Capsaicin: Cellular Targets, Mechanisms of Action, and 3.00/0
merican Society for Pharmacology and Experimental Therapeutics
Nechanisms of Action
Selectivity for Thin Sensory Neurons*
FETER HOLZER† PETER HOLZERt *Department* of *Experimental and Clinical Pharmacology, University of Graz, Graz, Austria*

I. Introduction

I. Introduction
THE function of primary afferent neurons is to receive
and transmit information from the internal and external
environment and thereby contribute to the organism's I. Introduction
THE function of primary afferent neurons is to receive
and transmit information from the internal and external
environment and thereby contribute to the organism's

THE function of primary afferent neurons is to receive
and transmit information from the internal and external
and external sensory ganglia and send fibers in both
anyironment and thereby contribute to the organism's
the c ability to maintain homeostasis. The cell bodies of primary afferent neurons are located in the cell bodies of pri-
mary afferent neurons are located in the spinal (dorsal
root) or cranial sensory ganglia and send fibers in both root) ability to maintain homeostasis. The cell bodies of pri-
mary afferent neurons are located in the spinal (dorsal
root) or cranial sensory ganglia and send fibers in both
the central and peripheral directions. The end ability to maintain homeostasis. The cell bodies of primary afferent neurons are located in the spinal (dorsal
root) or cranial sensory ganglia and send fibers in both
the central and peripheral directions. The endings of

HARN

PHARMACOLOGICAL REVIEWS

CAPSAIC
peripheral fibers may be either receptors themselves or
are connected to special sensory structures. Much of the CAPSAICI
peripheral fibers may be either receptors themselves or
are connected to special sensory structures. Much of the
current information concerning the histochemistry, In CA
peripheral fibers may be either receptors themselves
are connected to special sensory structures. Much of t
current information concerning the histochemisti
physiology, and pathophysiology of primary afferent ne peripheral fibers may be either receptors themselves on are connected to special sensory structures. Much of the current information concerning the histochemistry physiology, and pathophysiology of primary afferent neu-
ro peripheral fibers may be either receptors themselves or sare connected to special sensory structures. Much of the neurrent information concerning the histochemistry, Inphysiology, and pathophysiology of primary afferent ne are connected to special sensory structures. Much of the current information concerning the histochemistry, physiology, and pathophysiology of primary afferent neurons has been obtained in the last 15 years. This resulted current information concerning the histochemistry, In
physiology, and pathophysiology of primary afferent neu-
rons has been obtained in the last 15 years. This resulted co
not only from the advent of new experimental tech physiology, and pathophysiology of primary afferent ne
rons has been obtained in the last 15 years. This result
not only from the advent of new experimental techniqu
but also from the availability of capsaicin which, durit rons has been obtained in the
not only from the advent of
but also from the availabilit
this time, proved to be an
tool in sensory neuroscience
Capsaicin is the pungent t only from the advent of new experimental techniques cit also from the availability of capsaicin which, during us
is time, proved to be an important pharmacological to
ol in sensory neuroscience.
Capsaicin is the pungent

but also from the availability of capsaicin which, during usu
this time, proved to be an important pharmacological to s
tool in sensory neuroscience. The capsaicin is the pungent ingredient in a wide variety diss
of red pe this time, proved to be an important pharm
tool in sensory neuroscience.
Capsaicin is the pungent ingredient in a wiver
of red peppers of the genus Capsicum. Chemica
derivative of vanillyl amide, 8-methyl-N-van
nenamide (f tool in sensory neuroscience.
Capsaicin is the pungent ingredient in a wide variety
of red peppers of the genus *Capsicum*. Chemically, it is a
derivative of vanillyl amide, 8-methyl-N-vanillyl-6-no-
nenamide (fig. 1) and Capsaicin is the pungent ingredient in a wide variety diversed of red peppers of the genus Capsicum. Chemically, it is a anderivative of vanillyl amide, 8-methyl-N-vanillyl-6-no-
nenamide (fig. 1) and has a molecular weig of red peppers of the genus Capsicum. Chemically, it is a derivative of vanillyl amide, 8-methyl-N-vanillyl-6-no-
nenamide (fig. 1) and has a molecular weight of 305.42.
Hot peppers have been eaten and used by humans since derivative of vanillyl amide, 8-methyl-N-vanillyl-6-no-
nenamide (fig. 1) and has a molecular weight of 305.42. M
Hot peppers have been eaten and used by humans since
prehistorical times (Lembeck, 1987b). A. Högyes (1878) nenamide (fig. 1) and has a molecular weight of 305.42. M
Hot peppers have been eaten and used by humans since ta
prehistorical times (Lembeck, 1987b). A. Högyes (1878) ex
was the first to state that the pungent and irrita Hot peppers have been eaten and used by humans since to prehistorical times (Lembeck, 1987b). A. Högyes (1878) exas the first to state that the pungent and irritant action cof capsicol, an extract of *Capsicum*, is mediat prehistorical times (Lembeck, 1987b). A. Högyes (1878)
was the first to state that the pungent and irritant action
of capsicol, an extract of *Capsicum*, is mediated mainl
by sensory nerves. It was not before the middle of was the first to state that the pungent and irritant action
of capsicol, an extract of *Capsicum*, is mediated mainly
by sensory nerves. It was not before the middle of this
century, however, that another Hungarian investi of capsicol, an extract of *Capsicum*, is mediated mainly outly sensory nerves. It was not before the middle of this valentury, however, that another Hungarian investigator, m.
N. Jancsó, realized that capsaicin, the pure by sensory nerves. It was not before the middle of this century, however, that another Hungarian investigator, N. Jancsó, realized that capsaicin, the pure substance, also exerts a long-term sensory receptor-blocking actio N. Jancsó, realized that capsaicin, the pure substance, also exerts a long-term sensory receptor-blocking action which can be made use of in the functional investigation of afferent neurons (Jancsó, 1960, 1968; Szolcsányi, N. Jancsó, realized that capsaicin, the pure substanalso exerts a long-term sensory receptor-blocking act which can be made use of in the functional investigat of afferent neurons (Jancsó, 1960, 1968; Szolcsányi, 19
1984a) also exerts a long-term sensory receptor-blocking action 198
which can be made use of in the functional investigation 198
of afferent neurons (Jancsó, 1960, 1968; Szolcsányi, 1982, Cha
1984a). A large number of studies hav which can be made use of in the functional investigation 19
of afferent neurons (Jancsó, 1960, 1968; Szolcsányi, 1982, Cl
1984a). A large number of studies have since corrobo-
rated this discovery and established capsaicin of afferent neurons (Jancsó, 1960, 1968; Szolcsányi, 1982, Chassen (1984a). A large number of studies have since corrobo-
rated this discovery and established capsaicin as an comportant probe for sensory neuron mechanisms. 1984a). A large number of studies have since corroborated this discovery and established capsaicin as an important probe for sensory neuron mechanisms. The last few years have witnessed important insights into the mechanis rated this discovery and established capsaicin as an comportant probe for sensory neuron mechanisms. The last few years have witnessed important insights into the mechanism of action of capsaicin, and with these advances i important probe for sensory neuron mechanisms. The last few years have witnessed important insights into the mechanism of action of capsaicin, and with these advances it has become possible to put forward a framework hypot last few years have witnessed important in
mechanism of action of capsaicin, and v
vances it has become possible to put forware
hypothesis that explains the selectivity
action on a molecular and cellular basis.
With respec schanism of action of capsaicin, and with these ad-
nces it has become possible to put forward a framework
apothesis that explains the selectivity of capsaicin's
ation on a molecular and cellular basis.
With respect to pot hypothesis that explains the selectivity of capsaicin's and mechanisms of action.
action on a molecular and cellular basis.
With respect to potency, target, and mechanism of \quad II. Phenomenology and
action, two effects

hypothesis that explains the selectivity of capsaicin's action on a molecular and cellular basis.
With respect to potency, target, and mechanism of action, two effects of capsaicin can be differentiated: (*a*) One action i action on a molecular and cellular basis.
With respect to potency, target, and mechanism of
action, two effects of capsaicin can be differentiated: (a)
One action is grossly selective for thin afferent neurons
of mammali With respect to potency, target, and mechanism
action, two effects of capsaicin can be differentiated: (
One action is grossly selective for thin afferent neuro
of mammalian species and expresses itself in an init
short-la action, two effects of capsaicin can be differentiated: (a)
One action is grossly selective for thin afferent neurons
of mammalian species and expresses itself in an initial
short-lasting stimulation that can be followed b of mammalian species and expresses itself in an initial
short-lasting stimulation that can be followed by desen-
sitization of primary afferent neurons accord-
sitization to capsaicin and other stimuli of sensory neu-
ing of mammalian species and expresses itself in an initial
short-lasting stimulation that can be followed by desen-
sitization to capsaicin and other stimuli of sensory neu-
irons. With clearly suprathreshold doses of capsai short-lasting stimulation that can be followed by desensitization to capsaicin and other stimuli of sensory neurons. With clearly suprathreshold doses of capsaicin a term of long-term functional or even morphological abla sitization to capsaicin and other stimuli of sensory neu-
rons. With clearly suprathreshold doses of capsaicin a
long-term functional or even morphological ablation of
thin sensory neurons is achieved. Both the stimulant a rons. With clearly suprathreshold doses of capsaicin a long-term functional or even morphological ablation of $\frac{1}{2}$ thin sensory neurons is achieved. Both the stimulant and $\frac{1}{2}$ clong-term inhibitory effects of c long-term functional or even morphological ablation of
thin sensory neurons is achieved. Both the stimulant and
long-term inhibitory effects of capsaicin appear to arise
from a common mechanism of action, i.e., activation

FIG. 1. Chemical structures of capsaicin and resiniferatoxin.

sensory neurons. *(b)* The other action of capsaicin is cell 145
sensory neurons. (b) The other action of capsaicin is cell
nonselective and is seen throughout the animal kingdom.
In many, but not all, cases, it manifests itself as a IGIN

Sensory neurons. (b) The other action of capsaicin is cell

nonselective and is seen throughout the animal kingdom.

In many, but not all, cases, it manifests itself as a

transient depression of excitability with n sensory neurons. (b) The other action of capsaicin is cell
nonselective and is seen throughout the animal kingdom.
In many, but not all, cases, it manifests itself as a
transient depression of excitability with no long-las sensory neurons. (b) The other action of capsaicin is a nonselective and is seen throughout the animal kingdo In many, but not all, cases, it manifests itself as transient depression of excitability with no long-lastic co nonselective and is seen throughout the animal kingdom.
In many, but not all, cases, it manifests itself as a
transient depression of excitability with no long-lasting
consequences for the cell. The concentrations of capsa In many, but not all, cases, it manifests itself as a transient depression of excitability with no long-lasting consequences for the cell. The concentrations of capsaicin needed to elicit these cell-nonselective effects ar transient depression of excita
consequences for the cell. The
cin needed to elicit these ce
usually orders of magnitude h
to stimulate sensory neurons.
The scope of the present nsequences for the cell. The concentrations of capsai-
n needed to elicit these cell-nonselective effects are
ually orders of magnitude higher than those sufficient
stimulate sensory neurons.
The scope of the present artic

cin needed to elicit these cell-nonselective effects a
usually orders of magnitude higher than those sufficie
to stimulate sensory neurons.
The scope of the present article is to describe and
iscuss the phenomenology, cell usually orders of magnitude higher than those sufficient
to stimulate sensory neurons.
The scope of the present article is to describe and
discuss the phenomenology, cellular targets, and mech-
anisms of action of capsaici to stimulate sensory neurons.
The scope of the present article is to describe and
discuss the phenomenology, cellular targets, and mech-
anisms of action of capsaicin and to present an integrated
summary of the current neu discuss the phenomenology, cellular targets, and mechanisms of action of capsaicin and to present an integrated
summary of the current neuropharmacology of this drug.
My review concentrates on papers in which the cellular
 discuss the phenomenology, cellular targets, and mech-
anisms of action of capsaicin and to present an integrated
summary of the current neuropharmacology of this drug.
My review concentrates on papers in which the cellula anisms of action of capsaicin and to present an integrated
summary of the current neuropharmacology of this drug.
My review concentrates on papers in which the cellular
target and mechanism of the actions of capsaicin were summary of the current neuropharmacology of this drug.
My review concentrates on papers in which the cellular
target and mechanism of the actions of capsaicin were
explored and attempts to address the practical value of
ca My review concentrates on papers in which the cellular
target and mechanism of the actions of capsaicin were
explored and attempts to address the practical value of
capsaicin as a pharmacological research tool and to point target and mechanism of the actions of capsaicin werexplored and attempts to address the practical value of capsaicin as a pharmacological research tool and to poin out the limitations of its usefulness. Many other advance explored and attempts to address the practical value of capsaicin as a pharmacological research tool and to point out the limitations of its usefulness. Many other advances arising from the use of capsaicin have been summa capsaicin as a pharmacological research tool and to point
out the limitations of its usefulness. Many other ad-
vances arising from the use of capsaicin have been sum-
marized in various reviews (Nagy, 1982; Szolcsányi, 19 out the limitations of its usefulness. Many other advances arising from the use of capsaicin have been summarized in various reviews (Nagy, 1982; Szolcsányi, 1982, 1984a,b, 1990; Fitzgerald, 1983; Coleridge and Coleridge, vances arising from the use of capsaicin have been sum-
marized in various reviews (Nagy, 1982; Szolcsányi, 1982,
1984a,b, 1990; Fitzgerald, 1983; Coleridge and Coleridge,
1984; Russell and Burchiel, 1984; Marley and Livet 1984a,b, 1990; Fitzgerald, 1983; Coleridge and Coleridge, 1984; Russell and Burchiel, 1984; Marley and Livett, 1985; Buck and Burks, 1986; Lembeck, 1987a, 1988; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Don-nerer et 1984a,b, 1990; Fitzgerald, 1983; Coleridge and Coleridge,
1984; Russell and Burchiel, 1984; Marley and Livett,
1985; Buck and Burks, 1986; Lembeck, 1987a, 1988;
Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Don-
nerer e 1984; Russell and Burchiel, 1984; Marley and Livett, 1985; Buck and Burks, 1986; Lembeck, 1987a, 1988; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Donnerer et al., 1990; Lynn, 1990; Maggi, 1991) and are considered her 1985; Buck and Burks, 1986; Lembeck, 1987a, 1988;
Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Don-
nerer et al., 1990; Lynn, 1990; Maggi, 1991) and are
considered here only marginally. The disposition of the
article f Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Donnerer et al., 1990; Lynn, 1990; Maggi, 1991) and an considered here only marginally. The disposition of the acute to the inter-
acute follows the time course of capsaicin merer et al., 1990; Lynn, 1990; Maggi, 1991) and are considered here only marginally. The disposition of the article follows the time course of capsaicin's action on sensory neurons, proceeding from the acute to the interm considered here only marginally. The disposition of the article follows the time course of capsaicin's action on sensory neurons, proceeding from the acute to the intermediate and long-term effects of the drug. This order article follows the time cousensory neurons, proceeding
mediate and long-term effected
adhered to in the description
and mechanisms of action. II. **Phenomenology and Selectivity of the Actions**
II. **Phenomenology and Selectivity of the Actions**
II. **Phenomenology and Selectivity of the Actions**
of Capsaicin on Primary Afferent Neurons **of the description of both its cellular targe mechanisms of action.**
 Phenomenology and Selectivity of the Action of Capsaicin on Primary Afferent Neurons

Notes of Primary Afferent Neurons

A. Types of Primary Afferent Neurons II. Phenomenology and Selectivity of the Actions

of Capsaicin on Primary Afferent Neurons
A. Types of Primary Afferent Neurons
The classification of primary afferent neurons accord-
ing to morphological, functional, and neurochemical cri-
teria is dealt with here only to A. Types of Primary Afferent Neurons
The classification of primary afferent neurons accord-
ing to morphological, functional, and neurochemical cri-
teria is dealt with here only to the extent that the target
of action of A. 1 ypes of *Primary Afferent Neurons*

The classification of primary afferent neurons acc

ing to morphological, functional, and neurochemical

teria is dealt with here only to the extent that the ta

of action of capsai The classification of primary afferent neurons according to morphological, functional, and neurochemical criteria is dealt with here only to the extent that the target of action of capsaicin can be appreciated. *Morphologi* ing to morphological, functional, and neurochemical criteria is dealt with here only to the extent that the target
of action of capsaicin can be appreciated. Morphologi-
cally, primary afferent neurons are divided into tho teria is dealt with here only to the extent that the target
of action of capsaicin can be appreciated. *Morphologi-*
cally, primary afferent neurons are divided into those
having large light somata (A-type neurons) and tho of action of capsaicin can be appreciated. Morphologi-
cally, primary afferent neurons are divided into those
having large light somata (A-type neurons) and those
having small dark somata (B-type neurons), although
there i cally, primary afferent neurons are divided into those having large light somata (A-type neurons) and those having small dark somata (B-type neurons), although there is no sharp separation with respect to cell body diamete having large light somata (A-type neurons) and those having small dark somata (B-type neurons), although there is no sharp separation with respect to cell body diameter (for example, see Lawson and Harper, 1984). The size having small dark somata (B-type neurons), although
there is no sharp separation with respect to cell body
diameter (for example, see Lawson and Harper, 1984).
The size of the cell bodies is grossly, but not strictly,
rel there is no sharp separation with respect to cell body
diameter (for example, see Lawson and Harper, 1984).
The size of the cell bodies is grossly, but not strictly,
related to the diameter of the fibers that arise from th diameter (for example, see Lawson and Harper, 1984).
The size of the cell bodies is grossly, but not strictly,
related to the diameter of the fibers that arise from them
(Harper and Lawson, 1985; Hoheisel and Mense, 1986). The size of the cell bodies is grossly, but not strictly,
related to the diameter of the fibers that arise from them
(Harper and Lawson, 1985; Hoheisel and Mense, 1986).
Three groups of afferent nerve fibers can be separat related to the diameter of the fibers that arise from them (Harper and Lawson, 1985; Hoheisel and Mense, 1986).
Three groups of afferent nerve fibers can be separated:
(a) thick myelinated, (b) thin myelinated, and (c) th (Harper and Lawson, 1985; Hoheisel and Mense, 1986).
Three groups of afferent nerve fibers can be separated:
 (a) thick myelinated, (b) thin myelinated, and (c) thin
unmyelinated. This morphological heterogeneity of af-Three groups of afferent nerve fibers can be separated:

(a) thick myelinated, (b) thin myelinated, and (c) thin

unmyelinated. This morphological heterogeneity of af-

ferent nerve fibers is closely paralleled by a fun (a) thick myelinated, (b) thin myelinated, and (c) thin unmyelinated. This morphological heterogeneity of afferent nerve fibers is closely paralleled by a functional heterogeneity with regard to projection into differ unmyelinated. This morphological heterogeneent nerve fibers is closely paralleled by a heterogeneity with regard to projection integers of the spinal cord or medulla, conductional sensory modality (Salt and Hill, 1983). Ph *Physiologically* paralleled by a functional terogeneity with regard to projection into different wers of the spinal cord or medulla, conduction velocity, d sensory modality (Salt and Hill, 1983). *Physiologically*, the t heterogeneity with regard to projection into differen
layers of the spinal cord or medulla, conduction velocity
and sensory modality (Salt and Hill, 1983).
Physiologically, the thick myelinated fibers have the
highest c

hayers of the spinal cord or medulla, conduction velocity,
and sensory modality (Salt and Hill, 1983).
Physiologically, the thick myelinated fibers have the
highest conduction velocities ($A\alpha\beta$ -fibers) and carry non-

HOL
muscle. The thin unmyelinated fibers have the slowest
conduction velocities (C-fibers) and are primarily noci-He
muscle. The thin unmyelinated fibers have the slowes
conduction velocities (C-fibers) and are primarily noci-
ceptors (polymodal nociceptors, chemonociceptors 146
muscle. The thin unmyelinated fibers have the slowe
conduction velocities (C-fibers) and are primarily not
ceptors (polymodal nociceptors, chemonociceptor
which respond to noxious mechanical, thermal, and/ muscle. The thin unmyelinated fibers have the slowest
conduction velocities (C-fibers) and are primarily noci-
ceptors (polymodal nociceptors, chemonociceptors)
which respond to noxious mechanical, thermal, and/or
chemical muscle. The thin unmyelinated fibers have the slowest in
conduction velocities (C-fibers) and are primarily noci-
reptors (polymodal nociceptors, chemonociceptors) ac
which respond to noxious mechanical, thermal, and/or
ph conduction velocities (C-fibers) and are primarily inceptors (polymodal nociceptors, chemonocicep-
which respond to noxious mechanical, thermal, an
chemical stimuli. In addition, they also comprise appecific thermonocicept ceptors (polymodal nociceptors, chemonociceptors)
which respond to noxious mechanical, thermal, and/or
chemical stimuli. In addition, they also comprise some
specific thermonociceptors as well as some nonnocicep-
tive mec which respond to noxious mechanical, thermal, and/or
chemical stimuli. In addition, they also comprise some neur
specific thermonociceptors as well as some nonnocicep-
and
tive mechanical, warmth, and cold receptors. The chemical stimuli. In addition, they also comprise sor
specific thermonociceptors as well as some nonnocice
tive mechanical, warmth, and cold receptors. The sm
myelinated fibers conduct at intermediate velocities (A
fibers) specific thermonociceptors as well as some nonnociceptive mechanical, warmth, and cold receptors. The small myelinated fibers conduct at intermediate velocities ($A\delta$) fibers) and carry both nociceptive (mechanonocicepto tive mechanical, warmth, and cold receptors. The small
myelinated fibers conduct at intermediate velocities $(A\delta$ -
fibers) and carry both nociceptive (mechanonociceptors e
and polymodal nociceptors) and nonnociceptive (me myelinated fibers conduct at intermediate velocities (*A* fibers) and carry both nociceptive (mechanonociceptors) and polymodal nociceptors) and nonnociceptive (mechanoreceptors, cold receptors) information. The relation p fibers) and carry both nociceptive (mechanonociceptors
and polymodal nociceptors) and nonnociceptive (me-
chanoreceptors, cold receptors) information. The relative
proportions of these sensory receptors among the respec-
t

proportions of these sensory receptors among the respective afferent fiber classes show marked species differences.

Primary afferent neurons can be further differentiated

by their ultrastructural and by their *biochemica* tive afferent fiber classes show marked species differences.

Primary afferent neurons can be further differentiated

by their ultrastructural and by their *biochemical* and

histochemical properties. A large number of bio ences.

Primary afferent neurons can be further differentiated $\frac{8}{9}$

by their ultrastructural and by their *biochemical* and
 histochemical properties. A large number of bio- and $\frac{1}{1}$

histochemical markers ha Primary afferent neurons can be further differentiated
by their ultrastructural and by their biochemical and
histochemical properties. A large number of bio- and
histochemical markers has been found to be associated
with p histochemical properties. A large number of bio- and histochemical markers has been found to be associated with primary afferent neurons. The A-type neurons in the rat can be labeled selectively with RT97, a monoclo- nal a histochemical markers has been found to be associated histochemical markers has been found to be associated
with primary afferent neurons. The A-type neurons in
the rat can be labeled selectively with RT97, a monoclo-
nal antibody to a neurofilament protein that is absent
 C with primary afferent neurons. The A-type neurons in
the rat can be labeled selectively with RT97, a monoclo-
nal antibody to a neurofilament protein that is absent C_i
from B-type neurons (Lawson and Harper, 1984; Lawso the rat can be labeled selectively with RT97, a monoclo-
nal antibody to a neurofilament protein that is absent Ca
from B-type neurons (Lawson and Harper, 1984; Lawson et
et al., 1984; Kai-Kai et al., 1986; Winter, 1987). nal antibody to a neurofilament protein that is absent C
from B-type neurons (Lawson and Harper, 1984; Lawson
et al., 1984; Kai-Kai et al., 1986; Winter, 1987). Some this
biochemical and histochemical markers that have bee from B-type neurons (Lawson and Harper, 1984; Lawson et al., 1989). This painful sensation is produced by a
et al., 1984; Kai-Kai et al., 1986; Winter, 1987). Some threshold concentration of 30 nM capsaicin on the rat
bioc

en
include a number of peptides such as substance P, neu-
rokinin A, calcitonin gene-related peptide, galanin, vaso-ER
include a number of peptides such as substance P, neu
rokinin A, calcitonin gene-related peptide, galanin, vaso-
active intestinal polypeptide, and somatostatin whic ER
include a number of peptides such as substance P, neu-
rokinin A, calcitonin gene-related peptide, galanin, vaso-
active intestinal polypeptide, and somatostatin which
play a role in the communication of primary sensory include a number of peptides such as substance P, neurokinin A, calcitonin gene-related peptide, galanin, vaso-
active intestinal polypeptide, and somatostatin which
play a role in the communication of primary sensory
neur rokinin A, calcitonin gene-related peptide, galanin, vaso-
active intestinal polypeptide, and somatostatin which
play a role in the communication of primary sensory
neurons with other neuronal and nonneuronal cells (Salt
a and Hill, 1983; Weihe, 1990). The peptide markers are active intestinal polypeptide, and somatostatin which
play a role in the communication of primary sensory
neurons with other neuronal and nonneuronal cells (Salt
and Hill, 1983; Weihe, 1990). The peptide markers are
by no play a role in the communication of primary sensory
neurons with other neuronal and nonneuronal cells (Salt
and Hill, 1983; Weihe, 1990). The peptide markers are
by no means exclusive for afferent neurons but also label
ma meurons with other neuro
and Hill, 1983; Weihe, 1
by no means exclusive for
many neurons of the centeric nervous systems.
B. Acute Excitatory Effec and Tim, 1983, Welle, 1990). The peptide markets are
by no means exclusive for afferent neurons but also label
many neurons of the central, motor, autonomic, and
enteric nervous systems.
B. Acute Excitatory Effects of Caps *Sy* no means exclusion
many neurons of
enteric nervous sys
B. Acute Excitatory
Sensory Neurons
1. Excitatory thre

1. Acute Excitatory Effects of Capsaicin on Mammalian
1. Excitatory threshold doses or concentrations. On first
1. *Excitatory threshold doses or concentrations.* On first
ntact with capsaicin, afferent neurons are inv B. Acute Excitatory Effects of Capsaicin on Mammalian
Sensory Neurons
1. Excitatory threshold doses or concentrations. On first
contact with capsaicin, afferent neurons are invariably
stimulated, and there seems to be no g B. Acute Excitatory Effects of Capsaicin on Mammalian
Sensory Neurons
1. Excitatory threshold doses or concentrations. On first
contact with capsaicin, afferent neurons are invariably
stimulated, and there seems to be no g Sensory Neurons
1. Excitatory threshold doses or concentrations. On first
contact with capsaicin, afferent neurons are invariably
stimulated, and there seems to be no gross difference
whether the drug is applied to the per 1. Excitatory threshold doses or concentrations. On ficontact with capsaicin, afferent neurons are invarial stimulated, and there seems to be no gross different whether the drug is applied to the peripheral or cent endings contact with capsaicin, afferent neurons are invariably
stimulated, and there seems to be no gross difference
whether the drug is applied to the peripheral or central
endings or to the cell bodies of sensory neurons. Admin stimulated, and there seems to be no gross differen
whether the drug is applied to the peripheral or cent
endings or to the cell bodies of sensory neurons. Admi
istration of capsaicin to the peripheral nerve endir
results whether the drug is applied to the peripheral or central
endings or to the cell bodies of sensory neurons. Administration of capsaicin to the peripheral nerve endings
results in depolarization and discharge of action poten endings or to the cell bodies of sensory neurons. Administration of capsaicin to the peripheral nerve endings
results in depolarization and discharge of action potentials, which in turn evokes burning pain (Pórszász and
Ja istration of capsaicin to the peripheral nerve endings

results in depolarization and discharge of action poten-

tials, which in turn evokes burning pain (Pórszász and

Jancsó, 1959; Jancsó et al., 1968; Bernstein et al. results in depolarization and discharge of action potentials, which in turn evokes burning pain (Pórszász and Jancsó, 1959; Jancsó et al., 1968; Bernstein et al., 1981; Garpenter and Lynn, 1981; Geppetti et al., 1988b; Stj tials, which in turn evokes burning pain (Pórszász and Jancsó, 1959; Jancsó et al., 1968; Bernstein et al., 1981; Carpenter and Lynn, 1981; Geppetti et al., 1988b; Stjärne et al., 1989). This painful sensation is produced Jancsó, 1959; Jancsó et al., 1968; Bernstein et al., 1981;
Carpenter and Lynn, 1981; Geppetti et al., 1988b; Stjärne
et al., 1989). This painful sensation is produced by a
threshold concentration of 30 nM capsaicin on the Carpenter and Lynn, 1981; Geppetti et al., 1988b; Stjärne
et al., 1989). This painful sensation is produced by a
threshold concentration of 30 nM capsaicin on the rat
eye (Szolcsányi and Jancsó-Gábor, 1975) or blister base et al., 1989). This painful sensation is produced by a threshold concentration of 30 nM capsaicin on the rat eye (Szolcsányi and Jancsó-Gábor, 1975) or blister base in human skin (Szolcsányi, 1977), whereas the threshold c

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

TABLE 1

TABLE 1 Some markers of capsaicin-sensitive primary afferent neurons	
Adenosine deaminase	Nagy and Daddona, 1985
Arginine vasopressin	Kai-Kai et al., 1986
Bombesin/gastrin-releasing peptide	Decker et al., 1985
Calbindin D28k	Kashiba et al., 1990b
Calcitonin gene-related peptide	Gibbins et al., 1985; Lundberg et al., 1985; Skofitsch and Jacobowitz, 1985b; Franco- Cereceda et al., 1987b; Gibbins et al., 1987; Carr et al., 1990; Kashiba et al., 1990a
Cholecystokinin*	Jancsó et al., 1981; Gibbins et al., 1987
Cholecystokinin receptor binding	Ladenheim et al., 1986
Corticotropin-releasing factor†	Skofitsch et al., 1985
Dynorphin	Gibbins et al., 1987; Weihe, 1990
Fluoride-resistant acid phosphatase	Jancsó and Knyihár, 1975; Jessel et al., 1978; Ainsworth et al., 1981; Nagy et al., 1981a,b; Gamse et al., 1982; McDougal et al., 1983, 1985
GABA receptor binding	Singer and Placheta, 1980
Galanin	Skofitsch and Jacobowitz, 1985a
<i>ß-Glycerophosphatase</i>	Bucsics et al., 1988
5-Hydroxytryptamine receptor binding	Hamon et al., 1989
Lactoseries carbohydrate antigens	Kirchgessner et al., 1988
Leucine enkephalin	Weihe, 1990
Neurokinin A	Maggio and Hunter, 1984; Hua et al., 1985
Opiate receptor binding	Gamse et al., 1979a; Nagy et al., 1980; Laduron, 1984
Peptide histidine methionine	Chéry-Croze et al., 1989
Peripherin	Ferri et al., 1990
Somatostatin	Gamse et al., 1981b; Jancsó et al., 1981; Nagy et al., 1981a,b
Substance P	Jessell et al., 1978; Gamse et al., 1980, 1981b; Hayes and Tyers, 1980; Nagy et al., 1980, 1981a.b: Jancsó et al., 1981
Thiamine monophosphatase	Inomata and Nasu, 1984; Bucsics et al., 1988
Vasoactive intestinal polypeptide	Jancsó et al., 1981; Skofitsch et al., 1985

1986). thomata and Nasu, 1993; Butsics et al., 1995
soactive intestinal polypeptide
* Cholecystokinin-like immunoreactivity in rat sensory neurons (Jancsó et al., 1981) may represent calcitonin gene-related peptide (Ju et al., 19

et al., 1986).

CAPSAICIN
1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and of
1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and of
Harris, 1985). When given as an aerosol by nebulising resp CAPSAIC
humans is about 0.7 μ M (Szolcsányi and Jancsó-Gábor, e
1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and c
Harris, 1985). When given as an aerosol by nebulising r
solutions of capsaicin, concentrations of humans is about 0.7 μ M (Szolcsányi and Jancsó-Gábor, e
1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and c
Harris, 1985). When given as an aerosol by nebulising r
solutions of capsaicin, concentrations of $\geq 2 \mu$ humans is about 0.7 μ M (Szolcsányi and Jancsó-Gábor, 1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and Harris, 1985). When given as an aerosol by nebulising solutions of capsaicin, concentrations of $\geq 2 \mu$ M prod 1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and of Harris, 1985). When given as an aerosol by nebulising resolutions of capsaicin, concentrations of $\geq 2 \mu M$ produce Szoughing in humans (Collier and Fuller, 1984). solutions of capsaicin, concentrations of ≥ 2 μ M produce coughing in humans (Collier and Fuller, 1984). In the rat and monkey, intradermal doses of 30 nmol capsaicin are sufficient to activate polymodal nociceptors solutions of capsaicin, concentrations of ≥ 2 μ M produce Szolcsányi, 1987, 1990).
coughing in humans (Collier and Fuller, 1984). In the rat In the dog skeletal muscle, capsaicin has been found
and monkey, intraderm coughing in humans (Collier and Fuller, 1984). In the rat
and monkey, intradermal doses of 30 nmol capsaicin are
sufficient to activate polymodal nociceptors and to elicit
pain (Martin et al., 1987; LaMotte et al., 1988). and monkey, intradermal doses of 30 nmol capsaicin are to s
sufficient to activate polymodal nociceptors and to elicit grove
pain (Martin et al., 1987; LaMotte et al., 1988). Injected et a
close arterially to exteroceptive sufficient to activate polymodal nociceptors and to elicit
pain (Martin et al., 1987; LaMotte et al., 1988). Injected
close arterially to exteroceptive fields, doses of 0.07 nmol
in the cat (Szolcsányi, 1977) and guinea pi close arterially to exteroceptive fields, doses of 0.07 nmol
capsaicin in the cat (Szolcsányi, 1977) and guinea pig
(Szolcsányi et al., 1986), 0.3 nmol in the rat (Szolcsányi
et al., 1988), and 7 nmol in the rabbit (Szolcs capsaicin in the cat
(Szolcsányi et al., 19
et al., 1988), and 7 r
are suprathreshold
or producing pain.
This high potenc zolcsányi et al., 1986), 0.3 nmol in the rat (Szolcsányi stil al., 1988), and 7 nmol in the rabbit (Szolcsányi, 1987) appertually appertually a seen in vitro seen in vitro moducing pain.
This high potency of capsaicin is a

are suprathreshold in activating polymodal nociceptors
or producing pain.
This high potency of capsaicin is also seen in vitro
(Dray et al., 1989a, 1990a,b,d) and when capsaicin is
administered to the axons or somata of af or producing pain.
This high potency of capsaicin is also seen in vitro
(Dray et al., 1989a, 1990a,b,d) and when capsaicin is
administered to the axons or somata of afferent neurons.
Periaxonal concentrations as low as 30 This high potency of capsaicin is also seen in vitro mos
(Dray et al., 1989a, 1990a,b,d) and when capsaicin is 198-
administered to the axons or somata of afferent neurons. in k
Periaxonal concentrations as low as 30 to 10 (Dray et al., 1989a, 1990a,b,d) and when capsaicin is
administered to the axons or somata of afferent neurons.
Periaxonal concentrations as low as 30 to 100 nM cap-
saicin are capable of depolarizing afferent nerve fibers Periaxonal concentrations as low as 30 to 100 nM cap-
saicin to the rat vagus nerve depolarizes only
saicin are capable of depolarizing afferent nerve fibers in C-fibers (Bevan et al., 1987).
the rat isolated vagus, sciati Periaxonal concentrations as low as 30 to 100 nM capsaicin are capable of depolarizing afferent nerve fibers in
the rat isolated vagus, sciatic and sural nerves, or lumbar
dorsal roots (Ault and Evans, 1980; Yanagisawa et saicin are capable of depolarizing afferent nerve fibers in
the rat isolated vagus, sciatic and sural nerves, or lumbar
dorsal roots (Ault and Evans, 1980; Yanagisawa et al.,
1980; Hayes et al., 1984a; Bevan et al., 1987; the rat isolated vagus, sciatic and sural nerves, or lumbar
dorsal roots (Ault and Evans, 1980; Yanagisawa et al., ser
1980; Hayes et al., 1984a; Bevan et al., 1987; Marsh et On
al., 1987). Similar concentrations of capsai dorsal roots (Ault and Evans, 1980; Yanagisawa et al.
1980; Hayes et al., 1984a; Bevan et al., 1987; Marsh et
al., 1987). Similar concentrations of capsaicin depolarize
dorsal root and nodose ganglion cells of the rat in v 1980; Hayes et al., 1984a; Bevan et al., 1987; Marsh et On
al., 1987). Similar concentrations of capsaicin depolarize pr
dorsal root and nodose ganglion cells of the rat in vitro ne
or in culture (Williams and Zieglgänsber al., 1987). Similar concentrations of capsaicin depolarize
dorsal root and nodose ganglion cells of the rat in vitro
or in culture (Williams and Zieglgänsberger, 1982; Bac-
caglini and Hogan, 1983; Heyman and Rang, 1985; B dorsal root and nodose ganglion cells of the rat in vior in culture (Williams and Zieglgänsberger, 1982; Beaglini and Hogan, 1983; Heyman and Rang, 1985; Beart al., 1987; Marsh et al., 1987; Winter et al., 198
Behavioural or in culture (Williams and Zieglgänsberger, 1982; Bac-
caglini and Hogan, 1983; Heyman and Rang, 1985; Bevan to a
et al., 1987; Marsh et al., 1987; Winter et al., 1990). (La
Behavioural evidence indicates that intrathecal caglini and Hogan, 1983; Heyman and Rang, 1985; Beverting and Hogar, 1987; Winter et al., 1987; Winter et al., 1987; Behavioural evidence indicates that intrathecal, intradernal, or intracerebroventricular injection of 33 et al., 1987; Marsh et al., 1987; Winter et al., 1990). (Behavioural evidence indicates that intrathecal, intracisternal, or intracerebroventricular injection of 33 to 330 [1] mmol capsaicin activate the central endings of Behavioural evidence indicternal, or intracerebrovent
nmol capsaicin activate th
tive afferent nerve fibers
al., 1981b; Jancsó, 1981).
2. Targets and selectivity rnal, or intracerebroventricular injection of 33 to 330 Theorem and capsaicin activate the central endings of nocicepcare afferent nerve fibers (Yaksh et al., 1979; Gamse et the 1981b; Jancsó, 1981).

2. *Targets and selec*

nmol capsaicin activate the central endings of notive afferent nerve fibers (Yaksh et al., 1979; Gan al., 1981b; Jancsó, 1981).
2. Targets and selectivity of the excitatory action conjecture that pain receptors, but not me tive afferent nerve fibers (Yaksh et al., 1979; Gamse et the al., 1981b; Jancsó, 1981).

2. *Targets and selectivity of the excitatory action*. The all conjecture that pain receptors, but not mechanorecep-

tors, are activ al., 1981b; Jancsó, 1981).

2. Targets and selectivity of the excitatory action. The

conjecture that pain receptors, but not mechanorecep-

tors, are activated by capsaicin (Pórszász and Jancsó,

1959; Jancsó, 1968) was l 2. Targets and selectivity of the excitatory action. The conjecture that pain receptors, but not mechanoreceptors, are activated by capsaicin (Pórszász and Jancsó, 1959; Jancsó, 1968) was later confirmed by single-unit rec conjecture that pain receptors, but not mechanorecep-
tors, are activated by capsaicin (Pórszász and Jancsó, a
1959; Jancsó, 1968) was later confirmed by single-unit
recordings from cutaneous nerves. It is now evident that tors, are activated by capsaicin (Pórszász and Jancsó, al., 1959; Jancsó, 1968) was later confirmed by single-unit stine recordings from cutaneous nerves. It is now evident that hist the primary targets of the excitatory a 1959; Jancsó, 1968) was later confirmed by single-unit stinct recordings from cutaneous nerves. It is now evident that his the primary targets of the excitatory action of capsaicin otlare thin primary afferent neurons that recordings from cutaneous nerves. It is now evident that
the primary targets of the excitatory action of capsaicin
are thin primary afferent neurons that are connected to
distinct sensory receptors (table 2). When capsaici the primary targets of the excitatory action of capsaicin
are thin primary afferent neurons that are connected to
distinct sensory receptors (table 2). When capsaicin is
administered to the peripheral endings of cutaneous are thin primary afferent neurons that are connected to distinct sensory receptors (table 2). When capsaicin is administered to the peripheral endings of cutaneous sensory neurons of humans, cat, rabbit, and rat, many, but distinct sensory receptors (table 2). When capsaicin is and renal nerves (Coleridge and Coleridge, 1977, 1984;
administered to the peripheral endings of cutaneous sen-
sory neurons of humans, cat, rabbit, and rat, many, bu administered to the peripheral endings of cutaneous sensory neurons of humans, cat, rabbit, and rat, many, but
not all, C-fiber polymodal nociceptors (Szolcsányi, 1977,
1987; Foster and Ramage, 1981; Kenins, 1982; Konietzn sory neurons of humans, cat, rabbit, and rat, many, but
not all, C-fiber polymodal nociceptors (Szolcsányi, 1977,
1987; Foster and Ramage, 1981; Kenins, 1982; Konietzny
and Hensel, 1983; Martin et al., 1987; Szolcsányi et not all, C-fiber polymodal nociceptors (Szolcsányi, 1977
1987; Foster and Ramage, 1981; Kenins, 1982; Konietzn
and Hensel, 1983; Martin et al., 1987; Szolcsányi et al
1988; Lang et al., 1990), some C-fiber warmth receptor
 1987; Foster and Ramage, 1981; Kenins, 1982; Konietzny
and Hensel, 1983; Martin et al., 1987; Szolcsányi et al.,
1988; Lang et al., 1990), some C-fiber warmth receptors
(Szolcsányi, 1977, 1983a; Foster and Ramage, 1981; Ke and Hensel, 1983; Martin et al., 1987; Szolcsányi et al., 1988; Lang et al., 1990), some C-fiber warmth receptors is
(Szolcsányi, 1977, 1983a; Foster and Ramage, 1981; Kennis, 1982), and some Aô-fiber polymodal nociceptors 1988; Lang et al., 1990), some C-fiber warmth receptors (Szolcsányi, 1977, 1983a; Foster and Ramage, 1981; Kenins, 1982), and some $A\delta$ -fiber polymodal nociceptors (Matsumiya et al., 1983; Szolcsányi et al., 1988; Hartun (Szolcsányi, 1977, 1983a; Foster and Ramage, 1981; Kerins, 1982), and some A δ -fiber polymodal nociceptor (Matsumiya et al., 1983; Szolcsányi et al., 1988; Harturet al., 1989) are stimulated. Accordingly, perineural app ins, 1982), and some A δ -fiber polymodal nociceptors characteristic (Matsumiya et al., 1983; Szolcsányi et al., 1988; Hartung idet al., 1989) are stimulated. Accordingly, perineural apimplication of capsaicin to the cat (Matsumiya et al., 1983; Szolcsányi et al., 1988; Hartung ide
et al., 1989) are stimulated. Accordingly, perineural ap-
plication of capsaicin to the cat saphenous nerve depo-
tion
larizes C-fibers and some $A\delta$ -fibers (plication of capsaicin to the cat saphenous nerve depo-
larizes C-fibers and some A δ -fibers (Such and Jancsó, nociceptors remains to be determined.
1986). Other types of cutaneous C-fiber afferents such When administere plication of capsaicin to the cat saphenous nerve depolarizes C-fibers and some A δ -fibers (Such and Jancsó, 1986). Other types of cutaneous C-fiber afferents such as low- and high-threshold mechanoreceptors and cold rec larizes C-fibers and some A δ -fibers (Such and Jancsó, no
1986). Other types of cutaneous C-fiber afferents such
as low- and high-threshold mechanoreceptors and cold
receptors are not affected by capsaicin (Kenins, 1982;

humans is about 0.7 μ M (Szolcsányi and Jancsó-Gábor, exception of some A δ -fiber polymodal nociceptors, none
1975; Szolcsányi, 1977; Rozin et al., 1981; Sizer and of the cutaneous A δ - and A β -fiber afferents app EXEMBLE 147

exception of some A δ -fiber polymodal nociceptors, none

of the cutaneous A δ - and A β -fiber afferents appear to CIN
exception of some A δ -fiber polymodal nociceptors, none
of the cutaneous A δ - and A β -fiber afferents appear to
respond to capsaicin (Foster and Ramage, 1981; 147
exception of some $A\delta$ -fiber polymodal nociceptors, none
of the cutaneous $A\delta$ - and $A\beta$ -fiber afferents appear to
respond to capsaicin (Foster and Ramage, 1981;
Szolcsányi, 1987, 1990). respond to capsaicin (Foster and Ramage, 1981;
Szolcsányi, 1987, 1990).
In the dog skeletal muscle, capsaicin has been found ception of some $A\delta$ -fiber polymodal nociceptors, none
the cutaneous $A\delta$ - and $A\beta$ -fiber afferents appear to
spond to capsaicin (Foster and Ramage, 1981;
olcsányi, 1987, 1990).
In the dog skeletal muscle, capsaicin ha

close arterially to exteroceptive fields, doses of 0.07 nmol in the knee joint of the cat in which most of the group
capsaicin in the cat (Szolcsányi, 1977) and guinea pig IV and some of the group III articular afferents a are suprathreshold in activating polymodal nociceptors afferent neurons as it does with somatic afferents; cap-
or producing pain.
This high potency of capsaicin is also seen in vitro mosensitive $A\delta$ -fibers (Coleridge a of the cutaneous $A\delta$ - and $A\beta$ -fiber afferents appear to
respond to capsaicin (Foster and Ramage, 1981;
Szolcsányi, 1987, 1990).
In the dog skeletal muscle, capsaicin has been found
to stimulate the majority of group I respond to capsaicin (Foster and Ramage, 1981;
Szolcsányi, 1987, 1990).
In the dog skeletal muscle, capsaicin has been found
to stimulate the majority of group IV (C-fiber) and some
group III (A δ -fiber) skeletal muscle Szolcsányi, 1987, 1990).

In the dog skeletal muscle, capsaicin has been found

to stimulate the majority of group IV (C-fiber) and some

group III (A δ -fiber) skeletal muscle afferents (Kaufman

et al., 1982). Exactly In the dog skeletal muscle, capsaicin has been found
to stimulate the majority of group IV (C-fiber) and some
group III (A δ -fiber) skeletal muscle afferents (Kaufman
et al., 1982). Exactly the same spectrum of action i to stimulate the majority of group IV (C-fiber) and some
group III (A δ -fiber) skeletal muscle afferents (Kaufman
et al., 1982). Exactly the same spectrum of action is seen
in the knee joint of the cat in which most of et al., 1982). Exactly the same spectrum of action is seen in the knee joint of the cat in which most of the group in the knee joint of the cat in which most of the group IV and some of the group III articular afferents are stimulated by the drug (He et al., 1988, 1990). Capsaicin appears to have an equivalent target of action on visce IV and some of the group III articular afferents are
stimulated by the drug (He et al., 1988, 1990). Capsaicin
appears to have an equivalent target of action on visceral
afferent neurons as it does with somatic afferents; stimulated by the drug (He et al., 1988, 1990). Capsaicin
appears to have an equivalent target of action on visceral
afferent neurons as it does with somatic afferents; cap-
saicin preferentially stimulates C- but also so afferent neurons as it does with somatic afferents; capafferent neurons as it does with somatic afferents; c
saicin preferentially stimulates C- but also some c
mosensitive A δ -fibers (Coleridge and Coleridge, 19
1984; Longhurst et al., 1984; Szolcsányi, 1984b). This
in kee saicin preferentially stimulates C- but also some chemosensitive $A\delta$ -fibers (Coleridge and Coleridge, 1977, 1984; Longhurst et al., 1984; Szolcsányi, 1984b). This is in keeping with the observation that perineural appli mosensitive A δ -fibers (Colerian 1984; Sin keeping with the observation of capsaicin to the rat vage.
C-fibers (Bevan et al., 1987).
Polymodal nociceptors are u 84; Longhurst et al., 1984; Szolcsányi, 1984b). This is
keeping with the observation that perineural applica-
on of capsaicin to the rat vagus nerve depolarizes only
fibers (Bevan et al., 1987).
Polymodal nociceptors are u tion of capsaicin to the rat vagus nerve depolarizes only C-fibers (Bevan et al., 1987).
Polymodal nociceptors are usually identified by their

tion of capsaicin to the rat vagus nerve depolarizes only C-fibers (Bevan et al., 1987).

Polymodal nociceptors are usually identified by their

sensitivity to mechanical and thermal noxious stimuli.

Only recently has it C-fibers (Bevan et al., 1987).

Polymodal nociceptors are usually identified by their

sensitivity to mechanical and thermal noxious stimuli.

Only recently has it been recognized that a considerable

proportion of C-fiber Polymodal nociceptors are usually identified by their
sensitivity to mechanical and thermal noxious stimuli
Only recently has it been recognized that a considerable
proportion of C-fiber afferents in somatic and viscers
ne sensitivity to mechanical and thermal noxious stimuli.
Only recently has it been recognized that a considerable
proportion of C-fiber afferents in somatic and visceral
nerves do not respond to excessive mechanical and ther Only recently has it been recognized that a considerable
proportion of C-fiber afferents in somatic and visceral
nerves do not respond to excessive mechanical and ther-
mal stimulation ("silent nociceptors") but are sensit proportion of C-fiber afferents in somatic and visceral
nerves do not respond to excessive mechanical and ther-
mal stimulation ("silent nociceptors") but are sensitive
to algesic chemicals such as bradykinin and histamine nerves do not respond to excessive mechanical and thermal stimulation ("silent nociceptors") but are sensitive
to algesic chemicals such as bradykinin and histamine
(LaMotte et al., 1988; Schaible and Schmidt, 1988;
Häbler mal stimulation ("silent nociceptors") but are sensito algesic chemicals such as bradykinin and histam (LaMotte et al., 1988; Schaible and Schmidt, 19
Häbler et al., 1990; McMahon and Koltzenburg, 19
These chemonociceptors to algesic chemicals such as bradykinin and histamine (LaMotte et al., 1988; Schaible and Schmidt, 1988; Häbler et al., 1990; McMahon and Koltzenburg, 1990).
These chemonociceptors acquire sensitivity to mechanical stimuli Häbler et al., 1990; McMahon and Koltzenburg, 1990).
These chemonociceptors acquire sensitivity to mechanical stimuli during inflammation. All afferent C-fibers in
the rabbit great auricular nerve that respond to brady-
ki Häbler et al., 1990; McMahon and Koltzenburg, 1
These chemonociceptors acquire sensitivity to mech
cal stimuli during inflammation. All afferent C-fibe
the rabbit great auricular nerve that respond to bi
kinin are also sen These chemonociceptors acquire sensitivity to mechani-
cal stimuli during inflammation. All afferent C-fibers in
the rabbit great auricular nerve that respond to brady-
kinin are also sensitive to capsaicin injected intraa cal stimuli during inflammation. All afferent C-fibers in
the rabbit great auricular nerve that respond to brady-
kinin are also sensitive to capsaicin injected intraarteri-
ally into the ear (Szolcsányi, 1987). Similarly, the rabbit great auricular nerve that respond to brady-
kinin are also sensitive to capsaicin injected intraarteri-
ally into the ear (Szolcsányi, 1987). Similarly, those
afferent C-fibers in the skin of the monkey (LaMott kinin are also sensitive to capsaicin injected intraarterially into the ear (Szolcsányi, 1987). Similarly, those afferent C-fibers in the skin of the monkey (LaMotte et al., 1988) and the rat (Lang et al., 1990) which are ally into the ear (Szolcsányi, 1987). Similarly, those
afferent C-fibers in the skin of the monkey (LaMotte et
al., 1988) and the rat (Lang et al., 1990) which are
stimulated by capsaicin are, in addition, responsive to
hi afferent C-fibers in the skin of the monkey (LaMotte et al., 1988) and the rat (Lang et al., 1990) which are stimulated by capsaicin are, in addition, responsive to histamine or bradykinin. Sensitivity to capsaicin and oth al., 1988) and the rat (Lang et al., 1990) which are stimulated by capsaicin are, in addition, responsive to histamine or bradykinin. Sensitivity to capsaicin and other algesic chemicals is shared in an analogous manner by stimulated by capsaicin are, in addition, responsive to
histamine or bradykinin. Sensitivity to capsaicin and
other algesic chemicals is shared in an analogous manner
by visceral afferent C-fibers in, for example, the vaga histamine or bradykinin. Sensitivity to capsaicin and
other algesic chemicals is shared in an analogous manner
by visceral afferent C-fibers in, for example, the vagal
and renal nerves (Coleridge and Coleridge, 1977, 1984; other algesic chemicals is shared in an analogous manner
by visceral afferent C-fibers in, for example, the vagal
and renal nerves (Coleridge and Coleridge, 1977, 1984;
Longhurst et al., 1984; Szolcsányi, 1984b). In contra by visceral afferent C-fibers in, for example, the vagal
and renal nerves (Coleridge and Coleridge, 1977, 1984;
Longhurst et al., 1984; Szolcsányi, 1984b). In contrast,
there is much less overlap between cutaneous units se and renal nerves (Coleridge and Coleridge, 1977, 1984;
Longhurst et al., 1984; Szolcsányi, 1984b). In contrast,
there is much less overlap between cutaneous units sen-
sitive to capsaicin and units responsive to mechanical Longhurst et al., 1984; Szolcsányi, 1984b). In contrast,
there is much less overlap between cutaneous units sensitive to capsaicin and units responsive to mechanical
noxious stimulation (LaMotte et al., 1988; Lang et al.,
 there is much less overlap between cutaneous units s
sitive to capsaicin and units responsive to mechan
noxious stimulation (LaMotte et al., 1988; Lang et
1990). Thus, it appears as if responsiveness to capsai
is a particu sitive to capsaicin and units responsive to mechanical
noxious stimulation (LaMotte et al., 1988; Lang et al.,
1990). Thus, it appears as if responsiveness to capsaicin
is a particular property of C-fiber chemonociceptors, noxious stimulation (LaMotte et al., 1988; Lang et al., 1990). Thus, it appears as if responsiveness to capsaicin
is a particular property of C-fiber chemonociceptors,
which might be of great practical value in probing the 1990). Thus, it appears as if responsiveness to capsaicin
is a particular property of C-fiber chemonociceptors,
which might be of great practical value in probing the
chemical sensitivity of polymodal nociceptors and in
id is a particular property of C-fiber chemonociceptors
which might be of great practical value in probing the
chemical sensitivity of polymodal nociceptors and in
identifying silent nociceptors as suggested by Szolcsány
in 1 which might be of great practical value in probing the chemical sensitivity of polymodal nociceptors and in identifying silent nociceptors as suggested by Szolcsányi in 1984 (Szolcsányi, 1984b). However, the precise relati chemical sensitivity of polymodal ridentifying silent nociceptors as sugge
in 1984 (Szolcsányi, 1984b). Howeve
tionship between capsaicin-sensitive
nociceptors remains to be determined
When administered to the cell bod entifying silent nociceptors as suggested by Szolcsányi
1984 (Szolcsányi, 1984b). However, the precise rela-
onship between capsaicin-sensitive afferents and silent
ciceptors remains to be determined.
When administered to

in 1984 (Szolcsányi, 1984b). However, the precise relationship between capsaicin-sensitive afferents and silent nociceptors remains to be determined.
When administered to the cell bodies of afferent neurons, capsaicin stim tionship between capsaicin-sensitive afferents and silent
nociceptors remains to be determined.
When administered to the cell bodies of afferent neu-
rons, capsaicin stimulates only somata that are con-
nected to C-fibers nociceptors remains to be determined.
When administered to the cell bodies of afferent neu-
rons, capsaicin stimulates only somata that are con-
nected to C-fibers as observed both in vitro (Heyman
and Rang, 1985; Bevan et

148 HOLZER

TABLE 2

- -
- Targets and selectivity of capsaicin's actions on excitable cells in mammals*

Acute effects

1. Excitation of primary afferent neurons (high potency)

a. Application of capsaicin to peripheral endings of sensory neurons:
 ation of primary afferent neurons (high potency)
pplication of capsaicin to peripheral endings of sensory neurons:
Excitation of most, if not all, unmyelinated afferent axons (C-fibers) c
Excitation of some afferent C-fibe pplication of capsaicin to peripheral endings of sensory neurons:
Excitation of most, if not all, unmyelinated afferent axons (C-fibers) connected to chemonociceptors
Excitation of many unmyelinated afferent axons (C-fibe Excitation of most, if not all, unmyelinated afferent axons (C-fibers) connected to chemonociceptors

Excitation of many unmyelinated afferent axons (C-fibers, group IV afferents) connected to polymodal nociceptors

Excit
- *2. Excitation of some afferent C-fibers connected to warmth receptors*
 2. Excitation of capsaicin to cell bodies in sensory ganglia:
 2. Excitation of thermosensitive neurons in the preoptic region of the hypothalamus
-
-
-
- *3. Contraction of thermosensitive neurons in the preoptic region of the hypothalamus*
 4. *Inhibition of the activity of cardiac and visceral smooth muscle (low potency)*

5. *Variable effects on a variety of excitable* **5. Excitation of thermosensitive neurons in the preoptic region of the hypothalamus**
5. Contraction of the activity of cardiac and visceral smooth muscle (low potency)
4. Inhibition of the activity of cardiac and visce Variable effects on a variety of excitable cells (effects on the cell membrane and on cytoplasmic systems, typically produced by very hieron concentrations of capsaicin)
 a. Ablation of primary afferent neurons
 a. Abl

-
- **E.** Long-term neurotoxic effects
2. Ablation of primary afferent neurons
a. Ablation of majority of afferent neurons with small-diameter somata (small dark B-type somata, neurofilament protein-negative, nentrations of capsaicin)

m neurotoxic effects

n of primary afferent neurons

tion of majority of afferent neurons with small-diar

typically containing the markers listed in table 1)

tion of minority of afferent neuron
	-
	- **Ablation of primary afferent neurons**
 Ablation of primary afferent neurons
 Ablation of majority of afferent neurons
 Ablation of majority of afferent neurons with small-diameter somata (small dark B-type somata, typically containing the markers listed in table 1)
b. Ablation of minority of afferent neurons with somata of intermediate diameter (light A-type somata, neurofilament prot
c. Ablation of majority of afferent neurons with 2. Ablation of majority of afferent neurons with unmyelinated axons (C-ficted components), or warmth receptors
d. Ablation of minority of afferent neurons with thinly myelinated axons (a)
2. Secondary effects on systems re c. Ablation of majority of afferent neurons with unmyelinated axons
chemoceptors, or warmth receptors
d. Ablation of minority of afferent neurons with thinly myelinated axo
Secondary effects on systems related to capsaicin chemoceptors, or warmth receptors

	d. Ablation of minority of afferent neurons with thinly myelinated axons $(A\delta$ -fibers) connected to polymodal nociceptors

	2. Secondary effects on systems related to capsaicin-sensitive
		-
		-
		- d. Ablation of minority of afferent neurons with thinly my
Secondary effects on systems related to capsaicin-sensitive a
a. Reorganization of capsaicin-insensitive primary afferent
b. Alterations in second and higher-order
		-
		-
	-
	-

2. Secondary effects on systems related to capsaicin-sensitive afferent neurons
a. Reorganization of capsaicin-insensitive primary afferent neurons
b. Alterations in second and higher-order afferent pathways in the central

3. Ablation of some neurons in the preoptic region of the hypothalamu 4. Ablation of some neurons in certain forebrain nuclei, in the retina, \cdot Potency and effectiveness of capsaicin depend on route of administre and in 1988), albeit one report holds that the drug activates and in tissue culture (Bevan et al., 1987; Wood et al., 1988), albeit one report holds that the drug activates somata connected to both C- and A-fibers (Williams and Fousney and enectiveness or capsaicin depend on route or administration
and in tissue culture (Bevan et al., 1987; Wood et al., of
1988), albeit one report holds that the drug activates (Sz
somata connected to both C- and and in tissue culture (B
1988), albeit one report
somata connected to bot!
Zieglgänsberger, 1982).
Taken together, capsa d in tissue culture (Bevan et al., 1987; Wood et al., 1988), albeit one report holds that the drug activates mata connected to both C- and A-fibers (Williams and eglgänsberger, 1982).
Taken together, capsaicin is selective 1988), albeit one report holds that the drug activates
somata connected to both C- and A-fibers (Williams and
Zieglgänsberger, 1982).
Taken together, capsaicin is selective in *stimulating*
primary afferent C- and A δ -f 4. Ablation of some neurons in certain forebrain nuclei, in the retina, and in the enteric nervous system (to be corroborated)

Potency and effectiveness of capsaicin depend on route of administration and age, strain, and

somata connected to both C- and A-fibers (Williams and cor

Zieglgänsberger, 1982).

Taken together, capsaicin is selective in *stimulating* glic

primary afferent C- and Aô-fibers, although a few other glic

A-fibers als Zieglgänsberger, 1982).

Taken together, capsaicin is selective in *stimulating*

primary afferent C- and A δ -fibers, although a few other

A-fibers also might respond to the drug (Williams and

Zieglgänsberger, 1982; L Taken together, capsaicin is selective in *stimulating* gl

primary afferent C- and $A\delta$ -fibers, although a few other

A-fibers also might respond to the drug (Williams and 19

Zieglgänsberger, 1982; Longhurst et al., 19 primary afferent C- and $A\delta$ -fibers, although a few otl
A-fibers also might respond to the drug (Williams a
Zieglgänsberger, 1982; Longhurst et al., 1984). Howev
not all C- and $A\delta$ -fibers and not all sensory neur
somat A-fibers also might respond to the drug (Williams and Zieglgänsberger, 1982; Longhurst et al., 1984). However, not all C- and A δ -fibers and not all sensory neuron somata connected to these fibers are sensitive to capsa Zieglgänsberger, 1982; Longhurst et al., 1984). However, et not all C- and A δ -fibers and not all sensory neuron (S somata connected to these fibers are sensitive to capsaicin. In terms of sensory receptors, it is nocic not all C- and $A\delta$ -fibers and not all sensory neuron (S
somata connected to these fibers are sensitive to capsai-
cin. In terms of sensory receptors, it is nociceptors (po-
lymodal nociceptors, silent nociceptors) and s cin. In terms of sensory receptors, it is nociceptors (po-
lymodal nociceptors, silent nociceptors) and some
warmth receptors that are stimulated by the drug. The
capsaicin-sensitive nociceptors seem to be characterized
by cin. In terms of sensory receptors, it is nociceptors (po-
lymodal nociceptors, silent nociceptors) and some S
warmth receptors that are stimulated by the drug. The T
capsaicin-sensitive nociceptors seem to be characterize lymodal nociceptors, silent nociceptors) and so
warmth receptors that are stimulated by the drug. "
capsaicin-sensitive nociceptors seem to be characteri
by their particular responsiveness to a variety of algo
chemicals an warmth receptors that are stimulated by the drug. The capsaicin-sensitive nociceptors seem to be characterized
by their particular responsiveness to a variety of algesic
chemicals and may, therefore, be designated as chemo capsaicin-sensitive nociceptors seem to be characterized chy their particular responsiveness to a variety of algesic refleming chemicals and may, therefore, be designated as chemonociceptors. Because there is indirect evid by their particular responsiveness to a variety of algesi
chemicals and may, therefore, be designated as chemor
ociceptors. Because there is indirect evidence that cap
saicin-sensitive afferents might, in addition, be acti chemicals and may, therefore, be designated as chemon-
ociceptors. Because there is indirect evidence that cap-
saicin-sensitive afferents might, in addition, be activated me
by innocuous chemical stimuli (for example, see ociceptors. Because there is indirect evidence that capsaicin-sensitive afferents might, in addition, be activated
by innocuous chemical stimuli (for example, see Mac-
Lean, 1985; Amann and Lembeck, 1986; Raybould and
Tach saicin-sensitive afferents might, in addition, be activated
by innocuous chemical stimuli (for example, see Mac-
Lean, 1985; Amann and Lembeck, 1986; Raybould and
Taché, 1988; South and Ritter, 1988; Forster et al., 1990), Lean, 1985; Amann and Lembeck, 1986; Raybould and Taché, 1988; South and Ritter, 1988; Forster et al., 1990), it is conceivable that sensitivity to capsaicin is a distinct trait of chemoceptive afferent neurons in general. aché, 1988; South and Ritter, 1988; Forster et al., 1990), s
is conceivable that sensitivity to capsaicin is a distinct ⁷
ait of chemoceptive afferent neurons in general. This
mjecture, however, requires direct experimen

trait of chemoceptive afferent neurons in general. This conjecture, however, requires direct experimental proof.
The selectivity of the excitatory action of capsaicin toward sensory neurons is best exemplified by the lack conjecture, however, requires direct experimental proof. of
The selectivity of the excitatory action of capsaicin tai
toward sensory neurons is best exemplified by the lack
prof a direct excitatory action on neurons other

cord (Ault and Evans, 1980; Marsh et al., 1987). fibers of cord and age, strain, and species of the mammat under study.

(Szolcsányi, 1982; Hori, 1984). Ventral roots of the spinal

cord (Ault and Evans, 1980; Marsh et al., 1987), fibers of

the optic nerve (Marsh et al., 1987), p of thermosensitive neurons in the hypothalar (Szolcsányi, 1982; Hori, 1984). Ventral roots of the spicord (Ault and Evans, 1980; Marsh et al., 1987), fiber the optic nerve (Marsh et al., 1987), pre- and postgalionic sympat of thermosensitive neurons in the hypothalamus
(Szolcsányi, 1982; Hori, 1984). Ventral roots of the spina
cord (Ault and Evans, 1980; Marsh et al., 1987), fibers of
the optic nerve (Marsh et al., 1987), pre- and postgan-
g (Szolcsányi, 1982; Hori, 1984). Ventral roots of the spinal
cord (Ault and Evans, 1980; Marsh et al., 1987), fibers of
the optic nerve (Marsh et al., 1987), pre- and postgan-
glionic sympathetic nerve fibers and sympatheti cord (Ault and Evans, 1980; Marsh et al., 1987), fibers of
the optic nerve (Marsh et al., 1987), pre- and postgan-
glionic sympathetic nerve fibers and sympathetic gan-
glion cells (Ault and Evans, 1986; Beccaglini and Hog the optic nerve (Marsh et al., 1987), pre- and postgan-
glionic sympathetic nerve fibers and sympathetic gan-
glion cells (Ault and Evans, 1980; Baccaglini and Hogan,
1983; Such and Jancsó, 1986; Bevan et al., 1987; Marsh
 glionic sympathetic nerve fibers and sympathetic ganglion cells (Ault and Evans, 1980; Baccaglini and Hogan, 1983; Such and Jancsó, 1986; Bevan et al., 1987; Marsh et al., 1987; Wood et al., 1988), and cerebellar neurons (ion cells (Ault and Evans, 1980; Baccaglini and Hogan, 1983; Such and Jancsó, 1986; Bevan et al., 1987; Marsh al., 1987; Wood et al., 1988), and cerebellar neurons salt and Hill, 1980) are not stimulated by capsaicin. Ther

by innocuous chemical stimuli (for example, see Mac-
Lean, 1980; Andoh et al., 1982; Braga et al.,
Lean, 1985; Amann and Lembeck, 1986; Raybould and
Taché, 1988; South and Ritter, 1988; Forster et al., 1990),
secondary con trait of chemoceptive afferent neurons in general. This stances and one cannot rule out that capsaicin is capable
conjecture, however, requires direct experimental proof. of activating certain nonsensory neurons. This unce 1983; Such and Jancsó, 1986; Bevan et al., 1987; Marsh
et al., 1987; Wood et al., 1988), and cerebellar neurons
(Salt and Hill, 1980) are not stimulated by capsaicin.
There is indirect evidence that neurons of the enteric
 et al., 1987; Wood et al., 1988), and cerebellar neurons (Salt and Hill, 1980) are not stimulated by capsaicin.
There is indirect evidence that neurons of the enteric
nervous system are not activated either (Barthó and
Szo (Salt and Hill, 1980) are not stimulated by capsaicin.
There is indirect evidence that neurons of the enteric
nervous system are not activated either (Barthó and
Szolcsányi, 1978; Barthó et al., 1982a; Holzer, 1984;
Takaki There is indirect evidence that neurons of the enteric
nervous system are not activated either (Barthó and
Szolcsányi, 1978; Barthó et al., 1982a; Holzer, 1984;
Takaki and Nakayama, 1989). The excitatory actions of
capsaic nervous system are not activated either (Barthó and Szolcsányi, 1978; Barthó et al., 1982a; Holzer, 1984; Takaki and Nakayama, 1989). The excitatory actions of capsaicin seen, for example, in neurons of the enteric nervous Szolcsányi, 1978; Barthó et al., 1982a; Holzer, 1984;
Takaki and Nakayama, 1989). The excitatory actions of
capsaicin seen, for example, in neurons of the enteric
nervous system (Barthó and Szolcsányi, 1978; Takaki
and Nak Takaki and Nakayama, 1989). The excitatory actions of capsaicin seen, for example, in neurons of the enteric nervous system (Barthó and Szolcsányi, 1978; Takaki and Nakayama, 1989), in the spinal cord (Yanagisawa et al., 1 capsaicin seen, for example, in neurons of the enteric
nervous system (Barthó and Szolcsányi, 1978; Takaki
and Nakayama, 1989), in the spinal cord (Yanagisawa et
al., 1980; Chung et al., 1985a; Urbán et al., 1985), in the
 nervous system (Barthó and Szolcsányi, 1978; Takaki
and Nakayama, 1989), in the spinal cord (Yanagisawa et
al., 1980; Chung et al., 1985a; Urbán et al., 1985), in the
medulla (Salt and Hill, 1980), and in certain areas of and Nakayama, 1989), in the spinal cord (Yanagisawa et al., 1980; Chung et al., 1985a; Urbán et al., 1985), in the medulla (Salt and Hill, 1980), and in certain areas of the brain (Rabe et al., 1980; Andoh et al., 1982; Br medulla (Salt and Hill, 1980), and in certain areas of the medulla (Salt and Hill, 1980), and in certain areas of the
brain (Rabe et al., 1980; Andoh et al., 1982; Braga et al.,
1987; Zagami and Lambert, 1991) are considered to be
secondary consequences of sensory neuron stimulati brain (Rabe et al., 1980; Andoh et al., 1982; Braga et al., 1987; Zagami and Lambert, 1991) are considered to be secondary consequences of sensory neuron stimulation. This argument, however, is not conclusive in all instan This argument, however, is not conclusive in all insecondary consequences of sensory neuron stimulation.
This argument, however, is not conclusive in all in-
stances and one cannot rule out that capsaicin is capable
of activating certain nonsensory neurons. This uncer-
tai This argument, however, is not conclusive in all instances and one cannot rule out that capsaicin is capable
of activating certain nonsensory neurons. This uncer-
tainty also applies to the finding that systemic capsaicin
 stances and one cannot rule out that capsaicin is capable of activating certain nonsensory neurons. This unce
tainty also applies to the finding that systemic capsaic
produces acute changes in the synthesis rate and leve
o of activating certain nonsensory neurons. This uncertainty also applies to the finding that systemic capsaicin
produces acute changes in the synthesis rate and levels
of monoamines in substantia nigra, striatum, and hypo-

aspet

utilization in certain forebrain nuclei (Szikszay and Lonutilization in
don, 1988).
The acute

CAPS
ilization in certain forebrain nuclei (Szikszay and Lon-
m, 1988).
The acute actions of capsaicin, however, are not re-
ricted to neurons (table 2), and there are a number of utilization in certain forebrain nuclei (Szikszay and London, 1988).

The acute actions of capsaicin, however, are not re-

stricted to neurons (table 2), and there are a number of the

reports of capsaicin influencing non utilization in certain forebrain nuclei (Szikszay and Lon-
don, 1988).
The acute actions of capsaicin, however, are not re-
stricted to neurons (table 2), and there are a number of
reports of capsaicin influencing nonneura don, 1988).
The acute actions of capsaicin, however, are not re-
stricted to neurons (table 2), and there are a number of
reports of capsaicin influencing nonneural systems.
These *cell-nonselective* effects of capsaicin a The acute actions of capsaicin, however, are not
stricted to neurons (table 2), and there are a numbe
reports of capsaicin influencing nonneural syste
These *cell-nonselective* effects of capsaicin and capsa
congeners incl stricted to neurons (table 2), and there are a number of reports of capsaicin influencing nonneural systems.
These *cell-nonselective* effects of capsaicin and capsaicin congeners include inhibition of cardiac muscle excit reports of capsaicin influencing nonneural systems. fr
These *cell-nonselective* effects of capsaicin and capsaicin Ir
congeners include inhibition of cardiac muscle excitabil-
ity (Zernig et al., 1984; Franco-Cereceda and These cell-nonselective effects of capsaicin and capsaicin
congeners include inhibition of cardiac muscle excitabil-
ity (Zernig et al., 1984; Franco-Cereceda and Lundberg,
1988), inhibition of visceral smooth muscle activ congeners include inhibition of cardiac muscle excitabil-
ity (Zernig et al., 1984; Franco-Cereceda and Lundberg,
1988), inhibition of visceral smooth muscle activity
(Szolcsányi and Barthó, 1978; Holzer and Lembeck,
1979; ity (Zernig et al., 1984; Franco-Cereceda and Lundberg, 1988), inhibition of visceral smooth muscle activity (Szolcsányi and Barthó, 1978; Holzer and Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, 1989b; T 1988), inhibition of visceral smooth muscle activity (Szolcsányi and Barthó, 1978; Holzer and Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, 1989b; Takaki et al., 1990), and contraction of vascular smooth (Szolcsányi and Barthó, 1978; Holzer and Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, 1989b; Takaki et al., 1990), and contraction of vascular smooth muscle (Donnerer and Lembeck, 1982; Duckles, 1986; Sa 1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, 1989b; Takaki et al., 1990), and contraction of vascular smooth muscle (Donnerer and Lembeck, 1982; Duckles, 1986; Saito et al., 1988; Bény et al., 1989; Edvinsson et 1989b; Takaki et al., 1990), and contraction of vascular smooth muscle (Donnerer and Lembeck, 1982; Duckles, 1986; Saito et al., 1988; Bény et al., 1989; Edvinsson et al., 1990; Holzer et al., 1990b). Contradictory data su smooth muscle (Donnerer and Lembeck, 1982; Duckles, 1986; Saito et al., 1988; Bény et al., 1989; Edvinsson et al., 1990; Holzer et al., 1990b). Contradictory data suggest that capsaicin and related substances might either 1986; Saito et al., 1988; Bény et al., 1989; Edvinsson et tem
al., 1990; Holzer et al., 1990b). Contradictory data suggest rise
that capsaicin and related substances might either en-
hance (Juan et al., 1980; Moritoki et a al., 1990; Holzer et al., 1990b). Contradictory data sugges
that capsaicin and related substances might either en
hance (Juan et al., 1980; Moritoki et al., 1990) or inhibi
(Flynn et al., 1986) the formation of prostanoids that capsaicin and related substances might either en-
hance (Juan et al., 1980; Moritoki et al., 1990) or inhibit 198
(Flynn et al., 1986) the formation of prostanoids in and
vascular tissue of rabbits and humans, respect hance (Juan et al., 1980; Moritoki et al., 1990) or inhibit (Flynn et al., 1986) the formation of prostanoids in vascular tissue of rabbits and humans, respectively, whereas no effect on prostanoid formation is observed in (Flynn et al., 1986) the formation of prostanoids in and vascular tissue of rabbits and humans, respectively, strees whereas no effect on prostanoid formation is observed in Sau the rat gastric mucosa (Holzer et al., 1990a vascular tissue of rabbits and humans, respectively, whereas no effect on prostanoid formation is observed in the rat gastric mucosa (Holzer et al., 1990a) and other tissues (Brand et al., 1990). In addition, capsaicin and whereas no effect on prostanoid formation is observed in
the rat gastric mucosa (Holzer et al., 1990a) and other
tissues (Brand et al., 1990). In addition, capsaicin and
its congeners have been reported to inhibit platelet the rat gastric mucosa (Holzer et al., 1990a) and oth
tissues (Brand et al., 1990). In addition, capsaicin ar
its congeners have been reported to inhibit platelet a
gregation (Wang et al., 1984, 1985; Brand et al., 1999
an tissues (Brand et al., 1990). In addition, capsaicin and
its congeners have been reported to inhibit platelet ag-
gregation (Wang et al., 1984, 1985; Brand et al., 1990)
and to influence a variety of enzymatic activities (its congeners have been reported to inhibit platelet ag-
gregation (Wang et al., 1984, 1985; Brand et al., 1990) et
and to influence a variety of enzymatic activities (Chu-
Sz
dapongse and Janthasoot, 1981; Ki et al., 1982 gregation (Wang et al., 1984, 1985; Brand et al., 1990)
and to influence a variety of enzymatic activities (Chu-
dapongse and Janthasoot, 1981; Ki et al., 1982; Miller et
al., 1983; Negulesco et al., 1983; Modly et al., 19 and to influence a variety of enzymatic activities (Chu-Sdapongse and Janthasoot, 1981; Ki et al., 1982; Miller et et al., 1983; Negulesco et al., 1983; Modly et al., 1986; De Sand Ghosh, 1989; Srinivasan and Satyanarayana dapongse and Janthasoot, 1981; Ki et al., 1982; Miller et al., 1983; Negulesco et al., 1983; Modly et al., 1986; De and Ghosh, 1989; Srinivasan and Satyanarayana, 1989; Savitha et al., 1990; Yagi 1990) and other cell and t al., 1983; Negulesco et al., 1983; Modly et al., 1986; De
and Ghosh, 1989; Srinivasan and Satyanarayana, 1989;
Savitha et al., 1990; Yagi 1990) and other cell and tissue
functions (Kenins et al., 1984; Nagabhushan and Bhid and Ghosh, 1989; Srinivasan and Satyanarayana, 1989; al., Savitha et al., 1990; Yagi 1990) and other cell and tissue and functions (Kenins et al., 1984; Nagabhushan and Bhide, 1985; Agarwal and Bhide, 1988; Gannett et al., Savitha et al., 1990; Yagi 1990) and other cell and tissue
functions (Kenins et al., 1984; Nagabhushan and Bhide,
1985; Agarwal and Bhide, 1988; Gannett et al., 1988;
Muralidhara and Narasimhamurthy, 1988; Lawson and
Ganne functions ()
1985; Agar
Muralidhar
Gannett, 19
al., 1990).
Importan 85; Agarwal and Bhide, 1988; Gannett et al., 1988; uralidhara and Narasimhamurthy, 1988; Lawson and sannett, 1989; Knyazev et al., 1990; Matucci-Cerinic et *lc*, 1990).
Importantly, many of the cell-nonselective effects of

Gannett, 1989; Knyazev et al., 1990; Matucci-Cerinic et al., 1990).

Importantly, many of the cell-nonselective effects of

capsaicin are produced by, or were studied with, doses of

the drug far in excess of those necessa al., 1990).
Importantly, many of the cell-nonselective effects
capsaicin are produced by, or were studied with, doses
the drug far in excess of those necessary to stimul
thin afferent neurons. For example, the sensory neur Importantly, many of the cell-nonselective effects of recapsaicin are produced by, or were studied with, doses of Chine drug far in excess of those necessary to stimulate so thin afferent neurons. For example, the sensory capsaicin are produced by, or were studied with, doses of Chate the drug far in excess of those necessary to stimulate son thin afferent neurons. For example, the sensory neuron-
selective and cell-nonselective effects of the drug far in excess of those necessary to stimulate
thin afferent neurons. For example, the sensory neuron-
selective and cell-nonselective effects of the drug in the
guinea pig ileum are separated by a dose ratio of 30 thin afferent neurons. For example, the sensory neuron-
selective and cell-nonselective effects of the drug in the
guinea pig ileum are separated by a dose ratio of 300 tc
3000 (Szolcsányi and Barthó, 1978; Barthó et al., selective and cell-nonselective effects of the drug in the smoguinea pig ileum are separated by a dose ratio of 300 to multipulant 3000 (Szolcsányi and Barthó, 1978; Barthó et al., 1987). gan In addition, capsaicin's nonse guinea pig ileum are separated by a dose ratio of 300
3000 (Szolcsányi and Barthó, 1978; Barthó et al., 198
In addition, capsaicin's nonselective actions differ pr
foundly from its stimulant action on sensory neurons
that 3000 (Szolcsányi and Barthó, 1978; Barthó et al., 1987).
In addition, capsaicin's nonselective actions differ pro-
foundly from its stimulant action on sensory neurons in
that they are sustained, do not undergo desensitiza In addition, capsaicin's nonselective actions differ pro-
foundly from its stimulant action on sensory neurons in
that they are sustained, do not undergo desensitization,
and are easily reproducible on reapplication of cap foundly from its stimulant action on sensory neurons in
that they are sustained, do not undergo desensitization,
and are easily reproducible on reapplication of capsaicin
(Szolcsányi and Barthó, 1978; Holzer and Lembeck,
1 that they are sustained, do not
and are easily reproducible on re
(Szolcsányi and Barthó, 1978;
1979; Barthó et al., 1982b, 198
1989b; Edvinsson et al., 1990).
3. Consequences of excitation: d are easily reproducible on reapplication of capsaicin
 *20*lcsányi and Barthó, 1978; Holzer and Lembeck,

79; Barthó et al., 1982b, 1987; Maggi et al., 1987c,

89b; Edvinsson et al., 1990).

3. Consequences of excitation (Szolcsányi and Barthó, 1978; Holzer and Lembeck, a
1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, ra
1989b; Edvinsson et al., 1990).
3. Consequences of excitation: afferent and local effector corpus of sensory neu

1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, rel

1989b; Edvinsson et al., 1990).

3. Consequences of excitation: afferent and local effector co

roles of sensory neurons. It is beyond the scope of this Tlarticl 1989b; Edvinsson et al., 1990). The
3. Consequences of excitation: afferent and local effector
roles of sensory neurons. It is beyond the scope of this
article to discuss all the functional consequences of the
capsaicin-i 3. Consequences of excitation: afferent and local effector roles of sensory neurons. It is beyond the scope of this article to discuss all the functional consequences of the capsaicin-induced stimulation of afferent neuron roles of sensory neurons. It is beyond the scope of this Thé article to discuss all the functional consequences of the 198 capsaicin-induced stimulation of afferent neurons. Given star the selectivity with which capsaicin article to discuss all the functional consequences of the capsaicin-induced stimulation of afferent neurons. Given the selectivity with which capsaicin stimulates thin afferent neurons, however, this drug was instrumental the selectivity with which capsaicin stimulates thin afferent neurons, however, this drug was instrumental in providing evidence (Jancsó, 1960, 1981) for a "dual sensory-efferent function" (Szolcsányi, 1984b) of afferent

neurons. Thus, excitation of nociceptive nerve fibers by
either capsaicin or other stimuli is followed not only by icin 149

neurons. Thus, excitation of nociceptive nerve fibers by

either capsaicin or other stimuli is followed not only by

conduction of nerve activity to the central nervous sys-149
neurons. Thus, excitation of nociceptive nerve fibers by
either capsaicin or other stimuli is followed not only by
conduction of nerve activity to the central nervous sys-
tem but also by the release of transmitter sub neurons. Thus, excitation of nociceptive nerve fibers by either capsaicin or other stimuli is followed not only by conduction of nerve activity to the central nervous system but also by the release of transmitter substance neurons. Thus, excitation of nociceptive nerve fibers by either capsaicin or other stimuli is followed not only by conduction of nerve activity to the central nervous system but also by the release of transmitter substance either capsaicin or other stimuli is followed not only conduction of nerve activity to the central nervous s
tem but also by the release of transmitter substan
from the activated peripheral nerve endings themsely
In additi conduction of nerve activity to the central nervous system but also by the release of transmitter substances
from the activated peripheral nerve endings themselves.
In addition, nerve activity may travel among the periph-
 tem but also by the release of transmitter substances
from the activated peripheral nerve endings themselves.
In addition, nerve activity may travel among the periph-
eral branches of sensory nerve fibers, and this process from the activated peripheral nerve endings themselves.
In addition, nerve activity may travel among the periph-
eral branches of sensory nerve fibers, and this process is
thought to account for local "axon reflexes" such In addition, nerve activity may travel among the peripheral branches of sensory nerve fibers, and this process is thought to account for local "axon reflexes" such as the spreading flare (vasodilatation) around a focal inj eral branches of sensory nerve fibers, and this proce
thought to account for local "axon reflexes" such a
spreading flare (vasodilatation) around a focal inju
the skin (for reviews of this concept, see Szolcs
1984b, 1988; ought to account for local "axon reflexes" such as the reading flare (vasodilatation) around a focal injury of e skin (for reviews of this concept, see Szolcsányi, 984b, 1988; Holzer, 1988; Maggi and Meli, 1988). The *affe*

spreading flare (vasodilatation) around a focal injury of
the skin (for reviews of this concept, see Szolcsányi,
1984b, 1988; Holzer, 1988; Maggi and Meli, 1988).
The *afferent function* of sensory neurons enables in-
form the skin (for reviews of this concept, see Szolcsányi, 1984b, 1988; Holzer, 1988; Maggi and Meli, 1988).
The *afferent function* of sensory neurons enables information to be transmitted to the central nervous system. Stimu 1984b, 1988; Holzer, 1988; Maggi and Meli, 1988).
The *afferent function* of sensory neurons enables information to be transmitted to the central nervous system. Stimulation of afferent neurons by capsaicin gives rise to a The *afferent function* of sensory neurons enables information to be transmitted to the central nervous system. Stimulation of afferent neurons by capsaicin gives rise to a painful sensation and activates protective reflex formation to be transmitted to the central nervous system. Stimulation of afferent neurons by capsaicin gives
rise to a painful sensation and activates protective re-
flexes including avoidance or escape reactions (Gamse,
 tem. Stimulation of afferent neurons by capsaicin
rise to a painful sensation and activates protectiv
flexes including avoidance or escape reactions (Ga
1982; Fitzgerald, 1983; Russell and Burchiel, 1984; 3
and Burks, 1986 rise to a painful sensation and activates protective re-
flexes including avoidance or escape reactions (Gamse,
1982; Fitzgerald, 1983; Russell and Burchiel, 1984; Buck
and Burks, 1986) or sneezing, coughing, and bronchoco flexes including avoidance or escape reactions (G₁
1982; Fitzgerald, 1983; Russell and Burchiel, 1984;
and Burks, 1986) or sneezing, coughing, and bronch
striction in response to airway irritation (Lundber;
Saria, 1987). 1982; Fitzgerald, 1983; Russell and Burchiel, 1984; B
and Burks, 1986) or sneezing, coughing, and bronchoc
striction in response to airway irritation (Lundberg
Saria, 1987). Other reflexes arising from capsaicin-
duced sti and Burks, 1986) or sneezing, coughing, and bronchoconstriction in response to airway irritation (Lundberg and Saria, 1987). Other reflexes arising from capsaicin-induced stimulation of sensory neurons involve thermoregula striction in response to airway irritation (Lundberg and Saria, 1987). Other reflexes arising from capsaicin-in-
duced stimulation of sensory neurons involve thermo-
regulatory (Rabe et al., 1980; Szikszay et al., 1982;
Sz Saria, 1987). Other reflexes arising from capsaicin-in-
duced stimulation of sensory neurons involve thermo-
regulatory (Rabe et al., 1980; Szikszay et al., 1982;
Szolcsányi, 1982; Donnerer and Lembeck, 1983; Hayes
et al., duced stimulation of sensory neurons involve thermo-
regulatory (Rabe et al., 1980; Szikszay et al., 1982;
Szolcsányi, 1982; Donnerer and Lembeck, 1983; Hayes
et al., 1984b; Hori, 1984; de Vries and Blumberg, 1989;
Szallas regulatory (Rabe et al., 1980; Szikszay et al., 1982;
Szolcsányi, 1982; Donnerer and Lembeck, 1983; Hayes
et al., 1984b; Hori, 1984; de Vries and Blumberg, 1989;
Szallasi and Blumberg, 1989), cardiovascular (Crayton
et al. Szolcsányi, 1982; Donnerer and Lembeck, 1983; Hayes
et al., 1984b; Hori, 1984; de Vries and Blumberg, 1989;
Szallasi and Blumberg, 1989), cardiovascular (Crayton
et al., 1981; Donnerer and Lembeck, 1982; Jancsó and
Such, 1 et al., 1984b; Hori, 1984; de Vries and Blumberg, 1989; Szallasi and Blumberg, 1989), cardiovascular (Crayton et al., 1981; Donnerer and Lembeck, 1982; Jancsó and Such, 1983; Ordway and Longhurst, 1983; Longhurst et al., 1 Szallasi and Blumberg, 1989), cardiovascular (Crayton
et al., 1981; Donnerer and Lembeck, 1982; Jancsó and
Such, 1983; Ordway and Longhurst, 1983; Longhurst et
al., 1984; Szolcsányi et al., 1986; Amann et al., 1989a),
and et al., 1981; Donnerer and
Such, 1983; Ordway and L
al., 1984; Szolcsányi et al.
and neuroendocrine (Mue
1988b) control mechanism
The local release of pept al., 1984; Szolcsányi et al., 1986; Amann et al., 1989a), and neuroendocrine (Mueller, 1981; Watanabe et al., 1988b) control mechanisms.
The local release of peptide mediators from peripheral

Muralidhara and Narasimhamurthy, 1988; Lawson and sensory nerve endings enables these neurons to exert a Gannett, 1989; Knyazev et al., 1990; Matucci-Cerinic et *local effector function* (Holzer, 1988), because the release al., 1984; Szolcsányi et al., 1986; Amann et al., 1989a),
and neuroendocrine (Mueller, 1981; Watanabe et al.,
1988b) control mechanisms.
The local release of peptide mediators from peripheral
sensory nerve endings enables and neuroendocrine (Mueller, 1981; Watanabe et al., 1988b) control mechanisms.
 The local release of peptide mediators from peripheral

sensory nerve endings enables these neurons to exert a
 local effector function (H 1988b) control mechanisms.
The local release of peptide mediators from peripheral
sensory nerve endings enables these neurons to exert a
local effector function (Holzer, 1988), because the released
peptides influence a var The local release of peptide mediators from peripheral
sensory nerve endings enables these neurons to exert a
local effector function (Holzer, 1988), because the released
peptides influence a variety of local tissue func sensory nerve endings enables these neurons to exert local effector function (Holzer, 1988), because the release
peptides influence a variety of local tissue functions (for
views, see Szolcsányi, 1984b; Lundberg and Saria, local effector function (Holzer, 1988), because the released
peptides influence a variety of local tissue functions (for
reviews, see Szolcsányi, 1984b; Lundberg and Saria, 1987;
Chahl, 1988; Holzer, 1988; Maggi and Meli, peptides influence a variety of local tissue functions (for
reviews, see Szolcsányi, 1984b; Lundberg and Saria, 1987;
Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Nils-
son, 1989; Donnerer et al., 1990). These include reviews, see Szolcsányi, 1984b; Lundberg and Saria, 1987;
Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Nils-
son, 1989; Donnerer et al., 1990). These include changes
in local blood flow, vascular permeability, cardiac Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Nils
son, 1989; Donnerer et al., 1990). These include change
in local blood flow, vascular permeability, cardiac an
smooth muscle activity, tissue growth and repair, im
muno son, 1989; Donnerer et al., 1990). These include chan
in local blood flow, vascular permeability, cardiac
smooth muscle activity, tissue growth and repair,
munological processes, and regulation of activity in p
ganglionic in local blood flow, vascular permeability, cardiac and
smooth muscle activity, tissue growth and repair, im-
munological processes, and regulation of activity in post-
ganglionic sympathetic efferents. Substance P, neurok smooth muscle activity, tissue growth and repair, im-
munological processes, and regulation of activity in post-
ganglionic sympathetic efferents. Substance P, neuroki-
nin A, calcitonin gene-related peptide, and vasoactiv ganglionic sympathetic efferents. Substance P, neurokinin A, calcitonin gene-related peptide, and vasoactive intestinal polypeptide are among the identified peptides released by capsaicin from peripheral endings of afferen ganglionic sympathetic efferents. Substance P, neurokinin A, calcitonin gene-related peptide, and vasoactive intestinal polypeptide are among the identified peptides released by capsaicin from peripheral endings of afferen nin A, calcitonin gene-related peptide, and vasoactive
intestinal polypeptide are among the identified peptides
released by capsaicin from peripheral endings of afferent
neurons (Holzer, 1988; Maggi and Meli, 1988; Saria e intestinal polypeptide are among the identified peptide
released by capsaicin from peripheral endings of afferer
neurons (Holzer, 1988; Maggi and Meli, 1988; Saria a
al., 1988; Maggi et al., 1989d). However, capsaicin als
 released by capsaicin from peripheral endings of afferent
neurons (Holzer, 1988; Maggi and Meli, 1988; Saria et
al., 1988; Maggi et al., 1989d). However, capsaicin also
releases substance P, somatostatin, and calcitonin ge neurons (Holzer, 1988; Maggi and Meli, 1988; Saria et al., 1988; Maggi et al., 1989d). However, capsaicin also releases substance P, somatostatin, and calcitonin generalated peptide from their central endings in the spinal al., 1988; Maggi et al., 1989d). However, capsaicin also releases substance P, somatostatin, and calcitonin generelated peptide from their central endings in the spinal cord in vitro and in vivo (Gamse et al., 1979b, 1981a releases substance P, somatostatin, and calcitonin gene-
related peptide from their central endings in the spinal
cord in vitro and in vivo (Gamse et al., 1979b, 1981a;
Thériault et al., 1979; Yaksh et al., 1980; Helke et related peptide from their central endings in the spinal
cord in vitro and in vivo (Gamse et al., 1979b, 1981a;
Thériault et al., 1979; Yaksh et al., 1980; Helke et al.,
1981b; Jhamandas et al., 1984; Saria et al., 1986). cord in vitro and in vivo (Gamse et al., 1979b, 1981a;
Thériault et al., 1979; Yaksh et al., 1980; Helke et al.,
1981b; Jhamandas et al., 1984; Saria et al., 1986). Sub-
stance P in neurons of the central (Gamse et al., 19 1981b; Jhamandas et al., 1984; Saria et al., 1986). Substance P in neurons of the central (Gamse et al., 1979b; Helke et al., 1981b) or enteric (Holzer, 1984) nervous system is not released by capsaicin. Likewise, the rel 1981b; Jhamandas et al., 1984; Saria et al., 1986). Substance P in neurons of the central (Gamse et al., 1979b; Helke et al., 1981b) or enteric (Holzer, 1984) nervous system is not released by capsaicin. Likewise, the rel stance P in neurons of the central (Gamse et al., 1979b;
Helke et al., 1981b) or enteric (Holzer, 1984) nervous
system is not released by capsaicin. Likewise, the release
of neurotransmitters such as glutamic acid (Akagi e

PHARMACOLOGICAL REVIEWS

(Akagi et al., 1980), 5-hydroxytryptamine (Bergstrom et essarily take place so that excitation of thin sensory al., 1983), vasoactive intestinal polypeptide, cholecysto- neurons (Kaufman et al., 1982; Kenins, 1982; Longhur 150
(Akagi et al., 1980), 5-hydroxytryptamine (Bergstro:
al., 1983), vasoactive intestinal polypeptide, cholecy
kinin (Yaksh et al., 1982; Jhamandas et al., 1984) kota Holze
(Akagi et al., 1980), 5-hydroxytryptamine (Bergstrom et
al., 1983), vasoactive intestinal polypeptide, cholecysto-
kinin (Yaksh et al., 1982; Jhamandas et al., 1984), or
bombesin (Moody et al., 1981) in the spin (Akagi et al., 1980), 5-hydroxytryptamine (Bergstrom et al., 1983), vasoactive intestinal polypeptide, cholecysto-
kinin (Yaksh et al., 1982; Jhamandas et al., 1984), or bombesin (Moody et al., 1981) in the spinal cord is (Akagi et al., 1980), 5
al., 1983), vasoactive
kinin (Yaksh et al.,
bombesin (Moody et
affected by capsaicin.
C. Intermediate Effect I., 1999), vascultive measurital polypepide, choiecystemin (Yaksh et al., 1982; Jhamandas et al., 1984), bombesin (Moody et al., 1981) in the spinal cord is neffected by capsaicin.
C. Intermediate Effects of Capsaicin on M **bombesin (Moody et al., 1981) in the spinal cord is not affected by capsaicin.**
C. Intermediate Effects of Capsaicin on Mammalian Sensory Neurons

Fected by capsaicin.
 Intermediate Effects of Capsaicin on Mammalian
 nsory Neurons
 1. Sensitization. Desensitization and blockade of nerve

reduction are very common but not exclusive sequelae C. Intermediate Effects of Capsaicin on Mammalian
Sensory Neurons
1. Sensitization. Desensitization and blockade of nerve
conduction are very common but not exclusive sequelae
of the excitatory action of capsaicin on sens C. Intermediate Effects of Capsaicin on Mammalian
Sensory Neurons
1. Sensitization. Desensitization and blockade of nerve
conduction are very common but not exclusive sequelae
of the excitatory action of capsaicin on senso Sensory Neurons
1. Sensitization. Desensitization and blockade of nerv
conduction are very common but not exclusive sequela
of the excitatory action of capsaicin on sensory neurons
Under certain conditions the opposite can conduction are very common but not exclusive sequelae
of the excitatory action of capsaicin on sensory neurons.
Under certain conditions the opposite can be seen; exci-
tation is followed by sensitization to thermal, mecha conduction are very common but not exclusive sequelae
of the excitatory action of capsaicin on sensory neurons.
Under certain conditions the opposite can be seen; excitation is followed by sensitization to thermal, mechani of the excitatory action of capsaicin on sensory neurons.

Under certain conditions the opposite can be seen; excitation is followed by sensitization to thermal, mechanical, and chemical stimuli, particularly if low doses Under certain conditions the opposite can be seen; excitation is followed by sensitization to thermal, mechanical, and chemical stimuli, particularly if low doses of b capsaicin are administered repeatedly. There is only tation is followed by sensitization to thermal, mechanical, and chemical stimuli, particularly if low doses of capsaicin are administered repeatedly. There is only one proport indicating that neuronal sensitivity to capsa cal, and chemical stimuli, particularly if low doses capsaicin are administered repeatedly. There is only of report indicating that neuronal sensitivity to capsaic can increase with repeated applications of the drug the hu report indicating that neuronal sensitivity to capsaicin
can increase with repeated applications of the drug to
the human tongue; paradoxically, a pause in the stimu-
lation cycle gives rise to desensitization (Green, 1989 report indicating that neuronal sensitivity to capsaicin
can increase with repeated applications of the drug to
the human tongue; paradoxically, a pause in the stimu-
lation cycle gives rise to desensitization (Green, 1989 can increase with repeated applications of the drug to (S_2)
the human tongue; paradoxically, a pause in the stimulation cycle gives rise to desensitization (Green, 1989).
The capsaicin-induced sensitization of C-fiber p the human tongue; paradoxically, a pause in the stimu-
lation cycle gives rise to desensitization (Green, 1989).
The capsaicin-induced sensitization of C-fiber polymodal
nociceptors to thermal (Kenins, 1982; Konietzny and
 lation cycle gives rise to desensitization (Green, 1989).
The capsaicin-induced sensitization of C-fiber polymodal
nociceptors to thermal (Kenins, 1982; Konietzny and
Hensel, 1983) and mechanical (Kenins, 1982) noxious
sti The capsaicin-induced sensitization of C-fiber polymoda
nociceptors to thermal (Kenins, 1982; Konietzny and
Hensel, 1983) and mechanical (Kenins, 1982) noxious
stimuli is a more frequent observation, and sensitization
appe nociceptors to thermal (Kenins, 1982; Konietzny and
Hensel, 1983) and mechanical (Kenins, 1982) noxious
stimuli is a more frequent observation, and sensitization
appears to precede desensitization (Kenins, 1982). Sen-
siti Hensel, 1983) and mechanical (Kenins, 1982) noxious
stimuli is a more frequent observation, and sensitization
appears to precede desensitization (Kenins, 1982). Sen-
sitization could have a bearing on the capsaicin-induced stimuli is a more frequent observation, and sensitization appears to precede desensitization (Kenins, 1982). Sensitization could have a bearing on the capsaicin-induced hyperalgesia to thermal (Jancsó, 1960; Szolcsányi, 19 appears to precede desensitization (Kenins, 1982). Sensitization could have a bearing on the capsaicin-induced
hyperalgesia to thermal (Jancsó, 1960; Szolcsányi, 1977,
1990; Carpenter and Lynn, 1981; Green, 1986; Simone et sitization could have a bearing on the capsaicin-induced
hyperalgesia to thermal (Jancsó, 1960; Szolcsányi, 1977,
1990; Carpenter and Lynn, 1981; Green, 1986; Simone et
al., 1987) and mechanical (Szolcsányi, 1977; Culp et hyperalgesia to thermal (Jancsó, 1960; Szolcsányi, 1977, 1990; Carpenter and Lynn, 1981; Green, 1986; Simone et al., 1987) and mechanical (Szolcsányi, 1977; Culp et al., 1989; Simone et al., 1989) stimuli, but it is not c 1990; Carpenter and Lynn, 1981; Green, 1986; Simone et

al., 1987) and mechanical (Szolcsányi, 1977; Culp et al.,

1989; Simone et al., 1989) stimuli, but it is not clear

whether hyperalgesia is mediated by those nerve f al., 1987) and mechanical (Szolcsányi, 1977; Culp et a 1989; Simone et al., 1989) stimuli, but it is not clember hyperalgesia is mediated by those nerve fiber-
that are desensitized to capsaicin. However, it is wonder-
tha 1989; Simone et al., 1989) stimuli, but it is not clear
whether hyperalgesia is mediated by those nerve fibers
that are desensitized to capsaicin. However, it is worth
mentioning in this context that the mechanical hyperwhether hyperalgesia is mediated by those nerve fibers that are desensitized to capsaicin. However, it is worth mentioning in this context that the mechanical hyperalgesia resulting from chronic paw inflammation in the ra that are desensitized t
mentioning in this complession resulting from
rat is mediated by affer
(Barthó et al., 1990).
2. Desensitization. A entioning in this context that the mechanical hypesia resulting from chronic paw inflammation in
t is mediated by afferent neurons sensitive to capsa
arthó et al., 1990).
2. *Desensitization*. A more typical feature of cap

algesia resulting from chronic paw inflammation in the rat is mediated by afferent neurons sensitive to capsaicin (Barthó et al., 1990).

2. Desensitization. A more typical feature of capsaicin-

induced stimulation of pri rat is mediated by afferent neurons sensitive to capsaici
(Barthó et al., 1990).
2. Desensitization. A more typical feature of capsaici
induced stimulation of primary afferent neurons is the
excitation soon subsides and th (Barthó et al., 1990).

2. Desensitization. A more typical feature of capsaicin-

induced stimulation of primary afferent neurons is that

excitation soon subsides and the neurons become unre-

sponsive to further applica 2. Desensitization. A more typical feature of capsaicin-
induced stimulation of primary afferent neurons is that
excitation soon subsides and the neurons become unre-
sponsive to further applications of the drug. Capsaici induced stimulation of primary afferent neurons is that excitation soon subsides and the neurons become unre-
sponsive to further applications of the drug. Capsaicin
desensitization has been observed both by recording the
 excitation soon subsides and the neurons become un sponsive to further applications of the drug. Capsa desensitization has been observed both by recording activity of sensory neurons and by examining the consequences of se sponsive to further applications of the drug. Capsaicin
desensitization has been observed both by recording the
activity of sensory neurons and by examining the con-
sequences of sensory neurons and by examining the con-
s desensitization has been observed both by recording the
activity of sensory neurons and by examining the con-
sequences of sensory neuron activation, e.g., neuropep-
freed release from peripheral and central terminals of
a activity of sensory neurons and by examining the consequences of sensory neuron activation, e.g., neuropep-
tide release from peripheral and central terminals of def
afferent neurons, depolarization of spinal dorsal horn c sequences of sensory neuron activation, e.g., neuropeptide release from peripheral and central terminals of afferent neurons, depolarization of spinal dorsal horn and ventral root neurons (Dickenson et al., 1990a,b), and b tide release from peripheral and central terminals of afferent neurons, depolarization of spinal dorsal horn and ventral root neurons (Dickenson et al., 1990a,b), and behavioural (pain) reactions. The rapidity and extent w afferent neurons, depolarization of spinal dorsal horn cand ventral root neurons (Dickenson et al., 1990a,b), and dehavioural (pain) reactions. The rapidity and extent with which desensitization to capsaicin develops is r behavioural (pain) reactions. The rapidity and extent the fact that most, if not all, long-term neurotoxic effects with which desensitization to capsaicin develops is re-
lated to the dose of, and the time of exposure to, behavioural (pain) reactions. The rapidity and extent the with which desensitization to capsaicin develops is re-
lated to the dose of, and the time of exposure to, capsaicin phand the time interval between consecutive dos with which desensitization to capsaicin develops is re-
lated to the dose of, and the time of exposure to, capsaicin
and the time interval between consecutive dosings
f(Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor, lated to the dose of, and the time of exposure to, capsaicin
and the time interval between consecutive dosings
(Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor,
1976; Szolcsányi, 1977, 1987; Barthó and Szolcsányi,
197 and the time interval between consecutive dosings (Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor, 1976; Szolcsányi, 1977, 1987; Barthó and Szolcsányi, 1978; Foster and Ramage, 1981; Kaufman et al., 1982; Zernig et a (Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor, 1976; Szolcsányi, 1977, 1987; Barthó and Szolcsányi, 1978; Foster and Ramage, 1981; Kaufman et al., 1982; Zernig et al., 1984; He et al., 1988, 1990; Maggi et al., 198 1976; Szolcsányi, 1978; Foster and Rand
Zernig et al., 1984; H
1988f, 1990a; Dray et
Winter et al., 1990).
With low suprathre

appropriate time intervals, desensitization does not nec-

neurons (Kaufman et al., 1982; Kenins, 1982; Longhurst essarily take place so that excitation of thin sensory et al., 1984; Szolcs and the scitation of thin sensory
neurons (Kaufman et al., 1982; Kenins, 1982; Longhurst
et al., 1984; Szolcsányi, 1987; Szolcsányi et al., 1988),
pain reactions (Szolcsányi et al., 1975; Szolcsányi an pain reactions (Szolcs #225)
pain reactions (Kaufman et al., 1982; Kenins, 1982; Longhurst
et al., 1984; Szolcsányi, 1987; Szolcsányi et al., 1988),
pain reactions (Szolcsányi et al., 1975; Szolcsányi and
Jancsó-Gábor, 197 essarily take place so that excitation of thin sensory
neurons (Kaufman et al., 1982; Kenins, 1982; Longhurst
et al., 1984; Szolcsányi, 1987; Szolcsányi et al., 1988),
pain reactions (Szolcsányi et al., 1975; Szolcsányi an neurons (Kaufman et al., 1982; Kenins, 1982; Longhur
et al., 1984; Szolcsányi, 1987; Szolcsányi et al., 1988
pain reactions (Szolcsányi et al., 1975; Szolcsányi ar
Jancsó-Gábor, 1976; Szolcsányi, 1977; Green, 1989; Dra
et et al., 1984; Szolcsányi, 1987; Szolcsányi et al., 1988),
pain reactions (Szolcsányi et al., 1975; Szolcsányi and
Jancsó-Gábor, 1976; Szolcsányi, 1977; Green, 1989; Dray
et al., 1989a, 1990b), cardiovascular responses (Lon pain reactions (Szolcsányi et al., 1975; Szolcsányi and
Jancsó-Gábor, 1976; Szolcsányi, 1977; Green, 1989; Dray
et al., 1989a, 1990b), cardiovascular responses (Lon-
ghurst et al., 1980; Donnerer and Lembeck, 1982;
Szolcsá Jancsó-Gábor, 1976; Szolcsányi, 1977; Green, 1989; Dray
et al., 1989a, 1990b), cardiovascular responses (Lon-
ghurst et al., 1980; Donnerer and Lembeck, 1982;
Szolcsányi et al., 1986; Amann et al., 1989a), and peptide
rele et al., 1989a, 1990b), cardiovascular responses (Lon-
ghurst et al., 1980; Donnerer and Lembeck, 1982;
Szolcsányi et al., 1986; Amann et al., 1989a), and peptide
release from peripheral sensory nerve endings (Dray et
al., ghurst et al., 1980; Donnerer and Lembeck, 1982;
Szolcsányi et al., 1986; Amann et al., 1989a), and peptide
release from peripheral sensory nerve endings (Dray et
al., 1989b; Amann, 1990) can be reproduced with each
applic Szolcsányi et al., 1986; Amann et al., 1989a), and pep
release from peripheral sensory nerve endings (Dra
al., 1989b; Amann, 1990) can be reproduced with ϵ
application of the drug. With higher doses of capsa
or prolonge release from peripheral sensory nerve endings (Dray et al., 1989b; Amann, 1990) can be reproduced with each application of the drug. With higher doses of capsaicin or prolonged exposure to the drug, however, desensitizatio al., 1989b; Amann, 1990) can be reproduced with
application of the drug. With higher doses of caps
or prolonged exposure to the drug, however, dese
zation ensues and consecutive applications of caps
become less effective o plication of the drug. With higher doses of capsaicin
prolonged exposure to the drug, however, desensiti-
tion ensues and consecutive applications of capsaicin
come less effective or fail to produce any effect.
Whereas des

or prolonged exposure to the drug, however, desensitization ensues and consecutive applications of capsaicin
become less effective or fail to produce any effect.
Whereas desensitization to comparatively low doses of
capsai zation ensues and consecutive applications of capsaicin
become less effective or fail to produce any effect.
Whereas desensitization to comparatively low doses of
capsaicin may be specific for this drug and its congeners
(become less effective or fail to produce any effect.

Whereas desensitization to comparatively low doses of

capsaicin may be specific for this drug and its congeners

(Szolcsányi, 1977; Bernstein et al., 1981; Dray et al. Whereas desensitization to comparatively low doses of capsaicin may be specific for this drug and its congeners (Szolcsányi, 1977; Bernstein et al., 1981; Dray et al., 1989a,b, 1990b,c; Winter et al., 1990), desensitizatio capsaicin may be specific for this drug and its congeners (Szolcsányi, 1977; Bernstein et al., 1981; Dray et al., 1989a,b, 1990b,c; Winter et al., 1990), desensitization to higher doses of the drug also is associated with (Szolcsányi, 1977; Bernstein et al., 1981; Dray et al.)
1989a,b, 1990b,c; Winter et al., 1990), desensitization t
higher doses of the drug also is associated with a loss c
responsiveness to other chemical (Jancsó, 1960
Szo 1989a,b, 1990b,c; Winter et al., 1990), desensitization to
higher doses of the drug also is associated with a loss of
responsiveness to other chemical (Jancsó, 1960;
Szolcsányi, 1977, 1987; Foster and Ramage, 1981; Ken-
in higher doses of the drug also is associated with a loss of responsiveness to other chemical (Jancsó, 1960; Szolcsányi, 1977, 1987; Foster and Ramage, 1981; Kenins, 1982; Jancsó and Such, 1983; Ueda et al., 1984; Geppetti e responsiveness to other chemical (Jancsó, 1960; Szolcsányi, 1977, 1987; Foster and Ramage, 1981; Kenins, 1982; Jancsó and Such, 1983; Ueda et al., 1984; Geppetti et al., 1988c; Dray et al., 1989a, 1990b; He et al., 1990; L Szolcsányi, 1977, 1987; Foster and Ramage, 1981; Kenins, 1982; Jancsó and Such, 1983; Ueda et al., 1984;
Geppetti et al., 1988c; Dray et al., 1989a, 1990b; He et
al., 1990; Lang et al., 1990), warmth (Szolcsányi, 1977,
198 ins, 1982; Jancsó and Such, 1983; Ueda et al., 198
Geppetti et al., 1988c; Dray et al., 1989a, 1990b; He
al., 1990; Lang et al., 1990), warmth (Szolcsányi, 197
1983a, 1987; Foster and Ramage, 1981; Kenins, 198
Williams and Geppetti et al., 1988c; Dray et al., 1989a, 1990b; He et al., 1990; Lang et al., 1990), warmth (Szolcsányi, 1977, 1983a, 1987; Foster and Ramage, 1981; Kenins, 1982; Williams and Zieglgänsberger, 1982), and noxious (high-t al., 1990; Lang et al., 1990), warmth (Szolcsányi, 1977,
1983a, 1987; Foster and Ramage, 1981; Kenins, 1982;
Williams and Zieglgänsberger, 1982), and noxious (high-
threshold) mechanical stimuli (Kenins, 1982; Szolcsányi, 1983a, 1987; Foster and Ramage, 1981; Kenins, 1982;
Williams and Zieglgänsberger, 1982), and noxious (high-
threshold) mechanical stimuli (Kenins, 1982; Szolcsányi,
1987; He et al., 1990; Lang et al., 1990) and to potassiu Williams and Zieglgänsberger, 1982), and noxious (high-
threshold) mechanical stimuli (Kenins, 1982; Szolcsányi,
1987; He et al., 1990; Lang et al., 1990) and to potassium
depolarization (Saria et al., 1983a; Dray et al., threshold) mechanical stimuli (Kenins, 1982; Szolcsányi, 1987; He et al., 1990; Lang et al., 1990) and to potassium
depolarization (Saria et al., 1983a; Dray et al., 1989b;
Amann, 1990; Donnerer and Amann, 1990; Maggi et a depolarization (Saria et al., 1983a; Dray et al., 1989b; Amann, 1990; Donnerer and Amann, 1990; Maggi et al., 1990b). Specific taste chemoreceptors, cold receptors, and low-threshold mechanoreceptors are not inhibited Amann, 1990; Donnerer and Amann, 1990; Maggi et al., 1990b). Specific taste chemoreceptors, cold receptors, and low-threshold mechanoreceptors are not inhibited by desensitization to capsaicin (Szolcsányi, 1977, 1990; Dray Amann, 1990; Donnerer and Amann, 1990; Maggi et al.
1990b). Specific taste chemoreceptors, cold receptors
and low-threshold mechanoreceptors are not inhibited
by desensitization to capsaicin (Szolcsányi, 1977, 1990
Dray et 1990b). Specific taste chemoreceptors, cold receptors,
and low-threshold mechanoreceptors are not inhibited
by desensitization to capsaicin (Szolcsányi, 1977, 1990;
Dray et al., 1989b, 1990b). Thus, only thin sensory neu-
 their other sensory modalities.
Nonspecific desensitization to capsaicin is probably by desensitization to capsaicin (Szolcsányi, 1977, 1990; rons appear to be rendered insensitive to capsaicin and Whereas desensitization to comparatively low doses of $\frac{5}{2}$ (Szolcsányi, 1977; Bernstein et al., 1981; Dray et al., 1989a,b, 1990b,c; Winter et al., 1990), desensitization to higher doses of the drug also is associate

1978; Foster and Ramage, 1981; Kaufman et al., 1982; in this latter sense only, it is not possible in many cases
Zernig et al., 1984; He et al., 1988, 1990; Maggi et al., to clearly distinguish between desensitization and their other sensory modalities.
Nonspecific desensitization to capsaicin is probably
the first manifestation of the long-term neurotoxic action
of the drug on sensory neurons, the adjective long-term
referring to a time sc Nonspecific desensitization to capsaicin is probably
the first manifestation of the long-term neurotoxic action
of the drug on sensory neurons, the adjective long-term
referring to a time scale of several weeks to months. the first manifestation of the long-term neurotoxic action
of the drug on sensory neurons, the adjective long-term
referring to a time scale of several weeks to months. The
frequent use of the term desensitization to denot of the drug on sensory neurons, the adjective long-term
referring to a time scale of several weeks to months. The
frequent use of the term desensitization to denote chronic
defunctionalization of sensory neurons has create referring to a time scale of several weeks to months. The
frequent use of the term desensitization to denote chronic
defunctionalization of sensory neurons has created some
confusion because it is at variance with the mean frequent use of the term desensitization to denote chronic
defunctionalization of sensory neurons has created some
confusion because it is at variance with the meaning of
desensitization in pharmacology. The problem relate defunctionalization of sensory neurons has created some
confusion because it is at variance with the meaning of
desensitization in pharmacology. The problem relates to
the fact that most, if not all, long-term neurotoxic e confusion because it is at variance with the meaning of desensitization in pharmacology. The problem relates to the fact that most, if not all, long-term neurotoxic effects of capsaicin involve morphological changes, where desensitization in pharmacology. The problem relates to
the fact that most, if not all, long-term neurotoxic effects
of capsaicin involve morphological changes, whereas the
pharmacological term desensitization implies a tr the fact that most, if not all, long-term neurotoxic effects
of capsaicin involve morphological changes, whereas the
pharmacological term desensitization implies a transient
functional refractoriness in the absence of long of capsaicin involve morphological changes, whereas the pharmacological term desensitization implies a transient functional refractoriness in the absence of long-lasting morphological or other toxic changes. Although in th pharmacological term desensitization implies a transient
functional refractoriness in the absence of long-lasting
morphological or other toxic changes. Although in the
present article I attempt to use the term desensitizat functional refractoriness in the absence of long-lasting
morphological or other toxic changes. Although in the
present article I attempt to use the term desensitization
in this latter sense only, it is not possible in many morphological or other toxic changes. Although in the present article I attempt to use the term desensitization in this latter sense only, it is not possible in many cases to clearly distinguish between desensitization and present article I attempt to use the term desensitization
in this latter sense only, it is not possible in many cases
to clearly distinguish between desensitization and neu-
rotoxicity because the reversibility of defuncti have not been examined.

The duration of the desensitization to capsaicin ap-

aspet

several hours but disappears within a day (Szolcsányi, 1977; Green, 1989). It is not possible, however, to deduce from these behavioural data whether the time course of the antinociceptive effects of capsaicin reflects tha

from these behavioural data whether the time course of
the antinociceptive effects of capsaicin reflects that of
nociceptor desensitization. Antinociceptive doses of cap-
saicin and the related compound, olvanil, produce

mociceptor desensitization. Antinociceptive doses of capsicin and the related compound, olvanil, produce
selective reduction in the responses of dorsal horn ne
rons to peripheral C- and $A\delta$ -fiber stimulation, and the
is saicin and the related compound, olvanil, produce a selective reduction in the responses of dorsal horn neurons to peripheral C- and $A\delta$ -fiber stimulation, and there is circumstantial evidence that capsaicin/olvanil-ind selective reduction in the responses of dorsal horn neu-
rons to peripheral C- and $A\delta$ -fiber stimulation, and there
is circumstantial evidence that capsaicin/olvanil-induced
antinociception may be due to inhibition of t rons to peripheral C- and A δ -fiber stimulation, and the
is circumstantial evidence that capsaicin/olvanil-induc
antinociception may be due to inhibition of transmissi
from afferent nerve terminals in the spinal cord ra

antinociception may be due to inhibition of transmission
from afferent nerve terminals in the spinal cord rather
than defunctionalization of the peripheral axons (Dick-
enson et al., 1990a,b).
3. Blockade of nerve conduct

than defunctionalization of the peripheral axons (Dick-
enson et al., 1990a,b).
3. Blockade of nerve conduction. Within a few minutes
from the application of capsaicin to axons of sensory
neurons, nerve conduction through enson et al., 1990a,b).
3. *Blockade of nerve conduction*. Within a few minutes
from the application of capsaicin to axons of sensory
neurons, nerve conduction through the treated segment
is blocked (Petsche et al., 1983; 3. Blockade of nerve conduction. Within a few minutes
from the application of capsaicin to axons of sensory
neurons, nerve conduction through the treated segment
is blocked (Petsche et al., 1983; Pini, 1983; Handwerker
et

Such and Jancsó, 1986; Marsh et al., 1987; Waddell and Lawson, 1989; Brugger et al., 1990). Capsaicin inhibit conduction in most, but not all, afferent C-fibers of the monkey sural nerve, polymodal C-fiber noci-
ceptors be Lawson, 1989; Brugger et al., 1990). Capsaicin inhibits
conduction in most, but not all, afferent C-fibers of the
rat coccygeal, saphenous, sciatic, sural, and vagus nerve
and of the monkey sural nerve, polymodal C-fiber n conduction in most, but not all, afferent C-fibers of the rat coccygeal, saphenous, sciatic, sural, and vagus nerve and of the monkey sural nerve, polymodal C-fiber nociceptors being most often affected (Petsche et al., 19

and of the monkey sural nerve, polymodal C-fiber nociceptors being most often affected (Petsche et al., 1983; Welk et al., 1983; Lynn et al., 1984; Chung et al., 1985a; Waddell and Lawson, 1989). Nerve conduction in the do

Welk et al., 1983; Lynn et al., 1984; Chung et al., 1985a; Waddell and Lawson, 1989). Nerve conduction in the dorsal roots of the rat is blocked as well (Brugger et al., 1990). Except in the ferret in which perineural caps Waddell and Lawson, 1989). Nerve conduction in the
dorsal roots of the rat is blocked as well (Brugger et al.,
1990). Except in the ferret in which perineural capsaicin
blocks C-fibers only (Baranowski et al., 1986), the c dorsal roots of the rat is blocked as well (Brugger et al., 1990). Except in the ferret in which perineural capsaicin blocks C-fibers only (Baranowski et al., 1986), the conduction in afferent A-fibers of the rat, rabbit, 1990). Except in the ferret in which perineural capsaicin
blocks C-fibers only (Baranowski et al., 1986), the con-
duction in afferent A-fibers of the rat, rabbit, guinea pig,
and monkey also is reduced to a minor degree (

and monkey also is reduced to a minor degree (Pini, 1983; Lynn et al., 1984; Chung et al., 1985a; Baranowski et al., 1986; Such and Jancsó, 1986; Marsh et al., 1987).
The conduction block in the A-fibers is primarily due
 Lynn et al., 1984; Chung et al., 1985a; Baranowski et al., 1986; Such and Jancsó, 1986; Marsh et al., 1987).
The conduction block in the A-fibers is primarily due
to a block of A δ -fibers, although some fast-conducting
 1986; Such and Jancsó, 1986; Marsh et al., 1987).
The conduction block in the A-fibers is primarily do a block of A δ -fibers, although some fast-conduction $A\alpha\beta$ -fibers can be affected as well. The potency of consider The conduction block in the A-fibers is primarily due
to a block of A δ -fibers, although some fast-conducting
 $A\alpha\beta$ -fibers can be affected as well. The potency of cap-
saicin in blocking C- and A δ -fibers, however,

blocks C-fibers only (Baranowski et al., 1986), the
duction in afferent A-fibers of the rat, rabbit, guine
and monkey also is reduced to a minor degree (Pini,
Lynn et al., 1984; Chung et al., 1985a; Baranowski
1986; Such a

CAPSAICIN 151 pears to be a matter of a few hours to a few days. In
not known whether there is any temporal relations
between desensitization and the presence of capsaicin
the tissue. In the rat, topical administration of appro
mately 1

CAPSAICI
pears to be a matter of a few hours to a few days. It is Land known whether there is any temporal relationship CAPSAI
pears to be a matter of a few hours to a few days. It is
not known whether there is any temporal relationship
between desensitization and the presence of capsaicin in CAPSAICIN
pears to be a matter of a few hours to a few days. It is Law
not known whether there is any temporal relationship reve
between desensitization and the presence of capsaicin in any,
the tissue. In the rat, topical pears to be a matter of a few hours to a few days. It is L
not known whether there is any temporal relationship re-
between desensitization and the presence of capsaicin in
the tissue. In the rat, topical administration o not known whether there is any temporal relationship reverse between desensitization and the presence of capsaicin in any, the tissue. In the rat, topical administration of approxi-cationately 100μ M capsaicin is necess between desensitization and the presence of capsaicin in
the tissue. In the rat, topical administration of approxicat
mately 100μ M capsaicin is necessary to make the cornea cap
insensitive to chemical noxious stimuli f the tissue. In the rat, topical administration of approximately 100μ M capsaicin is necessary to make the cornea insensitive to chemical noxious stimuli for at least 2 h (Szolcsányi et al., 1975; Szolcsányi and Jancsó-G mately 100 μ M capsaicin is necessary to make the cornea caps
insensitive to chemical noxious stimuli for at least 2 h and
(Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor, the
1976). Capsaicin-induced desensitizat insensitive to chemical noxious stimuli for at least 2 h and
(Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor, the
1976). Capsaicin-induced desensitization of a C-fiber com
warmth receptor also was noted to last for a (Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor,
1976). Capsaicin-induced desensitization of a C-fiber cutaneous warmth receptor also was noted to last for at least 2 h
(Szolcsányi, 1983a). When given systemically, 1976). Capsaicin-induced desensitization of a C-fiber
warmth receptor also was noted to last for at least 2 h
(Szolcsányi, 1983a). When given systemically, 1 to 400
mg/kg capsaicin are able to reduce cutaneous sensitivity
 warmth receptor also was noted to last for at least 2 h (Szolcsányi, 1983a). When given systemically, 1 to 400 mg/kg capsaicin are able to reduce cutaneous sensitivity to chemical (Szolcsányi et al., 1975; Hayes et al., 19 (Szolcsányi, 1983a). When given systemically, 1 to 40
mg/kg capsaicin are able to reduce cutaneous sensitivity
to chemical (Szolcsányi et al., 1975; Hayes et al., 1981b)
mechanical (Hayes et al., 1981b, 1984b), and therma
 mg/kg capsaicin are able to reduce cutaneous sensitivity
to chemical (Szolcsányi et al., 1975; Hayes et al., 1981b),
mechanical (Hayes et al., 1981b, 1984b), and thermal
noxious stimuli (Hayes et al., 1981b; Gamse, 1982; B to chemical (Szolcsányi et al., 1975; Hayes et al., 1981b), mechanical (Hayes et al., 1981b, 1984b), and thermal noxious stimuli (Hayes et al., 1981b; Gamse, 1982; Bitt-
ner and LaHann, 1985; Szolcsányi, 1990) for a few ho mechanical (Hayes et al., 1981b, 1984b), and thermal finoxious stimuli (Hayes et al., 1981b; Gamse, 1982; Bitt-
ner and LaHann, 1985; Szolcsányi, 1990) for a few hours fiup to several days. Likewise, desensitization of the noxious stimuli (Hayes et al., 1981b; Gamse, 1982; Bitt-
ner and LaHann, 1985; Szolcsányi, 1990) for a few hours
up to several days. Likewise, desensitization of the hu-
man tongue to low concentrations of capsaicin lasts
 ner and LaHann, 1985; Szolcsányi, 1990) for a few hours
up to several days. Likewise, desensitization of the human tongue to low concentrations of capsaicin lasts
several hours but disappears within a day (Szolcsányi,
1977 up to several days. Likewise, desensitization of the human tongue to low concentrations of capsaicin lasts neveral hours but disappears within a day (Szolcsányi, 1977; Green, 1989). It is not possible, however, to deduce t CIN 151
Lawson, 1989). Although the block of A $\alpha\beta$ -fibers is fully
reversible within 1 h, the C-fibers show only partial, if reversible within 1 h, the block of $A\alpha\beta$ -fibers is fully
reversible within 1 h, the C-fibers show only partial, if
any, recovery during the first 2 h after capsaicin appli-1!
Lawson, 1989). Although the block of $A\alpha\beta$ -fibers is ful
reversible within 1 h, the C-fibers show only partial,
any, recovery during the first 2 h after capsaicin appl
cation. The duration of the C-fiber block at the Lawson, 1989). Although the block of $A\alpha\beta$ -fibers is fully reversible within 1 h, the C-fibers show only partial, if any, recovery during the first 2 h after capsaicin application. The duration of the C-fiber block at t Lawson, 1989). Although the block of $A\alpha\beta$ -fibers is fully reversible within 1 h, the C-fibers show only partial, if any, recovery during the first 2 h after capsaicin application. The duration of the C-fiber block at t reversible within 1 h, the C-fibers show only partial, if any, recovery during the first 2 h after capsaicin application. The duration of the C-fiber block at the site of capsaicin application appears to last up to 3 days any, recovery during the first 2 h after capsaicin application. The duration of the C-fiber block at the site of capsaicin application appears to last up to 3 days (Jancsó and Such, 1983; Welk et al., 1983; Lynn et al., 19 capsaicin application appears to last up to 3 days (Jancsó
and Such, 1983; Welk et al., 1983; Lynn et al., 1984). In
the rat vagus nerve the C-fiber conduction block is
composed of two components, one that is reversible
w capsaicin application appears to last up to 3 days (Jancsof
and Such, 1983; Welk et al., 1983; Lynn et al., 1984). In
the rat vagus nerve the C-fiber conduction block is
composed of two components, one that is reversible
 and Such, 1983; Welk et al., 1983; Lynn et al., 1984). In the rat vagus nerve the C-fiber conduction block is composed of two components, one that is reversible within 90 min and another one that is produced by perineural within 90 min and another one that is produced by
perineural concentrations of capsaicin of $>1 \mu M$ that is
not reversible within this time frame (Waddell and Law-
son, 1989). There are also species differences in that Ccomposed of two components, one that is reversible within 90 min and another one that is produced by perineural concentrations of capsaicin of $>1 \mu M$ that is not reversible within this time frame (Waddell and Lawson, 198 within 90 min and another one that is produced by
perineural concentrations of capsaicin of $>1 \mu M$ that is
not reversible within this time frame (Waddell and Law-
son, 1989). There are also species differences in that Cperineural concentrations of capsaicin of $>1 \mu M$ that is
not reversible within this time frame (Waddell and Law-
son, 1989). There are also species differences in that C-
fibers in the saphenous nerve of the guinea pig a not reversible within this time frame (Waddell and Lawson, 1989). There are also species differences in that C-
fibers in the saphenous nerve of the guinea pig and rabbit
are less sensitive to capsaicin than those in the r son, 1989). There are also species differences in that fibers in the saphenous nerve of the guinea pig and rablare less sensitive to capsaicin than those in the rat, a full recovery from the conduction block produced by mu are less sensitive to capsaicin than those in the rat, and
full recovery from the conduction block produced by as
much as 33 mM capsaicin takes place within 1 h (Bara-
nowski et al., 1986).
Nerve conduction in sympathetic e less sensitive to capsaicin than those in the rat, and
il recovery from the conduction block produced by as
uch as 33 mM capsaicin takes place within 1 h (Bara-
wski et al., 1986).
Nerve conduction in sympathetic efferen

man tongue to low concentrations of capsaicin lasts nowski et al., 1986).
several hours but disappears within a day (Szolcsányi, Nerve conduction in sympathetic efferent fibers, ven-
1977; Green, 1989). It is not possible 1977; Green, 1989). It is not possible, however, to deduce train
from these behavioural data whether the time course of is related the antinociceptive effects of capsaicin reflects that of 198
mociceptor desensitization the antinociceptive effects of capsaicin reflects that of
nociceptor desensitization. Antinociceptive doses of cap-
saicin and the related compound, olvanil, produce a
selective reduction in the responses of dorsal horn n tinociception may be due to inhibition of transmission
bm afferent nerve terminals in the spinal cord rather
an defunctionalization of the peripheral axons (Dick-
son et al., 1990a,b).
3. *Blockade of nerve conduction*. Wi full recovery from the conduction block produced by as much as 33 mM capsaicin takes place within 1 h (Baranowski et al., 1986).
Nerve conduction in sympathetic efferent fibers, ventral roots of the spinal cord, or fibers much as 33 mM capsaicin takes place within 1 h (Bara-nowski et al., 1986).

Nerve conduction in sympathetic efferent fibers, ven-

tral roots of the spinal cord, or fibers of the optic nerve

is not altered (Handwerker et nowski et al., 1986).

Nerve conduction in sympathetic efferent fibers, ventral roots of the spinal cord, or fibers of the optic nerve

is not altered (Handwerker et al., 1984; Marsh et al.,

1987) or only temporarily redu Nerve conduction in sympathetic efferent fibers, ven-
tral roots of the spinal cord, or fibers of the optic nerve
is not altered (Handwerker et al., 1984; Marsh et al.,
1987) or only temporarily reduced (Such and Jancsó,
1 tral roots of the spinal cord, or fibers of the optic nerve
is not altered (Handwerker et al., 1984; Marsh et al.,
1987) or only temporarily reduced (Such and Jancsó,
1986). The latter observation could either represent an is not altered (Handwerker et al., 1984; Marsh et al., 1987) or only temporarily reduced (Such and Jancsó, 1986). The latter observation could either represent an example of the cell-nonselective effects of capsaicin or pa 1987) or only temporarily reduced (Such and Jancsó, 1986). The latter observation could either represent an example of the cell-nonselective effects of capsaicin or partly be due to the use of 10% ethanol in the vehicle wh 1986). The latter observation could either represent an example of the cell-nonselective effects of capsaicin or partly be due to the use of 10% ethanol in the vehicle which, by itself, can block nerve conduction (Wall and partly be due to the use of 10% ethanol in the vehicle
which, by itself, can block nerve conduction (Wall and
Fitzgerald, 1981). The use of paraffin or olive oil (Petsche interaction. Winch, by Ident, can block herve conduction (wan an Fitzgerald, 1981). The use of paraffin or olive oil (Petsclet al., 1983; Pini, 1983) avoids this element of vehic interaction.
D. Long-term Neurotoxic Effects of Capsaici *Magerand, 1991).* The use of part
et al., 1983; Pini, 1983) avoids
interaction.
D. Long-term Neurotoxic Effects
Mammalian Sensory Neurons
1. Effects of systemic capsaicii

from afferent nerve terminals in the spinal cord rather
than defunctionalization of the peripheral axons (Dick-
enson et al., 1990a,b).
3. Blockade of nerve conduction. Within a few minutes
from the application of capsaic from the application of capsaicin to axons of sensory a. in neurons, nerve conduction through the treated segment is blocked (Petsche et al., 1983; Pini, 1983; Handwerker et al., 1984; Baranowski et al., 1986; Such and Jan neurons, nerve conduction through the treated segment
is blocked (Petsche et al., 1983; Pini, 1983; Handwerker
et al., 1984; Lynn et al., 1984; Baranowski et al., 1986;
Such and Jancsó, 1986; Marsh et al., 1987; Waddell an is blocked (Petsche et al., 1983; Pini, 1983; Handwerker
et al., 1984; Lynn et al., 1984; Baranowski et al., 1986;
Such and Jancsó, 1986; Marsh et al., 1987; Waddell and
Lawson, 1989; Brugger et al., 1990). Capsaicin inhib et al., 1984; Lynn et al., 1984; Baranowski et al., 1986;
Such and Jancsó, 1986; Marsh et al., 1987; Waddell and
Lawson, 1989; Brugger et al., 1990). Capsaicin inhibits
conduction in most, but not all, afferent C-fibers of rat coccygeal, saphenous, sciatic, sural, and vagus nerve given
and of the monkey sural nerve, polymodal C-fiber noci-
ceptors being most often affected (Petsche et al., 1983; tal
Welk et al., 1983; Lynn et al., 1984; Chun ceptors being most often affected (Petsche et al., 1983; Welk et al., 1983; Lynn et al., 1984; Chung et al., 1985a; m
Waddell and Lawson, 1989). Nerve conduction in the norsal roots of the rat is blocked as well (Brugger interaction.
 1. Long-term Neurotoxic Effects of Capsaicin on
 Mammalian Sensory Neurons
 1. Effects of systemic capsaicin in newborn mammals.

a. RAT. **i. Morphological changes.** It had long been

assumed that the p D. Long-term Neurotoxic Effects of Capsaicin on
Mammalian Sensory Neurons
1. Effects of systemic capsaicin in newborn mammals.
a. RAT. **i. Morphological changes.** It had long been
assumed that the persistent inhibition of *Hammalian Sensory Neurons*
1. Effects of systemic capsaicin in newborn mammals
a. RAT. **i. Morphological changes.** It had long been
assumed that the persistent inhibition of sensory neuror
functions produced by systemic a 1. Effects of systemic capsaicin in newborn mammals.
a. RAT. i. Morphological changes. It had long been
assumed that the persistent inhibition of sensory neuron
functions produced by systemic administration of rela-
tively assumed that the persistent inhibition of sensory neuron
functions produced by systemic administration of rela-
tively large doses of capsaicin to adult rats merely re-
flected a sustained defunctionalization of these neur assumed that the persistent inhibition of sensory neuron
functions produced by systemic administration of rela-
tively large doses of capsaicin to adult rats merely re-
flected a sustained defunctionalization of these neur functions produced by systemic administration of rela-
tively large doses of capsaicin to adult rats merely re-
flected a sustained defunctionalization of these neurons.
In 1977, however, G. Jancsó and his associates (1977 tively large doses of capsaicin to adult rats merely re-
flected a sustained defunctionalization of these neurons.
In 1977, however, G. Jancsó and his associates (1977)
reported that a subcutaneous dose of 50 mg/kg capsaic In 1977, however, G. Jancsó and his associates (1977) reported that a subcutaneous dose of 50 mg/kg capsaicin given to newborn rats caused a lifelong degeneration of B-type primary afferent neurons. This degeneration ta In 1977, however, G. Jancsó and his associates (1977)
reported that a subcutaneous dose of 50 mg/kg capsaicin
given to newborn rats caused a lifelong degeneration of
B-type primary afferent neurons. This degeneration
takes reported that a subcutaneous dose of 50 mg/kg capsaicin
given to newborn rats caused a lifelong degeneration of
B-type primary afferent neurons. This degeneration
takes place within 30 min, is permanent, and involves
most given to newborn rats caused a lifelong degeneration of B-type primary afferent neurons. This degeneration takes place within 30 min, is permanent, and involves most B-type neurons and their peripheral and central nerve pr B-type primary afferent neurons. This degeneration
takes place within 30 min, is permanent, and involves
most B-type neurons and their peripheral and central
nerve processes (Jancsó et al., 1977; Jancsó and Király,
1980, 1 takes place within 30 min, is permanent,
most B-type neurons and their peripheral
nerve processes (Jancsó et al., 1977; Jancsó
1980, 1981; Nagy et al., 1980, 1983; Nagy and
Holje et al., 1983; Dinh and Ritter, 1987).
The n ost B-type neurons and their peripheral and central
rve processes (Jancsó et al., 1977; Jancsó and Király,
80, 1981; Nagy et al., 1980, 1983; Nagy and Hunt, 1983;
olje et al., 1983; Dinh and Ritter, 1987).
The neurotoxic e nerve processes (Jancsó et al., 1977; Jancsó and Király, 1980, 1981; Nagy et al., 1980, 1983; Nagy and Hunt, 1983;
Holje et al., 1983; Dinh and Ritter, 1987).
The neurotoxic effect of neonatal capsaicin is dose
dependent;

ction in afferent A-fibers of the rat, rabbit, guinea pig, depthed monkey also is reduced to a minor degree (Pini, 1983; degram et al., 1984; Chung et al., 1985a; Baranowski et al., ter 86; Such and Jancsó, 1986; Marsh et to a block of $A\delta$ -fibers, although some fast-conducting mo $A\alpha\beta$ -fibers can be affected as well. The potency of capsicin in blocking C- and $A\delta$ -fibers, however, is considuated in the capsity higher than that for fast 1980, 1981; Nagy et al., 1980, 1983; Nagy and Hunt, 1983;
Holje et al., 1983; Dinh and Ritter, 1987).
The neurotoxic effect of neonatal capsaicin is dose
dependent; the threshold dose of the drug in inducing
degeneration o Holje et al., 1983; Dinh and Ritter, 1987).
The neurotoxic effect of neonatal capsaicin is dose
dependent; the threshold dose of the drug in inducing
degeneration of unmyelinated dorsal root fibers and axon
terminals in th The neurotoxic effect of neonatal capsaicin is dose
dependent; the threshold dose of the drug in inducing
degeneration of unmyelinated dorsal root fibers and axon
terminals in the spinal cord lies between 5 and 15 mg/
kg (dependent; the threshold dose of the drug in inducing
degeneration of unmyelinated dorsal root fibers and axon
terminals in the spinal cord lies between 5 and 15 mg/
kg (Jancsó and Király, 1981; Nagy et al. 1983; Jancsó,
1 degeneration of unmyelinated dorsal root fibers and a
terminals in the spinal cord lies between 5 and 15 r
kg (Jancsó and Király, 1981; Nagy et al. 1983; Jano
1984). The dose of 50 mg/kg capsaicin, which now
most widely us terminals in the spinal cord lies between 5 and 15 mg/
kg (Jancsó and Király, 1981; Nagy et al. 1983; Jancsó,
1984). The dose of 50 mg/kg capsaicin, which now is
most widely used, is thought to cause maximal degener-
ation kg (Jancsó and Király, 1981; Nagy et al. 1983; Jancsó, 1984). The dose of 50 mg/kg capsaicin, which now is most widely used, is thought to cause maximal degeneration of unmyelinated afferent neurons. The loss of unmyelinat 1984). The dose of 50 mg/kg capsaicin, which now is
most widely used, is thought to cause maximal degener-
ation of unmyelinated afferent neurons. The loss of
unmyelinated fibers from the rat saphenous, inferior
alveolar, most widely used, is thought to cause maximal degeneration of unmyelinated afferent neurons. The loss of unmyelinated fibers from the rat saphenous, inferior alveolar, and mental nerves ranges from 40% (Lynn, 1984), 50%

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

152
and 64% (Scadding, 1980) to 67% (Jancsó et al., 1977,
1980a). This variability in nerve fiber loss is likely to be HOLZER
152 HOLZER
1980a). This variability in nerve fiber loss is likely to be me
1980a). This variability in nerve fiber loss is likely to be me
due to regional differences in the proportion of unmye-is and 64% (Scadding, 1980) to 67% (Jancsó et al., 1977, 1980a). This variability in nerve fiber loss is likely to be due to regional differences in the proportion of unmye-
linated afferent/efferent nerve fibers in mixed ner and 64% (Scadding, 1980) to 67% (Jancsó et al., 1977, 1980a). This variability in nerve fiber loss is likely to be due to regional differences in the proportion of unmyelinated afferent/efferent nerve fibers in mixed nerve and 64% (Scadding, 1980) to 67% (Jancsó et al., 1977, the 1980a). This variability in nerve fiber loss is likely to be mer due to regional differences in the proportion of unmye- is s linated afferent/efferent nerve fibers 1980a). This variability in nerve fiber loss is likely to be not due to regional differences in the proportion of unmye-
linated afferent/efferent nerve fibers in mixed nerves.
Furthermore, the proportion of B-/A-type cel due to regional differences in the proportion of unmye-
linated afferent/efferent nerve fibers in mixed nerves.
Furthermore, the proportion of B-/A-type cell bodies in
the dorsal root ganglia shows some regional variation
 linated afferent/efferent nerve fibers in mixed nerves. where the relative proportion of B-/A-type cell bodies in inthe dorsal root ganglia shows some regional variation Ne (Lawson et al., 1984), which implies a regional d Furthermore, the proportion of B-/A-type cell bodies in
the dorsal root ganglia shows some regional variation
(Lawson et al., 1984), which implies a regional difference
in the relative proportion of afferent neurons that the dorsal root ganglia shows some regional variation.
(Lawson et al., 1984), which implies a regional different
in the relative proportion of afferent neurons that a
sensitive to the neurodegenerative action of capsaid
(D (Lawson et al., 1984), which implies a regional difference
in the relative proportion of afferent neurons that are T
sensitive to the neurodegenerative action of capsaicin b
(Doucette et al., 1987). In addition, the numbe in the relative proportion of afferent neurons that are
sensitive to the neurodegenerative action of capsaicin
(Doucette et al., 1987). In addition, the number of degen-
erated axons also can differ within different branch sensitive to the neurodegenerative action of capsaicin by
(Doucette et al., 1987). In addition, the number of degen-
erated axons also can differ within different branches of an
a nerve. Thus, although the number of unmyel (Doucette et al., 1987). In addition, the number of degenerated axons also can differ within different branches of a nerve. Thus, although the number of unmyelinated fibers in the inferior alveolar and mental nerves of the et al., 1983; Fried et al., 1988).

rat is decreased by approximately 58% (Holje et al., 1983), no changes are found in the pulpal nerves (Holje et al., 1983; Fried et al., 1988).
The loss of thin afferent nerve fibers is associated with the degeneration of 1983), no changes are found in the pulpal nerves (Holje vat
et al., 1983; Fried et al., 1988). The loss of thin afferent nerve fibers is associated with was
the degeneration of cell bodies from the spinal and cra-
mial sen et al., 1983; Fried et al., 1988).
The loss of thin afferent nerve fibers is associated with
the degeneration of cell bodies from the spinal and cra-
nial sensory ganglia (Jancsó et al., 1977; Lawson and
Nickels, 1980; Ott The loss of thin afferent nerve fibers is associated with
the degeneration of cell bodies from the spinal and cra-
nial sensory ganglia (Jancsó et al., 1977; Lawson and
Nickels, 1980; Otten et al., 1983; Lawson and Harper, the degeneration of cell bodies from the spinal and cra-
nial sensory ganglia (Jancsó et al., 1977; Lawson and al., 1980
Nickels, 1980; Otten et al., 1983; Lawson and Harper, manent
1984; McDougal et al., 1985; Arvidsson a nial sensory ganglia (Jancsó et al., 1977; Lawson and
Nickels, 1980; Otten et al., 1983; Lawson and Harper,
1984; McDougal et al., 1985; Arvidsson and Ygge, 1986).
The loss of somata from the ganglia ranges between 28%
(Mc Nickels, 1980; Otten et al., 1983; Lawson and Harper, mateurs (1984; McDougal et al., 1985; Arvidsson and Ygge, 1986). (G
The loss of somata from the ganglia ranges between 28% state.
(McDougal et al., 1985), 43% (Arvidsso 1984; McDougal et al., 1985; Arvidsson and Ygge, 1986). (C
The loss of somata from the ganglia ranges between 28% st
(McDougal et al., 1985), 43% (Arvidsson and Ygge, 1986), m
and 44% (Otten et al., 1983). Although it is The loss of somata from the ganglia ranges between 28% st

(McDougal et al., 1985), 43% (Arvidsson and Ygge, 1986), m

and 44% (Otten et al., 1983). Although it is primarily the dos-

small dark somata that are destroyed, (McDougal et al., 1985), 43% (Arvidsson and Ygge, 1986), meand 44% (Otten et al., 1983). Although it is primarily the dors small dark somata that are destroyed, there also is some which degeneration of large light A-type and 44% (Otten et al., 1983). Although it is primarily the do small dark somata that are destroyed, there also is some when degeneration of large light A-type somata, especially if majores of capsaicin >50 mg/kg are use small dark somata that are destroyed, there also is some wedepeneration of large light A-type somata, especially if m doses of capsaicin >50 mg/kg are used (Lawson and al Harper, 1984). A major loss of afferent neurons a degeneration of large light A-type somata, especially if doses of capsaicin >50 mg/kg are used (Lawson and Harper, 1984). A major loss of afferent neurons also is demonstrated by a marked reduction in the number of dorsal doses of capsaicin >50 mg/kg are used (Lawson and ab
Harper, 1984). A major loss of afferent neurons also is
demonstrated by a marked reduction in the number of the
dorsal root ganglion cells that are labeled by retrograde Harper, 1984). A major loss of afferent neurons also is
demonstrated by a marked reduction in the number of the
dorsal root ganglion cells that are labeled by retrograde tre
transport of horseradish peroxidase injected int demonstrated by a marked reduction in the number of the dorsal root ganglion cells that are labeled by retrograde treationsport of horseradish peroxidase injected into the The urinary bladder wall (Jancsó and Maggi, 1987). dorsal root ganglion cells that are labeled by retrograde
transport of horseradish peroxidase injected into the
urinary bladder wall (Jancsó and Maggi, 1987). In the
spinal cord, transganglionic labeling is totally absent transport of horseradish peroxidase injected into the urinary bladder wall (Jancsó and Maggi, 1987). In the spinal cord, transganglionic labeling is totally absent in the central termination areas of primary afferent neuro urinary bladder wall (Jancsó and Maggi, 1987). In the sisspinal cord, transganglionic labeling is totally absent in the central termination areas of primary afferent neurons stapplying the urinary bladder (Jancsó and Maggi spinal cord, transganglionic labeling is totally absent in that
the central termination areas of primary afferent neurons star
supplying the urinary bladder (Jancsó and Maggi, 1987). of 6
Similarly, the number of trigemina the central termination areas of primary afferent neurons
supplying the urinary bladder (Jancsó and Maggi, 1987)
Similarly, the number of trigeminal ganglion cells, which
are labeled retrogradely by a fluorescent dye appli pplying the urinary bladder (Jancsó and Maggi, 1987). of 6
milarly, the number of trigeminal ganglion cells, which (Die
e labeled retrogradely by a fluorescent dye applied to alth
e cornea, is diminished by 87% (Ogilvy et

Similarly, the number of trigeminal ganglion cells, which
are labeled retrogradely by a fluorescent dye applied to
the cornea, is diminished by 87% (Ogilvy et al., 1991).
In the dorsal roots 72% (Arvidsson and Ygge, 1986) are labeled retrogradely by a fluorescent dye applied to alt
the cornea, is diminished by 87% (Ogilvy et al., 1991). un
In the dorsal roots 72% (Arvidsson and Ygge, 1986) to er
95% (Lawson and Nickels, 1980; Nagy et al., 1 the cornea, is diminished by 87% (Ogilvy et al., 1991).

In the dorsal roots 72% (Arvidsson and Ygge, 1986) to

95% (Lawson and Nickels, 1980; Nagy et al., 1981b, 1983;

Holje et al., 1983) of all unmyelinated fibers are In the dorsal roots 72% (Arvidsson and Ygge, 1986) to 95% (Lawson and Nickels, 1980; Nagy et al., 1981b, 1983; Holje et al., 1983) of all unmyelinated fibers are lost. The number of myelinated $A\delta$ -fibers is either uncha 95% (Lawson and Nickels, 1980; Nagy et al., 1981b, 1983; lead to Holje et al., 1983) of all unmyelinated fibers are lost. The mary at number of myelinated $A\delta$ -fibers is either unchanged related (Scadding, 1980; Nagy et Holje et al., 1983) of all unmyelinated fibers are lost. The manumber of myelinated $A\delta$ -fibers is either unchanged rel
(Scadding, 1980; Nagy et al., 1981b; Arvidsson and Ygge, ho
1986) or reduced by 10% (Jancsó et al., number of myelinated A δ -fibers is either unchanged r
(Scadding, 1980; Nagy et al., 1981b; Arvidsson and Ygge, h
1986) or reduced by 10% (Jancsó et al., 1980a) to 40% r
(Lawson and Nickels, 1980; Nagy and Hunt, 1983; Na (Scadding, 1980; Nagy et al., 1981b; Arvidsson and Ygge, hoursel) or reduced by 10% (Jancsó et al., 1980a) to 40% relu
(Lawson and Nickels, 1980; Nagy and Hunt, 1983; Nagy 198
et al., 1983) particularly if doses >50 mg/k 1986) or reduced by 10% (Jancsó et al., 1980a) to 40% (Lawson and Nickels, 1980; Nagy and Hunt, 1983; Nagy et al., 1983) particularly if doses >50 mg/kg capsaicin are used. Conversely, doses of only 10 to 25 mg/kg lead (Lawson and Nickels, 1980; Nagy and Hunt, 1983; Nagy 1
et al., 1983) particularly if doses >50 mg/kg capsaicin 1
are used. Conversely, doses of only 10 to 25 mg/kg lead r
to a selective loss of up to 95% of all unmye et al., 1983) particularly if doses >50 mg/kg capsaicin 1990), sere used. Conversely, doses of only 10 to 25 mg/kg lead neurons to a selective loss of up to 95% of all unmyelinated eceda et afferent nerve fibers without af are used. Conversely, doses of only 10 to 25 mg/kg l
to a selective loss of up to 95% of all unmyelina
afferent nerve fibers without affecting myelinated fit
(Nagy et al., 1983). Consistent with these figures, a 9
loss of to a selective loss of up to 95% of all unmyelinated econferent nerve fibers without affecting myelinated fibers Di (Nagy et al., 1983). Consistent with these figures, a 93% al. loss of type I synaptic glomeruli, thought t afferent nerve fibers without affecting myelinated fibers Die
(Nagy et al., 1983). Consistent with these figures, a 93% al.,
loss of type I synaptic glomeruli, thought to be termina-
has
tions of unmyelinated afferent fibe (Nagy et al., 1983). Consistent with these figures, a 93%
loss of type I synaptic glomeruli, thought to be termina-
tions of unmyelinated afferent fibers, is observed in the
dorsal horn of the rat spinal cord (Ribeiro-da-S loss of type I synaptic glomeruli, thought to be terminations of unmyelinated afferent fibers, is observed in the dorsal horn of the rat spinal cord (Ribeiro-da-Silva an Coimbra, 1984). These glomeruli could be related to tions of unmyelinated afferent fibers, is observed in the deplete
dorsal horn of the rat spinal cord (Ribeiro-da-Silva and ceral tl
Coimbra, 1984). These glomeruli could be related to low-
al., 19:
density synaptosomes con

the dorsal spinal cord following neonatal capsaicin treat-ER
the dorsal spinal cord following neonatal capsaicin treat-
ment (Bucsics et al., 1984). Axon terminal degeneration
is seen in all areas of the spinal cord and brainstem ER
the dorsal spinal cord following neonatal capsaicin treat-
ment (Bucsics et al., 1984). Axon terminal degeneration
is seen in all areas of the spinal cord and brainstem
which are known to receive primary afferent C-fibe the dorsal spinal cord following neonatal capsaicin treatment (Bucsics et al., 1984). Axon terminal degeneration
is seen in all areas of the spinal cord and brainstem
which are known to receive primary afferent C-fiber
inp the dorsal spinal cord following neonatal capsaicin treatment (Bucsics et al., 1984). Axon terminal degeneration
is seen in all areas of the spinal cord and brainstem
which are known to receive primary afferent C-fiber
inp ment (Bucsics et al., 1984). Axon terminal
is seen in all areas of the spinal cord an
which are known to receive primary aff
input (Jancsó et al., 1977; Jancsó and Királ;
Nagy et al., 1980; Dinh and Ritter, 1987).
ii. Neur seen in all areas of the spinal cord and brainsten
nich are known to receive primary afferent C-fiber
put (Jancsó et al., 1977; Jancsó and Király, 1980, 1981
agy et al., 1980; Dinh and Ritter, 1987).
ii. Neurochemical and

a nerve. Thus, although the number of unmyelinated markers associated with thin primary afferent neurons.

fibers in the inferior alveolar and mental nerves of the This depletion of markers is seen in sensory ganglia, in
 The loss of thin afferent nerve fibers is associated with was the first marker found to be depleted by capsaicin
e degeneration of cell bodies from the spinal and cra- treatment of newborn rats (Gamse et al., 1980; Nagy et which are known to receive primary afferent C-fiber
input (Jancsó et al., 1977; Jancsó and Király, 1980, 1981;
Nagy et al., 1980; Dinh and Ritter, 1987).
ii. Neurochemical and histochemical changes.
The morphological ablat input (Jancsó et al., 1977; Jancsó and Király, 1980, 198
Nagy et al., 1980; Dinh and Ritter, 1987).
 ii. Neurochemical and histochemical change

The morphological ablation of sensory neurons produce

by capsaicin in the Nagy et al., 1980; Dinh and Ritter, 1987).

ii. Neurochemical and histochemical change

The morphological ablation of sensory neurons produce

by capsaicin in the newborn rat is reflected by neu

and histochemical as well ii. Neurochemical and histochemical changes.
The morphological ablation of sensory neurons produced
by capsaicin in the newborn rat is reflected by neuro-
and histochemically, capsaicin leads to a depletion of
markers asso The morphological ablation of sensory neurons produced
by capsaicin in the newborn rat is reflected by neuro-
and histochemically, capsaicin leads to a depletion of
markers associated with thin primary afferent neurons.
Th by capsaicin in the newborn rat is reflected by neuro-
and histochemical as well as functional deficits. Neuro-
and histochemically, capsaicin leads to a depletion of
markers associated with thin primary afferent neurons.
 and histochemical as well as functional deficits. Neur
and histochemically, capsaicin leads to a depletion
markers associated with thin primary afferent neuror
This depletion of markers is seen in sensory ganglia,
nerves c and histochemically, capsaicin leads to a depletion of markers associated with thin primary afferent neurons.
This depletion of markers is seen in sensory ganglia, in nerves containing afferent fibers, and in tissues inner markers associated with thin primary afferent neurons.
This depletion of markers is seen in sensory ganglia, in
nerves containing afferent fibers, and in tissues inner-
vated by these fibers in the periphery and in the te This depletion of markers is seen in sensory ganglia, in
nerves containing afferent fibers, and in tissues inner-
vated by these fibers in the periphery and in the terminal
regions of the spinal cord and brainstem. Substan nerves containing afferent fibers, and in tissues inner-
vated by these fibers in the periphery and in the terminal
regions of the spinal cord and brainstem. Substance P
was the first marker found to be depleted by capsaic vated by these fibers in the periphery and in the terminal
regions of the spinal cord and brainstem. Substance P
was the first marker found to be depleted by capsaicin
treatment of newborn rats (Gamse et al., 1980; Nagy et regions of the spinal cord and brainstem. Substance P
was the first marker found to be depleted by capsaicin
treatment of newborn rats (Gamse et al., 1980; Nagy et
al., 1980; Holzer et al., 1982), the depletion being per-
 was the first marker found to be depleted by capsaicin
treatment of newborn rats (Gamse et al., 1980; Nagy et
al., 1980; Holzer et al., 1982), the depletion being per-
manent because no recovery is seen within 9 months
(G treatment of newborn rats (Gamse et al., 1980; Nagy et al., 1980; Holzer et al., 1982), the depletion being per-
manent because no recovery is seen within 9 months (Gamse et al. 1981b). Accordingly, the synthesis of subst al., 1980; Holzer et al., 1982), the depletion being per-
manent because no recovery is seen within 9 months
(Gamse et al. 1981b). Accordingly, the synthesis of sub-
stance P, as measured by the incorporation of $[^{36}S]$
 manent because no recovery is seen within 9 months
(Gamse et al. 1981b). Accordingly, the synthesis of sub-
stance P, as measured by the incorporation of $[^{36}S]$
methionine, is reduced by 80 to 90% in tissue cultures of (Gamse et al. 1981b). Accordingly, the synthesis of substance P, as measured by the incorporation of $[^{35}S]$ methionine, is reduced by 80 to 90% in tissue cultures of dorsal root ganglia taken from rats treated with cap stance P, as measured by the incorporation of [³⁵S]
methionine, is reduced by 80 to 90% in tissue cultures of
dorsal root ganglia taken from rats treated with capsaicin
while neonates (Harmar et al., 1981), indicating th methionine, is reduced by 80 t
dorsal root ganglia taken from
while neonates (Harmar et al.,
majority of substance P-conta
ablated by neonatal capsaicin.
Calcitonin gene-related pep rsal root ganglia taken from rats treated with capsaicin

ile neonates (Harmar et al., 1981), indicating that the

ajority of substance P-containing afferent neurons are

lated by neonatal capsaicin.

Calcitonin gene-rela

while neonates (Harmar et al., 1981), indicating that the majority of substance P-containing afferent neurons are ablated by neonatal capsaicin.
Calcitonin gene-related peptide also is depleted from the dorsal horn of the majority of substance P-containing afferent neurons are
ablated by neonatal capsaicin.
Calcitonin gene-related peptide also is depleted from
the dorsal horn of the spinal cord 10 days after capsaicin
treatment of newborn r ablated by neonatal capsaicin.
Calcitonin gene-related peptide also is depleted from
the dorsal horn of the spinal cord 10 days after capsaicin
treatment of newborn rats (Hammond and Ruda, 1989).
There is some controversy, Calcitonin gene-related peptide also is depleted from
the dorsal horn of the spinal cord 10 days after capsaicin
treatment of newborn rats (Hammond and Ruda, 1989).
There is some controversy, however, relating to the per-
 the dorsal horn of the spinal cord 10 days after capsaicin
treatment of newborn rats (Hammond and Ruda, 1989).
There is some controversy, however, relating to the per-
sistence of depletion in the spinal cord. Two reports treatment of newborn rats (Hammond and Ruda, 1989).
There is some controversy, however, relating to the per-
sistence of depletion in the spinal cord. Two reports hold
that calcitonin gene-related peptide, in contrast to s There is some controversy, however, relating to the per-
sistence of depletion in the spinal cord. Two reports hold
that calcitonin gene-related peptide, in contrast to sub-
stance P, can be replenished over a posttreatmen sistence of depletion in the spinal cord. Two reports hold
that calcitonin gene-related peptide, in contrast to sub-
stance P, can be replenished over a posttreatment period
of 6 to 16 weeks to near-normal levels in the sp that calcitonin gene-related peptide, in contrast to substance P, can be replenished over a posttreatment period of 6 to 16 weeks to near-normal levels in the spinal cord (Diez Guerra et al., 1988; Hammond and Ruda, 1989) stance P, can be replenished over a posttreatment periof 6 to 16 weeks to near-normal levels in the spinal consideration (Diez Guerra et al., 1988; Hammond and Ruda, 1984) although the cellular source of peptide replenishm of 6 to 16 weeks to near-normal levels in the spinal cord (Diez Guerra et al., 1988; Hammond and Ruda, 1989) although the cellular source of peptide replenishment is unknown. This observation may be explained by considerin (Diez Guerra et al., 1988; Hammond and Ruda, 1989)
although the cellular source of peptide replenishment is
unknown. This observation may be explained by consid-
ering that in the spinal cord chronic deafferentation can
le although the cellular source of peptide replenishment is
unknown. This observation may be explained by considering that in the spinal cord chronic deafferentation ca
lead to sprouting and synaptogenesis of surviving pr
mar unknown. This observation may be explained by considering that in the spinal cord chronic deafferentation can
lead to sprouting and synaptogenesis of surviving pri-
mary afferent nerve fibers containing calcitonin gene-
re ering that in the spinal cord chronic deafferentation calead to sprouting and synaptogenesis of surviving pr
mary afferent nerve fibers containing calcitonin generalated peptide (McNeill et al., 1990). Other report
however lead to sprouting and synaptogenesis of surviving pri
mary afferent nerve fibers containing calcitonin gene
related peptide (McNeill et al., 1990). Other reports
however, show that the depletion of calcitonin gene
related mary afferent nerve fibers containing calcitonin gene-
related peptide (McNeill et al., 1990). Other reports,
however, show that the depletion of calcitonin gene-
related peptide in spinal cord (Skofitsch and Jacobowitz,
1 related peptide (McNeill et al., 1990). Other reports,
however, show that the depletion of calcitonin gene-
related peptide in spinal cord (Skofitsch and Jacobowitz,
1985b; Carr et al., 1990; Marlier et al., 1990; Pohl et however, show that the depletion of calcitonin gelated peptide in spinal cord (Skofitsch and Jacobo
1985b; Carr et al., 1990; Marlier et al., 1990; Pohl e
1990), sensory ganglia, and peripheral targets of ser
neurons (Skof related peptide in spinal cord (Skofitsch and Jacobowitz, 1985b; Carr et al., 1990; Marlier et al., 1990; Pohl et al., 1990), sensory ganglia, and peripheral targets of sensory neurons (Skofitsch and Jacobowitz, 1985b; Fra 1985b; Carr et al., 1990; Marlier et al., 1990; Pohl et al., 1990), sensory ganglia, and peripheral targets of sensory neurons (Skofitsch and Jacobowitz, 1985b; Franco-Cereceda et al., 1987b; Sternini et al., 1987; Su et a 1990), sensory ganglia, and peripheral targets of sensory
neurons (Skofitsch and Jacobowitz, 1985b; Franco-Cer-
eceda et al., 1987b; Sternini et al., 1987; Su et al., 1987;
Diez Guerra et al., 1988; Geppetti et al., 1988a; neurons (Skofitsch and Jacobowitz, 1985b; Franco-Cer-
eceda et al., 1987b; Sternini et al., 1987; Su et al., 1987;
Diez Guerra et al., 1988; Geppetti et al., 1988a; Varro et
al., 1988; Carr et al., 1990; Pohl et al., 1990) eceda et al., 1987b; Sternini et al., 1987; Su et al., 1987; Diez Guerra et al., 1988; Geppetti et al., 1988a; Varro et al., 1988; Carr et al., 1990; Pohl et al., 1990) persists. It has also been found that neonatal capsai Diez Guerra et al., 1988; Geppetti et al., 1988a; Varro et al., 1988; Carr et al., 1990; Pohl et al., 1990) persists. It has also been found that neonatal capsaicin seems to deplete more calcitonin gene-related peptide fro al., 1988; Carr et al., 1990; Pohl et al., 1990) persists. It has also been found that neonatal capsaicin seems to deplete more calcitonin gene-related peptide from visceral than from somatic sensory pathways (Kashiba et a has also been found that neonatal capsaicin seems the deplete more calcitonin gene-related peptide from violental than from somatic sensory pathways (Kashiba e al., 1990a), but it is not known whether this factor contribut deplete more calcitonin gene-related peptide from visceral than from somatic sensory pathways (Kashiba et al., 1990a), but it is not known whether this factor contributes to the variability in the findings with calcitonin

HARM
REV

PHARMACOLOGICAL REVIEWS

aspet

CAF
A list of markers of afferent neurons, including the
substance P-related peptide neurokinin A, dynorphin
leucine-enkephalin, galanin, somatostatin, and vasoac C

A list of markers of afferent neurons, including t

substance P-related peptide neurokinin A, dynorph

leucine-enkephalin, galanin, somatostatin, and vasoa

tive intestinal polypeptide, all of which can be deplet A list of markers of afferent neurons, including the neubstance P-related peptide neurokinin A, dynorphin, cleucine-enkephalin, galanin, somatostatin, and vasoaccitive intestinal polypeptide, all of which can be depleted m A list of markers of afferent neurons, including the
substance P-related peptide neurokinin A, dynorphin, cl
leucine-enkephalin, galanin, somatostatin, and vasoac-
tive intestinal polypeptide, all of which can be depleted
 substance P-related peptide neurokinin A, dynorpleucine-enkephalin, galanin, somatostatin, and vaso
tive intestinal polypeptide, all of which can be deple
by neonatal capsaicin to varying degrees, is given in ta
1. The che leucine-enkephalin, galanin, somatostatin, and vasoactive intestinal polypeptide, all of which can be depleted
by neonatal capsaicin to varying degrees, is given in table
1. The chemical coding of afferent neurons is heter tive intestinal polypeptide, all of which can be depleted mot
by neonatal capsaicin to varying degrees, is given in table (L
1. The chemical coding of afferent neurons is heteroge-
neous in that the markers listed in table by neonatal capsaicin to varying degrees, is given in table (Le 1. The chemical coding of afferent neurons is heteroge-San neous in that the markers listed in table 1 are not present 198 in all afferent neurons, and there 1. The chemical coding of afferent neurons is heterogeneous in that the markers listed in table 1 are not present in all afferent neurons, and there are differences in the combinations of coexisting markers both within and neous in that the markers listed in table 1 are not present 19
in all afferent neurons, and there are differences in the Micombinations of coexisting markers both within and 19
across different species (Costa et al., 1986; in all afferent neurons, and there are differences in the combinations of coexisting markers both within and across different species (Costa et al., 1986; Gibbins et al., 1987; Weihe, 1990). As a further limitation, many o combinations of coexisting markers both within and
across different species (Costa et al., 1986; Gibbins et al.,
1987; Weihe, 1990). As a further limitation, many of the
neurochemical markers of capsaicin-sensitive afferen 1987; Weihe, 1990). As a further limitation, many of the
neurochemical markers of capsaicin-sensitive afferent
neurons also occur in afferent and nonafferent neurons
that are not sensitive to capsaicin.
The capsaicin-induc 87; Weihe, 1990). As a further limitation, many of the urochemical markers of capsaicin-sensitive afferent urons also occur in afferent and nonafferent neurons at are not sensitive to capsaicin.
The capsaicin-induced deple

meurochemical markers of capsaicin-sensitive afferencurons also occur in afferent and nonafferent neuro
that are not sensitive to capsaicin.
The capsaicin-induced depletion of peptides and oth
markers from sensory neurons neurons also occur in afferent and nonafferent neurons that are not sensitive to capsaicin.

The capsaicin-induced depletion of peptides and other 1

markers from sensory neurons (table 1) and the classi-

fication of caps that are not sensitive to capsaicin.
The capsaicin-induced depletion of peptides and othe
markers from sensory neurons (table 1) and the classi
fication of capsaicin-sensitive afferent neurons according
to different patter The capsaicin-induced depletion of peptides and other 1981
markers from sensory neurons (table 1) and the classi-
fication of capsaicin-sensitive afferent neurons according
to different patterns of chemical coding have bee markers from sensory neurons (table 1) and the classi-Magnetican of capsaicin-sensitive afferent neurons according A
to different patterns of chemical coding have been sum-saic
marized in other reviews (Marley and Livett, fication of capsaicin-sensitive afferent neurons accordin
to different patterns of chemical coding have been sum
marized in other reviews (Marley and Livett, 1985; Buc
and Burks, 1986). In addition to the markers referred to different patterns of chemical coding have been sum
marized in other reviews (Marley and Livett, 1985; Buc
and Burks, 1986). In addition to the markers referred t
in table 1, large light A-type sensory neurons are chan
 marized in other reviews (Marley and Livett, 1985; Buck
and Burks, 1986). In addition to the markers referred to
in table 1, large light A-type sensory neurons are char-
acterized by the selective presence of a neurofilame and Burks, 1986). In addition to the markers referred to
in table 1, large light A-type sensory neurons are char-
acterized by the selective presence of a neurofilament
protein that is absent in the small dark B-type neuro in table 1, large light A-type sensory neurons are characterized by the selective presence of a neurofilament
protein that is absent in the small dark B-type neurons
(Lawson and Harper, 1984; Kai-Kai et al., 1986). Al-
tho acterized by the selective presence of a neurofilamen
protein that is absent in the small dark B-type neuron
(Lawson and Harper, 1984; Kai-Kai et al., 1986). Al
though the majority of capsaicin-sensitive afferent neu
rons protein that is absent in the small dark B-type neurons (Lawson and Harper, 1984; Kai-Kai et al., 1986). Although the majority of capsaicin-sensitive afferent neurons fall within the group of neurofilament-negative B-type (Lawson and Harper, 1984; Kai-Kai et al., 1986). Although the majority of capsaicin-sensitive afferent neu-
rons fall within the group of neurofilament-negative B-
type neurons (Lawson and Harper, 1984; Kai-Kai et al.,
198 though the majority of capsaicin-sensitive afferent neu-
rons fall within the group of neurofilament-negative B-
type neurons (Lawson and Harper, 1984; Kai-Kai et al.,
1986), some of the neurofilament-containing A-type neu rons fall within the group of neurofilament-negative
type neurons (Lawson and Harper, 1984; Kai-Kai et
1986), some of the neurofilament-containing A-type n
rons also are destroyed by neonatal capsaicin, at leas
doses >50 m type neurons (Lawson and Harper, 1984; Kai-Kai et al., 1986), some of the neurofilament-containing A-type neurons also are destroyed by neonatal capsaicin, at least at doses >50 mg/kg (Lawson and Harper, 1984). Furthermo 1986), some of the neurofilament-containing A-type neurons also are destroyed by neonatal capsaicin, at least at doses >50 mg/kg (Lawson and Harper, 1984). Furthermore, capsaicin treatment of newborn rats leads to inhibiti rons also are destroyed by neonatal capsaicin, at least at sa
doses >50 mg/kg (Lawson and Harper, 1984). Further-
more, capsaicin treatment of newborn rats leads to in-
hibition of the axoplasmic transport of organelle-spe doses >50 mg/kg (Lawson and Harper, 1984). Furthermore, capsaicin treatment of newborn rats leads to inhibition of the axoplasmic transport of organelle-specific enzymes and the retrograde transport of nerve growth factor more, capsaicin treatment of newborn rats leads to in-
hibition of the axoplasmic transport of organelle-specific spi
enzymes and the retrograde transport of nerve growth I
factor in sensory, but not sympathetic, nerves of hibition of the axoplasmic transport of organelle-specific spenzymes and the retrograde transport of nerve growth factor in sensory, but not sympathetic, nerves of adult seemimals (McDougal et al., 1983). These changes can fibers. rector in sensory, but not sympathetic, nerves of adult sensitive imals (McDougal et al., 1983). These changes can be ciception plained by a deficit of thin primary afferent nerve cape reas.
 Functional changes. As might

animals (McDougal et al., 1983). These changes can be complained by a deficit of thin primary afferent nerve complements.

fibers. primary afferent neurons, capsaicing the morphological ablation of afferent neurons, capsai explained by a deficit of thin primary afferent nerve
fibers.
iii. Functional changes. As might be expected from
the morphological ablation of afferent neurons, capsaicin
treatment of newborn rats is associated with perman fibers. per iii. Functional changes. As might be expected from al.
the morphological ablation of afferent neurons, capsaicin al.
treatment of newborn rats is associated with permanent Du
sensory and functional deficits whi iii. Functional changes. As might be expected from
the morphological ablation of afferent neurons, capsaicin
treatment of newborn rats is associated with permanent
sensory and functional deficits which involve both the
aff the morphological ablation of afferent neurons, capsaicinfreatment of newborn rats is associated with permanent sensory and functional deficits which involve both the afferent and local effector functions of sensory neuron treatment of newborn rats is associated with permanent
sensory and functional deficits which involve both the
afferent and local effector functions of sensory neurons
(Nagy, 1982; Szolcsányi, 1982, 1990; Jancsó, 1984; Russensory and functional deficits which involve both the a
afferent and local effector functions of sensory neurons in
(Nagy, 1982; Szolcsányi, 1982, 1990; Jancsó, 1984; Rus-
sell and Burchiel, 1984; Buck and Burks, 1986; Ma afferent and local effector functions of sensory neurons i

(Nagy, 1982; Szolcsányi, 1982, 1990; Jancsó, 1984; Rus-

sell and Burchiel, 1984; Buck and Burks, 1986; Maggi (

and Meli, 1986, 1988; Lembeck, 1987b, 1988; Lundb (Nagy, 1982; Szolcsányi, 1982, 1990; Jancsó, 1984; Rus-
sell and Burchiel, 1984; Buck and Burks, 1986; Maggi Cer
and Meli, 1986, 1988; Lembeck, 1987b, 1988; Lundberg 198
and Saria, 1987; Chahl, 1988; Holzer, 1988; Donnerer sell and Burchiel, 1984; Buck and Burks, 1986; Maggi Cond Meli, 1986, 1988; Lembeck, 1987b, 1988; Lundberg 19
and Saria, 1987; Chahl, 1988; Holzer, 1988; Donnerer et et
al., 1990; Maggi, 1990, 1991). The activity of the dr and Meli, 1986, 1988; Lembeck, 1987b, 1988; Lundberg
and Saria, 1987; Chahl, 1988; Holzer, 1988; Donnerer et
al., 1990; Maggi, 1990, 1991). The activity of the drug to
induce neuronal degeneration correlates well with its
 and Saria, 1987; Chahl, 1988; Holzer, 1988; Donnerer et al., 1990; Maggi, 1990, 1991). The activity of the drug to induce neuronal degeneration correlates well with its ability to inhibit the function of fine afferent neur al., 1990; Maggi, 1990, 1991). The activity of the drug to induce neuronal degeneration correlates well with its ability to inhibit the function of fine afferent neurons (Jancsó, 1984). The many functional changes brought induce neuronal degeneration correlates well with its
ability to inhibit the function of fine afferent neurons
(Jancsó, 1984). The many functional changes brought
about by neonatal capsaicin are not detailed here except
th ility to inhibit the function of fine afferent neurons relations, 1984). The many functional changes brought (Historic by neonatal capsaicin are not detailed here except the at some salient features are discussed. Capsaici

about by neonatal capsaicin are not detailed here except
that some salient features are discussed.
Capsaicin treatment of newborn rats has been used
widely to explore the functional implications of capsai-
cin-sensitive af about by neonatal capsaicin are not detailed here except
that some salient features are discussed. 19
Capsaicin treatment of newborn rats has been used
prividely to explore the functional implications of capsai-
this appro that some salient features are discussed. The assume that capsaicin treatment of newborn rats has been used put
widely to explore the functional implications of capsai-
thin sensitive afferent neurons, this approach being

A list of markers of afferent neurons, including the neurons only. A number of local effector functions in-
substance P-related peptide neurokinin A, dynorphin, cluding vasodilatation, increase in vascular permeability, neurons only. A number of local effector functions in-
cluding vasodilatation, increase in vascular permeability, cluding vasodilatation, increase in vascular permeability
cluding vasodilatation, increase in vascular permeability,
changes in the activity of cardiac, bronchial, and viscera 153
neurons only. A number of local effector functions in-
cluding vasodilatation, increase in vascular permeability,
changes in the activity of cardiac, bronchial, and visceral
muscle, and changes in the activity of the i meurons only. A number of local effector functions in-
cluding vasodilatation, increase in vascular permeability,
changes in the activity of cardiac, bronchial, and visceral
muscle, and changes in the activity of the immun neurons only. A number of local effector functions in-
cluding vasodilatation, increase in vascular permeability,
changes in the activity of cardiac, bronchial, and visceral
muscle, and changes in the activity of the immun changes in the activity of cardiac, bronchial, and visceral
muscle, and changes in the activity of the immune system
(Lembeck and Holzer, 1979; Morton and Chahl, 1980;
Saria, 1984; Lundberg and Saria, 1987; Ahlstedt et al. changes in the activity of cardiac, bronchial, and visceral
muscle, and changes in the activity of the immune system
(Lembeck and Holzer, 1979; Morton and Chahl, 1980;
Saria, 1984; Lundberg and Saria, 1987; Ahlstedt et al. muscle, and changes in the activity of the immune system
(Lembeck and Holzer, 1979; Morton and Chahl, 1980;
Saria, 1984; Lundberg and Saria, 1987; Ahlstedt et al.,
1986; Helme et al., 1987; Chahl, 1988; Holzer, 1988;
Maggi (Lembeck and Holzer, 1979; Morton and Chahl, 1980;
Saria, 1984; Lundberg and Saria, 1987; Ahlstedt et al.,
1986; Helme et al., 1987; Chahl, 1988; Holzer, 1988;
Maggi and Meli, 1988; Nilsson, 1989; Donnerer et al.,
1990; Ma Saria, 1984; Lundberg and Saria, 1987; Ahlstedt et al., 1986; Helme et al., 1987; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988; Nilsson, 1989; Donnerer et al., 1990; Maggi, 1990) are inhibited or abolished by neonatal c Maggi and Meli, 1988; Nilsson, 1989; Donnerer et al., 1990; Maggi, 1990) are inhibited or abolished by neonatal capsaicin. The vulnerability of the gastric mucosa is enhanced (Holzer and Sametz, 1986), and the occurrence and persistence of lesions in skin and cornea of capsaicin-
treated animals are seen to reflect a trophic role of
sensory nerve endings in these tissues (Gamse et al., 1990; Maggi, 1990) are inhibited or abolished by neonatal capsaicin. The vulnerability of the gastric mucosa is
enhanced (Holzer and Sametz, 1986), and the occurrence
and persistence of lesions in skin and cornea of capsai capsaicin. The vulnerability of the gastric mucosa is
enhanced (Holzer and Sametz, 1986), and the occurrence
and persistence of lesions in skin and cornea of capsaicin-
treated animals are seen to reflect a trophic role of enhanced (Holzer and Sametz, 1986), and the occurrence
and persistence of lesions in skin and cornea of capsaicin-
treated animals are seen to reflect a trophic role of
sensory nerve endings in these tissues (Gamse et al., and persistence of lesions in skin and corn
treated animals are seen to reflect a t
sensory nerve endings in these tissues
1981b; Shimizu et al., 1984; Kjartansso
Maggi et al., 1987a; Ogilvy et al., 1991).
Afferent functio eated animals are seen to reflect a trophic role of nsory nerve endings in these tissues (Gamse et al., 81b; Shimizu et al., 1984; Kjartansson et al., 1987; aggi et al., 1987a; Ogilvy et al., 1991).
Afferent functions that

sensory nerve endings in these tissues (Gamse et al., 1981b; Shimizu et al., 1984; Kjartansson et al., 1987; Maggi et al., 1987a; Ogilvy et al., 1991).
Afferent functions that are impaired by neonatal capsaicin comprise wa 1981b; Shimizu et al., 1984; Kjartansson et al., 1987;
Maggi et al., 1987a; Ogilvy et al., 1991).
Afferent functions that are impaired by neonatal cap-
saicin comprise warmth reception and thermoregulation
(Hori and Tsuzuk Maggi et al., 1987a; Ogilvy et al., 1991).
Afferent functions that are impaired by neonatal capsaicin comprise warmth reception and thermoregulation
(Hori and Tsuzuki, 1981; Donnerer and Lembeck, 1983;
Dib, 1983; Hajós et Afferent functions that are impaired by neonatal capsaicin comprise warmth reception and thermoregulation (Hori and Tsuzuki, 1981; Donnerer and Lembeck, 1983; Dib, 1983; Hajós et al., 1983, 1986a; Obál et al., 1983; Jancsó saicin comprise warmth reception and thermoregulation
(Hori and Tsuzuki, 1981; Donnerer and Lembeck, 1983;
Dib, 1983; Hajós et al., 1983, 1986a; Obál et al., 1983;
Jancsó, 1984), cardiovascular reflexes (Bond et al., 1982; (Hori and Tsuzuki, 1981; Donnerer and Lembeck, 1983;
Dib, 1983; Hajós et al., 1983, 1986a; Obál et al., 1983;
Jancsó, 1984), cardiovascular reflexes (Bond et al., 1982;
Lembeck and Skofitsch, 1982; Lorez et al., 1983; Benn Dib, 1983; Hajós et al., 1983, 1986a; Obál et al., 1983;
Jancsó, 1984), cardiovascular reflexes (Bond et al., 1982;
Lembeck and Skofitsch, 1982; Lorez et al., 1983; Bennett
and Gardiner, 1984; Donnerer et al., 1989), visce Jancsó, 1984), cardiovascular reflexes (Bond et al., 19
Lembeck and Skofitsch, 1982; Lorez et al., 1983; Benn
and Gardiner, 1984; Donnerer et al., 1989), visceral
flexes (Cervero-and McRitchie, 1982; Sharkey et
1983; Santi Lembeck and Skofitsch, 1982; Lorez et al., 1983; Bennett
and Gardiner, 1984; Donnerer et al., 1989), visceral re-
flexes (Cervero and McRitchie, 1982; Sharkey et al.,
1983; Santicioli et al., 1985; Holzer et al., 1986), ne and Gardiner, 1984; Donnerer et al., 1989), visceral reflexes (Cervero and McRitchie, 1982; Sharkey et al
1983; Santicioli et al., 1985; Holzer et al., 1986), neuroen
docrine reflexes (Traurig et al., 1984a,b; Amann and
Le flexes (Cervero and McRitchie, 1982; Sharkey et al., 1983; Santicioli et al., 1985; Holzer et al., 1986), neuroen-
docrine reflexes (Traurig et al., 1984a,b; Amann and
Lembeck, 1986, 1987; Bennett and Gardiner, 1986; Don-
 1983; Santicioli et al., 1985; Holzer et al., 1986), neuroen-
docrine reflexes (Traurig et al., 1984a,b; Amann and
Lembeck, 1986, 1987; Bennett and Gardiner, 1986; Don-
nerer et al., 1989; Donnerer and Lembeck, 1990), and
 docrine reflexes (Traurig et al., 1984a,b; Amann and
Lembeck, 1986, 1987; Bennett and Gardiner, 1986; Don-
nerer et al., 1989; Donnerer and Lembeck, 1990), and
satiety (MacLean, 1985). These changes are likely to be
relate nerer et al., 1989; Donnerer and Lembeck, 1990), and
satiety (MacLean, 1985). These changes are likely to be
related to ablation of unmyelinated afferent neurons and
to inhibition of slow synaptic transmission in the dorsa nerer et al., 1989; Donnerer and
satiety (MacLean, 1985). These c
related to ablation of unmyelinate
to inhibition of slow synaptic trar
spinal cord (Urbán et al., 1985).
In keeping with the sensory m tiety (MacLean, 1985). These changes are likely to lated to ablation of unmyelinated afferent neurons inhibition of slow synaptic transmission in the do inal cord (Urbán et al., 1985). In keeping with the sensory modalitie

to inhibition of slow synaptic transmission in the dorsal
spinal cord (Urbán et al., 1985).
In keeping with the sensory modalities of capsaicin-
sensitive afferent neurons there also are changes in no-
ciception and nocice to inhibition of slow synaptic transmission in the dorsal
spinal cord (Urbán et al., 1985).
In keeping with the sensory modalities of capsaicin-
sensitive afferent neurons there also are changes in no-
ciception and nocice spinal cord (Urbán et al., 1985).
In keeping with the sensory modalities of capsaicin-
sensitive afferent neurons there also are changes in no-
ciception and nociception-associated avoidance and es-
cape reactions. Percept In keeping with the sensory modalities of capsaicin-
sensitive afferent neurons there also are changes in no-
ciception and nociception-associated avoidance and es-
cape reactions. Perception of chemical noxious stimuli is sensitive afferent neurons there also are changes in no-
ciception and nociception-associated avoidance and es-
cape reactions. Perception of chemical noxious stimuli is
permanently inhibited by neonatal capsaicin (Jancsó ciception and nociception-associated avoidance and escape reactions. Perception of chemical noxious stimuli is
permanently inhibited by neonatal capsaicin (Jancsó et
al., 1977, 1980a; Faulkner and Growcott, 1980; Gamse et
 cape reactions. Perception of chemical noxious stimuli i
permanently inhibited by neonatal capsaicin (Jancsó e
al., 1977, 1980a; Faulkner and Growcott, 1980; Gamse e
al., 1980; Hayes et al., 1981a; Gamse, 1982; Saumet an
D permanently inhibited by neonatal capsaicin (Jancsó et al., 1977, 1980a; Faulkner and Growcott, 1980; Gamse et al., 1980; Hayes et al., 1981a; Gamse, 1982; Saumet and Duclaux, 1982; Jancsó, 1984), but there is disagreement al., 1977, 1980a; Faulkner and Growcott, 1980; Gamse et
al., 1980; Hayes et al., 1981a; Gamse, 1982; Saumet and
Duclaux, 1982; Jancsó, 1984), but there is disagreement
as to whether mechano- and thermonociception also are
 al., 1980; Hayes et al., 1981a; Gamse, 1982; Saumet and
Duclaux, 1982; Jancsó, 1984), but there is disagreement
as to whether mechano- and thermonociception also are
impaired (Holzer et al., 1979; Faulkner and Growcott,
19 Duclaux, 1982; Jancsó, 1984), but there is disagreement
as to whether mechano- and thermonociception also are
impaired (Holzer et al., 1979; Faulkner and Growcott,
1980; Jancsó and Jancsó-Gábor, 1980; Nagy et al., 1980;
Ce as to whether mechano- and thermonociception also are
impaired (Holzer et al., 1979; Faulkner and Growcott,
1980; Jancsó and Jancsó-Gábor, 1980; Nagy et al., 1980;
Cervero and McRitchie, 1981; Hayes et al., 1981a; Gamse,
1 impaired (Holzer et al., 1979; Faulkner and Growcott,
1980; Jancsó and Jancsó-Gábor, 1980; Nagy et al., 1980;
Cervero and McRitchie, 1981; Hayes et al., 1981a; Gamse,
1982; Saumet and Duclaux, 1982; Jancsó, 1984; Doucette
 1980; Jancsó and Jancsó-Gábor, 1980; Nagy et al., 1980;
Cervero and McRitchie, 1981; Hayes et al., 1981a; Gamse,
1982; Saumet and Duclaux, 1982; Jancsó, 1984; Doucette
et al., 1987; Hammond and Ruda, 1989; Ogilvy et al.,
1 Cervero and McRitchie, 1981; Hayes et al., 1981a; Gamse, 1982; Saumet and Duclaux, 1982; Jancsó, 1984; Doucette
et al., 1987; Hammond and Ruda, 1989; Ogilvy et al.,
1991). The discrepant results are probably due to several 1982; Saumet and Duclaux, 1982; Jancsó, 1984; Doucette
et al., 1987; Hammond and Ruda, 1989; Ogilvy et al.,
1991). The discrepant results are probably due to several
factors including the use of different strains of rats, et al., 1987; Hammond and Ruda, 1989; Ogilvy et al., 1991). The discrepant results are probably due to several factors including the use of different strains of rats, agerelated changes in capsaicin-induced antinociception 1991). The discrepant results are probably due to several factors including the use of different strains of rats, age-
related changes in capsaicin-induced antinociception
(Hammond and Ruda, 1989), intrastrain variability factors including the use of different strains of rats, age-
related changes in capsaicin-induced antinociception
(Hammond and Ruda, 1989), intrastrain variability in
the sensitivity to capsaicin (Nagy and van der Koy,
198 related changes in capsaicin-induced antinociceptic (Hammond and Ruda, 1989), intrastrain variability the sensitivity to capsaicin (Nagy and van der Kontess), and differences in the experimental protocols a procedures. Thu (Hammond and Ruda, 1989), intrastrain variability in
the sensitivity to capsaicin (Nagy and van der Koy,
1983), and differences in the experimental protocols and
procedures. Thus, tests of nociception that use supra-
thres the sensitivity to capsaicin (Nagy and van der K
1983), and differences in the experimental protocols a
procedures. Thus, tests of nociception that use sup
threshold or even supramaximal strengths of stimuli
likely to give 1983), and differences in the experimental protocols and procedures. Thus, tests of nociception that use supra-
threshold or even supramaximal strengths of stimuli are
likely to give different results than tests that use t

ferences in the proportion of afferent nerve fibers sensi-HOL2
ferences in the proportion of afferent nerve fibers sensi-
tive to capsaicin (Holje et al., 1983; Doucette et al., 1987;
Fried et al., 1988) are likely to account for differences in HOLZER
ferences in the proportion of afferent nerve fibers sensi-1985
tive to capsaicin (Holje et al., 1983; Doucette et al., 1987; saic
Fried et al., 1988) are likely to account for differences in pep
capsaicin-induced an ferences in the proportion of afferent nerve fibers sensitive to capsaicin (Holje et al., 1983; Doucette et al., 1987; s
Fried et al., 1988) are likely to account for differences in proposaicin-induced antinociception in d ferences in the proportic
tive to capsaicin (Holje e
Fried et al., 1988) are lik
capsaicin-induced antinc
(Doucette et al., 1987).
iv. Secondary chang ve to capsaicin (Holje et al., 1983; Doucette et al., 1987; saived et al., 1988) are likely to account for differences in perposaicin-induced antinociception in different skin areas raisolated to al., 1987).
 iv. Secondar

Fried et al., 1988) are likely to account for differences in capsaicin-induced antinociception in different skin areas (Doucette et al., 1987).
 iv. Secondary changes in sensory pathways. The lack of a consistent effect capsaicin-induced antinociception in different skin areas raid (Doucette et al., 1987).

iv. Secondary changes in sensory pathways. The lack of a consistent effect of neonatal capsaicin on me-

chanical and thermal nocicep (Doucette et al., 1987).

iv. Secondary changes in sensory pathways. The

lack of a consistent effect of neonatal capsaicin on me-

chanical and thermal nociception is a paradox in view of

the permanent loss of unmyelinat iv. Secondary changes in sensory pathways. The
lack of a consistent effect of neonatal capsaicin on me-
chanical and thermal nociception is a paradox in view of
the permanent loss of unmyelinated afferent neurons
caused by lack of a consistent effect of neonatal capsaicin on me-
chanical and thermal nociception is a paradox in view of
the permanent loss of unmyelinated afferent neurons et
caused by this treatment. This paradox probably refle chanical and thermal nociception is a paradox in view of (1)
the permanent loss of unmyelinated afferent neurons et
caused by this treatment. This paradox probably reflects as
one of the many aspects of secondary changes i the permanent loss of unmyelinated afferent neuron
caused by this treatment. This paradox probably reflect
one of the many aspects of secondary changes in sensor
pathways that occur in response to ablation of primar
affere caused by this treatment. This paradox probably reflement of the many aspects of secondary changes in sense pathways that occur in response to ablation of prima afferent neurons by neonatal capsaicin. Hence, fultional alte one of the many aspects of secondary changes in sensory et al., pathways that occur in response to ablation of primary treatnes afferent neurons by neonatal capsaicin. Hence, functional alterations seen in adult rats treat pathways that occur in response to ablation of primary
afferent neurons by neonatal capsaicin. Hence, func-
tional alterations seen in adult rats treated with capsai-
cin as neonates cannot unequivocally be used to draw
st afferent neurons by neonatal capsaicin. Hence, functional alterations seen in adult rats treated with capsailies in as neonates cannot unequivocally be used to draw sentraightforward conclusions as to specific functional i tional alterations seen in adult rats treated with capsaicin as neonates cannot unequivocally be used to draw
straightforward conclusions as to specific functional im-
plications of capsaicin-sensitive afferent neurons. Gi cin as neonates cannot unequivocally be used to draw
straightforward conclusions as to specific functional im-
plications of capsaicin-sensitive afferent neurons. Given
lehe plasticity of the nervous system in the newborn straightforward conclusions as to specific functional im-
plications of capsaicin-sensitive afferent neurons. Given leit
the plasticity of the nervous system in the newborn rat, man
degeneration of the majority of unmyelin plications of capsaicin-sensitive afferent neurons. Given
the plasticity of the nervous system in the newborn rat,
degeneration of the majority of unmyelinated primary
afferent neurons is likely to have a significant impac the plasticity of the nervous system in the newborn radegeneration of the majority of unmyelinated primar
afferent neurons is likely to have a significant impact of
afferent nerves themselves, on second- and higher-orde
af degeneration of the majority of unmyelinated primate afferent neurons is likely to have a significant impact afferent neurons and related systems in the central neous system, and on systems associated with the peripheral e afferent neurons is likely to have
afferent nerves themselves, on se
afferent neurons and related syst
ous system, and on systems asso
eral endings of sensory neurons.
Reorganization of the primary Ferent nerves themselves, on second- and higher-order
ferent neurons and related systems in the central nerv-
s system, and on systems associated with the periph-
al endings of sensory neurons.
Reorganization of the primar

afferent neurons and related systems in the central nerv-
ous system, and on systems associated with the periph-
eral endings of sensory neurons.
Reorganization of the primary afferent system is in-
dicated by the findings ous system, and on systems associated with the periph-
eral endings of sensory neurons. an
Reorganization of the primary afferent system is in-
dicated by the findings that the loss of small sensory 19
ganglion cells and u eral endings of sensory neurons.
Reorganization of the primary afferent system is in-
dicated by the findings that the loss of small sensory
ganglion cells and unmyelinated afferent nerve fibers is
associated with a numeri Reorganization of the primary afferent system is in-
dicated by the findings that the loss of small sensory 1
ganglion cells and unmyelinated afferent nerve fibers is 1
associated with a numerical increase of dorsal root g dicated by the findings that the loss of small sensory ganglion cells and unmyelinated afferent nerve fibers is associated with a numerical increase of dorsal root ganglion cells which are of intermediate size and stain fo ganglion cells and unmyelinated afferent nerve fibers is
associated with a numerical increase of dorsal root gan-
glion cells which are of intermediate size and stain for
both peripherin and neurofilament triplet (Ferri et associated with a numerical increase of dorsal root ganglion cells which are of intermediate size and stain for both peripherin and neurofilament triplet (Ferri et al., 1990) and by changes in the diameter of the remaining glion cells which are of intermediate size and stain
both peripherin and neurofilament triplet (Ferri et
1990) and by changes in the diameter of the remain
populations of sensory ganglion cells (McDougal et
1985; Ferri et both peripherin and neurofilament triplet (Ferri et al., 1990) and by changes in the diameter of the remaining
populations of sensory ganglion cells (McDougal et al.,
1985; Ferri et al., 1990). Although the number of unmye 1990) and by changes in the diameter of the remaining
populations of sensory ganglion cells (McDougal et al.,
1985; Ferri et al., 1990). Although the number of unmye-
linated fibers is diminished by about 40 to 50% in aff populations of sensory ganglion cells (McDougal et al., of 1985; Ferri et al., 1990). Although the number of unmye-
linated fibers is diminished by about 40 to 50% in afferent to nerves of adult rats treated with capsaicin 1985; Ferri et al., 1990). Although the number of unmyelinated fibers is diminished by about 40 to 50% in afferent nerves of adult rats treated with capsaicin as neonates (Lynn, 1984; Welk et al., 1984), there is no change linated fibers is diminished by about 40 to 50% in affer
nerves of adult rats treated with capsaicin as neona
(Lynn, 1984; Welk et al., 1984), there is no change in t
proportions of the C-fiber receptor types (Lynn, 19
Wel nerves of adult rats treated with capsaicin as neonates (Lynn, 1984; Welk et al., 1984), there is no change in the proportions of the C-fiber receptor types (Lynn, 1984; Welk et al., 1984; Cervero and Sharkey, 1988). Accor (Lynn, 1984; Welk et al., 1984), there is no change in the correspondingly as the C-fiber receptor types (Lynn, 1984; Nelk et al., 1984; Cervero and Sharkey, 1988). Accordingly, application of capsaicin to afferent nerves proportions of the C-fiber receptor types (Lynn, 1984;
Welk et al., 1984; Cervero and Sharkey, 1988). Accord-
ingly, application of capsaicin to afferent nerves of cap-
saicin-treated rats produces excitation of (Szolcsány Welk et al., 1984; Cervero and Sharkey, 1988). Accordingly, application of capsaicin to afferent nerves of capsaicin-treated rats produces excitation of (Szolcsányi, 1990), and a conduction block in, (Welk et al., 1984) Cingly, application of capsaicin to afferent nerves of capsaicin-treated rats produces excitation of (Szolcsányi, p. 1990), and a conduction block in, (Welk et al., 1984) C- enfiber polymodal nociceptors, the magnitude of t saicin-treated rats produces excitation of (Szolcsányi, pa
1990), and a conduction block in, (Welk et al., 1984) C-
fiber polymodal nociceptors, the magnitude of these ef-
infects being similar to that found in control rat 1990), and a conduction block in, (Welk et al., 1984) C-
fiber polymodal nociceptors, the magnitude of these ef-
fects being similar to that found in control rats. These
data indicate that adult rats treated with capsaicin fiber polymodal nociceptors, the magnitude of these ef-
fects being similar to that found in control rats. These
data indicate that adult rats treated with capsaicin as
meonates possess capsaicin-sensitive afferent neurons fects being similar to that found in control rats. These data indicate that adult rats treated with capsaicin as neonates possess capsaicin-sensitive afferent neurons; lyet it is not known whether these neurons escaped or data indicate that adult rats treated with capsaicin as necessare possess capsaicin-sensitive afferent neurons; logically by the it is not known whether these neurons escaped or between survived the neonatal capsaicin trea neonates possess capsaicin-sensitive afferent neurons; lot it is not known whether these neurons escaped or by survived the neonatal capsaicin treatment or evolved at all a later stage. In the cornea, sprouting of the surv yet it is not known whether these neurons escaped or by survived the neonatal capsaicin treatment or evolved at al.
a later stage. In the cornea, sprouting of the surviving Absensory fibers occurs to the extent that the de survived the neonatal capsaicin treatment or evolved at all a later stage. In the cornea, sprouting of the surviving A sensory fibers occurs to the extent that the density of herve fibers in the epithelium is considerably a later stage. In the cornea, sprouting of the survivial sensory fibers occurs to the extent that the density nerve fibers in the epithelium is considerably higher the control animals, although the overall innervation the sensory fibers occurs to the extent that the density of nerve fibers in the epithelium is considerably higher that in control animals, although the overall innervation of the cornea by trigeminal afferent fibers is greatly nerve fibers in the epithelium is considerably higher than
in control animals, although the overall innervation of
taithe cornea by trigeminal afferent fibers is greatly dimin-
ished (Ogilvy et al., 1991). Sprouting of cal in control animals, although the overall innervation of the cornea by trigeminal afferent fibers is greatly dimini-
ished (Ogilvy et al., 1991). Sprouting of calcitonin generaleted peptide-containing afferent neurons may the cornea by trigeminal afferent fibers is greatly diminished (Ogilvy et al., 1991). Sprouting of calcitonin generelated peptide-containing afferent neurons may also take place in the spinal cord of rats treated with caps

1989; McNeill et al., 1990). This may explain why cap-ER
1989; McNeill et al., 1990). This may explain why cap-
saicin is able to release some calcitonin gene-related
peptide and neurokinin A into the blood stream of adult ER
1989; McNeill et al., 1990). This may explain why capsaicin is able to release some calcitonin gene-related
peptide and neurokinin A into the blood stream of adult
rats treated with capsaicin as neonates (Diez Guerra et 1989; McNeill et al., 1990). This may explain why capsaicin is able to release some calcitonin gene-related peptide and neurokinin A into the blood stream of adult rats treated with capsaicin as neonates (Diez Guerra et al 1989; McN_i
saicin is al
peptide and
rats treated
al., 1988).
In the co icin is able to release some calcitonin gene-related
ptide and neurokinin A into the blood stream of adult
ts treated with capsaicin as neonates (Diez Guerra et
, 1988).
In the central nervous system, the organization of
n

peptide and neurokinin A into the blood stream of adult
rats treated with capsaicin as neonates (Diez Guerra et
al., 1988).
In the central nervous system, the organization of
sensory pathways in the spinal cord and nucleus rats treated with capsaicin as neonates (Diez Guerra et al., 1988).

In the central nervous system, the organization of sensory pathways in the spinal cord and nucleus gracilis

(Nagy and Hunt, 1983; Réthelyi et al., 1986; al., 1988).
In the central nervous system, the organization of
sensory pathways in the spinal cord and nucleus gracilis
(Nagy and Hunt, 1983; Réthelyi et al., 1986; Shortland
et al., 1990), of the spinothalamic tract (Sapo In the central nervous system, the organization of sensory pathways in the spinal cord and nucleus gracilis (Nagy and Hunt, 1983; Réthelyi et al., 1986; Shortland et al., 1990), of the spinothalamic tract (Saporta, 1986), (Nagy and Hunt, 1983; Réthelyi et al., 1986; Shortland
et al., 1990), of the spinothalamic tract (Saporta, 1986),
and of the somatotopic maps in the cerebral cortex (Wall
et al., 1982a) is profoundly altered by neonatal c et al., 1990), of the spinothalamic tract (Saporta, 1986), and of the somatotopic maps in the cerebral cortex (Wall et al., 1982a) is profoundly altered by neonatal capsaicin treatment. Reorganization of 5-hydroxytryptamin et al., 1990), of the spinothalamic tract (Saporta, 1986)
and of the somatotopic maps in the cerebral cortex (We
et al., 1982a) is profoundly altered by neonatal capsaic
treatment. Reorganization of 5-hydroxytryptamine-con and of the somatotopic maps in the cerebral cortex (Wall
et al., 1982a) is profoundly altered by neonatal capsaicin
treatment. Reorganization of 5-hydroxytryptamine-con-
taining nerve fibers also occurs in the spinal cord et al., 1982a) is profoundly altered by neonatal capsaicin
treatment. Reorganization of 5-hydroxytryptamine-con-
taining nerve fibers also occurs in the spinal cord (Mar-
lier et al., 1990). As a consequence, the processin treatment. Reorganization of 5-hydroxytryptamine-c
taining nerve fibers also occurs in the spinal cord (M
lier et al., 1990). As a consequence, the processing
sensory information in the spinal cord (Wall, 1982; W
et al., 1 taining nerve fibers also occurs in the spinal cord (Mar-
lier et al., 1990). As a consequence, the processing of
sensory information in the spinal cord (Wall, 1982; Wall
et al., 1982b; Cervero et al., 1984; Cervero and Pl lier et al., 1990). As a consequence, the processing of sensory information in the spinal cord (Wall, 1982; Wall et al., 1982b; Cervero et al., 1984; Cervero and Plenderleith, 1987) and brainstem (Salt et al., 1982) shows controls. al., 1982b; Cervero et al., 1984; Cervero and Plender-
th, 1987) and brainstem (Salt et al., 1982) shows
arked differences when compared with vehicle-treated
ntrols.
In the periphery, neonatal capsaicin treatment can
ad to

leith, 1987) and brainstem (Salt et al., 1982) shows
marked differences when compared with vehicle-treated
controls.
In the periphery, neonatal capsaicin treatment can
lead to permanent changes in the morphology of the
cor marked differences when compared with vehicle-treated
controls.
In the periphery, neonatal capsaicin treatment can
lead to permanent changes in the morphology of the
cornea (Shimizu et al., 1984; Ogilvy et al., 1991; but s controls.
In the periphery, neonatal capsaicin treatment can
lead to permanent changes in the morphology of the
cornea (Shimizu et al., 1984; Ogilvy et al., 1991; but see
also Knyazev et al., 1990) and lung (Ahlstedt et al In the periphery, neonatal capsaicin treatment can
lead to permanent changes in the morphology of the
cornea (Shimizu et al., 1984; Ogilvy et al., 1991; but see
also Knyazev et al., 1990) and lung (Ahlstedt et al., 1986)
a lead to permanent changes in the morphology of the
cornea (Shimizu et al., 1984; Ogilvy et al., 1991; but see
also Knyazev et al., 1990) and lung (Ahlstedt et al., 1986)
and to increased tissue concentrations of histamine cornea (Shimizu et al., 1984; Ogilvy et al., 1991; but see
also Knyazev et al., 1990) and lung (Ahlstedt et al., 1986)
and to increased tissue concentrations of histamine and
5-hydroxytryptamine in the skin and lung (Holze also Knyazev et al., 1990) and lung (Ahlstedt et al., 1986)
and to increased tissue concentrations of histamine and
5-hydroxytryptamine in the skin and lung (Holzer et al.,
1981). The responsiveness of blood vessels (Jancs and to increased tissue concentrations of histamine
5-hydroxytryptamine in the skin and lung (Holzer e
1981). The responsiveness of blood vessels (Jancsó e
1980a; Jancsó, 1984) and mast cells (Skofitsch e
1983) to substanc 5-hydroxytryptamine in the skin and lung (Holzer et al., 1981). The responsiveness of blood vessels (Jancsó et al., 1980a; Jancsó, 1984) and mast cells (Skofitsch et al., 1983) to substance P, bradykinin, 5-hydroxytryptami 1981). The responsiveness of blood vessels (Jancsó et al., 1980a; Jancsó, 1984) and mast cells (Skofitsch et al., 1983) to substance P, bradykinin, 5-hydroxytryptamine, and histamine may be altered permanently. A direct re 1980a; Jancsó, 1984) and mast cells (Skofitsch et al., 1983) to substance P, bradykinin, 5-hydroxytryptamine, and histamine may be altered permanently. A direct relationship of these changes to sensory neuron ablation is n 1983) to substance P, bradykinin, 5-hydroxytryptami
and histamine may be altered permanently. A dir
relationship of these changes to sensory neuron ablati
is not clear. This also holds true for the transformati
of fast mus and histamine may be altered permanently. A direct
relationship of these changes to sensory neuron ablation
is not clear. This also holds true for the transformation
of fast muscle fibers to slow muscle fibers in the stern relationship of these changes to sensory neuron ablations is not clear. This also holds true for the transformation fast muscle fibers to slow muscle fibers in the stern hyoid superior muscle of the rat (Müntener, 1985) an is not clear. This also holds true for the transformation
of fast muscle fibers to slow muscle fibers in the sterno-
hyoid superior muscle of the rat (Müntener, 1985) and
to some ultrastructural alterations in the gastroin of fast muscle fibers to slow muscle fibers in the sterno-
hyoid superior muscle of the rat (Müntener, 1985) and
to some ultrastructural alterations in the gastrointestinal
mucosa (Pfeiffer and Evangelista, 1991), although hyoid superior muscle of the rat (Müntener, 1985) and
to some ultrastructural alterations in the gastrointestinal
mucosa (Pfeiffer and Evangelista, 1991), although bio-
chemical indices of the intestinal endocrine mucosa a 1991). ucosa (Pfeiffer and Evangelista, 1991), although bio-
emical indices of the intestinal endocrine mucosa and
ush border remain unchanged (McGregor and Conlon,
91).
An intriguing observation is the existence of an ap-
rent r

chemical indices of the intestinal endocrine mucosa and
brush border remain unchanged (McGregor and Conlon,
1991).
An intriguing observation is the existence of an ap-
parent reciprocal relationship between the peripheral
 brush border remain unchanged (McGregor and Con
1991).
An intriguing observation is the existence of an
parent reciprocal relationship between the periph
endings of sympathetic and sensory neurons. Capsai
induced long-term 1991).

An intriguing observation is the existence of an apparent reciprocal relationship between the peripheral

endings of sympathetic and sensory neurons. Capsaicin-

induced long-term elimination of afferent neurons re An intriguing observation is the existence of an apparent reciprocal relationship between the peripheral endings of sympathetic and sensory neurons. Capsaicin-
induced long-term elimination of afferent neurons results in a parent reciprocal relationship between the peripheral endings of sympathetic and sensory neurons. Capsaicin-
induced long-term elimination of afferent neurons results in an increase in the transmitter content and in-
nerva endings of sympathetic and sensory neurons. Capsaicin-
induced long-term elimination of afferent neurons re-
sults in an increase in the transmitter content and in-
nervation density of sympathetic nerve endings, whereas
l induced long-term elimination of afferent neurons results in an increase in the transmitter content and in-
nervation density of sympathetic nerve endings, whereas
long-term ablation of sympathetic neurons is followed
by a sults in an increase in the transmitter content and in-
nervation density of sympathetic nerve endings, whereas
long-term ablation of sympathetic neurons is followed
by an increase in the sensory innervation (Terenghi et
a nervation density of sympathetic nerve endings, whereas
long-term ablation of sympathetic neurons is followed
by an increase in the sensory innervation (Terenghi et
al., 1986; Nielsch and Keen, 1987; Luthman et al., 1989;
 long-term ablation of sympathetic neurons is followed
by an increase in the sensory innervation (Terenghi et
al., 1986; Nielsch and Keen, 1987; Luthman et al., 1989;
Aberdeen et al., 1990). One group (Aberdeen et al., 1990 by an increase in the sensory innervation (Tereng
al., 1986; Nielsch and Keen, 1987; Luthman et al., 1
Aberdeen et al., 1990). One group (Aberdeen et al., 1
holds that following sympathectomy in the neonate
guanethidine on al., 1986; Nielsch and Keen, 1987; Luthman et al., 1989;
Aberdeen et al., 1990). One group (Aberdeen et al., 1990)
holds that following sympathectomy in the neonate with
guanethidine only calcitonin gene-related peptide-co Aberdeen et al., 1990). One group (Aberdeen et al., 1990)
holds that following sympathectomy in the neonate with
guanethidine only calcitonin gene-related peptide-con-
taining sensory neurons react with increased transmitt holds that following sympathectomy in the neonate with
guanethidine only calcitonin gene-related peptide-con-
taining sensory neurons react with increased transmitter
levels and innervation density, whereas no such changes guanethidine only calcitonin gene-related peptide-containing sensory neurons react with increased transmitt levels and innervation density, whereas no such chang are seen with sensory neurons containing substance P vasoact taining sensory neurons react with increased transmitter
levels and innervation density, whereas no such changes
are seen with sensory neurons containing substance P or
vasoactive intestinal polypeptide. Whether these reci levels and innervation density, whereas no such changes
are seen with sensory neurons containing substance P or
vasoactive intestinal polypeptide. Whether these recip-
rocal changes arise from a competition of sensory and

aspet

population (Terenghi et al., 1986; Nielsch and 1987; Luthman et al., 1989; Aberdeen et al., 1990)
need of experimental verification.
v. Selectivity of the action of capsaicin. Th
no doubt that the primary target of the neu 1987; Luthman et al., 1989; Aberdeen et al., 1990), is in
meed of experimental verification. for
w. Selectivity of the action of capsaicin. There is
mo doubt that the primary target of the neurodegenera-
tive action of cap need of experimental verification.

v. Selectivity of the action of capsaicin. There

no doubt that the primary target of the neurodegene

tive action of capsaicin in the newborn rat is a group

fine primary afferent neuro **v. Selectivity of the action of capsaicin.** There is no
no doubt that the primary target of the neurodegenera-
tive action of capsaicin in the newborn rat is a group of de
fine primary afferent neurons. This inference is mo doubt that the primary target of the neurodegenera-
tive action of capsaicin in the newborn rat is a group of
fine primary afferent neurons. This inference is corrob-
reporated by the findings that, with the exception tive action of capsaicin in the newborn rat is a group of define primary afferent neurons. This inference is corrob-
orated by the findings that, with the exception of some obmyelinated $A\delta$ -fibers, other primary afferen fine primary afferent neurons. This inference is corrob-

orated by the findings that, with the exception of some ob

myelinated A δ -fibers, other primary afferent as well as

the efferent motor and autonomic neurons ar myelinated $A\delta$ -fibers, other primary afferent as well as throw some doubt on the exclusive selectivity of capsaicin efferent motor and autonomic neurons are not affected for primary afferent neurons.
by capsaicin. Thus, myelinated A δ -fibers, other primary afferent as well as
efferent motor and autonomic neurons are not affected
by capsaicin. Thus, myelinated afferent neurons such as
muscle stretch receptors (Soukup and Jancsó, 1987) a efferent motor and autonomic neurons are not affected
by capsaicin. Thus, myelinated afferent neurons such a
muscle stretch receptors (Soukup and Jancsó, 1987) and
the unmyelinated efferent fibers of the sympathetic
(Jancs by capsaicin. Thus, myelinated afferent neurons such as muscle stretch receptors (Soukup and Jancsó, 1987) and the unmyelinated efferent fibers of the sympathetic (Jancsó et al., 1980a; Cervero and McRitchie, 1982; Takano muscle stretch receptors (Soukup and Jancsó, 1987) and
the unmyelinated efferent fibers of the sympathetic
(Jancsó et al., 1980a; Cervero and McRitchie, 1982; Tak-
ano et al., 1988) and parasympathetic (Sharkey et al.,
198 the unmyelinated efferent fibers of the sympathetic n (Jancsó et al., 1980a; Cervero and McRitchie, 1982; Tak-
ano et al., 1988) and parasympathetic (Sharkey et al., subseted all and the systems are not damaged by neonatal (Jancsó et al., 1980a; Cervero and McRitchie, 1982; Tano et al., 1988) and parasympathetic (Sharkey et al., 1983) nervous systems are not damaged by neona capsaicin treatment. Whether all capsaicin-induced terations of sen ano et al., 1988) and parasympathetic (Sharkey et al., sue 1983) nervous systems are not damaged by neonatal do capsaicin treatment. Whether all capsaicin-induced al-
capsaicin treatment. Whether all capsaicin-induced al-
 1983) nervous systems are not damaged by neonatal capsaicin treatment. Whether all capsaicin-induced alterations of sensory pathway-related systems are secondary to the degeneration of primary afferent neurons is not yet c capsaicin treatment. Whether all capsaicin-induced alexterations of sensory pathway-related systems are second-
nery to the degeneration of primary afferent neurons is ten
not yet clear. The possibility, therefore, remains terations of sensory pathway-related systems are secondary to the degeneration of primary afferent neurons is
not yet clear. The possibility, therefore, remains that
capsaicin also has some direct effects on neuronal and
n not yet clear. The possibility, therefore, remains that alcapsaicin also has some direct effects on neuronal and G
nonneuronal systems other than primary afferent neurons. However, most neurons of the central nervous negys capsaicin also has some direct effects on neuronal and
nonneuronal systems other than primary afferent neu-
rons. However, most neurons of the central nervous
system are not susceptible to the neurotoxic effect of
neonatal nonneuronal
rons. Howev
system are n
neonatal caps
tral neurons.
The capsaid ns. However, most neurons of the central nervous
stem are not susceptible to the neurotoxic effect of
onatal capsaicin, although this is not true for all cen-
al neurons.
The capsaicin-induced degeneration of axon terminal

neonatal capsaicin, although this is not true for all central neurons.

The capsaicin-induced degeneration of axon terminals

in the dorsal horn of the spinal cord and in the brain

bot

stem (Jancsó et al., 1977; Jancsó, real neurons.

The capsaicin-induced degeneration of axon terminals

in the dorsal horn of the spinal cord and in the brain

is tem (Jancsó et al., 1977; Jancsó, 1978; Jancsó and

Király, 1980, 1981; Dinh and Ritter, 1987) The capsaicin-induced degeneration of axon terminals histon in the dorsal horn of the spinal cord and in the brain between (Jancsó et al., 1977; Jancsó, 1978; Jancsó and film Király, 1980, 1981; Dinh and Ritter, 1987) is c in the dorsal horn of the spinal cord and in the brain
stem (Jancsó et al., 1977; Jancsó, 1978; Jancsó and
Király, 1980, 1981; Dinh and Ritter, 1987) is considered
to reflect degeneration of the central endings of primary
 stem (Jancsó et al., 1977; Jancsó, 1978; Jancsó and
Király, 1980, 1981; Dinh and Ritter, 1987) is considered
to reflect degeneration of the central endings of primary
afferent neurons only, because markers of thick afferen Király, 1980, 1981; Dinh and Ritter, 1987) is considered to reflect degeneration of the central endings of primary pafferent neurons only, because markers of thick afferent as well as of spinal and brainstem neurons are n to reflect degeneration of the central endings of primary
afferent neurons only, because markers of thick afferent
as well as of spinal and brainstem neurons are not
depleted by capsaicin. Thus, the tissue levels of gluta afferent neurons only, because markers of thick afferent
as well as of spinal and brainstem neurons are not for
depleted by capsaicin. Thus, the tissue levels of glutamic n
acid, glutamic acid decarboxylase, γ -aminobut as well as of spinal and brainstem neurons are
depleted by capsaicin. Thus, the tissue levels of glut
acid, glutamic acid decarboxylase, γ -aminobutyric
glycine, glycine receptors, aspartic acid, taurine, ch
acetyltrans depleted by capsaicin. Thus, the tissue levels of glutamic macid, glutamic acid decarboxylase, γ -aminobutyric acid, the glycine, glycine receptors, aspartic acid, taurine, choline etacetyltransferase, noradrenaline, 5acid, glutamic acid decarboxylase, γ -aminobutyric acid, the glycine, glycine receptors, aspartic acid, taurine, choline et acetyltransferase, noradrenaline, 5-hydroxytryptamine, Island histamine are not decreased in th glycine, glycine receptors, aspartic acid, taurine, choline
acetyltransferase, noradrenaline, 5-hydroxytryptamine,
and histamine are not decreased in the dorsal horn of
the spinal cord of adult rats treated with capsaicin acetyltransferase, noradrenaline, 5-hydroxytryptamine,
and histamine are not decreased in the dorsal horn of
the spinal cord of adult rats treated with capsaicin as
neonates (Nagy et al., 1980; Singer and Placheta, 1980;
H and histamine are not decreased in the dorsal horn of al.
the spinal cord of adult rats treated with capsaicin as size
neonates (Nagy et al., 1980; Singer and Placheta, 1980;
Holzer et al., 1981; Jancsó et al., 1981; Singe the spinal cord of adult rats treated with capsaicin as size
neonates (Nagy et al., 1980; Singer and Placheta, 1980; I
Holzer et al., 1981; Jancsó et al., 1981; Singer et al., 1982; mo
Hajós et al., 1986b; Holzer-Petsche e neonates (Nagy et al., 1980; Singer and Placheta, 1980; 1981; Holzer et al., 1981; Jancsó et al., 1981; Singer et al., 1982; more laised was found was found was found was found (Holzer et al., 1981), whereas these changes Holzer et al., 1981; Jancsó et al., 1981; Singer et al., 1982; mouse, 50 mg/kg capsaicin leads to rapid degeneration Hajós et al., 1986b; Holzer-Petsche et al., 1986). In one of a proportion of B-type somata sending unmyel study even an increase in the 5-hydroxytryptamine and the levels of substance P, somatostatin, and other neuhistamine content of the dorsal spinal cord was found
(Holzer et al., 1981), whereas these changes were not
seen in another study (Hajós et al., 1986b). Furthermore,
the levels of substance P, somatostatin, and other neu-
 (Holzer et al., 1981), whereas these changes were not place-
seen in another study (Hajós et al., 1986b). Furthermore, sequelie levels of substance P, somatostatin, and other neu-
repeptides found both in primary afferent seen in another study (Hajós et al., 1986b). Furthermore,
the levels of substance P, somatostatin, and other neu-
ropeptides found both in primary afferent and central
neurons are not altered in the ventral spinal cord and the levels of substance P, somatostatin, and other neu-

ropeptides found both in primary afferent and central

neurons are not altered in the ventral spinal cord and in

reeds

regions of the brain above the brainstem (Ga ropeptides found both in primary afferent and central
neurons are not altered in the ventral spinal cord and in
regions of the brain above the brainstem (Gamse et al.,
1980, 1981b; Nagy et al., 1980; Helke et al., 1981a; J neurons are not altered in the ventral spinal cord and in
regions of the brain above the brainstem (Gamse et al.,
1980, 1981b; Nagy et al., 1980; Helke et al., 1981a; Jancsó
et al., 1981; Priestley et al., 1982; Panerai et regions of the brain above the brainstem (Gamse et a
1980, 1981b; Nagy et al., 1980; Helke et al., 1981a; Jance
et al., 1981; Priestley et al., 1982; Panerai et al., 1983
Likewise, neuropeptides not associated with sensory

case elimination of one nerve population might increase remain unaffected throughout the central nervous sys-
the availability of nerve growth factor for the other nerve tem (Gamse et al., 1981b; Jancsó et al., 1981; Pries CIN
remain unaffected throughout the central nervous sys-
tem (Gamse et al., 1981b; Jancsó et al., 1981; Priestley tem in unaffected throughout the central nervous sys-
tem (Gamse et al., 1981b; Jancsó et al., 1981; Priestley
et al., 1982; Singer et al., 1982; Panerai et al., 1983). 155
remain unaffected throughout the central nervous sys-
tem (Gamse et al., 1981b; Jancsó et al., 1981; Priestley
et al., 1982; Singer et al., 1982; Panerai et al., 1983).
There is, however, evidence that some neurons in remain unaffected throughout the central nervous sys-
tem (Gamse et al., 1981b; Jancsó et al., 1981; Priestley
et al., 1982; Singer et al., 1982; Panerai et al., 1983).
There is, however, evidence that some neurons in the
 remain unaffected throughout the central nervous system (Gamse et al., 1981b; Jancsó et al., 1981; Priestley
et al., 1982; Singer et al., 1982; Panerai et al., 1983).
There is, however, evidence that some neurons in the
fo et al., 1982; Singer et al., 1982; Panerai et al., 1983).
There is, however, evidence that some neurons in the forebrain and retina degenerate following pre- or neonatal capsaicin treatment (Dinh and Ritter, 1987; Ritter et al., 1982; Singer et al., 1982; Panerai et al., 1983).
There is, however, evidence that some neurons in the
forebrain and retina degenerate following pre- or neo-
natal capsaicin treatment (Dinh and Ritter, 1987; Ritte There is, however, evidence that some neurons in the forebrain and retina degenerate following pre- or neonatal capsaicin treatment (Dinh and Ritter, 1987; Ritter and Dinh, 1990) and that β -endorphin is permanently dep forebrain and retina degenerate following pre- or neo-
natal capsaicin treatment (Dinh and Ritter, 1987; Ritter
and Dinh, 1990) and that β -endorphin is permanently
depleted from the hypothalamus but not from other
regi natal capsaicin treatment (Dinh and Ritter, 1987; Ritter
and Dinh, 1990) and that β -endorphin is permanently
depleted from the hypothalamus but not from other
regions of the brain (Panerai et al., 1983). Although these and Dinh, 1990) and that β -endorphin is permanently depleted from the hypothalamus but not from other regions of the brain (Panerai et al., 1983). Although these observations are in need of further confirmation, they d depleted from the hypothals
regions of the brain (Panerai e
observations are in need of fun
throw some doubt on the exclu
for primary afferent neurons.
The unmyelinated neurons gions of the brain (Panerai et al., 1983). Although these
servations are in need of further confirmation, they do
row some doubt on the exclusive selectivity of capsaicin
r primary afferent neurons.
The unmyelinated neuron

not yet clear. The possibility, therefore, remains that al., 1987; Su et al., 1987; Green and Dockray, 1988; capsaicin also has some direct effects on neuronal and Geppetti et al., 1988a). The tissue levels of vasoactive n in the dorsal neurons.
In the capsaicin-induced degeneration of axon terminals hydrate antigen colocalized with the peptide is lost from
in the dorsal horn of the spinal cord and in the brain both fibers and somata (Kirchg The unmyelinated neurons of the enteric nervous systhrow some doubt on the exclusive selectivity of capsaicin
for primary afferent neurons.
The unmyelinated neurons of the enteric nervous sys-
tem seem to be insensitive to the neurotoxic effect of
neonatal capsaicin insofa for primary afferent neurons.

The unmyelinated neurons of the enteric nervous sys-

tem seem to be insensitive to the neurotoxic effect of

neonatal capsaicin insofar as gastrointestinal tissue lev-

els of peptides asso The unmyelinated neurons of the enteric nervous sys-
tem seem to be insensitive to the neurotoxic effect of
neonatal capsaicin insofar as gastrointestinal tissue lev-
els of peptides associated with the enteric nervous sys tem seem to be insensitive to the neurotoxic effect of neonatal capsaicin insofar as gastrointestinal tissue levels of peptides associated with the enteric nervous system such as substance P and calcitonin gene-related pep neonatal capsaicin insofar as gastrointestinal tissue lev-
els of peptides associated with the enteric nervous system
such as substance P and calcitonin gene-related peptide
do not change (Holzer et al., 1980; Geppetti et els of peptides associated with the enteric nervous system
such as substance P and calcitonin gene-related peptide
do not change (Holzer et al., 1980; Geppetti et al., 1988a),
except in the upper gastrointestinal tract whe such as substance P and calcitonin gene-related peptide
do not change (Holzer et al., 1980; Geppetti et al., 1988a),
except in the upper gastrointestinal tract where sensory
nerve endings contribute significantly to the ti do not change (Holzer et al., 1980; Geppetti et al., 1988a),
except in the upper gastrointestinal tract where sensory
nerve endings contribute significantly to the tissue con-
tent of these peptides (Sharkey et al., 1984; except in the upper gastrointestinal tract where sensory
nerve endings contribute significantly to the tissue con-
tent of these peptides (Sharkey et al., 1984; Sternini et
al., 1987; Su et al., 1987; Green and Dockray, 19 nerve endings contribute significantly to the tissue content of these peptides (Sharkey et al., 1984; Sternini et al., 1987; Green and Dockray, 1988; Geppetti et al., 1988a). The tissue levels of vasoactive intestinal poly tent of these peptides (Sharkey et al., 1984; Sternini et al., 1987; Su et al., 1987; Green and Dockray, 1988; Geppetti et al., 1988a). The tissue levels of vasoactive intestinal polypeptide in the gut remain unchanged aft al., 1987; Su et al., 1987; Green and Dockray, 1988;
Geppetti et al., 1988a). The tissue levels of vasoactive
intestinal polypeptide in the gut remain unchanged after
neonatal capsaicin treatment (McGregor and Conlon,
1991 Geppetti et al., 1988a). The tissue levels of vasoactive
intestinal polypeptide in the gut remain unchanged after
neonatal capsaicin treatment (McGregor and Conlon,
1991), but an immunohistochemical study has shown
that, a intestinal polypeptide in the gut remain unchanged aft
neonatal capsaicin treatment (McGregor and Conlc
1991), but an immunohistochemical study has show
that, although this peptide is depleted from fibers, b
not somata, of meonatal capsaicin treatment (McGregor and Conlon,
1991), but an immunohistochemical study has shown
that, although this peptide is depleted from fibers, but
not somata, of submucosal neurons, a lactoseries carbo-
hydrate 1991), but an immunohistochemical study has shown
that, although this peptide is depleted from fibers, but
not somata, of submucosal neurons, a lactoseries carbo-
hydrate antigen colocalized with the peptide is lost from
b that, although this peptide is depleted from fibers, heat consta, of submucosal neurons, a lactoseries cark
hydrate antigen colocalized with the peptide is lost fro
both fibers and somata (Kirchgessner et al., 1988). Th
fi not somata, of submucosal neurons, a lactoseries carbo-
hydrate antigen colocalized with the peptide is lost from
both fibers and somata (Kirchgessner et al., 1988). This
finding suggests that capsaicin might have some neu hydrate antigen colocalized with the peptide
both fibers and somata (Kirchgessner et al.,
finding suggests that capsaicin might have s
toxic effect on certain enteric nerve fibers,
proof of such a target of the drug is nee th fibers and somata (Kirchgessner et al., 1988). Thi
Inding suggests that capsaicin might have some neuro
xic effect on certain enteric nerve fibers, but furthe
cof of such a target of the drug is needed.
b. OTHER MAMMALS

finding suggests that capsaicin might have some neurotoxic effect on certain enteric nerve fibers, but further proof of such a target of the drug is needed.
b. OTHER MAMMALS. The neuropharmacological effects of neonatal ca toxic effect on certain enteric nerve fibers, but further
proof of such a target of the drug is needed.
b. OTHER MAMMALS. The neuropharmacological ef-
fects of neonatal capsaicin treatment have been studied
most extensivel proof of such a target of the drug is needed.

b. OTHER MAMMALS. The neuropharmacological effects of neonatal capsaicin treatment have been studied

most extensively in the rat, but there is some information

that treatme b. OTHER MAMMALS. The neuropharmacological effects of neonatal capsaicin treatment have been studied
most extensively in the rat, but there is some information
that treatment of newborn mice (Scadding, 1980; Jancsó
et al., fects of neonatal capsaicin treatment have been studied
most extensively in the rat, but there is some information
that treatment of newborn mice (Scadding, 1980; Jancsó
et al., 1985a; Hiura and Sakamoto, 1987b; Hiura and
 most extensively in the rat, but there is some informat
that treatment of newborn mice (Scadding, 1980; Jan
et al., 1985a; Hiura and Sakamoto, 1987b; Hiura a
Ishizuka, 1989; Hiura et al., 1990b) and dogs (Jancsé
al., 1985a that treatment of newb
et al., 1985a; Hiura an
Ishizuka, 1989; Hiura e
al., 1985a) also causes d
sized afferent neurons.
In the lumbar dors al., 1985a; Hiura and Sakamoto, 1987b; Hiura and
nizuka, 1989; Hiura et al., 1990b) and dogs (Jancsó et
, 1985a) also causes degeneration of small- to medium-
ed afferent neurons.
In the lumbar dorsal root ganglia of the n al., 1985a) also causes degeneration of small- to medium-
sized afferent neurons.
In the lumbar dorsal root ganglia of the newborn

al., 1985a) also causes degeneration of small- to medium-
sized afferent neurons.
In the lumbar dorsal root ganglia of the newborn
mouse, 50 mg/kg capsaicin leads to rapid degeneration
of a proportion of B-type somata send sized afferent neurons.
In the lumbar dorsal root ganglia of the newborn
mouse, 50 mg/kg capsaicin leads to rapid degeneration
of a proportion of B-type somata sending unmyelinated
fibers into the dorsal roots (Hiura and I In the lumbar dorsal root ganglia of the newborn
mouse, 50 mg/kg capsaicin leads to rapid degeneration
of a proportion of B-type somata sending unmyelinated
fibers into the dorsal roots (Hiura and Ishizuka, 1989).
Later, u mouse, 50 mg/kg capsaicin leads to rapid degeneration
of a proportion of B-type somata sending unmyelinated
fibers into the dorsal roots (Hiura and Ishizuka, 1989).
Later, ultrastructural and degenerative changes also take fibers into the dorsal roots (Hiura and Ishizuka, 1989). fibers into the dorsal roots (Hiura and Ishizuka, 1989).
Later, ultrastructural and degenerative changes also take
place in A-type somata with myelinated fibers. This
sequence of events is interpreted to indicate that dege Later, ultrastructural and degenerative changes also take
place in A-type somata with myelinated fibers. This
sequence of events is interpreted to indicate that degen-
eration of A-type somata is not due to a direct actio place in A-type somata with myelinated fibers. This
sequence of events is interpreted to indicate that degen-
eration of A-type somata is not due to a direct action of
capsaicin on these neurons, however this contention
ne sequence of events is interpreted to indicate that degeneration of A-type somata is not due to a direct action of capsaicin on these neurons, however this contention needs to be proven. Doses of 50 to 150 mg/kg capsaicin eration of A-type somata is not due to a direct action of capsaicin on these neurons, however this contention needs to be proven. Doses of 50 to 150 mg/kg capsaicin cause a 41 to 75% reduction of unmyelinated fibers and a capsaicin on these neurons, however this contention
needs to be proven. Doses of 50 to 150 mg/kg capsaicin
cause a 41 to 75% reduction of unmyelinated fibers and
a 6 to 12% loss of myelinated fibers in the dorsal roots;
t needs to be proven. Doses of 50 to 150 mg/kg capsaicin
cause a 41 to 75% reduction of unmyelinated fibers and
a 6 to 12% loss of myelinated fibers in the dorsal roots;
the number of small dorsal root ganglion cell bodies
 cause a 41 to 75% reduction of unmyelinated fibers and
a 6 to 12% loss of myelinated fibers in the dorsal roots;
the number of small dorsal root ganglion cell bodies
decreases by 51 to 77% and that of large somata by 14
t

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

aspet

156
tive changes are accompanied by a 50% loss of unmy
nated fibers from the sural nerve, whereas the num HOL:
tive changes are accompanied by a 50% loss of unmyeli-
nated fibers from the sural nerve, whereas the number
of myelinated fibers stays the same in response to 50 HOLZER
tive changes are accompanied by a 50% loss of unmyeli-
nated fibers from the sural nerve, whereas the number
of myelinated fibers stays the same in response to 50 caps
mg/kg capsaicin given to newborn mice (Scadding tive changes are accompanied by a 50% loss of unmyeli-
nated fibers from the sural nerve, whereas the number
of myelinated fibers stays the same in response to 50
mg/kg capsaicin given to newborn mice (Scadding, 1980).
A l tive changes are accompanied by a 50% loss of unmyeli-
nated fibers from the sural nerve, whereas the number
of myelinated fibers stays the same in response to 50 c
mg/kg capsaicin given to newborn mice (Scadding, 1980).
A nated fibers from the sural nerve, whereas the number
of myelinated fibers stays the same in response to 50
mg/kg capsaicin given to newborn mice (Scadding, 1980).
A loss of nerve axons also is seen in the cornea (Fujita
 of myelinated fibers stays the same in response to 50 mg/kg capsaicin given to newborn mice (Scadding, 1980).
A loss of nerve axons also is seen in the cornea (Fujita et al., 1984) and in the superficial dorsal horn (Hiura mg/kg capsaicin given to newborn mice (Scadding, 1980).
A loss of nerve axons also is seen in the cornea (Fujita a
et al., 1984) and in the superficial dorsal horn (Hiura et d
al., 1990b) of the mouse. The neurotoxic acti A loss of nerve axons also is seen in the cornea (Fujita a
et al., 1984) and in the superficial dorsal horn (Hiura et d
al., 1990b) of the mouse. The neurotoxic action of cap-
saicin in the newborn mouse is associated with et al., 1984) and in the superficial dorsal horn (Hiura et al., 1990b) of the mouse. The neurotoxic action of capsaicin in the newborn mouse is associated with depletion of substance P from the dorsal spinal cord and corne al., 1990b) of the mouse. The neurotoxic action of capsaicin in the newborn mouse is associated with depletion of substance P from the dorsal spinal cord and cornea and with deficits in chemo- but not thermonociception (Ha saicin in the newborn mouse is associated with depletion
of substance P from the dorsal spinal cord and cornea
and with deficits in chemo- but not thermonociception
(Hayes et al., 1981a; Gamse, 1982; Keen et al., 1982).
Va of substance P from the dorsal spinal cord and cornea
and with deficits in chemo- but not thermonociception
(Hayes et al., 1981a; Gamse, 1982; Keen et al., 1982).
Vascularization of, and lesions in, the cornea (Keen et lal and with deficits in chemo- but not thermonociception (Hayes et al., 1981a; Gamse, 1982; Keen et al., 1982). Vascularization of, and lesions in, the cornea (Keen et al., 1982; Shimizu et al., 1984, 1987; Fujita et al., 198 (Hayes et al., 1981a; Gamse, 1982; Keen et al., 1982).
Vascularization of, and lesions in, the cornea (Keen et al., 1982; Shimizu et al., 1984, 1987; Fujita et al., 1984)
and changes of the somatotopic maps in the cerebral Vascularization of, and lesions in, the cornea (Keen et al., 1982; Shimizu et al., 1984, 1987; Fujita et al., 1984) and changes of the somatotopic maps in the cerebral cortex (Wall et al., 1982a) are considered to represen al., 1982; Shimizu et al., 1984, 1987; Fujita et al., 1984)
and changes of the somatotopic maps in the cerebral
cortex (Wall et al., 1982a) are considered to represent
changes secondary to the removal of sensory neurons.
T and changes of the somatotopic maps in the cerebral Unit correct (Wall et al., 1982a) are considered to represent to 3 changes secondary to the removal of sensory neurons. mit The gustatory afferent and parasympathetic eff cortex (Wall et al., 1982a) are considered to represent changes secondary to the removal of sensory neurons.
The gustatory afferent and parasympathetic efferent nerve fibers in the chorda tympani are not affected by 50 mg/ 1990a). he gustatory afferent and parasympathetic efferent
rve fibers in the chorda tympani are not affected by
mg/kg capsaicin given to newborn mice (Hiura et al.,
90a).
Administration of 70 mg/kg capsaicin to newborn rab-
ts fai

nerve fibers in the chorda tympani are not affected by 50 mg/kg capsaicin given to newborn mice (Hiura et al., 1990a).
Administration of 70 mg/kg capsaicin to newborn rabbits fails to cause any long-term depletion of subst 50 mg/kg capsaicin given to newborn mice (Hiura et al., Szc.
1990a).
Administration of 70 mg/kg capsaicin to newborn rabutions fails to cause any long-term depletion of substance a f
P from the spinal cord and eye, althou deministration of 70 mg/kg capsaicin to newborn rab-
bits fails to cause any long-term depletion of substance
at the spinal cord and eye, although the miotic and
hyperaemic effects of acute intracameral injection of secaps Administration of 70 mg/kg capsaicin to newborn rab
bits fails to cause any long-term depletion of substanc
P from the spinal cord and eye, although the miotic an
hyperaemic effects of acute intracameral injection c
capsai bits fails to cause any long-term depletion of substance a
P from the spinal cord and eye, although the miotic and capperaemic effects of acute intracameral injection of sequestion are inhibited (Tervo, 1981). No morpholog P from the spinal cord and eye, although the miotic
hyperaemic effects of acute intracameral injectio
capsaicin are inhibited (Tervo, 1981). No morpholo
study of the neurotoxic effect of capsaicin in the new
rabbit has yet hyperaemic effects of acute intracameral injection of several capsaicin are inhibited (Tervo, 1981). No morphological eractively of the neurotoxic effect of capsaicin in the newborn do rabbit has yet been carried out. In c capsaicin are inhibited (Tervo, 1981). No morphological
study of the neurotoxic effect of capsaicin in the newborn
rabbit has yet been carried out. In contrast, administra-
tion of 200 mg/kg capsaicin to newborn cats has b study of the neurotoxic effect of capsaicin in the newborn
rabbit has yet been carried out. In contrast, administra-
tion of 200 mg/kg capsaicin to newborn cats has been
found to induce neuronal degeneration in the small i rabbit has yet been carried out. In contrast, administration of 200 mg/kg capsaicin to newborn cats has been found to induce neuronal degeneration in the small intestine when examined 24 to 72 h later (Fehér and Vajda, 198 tion of 200 mg/kg capsaicin to newborn cats has been bofound to induce neuronal degeneration in the small intestine when examined 24 to 72 h later (Fehér and Vajda, co 1982). Degenerating axons were seen in the myenteric p found to induce neuronal degeneration in the small in-
testine when examined 24 to 72 h later (Fehér and Vajda, co
1982). Degenerating axons were seen in the myenteric p
and submucosal plexuses, and a few cell bodies in th testine when examined 24 to 72 h later (Fehér and Vajda, 1982). Degenerating axons were seen in the myenteric and submucosal plexuses, and a few cell bodies in the two plexuses also were severely damaged. Whether this obse and submucosal plexuses, and a few cell bodies in the two plexuses also were severely damaged. Whether this observation points to degeneration of enteric neurons awaits further verification, particularly because no fur-
th ther analysis of the effect of capsaicin on primary affertwo plexuses also were severely damaged. Whetl
observation points to degeneration of enteric in
awaits further verification, particularly because
ther analysis of the effect of capsaicin on primar
ent neurons of the newbor **2.** Effects of systemic capsaicin of enteric neurons in a waits further verification, particularly because no further analysis of the effect of capsaicin on primary afferent neurons of the newborn cat has been made.
2. Ef

ther analysis of the effect of capsaicin on primary affect neurons of the newborn cat has been made.

2. Effects of systemic capsaicin in adult mammals.
 RAT. i. Morphological changes compared with the
 produced by neon ent neurons of the newborn cat has been made.

2. Effects of systemic capsaicin in adult mammals.

RAT. **i. Morphological changes compared with those**
 produced by neonatal capsaicin. In the rat, unmy

linated primary af 2. Effects of systemic capsaicin in adult mammals. a. is all RAT. **i. Morphological changes compared with those** Bark produced by neonatal capsaicin. In the rat, unmye-subclinated primary afferent neurons are particularly RAT. **i. Morphological changes compared with those** B
produced by neonatal capsaicin. In the rat, unmye-
slinated primary afferent neurons are particularly sensi-
tive to the neurotoxic action of capsaicin at the age of 1
 produced by neonatal capsaicin. In the rat, unmyesulinated primary afferent neurons are particularly sensitive to the neurotoxic action of capsaicin at the age of 1 compute 12 days, whereas when capsaicin is given at the a linated primary afferent neurons are particularly sensitive to the neurotoxic action of capsaicin at the age of 1
to 12 days, whereas when capsaicin is given at the age of
14 days or more no major degeneration of nerve fib tive to the neurotoxic action of capsaicin at the age of 1 control to 12 days, whereas when capsaicin is given at the age of ter 14 days or more no major degeneration of nerve fibers is approticeable (Jancsó and Király, 19 to 12 days, whereas when capsaicin is given at the age of 14 days or more no major degeneration of nerve fibers noticeable (Jancsó and Király, 1981). Accordingly, capsaicin treatment of 2- to 10-day-old rats leads to perma 14 days or more no major degeneration of nerve fiber noticeable (Jancsó and Király, 1981). Accordingly, cosaicin treatment of 2- to 10-day-old rats leads to permanent depletion of substance P from primary aftent pathways, noticeable (Jancsó and Király, 1981). Accordingly, capsaicin treatment of 2- to 10-day-old rats leads to a permanent depletion of substance P from primary afferent pathways, a permanent deficit in chemonociception, and a p saicin treatment of 2- to 10-day-old rats leads to a
permanent depletion of substance P from primary affer-
ent pathways, a permanent deficit in chemonociception,
and a permanent absence of sensory nerve-mediated
increases permanent depletion of substance P from primary afferent pathways, a permanent deficit in chemonociception, and a permanent absence of sensory nerve-mediated increases in vascular permeability (Jancsó et al., 1977, 1980a; ent pathways, a permanent deficit in chemonociception,
and a permanent absence of sensory nerve-mediated
increases in vascular permeability (Jancsó et al., 1977,
1980a; Gamse et al., 1980; Nagy et al., 1980). In contrast,
 and a permanent absence of sensory nerve-media
increases in vascular permeability (Jancsó et al., 19
1980a; Gamse et al., 1980; Nagy et al., 1980). In contr
treatment of 20-day-old or adult rats reversibly reduction
chemon increases in vascular permeability (Jancsó et al., 1977, 1980a; Gamse et al., 1980; Nagy et al., 1980). In contrast, treatment of 20-day-old or adult rats reversibly reduces chemonociception (Jancsó, 1960), sensory nerve-m 1980a; Gamse et al., 1980; Nagy et al., 1980). In contrast, treatment of 20-day-old or adult rats reversibly reduces chemonociception (Jancsó, 1960), sensory nerve-mediated increases in vascular permeability (Jancsó et al.

during the ontogeny of unmyelinated primary afferent
neurons during which they are especially vulnerable to ER
during the ontogeny of unmyelinated primary afferent
neurons during which they are especially vulnerable to
capsaicin. However, capsaicin can have a long-lasting ER
during the ontogeny of unmyelinated primary afferent
neurons during which they are especially vulnerable to
capsaicin. However, capsaicin can have a long-lasting
sensory neuron-blocking effect also when it is given to during the ontogeny of unmyelinated primary afferent
neurons during which they are especially vulnerable to
capsaicin. However, capsaicin can have a long-lasting
sensory neuron-blocking effect also when it is given to
adul during the ontogeny of unmyelinated primary afferent
neurons during which they are especially vulnerable to
capsaicin. However, capsaicin can have a long-lasting
sensory neuron-blocking effect also when it is given to
adul neurons during which they are especially vulnerable to capsaicin. However, capsaicin can have a long-lasting sensory neuron-blocking effect also when it is given to adult rats (Jancsó et al., 1967), and some functional def capsaicin. However, capsaicin can have a long-lasting sensory neuron-blocking effect also when it is given to adult rats (Jancsó et al., 1967), and some functional deficits produced by capsaicin in the adult rat are virtua sensory neuron-blocking effect also when it is given to adult rats (Jancsó et al., 1967), and some functional deficits produced by capsaicin in the adult rat are virtually irreversible (Jancsó-Gábor et al., 1970; Szolcsány adult rats (Jancsó et al., 1967), and some functional
deficits produced by capsaicin in the adult rat are vir-
tually irreversible (Jancsó-Gábor et al., 1970; Szolcsányi
et al., 1975). Adult rats given capsaicin show recov deficits produced by capsaicin in the adult rat are virtually irreversible (Jancsó-Gábor et al., 1970; Szolcsányi et al., 1975). Adult rats given capsaicin show recovery which may take several weeks to several months (Szol tually irreversible (Jancsó-Gábor et al., 1970; Szolcsányi
et al., 1975). Adult rats given capsaicin show recovery
which may take several weeks to several months
(Szolcsányi and Jancsó-Gábor, 1976; Jancsó et al., 1977;
Gam et al., 1975). Adult rats given capsaicin show recovery
which may take several weeks to several months
(Szolcsányi and Jancsó-Gábor, 1976; Jancsó et al., 1977;
Gamse et al., 1980, 1981b; Gamse, 1982; Bittner and
LaHann, 19 which may take several weeks to several n
(Szolcsányi and Jancsó-Gábor, 1976; Jancsó et al.,
Gamse et al., 1980, 1981b; Gamse, 1982; Bittne
LaHann, 1985; Maggi et al., 1987d; South and 1
1988; Gardiner et al., 1989; Szalla zolcsányi and Jancsó-Gábor, 1976; Jancsó et al., 1977;
amse et al., 1980, 1981b; Gamse, 1982; Bittner and
aHann, 1985; Maggi et al., 1987d; South and Ritter,
88; Gardiner et al., 1989; Szallasi et al., 1989).
Ultrastructur

Gamse et al., 1980, 1981b; Gamse, 1982; Bittner and
LaHann, 1985; Maggi et al., 1987d; South and Ritter,
1988; Gardiner et al., 1989; Szallasi et al., 1989).
Ultrastructurally, subcutaneous administration of 35
to 300 mg/k LaHann, 1985; Maggi et al., 1987d; South and Ritter, 1988; Gardiner et al., 1989; Szallasi et al., 1989).
Ultrastructurally, subcutaneous administration of 35
to 300 mg/kg capsaicin to adult rats causes swelling of
mitocho 1988; Gardiner et al., 1989; Szallasi et al., 1989).
Ultrastructurally, subcutaneous administration of 35
to 300 mg/kg capsaicin to adult rats causes swelling of
mitochondria in B-type sensory neurons, but not in A-
type a Ultrastructurally, subcutaneous administration of 35
to 300 mg/kg capsaicin to adult rats causes swelling of
mitochondria in B-type sensory neurons, but not in A-
type afferent or sympathetic efferent neurons, when ex-
ami to 300 mg/kg capsaicin to adult rats causes swelling of mitochondria in B-type sensory neurons, but not in A-type afferent or sympathetic efferent neurons, when examined 1 to 60 days posttreatment (Joó et al., 1969; Szolcs mitochondria in B-type sensory neurons, but not in A-type afferent or sympathetic efferent neurons, when examined 1 to 60 days posttreatment (Joó et al., 1969; Szolcsányi et al., 1975; Chiba et al., 1986). Although destruc type afferent or sympathetic efferent neurons, when ex-
amined 1 to 60 days posttreatment (Joó et al., 1969;
Szolcsányi et al., 1975; Chiba et al., 1986). Although
destruction of cell bodies was not identified in these
stu amined 1 to 60 days posttreatment (Joó et al., 1969;
Szolcsányi et al., 1975; Chiba et al., 1986). Although
destruction of cell bodies was not identified in these
studies, G. Jancsó and his associates found that within
a f Szolcsányi et al., 1975; Chiba et al., 1986). Although destruction of cell bodies was not identified in these studies, G. Jancsó and his associates found that within a few hours after systemic administration of similar cap destruction of cell bodies was not identified in the
studies, G. Jancsó and his associates found that with
a few hours after systemic administration of simil
capsaicin doses a proportion of the B-type somata exhil
severe u studies, G. Jancsó and his associates found that within
a few hours after systemic administration of similar
capsaicin doses a proportion of the B-type somata exhibit
severe ultrastructural changes thought to reflect degen a few hours after systemic administration of similar
capsaicin doses a proportion of the B-type somata exhibit
severe ultrastructural changes thought to reflect degen-
eration (Jancsó et al., 1985b). The effect of capsaici capsaicin doses a proportion of the B-type somata exhibit
severe ultrastructural changes thought to reflect degen-
eration (Jancsó et al., 1985b). The effect of capsaicin is
dose dependent; the dose of 100 mg/kg capsaicin severe ultrastructural changes thought to reflect degeration (Jancsó et al., 1985b). The effect of capsaicin
dose dependent; the dose of 100 mg/kg capsaicin
maximally effective and damages 17% of the B-type bodies in the d eration (Jancsó et al., 1985b). The effect of capsaicin is dose dependent; the dose of 100 mg/kg capsaicin is maximally effective and damages 17% of the B-type cell bodies in the dorsal root ganglia. In addition, degenerat dose dependent; the dose of 100 mg/kg capsaicin is
maximally effective and damages 17% of the B-type cell
bodies in the dorsal root ganglia. In addition, degener-
ating axon terminals are seen in those areas of the spinal
 maximally effective and damages 17% of the B-type cell
bodies in the dorsal root ganglia. In addition, degener-
ating axon terminals are seen in those areas of the spinal
cord and brainstem that are known to be the centra bodies in the dorsal root ganglia. In addition, degenerating axon terminals are seen in those areas of the spinal cord and brainstem that are known to be the central projection areas of thin primary afferent neurons (Jancs ating axon terminals are seen in those areas of the spinal
cord and brainstem that are known to be the central
projection areas of thin primary afferent neurons (Jancsó
et al., 1985b; Jancsó and Maggi, 1987; Ritter and Din cord and brainstem that are known to be the cent
projection areas of thin primary afferent neurons (Janc
et al., 1985b; Jancsó and Maggi, 1987; Ritter and Dir
1988). Six days after capsaicin treatment, the number
unmyelina et al., 1985b; Jancsó and Maggi, 1987; Ritter and Dinh, 1988). Six days after capsaicin treatment, the number of unmyelinated fibers in the rat saphenous nerve is diminished by 45%, whereas the number of myelinated fibers is reduced by only 16% (Jancsó et al., 1985b). 88). Six days after capsaicin treatment, the number of myelinated fibers in the rat saphenous nerve is dimin-
ned by 45% , whereas the number of myelinated fibers
reduced by only 16% (Jancsó et al., 1985b).
Extensive

unmyelinated fibers in the rat saphenous nerve is dimin-
ished by 45%, whereas the number of myelinated fibers
is reduced by only 16% (Jancsó et al., 1985b).
Extensive degeneration of axons and axon terminals
is also obser ished by 45%, whereas the number of myelinated fibers
is reduced by only 16% (Jancsó et al., 1985b).
Extensive degeneration of axons and axon terminals
is also observed in the ureter, duodenum (Hoyes and
Barber, 1981), and is reduced by only 16% (Jancsó et al., 1985b).
Extensive degeneration of axons and axon terminals
is also observed in the ureter, duodenum (Hoyes and
Barber, 1981), and trachea (Hoyes et al., 1981) 24 h after
subcutaneous Extensive degeneration of axons and axon terminals
is also observed in the ureter, duodenum (Hoyes and
Barber, 1981), and trachea (Hoyes et al., 1981) 24 h after
subcutaneous injection of 50 mg/kg capsaicin to adult
rats. is also observed in the ureter, duodenum (Hoyes and
Barber, 1981), and trachea (Hoyes et al., 1981) 24 h after
subcutaneous injection of 50 mg/kg capsaicin to adult
rats. Degeneration is confined to axons with terminals
co Barber, 1981), and trachea (Hoyes et al., 1981) 24 h after
subcutaneous injection of 50 mg/kg capsaicin to adult
rats. Degeneration is confined to axons with terminals
containing mainly large dense-cored vesicles. In the u subcutaneous injection of 50 mg/kg capsaicin to adult
rats. Degeneration is confined to axons with terminals
containing mainly large dense-cored vesicles. In the ure-
ter as many as 90% of all axons degenerate, whereas no
 rats. Degeneration is confined to axons with terminals
containing mainly large dense-cored vesicles. In the ure-
ter as many as 90% of all axons degenerate, whereas no
appreciable degeneration in the dorsal roots is noted
 containing mainly large dense-cored vesicles. In the ure-
ter as many as 90% of all axons degenerate, whereas no
appreciable degeneration in the dorsal roots is noted
(Chung et al., 1985b). Likewise, 49% of the axons in th ter as many as 90% of all axons degenerate, whereas no
appreciable degeneration in the dorsal roots is noted
(Chung et al., 1985b). Likewise, 49% of the axons in the
subepidermal nerve plexus are lost 1 to 112 days after
t appreciable degeneration in the dorsal roots is noted (Chung et al., 1985b). Likewise, 49% of the axons in the subepidermal nerve plexus are lost 1 to 112 days after treatment with 50 mg/kg capsaicin, whereas the number o (Chung et al., 1985b).
subepidermal nerve p
treatment with 50 mg,
of axons in the sural
(Chung et al., 1990).
Thus, capsaicin tre bepidermal nerve plexus are lost 1 to 112 days after
eatment with 50 mg/kg capsaicin, whereas the number
axons in the sural nerve is not significantly altered
hung et al., 1990).
Thus, capsaicin treatment of adult rats can

treatment of 20-day-old or adult rats reversibly reduces neurons and predominantly unmyelinated afferent nerve
chemonociception (Jancsó, 1960), sensory nerve-me-
diated increases in vascular permeability (Jancsó et al., an treatment with 50 mg/kg capsaicin, whereas the number
of axons in the sural nerve is not significantly altered
(Chung et al., 1990).
Thus, capsaicin treatment of adult rats can lead to
severe morphological changes in some of axons in the sural nerve is not significantly altered (Chung et al., 1990).

Thus, capsaicin treatment of adult rats can lead to

severe morphological changes in some small sensory

neurons and predominantly unmyelinate (Chung et al., 1990).
Thus, capsaicin treatment of adult rats can lead to
severe morphological changes in some small sensory
neurons and predominantly unmyelinated afferent nerve
fibers. A very important point is that, alt Thus, capsaicin treatment of adult rats can lead t
severe morphological changes in some small sensor
neurons and predominantly unmyelinated afferent nerv
fibers. A very important point is that, although somat
and nerve fib severe morphological changes in some small sensory
neurons and predominantly unmyelinated afferent nerve
fibers. A very important point is that, although somata
and nerve fibers show no or only moderate degeneration,
axon neurons and predominantly unmyelinated afferent nerve
fibers. A very important point is that, although somata
and nerve fibers show no or only moderate degeneration,
axon terminals in the periphery are destroyed to a much

PHARMACOLOGICAL REVIEWS

nounced than when capsaicin is given to the newborn CAPSAIC
1985b, 1990). Therefore, the extent of degeneration of
1980 somata and axons in the adult rat is clearly less pro-
1990 nounced than when capsaicin is given to the newborn
1987a), and real (Jancsó et al., 1977, 198 1985b, 1990). Therefore, the extent of degeneration of 1984 somata and axons in the adult rat is clearly less prover nounced than when capsaicin is given to the newborn (Ganimal (Jancsó et al., 1977, 1980a, 1985b, 1987a), 1985b, 1990). Therefore, the extent of degeneration of somata and axons in the adult rat is clearly less pro-
nounced than when capsaicin is given to the newborn
animal (Jancsó et al., 1977, 1980a, 1985b, 1987a), and
only somata and axons in the adult rat is clearly less pro-
nounced than when capsaicin is given to the newborn
animal (Jancsó et al., 1977, 1980a, 1985b, 1987a), and
only a subpopulation of capsaicin-sensitive afferent neu-
ro 1985b). imal (Jancsó et al., 1977, 1980a, 1985b, 1987a), and
ly a subpopulation of capsaicin-sensitive afferent neu-
ns appears to undergo degeneration (Jancsó et al.,
85b).
ii. Neurochemical and histochemical changes
mpared wi

only a subpopulation of capsaicin-sensitive afferent neu-
rons appears to undergo degeneration (Jancsó et al.,
1985b).
ii. Neurochemical and histochemical changes
compared with those produced by neonatal capsai-
cin. rons appears to undergo degeneration (Jancsó et al., 1985b).
 ii. Neurochemical and histochemical changes
 compared with those produced by neonatal capsai-
 cin. The neurochemical consequences of systemic cap-

saici duce ii. Neurochemical and histochemical changes imp
compared with those produced by neonatal capsaicion
cin. The neurochemical consequences of systemic cap-
saicin treatment of adult rats are qualitatively similar to prop ii. Neurochemical and histochemical change compared with those produced by neonatal capse cin. The neurochemical consequences of systemic casicin treatment of adult rats are qualitatively similar those in newborn rats, whe compared with those produced by neonatal capsaicin. The neurochemical consequences of systemic capsaicin treatment of adult rats are qualitatively similar to those in newborn rats, whereas the extent and reversibility of t cin. The neurochemical consequences of systemic cap-
saicin treatment of adult rats are qualitatively similar to
those in newborn rats, whereas the extent and reversi-
bility of the neurotoxic effect of capsaicin may diffe saicin treatment of adult rats are qualitatively similar
those in newborn rats, whereas the extent and rever
bility of the neurotoxic effect of capsaicin may diff
Depletion of substance P from sensory nerve pathwe
is produ those in newborn rats, whereas the extent and reversi-
bility of the neurotoxic effect of capsaicin may differ.
Depletion of substance P from sensory nerve pathways
is produced by 50 to 125 mg/kg capsaicin given subcu-
ta bility of the neurotoxic effect of capsaicin may differ. 19.
Depletion of substance P from sensory nerve pathways of
is produced by 50 to 125 mg/kg capsaicin given subcu-
taneously or intraperitoneally to adult rats (Gamse Depletion of substance P from sensory nerve pathways
is produced by 50 to 125 mg/kg capsaicin given subcu-
taneously or intraperitoneally to adult rats (Gamse et
al., 1981b; Gamse, 1982), the intraperitoneal route being
mo is produced by 50 to 125 mg/kg capsaicin given subcu-
taneously or intraperitoneally to adult rats (Gamse et ed., 1981b; Gamse, 1982), the intraperitoneal route being of
more effective than the subcutaneous one (Gamse et a taneously or intraperitoneally to adult rats (Gamse et al., 1981b; Gamse, 1982), the intraperitoneal route being more effective than the subcutaneous one (Gamse et al., 1981b). Subcutaneously, the dose of 125 mg/kg capsaic al., 1981b; Gamse, 1982), the intraperitoneal route being of t
more effective than the subcutaneous one (Gamse et al., arta
1981b). Subcutaneously, the dose of 125 mg/kg capsaicin ish
seems to be maximally effective (Gamse more effective than the subcutaneous one (Gamse et al., 1981b). Subcutaneously, the dose of 125 mg/kg capsaicin seems to be maximally effective (Gamse et al., 1981b), making it unnecessary to use doses as high as 950 mg/kg 1981b). Subcutaneously, the dose of 125 mg/kg capsaic
seems to be maximally effective (Gamse et al., 1981)
making it unnecessary to use doses as high as 9:
mg/kg (Jessell et al., 1978) which may give rise to ce
nonselectiv seems to be maximally effective (Gamse et al., 1981b), ce
making it unnecessary to use doses as high as 950 te
mg/kg (Jessell et al., 1978) which may give rise to cell-
nonselective neurotoxic effects (Harti, 1988). The de making it unnecessary to use doses as high as 950 mg/kg (Jessell et al., 1978) which may give rise to cell-
nonselective neurotoxic effects (Harti, 1988). The deple-
tion of substance P and somatostatin from sensory
pathwa mg/kg (Jessell et al., 1978) which may give rise to cell-
nonselective neurotoxic effects (Harti, 1988). The deple-
tion of substance P and somatostatin from sensory
pathways produced by 125 mg/kg capsaicin in adult
Spragu nonselective neurotoxic effects (Harti, 1988). The depletion of substance P and somatostatin from sensory pathways produced by 125 mg/kg capsaicin in adult Sprague-Dawley rats is less than that caused by 50 mg/kg capsaicin tion of substance P and somatostatin from sensory
pathways produced by 125 mg/kg capsaicin in adult
Sprague-Dawley rats is less than that caused by 50 mg/
kg capsaicin in newborn animals (Gamse et al., 1981b;
Gamse, 1982; Sprague-Dawley rats is less than that caused by 50 mg/
kg capsaicin in newborn animals (Gamse et al., 1981b;
Gamse, 1982; Priestley et al., 1982). Likewise, neonatal
capsaicin treatment is more effective in depleting vaso-Sprague-Dawley rats is less than that caused by 50 mg/ cep
kg capsaicin in newborn animals (Gamse et al., 1981b; cin
Gamse, 1982; Priestley et al., 1982). Likewise, neonatal Szc
capsaicin treatment is more effective in dep kg capsaicin in newborn animals (Gamse et al., 1981b;
Gamse, 1982; Priestley et al., 1982). Likewise, neonatal
capsaicin treatment is more effective in depleting vaso-
active intestinal polypeptide from the dorsal spinal c Gamse, 1982; Priestley et al., 1982). Likewise, neonatal Scapsaicin treatment is more effective in depleting vaso-
active intestinal polypeptide from the dorsal spinal cord numeral mediation and dult capsaicin treatment (S capsaicin treatment is more effective in depleting vaso-
active intestinal polypeptide from the dorsal spinal cord methan adult capsaicin treatment (Skofitsch et al., 1985). 19
In MRC Porton and Wistar rats, however, the d active messinal polypeptule from the dorsal spinal cold
than adult capsaicin treatment (Skofitsch et al., 1985).
In MRC Porton and Wistar rats, however, the depletion
of substance P and calcitonin gene-related peptide is t than adult capsaicin treatment (Skofitsch et al., 1985). 19
In MRC Porton and Wistar rats, however, the depletion and
of substance P and calcitonin gene-related peptide is the pr
same when capsaicin is given to newborn or In MRC Porton and Wistar rats, however, the depletion and of substance P and calcitonin gene-related peptide is the pressure when capsaicin is given to newborn or adult rats 19 (Salt et al., 1982; Geppetti et al., 1988a), of substance P and calcitonin gene-related peptide is th
same when capsaicin is given to newborn or adult rat
(Salt et al., 1982; Geppetti et al., 1988a), and 125 mg/k
capsaicin given to adult animals is no more effective same when capsaicin is given to newborn or adult rat (Salt et al., 1982; Geppetti et al., 1988a), and 125 mg/k
capsaicin given to adult animals is no more effective tha
50 mg/kg (Geppetti et al., 1988a). Opiate receptor bi (Satt et al., 1562, Geppetti et al., 1566a), and 125 mg/kg
capsaicin given to adult animals is no more effective than
50 mg/kg (Geppetti et al., 1988a). Opiate receptor bind-
ing in the dorsal horn of the spinal cord rema capsaicin given to adult animals is no more effective than
50 mg/kg (Geppetti et al., 1988a). Opiate receptor bind-
ing in the dorsal horn of the spinal cord remains unal-
tered after capsaicin treatment of adult rats (Jes 50 mg/kg (Geppetti et al., 1988a)
ing in the dorsal horn of the spi
tered after capsaicin treatment c
al., 1978) but is decreased by neo:
et al., 1979a; Nagy et al., 1980).
After capsaicin treatment of g in the dorsal horn of the spinal cord remains unal-
red after capsaicin treatment of adult rats (Jessell et
, 1978) but is decreased by neonatal capsaicin (Gamse
al., 1979a; Nagy et al., 1980).
After capsaicin treatment

pathways, but partial or total recovery of the marker et al., 1979a; Nagy et al., 1980).

After capsaicin treatment of newborn rats, peptide

markers (table 1) are permanently depleted from sensory

pathways, but partial or total recovery of the marker

levels takes place fol Figure 2.1 The recovery rates differ with tissue and peptide. After administration of 125 mg/kg capsaicin to the and the peptide. After administration of 125 mg/kg capsaicin to et a adult rats, substance P recovers complet pathways, but partial or total recovery of the marker of sievels takes place following capsaicin treatment of adult inhitients, although the recovery rates differ with tissue and treas peptide. After administration of 125 levels takes place following capsaicin treatment of adult inh
rats, although the recovery rates differ with tissue and tre-
peptide. After administration of 125 mg/kg capsaicin to et a
dult rats, substance P recovers compl rats, although the recovery rates differ with tissue and
peptide. After administration of 125 mg/kg capsaicin to
adult rats, substance P recovers completely within 4
months in the saphenous nerve, dorsal root ganglia, and
 peptide. After administration of 125 mg/kg capsaicin to et a adult rats, substance P recovers completely within 4 the months in the saphenous nerve, dorsal root ganglia, and duo dorsal roots, whereas in the cornea, vagus n adult rats, substance P recovers completely within 4 months in the saphenous nerve, dorsal root ganglia, and dorsal roots, whereas in the cornea, vagus nerve, dorsal spinal cord, and brainstem recovery is not complete even months in the saphenous nerve, dorsal root ganglia, and
dorsal roots, whereas in the cornea, vagus nerve, dorsal
espinal cord, and brainstem recovery is not complete even
after 9 months (Gamse et al., 1981b). In other stud found in the spinal cord and urinary bladder 39 to 60
spinal cord, and brainstem recovery is not complete even
however, a complete replenishment of substance P was
found in the spinal cord and urinary bladder 39 to 60 cer
 after 9 months (Gamse et al., 1981b). In other studies, however, a complete replenishment of substance P was found in the spinal cord and urinary bladder 39 to 60 days after administration of 50 to 100 mg/kg capsaicin to a

1985b, 1990). Therefore, the extent of degeneration of 1987d). The depletion of somatostatin is completely resomata and axons in the adult rat is clearly less pro- versible within 4 months in all tissues investigated EXTEE 157
1987d). The depletion of somatostatin is completely re-
1987d). The depletion of somatostatin is completely reversible within 4 months in all tissues investigated
versible within 4 months in all tissues investigated
(Gamse et al., 1981b). A relationship, if any, between 157
1987d). The depletion of somatostatin is completely re-
versible within 4 months in all tissues investigated
(Gamse et al., 1981b). A relationship, if any, between
replenishment of neurochemical markers and morpho-1987d). The depletion of somatostatin is completely versible within 4 months in all tissues investiga
(Gamse et al., 1981b). A relationship, if any, betwee replenishment of neurochemical markers and morp logical recovery o local recovers in all tissues investigates were versible within 4 months in all tissues invest (Gamse et al., 1981b). A relationship, if any, be replenishment of neurochemical markers and m logical recovery of sensory neur (Gamse et al., 1981b). A relationship, if any, between
replenishment of neurochemical markers and morpho-
logical recovery of sensory neurons is not known.
iii. Functional changes compared with those pro-

(Gamse et al., 1981b). A relationship, if any, between
replenishment of neurochemical markers and morpho-
logical recovery of sensory neurons is not known.
iii. Functional changes compared with those pro-
duced by neonatal duced by neonatal capsaicin. There are some very
important age-dependent differences in the functional
consequences of systemic capsaicin treatment. Whereas
capsaicin treatment of newborn rats does not change the logical recovery of sensory neurons is not known.
iii. Functional changes compared with those pro-
duced by neonatal capsaicin. There are some very
important age-dependent differences in the functional
consequences of syst iii. Functional changes compared with those pro-
duced by neonatal capsaicin. There are some very
important age-dependent differences in the functional
consequences of systemic capsaicin treatment. Whereas
capsaicin treatm duced by neonatal capsaicin. There are some very
important age-dependent differences in the functional
consequences of systemic capsaicin treatment. Whereas
capsaicin treatment of newborn rats does not change the
proportio important age-dependent differences in the functional consequences of systemic capsaicin treatment. Whereas capsaicin treatment of newborn rats does not change the proportion of relative receptor types in afferent nerves (consequences of systemic capsaicin treatment. Whereas
capsaicin treatment of newborn rats does not change the
proportion of relative receptor types in afferent nerves
(Lynn, 1984; Welk et al., 1984; Cervero and Sharkey,
19 capsaicin treatment of newborn rats does not change the
proportion of relative receptor types in afferent nerves
(Lynn, 1984; Welk et al., 1984; Cervero and Sharkey,
1988), there is a significant reduction in the proportio proportion of relative receptor types in afferent nerves (Lynn, 1984; Welk et al., 1984; Cervero and Sharkey, 1988), there is a significant reduction in the proportion of C-fiber polymodal nociceptors in the rat saphenous 1988), there is a significant reduction in the proportion
of C-fiber polymodal nociceptors in the rat saphenous
nerve following capsaicin treatment of adult rats (Lynn
et al., 1984; Szolcsányi et al., 1988). The responsive 1988), there is a significant reduction in the proportion
of C-fiber polymodal nociceptors in the rat saphenous
nerve following capsaicin treatment of adult rats (Lynn
et al., 1984; Szolcsányi et al., 1988). The responsive nerve following capsaicin treatment of adult rats (Lynn et al., 1984; Szolcsányi et al., 1988). The responsiveness of the remaining C-fiber polymodal nociceptors to close arterial injection of capsaicin is diminished but n nerve following capsaicin treatment of adult rats (
et al., 1984; Szolcsányi et al., 1988). The responsiv
of the remaining C-fiber polymodal nociceptors to
arterial injection of capsaicin is diminished but not
ished (Szolc et al., 1984; Szolcsányi et al., 1988). The responsiveness
of the remaining C-fiber polymodal nociceptors to close
arterial injection of capsaicin is diminished but not abol-
ished (Szolcsányi et al., 1988). In contrast, t of the remaining C-fiber polymodal nociceptors to close
arterial injection of capsaicin is diminished but not abol-
ished (Szolcsányi et al., 1988). In contrast, thermonoci-
ception seems to be impaired only temporarily by arterial injection of capsaicin is diminished but not abolished (Szolcsányi et al., 1988). In contrast, thermonociception seems to be impaired only temporarily by systemic capsaicin treatment of adult rats (Hayes et al., 1 Eshed (Szolcsanyi et al., 1986). In contrast, thermonoci-
ception seems to be impaired only temporarily by sys-
temic capsaicin treatment of adult rats (Hayes et al.,
1981b; Buck et al., 1982; Gamse, 1982; Bittner and
LaHa denic Capsaich treatment of adult rats (riayes et 1981b; Buck et al., 1982; Gamse, 1982; Bittner
LaHann, 1985; Szolcsányi, 1990), whereas perma
changes may occur after neonatal treatment (Holz
al., 1979; Nagy et al., 1980; LaHann, 1985; Szolcsányi, 1990), whereas permanent changes may occur after neonatal treatment (Holzer et al., 1979; Nagy et al., 1980; Gamse, 1982). Chemonociception, however, is reduced for a long time after capsai-
cin t LaHann, 1985; Szolcsányi, 1990), whereas permanent
changes may occur after neonatal treatment (Holzer et
al., 1979; Nagy et al., 1980; Gamse, 1982). Chemonoci-
ception, however, is reduced for a long time after capsai-
cin changes may occur after neonatal treatment (Holzer et al., 1979; Nagy et al., 1980; Gamse, 1982). Chemonoci-
ception, however, is reduced for a long time after capsai-
cin treatment of adult rats (Szolcsányi et al., 1975;
 ception, however, is reduced for a long time after capsaicin treatment of adult rats (Szolcsányi et al., 1975; Szolcsányi and Jancsó-Gábor, 1976; Hayes and Tyers, 1980; Gamse et al., 1981b; Gamse, 1982). In contrast, mecha ception, however, is reduced for a long time after capsaicin treatment of adult rats (Szolcsányi et al., 1975;
Szolcsányi and Jancsó-Gábor, 1976; Hayes and Tyers,
1980; Gamse et al., 1981b; Gamse, 1982). In contrast,
mecha cin treatment of adult rats (Szolcsányi et al., 1975;
Szolcsányi and Jancsó-Gábor, 1976; Hayes and Tyers,
1980; Gamse et al., 1981b; Gamse, 1982). In contrast,
mechanonociception is either unchanged (Barthó et al.,
1990), Szolcsányi and Jancsó-Gábor, 1976; Hayes and Tyers,
1980; Gamse et al., 1981b; Gamse, 1982). In contrast,
mechanonociception is either unchanged (Barthó et al.,
1990), facilitated (Szolcsányi, 1985), or inhibited (Hayes
an 1980; Gamse et al., 1981b; Gamse, 1982). In contrast, mechanonociception is either unchanged (Barthó et al., 1990), facilitated (Szolcsányi, 1985), or inhibited (Hayes and Tyers, 1980; Gamse, 1982), this variability being mechanonociception is either unchanged (Barthó et al., 1990), facilitated (Szolcsányi, 1985), or inhibited (Hayes and Tyers, 1980; Gamse, 1982), this variability being probably due to different nociception tests (Barthó et 1990), facilitated (Szolcsányi, 1985), or inhibited (Hayes and Tyers, 1980; Gamse, 1982), this variability being probably due to different nociception tests (Barthó et al., 1990). Mechanical hyperalgesia associated with ch and Tyers, 1980; Gamse, 1982), this variability being

probably due to different nociception tests (Barthó et al.,

1990). Mechanical hyperalgesia associated with chronic

paw inflammation, however, is markedly reduced by probably due t
1990). Mechar
paw inflamma
temic adminis
et al., 1990).
The differe Forthermannian interaction associated with emotion
w inflammation, however, is markedly reduced by sys-
mic administration of capsaicin to adult rats (Barthó
al., 1990).
The differences between the effects of neonatal and

tered after capsaicin treatment of adult rats (Jessell et adult capsaicin treatment can be explained in at least
al., 1978) but is decreased by neonatal capsaicin (Gamse two different ways. On the one hand, they could mirr paw inflammation, however, is markedly reduced by systemic administration of capsaicin to adult rats (Barthó et al., 1990).
The differences between the effects of neonatal and adult capsaicin treatment can be explained in tem administration of capsarent w adult rats (Bartho)
et al., 1990).
The differences between the effects of neonatal and
adult capsaicin treatment can be explained in at least
two different ways. On the one hand, they coul The differences between the effects of neonatal and
adult capsaicin treatment can be explained in at least
two different ways. On the one hand, they could mirror
different degrees of morphological and functional abla-
tion adult capsaicin treatment can be explained in at least
two different ways. On the one hand, they could mirror
different degrees of morphological and functional abla-
tion of sensory neurons. Such a difference, for instance two different ways. On the one hand, they could mirror
different degrees of morphological and functional abla-
tion of sensory neurons. Such a difference, for instance,
is reflected by the finding that capsaicin-induced re tion of sensory neurons. Such a difference, for instance, is reflected by the finding that capsaicin-induced release of substance P from the dorsal spinal cord in vitro is inhibited to a greater extent by neonatal capsaici treatment than by pretreatment of adult animals (Gamse of substance P from the dorsal spinal cord in vitro is inhibited to a greater extent by neonatal capsaicin pre-
treatment than by pretreatment of adult animals (Gamse of substance P from the dorsal spinal cord in vitro is
inhibited to a greater extent by neonatal capsaicin pre-
treatment than by pretreatment of adult animals (Gamse
et al., 1981a; Gamse, 1982). A further example relates inhibited to a greater extent by neonatal capsaicin pre-
treatment than by pretreatment of adult animals (Gamse
et al., 1981a; Gamse, 1982). A further example relates to
the catecholamine secretion from the adrenal gland i treatment than by pretreatment of adult animals (Gamse et al., 1981a; Gamse, 1982). A further example relates to the catecholamine secretion from the adrenal gland induced by an acute intravenous infusion of capsaicin. Thi et al., 1981a; Gamse, 1982). A further example relates to
the catecholamine secretion from the adrenal gland in-
duced by an acute intravenous infusion of capsaicin. This
effect, which is due to a neural reflex (Watanabe e the catecholamine secretion from the adrenal gland in-
duced by an acute intravenous infusion of capsaicin. This
effect, which is due to a neural reflex (Watanabe et al.,
1988b), is reduced by capsaicin pretreatment of new duced by an acute intravenous infusion of capsaicin. This
effect, which is due to a neural reflex (Watanabe et al.,
1988b), is reduced by capsaicin pretreatment of newborn
rats to a larger extent than by pretreatment of ad effect, which is due to a neural reflex (Watanabe e 1988b), is reduced by capsaicin pretreatment of new rats to a larger extent than by pretreatment of α animals (Watanabe et al., 1988a). On the other hermonoception ma 1988b), is reduced by capsaicin pretreatment of newborn
rats to a larger extent than by pretreatment of adult
animals (Watanabe et al., 1988a). On the other hand,
certain differences such as that found with thermonoci-
cep animals (Watanabe et al., 1988a). On the other hand, certain differences such as that found with thermonociception may be accounted for by changes at the level of second-order neurons in the spinal cord and medulla

aspet

(Salt et al., 1982). Thus, neonatal capsaicin treatment HOLZI
(Salt et al., 1982). Thus, neonatal capsaicin treatment
greatly reduces the number of brainstem cells responding
to noxious pressure and heat, whereas after treatment of HOLZE
(Salt et al., 1982). Thus, neonatal capsaicin treatment algreatly reduces the number of brainstem cells responding the
to noxious pressure and heat, whereas after treatment of seadult rats no major change is observed (Salt et al., 1982). Thus, neonatal capsaicin treatment greatly reduces the number of brainstem cells responding to noxious pressure and heat, whereas after treatment of adult rats no major change is observed (Salt et al., greatly reduces the number of brainstem cells responding
to noxious pressure and heat, whereas after treatment of
adult rats no major change is observed (Salt et al., 1982).
An analogous explanation could hold true for the greatly reduces the number of brainstem cells responding
to noxious pressure and heat, whereas after treatment of
adult rats no major change is observed (Salt et al., 1982).
An analogous explanation could hold true for the to noxious pressure and heat, whereas after treatment of adult rats no major change is observed (Salt et al., 1982).
An analogous explanation could hold true for the observation that analgesia induced by mechanical stimula adult rats no major change is observed (Salt et al., 1984).
An analogous explanation could hold true for the observation that analgesia induced by mechanical stimulat
of the rat vagina is blocked by neonatal, but not ad
ca n analogous explanation could hold true for the obsertion that analgesia induced by mechanical stimulation the rat vagina is blocked by neonatal, but not adult, long-term effects posicin treatment (Rodriguez-Sierra et al.,

vation that analgesia induced by mechanical stimulation gelpt of the rat vagina is blocked by neonatal, but not adult, 19 capsaicin treatment (Rodriguez-Sierra et al., 1988). Very pronounced differences in the long-term ef of the rat vagina is blocked by neonatal, but not adult, capsaicin treatment (Rodriguez-Sierra et al., 1988).
Very pronounced differences in the long-term effects
of capsaicin when given to newborn or adult rats are
eviden capsaicin treatment (Rodriguez-Sierra et al., 1988).
Very pronounced differences in the long-term effects
of capsaicin when given to newborn or adult rats are
evident with the micturition reflex. Capsaicin treatment
at any Very pronounced differences in the long-term effectof capsaicin when given to newborn or adult rats a evident with the micturition reflex. Capsaicin treatment arc any age impairs this reflex, probably by interferies with i of capsaicin when given to newborn or adult rats are evident with the micturition reflex. Capsaicin treatment at any age impairs this reflex, probably by interfering with its afferent arc only (Sharkey et al., 1983; Holzer evident with the micturition reflex. Capsaicin treatment
at any age impairs this reflex, probably by interfering
with its afferent arc only (Sharkey et al., 1983; Holzer-
Petsche and Lembeck, 1984; Maggi et al., 1984, 1987 at any age impairs this reflex, probably by interfering ray with its afferent arc only (Sharkey et al., 1983; Holzer-
Petsche and Lembeck, 1984; Maggi et al., 1984, 1987d, set
1989b; Santicioli et al., 1985; Maggi and Meli with its afferent arc only (Sharkey et al., 1983; Holzer-
Petsche and Lembeck, 1984; Maggi et al., 1984, 1987d,
1989b; Santicioli et al., 1985; Maggi and Meli, 1986).
Although the depletion of substance P from the urinary
 Petsche and Lembeck, 1984; Maggi et al., 1984, 1987d, 1989b; Santicioli et al., 1985; Maggi and Meli, 1986).
Although the depletion of substance P from the urinary
bladder is similar (Holzer et al., 1982; Maggi et al., 198 1989b; Santicioli et al., 1985; Maggi and Meli, 1986).
Although the depletion of substance P from the urinary
bladder is similar (Holzer et al., 1982; Maggi et al., 1987d;
Geppetti et al., 1988a), neonatal capsaicin treatm Although the depletion of substance P from the urinar
bladder is similar (Holzer et al., 1982; Maggi et al., 1987d
Geppetti et al., 1988a), neonatal capsaicin treatmen
leads to a permanent abolition of distension-induce
mi bladder is similar (Holzer et al., 1982; Maggi et al., 1987d;
Geppetti et al., 1988a), neonatal capsaicin treatment
leads to a permanent abolition of distension-induced
micturition and to pronounced hypertrophy of the blad Geppetti et al., 1988a), neonatal capsaicin treatment P f
leads to a permanent abolition of distension-induced app
micturition and to pronounced hypertrophy of the blad-
Hader (Sharkey et al., 1983; Santicioli et al., 1985 leads to a permanent abolition of distension-induced apmicturition and to pronounced hypertrophy of the blad-
der (Sharkey et al., 1983; Santicioli et al., 1985; Maggi et Do
al., 1989b), whereas treatment of adults with 25 micturition and to pronounced hypertrophy of the blad-
der (Sharkey et al., 1983; Santicioli et al., 1985; Maggi et
al., 1989b), whereas treatment of adults with 25 to 350
mg/kg capsaicin causes only a reversible increase pressure threshold of micturition (Maggi et al., 1984, mg/kg capsaicin causes only a reversible increase in the the pressure threshold of micturition (Maggi et al., 1984, net 1987d, 1989b). This has been taken to suggest that there and are two populations of capsaicin-sensitiv pressure threshold of micturition (Maggi et al., 1984, not not neglect that there are two populations of capsaicin-sensitive afferent neurons in the rat urinary bladder, one population being sensitive to the neurotoxic act 1987d, 1989b). This has been taken to suggest that there and the original are two populations of capsaicin-sensitive afferent neurons in the rat urinary bladder, one population being sensitive to the neurotoxic action of c are two populations of capsaicin-sensitive afferent neu-
rons in the rat urinary bladder, one population being
sensitive to the neurotoxic action of capsaicin at all ages
of life and the other vulnerable to capsaicin only rons in the rat urinary bladder, one population being
sensitive to the neurotoxic action of capsaicin at all ages
of life and the other vulnerable to capsaicin only in the
newborn rat (Maggi et al., 1987d, 1989b; Maggi and sensitive to the neurotoxic action of capsaicin at all ages saic of life and the other vulnerable to capsaicin only in the rest newborn rat (Maggi et al., 1987d, 1989b; Maggi and Meli, bect 1988; Szolcsányi, 1990). Because of life and the other vulnerable to capsaicin only in the newborn rat (Maggi et al., 1987d, 1989b; Maggi and Meli, 1988; Szolcsányi, 1990). Because morphological evidence for this proposition is not available, however, it newborn rat (Maggi et al., 1987d, 1989b; Maggi and Meli, battle 1988; Szolcsányi, 1990). Because morphological evidence cofor this proposition is not available, however, it ought to feed considered that there is only one p for this proposition is not available, however, it ought to
be considered that there is only one population of affer-
ent neurons whose sensitivity to the neurotoxic effect of
capsaicin diminishes as they mature.
Differenc r this proposition is not available, however, it ought to considered that there is only one population of affer-
t neurons whose sensitivity to the neurotoxic effect of psaicin diminishes as they mature.
Differences also e be considered that there is only one population of afferent neurons whose sensitivity to the neurotoxic effect of capsaicin diminishes as they mature.
Differences also exist with respect to inhibition of local effector fun

ent neurons whose sensitivity to the neurotoxic effect of glut
capsaicin diminishes as they mature. asset as a sensory are to inhibition of local Peter
effector functions of sensory nerve endings in peripheral enk
tissues. capsaicin diminishes as they mature. a
Differences also exist with respect to inhibition of local
effector functions of sensory nerve endings in peripheral
tissues. The exudation of plasma proteins induced by
cutaneous app Differences also exist with respect to inhibition of local Peta
effector functions of sensory nerve endings in peripheral enk
tissues. The exudation of plasma proteins induced by 198
cutaneous application of mustard oil ca effector functions of sensory nerve endings in peripheral
tissues. The exudation of plasma proteins induced by
cutaneous application of mustard oil can be inhibited for
a much longer time when capsaicin is administered to
 tissues. The exudation of plasma proteins induced by
cutaneous application of mustard oil can be inhibited for
the much longer time when capsaicin is administered to
newborn rather than to adults rats (Jancsó et al., 1967, cutaneous application of mustard oil can be inhibited for
a much longer time when capsaicin is administered to
newborn rather than to adults rats (Jancsó et al., 1967,
1977). Similarly, capsaicin treatment of newborn rats
 a much longer time when capsaicin is administered to mewborn rather than to adults rats (Jancsó et al., 1967, the 1977). Similarly, capsaicin treatment of newborn rats et results in a decreased basal blood flow in the supe newborn rather than to adults rats (Jancsó et al., 1967, the 1977). Similarly, capsaicin treatment of newborn rats et results in a decreased basal blood flow in the superior respecteric artery of adult rats, whereas treatm 1977). Similarly, capsaicin treatment of newborn rats et results in a decreased basal blood flow in the superior remesenteric artery of adult rats, whereas treatment of valuation is without effect (Hottenstein et al., 1991 results in a decreased basal blood flow in the superior remesenteric artery of adult rats, whereas treatment of viewed adults is without effect (Hottenstein et al., 1991). In the neerfused hindquarter from rats treated wit mesenteric artery of adult rats, whereas treatment of values is without effect (Hottenstein et al., 1991). In the networking perfused hindquarter from rats treated with capsaicin as adults, substance P is able to release h adults is without effect (Hottenstein et al., 1991). In the perfused hindquarter from rats treated with capsaicin as adults, substance P is able to release histamine as it does in untreated rats, whereas in rats treated wi perfused hindquarter from rats treated with capsaicin as An adults, substance P is able to release histamine as it does the in untreated rats, whereas in rats treated with capsaicin is in as neonates the peptide is inactiv adults, substance P is able to release histamine as it does the in untreated rats, whereas in rats treated with capsaicin is as neonates the peptide is inactive (Skofitsch et al., given 1983). An appraisal of these differe in untreated rats, whereas in rats treated with capsaicin
as neonates the peptide is inactive (Skofitsch et al.,
1983). An appraisal of these differences has to take into
account that some of the functional alterations cau as neonates the peptide is inactive (Skofitsch et al., given 1983). An appraisal of these differences has to take into relaccount that some of the functional alterations caused in by neonatal capsaicin treatment probably r 1983). An appraisal of these differences has to take into account that some of the functional alterations caused
by neonatal capsaicin treatment probably reflect changes
not only in sensory neurons but also in systems clos account that some of the functional alterations caused in the meaning of the functional alterations caused in the mot only in sensory neurons but also in systems closely in related to these neurons. It needs to be stressed by neonatal capsaicin treatment probably reflect changes
not only in sensory neurons but also in systems closely
related to these neurons. It needs to be stressed, however,
that capsaicin treatment of newborn and adult rat

ablation of sensory neurons. Thus, the vulnerability of ER
ablation of sensory neurons. Thus, the vulnerability of
the rat gastric mucosa by acid, ethanol, or indomethacin
seems to be aggravated to the same degree in rats treated ER
ablation of sensory neurons. Thus, the vulnerability of
the rat gastric mucosa by acid, ethanol, or indomethacin
seems to be aggravated to the same degree in rats treated
with capsaicin either as neonates (Holzer and Sa ablation of sensory neurons. Thus, the vulnerability of
the rat gastric mucosa by acid, ethanol, or indomethacin
seems to be aggravated to the same degree in rats treated
with capsaicin either as neonates (Holzer and Samet the rat gastric mucosa by acid, ethanol, or indomethacin
seems to be aggravated to the same degree in rats treated
with capsaicin either as neonates (Holzer and Sametz,
1986) or as adults (Szolcsányi and Barthó, 1981; Evan the rat gastric mucosa by acid, ethanol, or indomethacin seems to be aggravated to the same degree in rats treated with capsaicin either as neonates (Holzer and Sametz, 1986) or as adults (Szolcsányi and Barthó, 1981; Evan 1991). th capsaicin either as neonates (Holzer and Sam 86) or as adults (Szolcsányi and Barthó, 1981; Evista et al., 1986; Esplugues et al., 1989; Holzer et 91).
Wix. Comparison of the onset of morphologicurochemical, and functio

al., 1989b), whereas treatment of adults with 25 to 350 ganglia of adult rats can be preceded by an increase in mg/kg capsaicin causes only a reversible increase in the ganglionic levels of substance P (Lembeck and Don-
pr 1986) or as adults (Szolcsányi and Barthó, 1981; Evelista et al., 1986; Esplugues et al., 1989; Holzer et 1991).

iv. Comparison of the onset of morphologic

neurochemical, and functional changes. Degeneration of B-type se gelista et al., 1986; Esplugues et al., 1989; Holzer et al., 1991).
1991).
iv. Comparison of the onset of morphological,
neurochemical, and functional changes. Degenera-
tion of B-type sensory neurons takes place within 1 1991).

iv. Comparison of the onset of morphological,

neurochemical, and functional changes. Degenera-

tion of B-type sensory neurons takes place within 1 h

after subcutaneous administration of capsaicin to adult

rats iv. Comparison of the onset of morphological,
neurochemical, and functional changes. Degenera-
tion of B-type sensory neurons takes place within 1 h
after subcutaneous administration of capsaicin to adult
rats (Jancsó et a neurochemical, and functional changes. Degeneration of B-type sensory neurons takes place within 1 h after subcutaneous administration of capsaicin to adult rats (Jancsó et al., 1985b), and inhibition of the afferent and l tion of B-type sensory neurons takes place within 1 after subcutaneous administration of capsaicin to adu
rats (Jancsó et al., 1985b), and inhibition of the afferer
and local effector functions of sensory neurons is ol
ser after subcutaneous administration of capsaicin to adult
rats (Jancsó et al., 1985b), and inhibition of the afferent
and local effector functions of sensory neurons is ob-
served within a few minutes to 1 h after capsaicin rats (Jancsó et al., 1985b), and inhibition of the afferent and local effector functions of sensory neurons is
served within a few minutes to 1 h after capsaicin tre
ment (Hayes et al., 1981b; Lembeck and Donnerer, 19
Bitt and local effector functions of sensory neurons is observed within a few minutes to 1 h after capsaicin treatment (Hayes et al., 1981b; Lembeck and Donnerer, 1981; Bittner and LaHann, 1985; Maggi et al., 1987d; Dickenson e served within a few minutes to 1 h after capsaicin treatment (Hayes et al., 1981b; Lembeck and Donnerer, 1981; Bittner and LaHann, 1985; Maggi et al., 1987d; Dickenson et al., 1990a,b). In contrast, depletion of substance ment (Hayes et al., 1981b; Lembeck and Donnerer, 1981; Bittner and LaHann, 1985; Maggi et al., 1987d; Dickenson et al., 1990a,b). In contrast, depletion of substance P from peripheral targets of sensory neurons is not appr Bittner and LaHann, 1985; Maggi et al., 1987d; Dickenson et al., 1990a,b). In contrast, depletion of substance
P from peripheral targets of sensory neurons is not
appreciable until 3 h posttreatment (Bittner and La-Hann, 1 son et al., 1990a,b). In contrast, depletion of substance P from peripheral targets of sensory neurons is not appreciable until 3 h posttreatment (Bittner and La-Hann, 1985; Maggi et al., 1987d,e) or later (Lembeck and Don P from peripheral targets of sensory neurons is not
appreciable until 3 h posttreatment (Bittner and La-
Hann, 1985; Maggi et al., 1987d,e) or later (Lembeck and
Donnerer, 1981). Peptide depletion from the sensory
ganglia appreciable until 3 h posttreatment (Bittner and La
Hann, 1985; Maggi et al., 1987d,e) or later (Lembeck an
Donnerer, 1981). Peptide depletion from the sensor
ganglia of adult rats can be preceded by an increase is
the gan Hann, 1985; Maggi et al., 1987d,e) or later (Lembeck and Donnerer, 1981). Peptide depletion from the sensory ganglia of adult rats can be preceded by an increase in the ganglionic levels of substance P (Lembeck and Donnere Donnerer, 1981). Peptide depletion from the sensory
ganglia of adult rats can be preceded by an increase in
the ganglionic levels of substance P (Lembeck and Don-
nerer, 1981; Gamse et al., 1981b; Geppetti et al., 1988a)
a ganglia of adult rats can be preceded by an increase is
the ganglionic levels of substance P (Lembeck and Don
nerer, 1981; Gamse et al., 1981b; Geppetti et al., 1988a
and calcitonin gene-related peptide (Geppetti et al
198 e ganglionic levels of substance P (Lembeck and Don-
rer, 1981; Gamse et al., 1981b; Geppetti et al., 1988a)
d calcitonin gene-related peptide (Geppetti et al.,
88a) during the first 4 days after capsaicin treatment.
v. Se nerer, 1981; Gamse et al., 1981b; Geppetti et al., 1988a)
and calcitonin gene-related peptide (Geppetti et al.,
1988a) during the first 4 days after capsaicin treatment.
v. Selectivity of the action of capsaicin. The cap-

and calcitonin gene-related peptide (Geppetti et al., 1988a) during the first 4 days after capsaicin treatment.

v. Selectivity of the action of capsaicin. The capsaicin-induced depletion of substance P appears to be restr 1988a) during the first 4 days after capsaicin treatment.

v. Selectivity of the action of capsaicin. The cap-

saicin-induced depletion of substance P appears to be

restricted to areas containing primary afferent neurons v. Selectivity of the action of capsaicin. The capsaicin-induced depletion of substance P appears to b restricted to areas containing primary afferent neuron because the peptide concentrations in the ventral spinacord and saicin-induced depletion of substance P appears to be restricted to areas containing primary afferent neurons because the peptide concentrations in the ventral spinal cord and in the brain above the brainstem remain unaffe restricted to areas containing primary afferent neurons
because the peptide concentrations in the ventral spinal
cord and in the brain above the brainstem remain unaf-
fected (Hayes and Tyers, 1980; Gamse et al., 1981b;
Ga because the peptide concentrations in the ventral spinal
cord and in the brain above the brainstem remain unaf-
fected (Hayes and Tyers, 1980; Gamse et al., 1981b;
Gamse, 1982; Virus et al., 1982). Similarly, levels of
glu fected (Hayes and Tyers, 1980; Gamse et al., 1981b; Gamse, 1982; Virus et al., 1982). Similarly, levels of glutamic acid decarboxylase and choline acetyltransferase in the dorsal spinal cord (Jessell et al., 1978; Holzer-P fected (Hayes and Tyers, 1980; Gamse et al., 19
Gamse, 1982; Virus et al., 1982). Similarly, leve
glutamic acid decarboxylase and choline acetyltran
ase in the dorsal spinal cord (Jessell et al., 1978; Ho
Petsche et al., 1 Gamse, 1982; Virus et al., 1982). Similarly, levels of glutamic acid decarboxylase and choline acetyltransfer-
ase in the dorsal spinal cord (Jessell et al., 1978; Holzer-
Petsche et al., 1986) and of neurotensin and methi glutamic acid decarboxylase and choline acetyltransfer-
ase in the dorsal spinal cord (Jessell et al., 1978; Holzer-
Petsche et al., 1986) and of neurotensin and methionine-
enkephalin in the central nervous system (Gamse ase in the dorsal spinal cord (Jessell et al., 1978; Holzer-
Petsche et al., 1986) and of neurotensin and methionine-
enkephalin in the central nervous system (Gamse et al.,
1981b; Priestley et al., 1982) are not altered b Petsche et al., 1986) and of neurotensin and methionine-
enkephalin in the central nervous system (Gamse et al.,
1981b; Priestley et al., 1982) are not altered by capsaicin
treatment of adult rats. The tissue concentration enkephalin in the central nervous system (Gamse et al.,

1981b; Priestley et al., 1982) are not altered by capsaicin

treatment of adult rats. The tissue concentrations of

moradrenaline, dopamine, and 5-hydroxytryptamine 1981b; Priestley et al., 1982) are not altered by capsaicin
treatment of adult rats. The tissue concentrations of
noradrenaline, dopamine, and 5-hydroxytryptamine in
the spinal cord and brain either stay unchanged (Hajós
e treatment of adult rats. The tissue concentrations
noradrenaline, dopamine, and 5-hydroxytryptamine
the spinal cord and brain either stay unchanged (Haj
et al., 1986b) or may even increase (Virus et al., 1983)
response to noradrenaline, dopamine, and 5-hydroxytryptamine in
the spinal cord and brain either stay unchanged (Hajós
et al., 1986b) or may even increase (Virus et al., 1983) in
response to systemic capsaicin application. This obserthe spinal cord and brain either stay unchange
et al., 1986b) or may even increase (Virus et al.,
response to systemic capsaicin application. Th
vation indicates that monoamine systems in th
nervous system are not damaged al., 1986b) or may even increase (Virus et al., 1983) in sponse to systemic capsaicin application. This obsertion indicates that monoamine systems in the central rvous system are not damaged by the drug.
A synopsis of the

response to systemic capsaicin application. This observation indicates that monoamine systems in the central
nervous system are not damaged by the drug.
A synopsis of the literature supports the assumption
that the neuroto vation indicates that monoamine systems in the central
nervous system are not damaged by the drug.
A synopsis of the literature supports the assumption
that the neurotoxic effect of capsaicin given to adult rats
is more se nervous system are not damaged by the drug.
A synopsis of the literature supports the assumption
that the neurotoxic effect of capsaicin given to adult rats
is more selective for fine sensory neurons than when
given to new A synopsis of the literature supports the assumption
that the neurotoxic effect of capsaicin given to adult rats
is more selective for fine sensory neurons than when
given to newborn rats. This contention derives from the
 that the neurotoxic effect of capsaicin given to adult rats
is more selective for fine sensory neurons than when
given to newborn rats. This contention derives from the
relative inability of the drug to induce secondary ch is more selective for fine sensory neurons than when
given to newborn rats. This contention derives from the
relative inability of the drug to induce secondary changes
in sensory neuron-related systems of the adult rat, a
 given to newborn rats. This contention derives from the relative inability of the drug to induce secondary changes in sensory neuron-related systems of the adult rat, a finding that could be due to the weak effect of capsa relative inability of the drug to induce secondary changes
in sensory neuron-related systems of the adult rat, a
finding that could be due to the weak effect of capsaicin
in producing morphological ablation of primary affe in sensory neuron-related systems of the adult rat, a finding that could be due to the weak effect of capsaiciin producing morphological ablation of primary afferen neurons and/or to the lack of plasticity of the nervousy finding that could be due to the weak effect of capsaicin
in producing morphological ablation of primary afferent
neurons and/or to the lack of plasticity of the nervous
system in the adult animal. However, a systematic co

aspet

CAPSA
yet been made, and there is some indirect evidence that
capsaicin treatment of adult rats can lead to functional CAP:
yet been made, and there is some indirect evidence that
capsaicin treatment of adult rats can lead to functional
changes in both the central and autonomic nervous sys-CAP:
yet been made, and there is some indirect evidence that
capsaicin treatment of adult rats can lead to functional
changes in both the central and autonomic nervous sys-
tems (Jancsó-Gábor, 1980; Miller et al., 1983; Ho yet been made, and there is some indirect evidence that capsaicin treatment of adult rats can lead to functional changes in both the central and autonomic nervous systems (Jancsó-Gábor, 1980; Miller et al., 1983; Holzer, 1 yet been made, and there is some indirect evidence the capsaicin treatment of adult rats can lead to function
changes in both the central and autonomic nervous s
tems (Jancsó-Gábor, 1980; Miller et al., 1983; Holz
1986) as psaicin treatment of adult rats can lead to functional
anges in both the central and autonomic nervous sys-
ms (Jancsó-Gábor, 1980; Miller et al., 1983; Holzer, (86)
as well as nonneural tissues (Cui et al., 1990).
The abs

changes in both the central and autonomic nervous systems (Jancsó-Gábor, 1980; Miller et al., 1983; Holzer 1986) as well as nonneural tissues (Cui et al., 1990).
The absence of any capsaicin-induced depletion oneurochemica tems (Jancsó-Gábor, 1980; Miller et al., 1983; Holzer, 1986) as well as nonneural tissues (Cui et al., 1990).
The absence of any capsaicin-induced depletion of neurochemical markers from central neurons is at variance with 1986) as well as nonneural tissues (Cui et al., 1990). 1
The absence of any capsaicin-induced depletion of the
neurochemical markers from central neurons is at variance with the finding that intraperitoneal administration The absence of any capsaicin-induced depletion of the
neurochemical markers from central neurons is at vari-
ance with the finding that intraperitoneal administration
of 50 to 90 mg/kg capsaicin to adult rats can induce
an neurochemical markers from central neurons is at vari-
spinal cord and be finding that intraperitoneal administration
of 50 to 90 mg/kg capsaicin to adult rats can induce
nerve terminal degeneration not only in areas of th of 50 to 90 mg/kg capsaicin to adult rats can induce
nerve terminal degeneration not only in areas of the
spinal cord and brainstem known to be innervated by
primary sensory neurons but also in certain discrete fore-
and h nerve terminal degeneration not only in areas of the nerve terminal degeneration not only in areas of the spinal cord and brainstem known to be innervated primary sensory neurons but also in certain discrete for and hindbrain areas not yet associated with terminatio of prima spinal cord and brainstem known to be innervated b
primary sensory neurons but also in certain discrete fore
and hindbrain areas not yet associated with termination
of primary afferents (Ritter and Dinh, 1988). The obser
v and hindbrain areas not yet associated with termination of primary afferents (Ritter and Dinh, 1988). The obsevation of degenerating cell bodies in the ventromed midbrain tegmentum, supramammillary nucleus, a posterior hy of primary afferents (Ritter and Dinh, 1988). The obser-
vation of degenerating cell bodies in the ventromedial tion
midbrain tegmentum, supramammillary nucleus, and nun
posterior hypothalamus points to a permanent destruc vation of degenerating cell bodies in the ventromedial timidbrain tegmentum, supramammillary nucleus, and n
posterior hypothalamus points to a permanent destruc- di
tion of some central neurons by capsaicin (Ritter and P
D midbrain tegmentum, supramammillary nucleus, and nuposterior hypothalamus points to a permanent destruc-
tion of some central neurons by capsaicin (Ritter and P
Dinh, 1988). Because capsaicin-induced degeneration of ap
cen tion of some central neurons by capsaicin (Ritter and Dinh, 1988). Because capsaicin-induced degeneration of central neurons has been reported by one research group only (Dinh and Ritter, 1987; Ritter and Dinh, 1988, tion of some central neurons by capsaicin (Ritter and I
Dinh, 1988). Because capsaicin-induced degeneration of
central neurons has been reported by one research group
ionly (Dinh and Ritter, 1987; Ritter and Dinh, 1988, p
 Dinh, 1988). Because capsaici
central neurons has been repo
only (Dinh and Ritter, 1987
1990), it will be important to
by an independent laboratory
One group of central neur

only (Dinh and Ritter, 1987; Ritter and Dinh, 1988, precedent 1990), it will be important to see this finding confirmed 19
by an independent laboratory. The proper of central neurons that have long been being recognized as 1990), it will be important to see this finding confirmed
by an independent laboratory. $\frac{1}{2}$
One group of central neurons that have long been
recognized as being sensitive to capsaicin lie in the
preoptic region of t by an independent laboratory.

One group of central neurons that have long beer

recognized as being sensitive to capsaicin lie in the

preoptic region of the hypothalamus. Administration

30 to 70 mg/kg capsaicin to adult One group of central neurons that have long been berecognized as being sensitive to capsaicin lie in the opreoptic region of the hypothalamus. Administration of as 30 to 70 mg/kg capsaicin to adult rats produces ultra-
st recognized as being sensitive to capsaicin lie in the preoptic region of the hypothalamus. Administration of 30 to 70 mg/kg capsaicin to adult rats produces ultrastructural changes in these neurons including swelling of mi preoptic region of the hypothalamus. Administration of affection of any approximation of a structural changes in these neurons including swelling of not mitochondria (Szolcsányi et al., 1971). These neurons follower though 30 to 70 mg/kg capsaicin to adult rats produces ul structural changes in these neurons including swellin mitochondria (Szolcsányi et al., 1971). These neurons are thought to be thermosensitive neurons involved central the structural changes in these neurons including swelling
mitochondria (Szolcsányi et al., 1971). These neuro:
are thought to be thermosensitive neurons involved
central thermoregulation (Szolcsányi, 1982). Investig
tion of t mitochondria (Szolcsányi et al., 1971). These neurons
are thought to be thermosensitive neurons involved in
central thermoregulation (Szolcsányi, 1982). Investiga-
tion of the effect of capsaicin on thermoregulation, there are thought to be thermosensitive neurons involved in
central thermoregulation (Szolcsányi, 1982). Investiga-
tion of the effect of capsaicin on thermoregulation, there-
fore, is complicated by the fact that both periphera central thermoregulation (Szolcsányi, 1982). Investiga-
tion of the effect of capsaicin on thermoregulation, there-
fore, is complicated by the fact that both peripheral C-
fiber warmth receptors and central thermosensitiv tion of the effect of capsaicin on thermoregulation, there-
fore, is complicated by the fact that both peripheral C-
fiber warmth receptors and central thermosensitive neu-
rons are affected by the drug (for reviews see Sz fore, is complicated by the fact that both peripheral C-
fiber warmth receptors and central thermosensitive neu-
rons are affected by the drug (for reviews see Szolcsányi,
1982; Hori, 1984). Whereas warmth sensitivity medi fiber warmth receptors and central thermosensitive neu-
rons are affected by the drug (for reviews see Szolcsányi, ind
1982; Hori, 1984). Whereas warmth sensitivity mediated to !
by primary afferents is impaired by capsaic rons are affected by the drug (for reviews see Szolcsi
1982; Hori, 1984). Whereas warmth sensitivity medi
by primary afferents is impaired by capsaicin treatr
of both newborn and adult rats (Hajós et al., 1986a),
treatment 1982; Hori, 1984). Whereas warmth sensitivity mediated
by primary afferents is impaired by capsaicin treatment
of both newborn and adult rats (Hajós et al., 1986a), only
treatment of adult rats produces a long-term defunct by primary afferents is impaired by capsaicin treatment
of both newborn and adult rats (Hajós et al., 1986a), only
treatment of adult rats produces a long-term defunction-
alization of central thermosensitive neurons (Hori of both newborn and adult rats (Hajós et al., 1986a), only
treatment of adult rats produces a long-term defunction-
alization of central thermosensitive neurons (Hori, 1981;
Dib, 1983; Hajós et al., 1983; Obál et al., 1983 treatment of adult rats produces a long-term defunction-
alization of central thermosensitive neurons (Hori, 1981;
Dib, 1983; Hajós et al., 1983; Obál et al., 1983). Likewise,
only treatment of adult but not newborn rats w alization of central thermosensitive neurons (Hori, 1981; (Hori, 1983; Hajós et al., 1983; Obál et al., 1983). Likewise, (Hori, 1983; Obál et al., 1983). Likewise, (Hori) treatment of adult but not newborn rats with system Dib, 1983; Hajós et al., 1983; Obál et al., 1983). Likewise, (B
only treatment of adult but not newborn rats with systemic capsaicin abolishes the increases in the synthesis fect
rate and tissue level of monoamines produce only treatment of adult but not newborn
temic capsaicin abolishes the increases is
rate and tissue level of monoamines pro
capsaicin application in the area of the
and hypothalamus (Hajós et al., 1986b).
The enteric nervou mic capsaicin abolishes the increases in the synthesis fect
te and tissue level of monoamines produced by acute rela
psaicin application in the area of the preoptic region al.,
d hypothalamus (Hajós et al., 1986b). (Bu
The

capsaicin application in the area of the preoptic region all
and hypothalamus (Hajós et al., 1986b). (H
The enteric nervous system seems to be spared by (
(treatment of adult rats with capsaicin unless excessively T
high d and hypothalamus (Hajós et al., 1986b).
The enteric nervous system seems to be spared by
treatment of adult rats with capsaicin unless excessively
high doses (950 mg/kg) are used. Such doses can cause
the disappearance of The enteric nervous system seems to be spared by
treatment of adult rats with capsaicin unless excessively
high doses (950 mg/kg) are used. Such doses can cause
the disappearance of some nerve fibers containing sub-
stance treatment of adult rats with capsaicin unless excessively Thigh doses (950 mg/kg) are used. Such doses can cause p
the disappearance of some nerve fibers containing sub-
stance P from the myenteric plexus of the small inte degeneration of axon terminals seen in the enteric plexstance P from the myenteric plexus of the small intestine (Harti, 1988). There is no direct evidence that enteric neurons are damaged by 50 mg/kg capsaicin because the degeneration of axon terminals seen in the enteric ple (Harti, 1988). There is no direct evidence that enteric p
neurons are damaged by 50 mg/kg capsaicin because the d
degeneration of axon terminals seen in the enteric plex-
ness probably reflects destruction of primary affer

ICIN
of substance P and calcitonin gene-related peptide in the
enteric nervous system remain unaltered (Holzer et al., enteric 159
159 of substance P and calcitonin gene-related peptide in the
enteric nervous system remain unaltered (Holzer et al.,
1980; Geppetti et al., 1988a). Furthermore, morphological 15
15
1980; Geppetti et al., 1988a). Furthermore, morphological
1980; Geppetti et al., 1988a). Furthermore, morphologica
(Szolcsányi et al., 1975) and functional (Stein et al. of substance P and calcitonin gene-related peptide in the enteric nervous system remain unaltered (Holzer et al., 1980; Geppetti et al., 1988a). Furthermore, morphological (Szolcsányi et al., 1975) and functional (Stein et of substance P and calcitonin gene-related peptide in tenteric nervous system remain unaltered (Holzer et 1980; Geppetti et al., 1988a). Furthermore, morphologi (Szolcsányi et al., 1975) and functional (Stein et 1986) obse enteric nervous system remain unaltered (Holzer et a 1980; Geppetti et al., 1988a). Furthermore, morphologic (Szolcsányi et al., 1975) and functional (Stein et a 1986) observations indicate that neurons of the sympethetic (Szolcsányi et al., 1975) and functional (Stein et al., 1986) observations indicate that neurons of the sympathetic nervous system are not susceptible to the neurotoxic action of capsaicin in the adult rat.
b. GUINEA PIG. zolcsányi et al., 1975) and functional (Stein et 86) observations indicate that neurons of the synetic nervous system are not susceptible to the ne
xic action of capsaicin in the adult rat.
b. GUINEA PIG. **i. Morphological**

and hindbrain areas not yet associated with terminations 1984). Perivascular nerve endings containing substance
of primary afferents (Ritter and Dinh, 1988). The obser-
 P deteriorate within 5 min after the subcutaneous central neurons has been reported by one research group is in keeping with virtually irreversible functional deficits
only (Dinh and Ritter, 1987; Ritter and Dinh, 1988, produced by capsaicin in the adult guinea pig (Jancs 1986) observations indicate that neurons of the sympathetic nervous system are not susceptible to the neuro-
toxic action of capsaicin in the adult rat.
b. GUINEA PIG. **i. Morphological, neurochemical,**
and histochemical c thetic nervous system are not susceptible to the neuro-
toxic action of capsaicin in the adult rat.
b. GUINEA PIG. **i. Morphological, neurochemical,**
and histochemical changes. Systemic administration
of capsaicin to adult toxic action of capsaicin in the adult rat.
b. GUINEA PIG. **i. Morphological, neurochemica**
and histochemical changes. Systemic administration
f capsaicin to adult guinea pigs produces extensive ax
terminal degeneration in b. GUINEA PIG. i. **Morphological**, neurochemical,
and histochemical changes. Systemic administration
of capsaicin to adult guinea pigs produces extensive axon
terminal degeneration in the dorsal spinal cord, brain-
stem (J and histochemical changes. Systemic administration
of capsaicin to adult guinea pigs produces extensive axon
terminal degeneration in the dorsal spinal cord, brain-
stem (Jancsó et al., 1987a), and periphery (Papka et al.
 of capsaicin to adult guinea pigs produces extensive axon
terminal degeneration in the dorsal spinal cord, brain-
stem (Jancsó et al., 1987a), and periphery (Papka et al. terminal degeneration in the dorsal spinal cord, brain-
stem (Jancsó et al., 1987a), and periphery (Papka et al.
1984). Perivascular nerve endings containing substance
P deteriorate within 5 min after the subcutaneous inje stem (Jancsó et al., 1987a), and periphery (Papka et al.
1984). Perivascular nerve endings containing substance
P deteriorate within 5 min after the subcutaneous injec-
tion of 50 mg/kg capsaicin, and by 4 h posttreatment 1984). Perivascular nerve endings containing substance P deteriorate within 5 min after the subcutaneous injection of 50 mg/kg capsaicin, and by 4 h posttreatment the number of substance P-containing nerve fibers is visibl P deteriorate within 5 min after the subcutaneous injection of 50 mg/kg capsaicin, and by 4 h posttreatment the number of substance P-containing nerve fibers is visibly diminished (Papka et al., 1984). Depletion of substan tion of 50 mg/kg capsaicin, and by 4 h posttreatment the
number of substance P-containing nerve fibers is visibly
diminished (Papka et al., 1984). Depletion of substance
P and ultrastructural signs of axon degeneration are number of substance P-containing nerve fibers is visibly diminished (Papka et al., 1984). Depletion of substance P and ultrastructural signs of axon degeneration are appreciable for at least 1 year (Papka et al., 1984), wh diminished (Papka et al., 1984). Depletion of substance
P and ultrastructural signs of axon degeneration are
appreciable for at least 1 year (Papka et al., 1984), which
is in keeping with virtually irreversible functional P and ultrastructural signs of axon degeneration are
appreciable for at least 1 year (Papka et al., 1984), which
is in keeping with virtually irreversible functional deficits
produced by capsaicin in the adult guinea pig (appreciable for at least 1 year (Papka et al., 1984), which
is in keeping with virtually irreversible functional deficits
produced by capsaicin in the adult guinea pig (Jancsó,
1968; Jancsó-Gábor et al., 1970). Quantitativ is in keeping with virtually irreversible functional deficits
produced by capsaicin in the adult guinea pig (Jancsó,
1968; Jancsó-Gábor et al., 1970). Quantitatively, a dose
of 2.5 mg/kg capsaicin given subcutaneously appe produced by capsaicin in the adult guinea pig (Jancsó,
1968; Jancsó-Gábor et al., 1970). Quantitatively, a dose
of 2.5 mg/kg capsaicin given subcutaneously appears to
be suprathreshold, whereas 10 mg/kg capsaicin is capab of 2.5 mg/kg capsaicin given subcutaneously appears to be suprathreshold, whereas 10 mg/kg capsaicin is capable of producing maximal depletion of substance P from afferent neurons (Miller et al., 1982b; Buck et al., 1983) of 2.5 mg/kg capsaicin given subcutaneously appears to
be suprathreshold, whereas 10 mg/kg capsaicin is capable
of producing maximal depletion of substance P from
afferent neurons (Miller et al., 1982b; Buck et al., 1983) be suprathreshold, whereas 10 mg/kg capsaicin is capable
of producing maximal depletion of substance P from
afferent neurons (Miller et al., 1982b; Buck et al., 1983).
With low doses of capsaicin $(\leq 5 \text{ mg/kg})$ depletion d afferent neurons (Miller et al., 1982b; Buck et al., 1983).
With low doses of capsaicin $(\leq 5 \text{ mg/kg})$ depletion does
not become apparent before 2 days posttreatment, but
following administration of 50 mg/kg capsaicin the afferent neurons (Miller et al., 1982b; Buck et al., 1983).
With low doses of capsaicin $(\leq 5 \text{ mg/kg})$ depletion does
not become apparent before 2 days posttreatment, but
following administration of 50 mg/kg capsaicin the With low doses of capsaicin $(\leq 5 \text{ mg/kg})$ depletion does
not become apparent before 2 days posttreatment, but
following administration of 50 mg/kg capsaicin the sub-
stance P content of dorsal root ganglia and dorsal spin tion of 50 mg/kg capasicin, and by 4 h posttreatment the number of substance P-containing nerve fibers is visibly diminished (Papka et al., 1984). Depletion of substance P and ultrastructural signs of axon degeneration ar following administration of 50 mg/kg capsaicin the sub
stance P content of dorsal root ganglia and dorsal spina
cord is significantly diminished within 12 h (Buck et al.
1983). Depletion of substance P proceeds with time t stance P content of dorsal root ganglia and dorsal spinal
cord is significantly diminished within 12 h (Buck et al.,
1983). Depletion of substance P proceeds with time to
reach a maximum of 10 days after capsaicin treatmen cord is significantly diminished within 12 h (Buck et al., 1983). Depletion of substance P proceeds with time to reach a maximum of 10 days after capsaicin treatment.
The loss of substance P from the dorsal root ganglia i 1983). Depletion of substance P proceeds with time to reach a maximum of 10 days after capsaicin treatment.
The loss of substance P from the dorsal root ganglia induced by 10 mg/kg capsaicin can be approximately 80 to 90% reach a maximum of 10 days after capsaicin treatment.
The loss of substance P from the dorsal root ganglia
induced by 10 mg/kg capsaicin can be approximately 80
to 90%; this degree of depletion is not surpassed even by
dos The loss of substance P from the dorse
induced by 10 mg/kg capsaicin can be app
to 90%; this degree of depletion is not sur-
doses up to 1250 mg/kg capsaicin (Gams
Miller et al., 1982a,b; Buck et al., 1983).
The tissue lev duced by 10 mg/kg capsaicin can be approximately 80
90%; this degree of depletion is not surpassed even by
ses up to 1250 mg/kg capsaicin (Gamse et al., 1981c;
iller et al., 1982a,b; Buck et al., 1983).
The tissue levels o

capsaicin application in the area of the preoptic region al., 1985; Franco-Cereceda et al., 1987b), cholecystokinin
and hypothalamus (Hajós et al., 1986b). (Buck et al., 1983; Gibbins et al., 1987), and dynorphin
The enter the disappearance of some nerve fibers containing sub-
stance P from the myenteric plexus of the small intestine cord, dorsal roots, sensory ganglia, afferent nerves, and
(Harti, 1988). There is no direct evidence that ent to 90%; this degree of depletion is not surpassed even by doses up to 1250 mg/kg capsaicin (Gamse et al., 1981c; Miller et al., 1982a,b; Buck et al., 1983).
The tissue levels of vasoactive intestinal polypeptide (Buck et a doses up to 1250 mg/kg capsaicin (Gamse et al., 1981c;
Miller et al., 1982a,b; Buck et al., 1983).
The tissue levels of vasoactive intestinal polypeptide
(Buck et al., 1983; Della et al., 1983) and somatostatin
(Buck et al Miller et al., 1982a,b; Buck et al., 1983).
The tissue levels of vasoactive intestinal polypeptide
(Buck et al., 1983; Della et al., 1983) and somatostatin
(Buck et al., 1983) and those of substance P in the ventral
spinal The tissue levels of vasoactive intestinal polypeptic
(Buck et al., 1983; Della et al., 1983) and somatostati
(Buck et al., 1983) and those of substance P in the ventra
spinal cord and brain above the brainstem are not a
f (Buck et al., 1983) and those of substance P in the ventral spinal cord and brain above the brainstem are not affected (Buck et al., 1983). However, calcitonin gene-(Buck et al., 1983) and those of substance P in the ventral
spinal cord and brain above the brainstem are not af-
fected (Buck et al., 1983). However, calcitonin gene-
related peptide (Gibbins et al., 1985, 1987; Lundberg spinal cord and brain above the brainstem are not af-
fected (Buck et al., 1983). However, calcitonin gene-
related peptide (Gibbins et al., 1985, 1987; Lundberg et
al., 1985; Franco-Cereceda et al., 1987b), cholecystokini fected (Buck et al., 1983). However, calcitonin gene-
related peptide (Gibbins et al., 1985, 1987; Lundberg et
al., 1985; Franco-Cereceda et al., 1987b), cholecystokinin
(Buck et al., 1983; Gibbins et al., 1987), and dynor al., 1985; Franco-Cereceda et al., 1987b), cholecystokinin al., 1985; Franco-Cereceda et al., 1987b), cholecystokinin (Buck et al., 1983; Gibbins et al., 1987), and dynorphin (Gibbins et al., 1987) are depleted from sensory neurons.
The loss of substance P and calcitonin gene-rela (Buck et al., 1983; Gibbins et al., 1987), and dynorphin
(Gibbins et al., 1987) are depleted from sensory neurons.
The loss of substance P and calcitonin gene-related
peptide is seen in all areas containing primary afferen (Gibbins et al., 1987) are depleted from sensory neurons.
The loss of substance P and calcitonin gene-related
peptide is seen in all areas containing primary afferent
pathways including medulla oblongata, dorsal spinal
cor The loss of substance P and calcitonin gene-related
peptide is seen in all areas containing primary afferent
pathways including medulla oblongata, dorsal spinal
cord, dorsal roots, sensory ganglia, afferent nerves, and
per pathways including medulla oblongata, dorsal spinal pathways including medulla oblongata, dorsal spinal
cord, dorsal roots, sensory ganglia, afferent nerves, and
peripheral targets of sensory neurons such as skin, car-
diovascular system, respiratory tract, urogenital syste cord, dorsal roots, sensory ganglia, afferent nerves, and
peripheral targets of sensory neurons such as skin, car-
diovascular system, respiratory tract, urogenital system,
and parasympathetic and sympathetic ganglia (Gams peripheral targets of sensory neurons such as skin, cardiovascular system, respiratory tract, urogenital system,
and parasympathetic and sympathetic ganglia (Gamse et
al., 1981c; Furness et al., 1982; Matthews and Cuello,

PHARMACOLOGICAL REVIEWS

160
 HOLZER
 **al., 1984; Gibbins et al., 1985, 1987; Lundberg et al., 1985; adults than those pretreated as neonates, the degree of

Franco-Cereceda et al., 1987b).** substance P depletion from the spinal cord and sciati 160
al., 1984; Gibbins et al., 1985, 198
Franco-Cereceda et al., 1987b).
ii. Functional changes. The

HOLZE

1984; Gibbins et al., 1985, 1987; Lundberg et al., 1985; a

anco-Cereceda et al., 1987b).
 ii. Functional changes. The sensitivity of the cornea n

chemical noxious stimuli is abolished by the same g al., 1984; Gibbins et al., 1985, 1987; Lundberg et al., 1985; admonstrator-
Franco-Cereceda et al., 1987b).
 ii. Functional changes. The sensitivity of the cornea net

to chemical noxious stimuli is abolished by the same al., 1984; Gibbins et al., 1985, 1987; Lundberg et al., 1985;
Franco-Cereceda et al., 1987b).
 ii. Functional changes. The sensitivity of the cornea

to chemical noxious stimuli is abolished by the same

doses of capsaic Franco-Cereceda et al., 1987b).
 ii. Functional changes. The sensitivity of the cornea

to chemical noxious stimuli is abolished by the same

doses of capsaicin that reduce the substance P content

of sensory neurons (Bu ii. Functional changes. The sensitivity of the cornea ne
to chemical noxious stimuli is abolished by the same give
doses of capsaicin that reduce the substance P content the
of sensory neurons (Buck et al., 1983). Chemonoc to chemical noxious stimuli is abolished by the same
doses of capsaicin that reduce the substance P content
of sensory neurons (Buck et al., 1983). Chemonociception
came be impaired lifelong (Jancsó, 1960). Unlike in the
r doses of capsaicin that reduce the substance P content the of sensory neurons (Buck et al., 1983). Chemonociception cau may be impaired lifelong (Jancsó, 1960). Unlike in the 198 rat, capsaicin treatment of adult guinea pi of sensory neurons (Buck et al., 1983). Chemonociception
may be impaired lifelong (Jancsó, 1960). Unlike in the
rat, capsaicin treatment of adult guinea pigs also is
followed by cutaneous insensitivity to nonnoxious and
no may be impaired lifelong (Jancsó, 1960). Unlike in the rat, capsaicin treatment of adult guinea pigs also is followed by cutaneous insensitivity to nonnoxious and noxious heat, but these changes require doses of at least 1 rat, capsaicin treatment of adult guinea pigs also
followed by cutaneous insensitivity to nonnoxious a
noxious heat, but these changes require doses of at le
10 mg/kg capsaicin (Miller et al., 1982a; Buck et
1983). In cont followed by cutaneous insensitivity to nonnoxious and noxious heat, but these changes require doses of at least 10 mg/kg capsaicin (Miller et al., 1982a; Buck et al., 1983). In contrast, the cutaneous sensitivity to nonnox moxious heat, but these changes require doses of at least
10 mg/kg capsaicin (Miller et al., 1982a; Buck et al., a
1983). In contrast, the cutaneous sensitivity to nonnox-
is not changed by doses of capsaicin
mechanical st 10 mg/kg capsaicin (Miller et al., 1982a; Buck et al., an 1983). In contrast, the cutaneous sensitivity to nonnoxious and noxious cold and to nonnoxious and noxious comechanical stimuli is not changed by doses of capsaici ious and noxious cold and to nonnoxious and noxious corneal
mechanical stimuli is not changed by doses of capsaicin ment c
as high as 950 mg/kg (Buck et al., 1983). The loss of by exter
sensitivity to thermal noxious stimu mechanical stimuli is not changed by doses of capsaici
as high as 950 mg/kg (Buck et al., 1983). The loss of
sensitivity to thermal noxious stimuli induced by 50 mg
kg capsaicin precedes the depletion of substance P from
t as high as 950 mg/kg (Buck et al., 1983). The loss of b
sensitivity to thermal noxious stimuli induced by 50 mg/
kg capsaicin precedes the depletion of substance P from ju
the dorsal root ganglia (Miller et al., 1982a). L sensitivity to thermal noxious stimuli induced by 50 mg/kg capsaicin precedes the depletion of substance P from
the dorsal root ganglia (Miller et al., 1982a). Local effec-
tor functions of sensory nerve endings are also i kg capsaicin precedes the depletion of substance P from jet the dorsal root ganglia (Miller et al., 1982a). Local effec-
tor functions of sensory nerve endings are also inhibited roby systemic pretreatment of adult guinea the dorsal root ganglia (Miller et al., 1982a). Local effec-
tor functions of sensory nerve endings are also inhibited rab
by systemic pretreatment of adult guinea pigs with cap-
saicin, defunctionalization being best docu tor functions of sensory nerve endings are also inhibited
by systemic pretreatment of adult guinea pigs with cap-
saicin, defunctionalization being best documented for
the sensory nerve-mediated neurogenic inflammatory and by systemic pretreatment of adult guinea pigs with cap-
saicin, defunctionalization being best documented for
the sensory nerve-mediated neurogenic inflammatory and
constrictor processes in the respiratory tract (Szolcsány saicin, defunctionalization being besensory nerve-mediated neurogenic
constrictor processes in the respirate
and Barthó, 1982; Lundberg and Sar
et al., 1983b; Manzini et al., 1987).
iii. Selectivity of the action of constrictor processes in the respiratory tract (Szolcsányi
and Barthó, 1982; Lundberg and Saria, 1983, 1987; Saria
et al., 1983b; Manzini et al., 1987).
iii. Selectivity of the action of capsaicin. A selec-

constrictor processes in the respiratory tract (Szolcsányi tional Barthó, 1982; Lundberg and Saria, 1983, 1987; Saria no
et al., 1983b; Manzini et al., 1987). ey
iii. Selectivity of the action of capsaicin. A selec-
tive a and Barthó, 1982; Lundberg and Saria, 1983, 1987; Saria
et al., 1983b; Manzini et al., 1987).
iii. Selectivity of the action of capsaicin. A selec-
tive action of capsaicin on primary afferent neurons is
supported by the a et al., 1983b; Manzini et al., 1987).
 iii. Selectivity of the action of capsaicin. A selective action of capsaicin on primary afferent neurons is

supported by the absence of effects of capsaicin on non-

sensory centra iii. Selectivity of the action of capsaicin. A selective action of capsaicin on primary afferent neurons is supported by the absence of effects of capsaicin on nonsensory central neurons (Buck et al., 1983), autonomic offe tive action of capsaicin on primary afferent neurons is
supported by the absence of effects of capsaicin on non-
sensory central neurons (Buck et al., 1983), autonomic
efferent neurons (Matthews and Cuello, 1982; Della et
 supported by the absence of effects of capsaicin on non-
sensory central neurons (Buck et al., 1983), autonomic
efferent neurons (Matthews and Cuello, 1982; Della et
al., 1983), and enteric neurons (Gamse et al., 1981c;
Fu sensory central neurons (Buck et al., 1983), autonomic
efferent neurons (Matthews and Cuello, 1982; Della et
al., 1983), and enteric neurons (Gamse et al., 1981c;
Furness et al., 1982; Matthews and Cuello, 1982; Gibbins
et efferent neurons (Matthews and Cuello, 1982; Della et in
al., 1983), and enteric neurons (Gamse et al., 1981c; tid
Furness et al., 1982; Matthews and Cuello, 1982; Gibbins an
et al., 1985; Harti, 1988). Neurotransmission p al., 1983), and enteric neurons (Gamse et al., 1981c; tide a
Furness et al., 1982; Matthews and Cuello, 1982; Gibbins and is
et al., 1985; Harti, 1988). Neurotransmission processes of an
in autonomic efferent and enteric p Furness et al., 1982; Matthews and Cuello, 1982; Gibbins
et al., 1985; Harti, 1988). Neurotransmission processes
in autonomic efferent and enteric pathways also are
spared by capsaicin (Szolcsányi and Barthó, 1978; Barthó
 et al., 1985; Harti, 1988). Neurotransmission processes
in autonomic efferent and enteric pathways also are
spared by capsaicin (Szolcsányi and Barthó, 1978; Barthó
et al., 1982b; Donnerer et al., 1984; Szolcsányi, 1984b). in autonomic efferent and enteric pathways also are Cespared by capsaicin (Szolcsányi and Barthó, 1978; Barthó exect al., 1982b; Donnerer et al., 1984; Szolcsányi, 1984b). Alt is not known, however, whether the corneal and spared by capsaicin (Szolcsányi and Barthó, 1978; Barthó expet al., 1982b; Donnerer et al., 1984; Szolcsányi, 1984b). Alvi
It is not known, however, whether the corneal and cu-
taneous lesions produced by 950 mg/kg capsaic It is not known, however, whether the corneal and cutaneous lesions produced by 950 mg/kg capsaicin (Buck et al., 1983) reflect a trophic role of sensory neurons in these tissues or other effects of the drug. Capsaicin-It is not known, however, whether the corneal and cu-
taneous lesions produced by 950 mg/kg capsaicin (Buck 3. Effects of periaxonal administration of capsaicin. In
et al., 1983) reflect a trophic role of sensory neurons i taneous lesions produced by 950 mg/kg capsaicin (Buck et al., 1983) reflect a trophic role of sensory neurons in this these tissues or other effects of the drug. Capsaicincal
induced changes in the number of substance P-bi et al., 1983) reflect a trophic role of sensory neurons in these tissues or other effects of the drug. Capsaicin-
induced changes in the number of substance P-binding
sites in the vas deferens are considered to arise from these tissues or other effects of the drug. Capsaicin-
induced changes in the number of substance P-binding
sites in the vas deferens are considered to arise from the
elimination of presynaptic substance P receptors on sen sites in the vas deferens are considered to arise from the sensory neurons.

elimination of presynaptic substance P receptors on sen-

sory nerve endings and the upregulation of postsynaptic capsaicin to axons of afferent

the age of 2, 4, and 7 days and of adult mice with $50 \text{ mg}/$ compact al., 1989).

c. OTHER MAMMALS. Systemic treatment of mice at by

the age of 2, 4, and 7 days and of adult mice with 50 mg/ ror

kg capsaicin results in inhibition of thermo- and che- 1%

monociception, the magnitud c. OTHER MAMMALS. Systemic treatment of mice at the age of 2, 4, and 7 days and of adult mice with 50 mg/
kg capsaicin results in inhibition of thermo- and che-
monociception, the magnitude of which increases with
the age the age of 2, 4, and 7 days and of adult mice with 50 mg/ rom-
kg capsaicin results in inhibition of thermo- and che-
monociception, the magnitude of which increases with
ner-
the age at the time of the treatment (Gamse, 1 kg capsaicin results in inhibition of thermo- and che-
monociception, the magnitude of which increases with
the age at the time of the treatment (Gamse, 1982).
Chemonociception is almost completely abolished by
capsaicin t the age at the time of the treatment (Gamse, 1982).
Chemonociception is almost completely abolished by
capsaicin-treatment of 10-day-old or older mice (Gamse,
1982). Although the capsaicin-induced release of sub-
stance P the age at the time of the treatment (Gamse, 1982). s
Chemonociception is almost completely abolished by a
capsaicin treatment of 10-day-old or older mice (Gamse, ti
1982). Although the capsaicin-induced release of sub-
st Chemonociception is almost completely abolished by an capsaicin treatment of 10-day-old or older mice (Gamse, tic
1982). Although the capsaicin-induced release of sub-
stance P from the isolated spinal cord also is inhibit

1983). In contrast, the cutaneous sensitivity to nonnox-
is seen in the cornea, this effect being associated with
ious and noxious cold and to nonnoxious and noxious
corneal lesions (Fujita et al., 1984). Subcutaneous tre adults than those pretreated as neonates, the degree of ER
adults than those pretreated as neonates, the degree of
substance P depletion from the spinal cord and sciatic
nerve is the same. A lower dose of capsaicin, 10 mg/kg, ER
adults than those pretreated as neonates, the degree of
substance P depletion from the spinal cord and sciatic
nerve is the same. A lower dose of capsaicin, 10 mg/kg,
given to adult mice reduces the substance P content adults than those pretreated as neonates, the degree of substance P depletion from the spinal cord and sciatic nerve is the same. A lower dose of capsaicin, 10 mg/kg , given to adult mice reduces the substance P content adults than those pretreated as neonates, the degree of substance P depletion from the spinal cord and sciatic nerve is the same. A lower dose of capsaicin, 10 mg/kg, given to adult mice reduces the substance P content of substance P depletion from the spinal cord and sciatic
nerve is the same. A lower dose of capsaicin, 10 mg/kg,
given to adult mice reduces the substance P content of
the spinal cord, but not the sciatic nerve, and fails to nerve is the same. A lower dose of capsaicin, 10 mg/kg, given to adult mice reduces the substance P content of the spinal cord, but not the sciatic nerve, and fails to cause long-term changes in thermonociception (Gamse, 1 given to adult mice reduces the substance P content of
the spinal cord, but not the sciatic nerve, and fails to
cause long-term changes in thermonociception (Gamse,
1982). These observations suggest that primary afferent
n the spinal cord, but not the sciatic nerve, and fails to cause long-term changes in thermonociception (Gamse, 1982). These observations suggest that primary afferent neurons in the newborn mouse are not as susceptible to t cause long-term changes in thermonociception (Gamse, 1982). These observations suggest that primary afferent neurons in the newborn mouse are not as susceptible to the neurotoxic action of capsaicin as they are later in li neurons in the newborn mouse are not as susceptible to the neurotoxic action of capsaicin as they are later in life. However, morphological data concerning this issue are not yet available, except that a marked loss of axo neurons in the newborn mouse are not as susceptible to
the neurotoxic action of capsaicin as they are later in
life. However, morphological data concerning this issue
are not yet available, except that a marked loss of axo the neurotoxic action of capsaicin as they are later if life. However, morphological data concerning this issue are not yet available, except that a marked loss of axon is seen in the cornea, this effect being associated w life. However, morphological data concerning this issue
are not yet available, except that a marked loss of axons
is seen in the cornea, this effect being associated with
corneal lesions (Fujita et al., 1984). Subcutaneous are not yet available, except that a marked loss of axons
is seen in the cornea, this effect being associated with
corneal lesions (Fujita et al., 1984). Subcutaneous treat-
ment of adult cats with 50 mg/kg capsaicin is fo is seen in the cornea, this effect being associated with
corneal lesions (Fujita et al., 1984). Subcutaneous treat-
ment of adult cats with 50 mg/kg capsaicin is followed
by extensive axon terminal degeneration in areas of corneal lesions (Fujita et al., 1984). Subcutaneous treatment of adult cats with 50 mg/kg capsaicin is followed
by extensive axon terminal degeneration in areas of the
brainstem and spinal cord known to be the central proment of adult cats with 50 mg/kg capsaicin is followed
by extensive axon terminal degeneration in areas of the
brainstem and spinal cord known to be the central pro-
jection areas of primary sensory neurons (Jancsó et al., by extensive axon terminal degeneration in areas of the brainstem and spinal cord known to be the central projection areas of primary sensory neurons (Jancsó et al., 1987a). Injection of the same dose of capsaicin to adult brainstem and spinal cord known to be the central projection areas of primary sensory neurons (Jancsó et al., 1987a). Injection of the same dose of capsaicin to adult rabbits does not alter the heat thresholds of primary a jection areas of primary sensory neurons (Jancsó et al., 1987a). Injection of the same dose of capsaicin to adult rabbits does not alter the heat thresholds of primary afferent neurons in the saphenous nerve but abolishes 1987a). Injection of the same dose of capsaicin to a rabbits does not alter the heat thresholds of printifferent neurons in the saphenous nerve but abolithe acute excitatory effects of capsaicin application the skin (Lynn rabbits does not alter the heat thresholds of primary
afferent neurons in the saphenous nerve but abolishes
the acute excitatory effects of capsaicin application to
the skin (Lynn et al., 1984). Subcutaneous administra-
ti afferent neurons in the saphenous nerve but abolishes
the acute excitatory effects of capsaicin application to
the skin (Lynn et al., 1984). Subcutaneous administra-
tion of up to 280 mg/kg capsaicin to adult rabbits does
 the acute excitatory effects of capsaicin application to
the skin (Lynn et al., 1984). Subcutaneous administra-
tion of up to 280 mg/kg capsaicin to adult rabbits does
not alter the substance P content of the spinal cord a tion of up to 280 mg/kg capsaicin to adult rabbits does
not alter the substance P content of the spinal cord and
eye (Tervo, 1981) but reduces the miotic and hyperemic
effects of acute intracameral injection of capsaicin
(tion of up to 280 mg/kg capsaicin to adult rabbits does
not alter the substance P content of the spinal cord and
eye (Tervo, 1981) but reduces the miotic and hyperemic
effects of acute intracameral injection of capsaicin
(not alter the substance P content of the spinal cord and
eye (Tervo, 1981) but reduces the miotic and hyperemic
effects of acute intracameral injection of capsaicin
(Tervo, 1981) and the contractile effect of capsaicin on
 eye (Tervo, 1981) but reduces the miotic and hyperemic
effects of acute intracameral injection of capsaicin
(Tervo, 1981) and the contractile effect of capsaicin on
isolated bronchi (Manzini et al., 1990). Administration
o effects of acute intracameral injection of capsaicin (Tervo, 1981) and the contractile effect of capsaicin or isolated bronchi (Manzini et al., 1990). Administration of a cumulative dose of 50 mg/kg capsaicin to pigs resul (Tervo, 1981) and the contractile effect of capsaicin on isolated bronchi (Manzini et al., 1990). Administration of a cumulative dose of 50 mg/kg capsaicin to pigs results in a 50 to 90% depletion of calcitonin gene-relat isolated bronchi (Manzini et al., 1990). Administration
of a cumulative dose of 50 mg/kg capsaicin to pigs results
in a 50 to 90% depletion of calcitonin gene-related pep-
tide and neurokinin A from the skin, respiratory t of a cumulative dose of 50 mg/kg capsaicin to pigs result in a 50 to 90% depletion of calcitonin gene-related p
tide and neurokinin A from the skin, respiratory trand skeletal muscle and blocks the vasodilator eff
of an ac in a 50 to 90% depletion of calcitonin gene-related peptide and neurokinin A from the skin, respiratory tract, and skeletal muscle and blocks the vasodilator effect of an acute intradermal injection of capsaicin (Franco-Ce tide and neurokinin A from the skin, respiratory tract, and skeletal muscle and blocks the vasodilator effect of an acute intradermal injection of capsaicin (Franco-Cereceda and Lundberg, 1989; Alving et al., 1991) or expo and skeletal muscle and blocks the vasodilator effect
of an acute intradermal injection of capsaicin (Franco-
Cereceda and Lundberg, 1989; Alving et al., 1991) or
exposure to a capsaicin aerosol (Matran et al., 1990;
Alvin of an acute intra
Cereceda and Luexposure to a ca
Alving et al., 1991
are not available.
3. Effects of per Preceda and Lundberg, 1989; Alving et al., 1991) or

posure to a capsaicin aerosol (Matran et al., 1990;

ving et al., 1991). Data from other mammalian species

a not available.

3. Effects of periaxonal administration of

exposure to a capsaicin aerosol (Matran et al., 1990;
Alving et al., 1991). Data from other mammalian species
are not available.
3. Effects of periaxonal administration of capsaicin. In
this article, periaxonal or perineur Alving et al., 1991). Data from other mammalian species
are not available.
3. Effects of periaxonal administration of capsaicin. In
this article, periaxonal or perineural administration of
capsaicin denotes application of are not available.

3. Effects of periaxonal administration of capsaicin. In

this article, periaxonal or perineural administration of

capsaicin denotes application of the drug to nerve trunks

as opposed to application t 3. Effects of periaxonal administration of capsaicin. In this article, periaxonal or perineural administration of capsaicin denotes application of the drug to nerve trunks as opposed to application to cell bodies or ending

elimination of presynaptic substance P receptors on sen-
sory nerve endings and the upregulation of postsynaptic capsaicin to axons of afferent neurons not only results
receptors in response to sensory denervation (Mussap receptors in response to sensory denervation (Mussap et in acute excitation and reversible inhibition of nerve
al., 1989).
c. OTHER MAMMALS. Systemic treatment of mice at by long-term ablation of primary afferent C-fiber capsaicin denotes application of the drug to nerve trunks
as opposed to application to cell bodies or endings of
sensory neurons.
a. RAT. **i. Morphological changes.** Application of
capsaicin to axons of afferent neurons no as opposed to application to cell bodies or endings of
sensory neurons.
a. RAT. **i. Morphological changes.** Application of
capsaicin to axons of afferent neurons not only results
in acute excitation and reversible inhibiti sensory neurons.

a. RAT. **i. Morphological changes.** Application of

capsaicin to axons of afferent neurons not only results

in acute excitation and reversible inhibition of nerve

conduction in C- and some A-fibers but a. RAT. **i. Morphological changes.** Application of capsaicin to axons of afferent neurons not only results in acute excitation and reversible inhibition of nerve conduction in C - and some A-fibers but also is followed b capsaicin to axons of afferent neurons not only results
in acute excitation and reversible inhibition of nerve
conduction in C- and some A-fibers but also is followed
by long-term ablation of primary afferent C-fiber neu-
 in acute excitation and reversible inhibition of nerve
conduction in C- and some A-fibers but also is followed
by long-term ablation of primary afferent C-fiber neu-
rons. One to several days after periaxonal application o conduction in C- and some A-fibers but also is followed
by long-term ablation of primary afferent C-fiber neu-
rons. One to several days after periaxonal application of
 1% (33 mM) capsaicin to the saphenous and sciatic
 by long-term ablation of primary afferent C-fiber neurons. One to several days after periaxonal application of 1% (33 mM) capsaicin to the saphenous and sciation nerves swelling of numerous unmyelinated fibers is observed nerves swelling of numerous unmyelinated fibers is observed both distal and proximal to the application site, and 2 to 3 weeks posttreatment the structural organization of the nerves is changed (Handwerker et al., 1984; nerves swelling of numerous unmyelinated fibers is a served both distal and proximal to the application si and 2 to 3 weeks posttreatment the structural organition of the nerves is changed (Handwerker et al., 19 Jancsó et served both distal and proximal to the application site,
and 2 to 3 weeks posttreatment the structural organiza-
tion of the nerves is changed (Handwerker et al., 1984;
Jancsó et al., 1985a). This damage is confined to unm and 2 to 3 weeks posttreatment the structural organization of the nerves is changed (Handwerker et al., 1984; Jancsó et al., 1985a). This damage is confined to unmyelinated fibers (Handwerker et al., 1984) and involves the

PHARMACOLOGICAL REVIEWS

Lawson, 1990; Pini et al., 1990). Quantitatively, periax-CAPSA
Lawson, 1990; Pini et al., 1990). Quantitatively, periax-
onal administration of capsaicin to the rat saphenous
and sciatic nerves leads to a 34% reduction of cell bodies CAPSAIC
Lawson, 1990; Pini et al., 1990). Quantitatively, periax-

onal administration of capsaicin to the rat saphenous

and sciatic nerves leads to a 34% reduction of cell bodies

in the corresponding dorsal root ganglia Lawson, 1990; Pini et al., 1990). Quantitatively, periax-

onal administration of capsaicin to the rat saphenous ner

and sciatic nerves leads to a 34% reduction of cell bodies pol

in the corresponding dorsal root ganglia Lawson, 1990; Pini et al., 1990). Quantitatively, perional administration of capsaicin to the rat saphen
and sciatic nerves leads to a 34% reduction of cell bot
in the corresponding dorsal root ganglia (Jancsó a
Lawson, 19 onal administration of capsaicin to the rat saphenous
and sciatic nerves leads to a 34% reduction of cell bodies
in the corresponding dorsal root ganglia (Jancsó and
Lawson, 1990) and a 32 to 40% reduction of unmyeli-
nate and sciatic nerves leads to a 34% reduction of cell bodie
in the corresponding dorsal root ganglia (Jancsó and
Lawson, 1990) and a 32 to 40% reduction of unmyeli
nated fibers in the treated nerve (Lynn et al., 1987
Jancsó in the corresponding dorsal root ganglia (Jancsó and Lawson, 1990) and a 32 to 40% reduction of unmyeli-
nated fibers in the treated nerve (Lynn et al., 1987;
Jancsó and Lawson, 1990), whereas the number of mye-
linated fi Lawson, 1990) and a 32 to 40% reduction of unmyeli-
nated fibers in the treated nerve (Lynn et al., 1987;
Jancsó and Lawson, 1990), whereas the number of mye-
linated fibers remains unaltered. The degeneration ex-
tends tr nated fibers in the treated nerve (Lynn et al., 1987
Jancsó and Lawson, 1990), whereas the number of mye
linated fibers remains unaltered. The degeneration ex
tends transganglionically to the central terminals of sen
sory Jancsó and Lawson, 1990), whereas the number of myear-
linated fibers remains unaltered. The degeneration ex-
tends transganglionically to the central terminals of sen-
sory neurons in the dorsal spinal cord (Jancsó and La linated fibers remains unaltered. The degeneration ex-
tends transganglionically to the central terminals of sen-
sory neurons in the dorsal spinal cord (Jancsó and Law-
son, 1990). Thus, a considerable proportion of fine
 tends transganglionically to the ce
sory neurons in the dorsal spinal of
son, 1990). Thus, a considerable
afferent neurons is eliminated in a
capsaicin application in the rat.
ii. Neurochemical and histoc ry neurons in the dorsal spinal cord (Jancsó and Law-
ineuron, 1990). Thus, a considerable proportion of fine 198
ferent neurons is eliminated in response to periaxonal rom
posicin application in the rat. zeliu
ii. Neuroch

son, 1990). Thus, a considerable proportion of fine
afferent neurons is eliminated in response to periaxonal
capsaicin application in the rat.
ii. Neurochemical and histochemical changes. In
keeping with the degeneration o afferent neurons is eliminated in response to periaxor
capsaicin application in the rat.
ii. Neurochemical and histochemical changes.
keeping with the degeneration of thin afferent neuror
the neurochemical changes caused b capsaicin application in the rat.
 ii. Neurochemical and histochemical changes. In

keeping with the degeneration of thin afferent neurons,

the neurochemical changes caused by periaxonal capsai-

cin persist for a long ii. Neurochemical and histochemical changes. In
keeping with the degeneration of thin afferent neurons,
the neurochemical changes caused by periaxonal capsai-
cin persist for a long time (Jancsó and Lawson, 1988).
Three mo keeping with the degeneration of thin afferent neurons, if the neurochemical changes caused by periaxonal capsaicin persist for a long time (Jancsó and Lawson, 1988).
Three months after application of capsaicin to the rat the neurochemical changes caused by periaxonal capsaicin persist for a long time (Jancsó and Lawson, 1988).
Three months after application of capsaicin to the rat sciatic nerves, the proportions of small-sized cell bodies
 cin persist for a long time (Jancsó and Lawson, 1988). get
Three months after application of capsaicin to the rat
sciatic nerves, the proportions of small-sized cell bodies
Simmunoreactive for substance P, calcitonin gene-Three months after application of capsaicin to the rat
sciatic nerves, the proportions of small-sized cell bodies
immunoreactive for substance P, calcitonin gene-related
peptide, somatostatin, carbohydrate epitopes, or sen sciatic nerves, the proportions of small-sized cell bodies Sz
immunoreactive for substance P, calcitonin gene-related po
peptide, somatostatin, carbohydrate epitopes, or sensory aff
neuron-specific acid phosphatase in the immunoreactive for substance P, calcitonin gene-rela
peptide, somatostatin, carbohydrate epitopes, or sens
neuron-specific acid phosphatase in the fifth lum
dorsal root ganglia are decreased by 24 to 61%. To
contrary, the peptide, somatostatin, carbohydrate epitopes, or sensory affered neuron-specific acid phosphatase in the fifth lumbar to no dorsal root ganglia are decreased by 24 to 61%. To the stimu contrary, the percentage of large-siz neuron-specific acid phosphatase in the fifth lumbar
dorsal root ganglia are decreased by 24 to 61%. To the
contrary, the percentage of large-sized somata immuno-
reactive for neurofilament protein is enhanced (Jancsó
and dorsal root ganglia are decreased by 24 to 61%. To the
contrary, the percentage of large-sized somata immuno-
reactive for neurofilament protein is enhanced (Jancsó
of
and Lawson, 1988). Peptide depletion from the axons bl contrary, the percentage of large-sized somata immuno-
reactive for neurofilament protein is enhanced (Jancsó
and Lawson, 1988). Peptide depletion from the axons
and endings of sensory neurons is most probably related
to t reactive for neurofilament protein is enhanced (Jancsó
and Lawson, 1988). Peptide depletion from the axons
and endings of sensory neurons is most probably related
to the fact that application of capsaicin to nerve trunks
b and Lawson, 1988). Peptide depletion from the axons
and endings of sensory neurons is most probably related
to the fact that application of capsaicin to nerve trunks
blocks the ortho- and retrograde transport of peptides
a and endings of sensory neurons is most probably related
to the fact that application of capsaicin to nerve trunks
blocks the ortho- and retrograde transport of peptides
and macromolecules in afferent fibers in a dose-relat blocks the ortho- and retrograde transport of peptides 19
and macromolecules in afferent fibers in a dose-related A δ
manner (for a review see Jancsó et al., 1987b). Thus, on
when capsaicin is applied to the rat sciatic and macromolecules in afferent fibers in a dose-related
manner (for a review see Jancsó et al., 1987b). Thus,
when capsaicin is applied to the rat sciatic nerve, the
axoplasmic flow of substance P and somatostatin is
inhib manner (for a review see Jancsó et al., 1987b). Thus, only
when capsaicin is applied to the rat sciatic nerve, the al.,
axoplasmic flow of substance P and somatostatin is resu
inhibited (Gamse et al., 1982; Handwerker et a when capsaicin is applied to the rat sciatic nerve, the axoplasmic flow of substance P and somatostatin is inhibited (Gamse et al., 1982; Handwerker et al., 1984). This effect is seen 1 day posttreatment and depends on the inhibited (Gamse et al., 1982; Handwerker et al., 1984).
This effect is seen 1 day posttreatment and depends on
the dose of capsaicin (0.33 to 33 mM) (Gamse et al.,
1982). The retrograde transport of horseradish peroxi-
da inhibited (Gamse et al., 1982; Handwerker et al., 1984).
This effect is seen 1 day posttreatment and depends on
the dose of capsaicin (0.33 to 33 mM) (Gamse et al.,
1982). The retrograde transport of horseradish peroxi-
da This effect is seen 1 day posttreatment and depends on
the dose of capsaicin (0.33 to 33 mM) (Gamse et al.,
1982). The retrograde transport of horseradish peroxi-
dase toward the dorsal root ganglia also is significantly
r the dose of capsaicin (0.33 to 33 mM) (Gamse e 1982). The retrograde transport of horseradish pe dase toward the dorsal root ganglia also is significe reduced by perineural capsaicin (Jancsó et al., 1! 1987b). In contrast, 1982). The retrograde transport of horseradish peroxidase toward the dorsal root ganglia also is significantly treduced by perineural capsaicin (Jancsó et al., 1985a, s
1987b). In contrast, the axoplasmic flow of acetylch dase toward the dorsal root ganglia also is significantly reduced by perineural capsaicin (Jancsó et al., 1985a, 1987b). In contrast, the axoplasmic flow of acetylcholinesterase and noradrenaline is not interrupted, indica reduced by perineural capsaicin (Jancsó et al., 1985a, si
1987b). In contrast, the axoplasmic flow of acetylcholin-
esterase and noradrenaline is not interrupted, indicating T
that efferent motor and sympathetic nerve fibe 1987b). In contrast, the axoplasmic flow of acetylcholin-
esterase and noradrenaline is not interrupted, indicating T
that efferent motor and sympathetic nerve fibers are not
affected (Gamse et al., 1982). During the 1 to esterase and noradrenaline is not interrupted, indicating T
that efferent motor and sympathetic nerve fibers are not
affected (Gamse et al., 1982). During the 1 to 13 days the
after periaxonal capsaicin application to the that efferent motor and sympathetic nerve fibers are not the affected (Gamse et al., 1982). During the 1 to 13 days the after periaxonal capsaicin application to the sciatic and nerve, substance P is progressively lost fro affected (Gamse et al., 1982). During the 1 to 13 day after periaxonal capsaicin application to the sciat nerve, substance P is progressively lost from all parts afferent neurons, although distal to the treatment si the lo after periaxonal capsaicin application to the sciatic
nerve, substance P is progressively lost from all parts of
afferent neurons, although distal to the treatment site
the loss is maximal already by 4 days posttreatment
(nerve, substance P is progressively lost from all part
afferent neurons, although distal to the treatment
the loss is maximal already by 4 days posttreatn
(Gamse et al., 1982). Proximal to the treatment
peptide depletion b afferent neurons, although distal to the treatment site route the loss is maximal already by 4 days posttreatment de (Gamse et al., 1982). Proximal to the treatment site, erappetide depletion becomes maximal 2 weeks posttr the loss is maximal already by 4 days posttreatment (Gamse et al., 1982). Proximal to the treatment site, epeptide depletion becomes maximal 2 weeks posttreat-
peptide depletion becomes maximal 2 weeks posttreat-
following (Gamse et al., 1982). Proximal to the treatment speptide depletion becomes maximal 2 weeks posttre
ment and shows various degrees of recovery during following 4 to 6 months (Gamse et al., 1982; Gibson
al., 1982). In the sp peptide depletion becomes maximal 2 weeks posttreat-
ment and shows various degrees of recovery during the et a
following 4 to 6 months (Gamse et al., 1982; Gibson et Ray
al., 1982). In the spinal cord substance P and soma ment and shows various degrees of recovery during the following 4 to 6 months (Gamse et al., 1982; Gibson et lal., 1982). In the spinal cord substance P and somato-
statin, cholecystokinin-like immunoreactivity which in pa following 4 to 6 months (Gamse et al., 1982; Gibson et Raguel, 1982). In the spinal cord substance P and somato-Estatin, cholecystokinin-like immunoreactivity which in perfact may represent calcitonin gene-related peptide statin, cholecystokinin-like immunoreactivity which in peripheral sensory nerve endings are inhibited. Thus, fact may represent calcitonin gene-related peptide (Ju et vasodilatation and increase in vascular permeability in

Gibson et al., 1982) in a concentration-dependent man-

ner (0.1 to 49 mM). In contrast, vasoactive intestinal

polypeptide levels in the sciatic nerve and dorsal horn of 161

Gibson et al., 1982) in a concentration-dependent man-

ner (0.1 to 49 mM). In contrast, vasoactive intestinal

polypeptide levels in the sciatic nerve and dorsal horn of

the spinal cord are increased following peria Gibson et al., 1982) in a concentration-dependent manner (0.1 to 49 mM). In contrast, vasoactive intestin polypeptide levels in the sciatic nerve and dorsal horn the spinal cord are increased following periaxonal applicat Gibson et al., 1982) in a concentration-dependent man-
ner (0.1 to 49 mM). In contrast, vasoactive intestinal
polypeptide levels in the sciatic nerve and dorsal horn of
the spinal cord are increased following periaxonal ap ner (0.1 to 49 mM). In contrast, vasoactive intestinal polypeptide levels in the sciatic nerve and dorsal horn of the spinal cord are increased following periaxonal application of capsaicin (Anand et al., 1990). Substance polypeptide levels in the sciatic nerve and dorsal horn of
the spinal cord are increased following periaxonal appli-
cation of capsaicin (Anand et al., 1990). Substance P in
spinal cord regions not receiving primary affere the spinal cord are increased following periaxonal apportunion of capsaicin (Anand et al., 1990). Substance P
spinal cord regions not receiving primary afferent inp
as well as peptides primarily present in intrinsic neuro
 spinal cord regions not receiving primary afferent input, as well as peptides primarily present in intrinsic neurons of the spinal cord (neurotensin, neurophysin, methionine-enkephalin, bombesin), remains unchanged by perspinal cord regions not receiving primary afferent input,
as well as peptides primarily present in intrinsic neurons
of the spinal cord (neurotensin, neurophysin, methio-
nine-enkephalin, bombesin), remains unchanged by pe as well as peptides primarily present in intrinsic neurons
of the spinal cord (neurotensin, neurophysin, methio-
nine-enkephalin, bombesin), remains unchanged by per-
ineural capsaicin (Ainsworth et al., 1981; Gibson et al of the spinal cord (neurotensin, neurophysin, methiomine-enkephalin, bombesin), remains unchanged by perineural capsaicin (Ainsworth et al., 1981; Gibson et al. 1982). Likewise, noradrenergic sympathetic efferent neurons a nine-enkephalin, bombesin), remains un
ineural capsaicin (Ainsworth et al., 198
1982). Likewise, noradrenergic sympathe
rons are spared by perineural capsaicin
zelius et al., 1983; Jancsó et al., 1987b).
iii. **Functional c** eural capsaicin (Ainsworth et al., 1981; Gibson et a
82). Likewise, noradrenergic sympathetic efferent ne
ns are spared by perineural capsaicin treatment (G
lius et al., 1983; Jancsó et al., 1987b).
iii. **Functional change**

to the fact that application of capsaicin to nerve trunks al., 1985a; Marsh et al., 1987; Waddell and Lawson, blocks the ortho- and retrograde transport of peptides 1989). Initially, nerve conduction in polymodal C- and a 1982). Likewise, noradrenergic sympathetic efferent neurons are spared by perineural capsaicin treatment (Gazelius et al., 1983; Jancsó et al., 1987b).
 iii. Functional changes. Perineural capsaicin inhibitis chemo- and rons are spared by perineural capsaicin treatment (Ga
zelius et al., 1983; Jancsó et al., 1987b).
iii. **Functional changes.** Perineural capsaicin inhib
its chemo- and thermonociception in the areas suppliee
by the treated zelius et al., 1983; Jancsó et al., 1987b).

iii. Functional changes. Perineural capsaicin inhib-

its chemo- and thermonociception in the areas supplied

by the treated nerve (Jancsó et al., 1980b, 1987b; Fitz-

gerald an iii. Functional changes. Perineural capsaicin inhibits chemo- and thermonociception in the areas supplied
by the treated nerve (Jancsó et al., 1980b, 1987b; Fitz-
gerald and Woolf, 1982; Gamse et al., 1982; Gibson et
al., its chemo- and thermonociception in the areas supplied
by the treated nerve (Jancsó et al., 1980b, 1987b; Fitz-
gerald and Woolf, 1982; Gamse et al., 1982; Gibson et
al., 1982; Coderre et al., 1984; McMahon et al., 1984;
S by the treated nerve (Jancsó et al., 1980b, 1987b; Fitz-
gerald and Woolf, 1982; Gamse et al., 1982; Gibson et
al., 1982; Coderre et al., 1984; McMahon et al., 1984;
Szolcsányi, 1990); this effect is seen as early as 5 h
 al., 1982; Coderre et al., 1984; McMahon et al., 1984; Szolcsányi, 1990); this effect is seen as early as 5 h posttreatment, i.e., before substance P is depleted from afferent nerve fibers (Gamse et al., 1982). The sensiti posttreatment, i.e., before substance P is depleted from Szolcsányi, 1990); this effect is seen as early as 5 h
posttreatment, i.e., before substance P is depleted from
afferent nerve fibers (Gamse et al., 1982). The sensitivity
to noxious cold and noxious and nonnoxious mechani posttreatment, i.e., before substance P is depleted from
afferent nerve fibers (Gamse et al., 1982). The sensitivity
to noxious cold and noxious and nonnoxious mechanical
stimuli is not affected by periaxonal capsaicin (Fi afferent nerve fibers (Gamse et al., 1982). The sensitivity
to noxious cold and noxious and nonnoxious mechanical
stimuli is not affected by periaxonal capsaicin (Fitzgerald
and Woolf, 1982; Coderre et al., 1984). The earl to noxious cold and noxious and nonnoxious mechanical
stimuli is not affected by periaxonal capsaicin (Fitzgerald
and Woolf, 1982; Coderre et al., 1984). The early onset
of functional inhibition is in keeping with the prom stimuli is not affected by periaxonal capsaicin (Fitzgerald and Woolf, 1982; Coderre et al., 1984). The early onset of functional inhibition is in keeping with the prompt blockade of nerve conduction caused by periaxonal c and Woolf, 1982; Coderre et al., 1984). The early onset
of functional inhibition is in keeping with the prompt
blockade of nerve conduction caused by periaxonal cap-
saicin (Petsche et al., 1983; Lynn et al., 1984; Chung e of functional inhibition is in keeping with the prompt
blockade of nerve conduction caused by periaxonal cap-
saicin (Petsche et al., 1983; Lynn et al., 1984; Chung et
al., 1985a; Marsh et al., 1987; Waddell and Lawson,
1 blockade of nerve conduction caused by periaxonal capsaicin (Petsche et al., 1983; Lynn et al., 1984; Chung et al., 1985a; Marsh et al., 1987; Waddell and Lawson, 1989). Initially, nerve conduction in polymodal C- and $A\delta$ saicin (Petsche et al., 1983; Lynn et al., 1984; Chung et al., 1985a; Marsh et al., 1987; Waddell and Lawson, 1989). Initially, nerve conduction in polymodal C- and $A\delta$ -fiber nociceptors is inhibited at the treatment si al., 1985a; Marsh et al., 1987; Waddell and Lawson, 1989). Initially, nerve conduction in polymodal C- and $A\delta$ -fiber nociceptors is inhibited at the treatment site only (Petsche et al., 1983; Lynn et al., 1984; Chung et 1989). Initially, nerve conduction in polymodal C- and $A\delta$ -fiber nociceptors is inhibited at the treatment site only (Petsche et al., 1983; Lynn et al., 1984; Chung et al., 1985a). Whereas conduction in the A-fibers is $A\delta$ -fiber nociceptors is inhibited at the treatment site
only (Petsche et al., 1983; Lynn et al., 1984; Chung et
al., 1985a). Whereas conduction in the A-fibers is soon
resumed, the polymodal C-fiber nociceptors remain only (Petsche et al., 1983; Lynn et al., 1984; Chung et al., 1985a). Whereas conduction in the A-fibers is soon resumed, the polymodal C-fiber nociceptors remain unresponsive to their natural sensory modalities (Welk et al al., 1985a). Whereas conduction in the A-fibers is soon
resumed, the polymodal C-fiber nociceptors remain un-
responsive to their natural sensory modalities (Welk et
al., 1983; Handwerker et al., 1984; Lynn et al., 1984).
 resumed, the polymodal C-fiber nociceptors remain un-
responsive to their natural sensory modalities (Welk et
al., 1983; Handwerker et al., 1984; Lynn et al., 1984).
The proportion of C-fibers responding only to noxious
he responsive to their natural sensory modalities (Welk e
al., 1983; Handwerker et al., 1984; Lynn et al., 1984
The proportion of C-fibers responding only to noxiou
heat can be increased 1 day after perineural capsaici:
treat al., 1983; Handwerker et al., 1984; Lynn et al., 1984
The proportion of C-fibers responding only to noxiou
heat can be increased 1 day after perineural capsaici:
treatment (Welk et al., 1983), which may reflect a tran
sien heat can be increased 1 day after perineural capsaicin
treatment (Welk et al., 1983), which may reflect a tran-
sient stage in the gradual defunctionalization of poly-
modal C-fiber nociceptors (Handwerker et al., 1984).
T heat can be increased 1 day after perineural capsaicin
treatment (Welk et al., 1983), which may reflect a tran-
sient stage in the gradual defunctionalization of poly-
modal C-fiber nociceptors (Handwerker et al., 1984).
T treatment (Welk et al., 1983), which may reflect a transient stage in the gradual defunctionalization of poly-
modal C-fiber nociceptors (Handwerker et al., 1984).
Thirteen to 21 days posttreatment nerve conduction in
the sient stage in the gradual defunctionalization of poly-
modal C-fiber nociceptors (Handwerker et al., 1984).
Thirteen to 21 days posttreatment nerve conduction in
the surviving C-fibers appears to be rather normal, al-
tho modal C-fiber nociceptors (Handwerker
Thirteen to 21 days posttreatment nerve
the surviving C-fibers appears to be rath
though the conduction velocity may still b
and Fitzgerald, 1981; Lynn et al., 1984).
As is expected fr nirteen to 21 days posttreatment nerve conduction in
e surviving C-fibers appears to be rather normal, al-
ough the conduction velocity may still be slowed (Wall
d Fitzgerald, 1981; Lynn et al., 1984).
As is expected from the surviving C-fibers appears to be rather normal, although the conduction velocity may still be slowed (Wall
and Fitzgerald, 1981; Lynn et al., 1984).
As is expected from the degeneration of sensory neu-
rons (Lynn et al

though the conduction velocity may still be slowed (Wall
and Fitzgerald, 1981; Lynn et al., 1984).
As is expected from the degeneration of sensory neu-
rons (Lynn et al., 1987; Jancsó and Lawson, 1990),
defunctionalization and Fitzgerald, 1981; Lynn et al., 1984).

As is expected from the degeneration of sensory neu-

rons (Lynn et al., 1987; Jancsó and Lawson, 1990),

defunctionalization of afferent C-fibers persists for sev-

eral months (As is expected from the degeneration of sensory neurons (Lynn et al., 1987; Jancsó and Lawson, 1990), defunctionalization of afferent C-fibers persists for several months (Lynn and Pini, 1985; Pini et al., 1990). Both the rons (Lynn et al., 1987; Jancsó and Lawson, 1990),
defunctionalization of afferent C-fibers persists for sev-
eral months (Lynn and Pini, 1985; Pini et al., 1990).
Both the afferent functions of sensory neurons (Jancsó
et defunctionalization of afferent C-fibers persists for several months (Lynn and Pini, 1985; Pini et al., 1990).
Both the afferent functions of sensory neurons (Jancsó
et al., 1980b; Gamse et al., 1982; Gibson et al., 1982;
 eral months (Lynn and Pini, 1985; Pini et al., 1990).
Both the afferent functions of sensory neurons (Jancsó
et al., 1980b; Gamse et al., 1982; Gibson et al., 1982;
Raybould and Taché, 1988, 1989; South and Ritter, 1988;
E Both the afferent functions of sensory neurons (Jancsó
et al., 1980b; Gamse et al., 1982; Gibson et al., 1982;
Raybould and Taché, 1988, 1989; South and Ritter, 1988;
Esplugues et al., 1990) and the local effector function et al., 1980b; Gamse et al., 1982; Gibson et al., 1982;
Raybould and Taché, 1988, 1989; South and Ritter, 1988;
Esplugues et al., 1990) and the local effector functions of
peripheral sensory nerve endings are inhibited. Th Raybould and Taché, 1988, 1989; South and Ritter, 1988;
Esplugues et al., 1990) and the local effector functions of
peripheral sensory nerve endings are inhibited. Thus,
vasodilatation and increase in vascular permeability Esplugues et al., 1990) and the local effector functions of
peripheral sensory nerve endings are inhibited. Thus,
vasodilatation and increase in vascular permeability in-
duced by electrical or chemical stimulation of sens

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

162
cin treatment (Jancsó et al., 1980b, 1987b; Gamse et al.,
1982; Coderre et al., 1984; Pertovaara, 1988; Raybould et 162
cin treatment (Jancsó et al., 1980b, 1987b; Gamse et al.,
1982; Coderre et al., 1984; Pertovaara, 1988; Raybould et
al., 1991). The onset of this effect of perineural capsaicin HOLZE
cin treatment (Jancsó et al., 1980b, 1987b; Gamse et al., o
1982; Coderre et al., 1984; Pertovaara, 1988; Raybould et c
al., 1991). The onset of this effect of perineural capsaicin
parallels that of substance P deple cin treatment (Jancsó et al., 1980b, 1987b; Gamse et al., 1982; Coderre et al., 1984; Pertovaara, 1988; Raybould et al., 1991). The onset of this effect of perineural capsaicin parallels that of substance P depletion from cin treatment (Jancsó et al., 1980b, 1987b; Gamse et al., 1982; Coderre et al., 1984; Pertovaara, 1988; Raybould et al., 1991). The onset of this effect of perineural capsaicin parallels that of substance P depletion from 1982; Coderre et al., 1984; Pertovaara, 1988; Raybould et al., 1991). The onset of this effect of perineural capsaicin parallels that of substance P depletion from afferent nerve fibers distal to the treatment site (Gamse al., 1991). The onset of this effect of perineural capsaint parallels that of substance P depletion from affer
nerve fibers distal to the treatment site (Gamse et
1982). The reduction of thermonociception does not
verse wi parallels that of substance P depletion from afferent
nerve fibers distal to the treatment site (Gamse et al.,
1982). The reduction of thermonociception does not re-
verse within 3 months (Szolcsányi, 1990), and cholecys-
 nerve fibers distal to the treatment site (Gamse et al., 1982). The reduction of thermonociception does not reverse within 3 months (Szolcsányi, 1990), and cholecys-
tokinin-induced satiety, which is attenuated by perivaga 1982). The reduction of thermonociception does not reverse within 3 months (Szolcsányi, 1990), and cholecystokinin-induced satiety, which is attenuated by perivagal capsaicin, takes as many as 5 months for full recovery (S verse within 3 months (Szolcsányi, 1990), and cholecys-
tokinin-induced satiety, which is attenuated by perivagal g
capsaicin, takes as many as 5 months for full recovery n
(South and Ritter, 1988). Functional recovery may tokinin-induced satiety, which is attenuated by perivagal capsaicin, takes as many as 5 months for full recovery
(South and Ritter, 1988). Functional recovery may not
take place even within 1 year from perineural capsaicin psaicin, takes as many as 5 months for full recovery
outh and Ritter, 1988). Functional recovery may not
ke place even within 1 year from perineural capsaicin
aatment (Jancsó and Király, 1984; Jancsó et al., 1987b).
The pr

(South and Ritter, 1988). Functional recovery may not take place even within 1 year from perineural capsaicin treatment (Jancsó and Király, 1984; Jancsó et al., 1987b). The processing of sensory information in the spinal c take place even within 1 year from perineural capsaicin kitestment (Jancsó and Király, 1984; Jancsó et al., 1987b).
The processing of sensory information in the spinal (Scord also is altered by perineural capsaicin. The nu treatment (Jancsó and Király, 1984; Jancsó et al., 1987b). subs
The processing of sensory information in the spinal (Sou
cord also is altered by perineural capsaicin. The number that
of cells in the dorsal horn of the spin The processing of sensory information in the spinal (Scord also is altered by perineural capsaicin. The number the of cells in the dorsal horn of the spinal cord that respond m to noxious heating of the skin is significant cord also is altered by perineural capsaicin. The number the of cells in the dorsal horn of the spinal cord that respond m
to noxious heating of the skin is significantly reduced 1 by
day after capsaicin application to the of cells in the dorsal horn of the spinal cord that respond
to noxious heating of the skin is significantly reduced 1 by
day after capsaicin application to the rat sciatic nerve
new (Fitzgerald and Woolf, 1982). In contras to noxious heating of the skin is significantly reductor day after capsaicin application to the rat sciatic n
(Fitzgerald and Woolf, 1982). In contrast, the number dorsal horn cells responding to electrical stimulation
aff day after capsaicin application to the rat sciatic ne (Fitzgerald and Woolf, 1982). In contrast, the number dorsal horn cells responding to electrical stimulation afferent C-fibers does not decrease until day 3 posttre men (Fitzgerald and Woolf, 1982). In contrast, the number of are v
dorsal horn cells responding to electrical stimulation of ical
afferent C-fibers does not decrease until day 3 posttreat-
intra-
ment, this effect reaching a m dorsal horn cells responding to electrical stimulation of
afferent C-fibers does not decrease until day 3 posttreat-
ment, this effect reaching a maximum on day 7 (Fitzger-
ald and Woolf, 1982) and remaining constant up to afferent C-fibers does not decrease until day 3 posttreat-
ment, this effect reaching a maximum on day 7 (Fitzger-
ald and Woolf, 1982) and remaining constant up to 3
weeks (Wall and Fitzgerald, 1981; Fitzgerald, 1982; F
M ment, this effect reaching a maximum on day 7 (Fitzger-
ald and Woolf, 1982) and remaining constant up to 3 dia
weeks (Wall and Fitzgerald, 1981; Fitzgerald, 1982; Fir
McMahon et al., 1984). The number of dorsal horn cells ald and Woolf, 1982) and remaining constant up to
weeks (Wall and Fitzgerald, 1981; Fitzgerald, 198
McMahon et al., 1984). The number of dorsal horn ce
responding to noxious mechanical stimulation of the sl
(Fitzgerald, 19 weeks (Wall and Fitzgerald, 1981; Fitzgerald, 1982
McMahon et al., 1984). The number of dorsal horn cells
responding to noxious mechanical stimulation of the skin
(Fitzgerald, 1982; Fitzgerald and Woolf, 1982) or electri-
 McMahon et al., 1984). The number of dorsal horn cells
responding to noxious mechanical stimulation of the skin
(Fitzgerald, 1982; Fitzgerald and Woolf, 1982) or electri-
cal stimulation of afferent A-fibers (Wall and Fitz responding to noxious mechanical stimulation of the skintify its increased for the skintical stimulation of afferent A-fibers (Wall and Fitzgerald, cal stimulation of afferent A-fibers (Wall and Fitzgerald, cal 1981) is no (Fitzgerald, 1982; Fitzgerald and Woolf, 1982) or electrical stimulation of afferent A-fibers (Wall and Fitzgerald, 1981) is not altered. In addition, the size of cutaneous receptive fields is increased for many dorsal hor cal stimulation of afferent A-fibers (Wall and Fitzgerald, 1981) is not altered. In addition, the size of cutaneous receptive fields is increased for many dorsal horn cells ipsilateral to the sciatic nerve treated with per 1981) is not altered. In addition, the size of cutaneous
receptive fields is increased for many dorsal horn cells
ipsilateral to the sciatic nerve treated with periaxonal
capsaicin (Fitzgerald, 1982; Wall et al., 1982b), w receptive fields is increased for many dorsal horn cells sipsilateral to the sciatic nerve treated with periaxonal trapsaicin (Fitzgerald, 1982; Wall et al., 1982b), whereas a other dorsal horn cells may have an ill-define ipsilateral to the sciatic nerve treated with periaxonal capsaicin (Fitzgerald, 1982; Wall et al., 1982b), whereas other dorsal horn cells may have an ill-defined receptive field (McMahon et al., 1984). Furthermore, excita capsaicin (Fitzgerald, 1982; Wall et al., 1982b), whereas
other dorsal horn cells may have an ill-defined receptive
field (McMahon et al., 1984). Furthermore, excitatory
receptive fields are seen not only in the ipsilatera other dorsal horn cells may have an ill-defined receptive an field (McMahon et al., 1984). Furthermore, excitatory ne receptive fields are seen not only in the ipsilateral but lalso in the contralateral dorsal horn of the field (McMahon et al., 1984). Furthermore, excitatory receptive fields are seen not only in the ipsilateral but also in the contralateral dorsal horn of the spinal cord, whereas in control rats these contralateral inputs a 1982b). io in the contralateral dorsal horn of the spinal cornereas in control rats these contralateral inputs and variably inhibitory (Fitzgerald, 1982; Wall et al.
82b).
iv. Topical selectivity of the action of periaxons
psaicin

whereas in control rats these contralateral inputs are provariably inhibitory (Fitzgerald, 1982; Wall et al., stated 1982b).

1982b).

iv. Topical selectivity of the action of periaxonal behavior. Periaxonal capsaicin prod invariably inhibitory (Fitzgerald, 1982; Wall et al., sub-
1982b).
 iv. Topical selectivity of the action of periaxonal bit
 capsaicin. Periaxonal capsaicin produces a selective that

long-term ablation of primary affe 1982b).

iv. Topical selectivity of the action of periaxona

capsaicin. Periaxonal capsaicin produces a selective

long-term ablation of primary afferent C-fibers with

polymodal nociceptors, whereas other afferent or noniv. Topical selectivity of the action of periaxonal bit
capsaicin. Periaxonal capsaicin produces a selective the
long-term ablation of primary afferent C-fibers with in
polymodal nociceptors, whereas other afferent or noncapsaicin. Periaxonal capsaicin produces a selective that
long-term ablation of primary afferent C-fibers with in the
polymodal nociceptors, whereas other afferent or non-liga
sensory (efferent motor and autonomic) nerve f long-term ablation of primary afferent C-fibers with inpolymodal nociceptors, whereas other afferent or non-
sensory (efferent motor and autonomic) nerve fibers are the action are restricted are whether the actions of peri polymodal nociceptors, whereas other afferent or non-
sensory (efferent motor and autonomic) nerve fibers are
not directly affected. The question arises, however, as to
whether the actions of periaxonal capsaicin are restr sensory (efferent motor and autonomic) nerve fibers are
not directly affected. The question arises, however, as to
whether the actions of periaxonal capsaicin are restricted
to afferent fibers of the treated nerve or wheth not directly affected. The question arises, however, as to whether the actions of periaxonal capsaicin are restricted to afferent fibers of the treated nerve or whether afferent fibers in other nerves are affected as well. whether the actions of periaxonal capsaicin are restricted plit to afferent fibers of the treated nerve or whether afferent The fibers in other nerves are affected as well. The latter phossibility is not unlikely because s to afferent fibers of the treated nerve or whether afferent fibers in other nerves are affected as well. The latter possibility is not unlikely because systemic parenteral comministration of capsaicin to the rat results in fibers in other nerves are affected as well. The latter phological possibility is not unlikely because systemic parenteral days after administration of capsaicin to the rat results in rapid ous nerved intribution of the d possibility is not unlikely because systemic parenteral
administration of capsaicin to the rat results in rapid
distribution of the drug throughout the body (Saria et
al., 1982). Indeed, 30 min after application of a 33 m administration of capsaicin to the rat results in rapid ou
distribution of the drug throughout the body (Saria et is
al., 1982). Indeed, 30 min after application of a 33 mM va
solution of capsaicin (maximal estimated dose distribution of the drug throughout the body (Saria e al., 1982). Indeed, 30 min after application of a 33 misolution of capsaicin (maximal estimated dose: 1.6 μ moto the rat sciatic nerve, the drug is found not only in al., 1982). Indeed, 30 min after application of a 33 mm solution of capsaicin (maximal estimated dose: 1.6 μ mol) to the rat sciatic nerve, the drug is found not only in the treated nerve segment and the adjacent distal solution of capsaicin (maximal estimated dose: 1.6μ mol) boto the rat sciatic nerve, the drug is found not only in the metreated nerve segment and the adjacent distal and prox-
imal segments but also in the blood (Gamse

of capsaicin to other tissues. However, the amounts of ER
of capsaicin to other tissues. However, the amounts of
capsaicin delivered to other tissues are too small to exert
a long-term neurotoxic effect on nerves other than the ER
of capsaicin to other tissues. However, the amounts of
capsaicin delivered to other tissues are too small to exert
a long-term neurotoxic effect on nerves other than the
treated one (Jancsó et al., 1980b, 1987b; Gamse e of capsaicin to other tissues. However, the amounts of capsaicin delivered to other tissues are too small to exert a long-term neurotoxic effect on nerves other than the treated one (Jancsó et al., 1980b, 1987b; Gamse et a capsaicin delivered to other tissues are too small to exert
a long-term neurotoxic effect on nerves other than the
treated one (Jancsó et al., 1980b, 1987b; Gamse et al.,
1982; South and Ritter, 1988).
A particularly valua psaicin delivered to other tissues are too small to exert
long-term neurotoxic effect on nerves other than the
eated one (Jancsó et al., 1980b, 1987b; Gamse et al.,
82; South and Ritter, 1988).
A particularly valuable stud

a long-term neurotoxic effect on nerves other than the
treated one (Jancsó et al., 1980b, 1987b; Gamse et al.,
1982; South and Ritter, 1988).
A particularly valuable study in this respect was one
in which the effects of ca treated one (Jancsó et al., 1980b, 1987b; Gamse et al., 1982; South and Ritter, 1988).
A particularly valuable study in this respect was one
in which the effects of capsaicin were compared when
given intraperitoneally (225 1982; South and Ritter, 1988).

A particularly valuable study in this respect was o

in which the effects of capsaicin were compared wh

given intraperitoneally (225 mg/kg), perivagally (1

mM), peripylorically (165 mM), A particularly valuable study in this respect was
in which the effects of capsaicin were compared w
given intraperitoneally (225 mg/kg), perivagally
mM), peripylorically (165 mM), intracerebroventricul
(330 nmol), or intra in which the effects of capsaicin were compared when
given intraperitoneally (225 mg/kg), perivagally (165
mM), peripylorically (165 mM), intracerebroventricularly
(330 nmol), or intrathecally (330 nmol) on cholecysto-
kin given intraperitoneally (225 mg/kg), perivagally (165 mM), peripylorically (165 mM), intracerebroventricularly (330 nmol), or intrathecally (330 nmol) on cholecysto-
kinin-induced satiety, chemosensitivity of the eye, and mM), peripylorically (165 mM), intracerebroventricularly
(330 nmol), or intrathecally (330 nmol) on cholecysto-
kinin-induced satiety, chemosensitivity of the eye, and
substance P tissue levels in the spinal cord and brain (330 nmol), or intrathecally (330 nmol) on cholecysto-
kinin-induced satiety, chemosensitivity of the eye, and
substance P tissue levels in the spinal cord and brainstem
(South and Ritter, 1988). Consistent with the conclu kinin-induced satiety, chemosensitivity of the eye, and
substance P tissue levels in the spinal cord and brainstem
(South and Ritter, 1988). Consistent with the conclusion
that cholecystokinin-induced inhibition of food in substance P tissue levels in the spinal cord and brain
(South and Ritter, 1988). Consistent with the conclu
that cholecystokinin-induced inhibition of food inta
mediated by vagal afferent neurons, satiety is preve
by periv (South and Ritter, 1988). Consistent with the conclusion
that cholecystokinin-induced inhibition of food intake is
mediated by vagal afferent neurons, satiety is prevented
by perivagal, intracerebroventricular, and intrape that cholecystokinin-induced inhibition of food intake
mediated by vagal afferent neurons, satiety is prevent
by perivagal, intracerebroventricular, and intraperit
neal capsaicin and peripyloric and intrathecal capsaic
are mediated by vagal afferent neurons, satiety is prevented
by perivagal, intracerebroventricular, and intraperito-
neal capsaicin and peripyloric and intrathecal capsaicin
are without effect. The sensitivity of the cornea to by perivagal, intracerebroventricular, and intraperito-
neal capsaicin and peripyloric and intrathecal capsaicin
are without effect. The sensitivity of the cornea to chem-
ical noxious stimuli, on the other hand, is abolis neal capsaicin and peripyloric and intrathecal capsaicin
are without effect. The sensitivity of the cornea to chem-
ical noxious stimuli, on the other hand, is abolished by
intraperitoneal and intracerebroventricular capsa are without effect. The sensitivity of the cornea to chemical noxious stimuli, on the other hand, is abolished by intraperitoneal and intracerebroventricular capsaicin only, which is in keeping with trigeminal afferents me ical noxious stimuli, on the other hand, is abolished by
intraperitoneal and intracerebroventricular capsaicin
only, which is in keeping with trigeminal afferents me-
diating corneal nociception (South and Ritter, 1988).
F intraperitoneal and intracerebroventricular caps
only, which is in keeping with trigeminal afferents
diating corneal nociception (South and Ritter, 19
Finally, substance P in the brainstem is deplete
intraperitoneal and in only, which is in keeping with trigeminal afferents me-
diating corneal nociception (South and Ritter, 1988).
Finally, substance P in the brainstem is depleted by
intraperitoneal and intracerebroventricular administra-
tio diating corneal nociception (South and Ritter, 1988)
Finally, substance P in the brainstem is depleted by
intraperitoneal and intracerebroventricular administra-
tion of capsaicin, whereas the substance P content of the
sp Finally, substance P in the brainstem is deplete
intraperitoneal and intracerebroventricular admini
tion of capsaicin, whereas the substance P content o
spinal cord is reduced by intraperitoneal and intratl
capsaicin only. intraperitoneal and intracerebroventricular administra-
tion of capsaicin, whereas the substance P content of the
spinal cord is reduced by intraperitoneal and intrathecal
capsaicin only. The perivagal and peripyloric admi tion of capsaicin, whereas the substance P conter
spinal cord is reduced by intraperitoneal and int
capsaicin only. The perivagal and peripyloric adm
tion of capsaicin has no effect on spinal or n
substance P levels as mea spinal cord is reduced by intraperitoneal and intrathecal
capsaicin only. The perivagal and peripyloric administra-
tion of capsaicin has no effect on spinal or medullar
substance P levels as measured by immunohistochemiscapsaicin only. The perivagal and peripyloric administra-
tion of capsaicin has no effect on spinal or medullar
substance P levels as measured by immunohistochemis-
try (South and Ritter, 1988). Thus, perineural capsaicin
 tion of capsaicin has no effect on spinal or medullar substance P levels as measured by immunohistochemis-
try (South and Ritter, 1988). Thus, perineural capsaicin
ablates afferent nerve fibers in the treated nerve only
an neuroanatomy. ablates afferent nerve fibers in the treated nerve only
and, hence, represents an important tool for functional
neuroanatomy.
b. OTHER MAMMALS. As in the rat, periaxonal appli-
cation of capsaicin (33 mM) to the sciatic ne

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

ablates afferent nerve fibers in the treated nerve only
and, hence, represents an important tool for functional
neuroanatomy.
b. OTHER MAMMALS. As in the rat, periaxonal appli-
cation of capsaicin (33 mM) to the sciatic ne and, hence, represents an important tool for functional
neuroanatomy.
b. OTHER MAMMALS. As in the rat, periaxonal appli-
cation of capsaicin (33 mM) to the sciatic nerves of guinea
pig, cat, and rabbit inhibits the axoplas neuroanatomy.

b. OTHER MAMMALS. As in the rat, periaxonal appli-

cation of capsaicin (33 mM) to the sciatic nerves of guinea

pig, cat, and rabbit inhibits the axoplasmic transport of

substance P (Gamse et al., 1982). H b. OTHER MAMMALS. As in the rat, periaxonal application of capsaicin (33 mM) to the sciatic nerves of guine-
pig, cat, and rabbit inhibits the axoplasmic transport of
substance P (Gamse et al., 1982). However, whereas in
t cation of capsaicin (33 mM) to the sciatic nerves of guinea
pig, cat, and rabbit inhibits the axoplasmic transport of
substance P (Gamse et al., 1982). However, whereas in
the rat, guinea pig, and cat the capsaicin-induced pig, cat, and rabbit inhibits the axoplasmic transport of substance P (Gamse et al., 1982). However, whereas in the rat, guinea pig, and cat the capsaicin-induced inhibition of substance P transport is of the same degree a substance P (Gamse et al., 1982). However, whereas in
the rat, guinea pig, and cat the capsaicin-induced inhi-
bition of substance P transport is of the same degree as
that produced by nerve ligation, the effect of capsaic the rat, guinea pig, and cat the capsaicin-induced inhibition of substance P transport is of the same degree as that produced by nerve ligation, the effect of capsaicin in the rabbit is less than one-half of that caused by bition of substance P transport is of the same degree as
that produced by nerve ligation, the effect of capsaicin
in the rabbit is less than one-half of that caused by nerve
ligation (Gamse et al., 1982). In addition, caps that produced by nerve ligation, the effect of capsaicin
in the rabbit is less than one-half of that caused by nerve
ligation (Gamse et al., 1982). In addition, capsaicin has
to be injected subepineurally in the rabbit to in the rabbit is less than one-half of that caused by nerve ligation (Gamse et al., 1982). In addition, capsaicin has to be injected subepineurally in the rabbit to inhibit the axonal transport of substance P, whereas peri ligation (Gamse et al., 1982). In addition, capsaicin ha
to be injected subepineurally in the rabbit to inhibit the
axonal transport of substance P, whereas perineural ap
plication with a cuff is ineffective (Gamse et al., to be injected subepineurally in the rabbit to inhibit the axonal transport of substance P, whereas perineural application with a cuff is ineffective (Gamse et al., 1982). This observation is consistent with the absence of axonal transport of substance P, whereas perineural
plication with a cuff is ineffective (Gamse et al., 198
This observation is consistent with the absence of m
phological or functional signs of axon degeneration
days afte plication with a cuff is ineffective (Gamse et al., 1982).
This observation is consistent with the absence of mor-
phological or functional signs of axon degeneration 10
days after application of capsaicin to the rabbit sa This observation is consistent with the absence of morphological or functional signs of axon degeneration 10 days after application of capsaicin to the rabbit saphen-
ous nerve, although the substance P content of the skin phological or functional signs of axon degeneration
days after application of capsaicin to the rabbit sapl
ous nerve, although the substance P content of the :
is diminished and sensory nerve-mediated increase
vascular per days after application of capsaicin to the rabbit saphen-
ous nerve, although the substance P content of the skin
is diminished and sensory nerve-mediated increases in
vascular permeability are reduced (Lynn and Shakhan-
b ous nerve, although the substance P content of the skiin is diminished and sensory nerve-mediated increases is
vascular permeability are reduced (Lynn and Shakhan
beh, 1988). Periaxonal application of capsaicin to so
matic is diminished and sensory nerve-mediated increases in vascular permeability are reduced (Lynn and Shakhan-
beh, 1988). Periaxonal application of capsaicin to so-
matic nerves of the guinea pig is followed by a long-
lastin vascular permeability are reduced (Lynn and Shakhan-
beh, 1988). Periaxonal application of capsaicin to so-
matic nerves of the guinea pig is followed by a long-
lasting inhibition of thermonociception (Szolcsányi,
1990). beh, 1988). Periaxonal application of capsaicin to somatic nerves of the guinea pig is followed by a long-
lasting inhibition of thermonociception (Szolcsányi, 1990). In the cat, perivagal capsaicin treatment impairs
vagal

aspet

CAPSAICIN
which are blocked 3 to 5 days posttreatment (Jancsó and et as
vas which are bloc
Such, 1983).
4. Effects of

CAF
1983).
4. *Effects of capsaicin administered to the central end-*
4. *Effects of capsaicin administered to the central end-*
gs *of afferent neurons*. a. INTRATHECAL, INTRACISTERwhich are blocked 3 to 5 days posttreatment (Jancsó
Such, 1983).
4. *Effects of capsaicin administered to the central*
ings of afferent neurons. a. INTRATHECAL, INTRACIS
NAL, OR EPIDURAL APPLICATION OF CAPSAICIN. I Such, 1983).
4. *Effects of capsaicin administered to the central end-*
ings of afferent neurons. a. INTRATHECAL, INTRACISTER-
NAL, OR EPIDURAL APPLICATION OF CAPSAICIN. Local
administration of 100 to 130 nmol capsaicin in 4. Effects of capsaicin administered to the central end-
ings of afferent neurons. a. INTRATHECAL, INTRACISTER-
NAL, OR EPIDURAL APPLICATION OF CAPSAICIN. Local
administration of 100 to 130 nmol capsaicin into the rat
acis ings of afferent neurons. a. INTRATHECAL, INTRACISTER-
NAL, OR EPIDURAL APPLICATION OF CAPSAICIN. Local
administration of 100 to 130 nmol capsaicin into the rat
cisterna magna (Jancsó, 1981; Gamse et al., 1984) or
lumbar/c NAL, OR EPIDURAL APPLICATION OF CAPSAICIN. Local
administration of 100 to 130 nmol capsaicin into the rat
cisterna magna (Jancsó, 1981; Gamse et al., 1984) or
lumbar/cervical subarachnoid space (Palermo et al.,
1981; Ribei administration of 100 to 130 nmol capsaicin into the rat cisterna magna (Jancsó, 1981; Gamse et al., 1984) or lumbar/cervical subarachnoid space (Palermo et al., 1981; Ribeiro-da-Silva and Coimbra, 1984) leads to destructi cisterna magna (Jancsó, 1981; Gamse et al., 1984)
lumbar/cervical subarachnoid space (Palermo et a
1981; Ribeiro-da-Silva and Coimbra, 1984) leads to c
struction of axon terminals in the primary afferent t
minal regions of lumbar/cervical subarachnoid space (Palermo et al., 1981; Ribeiro-da-Silva and Coimbra, 1984) leads to destruction of axon terminals in the primary afferent ter-
minal regions of the brainstem and spinal cord. Degeneration 1981; Ribeiro-da-Silva and Coimbra, 1984) leads to de-
struction of axon terminals in the primary afferent ter-
minal regions of the brainstem and spinal cord. Degen-
teration is confined to the glomerular C-type nerve ter struction of axon terminals in the primary afferent ter-
minal regions of the brainstem and spinal cord. Degen-
eration is confined to the glomerular C-type nerve ter-
minals (Palermo et al., 1981) or glomerular type I ner minal regions of the brainstem and spinal cord. Deger
eration is confined to the glomerular C-type nerve terminals (Palermo et al., 1981) or glomerular type I nerv
terminals (Ribeiro-da-Silva and Coimbra, 1984) whic
are co ention is confined to the glomerular C-type nerve ter-
minals (Palermo et al., 1981) or glomerular type I nerve
mat and mouse (Yaksh et al., 1979; Palermo et al., 1981;
terminals (Ribeiro-da-Silva and Coimbra, 1984) which minals (Palermo et al., 1981) or glomerular type I nerve
terminals (Ribeiro-da-Silva and Coimbra, 1984) which
are considered to be terminations of unmyelinated affer-
ents. One to 2 days posttreatment 53 to 56% of the type are considered to be terminations of unmyelinated afferents. One to 2 days posttreatment 53 to 56% of the type I nerve terminals have degenerated, whereas the number of type II nerve terminals thought to arise from myelin are considered to be terminations of unmyelinated a
ents. One to 2 days posttreatment 53 to 56% of the
I nerve terminals have degenerated, whereas the nur
of type II nerve terminals thought to arise from m
nated afferents ents. One to 2 days posttreatment 53 to 56% of the type
I nerve terminals have degenerated, whereas the number
of type II nerve terminals thought to arise from myeli-
nated afferents are reduced by only 2 to 5% (Ribeiro-da I nerve terminals have degenerated, whereas the number
of type II nerve terminals thought to arise from myeli-
nated afferents are reduced by only 2 to 5% (Ribeiro-da-
Silva and Coimbra, 1984). Importantly, the neurotoxic
 of type II nerve terminals thought to arise from myeli-
nated afferents are reduced by only 2 to 5% (Ribeiro-da-
Silva and Coimbra, 1984). Importantly, the neurotoxic neffect of capsaicin administered into the subarachnoid nated afferents are reduced by only 2 to 5% (Ribeiro-da-19
Silva and Coimbra, 1984). Importantly, the neurotoxic no
effect of capsaicin administered into the subarachnoid be
space is restricted to the central endings of pr Silva and Coimbra, 1984). Importantly, the neurotoxic not effect of capsaicin administered into the subarachnoid bet space is restricted to the central endings of primary cat afferent neurons, because no signs of degenerat effect of capsaicin administered into the subarachr space is restricted to the central endings of prim afferent neurons, because no signs of degeneration moted in the trigeminal roots, trigeminal ganglion, maxillary nerve afferent neurons, because no signs of degeneration are nociception is only temporarily diminished by intrathe-
noted in the trigeminal roots, trigeminal ganglion, and cal capsaicin (Hayes et al., 1981b) but unchanged in th

afferent neurons, because no signs of degeneration are noted in the trigeminal roots, trigeminal ganglion, and cal maxillary nerve (Jancsó, 1981; Gamse et al., 1984). lon
The topical selectivity of intracisternal capsaicin noted in the trigeminal roots, trigeminal ganglion, and cal constitutive maxillary nerve (Jancsó, 1981; Gamse et al., 1984). Iong
The topical selectivity of intracisternal capsaicin is Tunderlined by a selective depletion maxillary nerve (Jancsó, 1981; Gamse et al., 1984).
The topical selectivity of intracisternal capsaicin is
underlined by a selective depletion of substance P and
neurokinin A from the sensory nerve terminal areas in
the me The topical selectivity of intracisternal capsaicin is
underlined by a selective depletion of substance P and line
neurokinin A from the sensory nerve terminal areas in site
the medulla but not from the trigeminal roots, t underlined by a selective depletion of substance P and lineurokinin A from the sensory nerve terminal areas in sithe medulla but not from the trigeminal roots, trigeminal capanglion, and maxillary nerve of the rat and guin neurokinin A from the sensory nerve terminal areas in site
the medulla but not from the trigeminal roots, trigeminal cat
ganglion, and maxillary nerve of the rat and guinea pig era
(Gamse et al., 1984, 1986). Intrathecal a the medulla but not from the trigeminal roots, trigeminal
ganglion, and maxillary nerve of the rat and guinea pig
(Gamse et al., 1984, 1986). Intrathecal administration of
capsaicin (50 to 1000 nmol) at the lumbar level ca ganglion, and maxillary nerve of the rat and guinea pig
(Gamse et al., 1984, 1986). Intrathecal administration of
capsaicin (50 to 1000 nmol) at the lumbar level causes a
ilong-term depletion of substance P and somatostati (Gamse et al., 1984, 1986). Intrathecal administration of capsaicin (50 to 1000 nmol) at the lumbar level causes a
long-term depletion of substance P and somatostatin prom the dorsal spinal cord of rat and mouse (Yaksh et capsaicin (50 to 1000 nmol) at the lumbar level causes a
long-term depletion of substance P and somatostatin
from the dorsal spinal cord of rat and mouse (Yaksh et
al., 1979; Nagy et al., 1981a; Gamse, 1982; Micevych et
al long-term depletion of substance P and somatostatin pe
from the dorsal spinal cord of rat and mouse (Yaksh et (Y
al., 1979; Nagy et al., 1981a; Gamse, 1982; Micevych et
al., 1983; Jhamandas et al., 1984; South and Ritter, from the dorsal spinal cord of rat and mouse (Yaksh et (Yaksh).

al., 1979; Nagy et al., 1981a; Gamse, 1982; Micevych et al., 1983; Jhamandas et al., 1984; South and Ritter, 1988). SAI

Substance P also is depleted from t al., 1983; Jhamandas et al., 1984; South and Ritter, 1988).
Substance P also is depleted from the dorsal roots of the
rat but rather increased in the dorsal root ganglia and al., 1983; Jhamandas et al., 1984; South and Ritter, 1988). S.
Substance P also is depleted from the dorsal roots of the sprat but rather increased in the dorsal root ganglia and cisciatic nerve when measured 6 days posttr Substance P also is depleted from the dorsal roots of the spinal cut rather increased in the dorsal root ganglia and cisclatic nerve when measured 6 days posttreatment in (Gamse, 1982). Substance P levels in the ventral ha rat but rather increased in the dorsal root ganglia and sciatic nerve when measured 6 days posttreatment (Gamse, 1982). Substance P levels in the ventral half of the spinal cord and in areas remote from the injection site, (Gamse, 1982). Substance P levels in the ventral half of content of substance P, but not somatostatin and neu-
the spinal cord and in areas remote from the injection rotensin, in the medulla oblongata, with no changes in
 (Gamse, 1982). Substance P levels in the ventral half of
the spinal cord and in areas remote from the injection
site, i.e., cervical spinal cord, brainstem, and forebrain,
are not changed by intrathecal capsaicin (Yaksh et the spinal cord and in areas remote from the injection rosite, i.e., cervical spinal cord, brainstem, and forebrain, other not changed by intrathecal capsaicin (Yaksh et al., (G) 1979; Nagy et al., 1981a; South and Ritter, site, i.e., cervical spinal cord, brainstem, and forebrain, are not changed by intrathecal capsaicin (Yaksh et al., 1979; Nagy et al., 1981a; South and Ritter, 1988). Other markers of sensory and nonsensory neurons such as are not changed by intrathecal capsaicin (Yaksh et al., 1979; Nagy et al., 1981a; South and Ritter, 1988). Other markers of sensory and nonsensory neurons such as vasoactive intestinal polypeptide and cholecystokinin (Jham markers of sensory and nonsensory neurons such as content in the medulla is rather small (Gamse et al., vasoactive intestinal polypeptide and cholecystokinin 1981b), making it difficult to be picked up by immuno-
(Jhamand markers of sensory and nonsensory neurons such as consolative intestinal polypeptide and cholecystokinin 19. (Jhamandas et al., 1984), glutamic acid decarboxylase high (Yaksh et al., 1979; Nagy et al., 1981a), neurotensin vasoactive intestinal polypeptide and cholecystokir (Jhamandas et al., 1984), glutamic acid decarboxyle (Yaksh et al., 1979; Nagy et al., 1981a), neurotenine-enkephalin (Micev-brythemine, and methionine-enkephalin (Micev-b (Jhamandas et al., 1984), glutamic acid decarboxy
(Yaksh et al., 1979; Nagy et al., 1981a), neuroter
(Gamse, 1982), noradrenaline (Yaksh et al., 1979)
hydroxytryptamine, and methionine-enkephalin (Mi
ych et al., 1983) rema (Yaksh et al., 1979; Na)
(Gamse, 1982), noradre
hydroxytryptamine, and
ych et al., 1983) remain
cal capsaicin application
Although the nocicept hydroxytryptamine, and methionine-enkephalin (Micev-
ych et al., 1983) remain grossly unaltered after intrathe-
cal capsaicin application.
Although the nociceptive functions of sensory neurons
are inhibited by intracistern

ych et al., 1983) remain grossly unaltered after intrathe-

cal capsaicin application. m

Although the nociceptive functions of sensory neurons

1982

are inhibited by intracisternal capsaicin for several (C

months, the l nerve endings application. The Although the nociceptive functions of sensory neurons are inhibited by intracisternal capsaicin for several (when the local effector functions of peripheral sensory share endings remain unaff

Such, 1983).

4. Effects of capsaicin administered to the central end-

1. Effects of capsaicin administered to the central end-

1. The capsaic and subsessive of afferent neurons. a. INTRATHECAL, INTRACISTER-

1. CORE SAI et al., 1984). Thus, sensory nerve-mediated increases in cortage 163
et al., 1984). Thus, sensory nerve-mediated increases in
vascular permeability in the skin of the rat cheek and
nose are virtually unchanged, whereas the sensitivity to 163
et al., 1984). Thus, sensory nerve-mediated increases in
vascular permeability in the skin of the rat cheek and
nose are virtually unchanged, whereas the sensitivity to
chemical noxious stimuli in the ears, eyes, and f et al., 1984). Thus, sensory nerve-mediated increases in vascular permeability in the skin of the rat cheek and mose are virtually unchanged, whereas the sensitivity to chemical noxious stimuli in the ears, eyes, and forep et al., 1984). Thus, sensory nerve-mediated increases in
vascular permeability in the skin of the rat cheek and
nose are virtually unchanged, whereas the sensitivity to
chemical noxious stimuli in the ears, eyes, and forep vascular permeability in the skin of the rat cheek and nose are virtually unchanged, whereas the sensitivity to chemical noxious stimuli in the ears, eyes, and forepaws of the rat and guinea pig is greatly diminished as ea chemical noxious stimuli in the ears, eyes, and forepaws chemical noxious stimuli in the ears, eyes, and forepaws
of the rat and guinea pig is greatly diminished as early
as 1 h posttreatment (Jancsó, 1981; Gamse et al., 1984,
1986). Whereas chemonociception in the corresponding of the rat and guinea pig is greatly diminished as early
as 1 h posttreatment (Jancsó, 1981; Gamse et al., 1984,
1986). Whereas chemonociception in the corresponding
ecteroceptive areas also is lost after intrathecal or ep as 1 h posttreatment (Jancsó, 1981; Gamse et al., 1984, 1986). Whereas chemonociception in the corresponding ecteroceptive areas also is lost after intrathecal or epidural application of capsaicin (Yaksh et al., 1979; Janc 1986). Whereas chemonociception in the corresponding
ecteroceptive areas also is lost after intrathecal or epi-
dural application of capsaicin (Yaksh et al., 1979; Jancsó,
1981; Gamse, 1982; Eimerl and Papir-Kricheli, 1987 ecteroceptive areas also is lost after intrathecal or epi-
dural application of capsaicin (Yaksh et al., 1979; Jancsó,
1981; Gamse, 1982; Eimerl and Papir-Kricheli, 1987),
thermonociception is either reduced for up to 5 mo dural application of capsaicin (Yaksh et al., 1979; Jancsó, 1981; Gamse, 1982; Eimerl and Papir-Kricheli, 1987), thermonociception is either reduced for up to 5 months after intrathecal or epidural injection of capsaicin i 1981; Gamse, 1982; Eimerl and Papir-Kricheli, 1987),
thermonociception is either reduced for up to 5 months
after intrathecal or epidural injection of capsaicin in the
rat and mouse (Yaksh et al., 1979; Palermo et al., 198 thermonociception is either reduced for up to 5 mon
after intrathecal or epidural injection of capsaicin in
rat and mouse (Yaksh et al., 1979; Palermo et al., 19
Gamse, 1982; Micevych et al., 1983; Jhamandas et
1984; Eimer after intrathecal or epidural injection of capsaicin in the
rat and mouse (Yaksh et al., 1979; Palermo et al., 1981;
Gamse, 1982; Micevych et al., 1983; Jhamandas et al.,
1984; Eimerl and Papir-Kricheli, 1987) or not consi rat and mouse (Yaksh et al., 1979; Palermo et al., 1981;
Gamse, 1982; Micevych et al., 1983; Jhamandas et al.,
1984; Eimerl and Papir-Kricheli, 1987) or not consist-
ently changed (Hayes et al., 1981b; Nagy et al., 1981a). Gamse, 1982; Micevych et al., 1983; Jhamandas et al., 1984; Eimerl and Papir-Kricheli, 1987) or not consistently changed (Hayes et al., 1981b; Nagy et al., 1981a). These discrepancies may be related, in part, to variabilit 1984; Eimerl and Papir-Kricheli, 1987) or not consistently changed (Hayes et al., 1981b; Nagy et al., 1981a).
These discrepancies may be related, in part, to variability
between different experimental animals (Yaksh et al. ently changed (Hayes et al., 1981b; Nagy et al., 1981a).
These discrepancies may be related, in part, to variability
between different experimental animals (Yaksh et al.,
1979; Nagy et al., 1981a; Palermo et al., 1981), di These discrepancies may be related, in part, to variability
between different experimental animals (Yaksh et al.,
1979; Nagy et al., 1981a; Palermo et al., 1981), different
nociception tests (Gamse, 1982), nonspecific inte between different experimental animals (Yaksh et
1979; Nagy et al., 1981a; Palermo et al., 1981), differ
nociception tests (Gamse, 1982), nonspecific interacti
between capsaicin and its vehicle (Jancsó, 1981), or
catheteri 1979; Nagy et al., 1981a; Palermo et al., 1981), differenciception tests (Gamse, 1982), nonspecific interactifictively interactively diminished by intrathe-
interation procedure (Nagy et al., 1981a). Mechanociception is on nociception tests (Gamse, 1982), nonspecific interactions
between capsaicin and its vehicle (Jancsó, 1981), or the
catheterization procedure (Nagy et al., 1981a). Mechano-
nociception is only temporarily diminished by intr between capsaicin and its vehicl
catheterization procedure (Nagy
nociception is only temporarily
cal capsaicin (Hayes et al., 1981
long term (Yaksh et al., 1979).
Taken together, only the cent nociception is only temporarily diminished by intrathe-

nociception is only temporarily diminished by intrathe-
cal capsaicin (Hayes et al., 1981b) but unchanged in the
long term (Yaksh et al., 1979).
Taken together, only the central terminals of unmye-
linated afferent neurons cal capsaicin (Hayes et al., 1981b) but unchanged in the long term (Yaksh et al., 1979).
Taken together, only the central terminals of unmy
linated afferent neurons in the vicinity of the injectic
site are ablated after in long term (Yaksh et al., 1979).
Taken together, only the central terminals of unm
linated afferent neurons in the vicinity of the injecti
site are ablated after intrathecal or intracisternal app
cation of capsaicin, wherea Taken together, only the central terminals of unmye-
linated afferent neurons in the vicinity of the injection
site are ablated after intrathecal or intracisternal appli-
cation of capsaicin, whereas the cell bodies and pe cation of capsaicin, whereas the cell bodies and peripheral processes of these neurons are left intact. When doses of capsaicin shown to be effective intrathecally or intracisternally are administered intravenously or intr site are ablated after intrathecal or intracisternal appleation of capsaicin, whereas the cell bodies and peripleral processes of these neurons are left intact. When doses of capsaicin shown to be effective intrathecally i cation of capsaicin, whereas the cell bodies and peripheral processes of these neurons are left intact. When doses of capsaicin shown to be effective intrathecally or intracisternally are administered intravenously or intr eral processes of these neurons are left
doses of capsaicin shown to be effective i
intracisternally are administered intraver
peritoneally, no long-term neurotoxic efi
(Yaksh et al., 1979; Gamse et al., 1986).
b. INTRACER intracisternally are administered intravenously or intra-
peritoneally, no long-term neurotoxic effects are noted
(Yaksh et al., 1979; Gamse et al., 1986).
b. INTRACEREBROVENTRICULAR APPLICATION OF CAP-
sAICIN. Morphologic

hydroxytryptamine, and methionine-enkephalin (Micev-

ych et al., 1983) remain grossly unaltered after intrathe-

cal capsaicin application.

cal capsaicin application.

cal capsaicin application.

Although the nociceptiv peritoneally, no long-term neurotoxic effects are not
(Yaksh et al., 1979; Gamse et al., 1986).
b. INTRACEREBROVENTRICULAR APPLICATION OF CA
SAICIN. Morphological changes that might occur in
sponse to intracerebroventricul (Yaksh et al., 1979; Gamse et al., 1986).
b. INTRACEREBROVENTRICULAR APPLICATION OF
sAICIN. Morphological changes that might occur is
sponse to intracerebroventricular application of cap
cin have not yet been examined. Int b. INTRACEREBROVENTRICULAR APPLICATION OF CAPSAICIN. Morphological changes that might occur in response to intracerebroventricular application of capsaicin have not yet been examined. Intracerebroventricular injection of 6 SAICIN. Morphological changes that might occur in response to intracerebroventricular application of capsaicin have not yet been examined. Intracerebroventricular injection of 650 to 1000 nmol capsaicin reduces the content sponse to intracerebroventricular application of capsaicin have not yet been examined. Intracerebroventricular
injection of 650 to 1000 nmol capsaicin reduces the
content of substance P, but not somatostatin and neu-
roten cin have not yet been examined. Intracerebroventricular
injection of 650 to 1000 nmol capsaicin reduces the
content of substance P, but not somatostatin and neu-
rotensin, in the medulla oblongata, with no changes in
other injection of 650 to 1000 nmol capsaicin reduces the content of substance P, but not somatostatin and neurotensin, in the medulla oblongata, with no changes in other brain areas, spinal cord, and trigeminal ganglion (Gamse content of substance P, but not somatostatin and neurotensin, in the medulla oblongata, with no changes in other brain areas, spinal cord, and trigeminal ganglion (Gamse et al., 1981b; Bodnar et al., 1982; South and Ritte rotensin, in the medulla oblongata, with no changes in
other brain areas, spinal cord, and trigeminal ganglion
(Gamse et al., 1981b; Bodnar et al., 1982; South and
Ritter, 1988). The reduction (30%) of the substance P
cont other brain areas, spinal cord, and trigeminal gang

(Gamse et al., 1981b; Bodnar et al., 1982; South

Ritter, 1988). The reduction (30%) of the substanc

content in the medulla is rather small (Gamse et

1981b), making it (Gamse et al., 1981b; Bodnar et al., 1982; South
Ritter, 1988). The reduction (30%) of the substant
content in the medulla is rather small (Gamse et
1981b), making it difficult to be picked up by immu
histochemistry (Bodn Ritter, 1988). The reduction (30%) of the substance content in the medulla is rather small (Gamse e 1981b), making it difficult to be picked up by imm histochemistry (Bodnar et al., 1982). In the hypot mus, however, β content in the medulla is rather small (Gamse et al., 1981b), making it difficult to be picked up by immuno-
histochemistry (Bodnar et al., 1982). In the hypothala-
mus, however, β -endorphin is depleted by intracerebro 1981b), making it difficult to be picked up by immuno-
histochemistry (Bodnar et al., 1982). In the hypothala-
mus, however, β -endorphin is depleted by intracerebro-
ventricular injection of capsaicin for 2 weeks, wher histochemistry (Bodnar et al., 1982). In the hypothala-
mus, however, β -endorphin is depleted by intracerebro-
ventricular injection of capsaicin for 2 weeks, whereas
the β -endorphin content of other brain areas and mus, however, β -endorphin is depleted by intracerebro-
ventricular injection of capsaicin for 2 weeks, whereas
the β -endorphin content of other brain areas and the
hypothalamic content of substance P, somatostatin, ventricular injection of capsaicin for 2 weeks, whereas
the β -endorphin content of other brain areas and the
hypothalamic content of substance P, somatostatin, and
methionine-enkephalin are left unaltered (Panerai et a the β -endorphin content of other brain areas and the hypothalamic content of substance P, somatostatin, and methionine-enkephalin are left unaltered (Panerai et al. 1983). Functionally, chemonociception in the cornea (hypothalamic content of substance P, somatostatin, and
methionine-enkephalin are left unaltered (Panerai et al.
1983). Functionally, chemonociception in the cornea
(Gamse et al., 1981b; South and Ritter, 1988), but not in
 methionine-enkephalin are left unaltered (Panerai e 1983). Functionally, chemonociception in the co (Gamse et al., 1981b; South and Ritter, 1988), but no skin areas supplied by the lumbar spinal cord (Yaks al., 1979), is g

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

EMB4

164

capsaicin also attenuates cholecystokinin-induced sa-

tiety; this functional deficit takes as many as 5 month tiety; this functional deficit takes as many as 5 months for full recovery (South and Ritter, 1988). ¹⁶⁴

reapsaicin also attenuates cholecystokinin-induced sa

tiety; this functional deficit takes as many as 5 month

for full recovery (South and Ritter, 1988).

c. TOPICAL ADMINISTRATION OF CAPSAICIN TO SPE

CIFIC BRAIN

capsaicin also attenuates cholecystokinin-induced satiety; this functional deficit takes as many as 5 months for full recovery (South and Ritter, 1988).

c. TOPICAL ADMINISTRATION OF CAPSAICIN TO SPECIFIC BRAIN REGIONS. Mi tiety; this functional deficit takes as many as 5 momoder for full recovery (South and Ritter, 1988).

c. TOPICAL ADMINISTRATION OF CAPSAICIN TO :

CIFIC BRAIN REGIONS. Microinjection of 2 to 83 r.

capsaicin into the preo for full recovery (South and Ritter, 1988).

c. TOPICAL ADMINISTRATION OF CAPSAICIN TO SPE-

CIFIC BRAIN REGIONS. Microinjection of 2 to 83 nmol

capsaicin into the preoptic region of the rat hypothala-

mus causes hypothe c. TOPICAL ADMINISTRATION OF CAPSAICIN TO SPECIFIC BRAIN REGIONS. Microinjection of 2 to 83 nmol
capsaicin into the preoptic region of the rat hypothala-
mus causes hypothermia; this response is absent after
systemic or in CIFIC BRAIN REGIONS. Microinjection of 2 to 83 nmol
capsaicin into the preoptic region of the rat hypothala-
mus causes hypothermia; this response is absent after
systemic or intrahypothalamic treatment of the animals
with capsaicin into the preoptic region of the rat hypothala-
mus causes hypothermia; this response is absent after
systemic or intrahypothalamic treatment of the animals
with this drug (see Szolcsányi, 1982). Furthermore, in-
 mus causes hypothermia; this response is absent after systemic or intrahypothalamic treatment of the animals with this drug (see Szolcsányi, 1982). Furthermore, intrahypothalamic injection of nanomole to micromole doses of systemic or intrahypothalamic treatment of the animals 19
with this drug (see Szolcsányi, 1982). Furthermore, in-
trahypothalamic injection of nanomole to micromole va
doses of capsaicin results in a long-lasting impairmen with this drug (see Szolcsányi, 1982). Furthermore, in-
trahypothalamic injection of nanomole to micromole
doses of capsaicin results in a long-lasting impairment
of thermoregulation against overheating in rats and cats
(trahypothalamic injection of nanomole to micromole doses of capsaicin results in a long-lasting impairment of thermoregulation against overheating in rats and cats (see Szolcsányi, 1982). Topical administration of a capsa doses of capsaicin results in a long-lasting impairment
of thermoregulation against overheating in rats and cats
(see Szolcsányi, 1982). Topical administration of a cap-
saicin solution (320 μ M) to the brainstem of the of thermoregulation against overheating in rats and cats
(see Szolcsányi, 1982). Topical administration of a cap-
saicin solution (320 μ M) to the brainstem of the cat
causes degeneration of nerve terminals in a specifi (see Szolcsányi, 1982). Topical administration of a cap
saicin solution $(320 \mu M)$ to the brainstem of the cardiovascular
causes degeneration of nerve terminals in a specific region of the ventral medulla oblongata, these saicin solution $(320 \mu M)$ to the brainstem of the causes degeneration of nerve terminals in a specific region of the ventral medulla oblongata, these structure being involved in the regulation of the cardiovasculand resp causes degeneration of nerve terminals in a specific re-
gion of the ventral medulla oblongata, these structures the
being involved in the regulation of the cardiovascular 198
and respiratory systems (Jancsó and Such, 1985 and respiratory systems (Jancsó and Such, 1985). Injection of 80 nmol capsaicin into the area postrema and padjacent nucleus tractus solitarii of the rat brainstem wesults in overconsumption of preferred food (South and ti tion of 80 nmol capsaicin into the area postrema and padjacent nucleus tractus solitarii of the rat brainstem wiresults in overconsumption of preferred food (South and tion Ritter, 1983). No other long-term effects of caps adjacent nucleus tractus solitarii of the rat brainst
results in overconsumption of preferred food (South a
Ritter, 1983). No other long-term effects of capsaid
injected topically into the central nervous system ha
been re results in overconsumption of preferred food (South and
Ritter, 1983). No other long-term effects of capsaicin
injected topically into the central nervous system have
been reported. The behavioural and biochemical altera-
 Ritter, 1983). No other long-term effects of capsaicin
injected topically into the central nervous system have
been reported. The behavioural and biochemical altera-
ions involving 5-hydroxytryptamine and dopamine neu-
ron injected topically into the central nervous system have
been reported. The behavioural and biochemical altera-
tions involving 5-hydroxytryptamine and dopamine neu-
rons in the substantia nigra and striatum, observed after been reported. The behavioural and biochemical altera-ical
tions involving 5-hydroxytryptamine and dopamine neu-
rons in the substantia nigra and striatum, observed after
injection of 100 nmol capsaicin into the rat substa tions involving 5-hydroxytryptamine an
rons in the substantia nigra and striature
injection of 100 nmol capsaicin into the
nigra, are only short lasting and have
posttreatment (Dawbarn et al., 1981).
5. Effects of capsaici In the substantia nigra and striatum, observed after existencies of 100 nmol capsaicin into the rat substantia gra, are only short lasting and have abated by day ϵ streatment (Dawbarn et al., 1981).
5. Effects of capsai

injection of 100 nmol capsaicin into the rat substantianigra, are only short lasting and have abated by day 6 posttreatment (Dawbarn et al., 1981).
5. Effects of capsaicin administered to peripheral end-
ings of sensory ne nigra, are only short lasting and have abated by day 6
posttreatment (Dawbarn et al., 1981).
5. Effects of capsaicin administered to peripheral end-
ings of sensory neurons. Repeated administration of cap-
tisaicin (66 nM posttreatment (Dawbarn et al., 1981).
5. Effects of capsaicin administered to peripheral er
ings of sensory neurons. Repeated administration of ca
saicin (66 nM to 33 mM) to the cornea of rats and guin
pigs causes insensit 5. Effects of capsaicin administered to peripheral endings of sensory neurons. Repeated administration of capsaicin (66 nM to 33 mM) to the cornea of rats and guinea pigs causes insensitivity to further instillation of cap ings of sensory neurons. Repeated administration of capsaicin (66 nM to 33 mM) to the cornea of rats and guinea
pigs causes insensitivity to further instillation of capsai-
cin-related drugs (Jancsó, 1968; Szolcsányi et al saicin (66 nM to 33 mM) to the cornea of rats and guinea
pigs causes insensitivity to further instillation of capsai-
cin-related drugs (Jancsó, 1968; Szolcsányi et al., 1975; tl
Szolcsányi and Jancsó-Gábor, 1976; Gamse et pigs causes insensitivity to further instillation of capsaicin-related drugs (Jancsó, 1968; Szolcsányi et al., 1975;
Szolcsányi and Jancsó-Gábor, 1976; Gamse et al., 1981b).
Inhibition of corneal chemonociception may last cin-related drugs (Jancsó, 1968; Szolcsányi et al., 1975;
Szolcsányi and Jancsó-Gábor, 1976; Gamse et al., 1981b).
Inhibition of corneal chemonociception may last for days
or weeks, depending on the dose applied, but is of Szolcsányi and Jancsó-Gábor, 1976; Gamse et al., 1981b).
Inhibition of corneal chemonociception may last for days
or weeks, depending on the dose applied, but is of shorter
duration than that produced by systemic administr Inhibition of corneal chemonociception may last for days
or weeks, depending on the dose applied, but is of shorter st
duration than that produced by systemic administration for
fol mg/kg or higher doses of capsaicin (Szol or weeks, depending on the dose applied, but is of shorter straturation than that produced by systemic administration function function function of 50 mg/kg or higher doses of capsaicin (Szolcsányi et (Lal., 1975; Gamse et duration than that produced by systemic administration of 50 mg/kg or higher doses of capsaicin (Szolcsányi el., 1975; Gamse et al., 1981b). Although capsaicin do not induce any gross or ultrastructural damage of the corne of 50 mg/kg or higher doses of capsaicin (Szolcsányi et al., 1975; Gamse et al., 1981b). Although capsaicin does not induce any gross or ultrastructural damage of the corneal epithelium, it produces swelling of mitochondri al., 1975; Gamse et al., 1981b). Although capsaicin does
not induce any gross or ultrastructural damage of the
corneal epithelium, it produces swelling of mitochondria,
disorganization of mitochondrial cristae, and a 90% r corneal epithelium, it produces swelling of mitochondria, disorganization of mitochondrial cristae, and a 90% reduction of the number of microvesicles in unmyelinated nerve endings of the cornea (Szolcsányi et al., 1975). corneal epithelium, it produces swelling of mitochondria, drug disorganization of mitochondrial cristae, and a 90% re-
duction of the number of microvesicles in unmyelinated time
nerve endings of the cornea (Szolcsányi et disorganization of mitochondrial cristae, and a 90% return duction of the number of microvesicles in unmyelinated time
nerve endings of the cornea (Szolcsányi et al., 1975). m
These ultrastructural changes, which are obser duction of the number of microvesicles in unmyelinated
nerve endings of the cornea (Szolcsányi et al., 1975).
These ultrastructural changes, which are observed 5 h
after repeated instillation of 33 mM capsaicin, are strict nerve endings of the cornea (Szolcsányi et al., 1975). m
These ultrastructural changes, which are observed 5 h
after repeated instillation of 33 mM capsaicin, are strictly co
confined to nerve endings which in the cornea a These ultrastructural changes, which are observed 5 h after repeated instillation of 33 mM capsaicin, are strictly confined to nerve endings which in the cornea are all unmyelinated (Szolcsányi et al., 1975). No direct sig after repeated instillation of 33 mM capsaicin, are strictle confined to nerve endings which in the cornea are a unmyelinated (Szolcsányi et al., 1975). No direct sign caxonal degeneration was seen by Szolcsányi et al. (19 confined to nerve endings which in the cornea are all summyelinated (Szolcsányi et al., 1975). No direct sign of baxonal degeneration was seen by Szolcsányi et al. (1975), cobut this issue calls for reinvestigation and con unmyelinated (Szolcsányi et al., 1975). No direct sign of baxonal degeneration was seen by Szolcsányi et al. (1975), c
but this issue calls for reinvestigation and confirmation. b
Repeated topical application of 33 mM caps axonal degeneration was seen by Szolcsányi et al. (1975), conduct this issue calls for reinvestigation and confirmation. be Repeated topical application of 33 mM capsaicin to the that eye also is followed, within 4 h, by but this issue calls for reinvestigation and confirmation. be the Repeated topical application of 33 mM capsaicin to the that rat eye also is followed, within 4 h, by an 80% depletion hund for substance P from the cornea, Repeated topical application of 33 mM orat eye also is followed, within 4 h, by an of substance P from the cornea, which refollowing 3 weeks as does the cornea chemogenic pain (Gamse et al., 1981b).

being involved in the regulation of the cardiovascular 1981; Carpenter and Lynn, 1981; Anand et al., 1983; and respiratory systems (Jancsó and Such, 1985). Injec- Tóth-Kása et al. 1983, 1986; Szolcsányi, 1990) are imtion o and respiratory systems (Jancsó and Such, 1985). Injec-
tion of 80 nmol capsaicin into the area postrema and
adjacent nucleus tractus solitarii of the rat brainstem with capsaicin, whereas mechanonociception and percep-
re Local application of capsaicin to the skin of primates
and rodents is followed by a long-term defunctionaliza-ER
Local application of capsaicin to the skin of pri
and rodents is followed by a long-term defunction
tion of sensory neurons supplying the treated are ER
Local application of capsaicin to the skin of primates
and rodents is followed by a long-term defunctionaliza-
tion of sensory neurons supplying the treated area. Re-
peated administration of 33 mM capsaicin to the monk Local application of capsaicin to the skin of primates
and rodents is followed by a long-term defunctionaliza-
tion of sensory neurons supplying the treated area. Re-
peated administration of 33 mM capsaicin to the monkey
 Local application of capsaicin to the skin of primates
and rodents is followed by a long-term defunctionaliza-
tion of sensory neurons supplying the treated area. Re-
peated administration of 33 mM capsaicin to the monkey
 and rodents is followed by a long-term defunctionalization of sensory neurons supplying the treated area. Repeated administration of 33 mM capsaicin to the monkey skin results in a significant reduction of the cutaneous su tion of sensory neurons supplying the treated area. Re-
peated administration of 33 mM capsaicin to the monkey
skin results in a significant reduction of the cutaneous
substance P content and in inhibition of neurally me-
 peated administration of 33 mM capsaicin to the monkey
skin results in a significant reduction of the cutaneous
substance P content and in inhibition of neurally me-
diated increases in vascular permeability (Alber et al., skin results in a significant reduction of the cutaneous
substance P content and in inhibition of neurally me-
diated increases in vascular permeability (Alber et al.,
1989). Likewise, application of several doses of 3.3 t substance P content and in inhibition of neurally me-
diated increases in vascular permeability (Alber et al.,
1989). Likewise, application of several doses of 3.3 to 33
mM capsaicin to the human skin inhibits the axon ref diated increases in vascular permeability (Alber et al., 1989). Likewise, application of several doses of 3.3 to 33 mM capsaicin to the human skin inhibits the axon reflex vasodilatation induced by histamine, substance P, 1989). Likewise, application of several doses of 3.3 to 33 mM capsaicin to the human skin inhibits the axon reflex vasodilatation induced by histamine, substance P, somatostatin, vasoactive intestinal polypeptide (Bernstei mM capsaicin to the human skin inhibits the axon reflex
vasodilatation induced by histamine, substance P, so-
matostatin, vasoactive intestinal polypeptide (Bernstein
et al., 1981; Anand et al., 1983; Tóth-Kása et al., 198 vasodilatation induced by histamine, substance P, somatostatin, vasoactive intestinal polypeptide (Bernstein
et al., 1981; Anand et al., 1983; Tóth-Kása et al., 1983;
Szolcsányi, 1988), allergen (Lundblad et al., 1987; Mcmatostatin, vasoactive intestinal polypeptide (Bernstein
et al., 1981; Anand et al., 1983; Tóth-Kása et al., 1983;
Szolcsányi, 1988), allergen (Lundblad et al., 1987; Mc-
Cusker et al., 1989), heat injury, or mechanical tr et al., 1981; Anand et al., 1983; Tóth-Kása et al., 1983; Szolcsányi, 1988), allergen (Lundblad et al., 1987; Mc-Cusker et al., 1989), heat injury, or mechanical trauma (Carpenter and Lynn, 1981). In addition, chemo- and t Szolcsányi, 1988), allergen (Lundblad et al., 1987; Mc-
Cusker et al., 1989), heat injury, or mechanical trauma
(Carpenter and Lynn, 1981). In addition, chemo- and
thermonociception (Jancsó, 1960, 1968; Bernstein et al.,
1 Cusker et al., 1989), heat injury, or mechanical trauma (Carpenter and Lynn, 1981). In addition, chemo- and thermonociception (Jancsó, 1960, 1968; Bernstein et al., 1981; Carpenter and Lynn, 1981; Anand et al., 1983; Tôththermonociception (Jancsó, 1960, 1968; Bernstein et al., 1981; Carpenter and Lynn, 1981; Anand et al., 1983; Tóth-Kása et al. 1983, 1986; Szolcsányi, 1990) are impaired for several days to weeks in the skin area treated with capsaicin, whereas mechanonociception and perception of touch and temperature remain unaltered in the long paired for several days to weeks in the skin area treated
with capsaicin, whereas mechanonociception and percep-
tion of touch and temperature remain unaltered in the
long term (Jancsó, 1960, 1968; Bernstein et al., 1981;
 with capsaicin, whereas mechanonociception and perception of touch and temperature remain unaltered in the long term (Jancsó, 1960, 1968; Bernstein et al., 1981; Tóth-Kása et al., 1983; Szolcsányi, 1990). Repeated top-
ica tion of touch and temperature remain unaltered in the
long term (Jancsó, 1960, 1968; Bernstein et al., 1981;
Tóth-Kása et al., 1983; Szolcsányi, 1990). Repeated top-
ical application of capsaicin (33 mM) to exposed blister long term (Jancsó, 1960, 1968; Bernstein et al., 1981; Tóth-Kása et al., 1983; Szolcsányi, 1990). Repeated topical application of capsaicin (33 mM) to exposed blister bases on the human forearm blocks the algesic effects o 1977). al application of capsaicin (33 mM) to exposed blister
ses on the human forearm blocks the algesic effects of
psaicin, bradykinin, and acetylcholine (Szolcsányi,
77).
Topical application of 3 to 30 mM capsaicin to the
sal

(Carpenter and Lynn, 1981). In addition, chemo- and L_3 menter and Lynn, 1981; Carpenter and Lynn, 1981; Asset et al., 1983; Tóth-Kása et al. 1983, 1986; Szolcsányi, 1990) are impaired for several days to weeks in the sk bases on the human forearm blocks the algesic effects of capsaicin, bradykinin, and acetylcholine (Szolcsányi, 1977).
1977). Topical application of 3 to 30 mM capsaicin to the nasal mucosa of the guinea pig results in long capsaicin, bradykinin, and acetylcholine (Szolcsán
1977).
Topical application of 3 to 30 mM capsaicin to t
nasal mucosa of the guinea pig results in long-lasti
depletion of substance P from the nasal mucosa, inhi
tion of p 1977).
Topical application of 3 to 30 mM capsaicin to the
nasal mucosa of the guinea pig results in long-lasting
depletion of substance P from the nasal mucosa, inhibi-
tion of protective reflexes in response to nasal irri Topical application of 3 to 30 mM capsaicin to the
nasal mucosa of the guinea pig results in long-lasting
depletion of substance P from the nasal mucosa, inhibi-
tion of protective reflexes in response to nasal irritation, nasal mucosa of the guinea pig results in long-lasting
depletion of substance P from the nasal mucosa, inhibi-
tion of protective reflexes in response to nasal irritation,
and block of sensory nerve-induced extravasation o depletion of substance P from the nasal mucosa, inhibition of protective reflexes in response to nasal irritation, and block of sensory nerve-induced extravasation of plasma proteins (Lundblad, 1984). These changes are of and block of sensory nerve-induced extravasation of plasma proteins (Lundblad, 1984). These changes are of the same magnitude as those produced by systemic capsaicin treatment; they are evident for at least 2 months after and block of sensory nerve-induced extravasation of plasma proteins (Lundblad, 1984). These changes are of the same magnitude as those produced by systemic capsaicin treatment; they are evident for at least 2 months after plasma proteins (Lundblad, 1984). These changes are of
the same magnitude as those produced by systemic cap-
saicin treatment; they are evident for at least 2 months
after the topical application of capsaicin and are re-
s the same magnitude as those produced by systemic capsaicin treatment; they are evident for at least 2 months after the topical application of capsaicin and are restricted to the treated organ as no neurochemical or functio saicin treatment; they are evident for at least 2 months
after the topical application of capsaicin and are re-
stricted to the treated organ as no neurochemical or
functional alterations are seen, for example, in the uret after the topical application of capsaicin and are restricted to the treated organ as no neurochemical or
functional alterations are seen, for example, in the ureter
(Lundblad, 1984). Similarly, repetitive administration stricted to the treated organ as no neurochemical or
functional alterations are seen, for example, in the ureter
(Lundblad, 1984). Similarly, repetitive administration of
250 nmol capsaicin to the human nasal mucosa leads functional alterations are seen, for example, in the ureter (Lundblad, 1984). Similarly, repetitive administration of 250 nmol capsaicin to the human nasal mucosa leads to abolition of the irritating and secretory effects (Lundblad, 1984). Similarly, repetitive administration of 250 nmol capsaicin to the human nasal mucosa leads to abolition of the irritating and secretory effects of the drug, which lasts for several weeks and is confined 250 nmol capsaicin to the human nasal mucosa leads to
abolition of the irritating and secretory effects of the
drug, which lasts for several weeks and is confined to the
treated nostril (Geppetti et al. 1988b). When appli abolition of the irritating and secretory effects of the drug, which lasts for several weeks and is confined to the treated nostril (Geppetti et al. 1988b). When applied 10 times within 40 min to the human tongue, capsaici drug, which lasts for several weeks and is confined to the treated nostril (Geppetti et al. 1988b). When applied 10 times within 40 min to the human tongue, capsaicin (33 mM) abolishes the burning sensation evoked by capsa treated nostril (Geppetti et al. 1988b). When applied 10
times within 40 min to the human tongue, capsaicin (33
mM) abolishes the burning sensation evoked by capsaicin
or mustard oil; responsiveness to these chemicals re-
 times within 40 min to the human tongue, capsaicin (33 mM) abolishes the burning sensation evoked by capsaicin
or mustard oil; responsiveness to these chemicals re-
covers during the following 2 days. However, taste, sen-
 mM) abolishes the burning sensation evoked by capsaicin
or mustard oil; responsiveness to these chemicals re-
covers during the following 2 days. However, taste, sen-
sitivity to tactile stimuli, and the cold sensation evo or mustard oil; responsiveness to these chemicals recovers during the following 2 days. However, taste, sensitivity to tactile stimuli, and the cold sensation evoked by menthol remain unaltered (Szolcsányi, 1977). Thus, co covers during the following 2 days. However, taste, sensitivity to tactile stimuli, and the cold sensation evoked
by menthol remain unaltered (Szolcsányi, 1977). Thus,
consumption of hot food rich in capsaicin is unlikely sitivity to tactile stimuli, and the cold sensation evoked
by menthol remain unaltered (Szolcsányi, 1977). Thus,
consumption of hot food rich in capsaicin is unlikely to
be toxic for the tongue, and there is, in fact, no e humans. n sumption of hot food rich in capsaicin is unlikely to
toxic for the tongue, and there is, in fact, no evidence
at ingested capsaicin exerts any neurotoxic effect in
mans.
The selective and reversible effects of capsaicin

be toxic for the tongue, and there is, in fact, no evidence
that ingested capsaicin exerts any neurotoxic effect in
humans.
The selective and reversible effects of capsaicin applied
locally to the skin or nasal mucosa are that ingested capsaicin exerts any neurotoxic effect in
humans.
The selective and reversible effects of capsaicin applied
locally to the skin or nasal mucosa are beginning to be
used as a treatment for certain neurological

PHARMACOLOGICAL REVIEWS

CAPSAICIN
involving sensory neurons. Thus, several applications of the
capsaicin into the nasal mucosa have been reported to gene
cure vasomotor rhinitis (Marabini et al., 1988; Saria and nals CAPSAICIN
involving sensory neurons. Thus, several applications of the
capsaicin into the nasal mucosa have been reported to ger
cure vasomotor rhinitis (Marabini et al., 1988; Saria and nal
Wolf, 1988) and to be beneficia involving sensory neurons. Thus, several applications of
capsaicin into the nasal mucosa have been reported to
cure vasomotor rhinitis (Marabini et al., 1988; Saria and
Wolf, 1988) and to be beneficial in cluster headache
 involving sensory neurons. Thus, several applications of capsaicin into the nasal mucosa have been reported to cure vasomotor rhinitis (Marabini et al., 1988; Saria and Wolf, 1988) and to be beneficial in cluster headache capsaicin into the nasal mucosa have been reported to genere vasomotor rhinitis (Marabini et al., 1988; Saria and na Wolf, 1988) and to be beneficial in cluster headache vertex (Sicuteri et al., 1989). In some, but not all cure vasomotor rhinitis (Marabini et al., 1988; Saria a Wolf, 1988) and to be beneficial in cluster headad (Sicuteri et al., 1989). In some, but not all, paties topical administration of 0.8 mM capsaicin to the skinable to Wolf, 1988) and to be beneficial in cluster headache (Sicuteri et al., 1989). In some, but not all, patients topical administration of 0.8 mM capsaicin to the skin is able to relieve pain associated with postherpetic neura (Sicuteri et al., 1989). In some, but not all, patients v
topical administration of 0.8 mM capsaicin to the skin is
able to relieve pain associated with postherpetic neural-
gia (Bernstein et al., 1987; Don, 1988; Watson e topical administration of 0.8 mM capsaicin to the skin is pable to relieve pain associated with postherpetic neural-
gia (Bernstein et al., 1987; Don, 1988; Watson et al., 1988; Bjerring et al., 1990), pain associated with able to relieve pain associated with postherpetic neural-
gia (Bernstein et al., 1987; Don, 1988; Watson et al.,
1988; Bjerring et al., 1990), pain associated with diabetic
neuropathy (Ross and Varipapa, 1989), pain associ gia (Bernstein et al., 1987; Don, 1988; Watson et al., 1988; Bjerring et al., 1990), pain associated with diabetic neuropathy (Ross and Varipapa, 1989), pain associated with psoriasis (Bernstein et al., 1986), postmastecto 1988; Bjerring et al., 1990), pain associated with diabetic
neuropathy (Ross and Varipapa, 1989), pain associated
with psoriasis (Bernstein et al., 1986), postmastectomy
pain (Watson et al., 1989), and local stump pain (Ra with psoriasis (Bernstein et al., 1986), postmastectomy
pain (Watson et al., 1989), and local stump pain (Rayner
et al., 1989). Treatment for several days may suppress
pain for several weeks.
Local injection of capsaicin i pain (Watson et al., 1989), and local stump pain (Rayner et al., 1989). Treatment for several days may suppress pain for several weeks.
Local injection of capsaicin into tissues is another route by which peripheral sensory

pain (Watson et al., 1989), and local stump pain (Rayner the al., 1989). Treatment for several days may suppress ide pain for several weeks. oricular for several weeks. The column for several weeks. The column for the peri et al., 1989). Treatment for several days may suppress ideal injection of capsaicin into tissues is another to
Local injection of capsaicin into tissues is another to
route by which peripheral sensory nerve endings can be
 pain for several weeks.
Local injection of capsaicin into tissues is anothe
route by which peripheral sensory nerve endings can b
defunctionalized, although in this case an axonal site c
action may also play a role. Inject Local injection of capsaicin into tissues is another to route by which peripheral sensory nerve endings can be celefunctionalized, although in this case an axonal site of (Naction may also play a role. Injection of 25 n route by which peripheral sensory nerve endings can be defunctionalized, although in this case an axonal site of action may also play a role. Injection of 25 nmol dihydrocapsaicin, a congener of capsaicin, into the footpad defunctionalized, although in this case an axonal site of action may also play a role. Injection of 25 nmol dihy-
drocapsaicin, a congener of capsaicin, into the footpad
skin of guinea pigs causes a prompt and long-lasting action may also play a role. Injection of 25 nmol dihy-
drocapsaicin, a congener of capsaicin, into the footpad toche
skin of guinea pigs causes a prompt and long-lasting and
inhibition of thermonociception in the area sur drocapsaicin, a congener of capsaicin, into the footposkin of guinea pigs causes a prompt and long-lastiinhibition of thermonociception in the area surroundine site of injection but does not deplete substance from dorsal r skin of guinea pigs causes a prompt and long-lastin
inhibition of thermonociception in the area surroundin
the site of injection but does not deplete substance
from dorsal root ganglia or inhibit the retrograde trans
port the site of injection but does not deplete substance P eration of sensory neurons exposed to capsaicin.

from dorsal root ganglia or inhibit the retrograde trans-

port of nerve growth factor (Miller et al., 1982a). How-
 the site of injection but does not deplete substance P eration dorsal root ganglia or inhibit the retrograde transport of nerve growth factor (Miller et al., 1982a). However, injection of a much higher dose of capsaicin From dotsal floot ganging of infinite the retrograde transport of nerve growth factor (Miller et al., 1982a). How-
ever, injection of a much higher dose of capsaicin (8 the μ mol) into the skin of the rat scrotum inhibi put of herve growth factor (whilet et al., 1582a). How-
ever, injection of a much higher dose of capsaicin (8
 μ mol) into the skin of the rat scrotum inhibits the
retrograde transport of horseradish peroxidase in the
pud μ mol) into the skin of the rat scrotum inhibits the retrograde transport of horseradish peroxidase in the pudendal nerve toward the sixth lumbar and first sacral dorsal root ganglia (Taylor et al., 1984, 1985). This ef (Taylor et al., 1985), seems to be permanent because it retrograde transport of horseradish peroxidase in the Ipudendal nerve toward the sixth lumbar and first sacral
dorsal root ganglia (Taylor et al., 1984, 1985). This effect, 1
which involves predominantly small afferent neu pudendal nerve toward the sixth lumbar and first sacral
dorsal root ganglia (Taylor et al., 1984, 1985). This effect,
which involves predominantly small afferent neurons L
(Taylor et al., 1985), seems to be permanent becau dorsal root ganglia (Taylor et al., 1984, 1985). This effect,
which involves predominantly small afferent neurons
(Taylor et al., 1985), seems to be permanent because it
is seen even 1 year posttreatment, although no sign which involves predominantly small afferent neurons L
(Taylor et al., 1985), seems to be permanent because it sis
is seen even 1 year posttreatment, although no sign of et
cell body degeneration in the dorsal root ganglia (Taylor et al., 1985), seems to be permanent because it
is seen even 1 year posttreatment, although no sign of
cell body degeneration in the dorsal root ganglia is ob-
served (Taylor et al., 1984). Retrobulbar injection o is seen even 1 year posttreatment, although no sign of ecell body degeneration in the dorsal root ganglia is observed (Taylor et al., 1984). Retrobulbar injection of we capsaicin (16 μ mol) into the rabbit eye inhibits cell body degeneration in the dorsal root ganglia is observed (Taylor et al., 1984). Retrobulbar injection of weeks, this effect being confined to the treated census inflammation in response to various irritant stimuli fo capsaicin $(16 \mu \text{mol})$ into the rabbit eye inhibits ocular inflammation in response to various irritant stimuli for several weeks, this effect being confined to the treated eye (Camras and Bito, 1980; Bynke, 1983). Likewi inflammation in response to various irritant stimuli for elicit several weeks, this effect being confined to the treated cells eye (Camras and Bito, 1980; Bynke, 1983). Likewise, these topical application of 33 mM capsaici several weeks, this effect being confined to the treated
eye (Camras and Bito, 1980; Bynke, 1983). Likewise,
topical application of 33 mM capsaicin to the exposed
urinary bladder of the adult rat depletes substance P
from eye (Calinas and Bio, 1960, Byike, 1960). Elkewise,
topical application of 33 mM capsaicin to the exposed
urinary bladder of the adult rat depletes substance P
from the urinary bladder, but not from the adjacent
ureter, an topical application of 33 mM capsaicin to the exposed
urinary bladder of the adult rat depletes substance P
from the urinary bladder, but not from the adjacent
ureter, and leaves chemonociceptive and local effector
functio driven the urinary bladder, but not from the adjacent
from the urinary bladder, but not from the adjacent
ureter, and leaves chemonociceptive and local effector
functions of sensory neurons unaltered in organs distant
from different and leaves chemonociceptive and local effector
functions of sensory neurons unaltered in organs distant
from the urinary bladder such as the skin and eye (Maggi
et al., 1989b). The neurochemical and functional ch runctions of sensory neurons unaitered in organs distant
from the urinary bladder such as the skin and eye (Maggi z
et al., 1989b). The neurochemical and functional changes
produced by local application of capsaicin to the et al., 1989b). The neurochemical and functional changes
produced by local application of capsaicin to the rat
urinary bladder are of the same magnitude as those
produced by systemic capsaicin treatment (Maggi et al., 1989b). atter of the same magnitude as those produced by systemic capsaicin treatment (Maggi et al., 1989b).
6. *Effects of capsaicin on sensory neurons in vitro*. After only a 5-min exposure to 640 μ M capsaicin, nerve fibers

only a 5-min exposure to 640 μ M capsaicin, nerve fibers in the epithelium of the isolated rat trachea exhibit in 1989b).
 in the epithelium of the isolated rat trachea exhibit

only a 5-min exposure to 640 μ M capsaicin, nerve fibers

in the epithelium of the isolated rat trachea exhibit

ultrastructural changes that are indi o. Effects of capsatch on sensory neurons in ouro. After Fionly a 5-min exposure to 640μ M capsatch, nerve fibers blin the epithelium of the isolated rat trachea exhibit lead ultrastructural changes that are indicative in the epithelium of the isolated rat trachea exhibit lest ultrastructural changes that are indicative of degenera-
tion (Hoyes et al., 1981). A significant increase in axon (M
diameter, a reduction in axoplasmic density,

involving sensory neurons. Thus, several applications of the most prominent morphological features. These de-
capsaicin into the nasal mucosa have been reported to generative alterations are confined to axons with termigenerative alterations are confined to axons with termigenerative alternations are confined to axons with term
generative alterations are confined to axons with term
nals containing a high proportion of large dense-cor 165
the most prominent morphological features. These de-
generative alterations are confined to axons with termi-
nals containing a high proportion of large dense-cored
vesicles and only scattered small vesicles, whereas a the most prominent morphological features. These degenerative alterations are confined to axons with terminals containing a high proportion of large dense-cored vesicles and only scattered small vesicles, whereas axons wit the most prominent morphological features. These de-
generative alterations are confined to axons with termi-
nals containing a high proportion of large dense-cored
vesicles and only scattered small vesicles, whereas axons generative attenuions are commed to axons with terminals containing a high proportion of large dense-cored vesicles and only scattered small vesicles, whereas axons with terminals containing large numbers of closely packed nals containing a high proportion of large dense-cored
vesicles and only scattered small vesicles, whereas axons
with terminals containing large numbers of closely
packed small vesicles are not affected (Hoyes et al., 1981 vesicles and only scattered small vesicles, whereas axons
with terminals containing large numbers of closely
packed small vesicles are not affected (Hoyes et al., 1981).
Exactly similar changes are seen in the isolated gu with terminals containing large numbers of closely
packed small vesicles are not affected (Hoyes et al., 1981).
Exactly similar changes are seen in the isolated guinea
pig ureter (Sikri et al., 1981) in which concentratio packed small vesicles are not affected (Hoyes et al., 1981).
Exactly similar changes are seen in the isolated guinea
pig ureter (Sikri et al., 1981) in which concentrations of
1 to 10 μ M capsaicin are able to produce d Exactly similar changes are seen in the isolated guinea
pig ureter (Sikri et al., 1981) in which concentrations of
1 to 10 μ M capsaicin are able to produce degeneration of
up to 70% of all axonal profiles when examined pig ureter (Sikri et al., 1981) in which concentrations of 1 to 10 μ M capsaicin are able to produce degeneration of up to 70% of all axonal profiles when examined 1 h after a 6-min exposure to the drug (Király et al., 1 to 10 μ M capsaicin are able to produce degeneration of up to 70% of all axonal profiles when examined 1 h after a 6-min exposure to the drug (Király et al., 1991). Although the origin of the degenerating axons has no up to 70% of all axonal profiles when examined 1 h after
a 6-min exposure to the drug (Király et al., 1991). Al-
though the origin of the degenerating axons has not been
identified, it is likely that they are of primary a a 6-min exposure to the drug (Király et al., 1991). Although the origin of the degenerating axons has not been
identified, it is likely that they are of primary afferent
origin, because the same concentrations of capsaici chough the origin of the degenerating axons has not been
identified, it is likely that they are of primary afferent
origin, because the same concentrations of capsaicin (1
to 10 μ M) induce ultrastructural damage of mos origin, because the same concentrations of capsaicin (1 to 10 μ M) induce ultrastructural damage of most small cell bodies in the isolated nodose ganglion of the rat (Marsh et al., 1987). Within 5 min of exposure to the to 10 μ M) induce ultrastructural damage of most sma
cell bodies in the isolated nodose ganglion of the ra
(Marsh et al., 1987). Within 5 min of exposure to the
drug, ultrastructural changes including swelling of m
toch cell bodies in the isolated nodose ganglion of the rat (Marsh et al., 1987). Within 5 min of exposure to the drug, ultrastructural changes including swelling of mitochondria, disruption of neurofilament organization, and f drug, ultrastructural changes including swelling of mitochondria, disruption of neurofilament organization. and fiber enlargement take place (Marsh et al., 1987).

capsaicin (16 μ mol) into the rabbit eye inhibits ocular inferior mesenteric ganglion of the guinea pig capsaicin
inflammation in response to various irritant stimuli for elicits a slow depolarization of the principal g The rapidity with which morphological changes take to 10 μ M) induce ultrastructural damage of most small
cell bodies in the isolated nodose ganglion of the rat
(Marsh et al., 1987). Within 5 min of exposure to the
drug, ultrastructural changes including swelling of mi-All of these observations indicate rapid in vitro degeneration of sensory neurons exposed to capsaicin.
The rapidity with which morphological changes take
place after in vitro exposure to capsaicin is paralleled by
the qui eration of sensory neurons exposed to capsaicin.
The rapidity with which morphological changes take
place after in vitro exposure to capsaicin is paralleled by
the quick onset of functional changes. Isolated muscle
tissues The rapidity with which morphological changes take
place after in vitro exposure to capsaicin is paralleled by
the quick onset of functional changes. Isolated muscle
tissues including cardiac muscle (Zernig et al., 1984;
F place after in vitro exposure to capsaicin is paralleled by
the quick onset of functional changes. Isolated muscle
tissues including cardiac muscle (Zernig et al., 1984;
Franco-Cereceda and Lundberg, 1988), visceral smooth the quick onset of functional changes. Isolated muscle tissues including cardiac muscle (Zernig et al., 1984; Franco-Cereceda and Lundberg, 1988), visceral smooth muscle (Barthó and Szolcsányi, 1978; Barthó et al., 1982a, Insues Including caluat muscle (Defing et al., 1987,
Franco-Cereceda and Lundberg, 1988), visceral smooth
muscle (Barthó and Szolcsányi, 1978; Barthó et al.,
1982a, 1987; Chahl, 1982; Hua and Lundberg, 1986;
Lundberg and S muscle (Barthó and Szolcsányi, 1978; Barthó et al., 1982a, 1987; Chahl, 1982; Hua and Lundberg, 1986; Lundberg and Saria, 1987; Maggi et al., 1987c), vascular smooth muscle (Toda et al., 1972; Duckles, 1986; Saito et al., 1982a, 1987; Chahl, 1982; Hua and Lundberg, 1986;
Lundberg and Saria, 1987; Maggi et al., 1987c), vascular
smooth muscle (Toda et al., 1972; Duckles, 1986; Saito
et al., 1988; Edvinsson et al., 1990), and the iris sphincte Lundberg and Saria, 1987; Maggi et al., 1987c), vascular
smooth muscle (Toda et al., 1972; Duckles, 1986; Saito
et al., 1988; Edvinsson et al., 1990), and the iris sphincter
muscle (Ueda et al., 1984) promptly respond to c smooth muscle (Toda et al., 1972; Duckles, 1986; Saito
et al., 1988; Edvinsson et al., 1990), and the iris sphincter
muscle (Ueda et al., 1984) promptly respond to capsaicin
with neurogenic contraction or relaxation. In th et al., 1988; Edvinsson et al., 1990), and the iris sphincter
muscle (Ueda et al., 1984) promptly respond to capsaicin
with neurogenic contraction or relaxation. In the isolated
inferior mesenteric ganglion of the guinea p muscle (Ueda et al., 1984) promptly respond to capsaicin
with neurogenic contraction or relaxation. In the isolated
inferior mesenteric ganglion of the guinea pig capsaicin
elicits a slow depolarization of the principal ga with neurogenic contraction or relaxation. In the isolated
inferior mesenteric ganglion of the guinea pig capsaicin
elicits a slow depolarization of the principal ganglion
cells (Tsunoo et al., 1982; Dun and Kiraly, 1983). inferior mesenteric ganglion of the guinea pig capsaicin elicits a slow depolarization of the principal ganglion cells (Tsunoo et al., 1982; Dun and Kiraly, 1983). All of these acute effects of capsaicin are short lasting elicits a slow depolarization of the principal ganglion cells (Tsunoo et al., 1982; Dun and Kiraly, 1983). All of these acute effects of capsaicin are short lasting and, within a few minutes, the tissues become unresponsiv cells (Tsunoo et al., 1982; Dun and Kiraly, 1983). All
these acute effects of capsaicin are short lasting an
within a few minutes, the tissues become unrespons
to both capsaicin and other means of sensory ner
stimulation. these acute effects of capsaicin are short lasting and, within a few minutes, the tissues become unresponsive to both capsaicin and other means of sensory nerve stimulation. It can be assumed that this state of "desensitiz to both capsaicin and other means of sensory nerve stimulation. It can be assumed that this state of "desensitization" reflects not only defunctionalization but also degeneration of sensory nerve fibers because desensitiza to both capsaicin and other means of sensory nerve
stimulation. It can be assumed that this state of "desen-
sitization" reflects not only defunctionalization but also
degeneration of sensory nerve fibers because desensit stimulation. It can be assumed that this state of desensitization" reflects not only defunctionalization but also
degeneration of sensory nerve fibers because desensiti-
zation to capsaicin is achieved by in vitro concent sitization" reflects not only defunctionalization but also
degeneration of sensory nerve fibers because desensiti-
zation to capsaicin is achieved by in vitro concentrations
of capsaicin in the range of 0.3 to 10 μ M wh degeneration of sensory nerve fibers because desensitization to capsaicin is achieved by in vitro concentrations of capsaicin in the range of 0.3 to 10μ M which are of the same magnitude as those producing degenerativ zation to capsaicin is achieved by in vitro concentrations
of capsaicin in the range of 0.3 to 10μ M which are of the
same magnitude as those producing degenerative changes
in the isolated ureter (Király et al., 1991) of capsaicin in the range of 0.3 to 10 μ M which are of the same magnitude as those producing degenerative changes
in the isolated ureter (Király et al., 1991) and nodose
ganglion of the rat (Marsh et al., 1987) and in same magnitude as those producing degenerative changes
in the isolated ureter (Király et al., 1991) and nodose
ganglion of the rat (Marsh et al., 1987) and in dorsal root
ganglia grown in tissue culture (Wood et al., 1988 in the isolated ureter (Király et al., 1991) and nodose ganglion of the rat (Marsh et al., 1987) and in dorsal root ganglia grown in tissue culture (Wood et al., 1988). Furthermore, a 5-min exposure of the isolated rat ur ganglion of the rat (Marsh et al., 1987) and in dorsal root ganglia grown in tissue culture (Wood et al., 1988).
Furthermore, a 5-min exposure of the isolated rat urinary bladder to a solution containing 1 to 10 μ M cap Furthermore, a 5-min exposure of the isolated rat urinary
bladder to a solution containing 1 to 10 μ M capsaicin
leads to substantial depletion of substance P, which does
not become appreciable, however, until 3 h postt leads to substantial depletion of substance P, which does adder to a solution containing 1 to 10 μ M capsaicin
Ids to substantial depletion of substance P, which does
t become appreciable, however, until 3 h posttreatment
Iaggi et al., 1987e).
7. *Effects of capsaicin on sensor* leads to substantial depletion of substance P, which does
not become appreciable, however, until 3 h posttreatment
(Maggi et al., 1987e).
7. Effects of capsaicin on sensory neurons in culture.
The sensitivity to the acute

HOLZEE
Capsaicin is maintained when dorsal root ganglia are m
grown in tissue culture. Like in vivo, two populations of sa
neurons, large light and small dark cell bodies, can be HOLZER
capsaicin is maintained when dorsal root ganglia are mo
grown in tissue culture. Like in vivo, two populations of said
neurons, large light and small dark cell bodies, can be Inh
distinguished in cultures of dorsal capsaicin is maintained when dorsal root ganglia are more s
grown in tissue culture. Like in vivo, two populations of saicin t
neurons, large light and small dark cell bodies, can be Inhibit
distinguished in cultures of do capsaicin is maintained when dorsal root ganglia are
grown in tissue culture. Like in vivo, two populations of
neurons, large light and small dark cell bodies, can be
distinguished in cultures of dorsal root ganglia from
n grown in tissue culture. Like in vivo, two populations of neurons, large light and small dark cell bodies, can be distinguished in cultures of dorsal root ganglia from newborn or adult rats (Winter, 1987; Wood et al., 1988 neurons, large light and small dark cell bodies, can be distinguished in cultures of dorsal root ganglia from newborn or adult rats (Winter, 1987; Wood et al., 1988; Winter et al., 1990). The large light neurons are select distinguished in cultures of dorsal root ganglia from
newborn or adult rats (Winter, 1987; Wood et al., 1988
Winter et al., 1990). The large light neurons are selectively labeled with an antibody to neurofilament protein
w newborn or adult rats (Winter, 1987; Wood et al., 1988; the Winter et al., 1990). The large light neurons are selectively labeled with an antibody to neurofilament protein, guideled with an antibody to neurofilament protei Winter et al., 1990). The large light neurons are selectively labeled with an antibody to neurofilament protein, guidely whereas the small dark cell bodies are neurofilament tree megative. Capsaicin stimulates a certain pr tively labeled with an antibody to neurofilament protein, guidely whereas the small dark cell bodies are neurofilament treepative. Capsaicin stimulates a certain proportion of when cultured dorsal root ganglion cells, exci whereas the small dark cell bodies are neurofilament trends the cultured dorsal root ganglion cells, excitation being fibre cultured dorsal root ganglion cells, excitation being fibre visualized by a cobalt uptake stain (W negative. Capsaicin stimulates a certain proportion of the cultured dorsal root ganglion cells, excitation being fivisualized by a cobalt uptake stain (Winter, 1987; Wood et al., 1988; Winter et al., 1990). Those cells tha the cultured dorsal root ganglion cells, excitation being
visualized by a cobalt uptake stain (Winter, 1987; Wood
et al., 1988; Winter et al., 1990). Those cells that are
sensitive to capsaicin are usually neurofilament ne visualized by a cobalt uptake stain (Winter, 1987; Wood a et al., 1988; Winter et al., 1990). Those cells that are (Esensitive to capsaicin are usually neurofilament negative of and fall totally within the population of sm et al., 1988; Winter et al., 1990). Those cells that are
sensitive to capsaicin are usually neurofilament negative
and fall totally within the population of small dark cells.
Approximately 50% of the neuronal cell bodies sensitive to capsaicin are usually neurofilament negative of subsets and fall totally within the population of small dark cells. guinearly 50% of the neuronal cell bodies derived the guident from neonatal dorsal root gang and fall totally within the population of small dark cells. guas
Approximately 50% of the neuronal cell bodies derived the
from neonatal dorsal root ganglia are sensitive to cap-
saicin, and overnight treatment of culture Approximately 50% of the neuronal cell bodies derived the from neonatal dorsal root ganglia are sensitive to capsaicin, and overnight treatment of cultures with 2μ M capsaicin results in the loss of most cell bodies whi from neonatal dorsal root ganglia are sensitive to capsaicin, and overnight treatment of cultures with 2μ M capsaicin results in the loss of most cell bodies which show cobalt staining in response to acute capsaicin or saicin, and overnight treatment of cultures with 2 μ M
capsaicin results in the loss of most cell bodies which
show cobalt staining in response to acute capsaicin or
the related resiniferatoxin (Winter, 1987; Wood et al capsaicin results in the loss of most cell bodies which
show cobalt staining in response to acute capsaicin or
the related resiniferatoxin (Winter, 1987; Wood et al.,
1988; Winter et al., 1990). Because prolonged exposure
 show cobalt staining in response to acute capsaicin or
the related resiniferatoxin (Winter, 1987; Wood et al.,
1988; Winter et al., 1990). Because prolonged exposure
to capsaicin also leads to a 37% reduction in the total
 the related resiniferatoxin (Winter, 1987; Wood et al., weaker inhibition of the axoplasmic transport of sub-
1988; Winter et al., 1990). Because prolonged exposure stance P in the rabbit when compared with the rat
to cap 1988; Winter et al., 1990). Because prolonged exposure
to capsaicin also leads to a 37% reduction in the total (number of cell bodies in the culture, it follows that most
of the capsaicin-sensitive cells are killed (Wood to capsaicin also leads to a 37% reduction in the total (G
number of cell bodies in the culture, it follows that most
of the capsaicin-sensitive cells are killed (Wood et al., ne
1988). Thus, degeneration of sensory neuro number of cell bodies in the culture, it follows that most
of the capsaicin-sensitive cells are killed (Wood et al.,
1988). Thus, degeneration of sensory neurons also takes
place in tissue cultures of dorsal root ganglia of the capsaicin-sensitive cells are killed (Wood et al., 1988). Thus, degeneration of sensory neurons also takes place in tissue cultures of dorsal root ganglia and the extent of cell loss is similar to that seen after sy 1988). Thus, degeneration of sensory neurons also takes wild
place in tissue cultures of dorsal root ganglia and the in
extent of cell loss is similar to that seen after systemic
proposaicin treatment of newborn rats (Ott place in tissue cultures of dorsal root ganglia and the extent of cell loss is similar to that seen after systemic
capsaicin treatment of newborn rats (Otten et al., 1983
McDougal et al., 1985; Arvidsson and Ygge, 1986). T extent of cell loss is similar to that seen after systemic P_{in} capsaicin treatment of newborn rats (Otten et al., 1983; are McDougal et al., 1985; Arvidsson and Ygge, 1986). The saic cellular specificity of capsaici capsaicin treatment of newborn rats (Otten et al., 1983; are
McDougal et al., 1985; Arvidsson and Ygge, 1986). The said
cellular specificity of capsaicin's and resiniferatoxin's
effects on cultured dorsal root ganglia is u McDougal et al., 1985; Arvidsson and Ygge, 1986). The
ellular specificity of capsaicin's and resiniferatoxies
ffects on cultured dorsal root ganglia is underlined
the finding that cultures of large light neurons at
monneu cellular specificity of capsaicin's and resiniferatoxin's
effects on cultured dorsal root ganglia is underlined by
the finding that cultures of large light neurons and
nonneuronal cells from the rat sciatic nerve, rat symp effects on cultured dorsal root ganglia is underlined by
the finding that cultures of large light neurons and defunctionalization (Barthó and Szolcsányi, 1980;
nonneuronal cells from rat dorsal root ganglia, nonneu-
ronal the finding that cultures of large light neurons and \overline{C}_8 nonneuronal cells from the rat sciatic nerve, rat sympathetic incurons, neural crest-derived neuroblastoma cells, and \overline{C}_8 hybrid cells derived from embr nonneuronal cells from rat dorsal root ganglia, nonneuronal cells from the rat sciatic nerve, rat sympathetic ineurons, neural crest-derived neuroblastoma cells, and hybrid cells derived from embryonal carcinoma cells are neurons, neural crest-derived neuroblastoma cells, and
hybrid cells derived from embryonal carcinoma cells are
not affected by the drugs (Bevan et al., 1987; Winter et
al., 1988, 1990; Wood et al., 1988).
E. Differences in *hybrid cells derived from embryonal carcinoma cells are* not affected by the drugs (Bevan et al., 1987; Winter et al., 1988, 1990; Wood et al., 1988).
E. Differences in the Sensitivity to Capsaicin among Mammalian Specie not affected by the drugs (Bevan et al., 1987; Winter et

tigated so far including humans, rat, mouse, guinea pig, E. Differences in the Sensitivity to Capsaicin among
Mammalian Species
Although capsaicin acts as a stimulant of thin sensory
neurons in all mammalian species that have been inves-
tigated so far including humans, rat, mou Mammalian Species

Although capsaicin acts as a stimulant of thin sensory

neurons in all mammalian species that have been inves-

tigated so far including humans, rat, mouse, guinea pig,

hamster, rabbit, cat, dog, goat (Although capsaicin acts as a stimulant of thin sensory
neurons in all mammalian species that have been inves-
tigated so far including humans, rat, mouse, guinea pig,
hamster, rabbit, cat, dog, goat (Glinsukon et al. 1980; neurons in all mammalian species that have been inves-
tigated so far including humans, rat, mouse, guinea pig,
hamster, rabbit, cat, dog, goat (Glinsukon et al. 1980;
Szolcsányi 1990), pig (Franco-Cereceda et al. 1987c;
F tigated so far including humans, rat, mouse, guinea pig, hamster, rabbit, cat, dog, goat (Glinsukon et al. 1980; Szolcsányi 1990), pig (Franco-Cereceda et al. 1987c; Franco-Cereceda and Lundberg, 1989; Matran et al., 1989, Szolcsányi 1990), pig (Franco-Cereceda et al. 1987c; Franco-Cereceda and Lundberg, 1989; Matran et al., 1989, 1990; Pierau and Szolcsányi, 1989; Alving et al., 1991), and bear (Rogers, 1984), there are considerable species Szolcsányi 1990), pig (Franco-Cereceda et al. 1987c;
Franco-Cereceda and Lundberg, 1989; Matran et al.,
1989, 1990; Pierau and Szolcsányi, 1989; Alving et al.,
1991), and bear (Rogers, 1984), there are considerable
species Franco-Cereceda and Lundberg, 1989; Matran et 1989, 1990; Pierau and Szolcsányi, 1989; Alving et 1991), and bear (Rogers, 1984), there are consideral species differences in the sensitivity of afferent neuro to capsaicin wh 1989, 1990; Pierau and Szolcsányi, 1989; Alving et al., 1991), and bear (Rogers, 1984), there are considerable rapicies differences in the sensitivity of afferent neurons at to capsaicin which have not yet been examined s 1991), and bear (Rogers, 1984), there are considerable rate species differences in the sensitivity of afferent neurons at to capsaicin which have not yet been examined system-diatically. While sensory neurons in the corne to capsaicin which have not yet been examined system-
atically. While sensory neurons in the cornea of guinea
pig and rat are similarly sensitive to the irritant effect of
capsaicin (Szolcsányi et al., 1986), there are som to capsaicin which have not yet been examined system-
atically. While sensory neurons in the cornea of guinea or spec
pig and rat are similarly sensitive to the irritant effect of al., 198
capsaicin (Szolcsányi et al., 198 atically. While sensory neurons in the cornea of guinea or
pig and rat are similarly sensitive to the irritant effect of
alcapsaicin (Szolcsányi et al., 1986), there are some differ-
exences in capsaicin's neurotoxic effec pig and rat are similarly sensitive to the irritant effect of all capsaicin (Szolcsányi et al., 1986), there are some differences in capsaicin's neurotoxic effect. As judged from sa dose-response relationships, thin affere

HOLZER

166 **HOLZER**

166 **HOLZER**

1693 capsaicin is maintained when dorsal root ganglia are more sensitive to the neurotoxic action of systemic cap-

1983).

1983). more sensitive to the neurotoxic action of systemic cap-ER
more sensitive to the neurotoxic action of systemic cap-
saicin than are those of newborn rats (Nagy et al., 1983).
Inhibition of the micturition reflex is more pronounced ER
more sensitive to the neurotoxic action of systemic cap-
saicin than are those of newborn rats (Nagy et al., 1983).
Inhibition of the micturition reflex is more pronounced
in guinea pigs treated as adults than in rats t more sensitive to the neurotoxic action of systemic capsaicin than are those of newborn rats (Nagy et al., 1983).
Inhibition of the micturition reflex is more pronounced
in guinea pigs treated as adults than in rats treate more sensitive to the neurotoxic action of systemic capsaicin than are those of newborn rats (Nagy et al., 1983).
Inhibition of the micturition reflex is more pronounced
in guinea pigs treated as adults than in rats treate saicin than are those of newborn rats (Nagy et al., 1983).
Inhibition of the micturition reflex is more pronounced
in guinea pigs treated as adults than in rats treated at
the same age (Maggi et al., 1987b), and the reduct Inhibition of the micturition reflex is more pronounced
in guinea pigs treated as adults than in rats treated at
the same age (Maggi et al., 1987b), and the reduction of
thermonociception is definitely more marked in adult in guinea pigs treated as adults than in rats treated at the same age (Maggi et al., 1987b), and the reduction of thermonociception is definitely more marked in adult guinea pigs (Buck et al., 1983) than in rats and mice t the same age (Maggi et al., 1987b), and the reduction of thermonociception is definitely more marked in adult guinea pigs (Buck et al., 1983) than in rats and mice treated as neonates or as adults (Gamse, 1982). However, w thermonociception is definitely more marked in adult guinea pigs (Buck et al., 1983) than in rats and mice treated as neonates or as adults (Gamse, 1982). However, when capsaicin is administered perineurally, afferent C-
f guinea pigs (Buck et al., 1983) than in rats and mice
treated as neonates or as adults (Gamse, 1982). However,
when capsaicin is administered perineurally, afferent C-
fibers of the guinea pig are significantly less sensit treated as neonates or as adults (Gamse, 1982). However,
when capsaicin is administered perineurally, afferent C-
fibers of the guinea pig are significantly less sensitive to
a conduction block than are C-fibers in the rat when capsaicin is administered perineurally, afferent C-
fibers of the guinea pig are significantly less sensitive to
a conduction block than are C-fibers in the rat and ferret
(Baranowski et al., 1986), although axoplasmi fibers of the guinea pig are significantly less sensitive to
a conduction block than are C-fibers in the rat and ferret
(Baranowski et al., 1986), although axoplasmic transport
of substance P is inhibited to the same degre a conduction block than are C-fibers in the rat and ferret (Baranowski et al., 1986), although axoplasmic transport of substance P is inhibited to the same degree in rat and guinea pig (Gamse et al. 1982) and thermonocicep of substance P is inhibited to the same degree in rat and
guinea pig (Gamse et al. 1982) and thermonociception in
the guinea pig is even more inhibited than in the rat
(Szolcsányi, 1990).
Afferent C-fibers of the rabbit al substance P is inhibited to the same degree in rat and
inea pig (Gamse et al. 1982) and thermonociception in
e guinea pig is even more inhibited than in the rat
zolcsányi, 1990).
Afferent C-fibers of the rabbit also are le

Although capsaicin acts as a stimulant of thin sensory

though capsaic acts as a stimulant of thin sensory

Although capsaicin acts as a stimulant of thin sensory

Although capsaicin acts as a stimulant of thin sensory

A guinea pig (Gamse et al. 1982) and thermonociception in
the guinea pig is even more inhibited than in the rat
(Szolcsányi, 1990).
Afferent C-fibers of the rabbit also are less sensitive
to a conduction block than those in the guinea pig is even more inhibited than in the rat (Szolcsányi, 1990).

Afferent C-fibers of the rabbit also are less sensitive

to a conduction block than those in the rat (Baranowski

et al., 1986), but this observati (Szolcsányi, 1990).

Afferent C-fibers of the rabbit also are less sensitive

to a conduction block than those in the rat (Baranowski

et al., 1986), but this observation is consistent with a

weaker inhibition of the axop Afferent C-fibers of the rabbit also are less sensitive
to a conduction block than those in the rat (Baranowski
et al., 1986), but this observation is consistent with a
weaker inhibition of the axoplasmic transport of subto a conduction block than those in the rat (Baranowski
et al., 1986), but this observation is consistent with a
weaker inhibition of the axoplasmic transport of sub-
stance P in the rabbit when compared with the rat
(Gams et al., 1986), but this observation is consistent with a weaker inhibition of the axoplasmic transport of substance P in the rabbit when compared with the rat (Gamse et al., 1982). Furthermore, no degeneration of axons is weaker inhibition of the axoplasmic transport of substance P in the rabbit when compared with the rat (Gamse et al., 1982). Furthermore, no degeneration of axons is seen after application of capsaicin to afferent nerve axo (Gamse et al., 1982). Furthermore, no degeneration of axons is seen after application of capsaicin to afferent
nerve axons of the rabbit (Lynn and Shakhanbeh, 1988),
whereas a considerable proportion of C-fibers degenerate
in the rat (Lynn et al., 1987; Jancsó and Lawson, 19 axons is seen after application of capsaicin to afferent
nerve axons of the rabbit (Lynn and Shakhanbeh, 1988),
whereas a considerable proportion of C-fibers degenerate
in the rat (Lynn et al., 1987; Jancsó and Lawson, 199 in the rat (Lynn et al., 1987; Jancsó and Lawson, 1990;
Pini et al., 1990). Thus, afferent neurons in the rabbit
are in general resistant to a long-term ablation by cap-
saicin, although this drug is able to produce acute whereas a considerable proportion of C-fibers degenerate
in the rat (Lynn et al., 1987; Jancsó and Lawson, 1990;
Pini et al., 1990). Thus, afferent neurons in the rabbit
are in general resistant to a long-term ablation by in the rat (Lynn et al., 1987; Jancsó and Lawson, 199
Pini et al., 1990). Thus, afferent neurons in the rablare in general resistant to a long-term ablation by ca
saicin, although this drug is able to produce acute effec
i and defunctionalization (Barthó and Szolcsányi, 1980; are in general resistant to a long-term ablation by capsaicin, although this drug is able to produce acute effects
indicative of sensory neuron stimulation, desensitization
and defunctionalization (Barthó and Szolcsányi, 1 saicin, although this drug is able to produce acute effect
indicative of sensory neuron stimulation, desensitization
and defunctionalization (Barthó and Szolcsányi, 1980
Camras and Bito, 1980; Tervo, 1981; Bynke, 1983; Bar However, the rabbit is about 20 times less sensitive to and defunctionalization (Barthó and Szolcsányi, 1980;
Camras and Bito, 1980; Tervo, 1981; Bynke, 1983; Bar-
anowski et al., 1986; Lynn and Shakhanbeh, 1988; Mor-
itoki et al., 1990; Manzini et al., 1990; Trad et al., 1990) Camras and Bito, 1980; Tervo, 1981; Bynke, 1983; Bar-
anowski et al., 1986; Lynn and Shakhanbeh, 1988; Mor-
itoki et al., 1990; Manzini et al., 1990; Trad et al., 1990).
However, the rabbit is about 20 times less sensitive anowski et al., 1986; Lynn and Shakhanbeh, 1988; Moritoki et al., 1990; Manzini et al., 1990; Trad et al., 1990).
However, the rabbit is about 20 times less sensitive to
the irritant effect of capsaicin than is the rat (Sz itoki et al., 1990; Manzini et al., 1990; Trad et al., 1990).
However, the rabbit is about 20 times less sensitive to
the irritant effect of capsaicin than is the rat (Szolcsányi,
1987). There also are species differences However, the rabbit is about 20 times less sensitive to
the irritant effect of capsaicin than is the rat (Szolcsányi,
1987). There also are species differences in the sensitivity
of afferent A-fibers to capsaicin. Whereas the irritant effect of capsaicin than is the rat (Szolcsányi, 1987). There also are species differences in the sensitivity of afferent A-fibers to capsaicin. Whereas perineural capsaicin induces a reversible conduction blo 1987). There also are species differences in the sensitivity
of afferent A-fibers to capsaicin. Whereas perineural
capsaicin induces a reversible conduction block primarily
in $A\delta$ -fibers of the rat, guinea pig, rabbit, of afferent A-fibers to capsaicin. Whereas perineural capsaicin induces a reversible conduction block primarily in A δ -fibers of the rat, guinea pig, rabbit, cat, and monkey (Lynn et al., 1984; Chung et al., 1985a; Baran capsaicin induces a reversible conduction block primarily
in A δ -fibers of the rat, guinea pig, rabbit, cat, and monkey
(Lynn et al., 1984; Chung et al., 1985a; Baranowski et
al., 1986; Such and Jancsó, 1986; Marsh et al in Aδ-fibers
(Lynn et al
al., 1986; S
only C-fibe
al., 1986).
Other sp ynn et al., 1984; Chung et al., 1985a; Baranowski e
, 1986; Such and Jancsó, 1986; Marsh et al., 1987
ly C-fibers are blocked in the ferret (Baranowski e
, 1986).
Other species differences in the excitatory and long
rm eff

al., 1986; Such and Jancsó, 1986; Marsh et al., 1987), only C-fibers are blocked in the ferret (Baranowski et al., 1986).

Other species differences in the excitatory and long-

term effects of capsaicin are not necessaril only C-fibers are blocked in the ferret (Baranowski et al., 1986).

Other species differences in the excitatory and long-

term effects of capsaicin are not necessarily due to dif-

ferences in sensory neuron sensitivity t al., 1986).
Other species differences in the excitatory and long
term effects of capsaicin are not necessarily due to dif
ferences in sensory neuron sensitivity to capsaicin-sensitive
rather to different distributions of c Other species differences in the excitatory and long-
term effects of capsaicin are not necessarily due to dif-
ferences in sensory neuron sensitivity to capsaicin but
rather to different distributions of capsaicin-sensiti term effects of capsaicin are not necessarily due to differences in sensory neuron sensitivity to capsaicin but rather to different distributions of capsaicin-sensitive afferent neurons, different neurotransmitter contents ferences in sensory neuron sensitivity to capsaicin but
rather to different distributions of capsaicin-sensitive
afferent neurons, different neurotransmitter contents,
different actions and functions of these afferent neur rather to different distributions of capsaicin-sensitive
afferent neurons, different neurotransmitter contents,
different actions and functions of these afferent neurons,
or species differences in the metabolic effects (Mi afferent neurons, different neurotransmitter contents, different actions and functions of these afferent neurons, or species differences in the metabolic effects (Miller et al., 1983) and pharmacokinetic fate of capsaicin. different actions and functions of these afferent neurons,
or species differences in the metabolic effects (Miller et
al., 1983) and pharmacokinetic fate of capsaicin. One
example refers to the indirect contractile effects or species differences in the metabolic effects (Miller et al., 1983) and pharmacokinetic fate of capsaicin. One example refers to the indirect contractile effects of capsaicin on isolated cardiac muscle, which is thought al., 1983) and pharmacokinetic fate of capsaicin. One example refers to the indirect contractile effects of capsaicin on isolated cardiac muscle, which is thought to reflect a local effector function of sensory neurons in

pig (Zernig et a!., 1984; Franco-Cereceda and Lundberg, effect, no such effect is apparent in the cardiac muscle CAPSAIC

pig (Zernig et al., 1984; Franco-Cereceda and Lundberg, c

1988) capsaicin causes a positive ino- and chronotropic le

effect, no such effect is apparent in the cardiac muscle A

of rabbit, dog (Toda et al., 1972) pig (Zernig et al., 1984; Franco-Cereceda and Lundb
1988) capsaicin causes a positive ino- and chronotro
effect, no such effect is apparent in the cardiac mus
of rabbit, dog (Toda et al., 1972), and man (Fran
Cereceda et a pig (Zernig et al., 1984; Franco-Cereceda and Lundberg, compose 1988) capsaicin causes a positive ino- and chronotropic lover
effect, no such effect is apparent in the cardiac muscle Archit, dog (Toda et al., 1972), and ma 1988) capsaicin causes a positive ino- and chronotropic leffect, no such effect is apparent in the cardiac muscle of rabbit, dog (Toda et al., 1972), and man (Franco-
Cereceda et al., 1987a). A similar situation applies t effect, no such effect is apparent in the cardiac muscle
of rabbit, dog (Toda et al., 1972), and man (Franco-
Cereceda et al., 1987a). A similar situation applies to the
motor effects of capsaicin on tracheobronchial (Lund of rabbit, dog (Toda et al., 1972), and man (Franco-
Cereceda et al., 1987a). A similar situation applies to the from
otor effects of capsaicin on tracheobronchial (Lundberg to
and Saria, 1987) and gastrointestinal (Barthó Cereceda et al., 1987a)
motor effects of capsaid
and Saria, 1987) and ge
Maggi et al., 1986, 199
varies among species.
Other examples inc otor effects of capsaicin on tracheobronchial (Lundberg to d Saria, 1987) and gastrointestinal (Barthó et al., 1987; alggi et al., 1986, 1987c, 1989d) smooth muscle which is used the examples include differences in the abi

and Saria, 1987) and gastrointestinal (Barthó et al., 19
Maggi et al., 1986, 1987c, 1989d) smooth muscle wh
varies among species.
Other examples include differences in the ability
capsaicin to release substance P or calcit Maggi et al., 1986, 1987c, 1989d) smooth muscle which ist
varies among species. Un
other examples include differences in the ability of du
capsaicin to release substance P or calcitonin gene-re-
lated peptide in the ureter varies among species.

Other examples include differences in the ability of

capsaicin to release substance P or calcitonin gene-re-

lated peptide in the ureter of rat and guinea pig, the

tissue levels of these peptides Other examples include differences in the ability of duccapsaicin to release substance P or calcitonin gene-re-
lated peptide in the ureter of rat and guinea pig, the by issue levels of these peptides being profoundly diss capsaicin to release substance P or calcitonin gene-re-
lated peptide in the ureter of rat and guinea pig, the
tissue levels of these peptides being profoundly dissimilar
in the two species (Amann et al., 1988). Because th lated peptide in the ureter of rat and guinea pig, the tissue levels of these peptides being profoundly dissimilar in the two species (Amann et al., 1988). Because the two peptides exert either relaxant (calcitonin gene-re tissue levels of these peptides being profoundly dissimilar
in the two species (Amann et al., 1988). Because the two
peptides exert either relaxant (calcitonin gene-related 19
peptide) or contractile (substance P) effects in the two species (Amann et al., 1988). Because the two poptides exert either relaxant (calcitonin gene-related 19 peptide) or contractile (substance P) effects on the ureter in (Hua and Lundberg, 1986), it is not unexpe peptides exert either relaxant (calcitonin gene-related 1988)
peptide) or contractile (substance P) effects on the ureter into
(Hua and Lundberg, 1986), it is not unexpected that the advector
contractile effects of capsaic peptide) or contractile (substance P) effects on the ureter (Hua and Lundberg, 1986), it is not unexpected that the contractile effects of capsaicin also differ in the ureter of the rat and guinea pig (Amann et al., 1988). (Hua and Lundberg, 1986), it is not unexpected that the contractile effects of capsaicin also differ in the ureter the rat and guinea pig (Amann et al., 1988). Unlike ithe rat skin in which intravenous capsaicin inducted
l contractile effects of capsaicin also differ in the ureter of potential the rat and guinea pig (Amann et al., 1988). Unlike in the rat skin in which intravenous capsaicin induces full leakage of plasma proteins (Saria et the rat and guinea pig (Amann et al., 1988). Unlike in be
the rat skin in which intravenous capsaicin induces fu
leakage of plasma proteins (Saria et al., 1983b), intra-
dermal capsaicin fails to produce extravasation in the rat skin in which intravenous capsaicin induces
leakage of plasma proteins (Saria et al., 1983b), intra-
dermal capsaicin fails to produce extravasation in the
skin of humans (Lundblad et al., 1987) and pigs (Alving
et leakage of plasma proteins (Saria et al., 1983b), intra-
dermal capsaicin fails to produce extravasation in the F .
skin of humans (Lundblad et al., 1987) and pigs (Alving Set al., 1991). However, capsaicin gives rise to dermal capsaicin fails to produce extravasation in the skin of humans (Lundblad et al., 1987) and pigs (Alviet al., 1991). However, capsaicin gives rise to chemo (conjunctival edema) when it comes into contact whe human ey skin of humans (Lundblad et al., 1987) and pigs (Alving
et al., 1991). However, capsaicin gives rise to chemosis
(conjunctival edema) when it comes into contact with
the human eye (J. Szolcsányi, personal communication).
F et al., 1991). However, capsaicin gives rise to chemosis (conjunctival edema) when it comes into contact with the human eye (J. Szolcsányi, personal communication). Furthermore, capsaicin increases vascular permeability in (conjunctival edema) when it comes into contact with
the human eye (J. Szolcsányi, personal communication).
Furthermore, capsaicin increases vascular permeability
in the urinary bladder of rat, mouse, and guinea pig but
fa the human eye (J. Szolcsányi, personal communication).
Furthermore, capsaicin increases vascular permeability
in the urinary bladder of rat, mouse, and guinea pig but
fails to do so in the hamster bladder (Maggi et al., 19 Furthermore, capsaicin increases vascular permeability
in the urinary bladder of rat, mouse, and guinea pig but
fails to do so in the hamster bladder (Maggi et al., 1987b).
Similarly, capsaicin elicits sensory nerve-media in the urinary bladder of rat, mouse, and guinea pig but fails to do so in the hamster bladder (Maggi et al., 1987b).
Similarly, capsaicin elicits sensory nerve-mediated contractions of urinary bladders from rat, mouse, an fails to do so in the hamster bladder (Maggi et al., 1987b).

Similarly, capsaicin elicits sensory nerve-mediated contractions of urinary bladders from rat, mouse, and guinea

pig but not from rabbit and hamster (Maggi et tractions of urinary bladders from rat, mouse, and guinea
pig but not from rabbit and hamster (Maggi et al., 1987b).
Substance P is considered to be the main mediator of
sensory neurons for increasing vascular permeability pig but not from rabbit and hamster (Maggi et al., 1987b).
Substance P is considered to be the main mediator of
sensory neurons for increasing vascular permeability and
causing smooth muscle contraction (Lundberg and Saria Substance P is considered to be the main mediator of increasing vascular permeability and causing smooth muscle contraction (Lundberg and Saria, 1987; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988), and it has been spec sensory neurons for increasing vascular permeability and
causing smooth muscle contraction (Lundberg and Saria,
1987; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988),
and it has been speculated that the inactivity of caps causing smooth muscle contraction (Lundberg and Saria, 1987; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988), and it has been speculated that the inactivity of capsaicin in the rabbit and hamster bladder is related to the 1987; Chahl, 1988; Holzer, 1988; Maggi and Meli, 1988), and it has been speculated that the inactivity of capsaicin in the rabbit and hamster bladder is related to the low substance P content of the rabbit bladder and the and it has been speculated that the inactivity of capsaicin
in the rabbit and hamster bladder is related to the low
substance P content of the rabbit bladder and the ab-
sence of this peptide from the hamster bladder (Magg in the rabbit and hamster bladder is related to the low
substance P content of the rabbit bladder and the absence of this peptide from the hamster bladder (Maggi
et al., 1987b). Altogether, the hamster seems to be a
mamma substance P content of the rabbit bladder and the absence of this peptide from the hamster bladder (Maggi cap
et al., 1987b). Altogether, the hamster seems to be a cap
mammalian species that is comparatively insensitive t sence of this peptide from the hamster bladder (Maggi cap
et al., 1987b). Altogether, the hamster seems to be a cap
mammalian species that is comparatively insensitive to
capsaicin because even systemic treatment with the et al., 1987b). Altogether, the hamster seems to be a
mammalian species that is comparatively insensitive to
capsaicin because even systemic treatment with the drug
is relatively well tolerated (Glinsukon et al., 1980) and mammalian species that is c
capsaicin because even syster
is relatively well tolerated ((
does not result in, for example
reflex (Maggi et al., 1987b).
Finally, the overall toxicity psaicin because even systemic treatment with the different vectors relatively well tolerated (Glinsukon et al., 1980) as not result in, for example, changes of the micturitifiex (Maggi et al., 1987b).
Finally, the overall

is relatively well tolerated (Glinsukon et al., 1980) and
does not result in, for example, changes of the micturition
reflex (Maggi et al., 1987b).
Finally, the overall toxicity of capsaicin, when admin-
istered systemical does not result in, for example, changes of the micturition
reflex (Maggi et al., 1987b).
Finally, the overall toxicity of capsaicin, when admin-
istered systemically to mammals (Glinsukon et al., 1980),
does not necessari reflex (Maggi et al., 1987b).

Finally, the overall toxicity of capsaicin, when admin-

istered systemically to mammals (Glinsukon et al., 1980),

does not necessarily correlate with the species sensitivity

of afferent ne Finally, the overall toxicity of capsaicin, when administered systemically to mammals (Glinsukon et al., 1980), does not necessarily correlate with the species sensitivity of afferent neurons to the drug. Capsaicin is an e istered systemically to mammals (Glinsukon et al., does not necessarily correlate with the species sens
of afferent neurons to the drug. Capsaicin is an extinitating substance that, by stimulating sensory ne
gives rise not does not necessarily correlate with the species sensitiv
of afferent neurons to the drug. Capsaicin is an extrem
irritating substance that, by stimulating sensory neuro
gives rise not only to nociception and nociception-as of afferent neurons to the drug. Capsaicin is an extrem
irritating substance that, by stimulating sensory neuro
gives rise not only to nociception and nociception-as
ciated reactions but also to peripheral release of neu
p irritating substance that, by stimulating sensory neurons, in
gives rise not only to nociception and nociception-asso-
ciated reactions but also to peripheral release of neuro-
peptides that cause generalized vasodilatatio gives rise not only to nociception and nociception-asso-
ciated reactions but also to peripheral release of neuro-
peptides that cause generalized vasodilatation, extrava-
sation of plasma protein, and bronchoconstriction.

consequences of sensory neuron stimulation, and even
low doses of systemic capsaicin (<1 mg/kg) may be fatal. low 167

167

consequences of sensory neuron stimulation, and even

low doses of systemic capsaicin (<1 mg/kg) may be fatal.

Another limiting factor in the use of capsaicin in the rat Another limiting factor in the use of capsaicin (\leq 1 mg/kg) may be fatal.
Another limiting factor in the use of capsaicin in the rat is the induction of the Bezold-Jarisch reflex which arises consequences of sensory neuron stimulation, and even
low doses of systemic capsaicin (<1 mg/kg) may be fatal.
Another limiting factor in the use of capsaicin in the rat
is the induction of the Bezold-Jarisch reflex which a consequences of sensory neuron stimulation, and even
low doses of systemic capsaicin $(<1 \text{ mg/kg})$ may be fatal.
Another limiting factor in the use of capsaicin in the rat
is the induction of the Bezold-Jarisch reflex which low doses of systemic capsaicin (<1 mg/kg) may be fatal.
Another limiting factor in the use of capsaicin in the rat
is the induction of the Bezold-Jarisch reflex which arises
from activation of pulmonary chemoreceptors and Another limiting factor in the use of capsaicin in the is the induction of the Bezold-Jarisch reflex which arifrom activation of pulmonary chemoreceptors and let to apnoea, hypotension, and bradycardia (Szolcsányi al., 199 is the induction of the Bezold-Jarisch reflex which arises
from activation of pulmonary chemoreceptors and leads
to apnoea, hypotension, and bradycardia (Szolcsányi et
al., 1990). As a consequence, capsaicin has to be admi from activation of pulmonary chemoreceptors and
to apnoea, hypotension, and bradycardia (Szolcsár
al., 1990). As a consequence, capsaicin has to be ad
istered to animals under general anaesthesia to
undue pain. Especially to apnoea, hypotension, and bradycardia (Szolcsányi et al., 1990). As a consequence, capsaicin has to be administered to animals under general anaesthesia to avoid undue pain. Especially in the guinea pig, capsaicin-induce al., 1990). As a consequence, capsaicin has to be administered to animals under general anaesthesia to avoid undue pain. Especially in the guinea pig, capsaicin-in-
duced bronchoconstriction, hypersecretion in the air-
way istered to animals under general anaesthesia to avoid
undue pain. Especially in the guinea pig, capsaicin-in-
duced bronchoconstriction, hypersecretion in the air-
ways, and leakage of plasma protein ought to be limited
b undue pain. Especially in the guinea pig, capsaicin-in
duced bronchoconstriction, hypersecretion in the air
ways, and leakage of plasma protein ought to be limite
by pretreatment of the experimental animals with drug
such duced bronchoconstriction, hypersecretion in the air-
ways, and leakage of plasma protein ought to be limited
by pretreatment of the experimental animals with drugs
such as theophylline, β_2 -adrenoceptor agonists, and ways, and leakage of plasma protein ought to be limited
by pretreatment of the experimental animals with drugs
such as theophylline, β_2 -adrenoceptor agonists, and atro-
pine (Jancsó, 1960; Gamse et al., 1981c; Buck et by pretreatment of the experimental animals with drugs
such as theophylline, β_2 -adrenoceptor agonists, and atro-
pine (Jancsó, 1960; Gamse et al., 1981c; Buck et al.,
1983). In addition, it is necessary to split the t such as theophylline, β_2 -adrenoceptor agonists, and at pine (Jancsó, 1960; Gamse et al., 1981c; Buck et al. 1983). In addition, it is necessary to split the total dosto a schedule of gradually increasing doses to keep pine (Jancsó, 1960; Gamse et al., 1981c; Buck et al., 1983). In addition, it is necessary to split the total dose into a schedule of gradually increasing doses to keep the adverse effects of the initial doses tolerable. Th 1983). In addition, it is necessary to split the total dose into a schedule of gradually increasing doses to keep the adverse effects of the initial doses tolerable. The "ultrapotent" analogue of capsaicin, resiniferatorin into a schedule of gradually increasing doses to keep the adverse effects of the initial doses tolerable. The "ultrapotent" analogue of capsaicin, resiniferatoxin, seems to be comparatively less toxic because it does not e 1990). Frotent analogue of capsaich, resimeration, see
the comparatively less toxic because it does not elifted
full Bezold-Jarisch reflex in the rat (Szolcsányi
1990).
F. Age and Strain Differences in the Capsaicin
Sensitivity o *Se* comparatively less toxic because if
full Bezold-Jarisch reflex in the rat
1990).
F. Age and Strain Differences in the
Sensitivity of Mammalian Species
Age-dependent differences in the

Finite is any of the neurotropic increasing vascular permeability and neurochemical consequences of the neurotoxic actions of through the neurotropic increasing vascular permeability and causing smooth muscle contraction (**Age and Strain Differences in the Capsaicin
** *Age-dependent* **differences in the effects of capsaicin
** *Age-dependent* **differences in the effects of capsaicin

nummalian species are best documented in the rat,** F. Age and Strain Differences in the Capsaicin
Sensitivity of Mammalian Species
Age-dependent differences in the effects of capsaicin
on mammalian species are best documented in the rat,
with some information also availabl F. Age and Strain Differences in the Capsaicin
Sensitivity of Mammalian Species
Age-dependent differences in the effects of capsaicin
on mammalian species are best documented in the rat,
with some information also availabl Sensitivity of Mammaiian Species
Age-dependent differences in the effects of capsaicin
on mammalian species are best documented in the rat
with some information also available for the mouse. In
the newborn rat, thin primar Age-dependent differences in the effects of capsaicin
on mammalian species are best documented in the rat,
with some information also available for the mouse. In
the newborn rat, thin primary afferent neurons are con-
side on mammalian species are best documented in the revith some information also available for the mouse.
the newborn rat, thin primary afferent neurons are co
siderably more susceptible to the neurotoxic action
capsaicin than with some information also available for the mouse. In the newborn rat, thin primary afferent neurons are considerably more susceptible to the neurotoxic action of capsaicin than they are in the adult animal. This differen the newborn rat, thin primary afferent neurons are considerably more susceptible to the neurotoxic action of capsaicin than they are in the adult animal. This difference certainly is true for the cell bodies and nerve axon siderably more susceptible to the neurotoxic action of capsaicin than they are in the adult animal. This difference certainly is true for the cell bodies and nerve axons, whereas degeneration of the peripheral terminals of capsaicin than they are in the adult animal. This difference certainly is true for the cell bodies and nerve axons, whereas degeneration of the peripheral terminals of thin sensory neurons in the adult rat may be as extens ence certainly is true for the cell bodies and nerve axons,
whereas degeneration of the peripheral terminals of thin
sensory neurons in the adult rat may be as extensive as
in the newborn animal (Chung et al., 1985b, 1990) sensory neurons in the adult rat may be as extensive as
in the newborn animal (Chung et al., 1985b, 1990).
Conversely, in the mouse it appears as if some functional
and neurochemical consequences of the neurotoxic ac-
tion sensory neurons in the adult rat may be as extensive as
in the newborn animal (Chung et al., 1985b, 1990).
Conversely, in the mouse it appears as if some functional
and neurochemical consequences of the neurotoxic ac-
tion in the newborn animal (Chung et al., 1985b, 1990).
Conversely, in the mouse it appears as if some functional
and neurochemical consequences of the neurotoxic ac-
tion of capsaicin are more pronounced in adults than in
neon Conversely, in the mouse it appears as if some functional
and neurochemical consequences of the neurotoxic ac-
tion of capsaicin are more pronounced in adults than in
neonates (Gamse, 1982), although morphological evi-
den and neurochemical consequences of the neurotoxic action of capsaicin are more pronounced in adults than in neonates (Gamse, 1982), although morphological evidence for such a difference is not yet available. The ontogeneti tion of capsaicin are more pronounced in adults than in
neonates (Gamse, 1982), although morphological evi-
dence for such a difference is not yet available. The
ontogenetic shift in the sensitivity of sensory neurons to
c neonates (Gamse, 1982), although morphological evidence for such a difference is not yet available. The ontogenetic shift in the sensitivity of sensory neurons to capsaicin also poses problems for the classification of cap dence for such a difference is not yet available. The ontogenetic shift in the sensitivity of sensory neurons to capsaicin also poses problems for the classification of capsaicin-sensitive sensory neurons because the neuro ontogenetic shift in the sensitivity of sensory neurons to capsaicin also poses problems for the classification of capsaicin-sensitive sensory neurons because the neurons that are vulnerable to the drug in the newborn anim capsaicin also poses problems for the classification of capsaicin-sensitive sensory neurons because the neurons that are vulnerable to the drug in the newborn animal are not completely identical with those affected in the capsaicin-sensitive sensory neurons because the neurons
that are vulnerable to the drug in the newborn animal
are not completely identical with those affected in the
adult animal (Jancsó et al., 1987a; Maggi and Meli, 1988 that are vulnerable to the drug in the newborn animal
are not completely identical with those affected in the
adult animal (Jancsó et al., 1987a; Maggi and Meli, 1988;
Szolcsányi, 1990). Hence, the existence of more than o are not completely identical with those affected in
adult animal (Jancsó et al., 1987a; Maggi and Meli, 1
Szolcsányi, 1990). Hence, the existence of more than
population of capsaicin-sensitive afferent neurons
been propose adult animal (Jancsó et al., 1987a; Maggi and Meli, 1988;
Szolcsányi, 1990). Hence, the existence of more than one
population of capsaicin-sensitive afferent neurons has
been proposed, the groups differing in their age-dep Szolcsányi, 1990). H
population of caps.
been proposed, the
ent sensitivity to
Szolcsányi, 1990).
The sensitivity to pulation of capsaicin-sensitive afferent neurons has
en proposed, the groups differing in their age-depend-
it sensitivity to capsaicin (Maggi and Meli, 1988;
olcsányi, 1990).
The sensitivity to, and the effectiveness of,

been proposed, the groups differing in their age-depend-
ent sensitivity to capsaicin (Maggi and Meli, 1988;
Szolcsányi, 1990).
The sensitivity to, and the effectiveness of, capsaicin
in the rat depends to some degree on t ent sensitivity to capsaicin (Maggi and Meli, 19.
Szolcsányi, 1990).
The sensitivity to, and the effectiveness of, capsaid
in the rat depends to some degree on the *strain* of t
animals and, in addition, may be influenced Szolcsányi, 1990).
The sensitivity to, and the effectiveness of, capsaicin
in the rat depends to some degree on the *strain* of the
animals and, in addition, may be influenced by experi-
mental conditions such as the anaes The sensitivity to, and the effectiveness of, capsaic
in the rat depends to some degree on the *strain* of the
animals and, in addition, may be influenced by exper
mental conditions such as the anaesthetic used (
Szolcsány in the rat depends to some degree on the *strain* of animals and, in addition, may be influenced by exp mental conditions such as the anaesthetic used Szolcsányi, personal communication). Following internous administration animals and, in addition, may be influenced by experimental conditions such as the anaesthetic used (J. Szolcsányi, personal communication). Following intravenous administration of capsaicin, Wistar and Sprague-Dawley rats

aspet

168
but, whereas Wistar rats also exhibit bradycardia and to be affected by the drug (Mason and M
apnoea, these effects are absent in Sprague-Dawley rats Geisthövel et al., 1986; Sann et al., 1987). 168
but, whereas Wistar rats also exhibit bradycardia and to
apnoea, these effects are absent in Sprague-Dawley rats G
(Donnerer and Lembeck, 1982). Differences between HOLZE
but, whereas Wistar rats also exhibit bradycardia and to
apnoea, these effects are absent in Sprague-Dawley rats G
(Donnerer and Lembeck, 1982). Differences between
these two strains of rats also are noted after syst but, whereas Wistar rats also exhibit bradycardia and
apnoea, these effects are absent in Sprague-Dawley rats (Donnerer and Lembeck, 1982). Differences between
these two strains of rats also are noted after systemic t
trea but, whereas Wistar rats also exhibit bradycardia and to apnoea, these effects are absent in Sprague-Dawley rats Ge (Donnerer and Lembeck, 1982). Differences between these two strains of rats also are noted after systemic apnoea, these effects are absent in Sprague-Dawley rat
(Donnerer and Lembeck, 1982). Differences between
these two strains of rats also are noted after systemi
treatment of adult animals with a high dose of the
capsaicin c (Donnerer and Lembeck, 1982). Differences between these two strains of rats also are noted after system treatment of adult animals with a high dose of capsaicin congener, nonanoyl vanilly lamide. The leterm alterations inc these two strains of rats also are noted after systemic tion
treatment of adult animals with a high dose of the cape
capsaicin congener, nonanoyl vanillylamide. The long-
and
term alterations include different weight losse treatment of adult animals with a high dose of the capsaicin congener, nonanoyl vanillylamide. The long-
term alterations include different weight losses posttreat-
the ment, different degrees of tachycardia in response to capsaicin congener, nonanoyl vanillylamide. The long-
term alterations include different weight losses posttreat-
ment, different degrees of tachycardia in response to
captopril, and different changes in the sensitivity to ment, different degrees of tachycardia in response to captopril, and different changes in the sensitivity to the anaesthetic methohexital (Gardiner et al., 1989). The extent of long-term peptide depletion from sensory neur

ment, different degrees of tachycardia in response to ure captopril, and different changes in the sensitivity to the permeas and the sense independent of the star rats may be independent of the capse of the animal treated captopril, and different changes in the sensitivity to the panaesthetic methohexital (Gardiner et al., 1989).
The extent of long-term peptide depletion from sensity neurons of Wistar rats may be independent of the cage of anaesthetic methohexital (Gardiner et al., 1989).
The extent of long-term peptide depletion from sen-
sory neurons of Wistar rats may be independent of the
cage of the animal treated with a high dose of capsaicin
(Geppetti The extent of long-term peptide depletion from sensory neurons of Wistar rats may be independent of the cage of the animal treated with a high dose of capsaicing (Geppetti et al., 1988a), whereas in Sprague-Dawley rats tr sory neurons of Wistar rats may be independent of the capage of the animal treated with a high dose of capsaicin a 4 (Geppetti et al., 1988a), whereas in Sprague-Dawley rats related treatment of newborn animals seems to be age of the animal treated with a high dose of capsaicin
(Geppetti et al., 1988a), whereas in Sprague-Dawley rats
treatment of newborn animals seems to be more effective
than is treatment of adults (Gamse et al., 1981b). In (Geppetti et al., 1988a), whereas in Sprague-Dawley rats
treatment of newborn animals seems to be more effective
than is treatment of adults (Gamse et al., 1981b). In
addition, following capsaicin treatment as neonates,
Ch treatment of newborn animals seems to be more effective
than is treatment of adults (Gamse et al., 1981b). In
addition, following capsaicin treatment as neonates,
Charles River and Wistar-Morini rats develop persistent
ski than is treatment of adults (Gamse et al., 1981b). In addition, following capsaicin treatment as neonates, Charles River and Wistar-Morini rats develop persistent skin wounds, whereas Sprague-Dawley rats do not (Gamse et a addition, following capsaicin treatment as neonat
Charles River and Wistar-Morini rats develop persist
skin wounds, whereas Sprague-Dawley rats do
(Gamse et al., 1981b; Maggi et al., 1987a). Differen
are also seen after ca Charles River and Wistar-Morini rats develop persis
skin wounds, whereas Sprague-Dawley rats do
(Gamse et al., 1981b; Maggi et al., 1987a). Differe
are also seen after capsaicin treatment of adult Wii
Kyoto and spontaneous skin wounds, whereas Sprague-Dawley rats do r (Gamse et al., 1981b; Maggi et al., 1987a). Difference also seen after capsaicin treatment of adult Wistakyoto and spontaneously hypertensive rats. Thermore ciception is impair (Gamse et al., 1981b; Maggi et al., 1987a). Differences
are also seen after capsaicin treatment of adult Wistar-
Kyoto and spontaneously hypertensive rats. Thermono-
ciception is impaired only in the spontaneously hyper-
t are also seen after capsaicin treatment of adult Wistar-
Kyoto and spontaneously hypertensive rats. Thermono-
ciception is impaired only in the spontaneously hyper-
tensive rats (Virus et al., 1981); additionally these an Kyoto and spontaneously hypertensive rats. Thermono-
ciception is impaired only in the spontaneously hyper-
tensive rats (Virus et al., 1981); additionally these ani-
syimals show a more pronounced substance P depletion a 1983). spinal cord than do Wistar-Kyoto rats (Virus et al., 1983).
G. Acute and Long-term Effects of Capsaicin in
Nonmammalian Species

Nonmammalian Species

Acute and Long-term Effects of Capsaicin in

physical in contrast to mammals, which in general are sensitive

the irritant and long-term inhibitory effects of capsai-G. Acute and Long-term Effects of Capsaicin in
Nonmammalian Species
In contrast to mammals, which in general are sensite
to the irritant and long-term inhibitory effects of caps
cin on sensory neurons, nonmammalian species contrast to manimals, which in general are sensitive
In contrast to mammals, which in general are sensitive
to the irritant and long-term inhibitory effects of capsai-
cin on sensory neurons, nonmammalian species appear
to In contrast to mammals, which in general are sensitive
to the irritant and long-term inhibitory effects of capsai-
cin on sensory neurons, nonmammalian species appear
to be only poorly sensitive to the drug. In a marsupial In contrast to mammals, which in general are sensitive
to the irritant and long-term inhibitory effects of capsai-
cin on sensory neurons, nonmammalian species appear
of n
to be only poorly sensitive to the drug. In a mar to the irritant and long-term inhibitory effects of capsaicin on sensory neurons, nonmammalian species appear
to be only poorly sensitive to the drug. In a marsupial red
species, the North American opossum, acute exposure cin on sensory neurons, nonmammalian species appear
to be only poorly sensitive to the drug. In a marsupial
species, the North American opossum, acute exposure to
capsaicin has been found to release substance P from the
m

peptide (Daniel et al., 1987).
Acute local or systemic administration of capsaicin in
pigeons and other birds, at concentrations of 33 mM or muscularis mucosae of the esophagus, whereas systemic pretreatment does not change the tissue level of the Speptide (Daniel et al., 1987).
Acute local or systemic administration of capsaicin in pigeons and other birds, at pretreatment does not change the tissue level of the beptide (Daniel et al., 1987).

Acute local or systemic administration of capsaicin in origineons and other birds, at concentrations of 33 mM or doese up to 600 mg/kg, peptide (Daniel et al., 1987).

Acute local or systemic administration of capsaicin in

pigeons and other birds, at concentrations of 33 mM or

doses up to 600 mg/kg, either fails to evoke pain or

reactions indicative of Acute local or systemic administration of capsaicin in
pigeons and other birds, at concentrations of 33 mM or
doses up to 600 mg/kg, either fails to evoke pain or
reactions indicative of pain or is only weakly active
(Maso pigeons and other birds, at concentrations of 33 mM or degenues does up to 600 mg/kg, either fails to evoke pain or tem reactions indicative of pain or is only weakly active line (Mason and Maruniak, 1983; Szolcsányi et al doses up to 600 mg/kg, either fails to evoke pain or ^t
reactions indicative of pain or is only weakly active ¹
(Mason and Maruniak, 1983; Szolcsányi et al., 1986;
Sann et al., 1987). Similar to the findings made in ^c reactions indicative of pain or is only weakly active (Mason and Maruniak, 1983; Szolcsányi et al., 1986; Sann et al., 1987). Similar to the findings made in mammalian species, both substance P and calcitonin gene-related (Mason and Maruniak, 1983; Szolcsányi et al., 1986; Sann et al., 1987). Similar to the findings made in mammalian species, both substance P and calcitonin gene-related peptide are markers of primary afferent neurons in th Sann et al., 1987). Similar to the findings made in other mammalian species, both substance P and calcitonin U gene-related peptide are markers of primary afferent seen neurons in the pigeon (Pierau et al., 1987; Harti et mammalian species, both substance P and calcitonin gene-related peptide are markers of primary afferent neurons in the pigeon (Pierau et al., 1987; Harti et al., 1987, 1989). Capsaicin (10 μ M), however, is unable to ev gene-related peptide are markers of primary afferent seem to be extremely sensitive to the irritant effect of
neurons in the pigeon (Pierau et al., 1987; Harti et al., capsaicin. When instilled into the crocodile's eye, c neurons in the pigeon (Pierau et al., 1987; Harti et al., 1987, 1989). Capsaicin (10 μ M), however, is unable to evoke a detectable release of substance P from the central endings of these neurons in pigeon spinal cord 1987, 1989). Capsaicin (10 μ M), however, is unable to convoke a detectable release of substance P from the central in endings of these neurons in pigeon spinal cord slices her (Pierau et al., 1987). No changes in chemo evoke a detectable release of substance P from the central in endings of these neurons in pigeon spinal cord slices hermore (Pierau et al., 1987). No changes in chemonociception relative been noted after systemic capsaicin endings of these neurons in pigeon spinal cord slices
(Pierau et al., 1987). No changes in chemonociception
have been noted after systemic capsaicin treatment of
pigeons (Szolcsányi et al., 1986). Thermoregulation has
been

ER
to be affected by the drug (Mason and Maruniak, 1983;
Geisthövel et al., 1986; Sann et al., 1987). ER
to be affected by the drug (Mason and Ma
Geisthövel et al., 1986; Sann et al., 1987).
In spite of the absence of persistent func

In spite of the absence of Mason and Maruniak, 198

In spite of the absence of persistent functional alterations, systemic treatment of pigeons with 950 mg/ to be affected by the drug (Mason and Maruniak, 1983;
Geisthövel et al., 1986; Sann et al., 1987).
In spite of the absence of persistent functional altera-
tions, systemic treatment of pigeons with 950 mg/kg
capsaicin give to be affected by the drug (Mason and Maruniak, 1983;
Geisthövel et al., 1986; Sann et al., 1987).
In spite of the absence of persistent functional altera-
tions, systemic treatment of pigeons with 950 mg/kg
capsaicin give Geisthövel et al., 1986; Sann et al., 1987).
In spite of the absence of persistent functional altera-
tions, systemic treatment of pigeons with 950 mg/kg
capsaicin gives rise to a partial depletion of substance P
and calci In spite of the absence of persistent functional alterations, systemic treatment of pigeons with 950 mg/kg capsaicin gives rise to a partial depletion of substance P and calcitonin gene-related peptide from nerve fibers in tions, systemic treatment of pigeons with 950 mg/kg
capsaicin gives rise to a partial depletion of substance P
and calcitonin gene-related peptide from nerve fibers in
the myenteric plexus of the small intestine (Harti, 19 capsaicin gives rise to a partial depletion of substance P
and calcitonin gene-related peptide from nerve fibers in
the myenteric plexus of the small intestine (Harti, 1988),
ureter, and cornea (Harti et al., 1989). A redu and calcitonin gene-related peptide from nerve fibers in
the myenteric plexus of the small intestine (Harti, 1988),
ureter, and cornea (Harti et al., 1989). A reduction of
peptide levels in the pigeon cornea also is seen a the myenteric plexus of the small intestine (Harti, 1988), ureter, and cornea (Harti et al., 1989). A reduction of peptide levels in the pigeon cornea also is seen after topical application of 33 mM capsaicin to this tissu ureter, and cornea (Harti et al., 1989). A reduction of peptide levels in the pigeon cornea also is seen after topical application of 33 mM capsaicin to this tissue (Harti et al., 1989). Likewise, application of 330 nmol c peptide levels in the pigeon cornea also is seen after topical application of 33 mM capsaicin to this tissu (Harti et al., 1989). Likewise, application of 330 nm capsaicin to the sciatic nerve of the pigeon gives rise to a topical application of 33 mM capsaicin to this tissue
(Harti et al., 1989). Likewise, application of 330 nmol
capsaicin to the sciatic nerve of the pigeon gives rise to
a 40% depletion of substance P and calcitonin gene-
r (Harti et al., 1989). Likewise, application of 330 nmol
capsaicin to the sciatic nerve of the pigeon gives rise to
a 40% depletion of substance P and calcitonin gene-
related peptide from the nerve axons, whereas these
pep capsaicin to the sciatic nerve of the pigeon gives rise 40% depletion of substance P and calcitonin grelated peptide from the nerve axons, whereas the peptides accumulate in the dorsal horn of the spinal (Harti et al., 198 a 40% depletion of substance P and calcitonin gene-
related peptide from the nerve axons, whereas these
peptides accumulate in the dorsal horn of the spinal cord
(Harti et al., 1987). Taken collectively, these neurochem-
i related peptide from the nerve axons, whereas these
peptides accumulate in the dorsal horn of the spinal cord
(Harti et al., 1987). Taken collectively, these neurochem-
ical changes have been taken to suggest that systemic peptides accumulate in the dorsal horn of the spinal cord (Harti et al., 1987). Taken collectively, these neurochemical changes have been taken to suggest that systemic capsaicin acts primarily on axons but not on nerve te (Harti et al., 1987). Taken collectively, these neurochemical changes have been taken to suggest that systemic capsaicin acts primarily on axons but not on nerve terminals of sensory neurons (Harti et al., 1989). It is not ical changes have been taken to suggest that systemic capsaicin acts primarily on axons but not on nerve terminals of sensory neurons (Harti et al., 1989). It is not known, however, whether peptide depletion in the pigeon capsaicin acts
minals of sen:
known, howev
is associated a
sory neurons.
Morphologi inals of sensory neurons (Harti et al., 1989). It is not lown, however, whether peptide depletion in the pigeon
associated at all with degenerative alterations in sen-
ry neurons.
Morphological changes are unlikely to occu

tensive rats (Virus et al., 1981); additionally these ani-
mals show a more pronounced substance P depletion and
5-hydroxytryptamine/noradrenaline accumulation in the
spinal cord than do Wistar-Kyoto rats (Virus et al., to be only poorly sensitive to the drug. In a marsupial
species, the North American opossum, acute exposure to
species, the North American opossum, acute exposure to
capsaicin has been found to release substance P from the pretreatment does not change the tissue level of the Sakamoto, 1987a). Because degeneration of nerve cell
peptide (Daniel et al., 1987).
Acute local or systemic administration of capsaicin in of cultured chick sensory neu known, however, whether peptide depletion in the pigeonis associated at all with degenerative alterations in sen
sory neurons.
Morphological changes are unlikely to occur because
systemic application of 500 mg/kg capsaicin is associated at all with degenerative alterations in sensory neurons.

Morphological changes are unlikely to occur because

systemic application of 500 mg/kg capsaicin to the new-

born chick fails to cause degeneration o sory neurons.
Morphological changes are unlikely to occur because
systemic application of 500 mg/kg capsaicin to the new-
born chick fails to cause degeneration of dorsal root
ganglion cells (Jancsó et al., 1985a). This la Morphological changes are unlikely to occur because
systemic application of 500 mg/kg capsaicin to the new-
born chick fails to cause degeneration of dorsal root
ganglion cells (Jancsó et al., 1985a). This lack of effect
i systemic application of 500 mg/kg capsaicin to the new-
born chick fails to cause degeneration of dorsal root
ganglion cells (Jancsó et al., 1985a). This lack of effect
is in keeping with the finding that cultured dorsal r born chick fails to cause degeneration of dorsal root ganglion cells (Jancsó et al., 1985a). This lack of effect is in keeping with the finding that cultured dorsal root ganglia from the newborn chick do not respond to cap ganglion cells (Jancsó et al., 1985a). This lack of effect
is in keeping with the finding that cultured dorsal root
ganglia from the newborn chick do not respond to cap-
saicin or resiniferatoxin in the cobalt stain assay is in keeping with the finding that cultured dorsal root ganglia from the newborn chick do not respond to capsaicin or resiniferatoxin in the cobalt stain assay (Bevan et al., 1987; Wood et al., 1988; Winter et al., 1990) ganglia from the newborn chick do not respond to capsaicin or resiniferatoxin in the cobalt stain assay (Bevan
et al., 1987; Wood et al., 1988; Winter et al., 1990). In
contrast, exposure (30 min to 28 h) of cultured chic saicin or resiniferatoxin in the cobalt stain assay (Bevan
et al., 1987; Wood et al., 1988; Winter et al., 1990). In
contrast, exposure (30 min to 28 h) of cultured chick
sensory neurons to 32 to 160 μ M capsaicin has b et al., 1987; Wood et al., 1988; Winter et al., 1990). In contrast, exposure (30 min to 28 h) of cultured chick sensory neurons to 32 to 160 μ M capsaicin has been reported to cause a concentration-dependent retardation contrast, exposure (30 min to 28 h) of cultured chick
sensory neurons to 32 to 160 μ M capsaicin has been
reported to cause a concentration-dependent retardation
of neurite outgrowth (Hiura and Sakamoto, 1987a). This
re sensory neurons to 32 to 160 μ M capsaicin has been
reported to cause a concentration-dependent retardation
of neurite outgrowth (Hiura and Sakamoto, 1987a). This
retardation is associated with a disappearance of the
ne reported to cause a concentration-dependent retardation
of neurite outgrowth (Hiura and Sakamoto, 1987a). This
retardation is associated with a disappearance of the
neurite tips due to degeneration but does not seem to be
 of neurite outgrowth (Hiura and Sakamoto, 1987a). This
retardation is associated with a disappearance of the
neurite tips due to degeneration but does not seem to be
permanent because quick neurite regeneration may occur
e retardation is associated with a disappearance of the
neurite tips due to degeneration but does not seem to be
permanent because quick neurite regeneration may occur
even in the continued presence of capsaicin (Hiura and
S neurite tips due to degeneration but does not seem to be
permanent because quick neurite regeneration may occur
even in the continued presence of capsaicin (Hiura and
Sakamoto, 1987a). Because degeneration of nerve cell
bo permanent because quick neurite regeneration may occur
even in the continued presence of capsaicin (Hiura and
Sakamoto, 1987a). Because degeneration of nerve cell
bodies has not been noted, it would seem that the somata
of even in the continued presence of capsaicin (Hiura and Sakamoto, 1987a). Because degeneration of nerve cell bodies has not been noted, it would seem that the somata of cultured chick sensory neurons are resistant to the de Sakamoto, 1987a). Because degeneration of nerve cell
bodies has not been noted, it would seem that the somata
of cultured chick sensory neurons are resistant to the
degenerative action of capsaicin, whereas neurites may
te bodies has not been noted, it would seem that the somata
of cultured chick sensory neurons are resistant to the
degenerative action of capsaicin, whereas neurites may
temporarily be damaged by the drug. This inference is i of cultured chick sensory neurons are resistant to the degenerative action of capsaicin, whereas neurites may temporarily be damaged by the drug. This inference is in line with the suggestion that in the pigeon capsaicin r degenerative action of capsaicin, whereas neurites temporarily be damaged by the drug. This inference line with the suggestion that in the pigeon capse receptors are present only on the axons but not on other parts of sens mporarily be damaged by the drug. This inference is in
the with the suggestion that in the pigeon capsaicin
ceptors are present only on the axons but not on the
her parts of sensory neurons (Harti et al., 1989).
Unlike bir

line with the suggestion that in the pigeon capsaicin
receptors are present only on the axons but not on the
other parts of sensory neurons (Harti et al., 1989).
Unlike birds, reptiles such as the African crocodile
seem to receptors are present only on the axons but not on the other parts of sensory neurons (Harti et al., 1989).
Unlike birds, reptiles such as the African crocodile seem to be extremely sensitive to the irritant effect of caps other parts of sensory neurons (Harti et al., 1989).
Unlike birds, reptiles such as the African crocodile
seem to be extremely sensitive to the irritant effect of
capsaicin. When instilled into the crocodile's eye, con-
ce Unlike birds, reptiles such as the African crocodile
seem to be extremely sensitive to the irritant effect of
capsaicin. When instilled into the crocodile's eye, con-
centrations of capsaicin as low as 3.3 nM cause reactio seem to be extremely sensitive to the irritant effect of capsaicin. When instilled into the crocodile's eye, concentrations of capsaicin as low as 3.3 nM cause reactions indicative of pain (Kanui et al., 1990). This reacti capsaicin. When instilled into the crocodile's eye, concentrations of capsaicin as low as 3.3 nM cause reactions indicative of pain (Kanui et al., 1990). This reaction, however, does not show any desensitization, because r centrations of capsaicin as low as 3.3 nM cause reactions
indicative of pain (Kanui et al., 1990). This reaction,
however, does not show any desensitization, because
repeated instillation of the drug produces consistent pa indicative of pain (Kanui et al., 1990). This reaction,
however, does not show any desensitization, because
repeated instillation of the drug produces consistent pain
reactions (Kanui et al., 1990). In contrast, amphibian
 however, does not show any desensitization, because
repeated instillation of the drug produces consistent pain
reactions (Kanui et al., 1990). In contrast, amphibian
species appear to be insensitive to the irritant (Szolcs

PHARM
REV

PHARMACOLOGICAL REVIEWS

CAP
ing systemic treatment with up to 100 mg/kg of capsaicin,
frogs do not exhibit any long-term peptide depletion CAPSAIC
ing systemic treatment with up to 100 mg/kg of capsaicin,
frogs do not exhibit any long-term peptide depletion
from, or defunctionalization of, sensory neurons (Chéry-o CAPS
ing systemic treatment with up to 100 mg/kg of capsaicin,
frogs do not exhibit any long-term peptide depletion
from, or defunctionalization of, sensory neurons (Chéry-
Croze et al., 1985). However, overnight exposure ing systemic treatment with up to 100 mg/kg of capsaicin, so
frogs do not exhibit any long-term peptide depletion sit
from, or defunctionalization of, sensory neurons (Chéry-or
Croze et al., 1985). However, overnight expo ing systemic treatment with up to 100 mg/kg of capsaicin, so frogs do not exhibit any long-term peptide depletion sifrom, or defunctionalization of, sensory neurons (Chéry-or Croze et al., 1985). However, overnight exposur frogs do not exhibit any long-term peptide depletion
from, or defunctionalization of, sensory neurons (Chéry-
Croze et al., 1985). However, overnight exposure of the
isolated ileum of the toad to 300 μ M capsaicin is fo from, or defunctionalization of, sensory neurons (Chéry-
Croze et al., 1985). However, overnight exposure of the
isolated ileum of the toad to 300 μ M capsaicin is followed
19 the disappearance of most substance P-conta Croze et al., 1985). However, overnight exposure of the
isolated ileum of the toad to 300 μ M capsaicin is followed
by the disappearance of most substance P-containing
nerve fibers from the intestinal wall and by inhibi isolated ileum of the toad to 300μ M capsaicin is follow
by the disappearance of most substance P-containi
nerve fibers from the intestinal wall and by inhibition
contractions due to extrinsic nerve stimulation (Osbor
a by the disappearance of most substance P-containinerve fibers from the intestinal wall and by inhibition contractions due to extrinsic nerve stimulation (Osborand Campbell, 1986). The cellular specificity of caps cin's eff contractions due to extrinsic nerve stimulation (Osborne

and Campbell, 1986). The cellular specificity of capsai-

cin's effects in the toad has not yet been characterized.
 H. Summary: Targets of Action

1. Capsaicin-s

H. Summary: Targets of Action
1. Capsaicin-sensitive neurons. It has become common
usage to refer to those afferent neurons which, in the
rat, are excited and subsequently inhibited by nanomolar
concentrations of capsaicin *concentrations of Action*
 concentrative neurons. It has become common

usage to refer to those afferent neurons which, in the

rat, are excited and subsequently inhibited by nanomolar

concentrations of capsaicin as " usage to refer to those afferent neurons which, in the rat, are excited *and subsequently* inhibited by nanomolar concentrations of capsaicin as "capsaicin-sensitive sensory neurons" (Szolcsányi and Barthó, 1978; Szolcsány rat, are excited *and subsequently* inhibited by nanomolar concentrations of capsaicin as "capsaicin-sensitive sensory neurons" (Szolcsányi and Barthó, 1978; Szolcsányi, 1982, 1984b). Their sensitivity to these actions of sory neurons" (Szolcsányi and Barthó, 1978; Szolcsányi, 1982, 1984b). Their sensitivity to these actions of capsaicin appears to be mediated by a specific membrane recognition site for the drug (see below). The main classi sory neurons" (Szolcsányi and Barthó, 1978; Szolcsányi, 1982, 1984b). Their sensitivity to these actions of capsaicin appears to be mediated by a specific membrane fire recognition site for the drug (see below). The main 1982, 1984b). Their sensitivity to these actions of capsaicin appears to be mediated by a specific membrane recognition site for the drug (see below). The main classification traits of the neurons that are the target of th saicin appears to be mediated by a specific membrane recognition site for the drug (see below). The main classification traits of the neurons that are the target of the tensory neuron-selective effects of capsaicin are su recognition site for the drug (see below). The main classification traits of the neurons that are the target of the sensory neuron-selective effects of capsaicin are summarized in table 2. Apart from the trait of capsaicin sification traits of the neurons that are the target of the sensory neuron-selective effects of capsaicin are summarized in table 2. Apart from the trait of capsaicin sensitivity, however, capsaicin-sensitive afferent neu sensory neuron-selective effects of capsaicin are sum-
marized in table 2. Apart from the trait of capsaicin
sensitivity, however, capsaicin-sensitive afferent neurons
are difficult to define because they do not completely marized in table 2. Apart from the trait of capsaic
sensitivity, however, capsaicin-sensitive afferent neuro-
are difficult to define because they do not complete
overlap with any population of afferent neurons thave been sensitivity, however, capsaicin-se
are difficult to define because
overlap with any population of
have been classified according t
chemical, or functional criteria.
First, the majority of capsaicing e difficult to define because they do not completely
erlap with any population of afferent neurons that
we been classified according to morphological, neuro-
emical, or functional criteria.
First, the majority of capsaicin

overlap with any population of afferent neurons that
have been classified according to morphological, neuro-
chemical, or functional criteria.
First, the majority of capsaicin-sensitive afferent neu-
rons have small- to m have been classified according to morphological, neuro-
chemical, or functional criteria.
First, the majority of capsaicin-sensitive afferent neu-
rons have small- to medium-sized cell bodies that are
connected to unmyeli chemical, or functional criteria.

First, the majority of capsaicin-sensitive afferent neu-

rons have small- to medium-sized cell bodies that are

connected to unmyelinated (C) or thinly myelinated $(A\delta)$

nerve fibers (First, the majority of capsaicin-sensitive afferent neurons have small- to medium-sized cell bodies that are connected to unmyelinated (C) or thinly myelinated $(A\delta)$ nerve fibers (Lawson and Harper, 1984). However, not a rons have small- to medium-sized cell bodiconnected to unmyelinated (C) or thinly myel
nerve fibers (Lawson and Harper, 1984). Hall unmyelinated afferent neurons conductin
and $A\delta$ -fiber range are sensitive to capsaicin. mected to unmyelinated (C) or thinly myelinated $(A\delta)$

rve fibers (Lawson and Harper, 1984). However, not

unmyelinated afferent neurons conducting in the C-

of $A\delta$ -fiber range are sensitive to capsaicin.

Second, cap

nerve fibers (Lawson and Harper, 1984). However, not
all unmyelinated afferent neurons conducting in the C-
and A δ -fiber range are sensitive to capsaicin.
Second, capsaicin-sensitive afferent neurons contain a
variety o all unmyelinated afferent neurons conducting in the C-
and A δ -fiber range are sensitive to capsaicin.
Second, capsaicin-sensitive afferent neurons contain a
variety of peptides that are thought to play a transmitter
or and $A\delta$ -fiber range are sensitive to capsaicin.
Second, capsaicin-sensitive afferent neurons contain a
variety of peptides that are thought to play a transmitter
or mediator role. The best known among these peptides
are Second, capsaicin-sensitive afferent neurons contain a
variety of peptides that are thought to play a transmitter
or mediator role. The best known among these peptides
are substance P and calcitonin gene-related peptide, variety of peptides that are thought to play a transmitter
or mediator role. The best known among these peptides
are substance P and calcitonin gene-related peptide, but
there is a long list of peptide and other markers o or mediator role. The best known among these pept
are substance P and calcitonin gene-related peptide,
there is a long list of peptide and other markers of
neurons under consideration (table 1). However, non
these markers are substance P and calcitonin gene-related peptide, but
there is a long list of peptide and other markers of the
neurons under consideration (table 1). However, none of
these markers is an exclusive constituent of capsaic there is a long list of peptide and other markers of the neurons under consideration (table 1). However, none of sthese markers is an exclusive constituent of capsaicinsensitive sensory neurons because not all afferent ne neurons under consideration (table 1). However, none of these markers is an exclusive constituent of capsaicin-
sensitive sensory neurons because not all afferent neurons containing, for example, substance P or calcitoning these markers is an exclusive constituent of capsaicin-
sensitive sensory neurons because not all afferent neu-
rons containing, for example, substance P or calcitonin
gene-related peptide are sensitive to capsaicin, and t sensitive sensory neurons because not all afferent neurons containing, for example, substance P or calcitonin for gene-related peptide are sensitive to capsaicin, and these group peptides also are contained in nonsensory n rons containing, for example, substance P or calcitonin¹
gene-related peptide are sensitive to capsaicin, and these
peptides also are contained in nonsensory neurons. There
is, in fact, no specific histochemical marker f gene-related peptide are sensitive to capsaicin, and these
peptides also are contained in nonsensory neurons. There
is, in fact, no specific histochemical marker for this group
of neurons (Lawson and Harper, 1984; Kirchges ptides also are contained in nonsensory neurons. The
in fact, no specific histochemical marker for this grou
neurons (Lawson and Harper, 1984; Kirchgessner
, 1988).
Third, capsaicin-sensitive afferent neurons are hete
eneo is, in fact, no specific histochemical marker for this group
of neurons (Lawson and Harper, 1984; Kirchgessner et
al., 1988).
Third, capsaicin-sensitive afferent neurons are heter-
be-
ogeneous in terms of their sensory mo

of neurons (Lawson and Harper, 1984; Kirchgessner et al., 1988).

Third, capsaicin-sensitive afferent neurons are heter-

ogeneous in terms of their sensory modality and the

functions they subserve. The most consistent fu al., 1988).
Third, capsaicin-sensitive afferent neurons are heter-
ogeneous in terms of their sensory modality and the
functions they subserve. The most consistent functional
is change associated with the neurotoxic effect Third, capsaicin-sensitive afferent neurons are heter-
ogeneous in terms of their sensory modality and the
functions they subserve. The most consistent functional in
change associated with the neurotoxic effect of capsaici ogeneous in terms of their sensory modality and the functions they subserve. The most consistent functional change associated with the neurotoxic effect of capsaicin is a long-term inhibition of chemonociception, which und functions they subserve. The most consistent functional change associated with the neurotoxic effect of capsaicin
is a long-term inhibition of chemonociception, which
underlines the concept that capsaicin-sensitive afferen change associated with the neurotoxic effect of capsaicin the
is a long-term inhibition of chemonociception, which Caj
underlines the concept that capsaicin-sensitive afferents pre
are chemoceptive neurons (Szolcsányi, 198 is a long-term inhibition of chemonociception, which Cajunderlines the concept that capsaicin-sensitive afferents preare chemoceptive neurons (Szolcsányi, 1984b). However, prinche somatic capsaicin-sensitive afferents incl

some warmth receptors. Visceral afferent neurons sensitive to capsaicin have been found to respond to noxious cin
some warmth receptors. Visceral afferent neurons sensitive to capsaicin have been found to respond to noxious
or potentially noxious (Coleridge and Coleridge, 1977, 169
some warmth receptors. Visceral afferent neurons sensitive to capsaicin have been found to respond to noxious
or potentially noxious (Coleridge and Coleridge, 1977,
1984; Cervero and McRitchie, 1982; Longhurst et al., Some warmth receptors. Visceral afferent neurons sensitive to capsaicin have been found to respond to noxious or potentially noxious (Coleridge and Coleridge, 1977, 1984; Cervero and McRitchie, 1982; Longhurst et al., 1984 some warmth receptors. Visceral afferent neurons sensitive to capsaicin have been found to respond to noxious
or potentially noxious (Coleridge and Coleridge, 1977,
1984; Cervero and McRitchie, 1982; Longhurst et al.,
1984 sitive to capsaicin have been found to respond to noxious
or potentially noxious (Coleridge and Coleridge, 1977,
1984; Cervero and McRitchie, 1982; Longhurst et al.,
1984; Szolcsányi, 1984b; Stein et al., 1986; Martling an or potentially noxious (Coleridge and Coleridge, 1977, 1984; Cervero and McRitchie, 1982; Longhurst et al., 1984; Szolcsányi, 1984b; Stein et al., 1986; Martling and Lundberg, 1988; Geppetti et al., 1990, 1991; Forster et 1984; Cervero and McRitchie, 1982; Longhurst et al., 1984; Szolcsányi, 1984b; Stein et al., 1986; Martling and Lundberg, 1988; Geppetti et al., 1990, 1991; Forster et al., 1990; Holzer et al., 1991) as well as nonnoxious " 1984; Szolcsányi, 1984b; Stein et al., 1986; Martling and Lundberg, 1988; Geppetti et al., 1990, 1991; Forster et al., 1990; Holzer et al., 1991) as well as nonnoxious "physiological" stimuli (MacLean, 1985; McCann et al., Lundberg, 1988; Geppetti et al., 1990, 1991; Forster et al., 1990; Holzer et al., 1991) as well as nonnoxious
"physiological" stimuli (MacLean, 1985; McCann et al., 1988; Raybould and Taché, 1988, 1989; South and Ritter,
1 al., 1990; Holzer et a
"physiological" stimul
1988; Raybould and T
1988; Yox and Ritter,
Forster et al., 1990).
Fourth, age, strain, hysiological" stimuli (MacLean, 1985; McCann et al., 88; Raybould and Taché, 1988, 1989; South and Ritter, 88; Yox and Ritter, 1988; Rózsa and Jacobson, 1989; rster et al., 1990).
Fourth, age, strain, and species differenc

and Campbell, 1986). The cellular specificity of capsai-

1988; Raybould and Taché, 1988; 1989; South and Ritter,

cin's effects in the toad has not yet been characterized.

1988; Yox and Ritter, 1988; Rózsa and Jacobson, In Summary. I argue of House Photon.
I. Capsaicin-sensitive neurons. It has become common
usage to refer to those afferent neurons which, in the
rat, are excited and subsequently inhibited by nanomolar
sitive neurons. 1988; Raybould and Taché, 1988, 1989; South and Ritter, 1988; Yox and Ritter, 1988; Rózsa and Jacobson, 1989;
Forster et al., 1990).
Forster et al., 1990).
Fourth, age, strain, and species differences in the sen-
sory neur 1988; Yox and Ritter, 1988; Rózsa and Jacobson,
Forster et al., 1990).
Fourth, age, strain, and species differences in the
sory neuron-selective effects of capsaicin are othe
tors that complicate the classification of caps Forster et al., 1
Fourth, age, i
sory neuron-se
tors that comp
sitive neurons.
2. Neurons

2. *Neurons not sensitive to the neurotoxic action of* sory neuron-selective effects of capsaicin are other factors that complicate the classification of capsaicin-sensitive neurons.

2. Neurons not sensitive to the neurotoxic action of capsaicin. Although some afferent neuro tors that complicate the classification of capsaicin-sensitive neurons.

2. Neurons not sensitive to the neurotoxic action of capsaicin. Although some afferent neurons with thickly myelinated axons conducting in the $A\alpha$ sitive neurons.

2. Neurons not sensitive to the neurotoxic action of capsaicin. Although some afferent neurons with thickly myelinated axons conducting in the A α and A β range are first stimulated and then blocked t 2. Neurons not sensitive to the neurotoxic action of capsaicin. Although some afferent neurons with thickly myelinated axons conducting in the $A\alpha$ and $A\beta$ range are first stimulated and then blocked transiently by acu capsaicin. Although some afferent neurons with thickly myelinated axons conducting in the $A\alpha$ and $A\beta$ range are first stimulated and then blocked transiently by acute administration of capsaicin, there is consistent e myelinated axons conducting in the $A\alpha$ and $A\beta$ range are first stimulated and then blocked transiently by acute administration of capsaicin, there is consistent evidence that this population of afferent neurons is not first stimulated and then blocked transiently by acut
administration of capsaicin, there is consistent evidence
that this population of afferent neurons is not sensitiv
to the long-term neurotoxic action of the drug. Likew administration of capsaicin, there is consistent evidence
that this population of afferent neurons is not sensitive
to the long-term neurotoxic action of the drug. Likewise,
efferent motor neurons and efferent neurons of t that this population of afferent neurons is not sensitive
to the long-term neurotoxic action of the drug. Likewise,
efferent motor neurons and efferent neurons of the auto-
nomic nervous system are not directly sensitive t to the long-term neurotoxic action of the drug. Likewise,
efferent motor neurons and efferent neurons of the auto-
nomic nervous system are not directly sensitive to the
excitatory or neurotoxic action of capsaicin (Szolcs efferent motor neurons and efferent neurons of the auto
nomic nervous system are not directly sensitive to the
excitatory or neurotoxic action of capsaicin (Szolcsány
et al., 1975; Ault and Evans, 1980; Jancsó et al., 1980 nomic nervous system are not directly sensitive to the excitatory or neurotoxic action of capsaicin (Szolcsányi et al., 1975; Ault and Evans, 1980; Jancsó et al., 1980a; Cervero and McRitchie, 1982; Gamse et al., 1982; Mat 2. Neurons.

2. Neurons not sensitive to the neurotoxic action of $2.$ Neurons and sensitive to the neurotoxic action of capsacin, Although some afferent neurons with thickly myelinated anons conducting in the $A\alpha$ and et al., 1975; Ault and Evans, 1980; Jancsó et al., 1980a;
Cervero and McRitchie, 1982; Gamse et al., 1982; Mat-
thews and Cuello, 1982; Della et al., 1983; Sharkey et al.,
1983; Handwerker et al., 1984; Stein et al., 1986; Cervero and McRitchie, 1982; Gamse et al., 1982; Matthews and Cuello, 1982; Della et al., 1983; Sharkey et al., 1983; Handwerker et al., 1984; Stein et al., 1986; Such and Jancsó, 1986; Bevan et al., 1987; Marsh et al., 19 thews and Cuello, 1982; Della et al., 1983; Sharkey et al., 1983; Handwerker et al., 1984; Stein et al., 1986; Such and Jancsó, 1986; Bevan et al., 1987; Marsh et al., 1987; Takano et al., 1988; Wood et al., 1988). The ent 1983; Handwerker et al., 1984; Stein et al., 1986; Such
and Jancsó, 1986; Bevan et al., 1987; Marsh et al., 1987;
Takano et al., 1988; Wood et al., 1988). The enteric
nervous system also is believed to be grossly insensiti and Jancsó, 1986; Bevan et al., 1987; Marsh et al., 1987; Takano et al., 1988; Wood et al., 1988). The enteric
nervous system also is believed to be grossly insensitive
to capsaicin (Barthó and Holzer, 1985), and the repor Takano et al., 1988; Wood et al., 1988). The enteric
nervous system also is believed to be grossly insensitive
to capsaicin (Barthó and Holzer, 1985), and the reports
that a minority of enteric neurons is susceptible to th nervous system also is believed to be grossly insensitive
to capsaicin (Barthó and Holzer, 1985), and the reports
that a minority of enteric neurons is susceptible to the
neurotoxic action of the drug (Fehér and Vajda, 198 to capsaicin (Barthó and Holzer, 1985), and the reports
that a minority of enteric neurons is susceptible to the
neurotoxic action of the drug (Fehér and Vajda, 1982;
Harti, 1988; Kirchgessner et al., 1988) need to be conthat a minority of enteric neurons is susceptible to the meurotoxic action of the drug (Fehér and Vajda, 198
Harti, 1988; Kirchgessner et al., 1988) need to be cofirmed. A similar restriction applies to neurons in the cent neurotoxic action of the drug (Fehér and Vajda, 1982;
Harti, 1988; Kirchgessner et al., 1988) need to be confirmed. A similar restriction applies to neurons in the
central nervous system, the majority of which are insensit firmed. A similar restriction applies to neurons in the central nervous system, the majority of which are insensitive to the acute and long-term effects of capsaicin. However, the situation is not yet clear and calls for f sitive to the acute and long-term effects of capsaicin.
However, the situation is not yet clear and calls for
further examination. It needs to be emphasized, there-
fore, that the selectivity with which capsaicin acts on a central nervous system, the majority of which are insensitive to the acute and long-term effects of capsaicin.
However, the situation is not yet clear and calls for further examination. It needs to be emphasized, therefore sitive to the acute and long-term effects of capsaicin.
However, the situation is not yet clear and calls for
further examination. It needs to be emphasized, there-
fore, that the selectivity with which capsaicin acts on a However, the situation is not yet clear and calls for further examination. It needs to be emphasized, therefore, that the selectivity with which capsaicin acts on group of unmyelinated and thinly myelinated primar afferent lute. group of unmyelinated and thinly myelinated primary
afferent neurons is exceptional but certainly not abso-
lute.
3. Cell-nonselective effects of capsaicin. Apart from its
sensory neuron-selective effects, capsaicin exerts

group of unmyelinated and thinly myelinated primar
afferent neurons is exceptional but certainly not absolute.
3. Cell-nonselective effects of capsaicin. Apart from it
sensory neuron-selective effects, capsaicin exerts a n afferent neurons is exceptional but certainly not absolute.
3. Cell-nonselective effects of capsaicin. Apart from its
sensory neuron-selective effects, capsaicin exerts a num-
ber of "nonselective" effects which can be dif lute.
3. Cell-nonselective effects of capsaicin. Apart from its
sensory neuron-selective effects, capsaicin exerts a num-
ber of "nonselective" effects which can be differentiated
into three categories. (a) Capsaicin can, 3. Cell-nonselective effects of capsaicin. Apart from its
sensory neuron-selective effects, capsaicin exerts a num-
ber of "nonselective" effects which can be differentiated
into three categories. (a) Capsaicin can, both sensory neuron-selective effects, capsaicin exerts a number of "nonselective" effects which can be differentiated into three categories. (a) Capsaicin can, both acutely and in the long term, affect neural and nonneural sys ber of "nonselective" effects which can be differentiate
into three categories. (a) Capsaicin can, both acutely an
in the long term, affect neural and nonneural system
that are functionally related to primary afferent n in the long term, affect neural and nonneural systems
that are functionally related to primary afferent neurons.
Capsaicin-induced changes in these systems are inter-
preted to be secondary to the action of capsaicin on
pr primary afferent neurons. *(b)* Certain long-term neurothat are functionally related to primary afferent neurons.
Capsaicin-induced changes in these systems are inter-
preted to be secondary to the action of capsaicin on
primary afferent neurons. (b) Certain long-term neuro-
t Capsaicin-induced changes in these systems are inter-
preted to be secondary to the action of capsaicin on
primary afferent neurons. (b) Certain long-term neuro-
toxic actions of capsaicin on neurons in the central and
en

HOLZER
 A secondary sequel of sensory denervation but appear to the position of the amide (NH) and carbonyl (CO) func-
 A reflect a direct effect of the drug on these neurons. Thus, tions is reversed, but excitatory ac HOL
a secondary sequel of sensory denervation but appear to
reflect a direct effect of the drug on these neurons. Thus,
a group of thermosensitive neurons in the preoptic region HOLZER
a secondary sequel of sensory denervation but appear to
reflect a direct effect of the drug on these neurons. Thus, tic
a group of thermosensitive neurons in the preoptic region (S
of the hypothalamus is defunctiona a secondary sequel of sensory denervation but appear to
reflect a direct effect of the drug on these neurons. Thus,
a group of thermosensitive neurons in the preoptic region
of the hypothalamus is defunctionalized by syste a secondary sequel of sensory denervation but appear to
reflect a direct effect of the drug on these neurons. Thus,
a group of thermosensitive neurons in the preoptic region
of the hypothalamus is defunctionalized by syste reflect a direct effect of the drug on these neurons. Thus, tion
a group of thermosensitive neurons in the preoptic region (Sz
of the hypothalamus is defunctionalized by systemic of t
capsaicin given to adult rats, and som a group of thermosensitive neurons in the preoptic region
of the hypothalamus is defunctionalized by systemic
capsaicin given to adult rats, and some neurons in other
nuclei of the brain appear to degenerate in response to of the hypothalamus is defunctionalized by systemic of capsaicin given to adult rats, and some neurons in other muclei of the brain appear to degenerate in response to grade the drug (Dinh and Ritter, 1987; Ritter and Dinh capsaicin given to adult rats, and some neurons in oth
nuclei of the brain appear to degenerate in response
the drug (Dinh and Ritter, 1987; Ritter and Dinh, 1988
(c) Capsaicin exerts a transient effect on many neural α nuclei of the brain appear to degenerate in response the drug (Dinh and Ritter, 1987; Ritter and Dinh, 1988)
(c) Capsaicin exerts a transient effect on many neural a
well as nonneural systems in both vertebrate and inve-
t the drug (Dinh and Ritter, 1987; Ritter and Dinh, 1988). of Constantine exerts a transient effect on many neural as New Well as nonneural systems in both vertebrate and invertibrate species, which seem to be unrelated to i (c) Capsaicin exerts a transient effect on many neural as
well as nonneural systems in both vertebrate and inver-
tebrate species, which seem to be unrelated to its excit-
atory action on thin primary afferent neurons. A well as nonneural systems in both vertebrate and invertebrate species, which seem to be unrelated to its excitatory action on thin primary afferent neurons. Although the potency of capsaicin in producing these cell-nonsele tebrate species, which seem to be unrelated to its excit-
atory action on thin primary afferent neurons. Although mathe potency of capsaicin in producing these cell-nonse-
lective effects is, in most cases, orders of magni the potency of capsaicin in producing these cell-nonselective effects is, in most cases, orders of magnitude lower than that in exciting sensory neurons, it follows that the acute effects of capsaicin are less selective fo the potency of capsaicin in producing thes
lective effects is, in most cases, orders of mag
than that in exciting sensory neurons, it foll
acute effects of capsaicin are less selective fient neurons than are its long-term hat in exciting sensory neurons, it follows that
effects of capsaicin are less selective for thin at
urons than are its long-term effects.
III. Mechanisms of Action of Capsaicin
dence for the Presence of a Specific Recogni

A. Evidence for the Presence of a Specific Recognition
A. Evidence for the Presence of a Specific Recognition
A. Evidence for the Presence of a Specific Recognition
Site for Capsaicin **Site for Capsaicing TII. Mechanis:**
A. Evidence for the Piste for Capsaicin
1. Structure-activity

111. Mechanisms of Action of Capsaicin
Evidence for the Presence of a Specific Recognition
te for Capsaicin
1. Structure-activity relationship for the excitatory ef-
t of capsaicinoids on sensory neurons. Ever since th *A. Evidence for the Presence of a Specific Recognition* dif
 Site for Capsaicin
 1. Structure-activity relationship for the excitatory effect of capsaicinoids on sensory neurons. Ever since the
 acutely stimulant and Equivalently relationship for the excitatory of
Site for Capsaicin
1. Structure-activity relationship for the excitatory ef-
fect of capsaicinoids on sensory neurons. Ever since the
acutely stimulant and long-term inhibit I. Structure-activity relationship for the excitatory
fect of capsaicinoids on sensory neurons. Ever since
acutely stimulant and long-term inhibitory actions
capsaicin on afferent neurons were disclosed, invest
tors were i 1. Structure-activity relationship for the excitatory effect of capsaicinoids on sensory neurons. Ever since the actively stimulant and long-term inhibitory actions of capsaicin on afferent neurons were disclosed, investi fect of capsaicinoids on sensory neurons. Ever since the
acutely stimulant and long-term inhibitory actions of
capsaicin on afferent neurons were disclosed, investiga-
tors were intrigued by the remarkable selectivity of acutely stimulant and long-term inhibitory actions of capsaicin on afferent neurons were disclosed, investigators were intrigued by the remarkable selectivity of these actions for thin sensory neurons. The finding of Szolc capsaicin on afferent neurons were disclosed, investiga-
tors were intrigued by the remarkable selectivity of these
actions for thin sensory neurons. The finding of
Szolcsányi and Jancsó-Gábor (1975, 1976) that the ef-
fec tors were intrigued by the remarkable selectivity of these actions for thin sensory neurons. The finding of Szolcsányi and Jancsó-Gábor (1975, 1976) that the effects of capsaicin are shared by structurally related analogue neurons are finding of Szolcsányi and Jancsó-Gábor (1975, 1976) that the effects of capsaicin are shared by structurally related analogues of the drug first suggested that certain afferent neurons are sensitive to capsaici Szolcsányi and Jancsó-Gábor (1975, 1976) that the fects of capsaicin are shared by structurally related alogues of the drug first suggested that certain affer
neurons are sensitive to capsaicin because they poss
a selectiv fects of capsaicin are shared by structurally related analogues of the drug first suggested that certain afferent resiment of the drug first suggested that certain afferent of $\frac{1}{1}$ responses a selective recognition s alogues of the drug first suggested that certain afferent
neurons are sensitive to capsaicin because they possess
a selective recognition site for capsaicinoids, a pharma-
cological receptor that mediates the cellular res neurons are sensitive to capsaicin because they possess
a selective recognition site for capsaicinoids, a pharma-
cological receptor that mediates the cellular responses to
the drug. As shown in fig. 1, capsaicin consists cological receptor that mediates the cellular responses to
the drug. As shown in fig. 1, capsaicin-consists of a
vanillyl moiety, an acylamide group, and an alkyl chain,
certain features of which are required for capsaicin activity. e drug. As shown in fig. 1, capsaicin consists of
nillyl moiety, an acylamide group, and an alkyl chai
rtain features of which are required for capsaicin-lil
tivity.
The acutely stimulant activity of capsaicin is dete
ined

vanillyl moiety, an acylamide group, and an alkyl chain,
certain features of which are required for capsaicin-like
activity.
The acutely stimulant activity of capsaicin is deter-
mined by the presence of a 4-hydroxy-3-meth certain features of which are required for capsaicin-like
activity.
The acutely stimulant activity of capsaicin is deter-
mined by the presence of a 4-hydroxy-3-methoxy benzyl
ring, the polar nature of the acylamide bond, activity.
The acutely stimulant activity of capsaicin is deter-
mined by the presence of a 4-hydroxy-3-methoxy benzyl
ring, the polar nature of the acylamide bond, and the
apolar nature of the alkyl chain. The substituted mined by the presence of a 4-hydroxy-3-methoxy benzyl
ring, the polar nature of the acylamide bond, and the
apolar nature of the alkyl chain. The substituted aro-
matic ring is essential for the excitatory activity of capring, the polar nature of the acylamide bond, and the applar nature of the alkyl chain. The substituted are Talmatic ring is essential for the excitatory activity of capsical medicines or excitatory activity of capsical co apolar nature of the alkyl chain. The substituted aro-
matic ring is essential for the excitatory activity of capsaicin congeners (Szolcsányi and Jancsó-Gábor, 1975; id
Hayes et al., 1984b; Dray et al., 1990c; Szallasi and matic ring is essential for the excitatory activity of capsaicin congeners (Szolcsányi and Jancsó-Gábor, 1975;
Hayes et al., 1984b; Dray et al., 1990c; Szallasi and
Blumberg, 1990b), and this structural requirement has
bee saicin congeners (Szolcsányi and Jancsó-Gábor, 1975;
Hayes et al., 1984b; Dray et al., 1990c; Szallasi and
Blumberg, 1990b), and this structural requirement has
been confirmed by studying the activity of capsaicin-like
pho Hayes et al., 1984b; Dray et al., 1990c; Szallasi and
Blumberg, 1990b), and this structural requirement has
been confirmed by studying the activity of capsaicin-like
photoaffinity probes on neurons cultured from rat dorsal Blumberg, 1990b), and this structural requirement has held confirmed by studying the activity of capsaicin-like on photoaffinity probes on neurons cultured from rat dorsal proot ganglia (James et al., 1988). Thus, aryl azi been confirmed by studying the activity of capsaicin-like only photoaffinity probes on neurons cultured from rat dorsal proot ganglia (James et al., 1988). Thus, aryl azido ana-
logues of capsaicin produce a long-lasting s photoaffinity probes on neurons cultured from rat dorsal

root ganglia (James et al., 1988). Thus, aryl azido ana-

logues of capsaicin produce a long-lasting stimulation of

calcium uptake after ultraviolet irradiation on root ganglia (James e
logues of capsaicin precalcium uptake after unalogues contain a
(James et al., 1988).
There is some flexik

calcium uptake after ultraviolet irradiation only if these be analogues contain a 4-hydroxy-3-methoxy benzyl ring the (James et al., 1988).

There is some flexibility in the polar bond because the (S: acylamide group can b analogues contain a 4-hydroxy-3-methoxy benzyl ring (James et al., 1988).

There is some flexibility in the polar bond because the

acylamide group can be replaced by an ester group

(Szolcsányi and Jancsó-Gábor, 1975), pa their (James et al., 1988). their the polar bond because the (Sza acylamide group can be replaced by an ester group 1988). (Szolcsányi and Jancsó-Gábor, 1975), particularly in re- Sza siniferatoxin (Szallasi and Blumberg, There is some flexibility in the polar bond because the acylamide group can be replaced by an ester group (Szolcsányi and Jancsó-Gábor, 1975), particularly in resiniferatoxin (Szallasi and Blumberg, 1989, 1990a,b). In caps

the position of the amide (NH) and carbonyl (CO) func-ER
the position of the amide (NH) and carbonyl (CO) func-
tions is reversed, but excitatory activity is retained
(Szolcsányi and Jancsó-Gábor, 1975). However, a change ER
the position of the amide (NH) and carbonyl (CO) func-
tions is reversed, but excitatory activity is retained
(Szolcsányi and Jancsó-Gábor, 1975). However, a change
of the secondary to a tertiary amide function (replace the position of the amide (NH) and carbonyl (CO) futions is reversed, but excitatory activity is retain (Szolcsányi and Jancsó-Gábor, 1975). However, a change of the secondary to a tertiary amide function (replament of the the position of the amide (NH) and carbonyl (CO) functions is reversed, but excitatory activity is retained (Szolcsányi and Jancsó-Gábor, 1975). However, a change of the secondary to a tertiary amide function (replacement tions is reversed, but excitatory activity is retained (Szolcsányi and Jancsó-Gábor, 1975). However, a change of the secondary to a tertiary amide function (replacement of the H in the NH group by, for example, an alkyl gr (Szolcsányi and Jancsó-Gábor, 1975). However, a change
of the secondary to a tertiary amide function (replace-
ment of the H in the NH group by, for example, an alkyl
group) strongly reduces noxious activity of capsaicinoi of the secondary to a tertiary amide function (replacement of the H in the NH group by, for example, an alkyl group) strongly reduces noxious activity of capsaicinoids on the rat cornea (Szolcsányi and Jancsó-Gábor, 1975). ment of the H in the NH group by, for example, an alkyl group) strongly reduces noxious activity of capsaicinoids
on the rat cornea (Szolcsányi and Jancsó-Gábor, 1975).
Most variability is permitted in the apolar residue w group) strongly reduces noxious activity of capsaicino
on the rat cornea (Szolcsányi and Jancsó-Gábor, 19'
Most variability is permitted in the apolar residue whi
in capsaicin, is an alkyl chain. It appears as if the optii on the rat cornea (Szolcsányi and Jancsó-Gábor, 1975).
Most variability is permitted in the apolar residue which,
in capsaicin, is an alkyl chain. It appears as if the optimal
chain length for activity on the rat cornea is Most variability is permitted in the apolar residue which,
in capsaicin, is an alkyl chain. It appears as if the optimal
chain length for activity on the rat cornea is approxi-
mately 8 to 10 carbon atoms because either an in capsaicin, is an alkyl chain. It appears as if the optimal
chain length for activity on the rat cornea is approxi-
mately 8 to 10 carbon atoms because either an increase
or decrease in the chain length reduces activity, chain length for activity on the rat cornea is approximately 8 to 10 carbon atoms because either an increase
or decrease in the chain length reduces activity, wherea
the introduction of a double bond in the alkyl chain ha
 mately 8 to 10 carbon atoms because either an increase
or decrease in the chain length reduces activity, whereas
the introduction of a double bond in the alkyl chain has
no effect (Szolcsányi and Jancsó-Gábor, 1975). The p or decrease in the chain length reduces activity, whereas
the introduction of a double bond in the alkyl chain has
no effect (Szolcsányi and Jancsó-Gábor, 1975). The pres-
ence of an alkyl chain as such is not essential be the introduction of a double bond in the alkyl chain has no effect (Szolcsányi and Jancsó-Gábor, 1975). The presence of an alkyl chain as such is not essential because its substitution by a cycloalkyl ring results in a com no effect (Szolcsányi and Jancsó-Gábor, 1975). The pres-
ence of an alkyl chain as such is not essential because its
substitution by a cycloalkyl ring results in a compound
that retains much of its activity (Szolcsányi and ence of an alkyl chain as such is not essential because its
substitution by a cycloalkyl ring results in a compound
that retains much of its activity (Szolcsányi and Jancsó-
Gábor, 1975); the exchange of the alkyl chain by substitution by a cycloalkyl ring results in a compound
that retains much of its activity (Szolcsányi and Jancsó-
Gábor, 1975); the exchange of the alkyl chain by a
diterpene, as occurs in the resiniferatoxin molecule, lea that retains much of its activity (Szolcsányi and Jancsó-Gábor, 1975); the exchange of the alkyl chain by a diterpene, as occurs in the resiniferatoxin molecule, leads to a markedly increased activity in a number of assays Gábor, 1975); the exchange of the alkyl chain by a diterpene, as occurs in the resiniferatoxin molecule, leads to a markedly increased activity in a number of assays (de Vries and Blumberg, 1989; Szallasi and Blumberg, 198 diterpene, as occurs in the resiniferatoxin i
to a markedly increased activity in a nur
(de Vries and Blumberg, 1989; Szallasi i
1989, 1990a,b; Szallasi et al., 1989; Dray
Maggi et al., 1990c; Winter et al., 1990).
Some ex a markedly increased activity in a number of ass

E Vries and Blumberg, 1989; Szallasi and Blumbe

89, 1990a,b; Szallasi et al., 1989; Dray et al., 199

aggi et al., 1990c; Winter et al., 1990).

Some exceptions to the des

mined by the presence of a 4-hydroxy-3-methoxy benzyl

ring, the polar nature of the acylamide bond, and the

apolar nature of the acylamide bond, and the

apolar nature of the akkyl chain. The substituted aro-

Takaki et (de Vries and Blumberg, 1989; Szallasi and Blumberg
1989, 1990a,b; Szallasi et al., 1989; Dray et al., 1990a
Maggi et al., 1990c; Winter et al., 1990).
Some exceptions to the described structural require
ments for capsaici Maggi et al., 1990c; Winter et al., 1990).
Some exceptions to the described structural require-
ments for capsaicin-like activity need to be mentioned.
Removal of the 3-methoxy substituent in the resinifera-
toxin molecule Maggi et al., 1990c; Winter et al., 1990).

Some exceptions to the described structural require-

ments for capsaicin-like activity need to be mentioned.

Removal of the 3-methoxy substituent in the resinifera-

toxin mol Some exceptions to the described structural require-
ments for capsaicin-like activity need to be mentioned.
Removal of the 3-methoxy substituent in the resinifera-
toxin molecule, such as is found in tinyatoxin, results i ments for capsaicin-like activity need to be mentioned.
Removal of the 3-methoxy substituent in the resiniferatoxin molecule, such as is found in tinyatoxin, results in
only a minor decrease in activity as compared with
r Removal of the 3-methoxy substituent in the resinifer
toxin molecule, such as is found in tinyatoxin, results
only a minor decrease in activity as compared wi
resiniferatoxin (Szallasi and Blumberg, 1990b). Musta
oil (all toxin molecule, such as is found in tinyatoxin, results in
only a minor decrease in activity as compared with
resiniferatoxin (Szallasi and Blumberg, 1990b). Mustard
oil (allyl isothiocyanate, $CH_2 = CH-CH_2$ -NCS) stimu-
late only a minor decrease in activity as compared with
resiniferatoxin (Szallasi and Blumberg, 1990b). Mustard
oil (allyl isothiocyanate, $CH_2 = CH-CH_2$ -NCS) stimu-
lates capsaicin-sensitive afferent nerve fibers (Jancsó et
al., resiniferatoxin (Szallasi and Blumberg, 1990b). Mustard

oil (allyl isothiocyanate, $CH_2 = CH - CH_2$ -NCS) stimu-

lates capsaicin-sensitive afferent nerve fibers (Jancsó et

al., 1967, 1977, 1980a; Lembeck and Holzer, 1979; Ga oil (allyl isothiocyanate, $CH_2 = CH - CH_2$ -NCS) stimu-
lates capsaicin-sensitive afferent nerve fibers (Jancsó et
al., 1967, 1977, 1980a; Lembeck and Holzer, 1979; Gamse
et al., 1980; Patacchini et al., 1990) of both the C an lates capsaicin-sensitive afferent nerve fibers (Jancsó dal., 1967, 1977, 1980a; Lembeck and Holzer, 1979; Gams
et al., 1980; Patacchini et al., 1990) of both the C and A
type (Harris and Ryall, 1988), although its chemic: al., 1967, 1977, 1980a; Lembeck and Holzer, 1979; Gamse
et al., 1980; Patacchini et al., 1990) of both the C and A δ
type (Harris and Ryall, 1988), although its chemical
constitution is very different from that of capsa et al., 1980; Patacchini et al., 1990) of both the C and A₀ type (Harris and Ryall, 1988), although its chemical constitution is very different from that of capsaicinoids.
Furthermore, piperine which lacks a polar moiety type (Harris and Ryall, 1988), although its chemical constitution is very different from that of capsaicinoids.
Furthermore, piperine which lacks a polar moiety in the place of capsaicin's acylamide retains considerable ca constitution is very different from that of capsaicinoids.
Furthermore, piperine which lacks a polar moiety in the
place of capsaicin's acylamide retains considerable cap-
saicin-like activity in certain assays (Micevych e Furthermore, piperine which lacks a polar moiety in the place of capsaicin's acylamide retains considerable capsaicin-like activity in certain assays (Micevych et al., 1983; Jhamandas et al., 1984; Miyauchi et al., 1989; T place of capsaicin's acylamide retains considerable capsaicin-like activity in certain assays (Micevych et al., 1983; Jhamandas et al., 1984; Miyauchi et al., 1989; Takaki et al., 1990). It is not totally clear, however, w saicin-like activity in certain assays (Micevych et al., 1983; Jhamandas et al., 1984; Miyauchi et al., 1989; Takaki et al., 1990). It is not totally clear, however, whether the cellular site of action of these compounds i 1983; Jhamandas et al., 1984; Miyauchi et al., 1989;

Takaki et al., 1990). It is not totally clear, however,

whether the cellular site of action of these compounds is

identical with that of capsaicin. This shortcoming c Takaki et al., 1990). It is not totally clear, however, whether the cellular site of action of these compounds is identical with that of capsaicin. This shortcoming curtails the validity of all structure-activity studies t whether the cellular site of action of these compounds is
identical with that of capsaicin. This shortcoming cur-
tails the validity of all structure-activity studies that do
not directly examine the stimulant effect of ca identical with that of capsaicin. This shortcoming curtails the validity of all structure-activity studies that do not directly examine the stimulant effect of capsaicinoids on sensory neurons but utilize effects subsequen tails the validity of all structure-activity studies than to directly examine the stimulant effect of capsaicin
on sensory neurons but utilize effects subsequent to
primary event, e.g., nociceptive reflexes or tissue
spons t directly examine the stimulant effect of capsaicinoids
sensory neurons but utilize effects subsequent to this
imary event, e.g., nociceptive reflexes or tissue re-
onses to the local release of sensory neurotransmitters.

logues of capsaicin produce a long-lasting stimulation of Despite these uncertainties, there is a good correlation
calcium uptake after ultraviolet irradiation only if these between the noxious activity of capsaicin congen on sensory neurons but utilize effects subsequent to this
primary event, e.g., nociceptive reflexes or tissue re-
sponses to the local release of sensory neurotransmitters.
Despite these uncertainties, there is a good corr primary event, e.g., nociceptive reflexes or tissue responses to the local release of sensory neurotransmitters.
Despite these uncertainties, there is a good correlation
between the noxious activity of capsaicin congeners sponses to the local release of sensory neurotransmitters.

Despite these uncertainties, there is a good correlation

between the noxious activity of capsaicin congeners on

the rat cornea (Szolcsányi and Jancsó-Gábor, 197 Despite these uncertainties, there is a good correlation
between the noxious activity of capsaicin congeners on
the rat cornea (Szolcsányi and Jancsó-Gábor, 1975) with
their potency in eliciting the Bezold-Jarisch reflex
(between the noxious activity of capsaicin congeners on
the rat cornea (Szolcsányi and Jancsó-Gábor, 1975) with
their potency in eliciting the Bezold-Jarisch reflex
(Szolcsányi, 1982), producing hypothermia (Szolcsányi,
198 the rat cornea (Szolcsányi and Jancsó-Gábor, 1975) with
their potency in eliciting the Bezold-Jarisch reflex
(Szolcsányi, 1982), producing hypothermia (Szolcsányi,
1982; Hayes et al., 1984b; de Vries and Blumberg, 1989;
Sz their potency in eliciting the Bezold-Jarisch reflex (Szolcsányi, 1982), producing hypothermia (Szolcsányi, 1982; Hayes et al., 1984b; de Vries and Blumberg, 1989; Szallasi and Blumberg, 1990b), causing contraction of the (Szolcsányi, 1982), producing hypothermia (Szolcsányi, 1982; Hayes et al., 1984b; de Vries and Blumberg, 1989;
Szallasi and Blumberg, 1990b), causing contraction of
the trachea (Szolcsányi, 1983b), and facilitating the re-

aspet

CAPSAIC
Lembeck, 1981; Jhamandas et al., 1984). The situation
is different, however, when capsaicin and resiniferatoxin CAPS/
Lembeck, 1981; Jhamandas et al., 1984). The situation
is different, however, when capsaicin and resiniferatoxin
are compared with each other. In some assays of capsai-C
Lembeck, 1981; Jhamandas et al., 1984). The situati
is different, however, when capsaicin and resiniferator
are compared with each other. In some assays of caps
cin-like activity (Szallasi and Blumberg, 1989; Maggi Lembeck, 1981; Jhamandas et al., 1984). The situation
is different, however, when capsaicin and resiniferatoxin
are compared with each other. In some assays of capsai-
cin-like activity (Szallasi and Blumberg, 1989; Maggi Lembeck, 1981; Jhamandas et al., 1984). The situation
is different, however, when capsaicin and resiniferatoxin
are compared with each other. In some assays of capsai-
cin-like activity (Szallasi and Blumberg, 1989; Maggi are compared with each other. In some assays of capsaicin-like activity (Szallasi and Blumberg, 1989; Maggi et al., 1990c), resiniferatoxin is not or is only marginally more active than capsaicin, whereas in other tests (d cin-like activity (Szallasi and Blumberg, 1989; Maggi et ideal., 1990c), resiniferatoxin is not or is only marginally sensore active than capsaicin, whereas in other tests (decompress and Blumberg, 1989; Szallasi and Blumb al., 1990c), resiniferatoxin is not or is only marginally stim
more active than capsaicin, whereas in other tests (decorr
Vries and Blumberg, 1989; Szallasi and Blumberg, 1989, bor,
1990a,b; Szallasi et al., 1989; Dray et more active than capsaicin
Vries and Blumberg, 1989;
1990a,b; Szallasi et al., 1989;
al., 1990c; Winter et al., 19
10,000 times more potent.
On the basis of the desc. ies and Blumberg, 1989; Szallasi and Blumberg, 1989, 90a,b; Szallasi et al., 1989; Dray et al., 1990a; Maggi et
, 1990c; Winter et al., 1990), resiniferatoxin is 100 to
,000 times more potent.
On the basis of the described

1990a,b; Szallasi et al., 1989; Dray et al., 1990a; Maggi et al., 1990c; Winter et al., 1990), resiniferatoxin is 100 to 10,000 times more potent.
On the basis of the described structural requirements for a capsaicin conge al., 1990c; Winter et al., 1990), resiniferatoxin is 100 to 10,000 times more potent.
10,000 times more potent.
On the basis of the described structural requirement
for a capsaicin congener to stimulate sensory neuron
Szol 10,000 times more potent.

On the basis of the described structural requirements

for a capsaicin congener to stimulate sensory neurons,

Szolcsányi and Jancsó-Gábor (1975) proposed a hypo-

thetical model of a capsaicin On the basis of the described structural requirements relation and an explorer to stimulate sensory neurons, relations between the capsaicin receptor in which multiple desinteractions between the capsaicin molecule and the for a capsaicin congener to stimulate sensory neurons, records a hypotometrical model of a capsaicin receptor in which multiple dinteractions between the capsaicin molecule and the interactions between the capsaicin molecu Szolcsányi and Jancsó-Gábor (1975) proposed a hypo-
thetical model of a capsaicin receptor in which multiple depenteractions between the capsaicin molecule and the in
recognition site determine optimal activity. In this 1 thetical model of a capsaicin receptor in which multiple
interactions between the capsaicin molecule and the
recognition site determine optimal activity. In this
model, the 4-hydroxy substitutent on the phenyl ring
and the interactions between the capsaicin molecule and the recognition site determine optimal activity. In this model, the 4-hydroxy substitutent on the phenyl ring and the carbonyl and NH functions in the acylamide moiety (or it recognition site determine optimal activity. In this 1984). The potency of a number of capsaicin congeners model, the 4-hydroxy substitutent on the phenyl ring in preventing labeling of cultured sensory neurons with and th and the carbonyl and NH functions in the acylamide a photoaffinity probe also correlates well with their po-
moiety (or its polar equivalents) interact with polar tency as agonists in the calcium uptake assay (James et
con and the carbonyl and NH functions in the acylamide a p
moiety (or its polar equivalents) interact with polar ten
constituents of the receptor, whereas the phenyl ring, as al.,
well as the alkyl chain or its apolar substitu moiety (or its polar equivalents) interact with polaconstituents of the receptor, whereas the phenyl ring, a well as the alkyl chain or its apolar substitution, provident apolar ligand-receptor interactions (Szolcsányi an constituents of the receptor, whereas the phenyl ring, as al., well as the alkyl chain or its apolar substitution, provide O
for apolar ligand-receptor interactions (Szolcsányi and excivations of irritant compounds with pa well as the alkyl chain or its apolar substitution, provident for apolar ligand-receptor interactions (Szolcsányi and Jancsó-Gábor, 1975). However, the capsaicin-like activities of irritant compounds with partial, little, for apolar ligand-receptor interactions (Szold
Jancsó-Gábor, 1975). However, the capsaicin
ities of irritant compounds with partial, lift
structural similarity to capsaicin such as xyle
tard oil are not accounted for by th ncsó-Gábor, 1975). However, the capsaicin-like actives of irritant compounds with partial, little, or no
ructural similarity to capsaicin such as xylene or mus-
rd oil are not accounted for by this model.
2. Structure-acti

ities of irritant compounds with partial, little, or no
structural similarity to capsaicin such as xylene or mus-
tard oil are not accounted for by this model.
2. Structure-activity relationships for the desensitizing
and structural similarity to capsaicin such as xylene or mutard oil are not accounted for by this model.
2. Structure-activity relationships for the desensitizities and neurotoxic effects of capsaicinoids on sensory neuror.
Th tard oil are not accounted for by this model.
2. Structure-activity relationships for the desensitizing
and neurotoxic effects of capsaicinoids on sensory neurons.
The activities of capsaicin analogues in inducing desen-
s 2. Structure-activity relationships for the desensitizing and neurotoxic effects of capsaicinoids on sensory neurons.
The activities of capsaicin analogues in inducing desensitization to their stimulant effect on sensory n and neurotoxic effects of capsaicinoids on sensory neurons.
The activities of capsaicin analogues in inducing desensitization to their stimulant effect on sensory neurons
are still poorly defined but, as it appears, do not The activities of capsaicin analogues in inducing desensitization to their stimulant effect on sensory neurons are still poorly defined but, as it appears, do not completely overlap with their excitatory activities (Szolcs sitization to their stimulant effect on sensory neurons
are still poorly defined but, as it appears, do not com-
pletely overlap with their excitatory activities
(Szolcsányi and Jancsó-Gábor, 1976; Hayes et al., 1984b;
Dic are still poorly defined but, as it appears, do not com-
pletely overlap with their excitatory activities chical
(Szolcsányi and Jancsó-Gábor, 1976; Hayes et al., 1984b; is
Dickenson et al., 1990b; Dray et al., 1990c). The pletely overlap with their excitatory activities (Szolcsányi and Jancsó-Gábor, 1976; Hayes et al., 1984b; Dickenson et al., 1990b; Dray et al., 1990c). These differences are best illustrated by the fact that there are caps (Szolcsányi and Jancsó-Gábor, 1976; Hayes et al., 1984b; is
Dickenson et al., 1990b; Dray et al., 1990c). These dif-
ferences are best illustrated by the fact that there are G
capsaicin analogues such as zingerone and homo ferences are best illustrated by the fact that there are Gábor, 1976), and the especially high desensitizing activ-
capsaicin analogues such as zingerone and homovanillic ity of resiniferatoxin with its diterpene substitue ferences are best illustrated by the fact that there are (capsaicin analogues such as zingerone and homovanillic inoctylester that exhibit noxious activity but are devoid of desensitizing activity on the rat cornea (Szolcs capsaicin analogues such as zingerone and homovanillic
octylester that exhibit noxious activity but are devoid of
desensitizing activity on the rat cornea (Szolcsányi and
Jancsó-Gábor, 1976) and that, in contrast, other an octylester that exhibit noxious activity but are devoid of desensitizing activity on the rat cornea (Szolcsányi and Jancsó-Gábor, 1976) and that, in contrast, other analogues such as olvanil are able to desensitize against desensitizing activity on the rat cornea (Szolcsányi and se
Jancsó-Gábor, 1976) and that, in contrast, other ana-
logues such as olvanil are able to desensitize against of
capsaicin in the absence of stimulant activity (Di Jancsó-Gábor, 1976) and that, in contrast, other as logues such as olvanil are able to desensitize agaic capsaicin in the absence of stimulant activity (Dickens et al., 1990b; Dray et al., 1990c). Furthermore, in so assays logues such as olvanil are able to desensitize against of capsaicin in the absence of stimulant activity (Dickenson set al., 1990b; Dray et al., 1990c). Furthermore, in some Gassays of capsaicin-like activity, such as corn capsaicin in the absence of stimulant activity (Dicker
et al., 1990b; Dray et al., 1990c). Furthermore, in s
assays of capsaicin-like activity, such as corneal noci-
tion (Szallasi and Blumberg, 1989) and contraction
the r et al., 1990b; Dray et al., 1990c). Furthermore, in some assays of capsaicin-like activity, such as corneal nociception (Szallasi and Blumberg, 1989) and contraction of the rat urinary bladder (Maggi et al., 1990c), resini assays of capsaicin-like activity, such a
tion (Szallasi and Blumberg, 1989) a
the rat urinary bladder (Maggi et al., 1
toxin is orders of magnitude more poter
than in exciting sensory nerve fibers.
It is not yet clear how the rat urinary bladder (Maggi et al., 1990c), resiniferatoxin is orders of magnitude more potent in desensitizing
than in exciting sensory nerve fibers.
It is not vet clear how the divergence in the stimulant the rat urinary bladder (Maggi et al., 1990c), resiniferation is orders of magnitude more potent in desensitizing than in exciting sensory nerve fibers.
It is not yet clear how the divergence in the stimulant and desensiti

is to be explained wore potent in desensitizing
than in exciting sensory nerve fibers. A
It is not yet clear how the divergence in the stimulant
and desensitizing activities of some capsaicin derivatives
is to be explained than in exciting sensory nerve fibers.
It is not yet clear how the divergence in the stimulant
and desensitizing activities of some capsaicin derivatives
is to be explained, but two possibilities are especially
worth consi It is not yet clear how the divergence in the stimula
and desensitizing activities of some capsaicin derivative
is to be explained, but two possibilities are especia
worth considering. One line of evidence suggests the
exc is to be explained, but two possibilities are especially worth considering. One line of evidence suggests that excitation, desensitization, and neurotoxicity of capsaicinoids are mediated by a common site of action and tha is to be explained, but two possibilities are especially genol, worth considering. One line of evidence suggests that variables excitation, desensitization, and neurotoxicity of capsai- overlap cinoids are mediated by a co worth considering. One line of evidence suggests that excitation, desensitization, and neurotoxicity of capsaicinoids are mediated by a common site of action and that mismatches in the activities of some congeners arise fr mismatches in the activities of some congeners arise from
differences in their pharmacokinetic behaviour and/or
metabolic stability or from differences in the ligand-

are compared with each other. In some assays of capsai-
cin-like activity (Szallasi and Blumberg, 1989; Maggi et ings that the potencies of many capsaicin congeners to
al., 1990c), resiniferatoxin is not or is only margina receptor interactions with respect to binding forces and
binding reversibility (Szolcsányi and Jancsó-Gábor, 171
binding reversibility (Szolcsányi and Jancsó-Gábor,
1976). Support for this contention comes from the find-177

1776). The interactions with respect to binding forces and

binding reversibility (Szolcsányi and Jancsó-Gábor

1976). Support for this contention comes from the find

ings that the potencies of many capsaicin congene receptor interactions with respect to binding forces and
binding reversibility (Szolcsányi and Jancsó-Gábor,
1976). Support for this contention comes from the find-
ings that the potencies of many capsaicin congeners to
st receptor interactions with respect to binding forces and
binding reversibility (Szolcsányi and Jancsó-Gábor,
1976). Support for this contention comes from the find-
ings that the potencies of many capsaicin congeners to
st binding reversibility (Szolcsányi and Jancsó-Gábor, 1976). Support for this contention comes from the findings that the potencies of many capsaicin congeners to stimulate and desensitize sensory neurons are grossly correla 1976). Support for this contention comes from the findings that the potencies of many capsaicin congeners to stimulate and desensitize sensory neurons are grossly correlated with each other (Szolcsányi and Jancsó-Gábor, 19 ings that the potencies of many capsaicin congeners to
stimulate and desensitize sensory neurons are grossly
correlated with each other (Szolcsányi and Jancsó-Gá-
bor, 1975, 1976; Szolcsányi, 1982; Hayes et al., 1984b;
Jam stimulate and desensitize sensory neurons are grossly
correlated with each other (Szolcsányi and Jancsó-Gá-
bor, 1975, 1976; Szolcsányi, 1982; Hayes et al., 1984b;
James et al., 1988) and with their potency to induce
affer correlated with each other (Szolcsányi and Jancsó-Gábor, 1975, 1976; Szolcsányi, 1982; Hayes et al., 1984b; James et al., 1988) and with their potency to induce afferent neuron degeneration in the newborn rat (Jancsó and K bor, 1975, 1976; Szolcsányi, 1982; Hayes et al., 1984b;
James et al., 1988) and with their potency to induce
afferent neuron degeneration in the newborn rat (Jancsó
and Király, 1981). Furthermore, the structure-activity
re James et al., 1988) and with their potency to induce
afferent neuron degeneration in the newborn rat (Jancsó
and Király, 1981). Furthermore, the structure-activity
relationships of intrathecal capsaicinoids for the acute
r afferent neuron degeneration in the newborn rat (Jancsó
and Király, 1981). Furthermore, the structure-activity
relationships of intrathecal capsaicinoids for the acute
release of substance P in the spinal cord, desensitiza and Király, 1981). Furthermore, the structure-activity relationships of intrathecal capsaicinoids for the acute release of substance P in the spinal cord, desensitization to this effect, long-lasting antinociception, and l relationships of intrathecal capsaicinoids for the acute
release of substance P in the spinal cord, desensitization
to this effect, long-lasting antinociception, and long-term
depletion of substance P from afferent nerve t release of substance P in the spinal cord, desensitization
to this effect, long-lasting antinociception, and long-term
depletion of substance P from afferent nerve terminals
in the spinal cord are comparable (Jhamandas et to this effect, long-lasting antinociception, and long-term
depletion of substance P from afferent nerve terminals
in the spinal cord are comparable (Jhamandas et al.,
1984). The potency of a number of capsaicin congeners
 depletion of substance P from afferent nerve terminals
in the spinal cord are comparable (Jhamandas et al.,
1984). The potency of a number of capsaicin congeners
in preventing labeling of cultured sensory neurons with
a ph in the spinal cord are comparable (Jhamandas et al., 1984). The potency of a number of capsaicin congeners in preventing labeling of cultured sensory neurons with a photoaffinity probe also correlates well with their poten 1984). The
in preventii
a photoaffii
tency as ag
al., 1988).
Other dat preventing labeling of cultured sensory neurons with
photoaffinity probe also correlates well with their po-
ncy as agonists in the calcium uptake assay (James et
, 1988).
Other data prompt speculation that capsaicin-induc

a photoaffinity probe also correlates well with their po-
tency as agonists in the calcium uptake assay (James et
al., 1988).
Other data prompt speculation that capsaicin-induced
excitation and desensitization of sensory n tency as agonists in the calcium uptake assay (James e
al., 1988).
Other data prompt speculation that capsaicin-induce
excitation and desensitization of sensory neurons involve
two different sites of action. In line with t al., 1988).

Other data prompt speculation that capsaicin-induced

excitation and desensitization of sensory neurons involve

two different sites of action. In line with this contention,

differences in the structural requ Other data prompt speculation that capsaicin-induced
excitation and desensitization of sensory neurons involve
two different sites of action. In line with this contention,
differences in the structural requirements for cap differences in the structural requirements for capsaicin
analogues to cause stimulation and desensitization of
sensory neurons are apparent. The most important dif-
ference seems to relate to the apolar moiety, because two different sites of action. In line with this contention,
differences in the structural requirements for capsaicin
analogues to cause stimulation and desensitization of
sensory neurons are apparent. The most important d differences in the structural requirements for capsaicin
analogues to cause stimulation and desensitization of
sensory neurons are apparent. The most important dif-
ference seems to relate to the apolar moiety, because
cha analogues to cause stimulation and desensitization of
sensory neurons are apparent. The most important dif-
ference seems to relate to the apolar moiety, because
changes in this group (e.g., olvanil) lead to a loss of
exci sensory neurons are apparent. The most important difference seems to relate to the apolar moiety, because changes in this group (e.g., olvanil) lead to a loss of excitatory activity, whereas desensitizing potency is mainta ference seems to relate to the apolar moiety, because
changes in this group (e.g., olvanil) lead to a loss of
excitatory activity, whereas desensitizing potency is
maintained (Dickenson et al., 1990b; Dray et al., 1990c).
 changes in this group (e.g., olvanil) lead to a loss of excitatory activity, whereas desensitizing potency is maintained (Dickenson et al., 1990b; Dray et al., 1990c). Furthermore, the optimal length of capsaicin's alkyl c excitatory activity, whereas desensitizing potency is
maintained (Dickenson et al., 1990b; Dray et al., 1990c).
Furthermore, the optimal length of capsaicin's alkyl
chain for desensitizing potency (10 to 12 carbon atoms)
i maintained (Dickenson et al., 1990b; Dray et al., 1990c).
Furthermore, the optimal length of capsaicin's alkyl
chain for desensitizing potency (10 to 12 carbon atoms)
is somewhat longer than that required for excitatory
ac Furthermore, the optimal length of capsaicin's alked thain for desensitizing potency (10 to 12 carbon atomis somewhat longer than that required for excitator activity (8 to 10 carbon atoms) (Szolcsányi and Jancs Gábor, 197 chain for desensitizing potency (10 to 12 carbon atoms)
is somewhat longer than that required for excitatory
activity (8 to 10 carbon atoms) (Szolcsányi and Jancsó-
Gábor, 1976), and the especially high desensitizing activ is somewhat longer than that required for excitatory
activity (8 to 10 carbon atoms) (Szolcsányi and Jancsó-
Gábor, 1976), and the especially high desensitizing activ-
ity of resiniferatoxin with its diterpene substituent
 activity (8 to 10 carbon atoms) (Szolcsányi and Jancsó-Gábor, 1976), and the especially high desensitizing activity of resiniferatoxin with its diterpene substituent underlines the importance of the apolar moiety for desen Gábor, 1976), and the especially high desensitizing activity of resiniferatoxin with its diterpene substituent
underlines the importance of the apolar moiety for desensitization (Szallasi and Blumberg, 1989, 1990b). An-
ot ity of resiniferatoxin with its diterpene substituent
underlines the importance of the apolar moiety for de-
sensitization (Szallasi and Blumberg, 1989, 1990b). An-
other point concerns the acylamide linkage, the presence
 underlines the importance of the apolar moiety for desensitization (Szallasi and Blumberg, 1989, 1990b). Another point concerns the acylamide linkage, the presence of which was previously believed to be required for desens sensitization (Szallasi and Blumberg, 1989, 1990b). Another point concerns the acylamide linkage, the presence
of which was previously believed to be required for de-
sensitizing activity (Jancsó, 1968; Szolcsányi and Janc other point concerns the acylamide linkage, the presence
of which was previously believed to be required for de-
sensitizing activity (Jancsó, 1968; Szolcsányi and Jancsó-
Gábor, 1976). This bond is not essential, however, of which was previously believed to be required for
sensitizing activity (Jancsó, 1968; Szolcsányi and Jan
Gábor, 1976). This bond is not essential, however,
cause resiniferatoxin, which has an ester group ins
of the acyla sensitizing activity (Jancsó, 1968; Szolcsányi
Gábor, 1976). This bond is not essential, h
cause resiniferatoxin, which has an ester gr
of the acylamide, displays a particularly high
ing potency (Szallasi and Blumberg, 198 ibor, 1976). This bond is not essential, however, be-
use resiniferatoxin, which has an ester group instead
the acylamide, displays a particularly high desensitiz-
g potency (Szallasi and Blumberg, 1989).
3. *Resiniferatox*

cause resiniferatoxin, which has an ester group instead
of the acylamide, displays a particularly high desensitiz-
ing potency (Szallasi and Blumberg, 1989).
3. Resiniferatoxin as a very potent capsaicin agonist.
Apart fro of the acylamide, displays a particularly high desensitizing potency (Szallasi and Blumberg, 1989).
3. Resiniferatoxin as a very potent capsaicin agonist.
Apart from capsaicin, there are a number of other natural
and synth ing potency (Szallasi and Blumberg, 1989).

3. Resiniferatoxin as a very potent capsaicin agonist.

Apart from capsaicin, there are a number of other natural

and synthetic pungent compounds, including zingerone,

shogaol, 3. Resiniferatoxin as a very potent capsaicin agonist.
Apart from capsaicin, there are a number of other natural
and synthetic pungent compounds, including zingerone,
shogaol, chavicine, piperine, guajacol, isoeugenol, eu-Apart from capsaicin, there are a number of other natureand synthetic pungent compounds, including zingeror
shogaol, chavicine, piperine, guajacol, isoeugenol, e
genol, xylene, curcumin, and mustard oil, that sho
variable and synthetic pungent compounds, including zingerone,
shogaol, chavicine, piperine, guajacol, isoeugenol, eu-
genol, xylene, curcumin, and mustard oil, that show
variable degrees of structural and/or pharmacological
overla genol, xylene, curcumin, and mustard oil, that show variable degrees of structural and/or pharmacological overlap with capsaicin (Jancsó, 1968; Szolcsányi and Jancsó-Gábor, 1975, 1976; Szolcsányi, 1982; Abelli et al., 1988 genol, xylene, curcumin, and mustard oil, that show
variable degrees of structural and/or pharmacological
overlap with capsaicin (Jancsó, 1968; Szolcsányi and
Jancsó-Gábor, 1975, 1976; Szolcsányi, 1982; Abelli et al.,
1988 variable degrees of structural and/or pharmacological
overlap with capsaicin (Jancsó, 1968; Szolcsányi and
Jancsó-Gábor, 1975, 1976; Szolcsányi, 1982; Abelli et al.,
1988; Miyauchi et al., 1989; Patacchini et al., 1990;
Ta overlap with capsaicin (Jancsó, 1968; Szolcsányi and Jancsó-Gábor, 1975, 1976; Szolcsányi, 1982; Abelli et al., 1988; Miyauchi et al., 1989; Patacchini et al., 1990; Takaki et al., 1990). Among these, capsaicin is by far t

tion and desensitization and sensory neuron ablation. HOLZE

tion and desensitization and sensory neuron ablation.

Another compound, resiniferatoxin, has been known for

some time to be a potent irritant whose mechanism of in HOLZE:

some and desensitization and sensory neuron ablation.

Another compound, resiniferatoxin, has been known for

some time to be a potent irritant whose mechanism of

in action is not understood. It is a substance tha tion and desensitization and sensory neuron ablation. ϵ Another compound, resiniferatoxin, has been known for ϵ some time to be a potent irritant whose mechanism of inaction is not understood. It is a substance that tion and desensitization and sensory neuron ablation.
Another compound, resiniferatoxin, has been known for
some time to be a potent irritant whose mechanism of
action is not understood. It is a substance that occurs
natur Another compound, resiniferatoxin, has been known for
some time to be a potent irritant whose mechanism of
action is not understood. It is a substance that occurs
naturally in the latex of certain species of *Euphorbia*.
S some time to be a potent irritant whose mechanism of action is not understood. It is a substance that occurs naturally in the latex of certain species of *Euphorbia*.
Structurally, it combines characteristics of the phorbo action is not understood. It is a substance that occurs
naturally in the latex of certain species of *Euphorbia*.
Structurally, it combines characteristics of the phorbol
esters and of capsaicin (fig. 1). Like capsaicin, i naturally in the latex of certain species of Euphorbia.
Structurally, it combines characteristics of the phorbol
esters and of capsaicin (fig. 1). Like capsaicin, it contains
a 4-hydroxy-3-methoxy benzyl (vanillyl) molecul Structurally, it combines characteristics of the phorbol Besters and of capsaicin (fig. 1). Like capsaicin, it contains D
a 4-hydroxy-3-methoxy benzyl (vanillyl) moiety con-S
nected to an ester group which, in the capsaici esters and of capsaicin (fig. 1). Like capsaicin, it contains Dranched activity benzyl (vanillyl) moiety connected to an ester group which, in the capsaicin molecule, resean replace the acylamide group in reversed position a 4-hydroxy-3-methoxy benzyl (vanillyl) moiety con-
nected to an ester group which, in the capsaicin molecule, resi
can replace the acylamide group in reversed position Jari
without loss of activity (Szolcsányi and Jancsónected to an ester group which, in the capsaicin molecule,
can replace the acylamide group in reversed position
without loss of activity (Szolcsányi and Jancsó-Gábor,
1975). This ester group connects the vanillyl moiety to can replace the acylamide group in reversed posi
without loss of activity (Szolcsányi and Jancsó-Gá
1975). This ester group connects the vanillyl moiet
the 20-hydroxyl substituent of the complex diterr
structure. Thus, unl without loss of activity (Szolcsányi and Jancsó-Gábor, 1975). This ester group connects the vanillyl moiety to the 20-hydroxyl substituent of the complex diterpene structure. Thus, unlike active phorbol esters, resiniferat 1975). This ester group connects the vanillyl moiety to age the 20-hydroxyl substituent of the complex diterpene al.
structure. Thus, unlike active phorbol esters, resinifera-extoxin lacks a free 20-hydroxyl group which i the 20-hydroxyl substituent of the complex diterpendstructure. Thus, unlike active phorbol esters, resiniferatorin lacks a free 20-hydroxyl group which is essentiator phorbol ester activity and thus fails to induce the typ structure. Thus, unlike active phorbol esters, resiniferatoxin lacks a free 20-hydroxyl group which is essential
for phorbol ester activity and thus fails to induce the
typical phorbol ester effects including tumor promoti for phorbol ester activity and thus fails to induce the typical phorbol ester effects including tumor promotion, binding to, and stimulation of, protein kinase C (Szallasi and Blumberg, 1989, 1990b; Dray et al., 1990a; Win typical phorbol ester effects including tumor promotion, pical phorbol ester effects including tumor promotion,
nding to, and stimulation of, protein kinase C (Szallasi
d Blumberg, 1989, 1990b; Dray et al., 1990a; Winter
al., 1990).
In keeping with the structural similarity betw

binding to, and stimulation of, protein kinase C (Szallasi al., and Blumberg, 1989, 1990b; Dray et al., 1990a; Winter fera et al., 1990).

In keeping with the structural similarity between re- (Sza

siniferatoxin and capsa and Blumberg, 1989, 1990b; Dray et al., 1990a; Winter fera
et al., 1990). rece
et al., 1990). The effects of capsaicin on the effects of capsaicin on (100
share most, if not all, of the effects of capsaicin on (100
sensory et al., 1990).
In keeping with the structural similarity between re-
siniferatoxin and capsaicin, resiniferatoxin appears to
share most, if not all, of the effects of capsaicin on
sensory neurons. Thus, resiniferatoxin dep siniferatoxin and capsaicin, resiniferatoxin appears to share most, if not all, of the effects of capsaicin on sensory neurons. Thus, resiniferatoxin depolarizes cultured neurons from rat dorsal root ganglia and increases share most, if not all, of the effects of capsaicin on sensory neurons. Thus, resiniferatoxin depolarizes cultured neurons from rat dorsal root ganglia and increases cation fluxes across the cell membrane but is approximat share most, if not all, of the effects of capsaicin on sensory neurons. Thus, resiniferatoxin depolarizes cultured neurons from rat dorsal root ganglia and increases cation fluxes across the cell membrane but is approximat sensory neurons. Thus, resiniferatoxin depolarizes cutured neurons from rat dorsal root ganglia and increased cation fluxes across the cell membrane but is appromately two orders of magnitude more potent than casaicin (Win tured neurons from rat dorsal root ganglia and increation fluxes across the cell membrane but is app
mately two orders of magnitude more potent than
saicin (Winter et al., 1990). A similar activity of re
feratoxin relative cation fluxes across the cell membrane but is approxi-
mately two orders of magnitude more potent than cap-
saicin (Winter et al., 1990). A similar activity of resini-
1989
feratoxin relative to capsaicin is seen with resi mately two orders of magnitude more potent than cap-
saicin (Winter et al., 1990). A similar activity of resini-
feratoxin relative to capsaicin is seen with resiniferatox-
res
in's stimulant effect on cutaneous nociceptor saicin (Winter et al., 1990). A similar activity of resini-
feratoxin relative to capsaicin is seen with resiniferatox-
in's stimulant effect on cutaneous nociceptors in an in
witro preparation of the neonatal rat tail-spi feratoxin relative to capsaicin is seen with resiniferatox-
in's stimulant effect on cutaneous nociceptors in an in neuron
vitro preparation of the neonatal rat tail-spinal cord treatm
(Dray et al., 1990a; Winter et al., 1 in's stimulant effect on cutaneous nociceptors in an in
vitro preparation of the neonatal rat tail-spinal cord
(Dray et al., 1990a; Winter et al., 1990) and on the release
of substance P and calcitonin gene-related peptid vitro preparation of the neonatal rat tail-spinal cord trail. (Dray et al., 1990a; Winter et al., 1990) and on the release of substance P and calcitonin gene-related peptide from rethe rat urinary bladder, rat spinal cord, (Dray et al., 1990a; Winter et al., 1990) and on the release of substance P and calcitonin gene-related peptide from rest
the rat urinary bladder, rat spinal cord, and rabbit ear log
(Maggi et al., 1990c). In other tests, of substance P and calcitonin gene-related peptide fr
the rat urinary bladder, rat spinal cord, and rabbit
(Maggi et al., 1990c). In other tests, such as induction
hypothermia (de Vries and Blumberg, 1989; Szallasi a
Blumb the rat urinary bladder, rat spinal cord, and rabbit ear lo (Maggi et al., 1990c). In other tests, such as induction of rehypothermia (de Vries and Blumberg, 1989; Szallasi and climberg, 1989), induction of plasma protein (Maggi et al., 1990c). In other tests, such as induction of rehypothermia (de Vries and Blumberg, 1989; Szallasi and che Blumberg, 1989), induction of plasma protein extravation (Szallasi and Blumberg, 1989) and inhibition hypothermia (de Vries and Blumberg, 1989; Szallasi and change all the Blumberg, 1989), induction of plasma protein extravation (Szallasi and Blumberg, 1989) and inhibition of orgelectrically induced twitch contractions of Blumberg, 1989), induction of plasma protein extravation (Szallasi and Blumberg, 1989) and inhibition of orgelectrically induced twitch contractions of the rat vas prodeferens (Maggi et al., 1990c), resiniferatorin is even sation (Szallasi and Blumberg, 1989) and inhibition
electrically induced twitch contractions of the rat
deferens (Maggi et al., 1990c), resiniferatoxin is e
three to four orders of magnitude more potent the
capsaicin. To c electrically induced twitch contractions of the rat vase deferens (Maggi et al., 1990c), resiniferatoxin is even three to four orders of magnitude more potent than capsaicin. To complicate the situation further, resinifera deferens (Maggi et al., 1990c), resiniferatoxin is even captive to four orders of magnitude more potent than A-t capsaicin. To complicate the situation further, resiniferentiation is not or only marginally more active than three to four orders of magnitude more potent than capsaicin. To complicate the situation further, resiniferatorin is not or only marginally more active than capsaicin in inducing corneal nociception (Szallasi and Blumberg capsaicin. To complicate the situation further, resiniferatoxin is not or only marginally more active than capsaicin in inducing corneal nociception (Szallasi and Blumberg, 1989), reflex hypotension, and urinary bladder co atoxin is not or only marginally more active than capsaicin in inducing corneal nociception (Szallasi and Blumberg, 1989), reflex hypotension, and urinary bladder contraction (Maggi et al., 1990c) and, unlike capsaicin, fa saicin in inducing corneal nociception (Szallasi and
Blumberg, 1989), reflex hypotension, and urinary bladder
contraction (Maggi et al., 1990c) and, unlike capsaicin,
fails to evoke the full Bezold-Jarisch reflex in the ra Blumberg, 1989), reflex hypotension, and urinary bladder contraction (Maggi et al., 1990c) and, unlike capsaicin, fails to evoke the full Bezold-Jarisch reflex in the rat (Szolcsányi et al., 1990). In the cat, however, the contraction (Maggi et al., 1990c) and, unlike capsaicin, a
fails to evoke the full Bezold-Jarisch reflex in the rat
(Szolcsányi et al., 1990). In the cat, however, the full J
Bezold-Jarisch reflex is evoked by resiniferato fails to evoke the full Bezold-Jarisch reflex in the rat (Szolcsányi et al., 1990). In the cat, however, the full Bezold-Jarisch reflex is evoked by resiniferatoxin (Szolcsányi et al., 1990). Thus, although the excitatory (Szolcsányi et al., 1990). In the cat, however, the full Bezold-Jarisch reflex is evoked by resiniferatoxin (Szolcsányi et al., 1990). Thus, although the excitatory effects of capsaicin and resiniferatoxin on sensory neuro Bezold-Jarisch reflex is evoked by resiniferatoxin resi
(Szolcsányi et al., 1990). Thus, although the excitatory era
effects of capsaicin and resiniferatoxin on sensory neu-
tox
mons are qualitatively similar, there are so drugs. Fects of capsaicin and resiniferatoxin on sensory neu-
ns are qualitatively similar, there are some important per
antitative differences between the potencies of the two
nugs.
There also are similarities and differences be rons are qualitatively similar, there are some important
quantitative differences between the potencies of the two
drugs.
There also are similarities and differences between the
intermediate (desensitizing) and long-term n

effects of the two drugs. In contrast to its stimulant effect, resiniferatoxin is generally more active in produc-ER
effects of the two drugs. In contrast to its stimula
effect, resiniferatoxin is generally more active in prod
ing desensitization to itself and capsaicin, the desensit ER
effects of the two drugs. In contrast to its stimu
effect, resiniferatoxin is generally more active in proving desensitization to itself and capsaicin, the desens
ing potency of resiniferatoxin exceeding that of capsa effects of the two drugs. In contrast to its stimulant effect, resiniferatoxin is generally more active in producing desensitization to itself and capsaicin, the desensitizing potency of resiniferatoxin exceeding that of c effects of the two drugs. In contrast to its stimulant
effect, resiniferatoxin is generally more active in produc-
ing desensitization to itself and capsaicin, the desensitiz-
ing potency of resiniferatoxin exceeding that ing potency of resiniferatoxin exceeding that of capsaicin
by three to four orders of magnitude (de Vries and
Blumberg, 1989; Szallasi and Blumberg, 1989, 1990b;
Dray et al. 1990a; Maggi et al., 1990c; Winter et al., 1990; ing desensitization to itself and capsaicin, the desensitiz-
ing potency of resiniferatoxin exceeding that of capsaicin
by three to four orders of magnitude (de Vries and
Blumberg, 1989; Szallasi and Blumberg, 1989, 1990b; ing potency of resiniferatoxin exceeding that of capsaicin
by three to four orders of magnitude (de Vries and
Blumberg, 1989; Szallasi and Blumberg, 1989, 1990b;
Dray et al. 1990a; Maggi et al., 1990c; Winter et al., 1990; by three to four orders of magnitude (de Vries a Blumberg, 1989; Szallasi and Blumberg, 1989, 1990 Dray et al. 1990a; Maggi et al., 1990c; Winter et al., 19
Szolcsányi et al., 1991). In the rat, intravenous doses resinifer Blumberg, 1989; Szallasi and Blumberg, 1989, 1990b;
Dray et al. 1990a; Maggi et al., 1990c; Winter et al., 1990;
Szolcsányi et al., 1991). In the rat, intravenous doses of
resiniferatoxin that are too low to evoke the Bezo Dray et al. 1990a; Maggi et al., 1990c; Winter et al., 1990;
Szolcsányi et al., 1991). In the rat, intravenous doses of
resiniferatoxin that are too low to evoke the Bezold-
Jarisch reflex are able to desensitize the pulmo Szolcsányi et al., 1991). In the rat, intravenous doses of resiniferatoxin that are too low to evoke the Bezold-Jarisch reflex are able to desensitize the pulmonary chemoreceptors, which are responsible for this reflex, ag resiniferatoxin that are too low to evoke the Bezold-Jarisch reflex are able to desensitize the pulmonary chemoreceptors, which are responsible for this reflex, against the excitatory action of capsaicin (Szolcsányi et al. Jarisch reflex are able to desensitize the pulmonary
chemoreceptors, which are responsible for this reflex,
against the excitatory action of capsaicin (Szolcsányi et
al., 1991). At low doses, desensitization involves only chemoreceptors, which are responsible for this reflex,
against the excitatory action of capsaicin (Szolcsányi et
al., 1991). At low doses, desensitization involves only the
excitatory responses to resiniferatoxin and capsa against the excitatory action of capsaicin (Szolcsányi et al., 1991). At low doses, desensitization involves only the excitatory responses to resiniferatoxin and capsaicin (Dray et al., 1990a; Winter et al., 1990), whereas al., 1991). At low doses, desensitization involves only the excitatory responses to resiniferatoxin and capsaicin (Dray et al., 1990a; Winter et al., 1990), whereas at higher doses insensitivity to all noxious stimuli of s excitatory responses to resiniferatoxin and capsaicin (Dray et al., 1990a; Winter et al., 1990), whereas at higher doses insensitivity to all noxious stimuli of sensory neurons is produced (Szallasi and Blumberg, 1989; Dra doses insensitivity to all noxious stimuli of sensory neurons is produced (Szallasi and Blumberg, 1989; Dray et al., 1990a; Winter et al., 1990). Unlike capsaicin, resiniferatorin is also able to desensitize pulmonary chem doses insensitivity to all noxious stimuli of sensory neurons is produced (Szallasi and Blumberg, 1989; Dray et al., 1990a; Winter et al., 1990). Unlike capsaicin, resiniferatorin is also able to desensitize pulmonary chem al., 1990a; Winter et al., 1990). Unlike capsaicin, resini-
feratoxin is also able to desensitize pulmonary chemo-
receptors to the excitatory effect of phenyldiguanide
(Szolcsányi et al., 1990).
Systemic treatment of adul , 1990a; Winter et al., 1990). Unlike capsaicin, resini-
ratoxin is also able to desensitize pulmonary chemo-
ceptors to the excitatory effect of phenyldiguanide
zolcsányi et al., 1990).
Systemic treatment of adult rats w

feratoxin is also able to desensitize pulmonary chemo-
receptors to the excitatory effect of phenyldiguanide
(Szolcsányi et al., 1990).
Systemic treatment of adult rats with resiniferatoxin
(100 to 400 μ g/kg) causes de receptors to the excitatory effect of phenyldiguanide
(Szolcsányi et al., 1990).
Systemic treatment of adult rats with resiniferatoxin
(100 to 400 μ g/kg) causes defunctionalization of sensory
neurons as shown by the ab (Szolcsányi et al., 1990).
Systemic treatment of adult rats with resiniferatoxin
(100 to 400 μ g/kg) causes defunctionalization of sensory
neurons as shown by the abolition of capsaicin- or resi-
niferatoxin-evoked hypo Systemic treatment of adult rats with resiniferatoxin
 $(100 \text{ to } 400 \mu g/kg)$ causes defunctionalization of sensory

neurons as shown by the abolition of capsaicin- or resi-

niferatoxin-evoked hypothermia, leakage of plasm (100 to 400 μ g/kg) causes defunctionalization of sensory
neurons as shown by the abolition of capsaicin- or resi-
niferatoxin-evoked hypothermia, leakage of plasma pro-
tein in the skin and trachea, and chemonociceptio neurons as shown by the abolition of capsaicin- or resi-
niferatoxin-evoked hypothermia, leakage of plasma pro-
tein in the skin and trachea, and chemonociception in
the cornea (Szallasi and Blumberg, 1989; Szallasi et al. niferatoxin-evoked hypothermia, leakage of plasma protein in the skin and trachea, and chemonociception in the cornea (Szallasi and Blumberg, 1989; Szallasi et al., 1989; Szolcsányi et al., 1990). In contrast, cardiovascul tein in the skin and trachea, and chemonociception in
the cornea (Szallasi and Blumberg, 1989; Szallasi et al.,
1989; Szolcsányi et al., 1990). In contrast, cardiovascular
responses to stimulation of parasympathetic effere neurons are not affected by systemic resiniferatoxin pre-
treatment (Szolcsányi et al., 1990).

(Dray et al., 1990a; Winter et al., 1990), whereas at higher
doses insensitivity to all noxious stimuli of sensory neurons
is produced (Szallasi and Blumberg, 1989; Dray et
al., 1990a; Winter et al., 1990). Unlike capsaic The defunctionalization of sensory neurons is due to resiniferatoxin given to adult rats induces ultrastructural treatment (Szolcsányi et al., 1990).
The defunctionalization of sensory neurons is due t
resiniferatoxin's neurotoxic action as shown by morpho
logical alterations in their cell bodies. Like capsaicir
resiniferatoxin given The defunctionalization of sensory neurons is due to
resiniferatoxin's neurotoxic action as shown by morpho-
logical alterations in their cell bodies. Like capsaicin,
resiniferatoxin given to adult rats induces ultrastruct resiniferatoxin's neurotoxic action as shown by morpho-
logical alterations in their cell bodies. Like capsaicin,
resiniferatoxin given to adult rats induces ultrastructural
changes in small dark neurons of the dorsal root logical alterations in their cell bodies. Like capsaicin,
resiniferatoxin given to adult rats induces ultrastructural
changes in small dark neurons of the dorsal root ganglia,
the alterations being characterized by swellin resiniferatoxin given to adult rats induces ultrastructural
changes in small dark neurons of the dorsal root ganglia,
the alterations being characterized by swelling and dis-
organization of mitochondria, but resiniferatox changes in small dark neurons of the dorsal root ganglia,
the alterations being characterized by swelling and dis-
organization of mitochondria, but resiniferatoxin is ap-
proximately three orders of magnitude more potent the alterations being characterized by swelling and disorganization of mitochondria, but resiniferatoxin is approximately three orders of magnitude more potent than capsaicin (Szallasi et al., 1989; Szolcsányi et al., 1990 organization of mitochondria, but resiniferatoxin is approximately three orders of magnitude more potent than capsaicin (Szallasi et al., 1989; Szolcsányi et al., 1990).
A-type neurons in dorsal root ganglia or sympathetic proximately three orders of magnitude more potent than capsaicin (Szallasi et al., 1989; Szolcsányi et al., 1990).
A-type neurons in dorsal root ganglia or sympathetic ganglion cells in the superior cervical ganglion are n capsaicin (Szallasi et al., 1989; Szolcsányi et al., 1984).
A-type neurons in dorsal root ganglia or sympathe ganglion cells in the superior cervical ganglion are affected by resiniferatoxin (Szolcsányi et al., 1990).
addi A-type neurons in dorsal root ganglia or sympathetic ganglion cells in the superior cervical ganglion are not affected by resiniferatoxin (Szolcsányi et al., 1990). In addition, systemic resiniferatoxin leads to the accumu ganglion cells in the superior cervical ganglion are not affected by resiniferatoxin (Szolcsányi et al., 1990). In addition, systemic resiniferatoxin leads to the accumulation of ionic calcium in some small sensory neurons affected by resiniferatoxin (Szolcsányi et al., 1990). In
addition, systemic resiniferatoxin leads to the accumu-
lation of ionic calcium in some small sensory neurons,
an effect that is more marked than that occurring wit addition, systemic resiniferatoxin leads to the accumulation of ionic calcium in some small sensory neurons, an effect that is more marked than that occurring with capsaicin (Szallasi et al., 1989) and which, according to lation of ionic calcium in some small sensory neuron
an effect that is more marked than that occurring wi
capsaicin (Szallasi et al., 1989) and which, according
Jancsó et al. (1978), could indicate that in the adult 1
resi an effect that is more marked than that occurring v
capsaicin (Szallasi et al., 1989) and which, accordin
Jancsó et al. (1978), could indicate that in the adult
resiniferatoxin causes more sensory neurons to de
erate than capsaicin (Szallasi et al., 1989) and which, according to Jancsó et al. (1978), could indicate that in the adult rat resiniferatoxin causes more sensory neurons to degenerate than does capsaicin. Neurochemically, resinifer Jancsó et al. (1978), could indicate that in the adult rat
resiniferatoxin causes more sensory neurons to degen-
erate than does capsaicin. Neurochemically, resinifera-
toxin has been found to deplete calcitonin gene-relat resiniferatoxin causes more sensory neurons to degenerate than does capsaicin. Neurochemically, resiniferatoxin has been found to deplete calcitonin gene-related peptide from the spinal and cranial sensory ganglia and the 1990). xin has been found to deplete calcitonin gene-related ptide from the spinal and cranial sensory ganglia and e dorsal horn of the spinal cord (Szolcsányi et al. 90).
Administration of resiniferatoxin (300 μ g/kg) to new peptide from the spinal and cranial sensory ganglia and
the dorsal horn of the spinal cord (Szolcsányi et al., 1990).
Administration of resiniferatoxin (300 μ g/kg) to new-
born rats leads to approximately a 50% degener

PHARMACOLOGICAL REVIEWS

CA
cell bodies in the dorsal root ganglia, which is associate
with an almost complete depletion of calcitonin gene-
related peptide from the spinal and cranial sensory gan CAP
cell bodies in the dorsal root ganglia, which is associated
with an almost complete depletion of calcitonin gene-
related peptide from the spinal and cranial sensory gan-
glia and the dorsal horn of the spinal cord (Sz cell bodies in the dorsal root ganglia, which is associated cordinal and and cranical sensory gan-
related peptide from the spinal and cranial sensory gan-
glia and the dorsal horn of the spinal cord (Szallasi et f
al., 19 cell bodies in the dorsal root ganglia, which is associate
with an almost complete depletion of calcitonin generelated peptide from the spinal and cranial sensory ganglia and the dorsal horn of the spinal cord (Szallasi $\$ with an almost complete depletion of calcitonin gene-lasi
related peptide from the spinal and cranial sensory gan-
glia and the dorsal horn of the spinal cord (Szallasi et find
al., 1990). These morphological and neurochem glia and the dorsal horn of the spinal cord (Szallasi et al., 1990). These morphological and neurochemical alterations induced by administration of resiniferatorin to newborn rats are paralleled by a complete loss of che-m glia and the dorsal horn of the spinal cord (Szallasi et al., 1990). These morphological and neurochemical alter-
ations induced by administration of resiniferatoxin to
newborn rats are paralleled by a complete loss of che al., 1990). These morphological and neurochemical alterations induced by administration of resiniferatoxin to newborn rats are paralleled by a complete loss of chemonociception in the cornea and by inhibition of neurogenic ations induced by administration of resiniferatoxin to showborn rats are paralleled by a complete loss of chemonociception in the cornea and by inhibition of neurogenic edema formation in the skin (Szallasi et al., showb). newborn rats are paralleled by a complete loss of che-
monociception in the cornea and by inhibition of neu-
rogenic edema formation in the skin (Szallasi et al., si
1990). The range and magnitude of the neurotoxic effects monociception in the cornea and by inhibition of neu-
rogenic edema formation in the skin (Szallasi et al.,
1990). The range and magnitude of the neurotoxic effects
produced by neonatal resiniferatoxin are similar to those rogenic edema formation in the skin (Szallasi et al., si
1990). The range and magnitude of the neurotoxic effects d
produced by neonatal resiniferatoxin are similar to those o
produced by neonatal capsaicin, but resinifera 1990). The range and magnitude of the neurotoxic effects diproduced by neonatal resiniferatoxin are similar to those of produced by neonatal capsaicin, but resiniferatoxin is at the deast two orders of magnitude more pote produced by neonatal resiniferatoxin are similar to those of a
produced by neonatal capsaicin, but resiniferatoxin is at that
least two orders of magnitude more potent than capsaicin of c
(Szallasi et al., 1990). Similarl least two orders of magnitude more potent than capsaicin of cells (Maggi et al., 1990c; Winter et al., 1990).

(Szallasi et al., 1990). Similarly, a 50-min exposure of 4. Capsazepine as a competitive antagonist of capsaic deast two orders of magnitude more potent than capsaicincy.

(Szallasi et al., 1990). Similarly, a 50-min exposure of

cultured sensory neurons from newborn rats to 10 to 100

nM resiniferatoxin causes the same extent of (Szallasi et
cultured ser
nM resinife
damage as el., 1990).
Further d Itured sensory neurons from newborn rats to 10 to
 i resiniferatoxin causes the same extent of neumage as exposure to 1 to 10 μ M capsaicin (Winte

, 1990).

Further differences between capsaicin and resinif

xin conc

nM resiniferatoxin causes the same extent of neuritic redamage as exposure to 1 to 10 μ M capsaicin (Winter et cal., 1990).

[Rurther differences between capsaicin and resiniferatoric concern the time course of their ac damage as exposure to 1 to 10 μ M capsaicin (Winter et al., 1990).

Further differences between capsaicin and resiniferatoxin concern the time course of their acutely excitatory

and long-term neurotoxic effects. Thus, al., 1990).
Further differences between capsaicin and resinifera-
toxin concern the time course of their acutely excitatory
and long-term neurotoxic effects. Thus, resiniferatoxin's
effects in depolarizing cultured sensory Further differences between capsaicin and resinifera-
toxin concern the time course of their acutely excitatory
and long-term neurotoxic effects. Thus, resiniferatoxin's
effects in depolarizing cultured sensory neurons (Wi toxin concern the time course of their acutely excitato:
and long-term neurotoxic effects. Thus, resiniferatoxin
effects in depolarizing cultured sensory neurons (Wint
et al., 1990), in producing corneal nociception (Szall effects in depolarizing cultured sensory neurons (Winter
et al., 1990), in producing corneal nociception (Szallasi
and Blumberg, 1989), in inducing plasma protein extra-
vasation in the skin (Szallasi and Blumberg, 1989), et al., 1990), in producing corneal nociception (Szallasi In c
and Blumberg, 1989), in inducing plasma protein extra-caps
vasation in the skin (Szallasi and Blumberg, 1989), and of ca
in depressing electrically evoked cont and Blumberg, 1989), in inducing plasma protein extivasation in the skin (Szallasi and Blumberg, 1989), a
in depressing electrically evoked contractions of the isolated vas deferens (Maggi et al., 1990c) are slower
onset b vasation in the skin (Szallasi and Blumberg, 1989), and
in depressing electrically evoked contractions of the rat
isolated vas deferens (Maggi et al., 1990c) are slower in
onset but longer lasting than those of capsaicin. in depressing electrically evoked contractions of the raisolated vas deferens (Maggi et al., 1990c) are slower is onset but longer lasting than those of capsaicin. Accordingly, the inhibitory effects of systemic resinifera isolated vas deferens (Maggi et al., 1990c) are slower in
onset but longer lasting than those of capsaicin. Accord-
ingly, the inhibitory effects of systemic resiniferatoxin
on sensory nerve-mediated chemical pain, hypothe onset but longer lasting than those of capsaicin. Accord-
ingly, the inhibitory effects of systemic resiniferatoxine
on sensory nerve-mediated chemical pain, hypothermia, [¹
and plasma protein leakage also take longer t on sensory nerve-mediated chemical pain, hypothermia, and plasma protein leakage also take longer to recover than do the equivalent effects of systemic capsaicin (Szallasi et al., 1989). There is evidence that the slower o and plasma protein leakage also take longer to recover set than do the equivalent effects of systemic capsaicin sa (Szallasi et al., 1989). There is evidence that the slower current of resiniferatoxin's acute effects is, a than do the equivalent effects of systemic capsaicin (Szallasi et al., 1989). There is evidence that the slower onset of resiniferatoxin's acute effects is, at least in part, due to a slower tissue penetration rate of this (Szallasi et al., 1989). There is evidence that the slower conset of resiniferatoxin's acute effects is, at least in part, in due to a slower tissue penetration rate of this drug as an compared with that of capsaicin (Magg onset of resiniferatoxin's acute effects is, at least in part, due to a slower tissue penetration rate of this drug as compared with that of capsaicin (Maggi et al., 1990c). This difference in the pharmacokinetic behaviour due to a slower tissue penetration rate of this drug as compared with that of capsaicin (Maggi et al., 1990c).
This difference in the pharmacokinetic behaviour of capsaicin and resiniferatorin could explain why the relativ compared with that of capsaicin (Maggi et al., 1990c).
This difference in the pharmacokinetic behaviour of
capsaicin and resiniferatoxin could explain why the rel-
ative potencies of the two drugs in acutely stimulating
se This difference in the pharmacokinetic behaviou capsaicin and resiniferatoxin could explain why the ative potencies of the two drugs in acutely stimula sensory neurons vary so much in different assay systembreas their rela capsaicin and resiniferatoxin could explain why the rel-
ative potencies of the two drugs in acutely stimulating caps
sensory neurons vary so much in different assay systems, Pain
whereas their relative activities in causi tion and neurotoxicity are less variable. Whether, in addition, a heterogeneity of receptors accounts for some of the differences in the actions of capsaicin and resini-feratoxin (Szallasi and Blumberg, 1990b) has not yet whereas their relative activities in causing desensitization and neurotoxicity are less variable. Whether, in addition, a heterogeneity of receptors accounts for some of the differences in the actions of capsaicin and resi tion and neurotoxicity are less variable. Whether, in mindled. and heterogeneity of receptors accounts for some corport of the differences in the actions of capsaicin and resiniby feratoxin (Szallasi and Blumberg, 1990b) addition, a heterogeneity of receptors accounts for some confined the differences in the actions of capsaicin and resiniby feratoxin (Szallasi and Blumberg, 1990b) has not yet tive been established. The two drugs have bee of the differences in the actions of capsaicin and resitents feratoxin (Szallasi and Blumberg, 1990b) has not y been established. The two drugs have been found to bit to a cellular recognition site, the kinetics of which a feratoxin (Szallasi and Blumberg, 1990b) has not youther a stablished. The two drugs have been found to bin to a cellular recognition site, the kinetics of which and best described by a one-site model (Szallasi and Blumber been established. The two drugs have been found to bind
to a cellular recognition site, the kinetics of which are
best described by a one-site model (Szallasi and Blum-
berg, 1990a). However, following resiniferatoxin trea to a cellular recognition site, the kinetics of which a best described by a one-site model (Szallasi and Blu berg, 1990a). However, following resiniferatoxin tre ment of newborn rats there is not only a permane reduction best described by a one-site model (Szallasi and Blum-
berg, 1990a). However, following resiniferatoxin treat-
ment of newborn rats there is not only a permanent preduction in the number of [³H]resiniferatoxin-binding c
 ment of newborn rats there is not only a permane
reduction in the number of [³H] resiniferatoxin-bindis
sites in sensory ganglia but also a 4- to 6-fold decrea
in the affinity of the remaining binding sites, a findi-
tha reduction in the number of [³H] resiniferaties in sensory ganglia but also a 4- to 6-
in the affinity of the remaining binding sithat is consistent with a heterogeneity of res
capsaicin receptors (Szallasi et al., 1990).

cell bodies in the dorsal root ganglia, which is associated capsaicin and resiniferatoxin on sensory neurons (Szal-
with an almost complete depletion of calcitonin gene- lasi and Blumberg, 1989; Szallasi et al., 1989; Dray cin
capsaicin and resiniferatoxin on sensory neurons (Szal-
lasi and Blumberg, 1989; Szallasi et al., 1989; Dray et al., ITS
23 capsaicin and resiniferatoxin on sensory neurons (Szallasi and Blumberg, 1989; Szallasi et al., 1989; Dray et al.,
1990a; Maggi et al., 1990c; Winter et al., 1990) is another 173

173

capsaicin and resiniferatoxin on sensory neurons (Szal-

lasi and Blumberg, 1989; Szallasi et al., 1989; Dray et al.,

1990a; Maggi et al., 1990c; Winter et al., 1990) is another

finding that may indicate a comm capsaicin and resiniferatoxin on sensory neurons (Szallasi and Blumberg, 1989; Szallasi et al., 1989; Dray et al., 1990a; Maggi et al., 1990c; Winter et al., 1990) is another finding that may indicate a common site of acti capsaicin and resiniferatoxin on sensory neurons (Szallasi and Blumberg, 1989; Szallasi et al., 1989; Dray et al., 1990a; Maggi et al., 1990c; Winter et al., 1990) is another finding that may indicate a common site of acti lasi and Blumberg, 1989; Szallasi et al., 1989; Dray et al., 1990a; Maggi et al., 1990c; Winter et al., 1990) is another finding that may indicate a common site of action of the two drugs. However, this argument is only va 1990a; Maggi et al., 1990c; Winter et al., 1990) is another
finding that may indicate a common site of action of the
two drugs. However, this argument is only valid for the
specific desensitization and cross-desensitizatio finding that may indicate a common site of action of t
two drugs. However, this argument is only valid for t
specific desensitization and cross-desensitization to ca
saicin/resiniferatoxin (Amann, 1990; Winter et
1990). In two drugs. However, this argument is only valid for the specific desensitization and cross-desensitization to capsaicin/resiniferatoxin (Amann, 1990; Winter et al., 1990). In the case of nonspecific desensitization, respon specific desensitization and cross-desensitization to capsaicin/resiniferatoxin (Amann, 1990; Winter et al., 1990). In the case of nonspecific desensitization, responsiveness to the drugs seems to be lost because of cell d saicin/resiniferatoxin (Amann, 1990; Winter et al., 1990). In the case of nonspecific desensitization, responsiveness to the drugs seems to be lost because of cell damage. Consequently, no inference as to a common site of siveness to the drugs seems to be lost because of cell damage. Consequently, no inference as to a common site of action can be made, and all that can be deduced is that the cross-desensitizing drugs act on the same group o of cells (Maggi et a!., 1990c; Winter et a!., 1990).

effects in depolarizing cultured sensory neurons (Winter agonistic activity (Bevan et al., 1991; Dray et al., 1991).
et al., 1990), in producing corneal nociception (Szallasi In cultured dorsal root ganglion cells from ne ingly, the inhibitory effects of systemic resiniferatoxin efflux from cultured dorsal root ganglion neurons and
on sensory nerve-mediated chemical pain, hypothermia, [¹⁴C]guanidinium efflux from isolated rat vagus nerve An important step in proving the existence of a specific of action can be made, and all that can be deduced is
that the cross-desensitizing drugs act on the same group
of cells (Maggi et al., 1990c; Winter et al., 1990).
4. Capsazepine as a competitive antagonist of capsaicin.
A that the cross-desensitizing drugs act on the same group
of cells (Maggi et al., 1990c; Winter et al., 1990).
4. Capsazepine as a competitive antagonist of capsaicin.
An important step in proving the existence of a specif of cells (Maggi et al., 1990c; Winter et al., 1990).
4. Capsazepine as a competitive antagonist of capsaicin.
An important step in proving the existence of a specific
recognition site for capsaicin was the development of a [2-(4-chloropheny!)ethylamino-thiocarbonylj-7,8-dihy-An important step in proving the existence of a speceognition site for capsaicin was the development competitive antagonist, capsazepine. This compound [2-(4-chlorophenyl)ethylamino-thiocarbonyl]-7,8-dih droxy-2,3,4,5-tetr recognition site for capsaicin was the development of a
competitive antagonist, capsazepine. This compound (2-
[2-(4-chlorophenyl)ethylamino-thiocarbonyl]-7,8-dihy-
droxy-2,3,4,5-tetrahydro-1H-2-benzazepine) is structur-
a competitive antagonist, capsazepine. This compound (2-
[2-(4-chlorophenyl)ethylamino-thiocarbonyl]-7,8-dihy-
droxy-2,3,4,5-tetrahydro-1H-2-benzazepine) is structur-
ally related to capsaicin and potently antagonizes all
se [2-(4-chlorophenyl)ethylamino-thiocarbonyl]-7,8-dihy-
droxy-2,3,4,5-tetrahydro-1H-2-benzazepine) is structur-
ally related to capsaicin and potently antagonizes all
sensory neuron-selective effects of capsaicin but lacks
a droxy-2,3,4,5-tetrahydro-1H-2-benzazepine) is structurally related to capsaicin and potently antagonizes all sensory neuron-selective effects of capsaicin but lacks agonistic activity (Bevan et al., 1991; Dray et al., 1991 sensory neuron-selective effects of capsaicin but lacks sensory neuron-selective effects of capsaicin but lacks
agonistic activity (Bevan et al., 1991; Dray et al., 1991).
In cultured dorsal root ganglion cells from newborn rats,
capsazepine reversibly antagonizes the excitator agonistic activity (Bevan et al., 1991; Dray et al., 1991).
In cultured dorsal root ganglion cells from newborn rats,
capsazepine reversibly antagonizes the excitatory action
of capsaicin. The concentration of the antagon In cultured dorsal root ganglion cells from newborn rats,
capsazepine reversibly antagonizes the excitatory action
of capsaicin. The concentration of the antagonist needed
to reduce capsaicin-evoked uptake and accumulatio capsazepine reversibly antagonizes the excitatory action
of capsaicin. The concentration of the antagonist needed
to reduce capsaicin-evoked uptake and accumulation of
 ${}^{45}Ca^{2+}$ in these neurons is 0.5 μ M (Bevan et of capsaicin. The concentration of the antagonist needed
to reduce capsaicin-evoked uptake and accumulation of
 ${}^{45}Ca^{2+}$ in these neurons is 0.5 μ M (Bevan et al., 1991).
Analysis of the inhibition of capsaicin-induc to reduce capsaicin-evoked uptake and accumulation of ${}^{45}Ca^{2+}$ in these neurons is 0.5 μ M (Bevan et al., 1991).
Analysis of the inhibition of capsaicin-induced ${}^{86}Rb^+$
efflux from cultured dorsal root ganglion Analysis of the inhibition of capsaicin-induced $^{86}Rb^+$ Analysis of the inhibition of capsaicin-induced ⁸⁶
efflux from cultured dorsal root ganglion neurons
[¹⁴C]guanidinium efflux from isolated rat vagus ne
segments indicates that the antagonism exerted by c
sazepine is co efflux from cultured dorsal root ganglion neurons and [¹⁴C]guanidinium efflux from isolated rat vagus nerve segments indicates that the antagonism exerted by capsazepine is competitive. Thus, log concentration-effect cur $[{}^{14}C]$ guanidinium efflux from isolated rat vagus nerve segments indicates that the antagonism exerted by capsazepine is competitive. Thus, log concentration-effect curves are shifted to the right in a parallel manner sazepine is competitive. Thus, log concentration-effect
sazepine is competitive. Thus, log concentration-effect
curves are shifted to the right in a parallel manner with
increasing concentrations of the antagonist. Schild sazepine is competitive. Thus, log concentration
curves are shifted to the right in a parallel mani-
increasing concentrations of the antagonist. Sch
are linear, display a slope very close to 1, and
estimates of 0.1 to 0.7 rves are shifted to the right in a parallel manner with
creasing concentrations of the antagonist. Schild plots
e linear, display a slope very close to 1, and give K_d
timates of 0.1 to 0.7 μ M (Bevan et al., 1991).
In

sensory neurons vary so much in different assay systems, Pain evoked by intradermal injection of capsaicin into
whereas their relative activities in causing desensitiza-
tion and neurotoxicity are less variable. Whether, i ment of newborn rats there is not only a permanent preparation from the neonatal rat $(IC_{50} 0.2 \mu M)$ and
reduction in the number of [³H]resiniferatoxin-binding capsaicin-induced activation of afferent C-fiber termi-
si that is consistent with a heterogeneity of resiniferatoxin/ duced reflex decrease in rat blood pressure, 50% reduc-
capsaicin receptors (Szallasi et al., 1990).
Cross-desensitization between the stimulant effects of ally, increasing concentrations of the antagonist. Schild plots
are linear, display a slope very close to 1, and give K_d
estimates of 0.1 to 0.7 μ M (Bevan et al., 1991).
In keeping with these pharmacological properties, ca are linear, display a slope very close to 1, and give K_d
estimates of 0.1 to 0.7 μ M (Bevan et al., 1991).
In keeping with these pharmacological properties, cap-
sazepine has been found to antagonize the effects of
ca estimates of 0.1 to 0.7 μ M (Bevan et al., 1991).
In keeping with these pharmacological properties, cap-
sazepine has been found to antagonize the effects of
capsaicin in various test preparations (Dray et al., 1991).
P In keeping with these pharmacological properties, cap-
sazepine has been found to antagonize the effects of
capsaicin in various test preparations (Dray et al., 1991).
Pain evoked by intradermal injection of capsaicin into capsaicin in various test preparations (Dray et al., 1991). capsaicin in various test preparations (Dray et al., 1991).
Pain evoked by intradermal injection of capsaicin into
human skin is inhibited by 50% after intradermal ad-
ministration of 10 to 100 pmol of the antagonist. The
 Pain evoked by intradermal injection of capsaicin in
human skin is inhibited by 50% after intradermal iministration of 10 to 100 pmol of the antagonist. T
concentration of capsazepine that is required to redu
by one-half t human skin is inhibited by 50% after intradermal administration of 10 to 100 pmol of the antagonist. The concentration of capsazepine that is required to reduce by one-half the capsaicin-evoked activation of nociceptive Cministration of 10 to 100 pmol of the antagonist. The
concentration of capsazepine that is required to reduce
by one-half the capsaicin-evoked activation of nocicep-
tive C-fiber units in an isolated preparation of the ra concentration of capsazepine that is required to reduce
by one-half the capsaicin-evoked activation of nocicep-
tive C-fiber units in an isolated preparation of the rat
saphenous nerve and hindpaw skin is approximately 1
 by one-half the capsaicin-evoked activation of nocitive C-fiber units in an isolated preparation of the saphenous nerve and hindpaw skin is approximate μ M (Dray et al., 1991). This potency of capsazer compares well wit tive C-fiber units in an isolated preparation of the rat saphenous nerve and hindpaw skin is approximately 1 μ M (Dray et al., 1991). This potency of capsazepine compares well with its activity in antagonizing capsaicin saphenous nerve and hindpaw skin is approximately 1 μ M (Dray et al., 1991). This potency of capsazepine compares well with its activity in antagonizing capsaicinevoked stimulation of nociceptors in the spinal cord-tail μ M (Dray et al., 1991). This potency of capsazepi
compares well with its activity in antagonizing capsaici
evoked stimulation of nociceptors in the spinal cord-t-
preparation from the neonatal rat (IC₅₀ 0.2 μ M) ar compares well with its activity in antagonizing capsaicinevoked stimulation of nociceptors in the spinal cord-tail preparation from the neonatal rat $(IC_{50} 0.2 \mu M)$ and capsaicin-induced activation of afferent C-fiber te preparation from the neonatal rat $(IC_{50} 0.2 \mu M)$ and preparation from the neonatal rat $(IC_{50} 0.2 \mu M)$ are capsaicin-induced activation of afferent C-fiber term rals in the isolated mouse spinal cord $(IC_{50} 1$ to 5 μN Furthermore, the antagonist blocks the capsaicin-id capsaicin-induced activation of afferent C-fiber tends in the isolated mouse spinal cord $(IC_{50} 1$ to 5
Furthermore, the antagonist blocks the capsaicinduced reflex decrease in rat blood pressure, 50% retion being seen w nals in the isolated mouse spinal cord $(IC_{50} 1$ to 5μ M).
Furthermore, the antagonist blocks the capsaicin-in-
duced reflex decrease in rat blood pressure, 50% reduc-
tion being seen with doses of 10 nmol given intraa

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

174 HOLZER
the guinea pig isolated ileum with an IC_{50} of 0.01 to 0.05 con
 μ M (Dray et al., 1991). Importantly, in all of these test scu **iMarting 174**
 i HOL2
 i the guinea pig isolated ileum with an IC_{60} of 0.01 to 0.05
 μ M (Dray et al., 1991). Importantly, in all of these test

preparations only responses to capsaicin, but not to other p_{μ} HOLZ
the guinea pig isolated ileum with an IC_{60} of 0.01 to 0.05
 μ M (Dray et al., 1991). Importantly, in all of these test
preparations only responses to capsaicin, but not to other
stimuli, are blocked by ca the guinea pig isolated ileum with an IC_{50} of 0.01 to 0.05 μ M (Dray et al., 1991). Importantly, in all of these test preparations only responses to capsaicin, but not to other stimuli, are blocked by capsazepine.
Th e guinea pig isolated ileum with an IC_{50} of 0.01 to 0.

If (Dray et al., 1991). Importantly, in all of these to eparations only responses to capsaicin, but not to oth

muli, are blocked by capsazepine.

The discovery o

 μ M (Dray et al., 1991). Importantly, in all of these test
preparations only responses to capsaicin, but not to other
stimuli, are blocked by capsazepine.
The discovery of capsazepine as a competitive antag-
onist of ca preparations only responses to capsaicin, but not to other
stimuli, are blocked by capsazepine.
The discovery of capsazepine as a competitive antag-
onist of capsaicin has added significant support to the
hypothesis that c stimuli, are blocked by capsazepine. the chiral contract the discovery of capsazepine as a competitive antag-
onist of capsaicin has added significant support to the cells
hypothesis that capsaicin's actions on sensory neu The discovery of capsazepine as a competitive antagonist of capsaicin has added significant support to the hypothesis that capsaicin's actions on sensory neurons are mediated by a specific recognition site with the pharmac onist of capsaicin has added significant support to the hypothesis that capsaicin's actions on sensory neurons are mediated by a specific recognition site with the pharmacological properties of a receptor. The availability hypothesis that capsaicin's actions on sensory neurons that are mediated by a specific recognition site with the gipharmacological properties of a receptor. The availability that of such an antagonist is a significant asse are mediated by a specific recognition site with the
pharmacological properties of a receptor. The availability
of such an antagonist is a significant asset in the further
exploration of the sensory neuron-selective action **Example 15. Example 15. Example 16. Example 16. Example 16. Example 16. Example 16. Example 16. Biochemical characterization of the recognition site** 5. **Biochemical characterization of the recognition sit**

of such an antagonist is a significant asset in the further exploration of the sensory neuron-selective actions of capsaicin, their mechanisms, and functional significance.
5. Biochemical characterization of the recognitio capsaicin, their mechanisms, and functional significance
5. Biochemical characterization of the recognition sit
for capsaicin. Biochemical characterization of the cellule
recognition site for capsaicin through a study of i 5. Biochemical characterization of the recognition site the composition. Biochemical characterization of the cellular recognition site for capsaicin through a study of its repecific binding has not been possible because o for capsaicin. Biochemical characterization of the cellular

recognition site for capsaicin through a study of its

specific binding has not been possible because of tech-

nical problems arising from the lipophilic nature recognition site for capsaicin through a study of its specific binding has not been possible because of technical problems arising from the lipophilic nature of this ligand (James et al., 1988). This problem was overcome w specific binding has not been possible because of tech-
nical problems arising from the lipophilic nature of this
ligand (James et al., 1988). This problem was overcome cin
when [³H] resiniferatoxin was used as the ligan nical problems arising from the lipophilic nature of this P
ligand (James et al., 1988). This problem was overcome c
when $[^3H]$ resiniferatoxin was used as the ligand (Szallasi
and Blumberg, 1990a). Binding studies with t ligand (James et al., 1988). This problem was overcome
when $[^{3}H]$ resiniferatoxin was used as the ligand (Szallasi
and Blumberg, 1990a). Binding studies with this labeled
compound have indicated the presence of a single when [³H] resiniferatoxin was used as the ligand (Szallasi
and Blumberg, 1990a). Binding studies with this labeled the
compound have indicated the presence of a single class bof specific saturable binding sites for [³ and Blumberg, 1990a). Binding studies with this labeled
compound have indicated the presence of a single class
of specific saturable binding sites for [³H] resiniferatoxin
on membranes from dorsal root and trigeminal ga compound have indicated the presence of a single class
of specific saturable binding sites for [³H] resiniferatoxin of t
on membranes from dorsal root and trigeminal ganglia Thu
(Szallasi and Blumberg, 1990a). This neuro of specific saturable binding sites for [³H] resiniferatoxin
on membranes from dorsal root and trigeminal ganglia
(Szallasi and Blumberg, 1990a). This neuronal binding
site for resiniferatoxin, characterized by a K_d o on membranes from dorsal root and trigeminal ganglia (Szallasi and Blumberg, 1990a). This neuronal binding of site for resiniferatoxin, characterized by a K_d of 0.13 to we 0.27 nm, is distinct from protein kinase C whic (Szallasi and Blumberg, 1990a). This neuronal binding ^{of}
site for resiniferatoxin, characterized by a K_d of 0.13 to
0.27 nM, is distinct from protein kinase C which seems
to recognize a different aspect of the diterpe site for resiniferatoxin, characterized by a K_d of 0.13 to
0.27 nM, is distinct from protein kinase C which seems
to recognize a different aspect of the diterpene moiety
(Szallasi and Blumberg, 1990a,b). Subcellularly, 0.27 nM, is distinct from protein kinase C which seems
to recognize a different aspect of the diterpene moiety
(Szallasi and Blumberg, 1990a,b). Subcellularly, most of
the binding sites for resiniferatoxin are located in t to recognize a different aspect of the diterpene moiety (Szallasi and Blumberg, 1990a,b). Subcellularly, most of the binding sites for resiniferatoxin are located in the amicrosomal/plasma membrane fraction of pig dorsal (Szallasi and Blumberg, 1990a,b). Subcellularly, most the binding sites for resiniferatoxin are located in the microsomal/plasma membrane fraction of pig dorsal roganglia (Szallasi and Blumberg, 1990a). The specific bindin the binding sites for resiniferatoxin are located in the
microsomal/plasma membrane fraction of pig dorsal root
ganglia (Szallasi and Blumberg, 1990a). The specific
binding of [³H] resiniferatoxin to sensory ganglion mem microsomal/plasma membrane fraction of pig dorsal root
ganglia (Szallasi and Blumberg, 1990a). The specific
binding of [³H]resiniferatoxin to sensory ganglion mem-
branes is displaced by resiniferatoxin, capsaicin, and
o ganglia (Szallasi and Blumberg, 1990a). The specific $\frac{1}{1}$
binding of [³H] resiniferatoxin to sensory ganglion mem-
branes is displaced by resiniferatoxin, capsaicin, and
other capsaicinoids, their relative potencie binding of [³H] resiniferatoxin to sensory ganglion membranes is displaced by resiniferatoxin, capsaicin, and other capsaicinoids, their relative potencies being similar to those in producing hypothermia and plasma prote branes is displaced by resiniferatoxin, capsaicin, and
other capsaicinoids, their relative potencies being similar
to those in producing hypothermia and plasma protein
leakage in vivo (Szallasi and Blumberg, 1989, 1990a).
 other capsaicinoids, their relative potencies being similar
to those in producing hypothermia and plasma protein
leakage in vivo (Szallasi and Blumberg, 1989, 1990a).
Inorganic calcium channel blockers (nickel and cad-
miu to those in producing hypothermia and plasma protein leakage in vivo (Szallasi and Blumberg, 1989, 1990a).
Inorganic calcium channel blockers (nickel and cadmium) and ruthenium red, which can block certain phases of capsai leakage in vivo (Szallasi and Blumberg, 1989, 1990a).
Inorganic calcium channel blockers (nickel and cadmium) and ruthenium red, which can block certain phases of capsaicin's and resiniferatoxin's stimulant effects on sens Inorganic calcium channel blockers (nickel and camium) and ruthenium red, which can block certs
phases of capsaicin's and resiniferatoxin's stimulant (fects on sensory neurons (Wood et al., 1988; Amann
al., 1989a; Maggi et mium) and ruthenium red, which can block certain
phases of capsaicin's and resiniferatoxin's stimulant ef-
fects on sensory neurons (Wood et al., 1988; Amann et
al., 1989a; Maggi et al., 1988d; Dray et al., 1990d) appar-
e phases of capsaicin's and resiniferatoxin's stimulant ef-
fects on sensory neurons (Wood et al., 1988; Amann et
grad., 1989a; Maggi et al., 1988d; Dray et al., 1990d) appar-
ently do not inhibit [³H]resiniferatoxin bindi al., 1989a; Maggi et al., 1988d; Dray et al., 1990d) apparently do not inhibit [³H] resiniferatoxin binding (Szallasi and Blumberg, 1990a,b). These compounds, therefore, do ently do not inhibit [³H] resiniferatoxin binding (Szallasi sin and Blumberg, 1990a,b). These compounds, therefore, do primet seem to interact with the recognition site for resiniferatoxin per se. Sodium deoxycholate, w and Blumberg, 1990a,b). These compounds, therefore, donot seem to interact with the recognition site for resiniferatoxin per se. Sodium deoxycholate, which has been reported to facilitate capsaicin's acute effects (Jin and feratoxin per se. Sodium deoxycholate, which has been reported to facilitate capsaicin's acute effects (Jin and Nakayama, 1990), is likewise without effect on the resiniferatoxin-binding site (Szallasi and Blumberg, 1990b) reported to facilitate capsaicin's acute effects (Jin and Nakayama, 1990), is likewise without effect on the resi-
niferatoxin-binding site (Szallasi and Blumberg, 1990b).
Specific recognition sites for [³H]resiniferatox

Nakayama, 1990), is likewise without effect on the resi-
niferatoxin-binding site (Szallasi and Blumberg, 1990b). Rai
Specific recognition sites for [³H] resiniferatoxin have et a
been found in dorsal root and trigeminal niferatoxin-binding site (Szallasi and Blumberg, 1990b). Reposition specific recognition sites for [³H] resiniferatoxin have et been found in dorsal root and trigeminal ganglia of rat, alpig, cow, and sheep but not in th Specific recognition sites for $[^{3}H]$ resiniferatoxin have
been found in dorsal root and trigeminal ganglia of rat,
pig, cow, and sheep but not in those of the chicken, a
species that is not responsive to the pungent act been found in dorsal root and trigeminal ganglia of r
pig, cow, and sheep but not in those of the chicken
species that is not responsive to the pungent action
capsaicin (Szallasi and Blumberg, 1990a). No speci
binding of r species that is not responsive to the pungent action of capsaicin (Szallasi and Blumberg, 1990a). No specific binding of resiniferatorin has been detected in the preoptic region of the brain, striatum, substantia nigra, ce bellum, and whole spinal cord of the rat, but one must

capsaicin, their mechanisms, and functional significance. the dorsal root ganglia of adult rats; the binding sites in
5. Biochemical characterization of the recognition site the trigeminal ganglion are reduced by 30 to 56 ER
consider that minor binding components could be ob-
scured by a high level of nonspecific binding of resinifer-ER
consider that minor binding components could be
scured by a high level of nonspecific binding of resini
atoxin (Szallasi and Blumberg, 1990a,b). Neverthel ER
consider that minor binding components could be ol
scured by a high level of nonspecific binding of resinife
atoxin (Szallasi and Blumberg, 1990a,b). Nevertheles
the available findings indicate that specific binding o The available finding components could be obscured by a high level of nonspecific binding of resiniferatorin (Szallasi and Blumberg, 1990a,b). Nevertheless, the available findings indicate that specific binding of [³H] r consider that minor binding components could be ob-
scured by a high level of nonspecific binding of resinifer-
atoxin (Szallasi and Blumberg, 1990a,b). Nevertheless,
the available findings indicate that specific binding o scured by a high level of nonspecific binding of resinife atoxin (Szallasi and Blumberg, 1990a,b). Neverthele
the available findings indicate that specific binding
[³H] resiniferatoxin reflects the existence of a speci
c atoxin (Szallasi and Blumberg, 1990a,b). Nevertheless,
the available findings indicate that specific binding of
[³H]resiniferatoxin reflects the existence of a specific
cellular recognition site for resiniferatoxin/capsa the available findings indicate that specific binding of [³H] resiniferatoxin reflects the existence of a specific cellular recognition site for resiniferatoxin/capsaicin that is exclusively present on membranes of senso [³H] resiniferatoxin reflects the existence of a specific cellular recognition site for resiniferatoxin/capsaicin that is exclusively present on membranes of sensory ganglia. This contention is underlined by the finding cellular recognition site for resiniferatoxin/capsaicin
that is exclusively present on membranes of sensory
ganglia. This contention is underlined by the finding
that resiniferatoxin treatment of newborn rats leads to
a 41 that is exclusively present on membranes of sensory
ganglia. This contention is underlined by the finding
that resiniferatoxin treatment of newborn rats leads to
a 41 to 53% loss of cell bodies and to a 79 to 91%
reductio ganglia. This contention is underlined by the finding
that resiniferatoxin treatment of newborn rats leads to
a 41 to 53% loss of cell bodies and to a 79 to 91%
reduction of specific [³H]resiniferatoxin-binding sites in that resiniferatoxin treatment of newborn rats leads
a 41 to 53% loss of cell bodies and to a 79 to 91
reduction of specific [³H]resiniferatoxin-binding sites
the dorsal root ganglia of adult rats; the binding sites
the a 41 to 53% loss of cell bodies and to a 79 to 91%
reduction of specific [³H]resiniferatoxin-binding sites in
the dorsal root ganglia of adult rats; the binding sites in
the trigeminal ganglion are reduced by 30 to 56% reduction of specific [³H] resiniferatoxin-binding sites in
the dorsal root ganglia of adult rats; the binding sites in
the trigeminal ganglion are reduced by 30 to 56% (Szal-
lasi et al., 1990). It can be anticipated t the dorsal root ganglia of adult rats; the binding sites in the trigeminal ganglion are reduced by 30 to 56% (Szallasi et al., 1990). It can be anticipated that the [³H] resiniferatoxin-binding assay will have great pote the trigeminal ganglion are reduced by 30 to 56 lasi et al., 1990). It can be anticipated that resiniferatoxin-binding assay will have great pot further unraveling the molecular structure, bio processing, and properties of lasi et al., 1
resiniferatox
further unra
processing, a
cin receptor.
The ability siniferatoxin-binding assay will have great potential in
rther unraveling the molecular structure, biochemical
ocessing, and properties of the resiniferatoxin/capsai-
n receptor.
The ability of photoaffinity probes to irre

further unraveling the molecular structure, biochemical
processing, and properties of the resiniferatoxin/capsai-
cin receptor.
The ability of photoaffinity probes to irreversibly label
the capsaicin recognition site (Jame processing, and properties of the resiniferatoxin/capsaicin receptor.

The ability of photoaffinity probes to irreversibly label

the capsaicin recognition site (James et al., 1988) has

been utilized in an attempt to isol cin receptor.
The ability of photoaffinity probes to irreversibly label
the capsaicin recognition site (James et al., 1988) has
been utilized in an attempt to isolate protein components
of the putative capsaicin receptor (The ability of photoaffinity probes to irreversibly label
the capsaicin recognition site (James et al., 1988) has
been utilized in an attempt to isolate protein components
of the putative capsaicin receptor (Wood et al., 1 the capsaicin recognition site (James et al., 1988) has
been utilized in an attempt to isolate protein components
of the putative capsaicin receptor (Wood et al., 1990).
Thus, a major protein with an apparent molecular wei been utilized in an attempt to isolate protein components
of the putative capsaicin receptor (Wood et al., 1990).
Thus, a major protein with an apparent molecular weight
of 58 kD and a minor protein with an apparent molecu of the putative capsaicin receptor (Wood et al., 1990).

Thus, a major protein with an apparent molecular weight

of 58 kD and a minor protein with an apparent molecular

weight of 42 kD can be isolated from rat and chick Thus, a major protein with an apparent molecular weight
of 58 kD and a minor protein with an apparent molecular
weight of 42 kD can be isolated from rat and chick dorsal
root ganglia but are absent from rat liver and cereb of 58 kD and a minor protein with an apparent molecu
weight of 42 kD can be isolated from rat and chick dor
root ganglia but are absent from rat liver and cerebell
(Wood et al., 1990). However, the inability of capsaid
to weight of 42 kD can be isolated from rat and chick dorsal
root ganglia but are absent from rat liver and cerebellum
(Wood et al., 1990). However, the inability of capsaicin
to protect these proteins from labeling with the root ganglia but are absent from rat liver and cerebellum (Wood et al., 1990). However, the inability of capsaicin
to protect these proteins from labeling with the photo-
affinity probe does not allow them to be designated (Wood et al., 1990). However, the inability of capsaicin
to protect these proteins from labeling with the photo-
affinity probe does not allow them to be designated as
part of the capsaicin recognition site (Wood et al., 1 to protect these proteins from labeling with the photo-
affinity probe does not allow them to be designated as
part of the capsaicin recognition site (Wood et al., 1990).
This inference is also supported by the finding tha affinity probe does not allow them to be designated as
part of the capsaicin recognition site (Wood et al., 1990).
This inference is also supported by the finding that the
labeled proteins are present in both rat and chick part of the capsaicin recognition site (Wood et al., 1990).
This inference is also supported by the finding that the
labeled proteins are present in both rat and chick dorsal
root ganglion neurons, although chick sensory n This inference is also supported by the finding that the labeled proteins are present in both rat and chick dorsa root ganglion neurons, although chick sensory neurons are insensitive to capsaicin in the calcium uptake ass labeled proteins are present in both rat and chick dorsal
root ganglion neurons, although chick sensory neurons
are insensitive to capsaicin in the calcium uptake assay
(Wood et al., 1988, 1990). Consequently, a possible r root ganglion neurons, although chick sen
are insensitive to capsaicin in the calcium
(Wood et al., 1988, 1990). Consequently, a
tionship of the labeled proteins to the capsa
cation channel complex remains unknown.
B. Mech are msensitive to capsaicm in the calcium update assay

(Wood et al., 1988, 1990). Consequently, a possible rela-

tionship of the labeled proteins to the capsaicin receptor/

cation channel complex remains unknown.
 B. M **1. Acute 1. Acute excitation of sensory Neuron-selective Effects**
 1. Acute excitation of sensory Neuron-selective Effects
 1. Acute excitation of sensory neurons. a. **PRIMARY**
 PECT: ACTIVATION OF A CATION CONDUCTA

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

al., 1989a; Maggi et al., 1988a; Dray et al., 1990a) apparties timulants of sensory neurons, capsaicin and re-
ently do not inhibit [³H] resiniferatoxin binding (Szallasi aniferatoxin depolarize both axons and somata of Nakayama, 1990), is likewise without effect on the resi-
niferatoxin-binding site (Szallasi and Blumberg, 1990b). Rang, 1985; Bevan et al., 1987; Marsh et al., 1987; Winter
Specific recognition sites for [³H]resiniferato Example 2.1 and 15 and 16.
 EFFECT: ACTIVATION OF A CATION CONDUCTANCE. As

potent stimulants of sensory neurons, capsaicin and re-B. Mechanisms of the Sensory Neuron-selective Effects
1. Acute excitation of sensory neurons. a. PRIMARY
EFFECT: ACTIVATION OF A CATION CONDUCTANCE. As
potent stimulants of sensory neurons, capsaicin and re-
siniferatoxin B. Mechanisms of the Sensory Neuron-selective Effects
1. Acute excitation of sensory neurons. a. PRIMARY
EFFECT: ACTIVATION OF A CATION CONDUCTANCE. As
potent stimulants of sensory neurons, capsaicin and re-
siniferatoxin 1. Acute excitation of sensory neurons. a. PRIMARY
EFFECT: ACTIVATION OF A CATION CONDUCTANCE. As
potent stimulants of sensory neurons, capsaicin and re-
siniferatoxin depolarize both axons and somata of rat
primary affere EFFECT: ACTIVATION OF A CATION CONDUCTANCE. As
potent stimulants of sensory neurons, capsaicin and re-
siniferatoxin depolarize both axons and somata of rat
primary afferent neurons. The depolarization derives
from an inwa potent stimulants of sensory neurons, capsaicin and resiniferatoxin depolarize both axons and somata of rat
primary afferent neurons. The depolarization derives
from an inward current which sometimes is followed by
an outw from an inward current which sometimes is followed by primary afferent neurons. The depolarization derives
from an inward current which sometimes is followed by
an outward current (Ault and Evans, 1980; Yanagisawa
et al., 1980; Williams and Zieglgänsberger, 1982; Baccag-
lini from an inward current which sometimes is followed by
an outward current (Ault and Evans, 1980; Yanagisawa
et al., 1980; Williams and Zieglgänsberger, 1982; Baccag-
lini and Hogan, 1983; Hayes et al., 1984a; Heyman and
Ran an outward current (Ault and Evans, 1980; Yanagisawa
et al., 1980; Williams and Zieglgänsberger, 1982; Baccag-
lini and Hogan, 1983; Hayes et al., 1984a; Heyman and
Rang, 1985; Bevan et al., 1987; Marsh et al., 1987; Winte et al., 1980; Williams and Zieglgänsberger, 1982; Baccag-
lini and Hogan, 1983; Hayes et al., 1984a; Heyman and
Rang, 1985; Bevan et al., 1987; Marsh et al., 1987; Winter
et al., 1988; Bevan and Szolcsányi, 1990; Bleakman lini and Hogan, 1983; Hayes et al., 1984a; Heyman a Rang, 1985; Bevan et al., 1987; Marsh et al., 1987; Wiret al., 1988; Bevan and Szolcsányi, 1990; Bleakmand., 1990; Dray et al., 1990d; Docherty et al., 1990
Because the i Rang, 1985; Bevan et al., 1987; Marsh et al., 1987; Winter
et al., 1988; Bevan and Szolcsányi, 1990; Bleakman et
al., 1990; Dray et al., 1990d; Docherty et al., 1991).
Because the inward current is associated with a conduc et al., 1988; Bevan and Szolcsányi, 1990; Bleakman et al., 1990; Dray et al., 1990d; Docherty et al., 1991). Because the inward current is associated with a conductance increase, it would follow that ion channels are opene al., 1990; Dray et al., 1990d; Docherty et al., 1991).
Because the inward current is associated with a conduct-
ance increase, it would follow that ion channels are
opened by the drugs. Indeed, ion flux (Wood et al., 1988, Because the inward current is associated with a conduct-
ance increase, it would follow that ion channels are
opened by the drugs. Indeed, ion flux (Wood et al., 1988,
1989; Winter et al., 1990) and patch clamp (Bevan and
 ance increase, it would follow that ion channels are opened by the drugs. Indeed, ion flux (Wood et al., 1988, 1989; Winter et al., 1990) and patch clamp (Bevan and Forbes, 1988; Forbes and Bevan, 1988; Bevan and Szolcsány

CA
indicate that capsaicin and resiniferatoxin open a men
brane ion channel that is relatively nonselective fo CAPSAIC
indicate that capsaicin and resiniferatoxin open a mem-
brane ion channel that is relatively nonselective for to
cations and which allows the passage of both mono- and c CAPSAICIN
indicate that capsaicin and resiniferatoxin open a mem-
brane ion channel that is relatively nonselective for tox
cations and which allows the passage of both mono- and cap
divalent cations including Na^+ , K^+ indicate that capsaicin and resiniferatoxin open a men
brane ion channel that is relatively nonselective for
cations and which allows the passage of both mono- an
divalent cations including $N_a^+, K^+, C_s^+, R_b^+, C_a^{2+}, M_g^{2}$
an indicate that capsaicin and resiniferatoxin open a mem-
brane ion channel that is relatively nonselective for
cations and which allows the passage of both mono- and
divalent cations including $Na^+, K^+, Cs^+, Rb^+, Ca^{2+}, Mg^{2+}$,
an brane ion channel that is relatively nonselective for to:
cations and which allows the passage of both mono- and
divalent cations including $Na^+, K^+, Cs^+, Rb^+, Ca^{2+}, Mg^{2+}, cyd$
and guanidium ions. The reversal potential for the in cations and which allows the passage of both mono- and cal
divalent cations including $Na^+, K^+, Cs^+, Rb^+, Ca^{2+}, Mg^{2+}, cy$
and guanidium ions. The reversal potential for the in-
ward current evoked by capsaicin and resiniferatorin divalent cations including $Na^+, K^+, Cs^+, Rb^+, Ca^{2+}, Mg^{2+}, cyc$
and guanidium ions. The reversal potential for the in-
ward current evoked by capsaicin and resiniferatoxin is thr
approximately 0 mV, which is also consistent with th and guanidium ions. The reversal potential for the in-
ward current evoked by capsaicin and resiniferatoxin is
approximately 0 mV, which is also consistent with the
et opening of a nonselective cation channel (Bevan and
Fo ward current evoked by capsaicin and resiniferatoxin is
approximately 0 mV, which is also consistent with the
opening of a nonselective cation channel (Bevan and
Forbes, 1988; Winter et al., 1990). In contrast, the efflux
 approximately 0 mV, which is also consistent with the opening of a nonselective cation channel (Bevan and Forbes, 1988; Winter et al., 1990). In contrast, the efflux of Cl⁻ is left unaltered by capsaicin (Wood et al., 19 opening of a nonselective cation channel (Bevan and Trorbes, 1988; Winter et al., 1990). In contrast, the efflux cap of Cl⁻ is left unaltered by capsaicin (Wood et al., 1988), age and it seems that Cl⁻ and other anions Forbes, 1988; Winter et al., 1990). In contrast, the efflux condiction of Cl⁻ is left unaltered by capsaicin (Wood et al., 1988), and it seems that Cl⁻ and other anions do not participate F directly in the conductance of Cl⁻ is left unaltered by capsaicin (Wood et al., 1988), age
and it seems that Cl⁻ and other anions do not participate Fir
directly in the conductance increase (Bevan and pre
Szolcsányi, 1990; Winter et al., 1990), and it seems that Cl⁻ and o
directly in the conduct.
Szolcsányi, 1990; Winter
could be a secondary increasions (Marsh et al., 1987).
The permeability sequen directly in the conductance increase (Bevan and Szolcsányi, 1990; Winter et al., 1990), although there could be a secondary increase in the conductance for Cl⁻
ions (Marsh et al., 1987). The permeability sequence of the

Szolcsányi, 1990; Winter et al., 1990), although there nal
could be a secondary increase in the conductance for Cl⁻ vol
ions (Marsh et al., 1987). The permeability sequence of the capsaicin-operated pin
cation channel i could be a secondary increase in the conductance for Cl⁻
ions (Marsh et al., 1987).
The permeability sequence of the capsaicin-operated
cation channel is $Ca^{2+} > Mg^{2+} > K^+ > Na^+$ (Bevan and
Szolcsányi, 1990). Thus, under p ions (Marsh et al., 1987).

The permeability sequence of the capsaicin-operated pincation channel is $Ca^{2+} > Mg^{2+} > K^+ > Na^+$ (Bevan and the Szolcsányi, 1990). Thus, under physiological conditions M₁ both Ca^{2+} and Na⁺ The permeability sequence of the capsaicin-operated pication channel is $Ca^{2+} > Mg^{2+} > K^+ > Na^+$ (Bevan and the Szolcsányi, 1990). Thus, under physiological conditions Moth Ca^{2+} and Na⁺ move into the cell and carry the both Ca²⁺ and Na⁺ move into the cell and carry the capsaicin/resiniferatoxin-induced inward current while K⁺ ions leave the cell (Wood et al., 1988; Bleakman et al., 1990; Dray et al., 1990d; Winter et al., 1990). R capsaicin/resiniferatoxin-induced inward current while
 K^+ ions leave the cell (Wood et al., 1988; Bleakman et

al., 1990; Dray et al., 1990d; Winter et al., 1990). Removal

of either Ca^{2+} or Na⁺ from the extracel K⁺ ions leave the cell (Wood et al., 1988; Bleakman et al., 1990; Dray et al., 1990d; Winter et al., 1990). Removal larger of either Ca^{2+} or Na⁺ from the extracellular fluid does denot abolish the inward current be al., 1990; Dray et al., 1990d; Winter et al., 1990). Remot either Ca^{2+} or Na⁺ from the extracellular fluid contrabolish the inward current because in this instation the inward current will be carried, at least in par of either Ca^{2+} or Na⁺ from the extracellular fluid does depoted but not abolish the inward current because in this instance end the inward current will be carried, at least in part, by the 1979 other cation (Bevan an not abolish the inward current because in this instance
the inward current will be carried, at least in part, by the
196ther cation (Bevan and Forbes, 1988). Thus, capsaicin-
Induced depolarization is reduced but not prev the inward current will be carried, at least in part, by the other cation (Bevan and Forbes, 1988). Thus, capsaicin-
induced depolarization is reduced but not prevented by removal of extracellular Na^+ (Bevan et al., 198 other cation (Bevan and Forbes, 1988). Thus, capsaicin-
induced depolarization is reduced but not prevented by
removal of extracellular Na⁺ (Bevan et al., 1987; Marsh
et al., 1987). In contrast, omission of extracellular induced depolarization is reduced but not prevented by
removal of extracellular Na^+ (Bevan et al., 1987; Marsh
et al., 1987). In contrast, omission of extracellular Ca^{2+}
completely fails to inhibit the excitatory act removal of extracellular Na⁺ (Bevan et al., 1987; Marsh et al., 1987). In contrast, omission of extracellular Ca²⁺ completely fails to inhibit the excitatory action of capsaicin but, if anything, enhances it (Yanagisaw et al., 1987). In contrast, omission of extracellular Ca²⁺ completely fails to inhibit the excitatory action of capsaicin but, if anything, enhances it (Yanagisawa et al., 1980; Baccaglini and Hogan, 1983; Marsh et al., completely fails to inhibit the excitat saicin but, if anything, enhances it (1980; Baccaglini and Hogan, 1983; N
Bettaney et al., 1988; Amann et al., 1990b; Docherty et al., 1991).
Turther analysis of the capsaicin/ icin but, if anything, enhances it (Yanagis 80; Baccaglini and Hogan, 1983; Marsh ettaney et al., 1988; Amann et al., 1989a; 190b; Docherty et al., 1991).
Further analysis of the capsaicin/resiniferated membrane current on

dependent kinase, calmodulin-dependent kinase, phos-
pholipase A₂, and cyclooxygenase does not affect the
tAbbreviations: AMP, adenosine monophosphate; GMP, guanosine
monophosphate; NGF, nerve growth factor. 1980; Baccaglini and Hogan, 1983; Marsh et al., 1987;
Bettaney et al., 1988; Amann et al., 1989a; Dray et al.,
1990b; Docherty et al., 1991).
Further analysis of the capsaicin/resiniferatoxin-in-
duced membrane current on Bettaney et al., 1988; Amann et al., 1989a; Dray et al.
1990b; Docherty et al., 1991).
Further analysis of the capsaicin/resiniferatoxin-ir
duced membrane current on outside-out membran
patches has shown that capsaicin evo 1990b; Docherty et al., 1991).

Further analysis of the capsaicin/resiniferatoxin-in-

duced membrane current on outside-out membrane

patches has shown that capsaicin evokes single-channel

currents which display the sam Further analysis of the capsaicin/resiniferatoxin-in-
duced membrane current on outside-out membrane
patches has shown that capsaicin evokes single-channel
currents which display the same cation permeability as
the current duced membrane current on outside-out membrane
patches has shown that capsaicin evokes single-channel
currents which display the same cation permeability as
the currents obtained from whole cell recordings (Forbes
and Beva patches has shown that capsaicin evokes single-channel

currents which display the same cation permeability as

the currents obtained from whole cell recordings (Forbes

and Bevan, 1988; Bevan and Szolcsányi, 1990; Dray et currents which display the same cation permeability as the currents obtained from whole cell recordings (Forbes and Bevan, 1988; Bevan and Szolcsányi, 1990; Dray et in the al., 1990d). The conductance of single channels o the currents obtained from whole cell recordings (Forbes in the and Bevan, 1988; Bevan and Szolcsányi, 1990; Dray et al., 1990d). The conductance of single channels opened synthety and resimiferatorin is approximately 100 and Bevan, 1988; Bevan and Szolcsányi, 1990; Dray et al., 1988; Sevan and Szolcsányi, 1990; Dray et al., 1990d). The conductance of single channels opened
by capsaicin and resiniferatoxin is approximately 100 pS
at +60 mV al., 1990d). The conductance of single channels opened
by capsaicin and resiniferatoxin is approximately 100 pS
at +60 mV and 20 to 30 pS at -60 mV (Forbes and
Bevan, 1988; Bevan and Szolcsányi, 1990). The data
obtained f by capsaicin and resiniferatoxin is approximately 100 pS
at +60 mV and 20 to 30 pS at -60 mV (Forbes and $\frac{1}{2}$ et a
Bevan, 1988; Bevan and Szolcsányi, 1990). The data in co
obtained from isolated membrane patches of s at $+60$ mV and 20 to 30 pS at -60 mV (Forbes and Europan membrane patches of sensory agreements in the plasma membrane without any intervention of a second-messenger system, a conclusion for which there Bevan, 1988; Bevan and Szolcsányi, 1990). The data
obtained from isolated membrane patches of sensory
neurons indicate that capsaicin-like drugs act directly on
the plasma membrane without any intervention of a
second-mes obtained from isolated membrane patches of sensory
neurons indicate that capsaicin-like drugs act directly on
the plasma membrane without any intervention of a
second-messenger system, a conclusion for which there
is also neurons indicate that capsaicin-like drugs act directly on the plasma membrane without any intervention of a second-messenger system, a conclusion for which there is also biochemical evidence (Wood et al. 1989; Bevan and S the plasma membrane without any intervention of a
second-messenger system, a conclusion for which there
is also biochemical evidence (Wood et al. 1989; Bevan
and Szolcsányi, 1990; Dray et al., 1990a,b; Winter et al.,
1990 second-messenger system, a conclusion for which there is also biochemical evidence (Wood et al. 1989; Bevan and Szolcsányi, 1990; Dray et al., 1990a,b; Winter et al., 1990). Accordingly, inhibition or activation of protein is also biochemical evidence (Wood et al. 1989; Beva
and Szolcsányi, 1990; Dray et al., 1990a,b; Winter et al
1990). Accordingly, inhibition or activation of protei
kinase C, cyclic AMP‡-dependent kinase, cyclic GMI
depend and Szolcsányi, 1990; Dray et al., 1990a,b; Winter et al., \rightarrow 1990). Accordingly, inhibition or activation of protein the skinase C, cyclic AMP‡-dependent kinase, cyclic GMP-dependent kinase, calmodulin-dependent kinase

sensory neuron responses to capsaicin and resiniferatoxin (Dray et al., 1990a,b; Winter et al., 1990). The toxin (175
sensory neuron responses to capsaicin and resinifera-
toxin (Dray et al., 1990a,b; Winter et al., 1990). The
capsaicin/resiniferatoxin-evoked increase in the levels of 175
sensory neuron responses to capsaicin and resinifera-
toxin (Dray et al., 1990a,b; Winter et al., 1990). The
capsaicin/resiniferatoxin-evoked increase in the levels of
cyclic GMP in sensory neurons does not have any be sensory neuron responses to capsaicin and resinifera-
toxin (Dray et al., 1990a,b; Winter et al., 1990). The
capsaicin/resiniferatoxin-evoked increase in the levels of
cyclic GMP in sensory neurons does not have any bearin sensory neuron responses to capsaicin and resinifera-
toxin (Dray et al., 1990a,b; Winter et al., 1990). The
capsaicin/resiniferatoxin-evoked increase in the levels of
cyclic GMP in sensory neurons does not have any bearin toxin (Dray et al., 1990a,b; Winter et al., 1990). The capsaicin/resiniferatoxin-evoked increase in the levels of cyclic GMP in sensory neurons does not have any bearing on the capsaicin/resiniferatoxin-evoked ion fluxes t cyclic GMP in sensory neurons does not have any bearing
on the capsaicin/resiniferatoxin-evoked ion fluxes
through the cell membrane (Wood et al., 1989; Winter
et al., 1990).

cation channel is $Ca^{2+} > Mg^{2+} > K^+ > Na^+$ (Bevan and the stimulant effect of capsaicin (Zernig et al., 1984;
Szolcsányi, 1990). Thus, under physiological conditions Maggi et al., 1988a,c,e, 1989c,e, 1990b; Wood et al., 1988 capsaicin/resiniferatoxin-induced inward current while

K⁺ ions leave the cell (Wood et al., 1988; Bleakman et (Lou et al., 1991). Third, local anaesthetics and particu-

al., 1990; Dray et al., 1990d; Winter et al., 19 There are several lines of evidence indicating that the capsaicin-operated cation channel is distinct from voltage-dependent cation channels in the cell membrane. on the capsaicin/resiniferatoxin-evoked ion fluxer
through the cell membrane (Wood et al., 1989; Winter
et al., 1990).
There are several lines of evidence indicating that the
capsaicin-operated cation channel is distinct f through the cell membrane (Wood et al., 1989; Winter
et al., 1990).
There are several lines of evidence indicating that the
capsaicin-operated cation channel is distinct from volt
age-dependent cation channels in the cell et al., 1990).
There are several lines of evidence indicating that the
capsaicin-operated cation channel is distinct from volt-
age-dependent cation channels in the cell membrane.
First, the effect of capsaicin to release There are several lines of evidence indicating that the capsaicin-operated cation channel is distinct from voltage-dependent cation channels in the cell membran First, the effect of capsaicin to release peptides is neprev capsaicin-operated cation channel is distinct from volt-
age-dependent cation channels in the cell membrane.
First, the effect of capsaicin to release peptides is not
prevented by K⁺ depolarization of sensory nerve termi age-dependent cation channels in the cell membrane.
First, the effect of capsaicin to release peptides is not
prevented by K⁺ depolarization of sensory nerve termi-
nals (Donnerer and Amann, 1990). Second, blockers of
v First, the effect of capsaicin to release peptides is r
prevented by K^+ depolarization of sensory nerve tern
nals (Donnerer and Amann, 1990). Second, blockers
voltage-dependent Ca²⁺ channels of the T-, N- and
type (s prevented by K⁺ depolarization of sensory nerve terminals (Donnerer and Amann, 1990). Second, blockers of voltage-dependent Ca²⁺ channels of the T-, N- and L-
type (such as nickel ions, omega-conotoxin, and nifedi-
pin voltage-dependent Ca^{2+} channels of the T-, N- and L-
type (such as nickel ions, omega-conotoxin, and nifedi-
pine or verapamil, respectively) fail, in general, to inhibit voltage-dependent Ca²⁺ channels of the T-, N- and L-
type (such as nickel ions, omega-conotoxin, and nifedi-
pine or verapamil, respectively) fail, in general, to inhibit
the stimulant effect of capsaicin (Zernig et al., type (such as nickel ions, omega-conotoxin, and nife
pine or verapamil, respectively) fail, in general, to inhi
the stimulant effect of capsaicin (Zernig et al., 19
Maggi et al., 1988a,c,e, 1989c,e, 1990b; Wood et al., 19
 pine or verapamil, respectively) fail, in general, to inhibit
the stimulant effect of capsaicin (Zernig et al., 1984;
Maggi et al., 1988a,c,e, 1989c,e, 1990b; Wood et al., 1988;
Dray et al., 1990b). The effect of low capsa the stimulant effect of capsaicin (Zernig et al., 19
Maggi et al., 1988a,c,e, 1989c,e, 1990b; Wood et al., 19
Dray et al., 1990b). The effect of low capsaicin conc
trations, however, may be reduced by omega-conoto
(Lou et Maggi et al., 1988a,c,e, 1989c,e, 1990b; Wood et al., 1988;
Dray et al., 1990b). The effect of low capsaicin concentrations, however, may be reduced by omega-conotoxin
(Lou et al., 1991). Third, local anaesthetics and part Dray et al., 1990b). The effect of low capsaicin concentrations, however, may be reduced by omega-conotoxin (Lou et al., 1991). Third, local anaesthetics and particularly tetrodotoxin are without effect on capsaicin's loca trations, however, may be reduced by omega-conotoxin (Lou et al., 1991). Third, local anaesthetics and particularly tetrodotoxin are without effect on capsaicin's local depolarizing and excitatory actions on sensory nerve (Lou et al., 1991). Third, local anaesthetics and particularly tetrodotoxin are without effect on capsaicin's local
depolarizing and excitatory actions on sensory nerve
endings and axons (Jancsó et al., 1968; Gamse et al., depolarizing and excitatory actions on sensory nerve
endings and axons (Jancsó et al., 1968; Gamse et al.,
1979b; Saria et al., 1983a; Szolcsányi, 1983b, 1984b;
Hayes et al., 1984a; Hua et al., 1986; Marsh et al., 1987;
Sa depolarizing and excitatory actions on sensory nerve
endings and axons (Jancsó et al., 1968; Gamse et al.,
1979b; Saria et al., 1983a; Szolcsányi, 1983b, 1984b;
Hayes et al., 1984a; Hua et al., 1986; Marsh et al., 1987;
Sa endings and axons (Jancsó et al., 1968; Gamse et al., 1979b; Saria et al., 1983a; Szolcsányi, 1983b, 1984b; Hayes et al., 1984a; Hua et al., 1986; Marsh et al., 1987; Santicioli et al., 1987; Maggi et al., 1989c, 1990b). T 1979b; Saria et al., 1983a; Szolcsányi, 1983b, 1984b;
Hayes et al., 1984a; Hua et al., 1986; Marsh et al., 1987;
Santicioli et al., 1987; Maggi et al., 1989c, 1990b). This
latter finding indicates that fast voltage-depende Hayes et al., 1984a
Santicioli et al., 19
latter finding indic
channels are not i
the cell membrane
The capsaicin/r inticioli et al., 1987; Maggi et al., 1989c, 1990b). This
tter finding indicates that fast voltage-dependent Na⁺
annels are not involved in the action of capsaicin on
e cell membrane.
The capsaicin/resiniferatoxin-induce type (such as nickel ions, omega-conotoxin, and nifedi-
pine or verapamil, respectively) fail, in general, to inhibit
the stimulant effect of capsaicin (Zernig et al., 1984;
Maggi et al., 1988a,c,e, 1989c,e, 1990b); Wood

latter finding indicates that fast voltage-dependent Na⁺
channels are not involved in the action of capsaicin on
the cell membrane.
The capsaicin/resiniferatoxin-induced activation of a
nonselective cation conductance l channels are not involved in the action of capsaicin on
the cell membrane.
The capsaicin/resiniferatoxin-induced activation of a
nonselective cation conductance leads to a sustained
increase in the intracellular concentra the cell membrane.

The capsaicin/resiniferatoxin-induced activation of a

nonselective cation conductance leads to a sustained

increase in the intracellular concentration of free Ca²⁺

(Bleakman et al., 1990; Dray et The capsaicin/resiniferatoxin-induced activation of a
nonselective cation conductance leads to a sustained
increase in the intracellular concentration of free Ca²⁺
(Bleakman et al., 1990; Dray et al., 1990d) and to a ne nonselective cation conductance leads to a sustained
increase in the intracellular concentration of free Ca^{2+}
(Bleakman et al., 1990; Dray et al., 1990d) and to a net
uptake of ⁴⁵ Ca^{2+} into the cell (Wood et al., 1 increase in the intracellular concentration of free Ca^{2+}
(Bleakman et al., 1990; Dray et al., 1990d) and to a net
uptake of ${}^{45}Ca^{2+}$ into the cell (Wood et al., 1988, 1989;
Winter et al., 1990). This Ca^{2+} uptake (Bleakman et al., 1990; Dray et al., 1990d) and to a net uptake of ${}^{45}Ca^{2+}$ into the cell (Wood et al., 1988, 1989; Winter et al., 1990). This Ca^{2+} uptake is a specific response of B-type sensory neurons of the rat uptake of ${}^{45}Ca^{2+}$ into the cell (Wood et al., 1988, 1989;
Winter et al., 1990). This Ca^{2+} uptake is a specific
response of B-type sensory neurons of the rat and mouse
(and probably other mammalian species) which i response of B-type sensory neurons of the rat and mouse
(and probably other mammalian species) which is absent
in the vast majority of rat A-type sensory neurons, in rat
sympathetic neurons, Schwann cells and fibroblasts, (and probably other mammalian species) which is absent
in the vast majority of rat A-type sensory neurons, in rat
sympathetic neurons, Schwann cells and fibroblasts, in
neuronal cell lines, and in chick sensory neurons (W in the vast majority of rat A-type sensory neurons, in rat
sympathetic neurons, Schwann cells and fibroblasts, in
neuronal cell lines, and in chick sensory neurons (Wood
et al., 1988; Winter et al., 1990). The activity of sympathetic neurons, Schwann cells and fibroblasts,
neuronal cell lines, and in chick sensory neurons (We
et al., 1988; Winter et al., 1990). The activity of capsai
in causing an influx of calcium (EC_{50} 100 to 300 r
ag neuronal cell lines, and in chick sensory neurons (Wood
et al., 1988; Winter et al., 1990). The activity of capsaicin
in causing an influx of calcium (EC₅₀ 100 to 300 nM)
agrees very well with estimates of its potency in et al., 1988; Winter et al., 1990). The activity of capsaicin
in causing an influx of calcium (EC_{50} 100 to 300 nM)
agrees very well with estimates of its potency in depolar-
izing sensory neurons (Marsh et al., 1987), in causing an influx of calcium (EC_{50} 100 to 300 nM
agrees very well with estimates of its potency in depola
izing sensory neurons (Marsh et al., 1987), activatin
nociceptors (Dray et al., 1990b), and evoking peptic
re agrees very well with estimates of its potency in depolarizing sensory neurons (Marsh et al., 1987), activating nociceptors (Dray et al., 1990b), and evoking peptide release from sensory nerve terminals (Amann, 1990). Div

nociceptors (Dray et al., 1990b), and evoking peptide
release from sensory nerve terminals (Amann, 1990).
Divalent cations (order of potency: cadmium \gg nickel
 \gg cobalt $>$ barium $>$ strontium $>$ manganese $>$ magrelease from sensory nerve terminals (Amann, 1990).

Divalent cations (order of potency: cadmium \gg nickel
 \gg cobalt $>$ barium $>$ strontium $>$ manganese $>$ mag-

nesium) can inhibit the capsaicin-induced uptake o Divalent cations (order of potency: cadmium \gg nickel
 \gg cobalt $>$ barium $>$ strontium $>$ manganese $>$ mag-
nesium) can inhibit the capsaicin-induced uptake of
 $^{46}Ca^{2+}$ into sensory neurons (Wood et al., 1988; \Rightarrow cobalt $>$ barium $>$ strontium $>$ manganese $>$ magnesium) can inhibit the capsaicin-induced uptake of $^{45}Ca^{2+}$ into sensory neurons (Wood et al., 1988; Bleakman et al., 1990). These data, however, do not necess nesium) can inhibit the capsaicin-induced uptake of ${}^{45}Ca^{2+}$ into sensory neurons (Wood et al., 1988; Bleakman
et al., 1990). These data, however, do not necessarily
indicate that the capsaicin-operated cation channel ^{4o}Ca²⁺ into sensory neurons (Wood et al., 1988; Bleakman et al., 1990). These data, however, do not necessarily indicate that the capsaicin-operated cation channel is blocked as well. Thus, cadmium fails to prevent th et al., 1990). These data, however, do not necessarily indicate that the capsaicin-operated cation channel is blocked as well. Thus, cadmium fails to prevent the capsaicin-induced increase in free intracellular Ca²⁺, and

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

176
capsaicin-induced Ca²⁺ uptake arises from inhibition of action
intracellular Ca²⁺ sequestration or cellular Ca²⁺ extru- up 176
capsaicin-induced Ca²⁺ uptake arises from inhibition
intracellular Ca²⁺ sequestration or cellular Ca²⁺ extr
sion (Dray et al., 1990d). Inhibition of cation influx al 176

strategy increases the multiplet of the capasaicin-induced Ca^{2+} uptake arises from inhibition of acceptation

intracellular Ca^{2+} sequestration or cellular Ca^{2+} extru-

indication (Dray et al., 1990d). Inhibi capsaicin-induced Ca^{2+} uptake arises from inhibition of intracellular Ca^{2+} sequestration or cellular Ca^{2+} extration (Dray et al., 1990d). Inhibition of cation influx als is ruled out by the finding that capsaicin capsaicin-induced Ca²⁺ uptake arises from inhibition of intracellular Ca²⁺ sequestration or cellular Ca²⁺ extrusion (Dray et al., 1990d). Inhibition of cation influx also is ruled out by the finding that capsaicin-i intracellular Ca²⁺ sequestration or cellular Ca²⁺ extru-
sion (Dray et al., 1990d). Inhibition of cation influx also
is ruled out by the finding that capsaicin-induced depo-
ilarization and activation of sensory nerve sion (Dray et al., 1990d). Inhibition of cation influx also
is ruled out by the finding that capsaicin-induced depo-
larization and activation of sensory nerve endings is not
blocked by either cadmium (Marsh et al., 1987; is ruled out by the finding that capsaicin-induced de
larization and activation of sensory nerve endings is
blocked by either cadmium (Marsh et al., 1987; Dra
al., 1990b,d) or nickel (Maggi et al., 1988e). It may
be that larization and activation of sensory nerve endings is n
blocked by either cadmium (Marsh et al., 1987; Dray
al., 1990b,d) or nickel (Maggi et al., 1988e). It may we
be that some of the divalent ions that block the capsaici blocked by either cadmium (Marsh et al., 1987; Dray et (V
al., 1990b,d) or nickel (Maggi et al., 1988e). It may well ce
be that some of the divalent ions that block the capsaicin-
cinduced Ca^{2+} uptake do so by entering al., 1990b,d) or nickel (Maggi et al., 1988e). It may well
be that some of the divalent ions that block the capsaicin-
induced Ca^{2+} uptake do so by entering the cells them-
selves instead of Ca^{2+} . Thus, cobalt appea be that some of the divalent ions that block the capsainduced Ca^{2+} uptake do so by entering the cells the selves instead of Ca^{2+} . Thus, cobalt appears to be tap via the capsaicin-operated cation channel, which plain induced Ca^{2+} uptake do so by entering the cells themselves instead of Ca^{2+} . Thus, cobalt appears to be taken up via the capsaicin-operated cation channel, which explains why cobalt staining is selective for capsaici selves instead of Ca²⁺. Thus, cobalt appears to be taken
up via the capsaicin-operated cation channel, which ex-
plains why cobalt staining is selective for capsaicin-
sensitive B-type sensory neurons (Winter, 1987; Wint up via the capsaicin-operated cation channel, which
plains why cobalt staining is selective for capsai
sensitive B-type sensory neurons (Winter, 1987; Wii
et al., 1988, 1990; Wood et al., 1988). In addition, of
mium itself plains why cobalt staining is selective for capsaicin-
sensitive B-type sensory neurons (Winter, 1987; Winter er
et al., 1988, 1990; Wood et al., 1988). In addition, cad-
mium itself has been reported to display some capsa et al., 1988, 1990; Wood et al., 1988). In addition, cad-
mium itself has been reported to display some capsaicin-
like stimulant activity on capsaicin-sensitive sensory
neurons (Patacchini et al., 1988).
The stimulant eff al., 1988, 1990; Wood et al., 1988). In addition, cad-
ium itself has been reported to display some capsaicin-
re stimulant activity on capsaicin-sensitive sensory
urons (Patacchini et al., 1988).
The stimulant effect of c

like stimulant activity on capsaicin-sensitive sensory
neurons (Patacchini et al., 1988).
The stimulant effect of capsaicin on sensory neurons
in vivo displays a high degree of temperature dependency.
The capsaicin-induced like stimulant activity on capsaicin-sensitive sensory do
neurons (Patacchini et al., 1988). the
The stimulant effect of capsaicin on sensory neurons (V
in vivo displays a high degree of temperature dependency. pl
The caps neurons (Patacchini et al., 1988). the stimulant effect of capsaicin on sensory neurons (V
in vivo displays a high degree of temperature dependency. ph
The capsaicin-induced burning sensation on the human in
tongue and ski The stimulant effect of capsaicin on sensory neurons (Wood et
in vivo displays a high degree of temperature dependency. phosphor
The capsaicin-induced burning sensation on the human nitropher
tongue and skin is inhibited o in vivo displays a high degree of temperature dependency.
The capsaicin-induced burning sensation on the human
tongue and skin is inhibited or even abolished by cooling
of the respective tissue to 24°C (Green, 1986) and 20 The capsaicin-induced burning sensation on the human
tongue and skin is inhibited or even abolished by cooling
of the respective tissue to 24°C (Green, 1986) and 20°C
(Szolcsányi, 1977), whereas warming augments burning.
C tongue and skin is inhibited or even abolished by cooling cius
of the respective tissue to 24° C (Green, 1986) and 20° C rel:
(Szolcsányi, 1977), whereas warming augments burning. al.,
Capsaicin-induced action pote of the respective tissue to 24°C (Green, 1986) and 20°C re (Szolcsányi, 1977), whereas warming augments burning. all Capsaicin-induced action potential activity in afferent wherve fibers is likewise inhibi (Szolcsányi, 1977), whereas warming augments burning.
Capsaicin-induced action potential activity in afferent
nerve fibers is likewise inhibited by cooling of the skin
(Szolcsányi, 1977). Thus, the temperature dependency o Capsaicin-induced action potential activity in afferent
nerve fibers is likewise inhibited by cooling of the skin
(Szolcsányi, 1977). Thus, the temperature dependency of
capsaicin's effect seems to be related to a peripher nerve fibers is likewise inhibited by cooling of the skin (Szolcsányi, 1977). Thus, the temperature dependency of capsaicin's effect seems to be related to a peripheral process occurring at, or close to, the sensory recep (Szolcsányi, 1977). Thus, the temperature dependency of b.
capsaicin's effect seems to be related to a peripheral (1
process occurring at, or close to, the sensory receptors m
(Szolcsányi, 1977, 1990). However, the capsai capsaicin's effect seems to be related to a peripheral process occurring at, or close to, the sensory receptors (Szolcsányi, 1977, 1990). However, the capsaicin-evoked uptake of Ca^{2+} into rat cultured dorsal root gangl process occurring at, or close to, the sensory receptors missues (Szolcsányi, 1977, 1990). However, the capsaicin-evoked supptake of Ca^{2+} into rat cultured dorsal root ganglion cells ler is not much different at 37° (Szolcsányi, 1977, 1990). However, the capsaicin-evoked uptake of Ca²⁺ into rat cultured dorsal root ganglion cells is not much different at 37° and 20°C (Wood et al., 1988), although peptide release from sensory nerve uptake of Ca²⁺ into rat cultured dorsal root ganglion cells
is not much different at 37° and 20° C (Wood et al., 1988),
although peptide release from sensory nerve terminals is
reduced at 18° C (Amann, 1990 is not much different at 37° and 20° C (Wood et al., 1988), 19
although peptide release from sensory nerve terminals is al.
reduced at 18° C (Amann, 1990). It would seem, therefore, al.
that the opening of ca although peptide release from sensory nerve terminals is reduced at 18°C (Amann, 1990). It would seem, therefore, that the opening of capsaicin-operated cation channels cannot blocked by cooling but that in some way the co reduced at 18°C (Amann, 1990). It would seem, therefore,
that the opening of capsaicin-operated cation channels
is not blocked by cooling but that in some way the
initiation of propagated action potentials is prevented
and that the opening of capsaicin-operated cation channels or relation to blocked by cooling but that in some way the on initiation of propagated action potentials is prevented thought and peptide release is reduced. This poor is not blocked by cool
initiation of propagated
and peptide release is r
aspect of capsaicin's act
be investigated further.
Taken together, the ε itiation of propagated action potentials is prevented
d peptide release is reduced. This poorly understood
pect of capsaicin's action on sensory neurons needs to
investigated further.
Taken together, the available evidence

and peptide release is reduced. This poorly understood
aspect of capsaicin's action on sensory neurons needs to
be investigated further.
Taken together, the available evidence indicates that
capsaicin stimulates sensory ne aspect of capsaicin's action on sensory neurons needs to
be investigated further.
Taken together, the available evidence indicates that
capsaicin stimulates sensory neurons by an interaction
with a specific recognition sit be investigated further.
Taken together, the available evidence indicates that
capsaicin stimulates sensory neurons by an interaction
with a specific recognition site on their cell membrane,
which in turn leads to activati Taken together, the available evidence indicates the capsaicin stimulates sensory neurons by an interactivith a specific recognition site on their cell membra which in turn leads to activation of a conductance the nonselec capsaicin stimulates sensory neurons by an interaction at a specific recognition site on their cell membre which in turn leads to activation of a conductance is nonselective for cations and different from volt dependent i with a specific recognition site on their cell membrane, which in turn leads to activation of a conductance that is nonselective for cations and different from voltage-dependent ion channels. Capsaicin-induced depolarizat which in turn leads to activation of a conductance that
is nonselective for cations and different from voltage-
dependent ion channels. Capsaicin-induced depolariza-
tion and Ca^{2+} influx through this mechanism, however dependent ion channels. Capsaicin-induced depolariza-
dependent ion channels. Capsaicin-induced depolariza-
exerts secondary effects on voltage-dependent and Ca^{2+} -
eviactivated membrane currents of sensory neurons. The tion and Ca²⁺ influx through this mechanism, however exerts secondary effects on voltage-dependent and Ca² activated membrane currents of sensory neurons. There are in the intracellular concentration of Ca²⁺ alleads exerts secondary effects of
activated membrane cur
increase in the intracellu
leads to activation of intr
mitter (peptide) release.
b. SECONDARY EFFECT tivated membrane currents of sensory neurons. Therease in the intracellular concentration of Ca²⁺ also to activation of intracellular enzymes and to tran itter (peptide) release.
b. SECONDARY EFFECTS. **i. Intracellular i**

increase in the intracellular concentration of Ca^{2+} alleads to activation of intracellular enzymes and to tran mitter (peptide) release.

b. SECONDARY EFFECTS. **i. Intracellular ion accumulation.** The capsaicin/resinif ing of a nonselective cation channel leads to the net

mulation. The capsaicin/resiniferatoxin-induced open-

ing of a nonselective cation channel leads to the net

uptake of Ca^{2+} and Na^+ (Wood et al., 1988; Winter e b. SECONDARY EFFECTS. **i. Intracellular ion accumulation.** The capsaicin/resiniferatoxin-induced opening of a nonselective cation channel leads to the net uptake of Ca^{2+} and Na⁺ (Wood et al., 1988; Winter et al., 199

accumulation in sensory neurons exposed to capsaicin is ER
accumulation in sensory neurons exposed to capsaicin is
unique in that no other stimuli have yet been identified
to cause a comparable accumulation. Quantitatively, it ER
accumulation in sensory neurons exposed to capsaicin is
unique in that no other stimuli have yet been identified
to cause a comparable accumulation. Quantitatively, it
is estimated that intracellular concentrations of u accumulation in sensory neurons exposed to capsaicin is
unique in that no other stimuli have yet been identified
to cause a comparable accumulation. Quantitatively, it
is estimated that intracellular concentrations of up accumulation in sensory neurons exposed to capsaich is
unique in that no other stimuli have yet been identified
to cause a comparable accumulation. Quantitatively, it
is estimated that intracellular concentrations of up t w cause a comparable accumulation. Quantitatively, it
is estimated that intracellular concentrations of up to 12
mM calcium can be reached in response to 1μ M capsaicin
(Wood et al., 1988). Calcium is thus concentrated mM calcium can be reached in response to 1 μ M capsaicin (Wood et al., 1988). Calcium is thus concentrated in the cell but, because the intracellular concentration of free Ca²⁺ does not exceed 0.6 to 0.9 μ M (Bleakm mM calcium can be reached in response to 1μ M capsaicin (Wood et al., 1988). Calcium is thus concentrated in the cell but, because the intracellular concentration of free Ca²⁺ does not exceed 0.6 to 0.9 μ M (Bleakma (Wood et al., 1988). Calcium is thus concentrated in the cell but, because the intracellular concentration of free Ca²⁺ does not exceed 0.6 to 0.9 μ M (Bleakman et al., 1990; Dray et al., 1990d), it follows that influ Ca²⁺ does not exceed 0.6 to 0.9 μ M (Bleakman et al., 1990; Dray et al., 1990d), it follows that influxing Ca²⁺ is sequestered by intracellular organelles. There are some data to indicate that the major part of Ca² 1990; Dray et al., 1990d), it follows that influxing Ca^{2+} is sequestered by intracellular organelles. There are some data to indicate that the major part of Ca^{2+} entering the cell is taken up by mitochondria rather is sequestered by intracellular organelles. There are some data to indicate that the major part of Ca^{2+} entering the cell is taken up by mitochondria rather than by the endoplasmic reticulum and that this process requi data to indicate that the major part of Ca^{2+} entering the cell is taken up by mitochondria rather than by the endoplasmic reticulum and that this process requires an oxidative energy supply (Wood et al., 1988). Thus, d cell is taken up by mitochondria rather than
endoplasmic reticulum and that this process requ
oxidative energy supply (Wood et al., 1988). Thus
known to interfere with the calcium binding of
doplasmic reticulum (e.g., caff endoplasmic reticulum and that this process requires an oxidative energy supply (Wood et al., 1988). Thus, drugs known to interfere with the calcium binding of the endoplasmic reticulum (e.g., caffeine, isobutylmethylxant Modular et al., 1988). In contrast, 1988). In the mitochondria binding of the endoplasmic reticulum (e.g., caffeine, isobutylmethylxanthine) do not inhibit capsaicin-induced uptake of calcium (Wood et al., 1988). In contra doplasmic reticulum (e.g., caffeine, isobutylmethylxanthine) do not inhibit capsaicin-induced uptake of calcium
(Wood et al., 1988). In contrast, uncoupling of oxidative
phosphorylation in the mitochondria by cyanide or di thine) do not inhibit capsaicin-induced uptake of calcium
(Wood et al., 1988). In contrast, uncoupling of oxidative
phosphorylation in the mitochondria by cyanide or d
nitrophenol inhibits the capsaicin-induced uptake of c (wood et al., 1566). In contrast, uncouping of oxidative
phosphorylation in the mitochondria by cyanide or di-
nitrophenol inhibits the capsaicin-induced uptake of cal-
cium (Wood et al., 1988) and release of calcitonin ge phosphorylation in the infoculoration by cyantie or di-
nitrophenol inhibits the capsaicin-induced uptake of cal-
cium (Wood et al., 1988) and release of calcitonin gene-
related peptide from sensory nerve endings, however cium (Wood et al., 1988) and release of calcitonin gene-
related peptide from sensory nerve endings (Amann et
al., 1990c). It is not clear from these findings, however,
whether the process of calcium accumulation is inhibi blockade of calcium sensory herve endings (Amami et al., 1990c). It is not clear from these findings, however, whether the process of calcium accumulation is inhibited because of energy deprivation of the cell or because o whether the process of calcium accumulation is inhibited
because of energy deprivation of the cell or because of
blockade of calcium sequestration in the mitochondria
(R. Amann, personal communication). Nevertheless, a
mit because of energy deprivation of the cell or because of
blockade of calcium sequestration in the mitochondria
(R. Amann, personal communication). Nevertheless, a
mitochondrial site of calcium accumulation is strongly
sugge blockade of calcium sequestration in the mitochondria (R. Amann, personal communication). Nevertheless, a mitochondrial site of calcium accumulation is strongly suggested by electron microscopical observations of swollen m (R. Amann, personal communication). Nevertheless, a
mitochondrial site of calcium accumulation is strongly
suggested by electron microscopical observations of swol-
len mitochondria (Joó et al., 1969; Szolcsányi et al., 19 mitochondrial site of calcium accumulation is strongly
suggested by electron microscopical observations of swol-
len mitochondria (Joó et al., 1969; Szolcsányi et al., 1975,
1990; Chiba et al., 1986; Marsh et al., 1987; Sz suggested by electron microscopical observations of swol-
len mitochondria (Joó et al., 1969; Szolcsányi et al., 1975,
1990; Chiba et al., 1986; Marsh et al., 1987; Szallasi et
al., 1989) and by mitochondrial Ca²⁺ deposi len mitochondria (Joó et al., 1969; Szolcsányi et al., 1975,
1990; Chiba et al., 1986; Marsh et al., 1987; Szallasi et
al., 1989) and by mitochondrial Ca²⁺ deposits (Jancsó et
al., 1978, 1984) in sensory neurons exposed 1990; Chiba et al., 1986; Marsh et al., 1987; Szallasi et al., 1989) and by mitochondrial Ca^{2+} deposits (Jancsó et al., 1978, 1984) in sensory neurons exposed to capsaicin or resiniferatoxin. The inhibitory effect of r al., 1989) and by mitochondrial Ca²⁺ deposits (Jancsó et al., 1978, 1984) in sensory neurons exposed to capsaicin or resiniferatoxin. The inhibitory effect of ruthenium red on capsaicin-induced uptake of calcium, previou al., 1978, 1984) in sensory neurons exposed to capsaicin
or resiniferatoxin. The inhibitory effect of ruthenium red
on capsaicin-induced uptake of calcium, previously
thought to occur by interference at a mitochondrial lev or resiniferatoxin. The inhibitory effect of ruthenium red
on capsaicin-induced uptake of calcium, previously
thought to occur by interference at a mitochondrial level
(Wood et al., 1988), is now thought to result from an
 on capsaicin-induced uptake of calcium, previously
thought to occur by interference at a mitochondrial level
(Wood et al., 1988), is now thought to result from an
action on the cell membrane (Chahl, 1989; Bleakman et
al., thought to occur by interference at a mitochondrial level (Wood et al., 1988), is now thought to result from an action on the cell membrane (Chahl, 1989; Bleakman et al., 1990; Dray et al. 1990d). The inhibitory effects of (Wood et al., 1988), is now thought to result from an action on the cell membrane (Chahl, 1989; Bleakman et al., 1990; Dray et al. 1990d). The inhibitory effects of cinnarizine and trifluoperazine on the capsaicin-induced action on the cell membrane (Chahl, 1989; Bleakman et al., 1990; Dray et al. 1990d). The inhibitory effects of cinnarizine and trifluoperazine on the capsaicin-induced accumulation of calcium are not understood in terms of al., 1990; Dray et al. 1990d). The inhibitory effects
cinnarizine and trifluoperazine on the capsaicin-indu
accumulation of calcium are not understood in terms
site and mechanism of action (Wood et al., 1988). T
fluoperazi cinnarizine and trifluoperazine on the ca
accumulation of calcium are not underst
site and mechanism of action (Wood et
fluoperazine does not block capsaicin-ir
tion of nociceptors (Dray et al., 1990b).
Capsaicin also caus cumulation of calcium are not understood in terms of
ce and mechanism of action (Wood et al., 1988). Tri-
ioperazine does not block capsaicin-induced stimula-
in of nociceptors (Dray et al., 1990b).
Capsaicin also causes a site and mechanism of action (Wood et al., 1988). Tri-
fluoperazine does not block capsaicin-induced stimula-
tion of nociceptors (Dray et al., 1990b).
Capsaicin also causes an influx of Na⁺ in cultured
sensory neurons (

fluoperazine does not block capsaicin-induced stimultion of nociceptors (Dray et al., 1990b).
Capsaicin also causes an influx of Na⁺ in culture
sensory neurons (Wood et al., 1988). There is indire
evidence that this ion, tion of nociceptors (Dray et al., 1990b).
Capsaicin also causes an influx of $Na⁺$ in cultured
sensory neurons (Wood et al., 1988). There is indirect
evidence that this ion, as it accumulates intracellularly,
is follo Capsaicin also causes an influx of $Na⁺$
sensory neurons (Wood et al., 1988). There
evidence that this ion, as it accumulates inti
is followed passively by Cl⁻, which results in a
of NaCl (Hogan, 1983; Winter et al. nsory neurons (Wood et al., 1988). There is indi
idence that this ion, as it accumulates intracellula
followed passively by Cl⁻, which results in a net up
NaCl (Hogan, 1983; Winter et al., 1990).
ii. Effects on voltageevidence that this ion, as it accumulates intracellula
is followed passively by Cl⁻, which results in a net upt
of NaCl (Hogan, 1983; Winter et al., 1990).
ii. Effects on voltage-dependent and calcit
activated membrane

is followed passively by Cl⁻, which results in a net uptake
of NaCl (Hogan, 1983; Winter et al., 1990).
 ii. Effects on voltage-dependent and calcium-
 activated membrane currents. Capsaicin administra-

tion can le of NaCl (Hogan, 1983; Winter et al., 1990).
 ii. Effects on voltage-dependent and calcium-
 activated membrane currents. Capsaicin administra-

tion can lead to activation of voltage-dependent Ca²⁺

channels in sens ii. Effects on voltage-dependent and calcius
activated membrane currents. Capsaicin administ
tion can lead to activation of voltage-dependent C.
channels in sensory neurons (Petersen et al., 1989), l
from ion flux studies activated membrane currents. Capsaicin administra-
tion can lead to activation of voltage-dependent Ca^{2+}
channels in sensory neurons (Petersen et al., 1989), but
from ion flux studies it appears as if this occurs secon tion can lead to activation of voltage-dependent Ca²⁺
channels in sensory neurons (Petersen et al., 1989), but
from ion flux studies it appears as if this occurs second-
arily to the capsaicin-induced depolarization thro

1990b).

(Wood et al., 1988, 1989). Those somata in the dorsal root ganglia of the guinea pig which respond to capsaicin

and intracellular perfusion conditions, capsaicin $(30 \mu M)$
activates selectively the fast-inactivating channel, which
may correspond to a T-type Ca²⁺ channel because it is
blocked by nickel ions (Petersen et al., 1989)

may correspond to a T-type Ca^{2+} channel because it is blocked by nickel ions (Petersen et al., 1989). The action of capsaicin manifests itself in acceleration of channel activation and inactivation and in an increase i

of capsaicin manifests itself in acceleration of channel activation and inactivation and in an increase in the Ca^{2+} current. In cultured rat dorsal root ganglion neurons, however, capsaicin was found to be unable to ac tivation and inactivation and in an increase in the Ca²⁺
rrent. In cultured rat dorsal root ganglion neurons,
wever, capsaicin was found to be unable to activate
ltage-dependent Ca²⁺ channels (Docherty et al., 1991).

activate a Ca²⁺-dependent K⁺ conductance, a contention
that is supported by both electrophysiological (Marsh et
al., 1987; Bleakman et al., 1990) and ion flux (Wood et
al., 1988; Winter et al., 1990) studies. Although

al., 1988; Winter et al., 1990) studies. Although the capsaicin-operated cation channel per se will allow K^+ to leave the cell (Bevan and Szolcsányi, 1990), it appears as if most of the capsaicin/resiniferatoxin-evoked

capsaicin-operated cation channel per se will allow K^+
to leave the cell (Bevan and Szolcsányi, 1990), it appears
as if most of the capsaicin/resiniferatoxin-evoked in-
crease in the efflux of K^+ (measured by the ef to leave the cell (Bevan and Szolcsányi, 1990), it appears
as if most of the capsaicin/resiniferatoxin-evoked in-
crease in the efflux of K^+ (measured by the efflux of
 $^{86}\text{Rb}^+$) reflects a Ca²⁺-activated K^+ o

crease in the efflux of K^+ (measured by the efflux of ${}^{86}Rb^+$) reflects a Ca²⁺-activated K^+ outward current, because it is inhibited in the absence of extracellular Ca²⁺ (Wood et al., 1988; Winter et al., 19

 Ca^{2+} (Wood et al., 1988; Winter et al., 1990). Blockade of this K⁺ outward current by removal of extracellular Ca^{2+} has been proposed to account for the facilitatory effect of Ca^{2+} removal on capsaicin's excita

Ca²⁺ has been proposed to account for the facilitatory effect of Ca²⁺ removal on capsaicin's excitatory effect on sensory neurons (Amann et al., 1989a). The argument goes that in the absence of extracellular Ca²⁺ ca

sensory neurons (Amann et al., 1989a). The argument
goes that in the absence of extracellular Ca^{2+} capsaicin
can still activate an inward current carried by Na⁺ but,
because of the absence of Ca^{2+} entry, the K⁺ goes that in the absence of extracellular Ca^{2+} capsaicin
can still activate an inward current carried by Na⁺ but,
because of the absence of Ca^{2+} entry, the K⁺ outward
current will be inhibited. Consequently, the

because of the absence of Ca^{2+} entry, the K⁺ outward current will be inhibited. Consequently, the inward current is enhanced because it is not cut short by the K⁺ outward current and depolarization of sensory neuro

rent is enhanced because it is not cut short by the K⁺
outward current and depolarization of sensory neurons
is augmented (Amann et al., 1989a). An alternative ex-
planation considers that Ca²⁺ ions normally impede th

is augmented (Amann et al., 1989a). An alternative ex-
planation considers that Ca^{2+} ions normally impede the
capsaicin-evoked passage of Na^{+} ions (Forbes and Bevan,
1988). If so, removal of external Ca^{2+} will fa

depolarization of sensory nerve endings (Dray et al., 1990b).
Second, capsaicin-evoked influx of Ca^{2+} leads to inhi-
bition of voltage-dependent Ca^{2+} channels (Bleakman et

bition of voltage-dependent Ca²⁺ channels (Bleakmar
al., 1990; Docherty et al., 1991). This effect of capsai
on cultured dorsal root ganglion cells, which is extrem
long lasting (>1 h), is seen only in neurons that
depo

on cultured dorsal root ganglion cells, which is extremely
long lasting $(>1 \text{ h})$, is seen only in neurons that are
depolarized by the drug (Docherty et al., 1991). Replace-
ment of Ca^{2+} by Mg^{2+} or Ba^{2+} either long lasting $(>1 \text{ h})$, is seen only in neurons that are
depolarized by the drug (Docherty et al., 1991). Replace-
ment of Ca^{2+} by Mg^{2+} or Ba^{2+} either strongly reduces
(Bleakman et al., 1990) or abolishes (Doch

(Wood et al., 1988, 1989). Those somata in the root ganglia of the guinea pig which respond to cap (about 50% of all somata) exhibit both fast- and inactivating Ca^{2+} channels, whereas the capsaicinsitive neurons displa

root ganglia of the guinea pig which respond to capsaicin cin depends on a substantial increase in the intracellular (about 50% of all somata) exhibit both fast- and slow- Ca^{2+} concentration (Bleakman et al., 1990; Doc (Wood et al., 1988, 1989). Those somata in the dorsal Ca³ root ganglia of the guinea pig which respond to capsaicin cin (about 50% of all somata) exhibit both fast- and slow-Ca³ inactivating Ca²⁺ channels, whereas t root ganglia of the guinea pig which respond to capsaicin circle (about 50% of all somata) exhibit both fast- and slow-
inactivating Ca²⁺ channels, whereas the capsaicin-insen-
sitive neurons display slow-inactivating c (about 50% of all somata) exhibit both fast- and slow-
inactivating Ca²⁺ channels, whereas the capsaicin-insensitive neurons display slow-inactivating currents only
(Petersen et al., 1989). As recorded under voltage cla sitive neurons display slow-inactivating currents only rents may be inhibited to a minor degree by the capsai-
(Petersen et al., 1989). As recorded under voltage clamp cin-induced activation of an outward current and/or b sitive neurons display slow-inactivating currents only respond (Petersen et al., 1989). As recorded under voltage clamp circular perfusion conditions, capsaicin $(30 \mu M)$ a sactivates selectively the fast-inactivating cha (Petersen et al., 1989). As recorded under voltage clamp cin and intracellular perfusion conditions, capsaicin $(30 \mu M)$ a in activates selectively the fast-inactivating channel, which al. may correspond to a T-type Ca²⁺ activates selectively the fast-inactivating channel, which may correspond to a T-type Ca^{2+} channel because it is blocked by nickel ions (Petersen et al., 1989). The action of capsaicin manifests itself in acceleration CIN
Ca²⁺ currents, which indicates that this effect of caps
cin depends on a substantial increase in the intracellu cm 177
Ca²⁺ currents, which indicates that this effect of capsai-
cin depends on a substantial increase in the intracellular
Ca²⁺ concentration (Bleakman et al., 1990; Docherty et 177
Ca²⁺ currents, which indicates that this effect of capsai-
cin depends on a substantial increase in the intracellular
Ca²⁺ concentration (Bleakman et al., 1990; Docherty et
al., 1991). In addition, voltage-gated C Ca^{2+} currents, which indicates that this effect of capsai-
cin depends on a substantial increase in the intracellular
 Ca^{2+} concentration (Bleakman et al., 1990; Docherty et
al., 1991). In addition, voltage-gated $Ca^{$ Ca^{2+} currents, which indicates that this effect of caps
cin depends on a substantial increase in the intracellu
 Ca^{2+} concentration (Bleakman et al., 1990; Docherty
al., 1991). In addition, voltage-gated Ca^{2+} inwa cin depends on a substantial increase in the intracellular Ca^{2+} concentration (Bleakman et al., 1990; Docherty et al., 1991). In addition, voltage-gated Ca^{2+} inward currents may be inhibited to a minor degree by the Ca²⁺ concentration (Bleakman et al., 1990; Docherty et al., 1991). In addition, voltage-gated Ca²⁺ inward currents may be inhibited to a minor degree by the capsaicin-induced activation of an outward current and/or by al., 1991). l
rents may l
cin-induced
a small dire
al., 1990).
iii. Pept nts may be inhibited to a minor degree by the capsai-
n-induced activation of an outward current and/or by
small direct blocking effect of the drug (Bleakman et
, 1990).
iii. Peptide release. Another consequence of the
p

blocked by nickel ions (Petersen et al., 1989). The action of capsaicin manifests itself in acceleration of channel functivation and inactivation and in an increase in the Ca^{2+} reurrent. In cultured rat dorsal root gan however, capsaicin was found to be unable to activate duced release of neuropeptides from the central and voltage-dependent Ca^{2+} channels (Docherty et al., 1991). peripheral endings of sensory neurons is inhibited by T however, capsaicin was found to be unable to activate du
voltage-dependent Ca^{2+} channels (Docherty et al., 1991). pe
The capsaicin/resiniferatoxin-induced influx of Ca^{2+} res
appears to have at least two secondary ef voltage-dependent Ca²⁺ channels (Docherty et al., 1991). peri

The capsaicin/resiniferatoxin-induced influx of Ca²⁺ rem

appears to have at least two secondary effects on Ca²⁺- iaul

dependent ion channels in the ce The capsaicin/resiniferatoxin-induced influx of Ca^{2+}
appears to have at least two secondary effects on Ca^{2+} -
dependent ion channels in the cell membrane. First, the
increase in the intracellular Ca^{2+} concentratio appears to have at least two secondary effects on Ca^{2+} -
dependent ion channels in the cell membrane. First, the
increase in the intracellular Ca^{2+} concentration seems to
activate a Ca^{2+} -dependent K^+ conductanc dependent ion channels in the cell membrane. First, the
increase in the intracellular Ca^{2+} concentration seems to
activate a Ca^{2+} -dependent K^+ conductance, a contention
that is supported by both electrophysiologi increase in the intracellular Ca^{2+} concentration seems to
activate a Ca^{2+} -dependent K^+ conductance, a contention the
that is supported by both electrophysiological (Marsh et fie
al., 1987; Bleakman et al., 1990) that is supported by both electrophysiological (Marsh et al., 1987; Bleakman et al., 1990) and ion flux (Wood et al., 1988; Winter et al., 1990) studies. Although the capsaicin-operated cation channel per se will allow K⁺ al., 1988; Winter et al., 1990) studies. Although the 19
capsaicin-operated cation channel per se will allow K⁺ no
to leave the cell (Bevan and Szolcsányi, 1990), it appears 19
as if most of the capsaicin/resiniferatoxi as if most of the capsaicin/resiniferatoxin-evoked in-
crease in the efflux of K^+ (measured by the efflux of
⁸⁶Rb⁺) reflects a Ca²⁺-activated K^+ outward current,
because it is inhibited in the absence of extra ²⁶Rb⁺) reflects a Ca²⁺-activated K⁺ outward current,
because it is inhibited in the absence of extracellular
Ca²⁺ (Wood et al., 1988; Winter et al., 1990). Blockade
of this K⁺ outward current by removal of ext because it is inhibited in the absence of extracellular introval Ca^{2+} (Wood et al., 1988; Winter et al., 1990). Blockade uptof this K^+ outward current by removal of extracellular pro Ca^{2+} has been proposed to acco of this K^+ outward current by removal of extracellular p Ca^{2+} has been proposed to account for the facilitatory lueffect of Ca^{2+} removal on capsaicin's excitatory effect on fisensory neurons (Amann et al., 1989a) effect of Ca^{2+} removal on capsaicin's excitatory effect on fremsory neurons (Amann et al., 1989a). The argument the goes that in the absence of extracellular Ca^{2+} capsaicin decause of the absence of Ca^{2+} entry, t can still activate an inward current carried by Na⁺ but,
because of the absence of Ca^{2+} entry, the K⁺ outward
current will be inhibited. Consequently, the inward cur-
rent is enhanced because it is not cut short by cin-induced activation of an outward current and/or by
a small direct blocking effect of the drug (Bleakman et
al., 1990).
iii. Peptide release. Another consequence of the
capsaicin-induced entry of Ca²⁺ is the release a small direct blocking effect of the drug (Bleakman et al., 1990).
 iii. Peptide release. Another consequence of the capsaicin-induced entry of Ca^{2+} is the release of peptides from sensory nerve endings. Exocytotic al., 1990).
 iii. Peptide release. Another consequence of the

capsaicin-induced entry of Ca^{2+} is the release of peptides

from sensory nerve endings. Exocytotic release of neu-

rotransmitter substances is a process iii. Peptide release. Another consequence of capsaicin-induced entry of Ca^{2+} is the release of pep from sensory nerve endings. Exocytotic release of rotransmitter substances is a process that depends of influx of extra capsaicin-induced entry of Ca^{2+} is the release of peptides
from sensory nerve endings. Exocytotic release of neu-
rotransmitter substances is a process that depends on an
influx of extracellular Ca^{2+} . Accordingly, c from sensory nerve endings. Exocytotic release of neu-
rotransmitter substances is a process that depends on an
influx of extracellular Ca^{2+} . Accordingly, capsaicin-in-
duced release of neuropeptides from the central a rotransmitter substances is a process that depends on a influx of extracellular Ca^{2+} . Accordingly, capsaicin-induced release of neuropeptides from the central are peripheral endings of sensory neurons is inhibited lare influx of extracellular Ca^{2+} . Accordingly, capsaicin-in-
duced release of neuropeptides from the central and
peripheral endings of sensory neurons is inhibited by
removal of extracellular Ca^{2+} (Gamse et al., 1979b; duced release of neuropeptides from the central and
peripheral endings of sensory neurons is inhibited by
removal of extracellular Ca²⁺ (Gamse et al., 1979b; Thér-
iault et al., 1979; Yanagisawa et al., 1980; Helke et al peripheral endings of sensory neurons is inhibited by
removal of extracellular Ca²⁺ (Gamse et al., 1979b; Thér-
iault et al., 1979; Yanagisawa et al., 1980; Helke et al.,
1981b; Hua et al., 1986; Maggi et al., 1988d, 198 removal of extracellular Ca²⁺ (Gamse et al., 1979b; Thériault et al., 1979; Yanagisawa et al., 1980; Helke et al., 1981b; Hua et al., 1986; Maggi et al., 1988d, 1989e; Amann et al., 1989a; Amann, 1990). However, whereas iault et al., 1979; Yanagisawa et al., 1980; Helke et
1981b; Hua et al., 1986; Maggi et al., 1988d, 198
Amann et al., 1989a; Amann, 1990). However, wher
the peptide release that occurs in response to electri
field stimulat Amann et al., 1989a; Amann, 1990). However, whereas
the peptide release that occurs in response to electrical
field stimulation is prevented by blockers of voltage-
dependent Ca^{2+} channels (Holz et al., 1988; Maggi et not blocked by Ca^{2+} channel inhibitors (Maggi et al., the peptide release that occurs in response to electrical
field stimulation is prevented by blockers of voltage-
dependent Ca²⁺ channels (Holz et al., 1988; Maggi et al.,
1989c, 1990b), peptide release induced by capsai field stimulation is prevented by blockers of voltage-
dependent Ca²⁺ channels (Holz et al., 1988; Maggi et al.,
1989c, 1990b), peptide release induced by capsaicin is
not blocked by Ca²⁺ channel inhibitors (Maggi et dependent Ca²⁺ channels (Holz et al., 1988; Maggi et 1989c, 1990b), peptide release induced by capsaicin not blocked by Ca²⁺ channel inhibitors (Maggi et 1988c,e, 1989e) or by K⁺ depolarization of the neterminals (D 1989c, 1990b), peptide release induced by capsaicinnot blocked by Ca^{2+} channel inhibitors (Maggi et 1988c,e, 1989e) or by K^+ depolarization of the numinals (Donnerer and Amann, 1990). This obsetion indicates that Ca not blocked by Ca^{2+} channel inhibitors (Maggi et al., 1988c,e, 1989e) or by K^+ depolarization of the nerve terminals (Donnerer and Amann, 1990). This observation indicates that Ca^{2+} entry through the capsaicinope 1988c,e, 1989e) or by K^+ depolarization of the nerve
terminals (Donnerer and Amann, 1990). This observa-
tion indicates that Ca^{2+} entry through the capsaicin-
operated nonselective cation channel provides sufficient terminals (Donnerer and Amann, 1990). This observa-
tion indicates that Ca^{2+} entry through the capsaicin-
operated nonselective cation channel provides sufficient
intracellular Ca^{2+} to induce peptide release. The ma operated nonselective cation channel provides sufficient
intracellular Ca^{2+} to induce peptide release. The massive
uptake of Ca^{2+} induced by capsaicin (Wood et al., 1988)
probably also explains why the requirements peripheral endings of sensory neurons is inhibited by
removal of extracellular Ca²⁺ (Games et al., 1978); Ther-
iault et al., 1979; Yanagisawa et al., 1980; Helke et al.,
1981b; Hua et al., 1988; Maggi et al., 1988d, 19 uptake of Ca^{2+} induced by capsaicin (Wood et al., 1988)
probably also explains why the requirements of extracel-
lular Ca^{2+} for capsaicin-induced release of substance P
from sensory nerve endings are substantially l uptake of Ca^{2+} induced by capsaicin (Wood et al., 1988)
probably also explains why the requirements of extracel-
lular Ca^{2+} for capsaicin-induced release of substance P
from sensory nerve endings are substantially l probably also explains why the requirements of extracel-
lular Ca²⁺ for capsaicin-induced release of substance P
from sensory nerve endings are substantially lower than
those necessary to maintain release induced by othe lular Ca²⁺ for c
from sensory ne
those necessary
depolarizing sti
1988e, 1989e).
iv. Enzyme Im sensory nerve endings are substantially lower the ose necessary to maintain release induced by oth polarizing stimuli (Gamse et al., 1979b; Maggi et a $88e$, 1989e).
iv. Enzyme activation. The buildup of Ca²⁺ in manthose necessary to maintain release induced by other depolarizing stimuli (Gamse et al., 1979b; Maggi et al., 1988e, 1989e).
 iv. Enzyme activation. The buildup of Ca^{2+} in mammalian sensory neurons also is likely to

current will be inhibited. Consequently, the inward cur-
rent is enhanced because it is not cut short by the K^+ act
outward current and depolarization of sensory neurons an
is augmented (Amann et al., 1989a). An altern outward current and depolarization of sensory neurons and is augmented (Amann et al., 1989a). An alternative explanation considers that Ca^{2+} ions normally impede the this capsaicin-evoked passage of Na⁺ ions (Forbes planation considers that Ca²⁺ ions normally impede the this biochemical change is unrelated to the drugs' pri-
capsaicin-evoked passage of Na⁺ ions (Forbes and Bevan, mary effects on the cell membrane (Wood et al., 19 entry of Na⁺ and thereby amplify the capsaicin-induced depolarization of sensory nerve endings (Dray et al., 1990b).
1990b). Second, capsaicin-evoked influx of Ca²⁺ leads to inhi-
bition of voltage-dependent Ca²⁺ ch depolarization of sensory nerve endings (Dray et al., V
1990b).

Second, capsaicin-evoked influx of Ca²⁺ leads to inhi-

bition of voltage-dependent Ca²⁺ channels (Bleakman et al., 1990; Docherty et al., 1991). This e 1990b).

Second, capsaicin-evoked influx of Ca^{2+} leads to inhi-

bition of voltage-dependent Ca^{2+} channels (Bleakman et

al., 1990; Docherty et al., 1991). This effect of capsaicin

on cultured dorsal root ganglion Second, capsaicin-evoked influx of Ca^{2+} leads to inhition of voltage-dependent Ca^{2+} channels (Bleakman et and., 1990; Docherty et al., 1991). This effect of capsaicin vivon cultured dorsal root ganglion cells, which depolarizing stimuli (Gamse et al., 1979b; Maggi et al., 1988e, 1989e).
 iv. Enzyme activation. The buildup of Ca²⁺ in mam-

malian sensory neurons also is likely to account for the

activation of Ca²⁺-dependent enzy 1988e, 1989e).
 iv. Enzyme activation. The buildup of Ca^{2+} in mam-

malian sensory neurons also is likely to account for the

activation of Ca^{2+} -dependent enzymes. Thus, capsaicin

and resiniferatoxin increase cyc iv. Enzyme activation. The buildup of Ca^{2+} in mam-
malian sensory neurons also is likely to account for the
activation of Ca^{2+} -dependent enzymes. Thus, capsaicin
and resiniferatoxin increase cyclic GMP levels in tho malian sensory neurons also is likely to account for the activation of Ca^{2+} -dependent enzymes. Thus, capsaicin and resiniferatoxin increase cyclic GMP levels in those sensory neurons that also show uptake of calcium, b activation of Ca²⁺-dependent enzymes. Thus, capsaicin
and resiniferatoxin increase cyclic GMP levels in those
sensory neurons that also show uptake of calcium, but
this biochemical change is unrelated to the drugs' pri-
 and resiniferatoxin increase cyclic GMP levels in those
sensory neurons that also show uptake of calcium, but
this biochemical change is unrelated to the drugs' pri-
mary effects on the cell membrane (Wood et al., 1989;
Wi sensory neurons that also show uptake of calcium, but
this biochemical change is unrelated to the drugs' pri-
mary effects on the cell membrane (Wood et al., 1989;
Winter et al., 1990). The levels of cyclic AMP are not
cha this biochemical change is unrelated to the drugs' pri-
mary effects on the cell membrane (Wood et al., 1989;
Winter et al., 1990). The levels of cyclic AMP are not
changed in cultured sensory neurons (Wood et al., 1989;
W mary effects on the cell membrane (Wood et al., 1989;
Winter et al., 1990). The levels of cyclic AMP are not
changed in cultured sensory neurons (Wood et al., 1989;
Winter et al., 1990) which contrasts with reports that
ca Winter et al., 1990). The levels of cyclic AMP are not
changed in cultured sensory neurons (Wood et al., 1989;
Winter et al., 1990) which contrasts with reports that
capsaicin can increase the levels of this phosphate in t changed in cultured sensory neurons (Wood et al., 1989;
Winter et al., 1990) which contrasts with reports that
capsaicin can increase the levels of this phosphate in the
rat brain (Horváth et al., 1979) and spinal cord (No Winter et al., 1990) which contrasts with reports that
capsaicin can increase the levels of this phosphate in the
rat brain (Horváth et al., 1979) and spinal cord (Northam
and Jones, 1984). However, this effect of capsaici rat brain (Horváth et al., 1979) and spinal cord (Northam
and Jones, 1984). However, this effect of capsaicin in
vivo may conceivably be an indirect action caused by
transmitter release (Wood et al., 1989).
2. Desensitizat *2. betain (Horváth et al., 1979) and spinal cord (Northam d Jones, 1984). However, this effect of capsaicin in*
2. Desensitization. a. SPECIFIC DESENSITIZATION. Al-
2. Desensitization. a. SPECIFIC DESENSITIZATION. Al-

al., 1990; Docherty et al., 1991). This effect of capsaicin
on cultured dorsal root ganglion cells, which is extremely
long lasting (>1 h), is seen only in neurons that are
depolarized by the drug (Docherty et al., 1991). and Jones, 1984). However, this effect of capsaicin in
vivo may conceivably be an indirect action caused by
transmitter release (Wood et al., 1989).
2. Desensitization. a. SPECIFIC DESENSITIZATION. Al-
though the phenomeno vivo may conceivably be an indirect action caused b
transmitter release (Wood et al., 1989).
2. Desensitization. a. SPECIFIC DESENSITIZATION. A
though the phenomenon of desensitization to capsaici
and structurally related transmitter release (Wood et al., 1989).

2. Desensitization. a. SPECIFIC DESENSITIZATION.

though the phenomenon of desensitization to capsaid

and structurally related substances has been well doo

mented, its mechanism though the phenomenon of desensitization to capsaicin
and structurally related substances has been well docu-
mented, its mechanism of action is still poorly under-
stood. Desensitization to capsaicin can be differentiated

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

into a process that is specific for this drug and related mon effect of capsaicin on sensory neurons. Like exci-
compounds (Szolcsányi, 1977, 1987; Bernstein et al., tation, specific desensitization does not involve any se HOLZ
into a process that is specific for this drug and related
compounds (Szolcsányi, 1977, 1987; Bernstein et al.,
1981; Dray et al., 1989a,b, 1990a,b; Amann, 1990; Winter HOL:

into a process that is specific for this drug and related

compounds (Szolcsányi, 1977, 1987; Bernstein et al.,

1981; Dray et al., 1989a,b, 1990a,b; Amann, 1990; Winter

et al., 1990) and a process that is drug nons into a process that is specific for this drug and related compounds (Szolcsányi, 1977, 1987; Bernstein et al., 1981; Dray et al., 1989a,b, 1990a,b; Amann, 1990; Winter et al., 1990) and a process that is drug nonspecific a into a process that is specific for this drug and related m
compounds (Szolcsányi, 1977, 1987; Bernstein et al., ta
1981; Dray et al., 1989a,b, 1990a,b; Amann, 1990; Winter of
et al., 1990) and a process that is drug nonsp compounds (Szolcsányi, 1977, 1987; Bernstein et al., tati
1981; Dray et al., 1989a,b, 1990a,b; Amann, 1990; Winter ond
et al., 1990) and a process that is drug nonspecific and, AM
hence, is better described as a defunction 1981; Dray et al., 1989a,b, 1990a,b; Amann, 1990; Winet al., 1990) and a process that is drug nonspecific an hence, is better described as a defunctionalization sensory neurons. Specific desensitization, as studied capsaic et al., 1990) and a process that is drug nonspecific and hence, is better described as a defunctionalization comparison of the described of neuropeptides from peripheral sensory nerve terminals, is restricted to low, nearhence, is better described as a defunctionalization of sensory neurons. Specific desensitization, as studied on capsaicin-evoked release of neuropeptides from peripheral sensory nerve terminals, is restricted to low, nearsensory neurons. Specific desensitization, as studied on clapsaicin-evoked release of neuropeptides from periph-
eral sensory nerve terminals, is restricted to low, near-
threshold concentrations of the drug (Dray et al., capsaicin-evoked release of neuropeptides from periph-

Feral sensory nerve terminals, is restricted to low, near-

threshold concentrations of the drug (Dray et al., 1989b;

siti

Amann, 1990). However, the range of conce eral sensory nerve terminals, is restricted to low, near-
threshold concentrations of the drug (Dray et al., 1989b;
Amann, 1990). However, the range of concentrations of
capsaicin producing specific desensitization seems t threshold concentrations of the drug (Dray et al., 1989b;
Amann, 1990). However, the range of concentrations of
capsaicin producing specific desensitization seems to be
extended by lowering the experimental temperature
(Dr capsaicin producing specific desensitization seems to be extended by lowering the experimental temperature (Dray et al., 1989b) so that, in the neonatal rat spinal cord-tail preparation kept in vitro at 24° C, specifi capsaicin producing specific desensitization seems to extended by lowering the experimental temperation (Dray et al., 1989b) so that, in the neonatal rat spin cord-tail preparation kept in vitro at 24° C, specific ese extended by lowering the experimental temperature.
(Dray et al., 1989b) so that, in the neonatal rat spins cord-tail preparation kept in vitro at 24°C, specific desensitization can be demonstrated with capsaicin concertra (Dray et al., 1989b) so that, in the neonatal rat spinal cord-tail preparation kept in vitro at 24° C, specific desensitization can be demonstrated with capsaicin concentrations up to 2μ M, a concentration that is s cord-tail preparation kept in vis
sensitization can be demonstrate
trations up to 2μ M, a concentration
with regard to nociceptor stimula
1990a,b,c; Winter et al., 1990).
As its definition implies, spec msitization can be demonstrated with capsaicin concentrions up to 2μ M, a concentration that is supramaximal
th regard to nociceptor stimulation (Dray et al., 1989a,
90a,b,c; Winter et al., 1990).
As its definition impl

trations up to 2μ M, a concentration that is supramaximal
with regard to nociceptor stimulation (Dray et al., 1989a,
1990a,b,c; Winter et al., 1990).
As its definition implies, specific desensitization will look affect with regard to nociceptor stimulation (Dray et al., 1989a, the 1990a, b,c; Winter et al., 1990).

As its definition implies, specific desensitization will lead only affect a signaling mechanism that is selectively afferen 1990a,b,c; Winter et al., 1990).
As its definition implies, specific desensitization will
only affect a signaling mechanism that is selectively
operated by capsaicin-like drugs and does not impair the
function of sensory n As its definition implies, specific desensitization will leading only affect a signaling mechanism that is selectively afferenced by capsaicin-like drugs and does not impair the Caption of sensory neurons. Consequently, sp only affect a signaling mechanism that is selectively affer
operated by capsaicin-like drugs and does not impair the Ca^{2+}
function of sensory neurons. Consequently, specific de-
sensitization may arise from either dese operated by capsaicin-like drugs and does not impair the (function of sensory neurons. Consequently, specific desensitization may arise from either desensitization of the capsaicin receptor itself (Szolcsányi and Jancsó-Gá function of sensory neurons. Consequently, specific d
sensitization may arise from either desensitization of the
capsaicin receptor itself (Szolcsányi and Jancsó-Gábo
1976; Dray et al., 1989a,b, 1990b; Amann 1990; Bleakma
 sensitization may arise from either desensitization of the capsaicin-receptor-itself (Szolcsányi and Jancsó-Gábor
1976; Dray et al., 1989a,b, 1990b; Amann 1990; Bleakman
et al., 1990) or desensitization of the specific cel capsaicin receptor itself (Szolcsányi and Jancsó-C
1976; Dray et al., 1989a,b, 1990b; Amann 1990; Bleal
et al., 1990) or desensitization of the specific cell i
brane response to capsaicin-like drugs (Amann,
Bleakman et al. et al., 1990) or desensitization of the specific cell membrane response to capsaicin-like drugs (Amann, 1990;
Bleakman et al., 1990). Like the temperature-dependent
desensitization of muscarinic acetylcholine receptors (El et al., 1990) or desensitization of the specific cell mem-
brane response to capsaicin-like drugs (Amann, 1990; ce
Bleakman et al., 1990). Like the temperature-dependent of
desensitization of muscarinic acetylcholine recep brane response to capsaicin-like drugs (Amann, 1990;
Bleakman et al., 1990). Like the temperature-dependent
desensitization of muscarinic acetylcholine receptors (El-
Fakahany and Richelson, 1980), desensitization to the
c Bleakman et al., 1990). Like the temperature-dependent of desensitization of muscarinic acetylcholine receptors (El-
Fakahany and Richelson, 1980), desensitization to the lattenuated peptide release from guinea pig ureter desensitization of muscarinic acetylcholine receptors (Fakahany and Richelson, 1980), desensitization to the capsaicin-induced peptide release from guinea pig ure and rat urinary bladder is attenuated by lowering temperatu Fakahany and Richelson, 1980), desensitization to the capsaicin-induced peptide release from guinea pig ureter and rat urinary bladder is attenuated by lowering the temperature from 37° to 18° to 20° C, even capsaicin-induced peptide release from guinea pig ureter
and rat urinary bladder is attenuated by lowering the
temperature from 37° to 18° to 20°C, even when concen-
trations of capsaicin are used that release as much pep and rat urinary bladder is attenuated by lowering the Dr.
temperature from 37° to 18° to 20° C, even when concentrations of capsaicin are used that release as much peptide as at 37°C (Dray et al., 1989b; Amann, 1 temperature from 37° to 18° to 20°C, even when concen-
trations of capsaicin are used that release as much pep-
tide as at 37°C (Dray et al., 1989b; Amann, 1990; Maggi th
et al., 1990a). Although this finding is compatibl trations of capsaicin are used that release as much pep-
tide as at 37°C (Dray et al., 1989b; Amann, 1990; Maggi
et al., 1990a). Although this finding is compatible with
the idea of receptor desensitization (Amann, 1990), tide as at 37°C (Dray et al., 1989b; Amann, 1990; Maggi the al., 1990a). Although this finding is compatible with action-induced opening of nonselective cation with the capsaicin-induced opening of nonselective cation with et al., 1990a). Although this finding is compatible with acther idea of receptor desensitization (Amann, 1990), this 19
possibility is difficult to reconcile with the observation kit
that the capsaicin-induced opening of n the idea of receptor desensitization (Amann, 1990), this possibility is difficult to reconcile with the observation that the capsaicin-induced opening of nonselective cation channels in isolated cell membrane patches from possibility is difficult to reconcile with the observation
that the capsaicin-induced opening of nonselective cation
channels in isolated cell membrane patches from sensory
neurons is sustained as long as the drug is prese that the capsaicin-induced opening of nonselective cation which
channels in isolated cell membrane patches from sensory de
neurons is sustained as long as the drug is present et
(Forbes and Bevan, 1988; Dray et al., 1990d) channels in isolated cell membrane patches from sensory
neurons is sustained as long as the drug is present
(Forbes and Bevan, 1988; Dray et al., 1990d). Thus,
receptor desensitization and rapid inactivation of the
capsaic neurons is sustained as long as the drug is present (Forbes and Bevan, 1988; Dray et al., 1990d). Thus, receptor desensitization and rapid inactivation of the capsaicin-operated cation channel are unlikely to account for d (Forbes and Bevan, 1988; Dray et al., 1990d). Thus,
receptor desensitization and rapid inactivation of the
capsaicin-operated cation channel are unlikely to ac-
count for desensitization provided that the temporal
characte receptor desensitization and rapid inactivation of the the capsaicin-operated cation channel are unlikely to accurate for desensitization provided that the temporal spharacteristics of this channel are identical in membran capsaicin-operated cation channel are unlikely to ac-
count for desensitization provided that the temporal spec
characteristics of this channel are identical in membrane the spatches and intact cells. Moreover, there is no count for desensitization provided that the temporal
characteristics of this channel are identical in membrane
patches and intact cells. Moreover, there is no loss of
resiniferatoxin-binding sites in dorsal root ganglia 12 characteristics of this channel are identical in membrane
patches and intact cells. Moreover, there is no loss of
resiniferatoxin-binding sites in dorsal root ganglia 12 h
after systemic treatment of rats with resiniferato patches and intact cells. Moreover, there is no loss
resiniferatoxin-binding sites in dorsal root ganglia 12
after systemic treatment of rats with resiniferator
(Szallasi and Blumberg, 1990a). The available da
therefore, s resiniferatoxin-binding sites in dorsal root ganglia 12
after systemic treatment of rats with resiniferatox
(Szallasi and Blumberg, 1990a). The available dat
therefore, suggest that specific desensitization to capsa
cin ar after systemic treatment of rats with resini
(Szallasi and Blumberg, 1990a). The availa
therefore, suggest that specific desensitization
cin arises from a mechanism beyond the capsaid
tor and the capsaicin-operated cation therefore, suggest that specific desensitization to capsaicin arises from a mechanism beyond the capsaicin receptor and the capsaicin-operated cation channel.
The time and dose relationships between capsaicintherefore, suggest that specific desensitization to capsai-
cin arises from a mechanism beyond the capsaicin recep-
tor and the capsaicin-operated cation channel.
The time and dose relationships between capsaicin-
induced

cin arises from a mechanism beyond the capsaicin receptor and the capsaicin-operated cation channel.
The time and dose relationships between capsaicin
induced excitation and desensitization suggest that thes
phenomena are

mon effect of capsaicin on sensory neurons. Like exci-ER
mon effect of capsaicin on sensory neurons. Like excitation, specific desensitization does not involve any sec-
ond-messenger system such as protein kinase C, cyclic ER
mon effect of capsaicin on sensory neurons. Like excitation, specific desensitization does not involve any sec-
ond-messenger system such as protein kinase C, cyclic
AMP-dependent kinase, cyclic GMP-dependent kinase, mon effect of capsaicin on sensory neurons. Like excitation, specific desensitization does not involve any second-messenger system such as protein kinase C, cyclic AMP-dependent kinase, cyclic GMP-dependent kinase, calmodu mon effect of capsaicin on sensory neurons. Like excitation, specific desensitization does not involve any second-messenger system such as protein kinase C, cyclic AMP-dependent kinase, cyclic GMP-dependent kinase, calmodu tation, specific desensitization does not involve any second-messenger system such as protein kinase C, cyclic AMP-dependent kinase, cyclic GMP-dependent kinase, calmodulin-dependent kinase, phospholipase A₂, or cyclooxy ond-messenger system such as protein kinase C, cyclic AMP-dependent kinase, calmodulin-dependent kinase, phospholipase A_2 , or cy-clooxygenase (Dray et al., 1990a,b; Winter et al., 1990).
Removal of external Na^+ fails AMP-dependent kinase, cyclic GMP-dependent kinase, calmodulin-dependent kinase, phospholipase A_2 , or clooxygenase (Dray et al., 1990a,b; Winter et al., 199
Removal of external Na⁺ fails to influence specific consisti calmodulin-dependent kinase, phospholipase A_2 , or c
clooxygenase (Dray et al., 1990a,b; Winter et al., 1990
Removal of external Na⁺ fails to influence specific d
sensitization, and neither excitation nor specific des clooxygenase (Dray et al., 1990a,b; Winter et al., 199
Removal of external Na⁺ fails to influence specific α
sensitization, and neither excitation nor specific dese
sitization of nociceptors requires the presence of Removal of external Na⁺ fails to influence specific desensitization, and neither excitation nor specific desensitization of nociceptors requires the presence of extracellular Ca^{2+} in the neonatal rat tail/spinal cord sensitization, and neither excitation nor specific desensitization of nociceptors requires the presence of extra-
cellular Ca^{2+} in the neonatal rat tail/spinal cord prepa-
ration (Dray et al., 1990b). This observation, sitization of nociceptors requires the presence of extra-
cellular Ca^{2+} in the neonatal rat tail/spinal cord prepa-
ration (Dray et al., 1990b). This observation, however, is
at variance with the finding that specific cellular Ca^{2+} in the neonatal rat tail/spinal cord preparation (Dray et al., 1990b). This observation, however, is at variance with the finding that specific desensitization to the capsaicin-evoked peptide release from ration (Dray et al., 1990b). This observation, however, is
at variance with the finding that specific desensitization
to the capsaicin-evoked peptide release from peripheral
sensory nerve terminals requires the presence of at variance with the finding that specific desensitizatio
to the capsaicin-evoked peptide release from periphers
sensory nerve terminals requires the presence of externs
Ca²⁺ (Amann, 1990). This discrepancy might be reso to the capsaicin-evoked peptide release from peripheral
sensory nerve terminals requires the presence of external
 Ca^{2+} (Amann, 1990). This discrepancy might be resolved
by speculating (R. Amann, personal communication) sensory nerve terminals requires the presence of external Ca^{2+} (Amann, 1990). This discrepancy might be resolved
by speculating (R. Amann, personal communication)
that desensitization to the stimulant effect of capsaic Ca^{2+} (Amann, 1990). This discrepancy might be resolved
by speculating (R. Amann, personal communication)
that desensitization to the stimulant effect of capsaicin
in the neonatal rat tail/spinal cord preparation may, a by speculating (R. Amann, personal communication)
that desensitization to the stimulant effect of capsaicin
in the neonatal rat tail/spinal cord preparation may, at
least in part, be due to blockade of nerve conduction in
 that desensitization to the stimulan
in the neonatal rat tail/spinal cord
least in part, be due to blockade of
afferent nerve fibers, a process tha
Ca²⁺ (Waddell and Lawson, 1989).
There are some data to suggest tha the neonatal rat tail/spinal cord preparation may, at
ast in part, be due to blockade of nerve conduction in
ferent nerve fibers, a process that is independent of
 a^{2+} (Waddell and Lawson, 1989).
There are some data to

least in part, be due to blockade of nerve conduction in
afferent nerve fibers, a process that is independent of
 Ca^{2+} (Waddell and Lawson, 1989).
There are some data to suggest that capsaicin-induced
excitation and spe afferent nerve fibers, a process that is independent Ca^{2+} (Waddell and Lawson, 1989).
There are some data to suggest that capsaicin-induc
excitation and specific desensitization are not related
each other but involve t Ca^{2+} (Waddell and Lawson, 1989).
There are some data to suggest that capsaicin-induced
excitation and specific desensitization are not related to
each other but involve two different sites and/or mech-
anisms of action There are some data to suggest that capsaicin-induce
excitation and specific desensitization are not related t
each other but involve two different sites and/or mech
anisms of action. Thus, specific desensitization can occ excitation and specific desensitization are not related to each other but involve two different sites and/or mechanisms of action. Thus, specific desensitization can occur independently of capsaicin-induced stimulation of each other but involve two different sites and/or mechanisms of action. Thus, specific desensitization can occur
independently of capsaicin-induced stimulation of nociceptors (Dray et al., 1990b). Furthermore, the potencie anisms of action. Thus, specific desensitization can occur
independently of capsaicin-induced stimulation of noci-
ceptors (Dray et al., 1990b). Furthermore, the potencies
of structurally related analogues of capsaicin in independently of capsaicin-induced stimulation of nociceptors (Dray et al., 1990b). Furthermore, the potencies of structurally related analogues of capsaicin in exciting and desensitizing sensory neurons do not always corr ceptors (Dray et al., 1990b). Furthermore, the potencies
of structurally related analogues of capsaicin in exciting
and desensitizing sensory neurons do not always corre-
late with each other (Szolcsányi and Jancsó-Gábor, Hayes et al., 1984b; Szallasi and Blumberg, 1989, 1990b; Dray et al., 1990c; Maggi et al., 1990c). These studies, however, have rarely considered that differences in the and desensitizing sensory neurons do not always corre-
late with each other (Szolcsányi and Jancsó-Gábor, 1976;
Hayes et al., 1984b; Szallasi and Blumberg, 1989, 1990b;
Dray et al., 1990c; Maggi et al., 1990c). These studi late with each other (Szolcsányi and Jancsó-Gábor, 1976;
Hayes et al., 1984b; Szallasi and Blumberg, 1989, 1990b;
Dray et al., 1990c; Maggi et al., 1990c). These studies,
however, have rarely considered that differences in Hayes et al., 1984b; Szallasi and Blumberg, 1989, 1990b;
Dray et al., 1990c; Maggi et al., 1990c). These studies,
however, have rarely considered that differences in the
activities may in part be determined by differences Dray et al., 1990c; Maggi et al., 1990c). These studies, however, have rarely considered that differences in the activities may in part be determined by differences in the rates with which the different compounds can gain however, have rarely considered that differences in
activities may in part be determined by difference
the rates with which the different compounds can
access to their sites of action in the tissue (Maggi et
1990c). It is activities may in part be determined by differences in
the rates with which the different compounds can gain
access to their sites of action in the tissue (Maggi et al.,
1990c). It is not known to what extent such pharmaco the rates with which the different compounds can gain
access to their sites of action in the tissue (Maggi et al.,
1990c). It is not known to what extent such pharmaco-
kinetic factors contribute to the activity profile of access to their sites of action in the tissue (Maggi et al., 1990c). It is not known to what extent such pharmaco-
kinetic factors contribute to the activity profile of olvanil
which is a capsaicin congener that can produc 1990c). It is not known to what extent such pharmaco-
kinetic factors contribute to the activity profile of olvanil
which is a capsaicin congener that can produce specific
desensitization in the absence of excitation (Dick kinetic factors contribute to the activity profile of olvanil
which is a capsaicin congener that can produce specific
desensitization in the absence of excitation (Dickenson
et al., 1990b; Dray et al., 1990c). The mechanis which is a capsaicin congener that can produce specific
desensitization in the absence of excitation (Dickenson
et al., 1990b; Dray et al., 1990c). The mechanism of
olvanil-induced desensitization to capsaicin requires fu desensitization in the absence of excitation (Dickenson
et al., 1990b; Dray et al., 1990c). The mechanism of
olvanil-induced desensitization to capsaicin requires fur-
ther exploration, particularly in view of the reports et al., 1990b; Dray et al., 1990c). The mechanism of olvanil-induced desensitization to capsaicin requires fur-
ther exploration, particularly in view of the reports that
in the tail of the neonatal rat 50 μ M olvanil p olvanil-induced desensitization to capsaicin requires fur-
ther exploration, particularly in view of the reports that
in the tail of the neonatal rat 50 μ M olvanil produces
specific desensitization (Dray et al., 1990c) ther exploration, particularly in view of the reports that
in the tail of the neonatal rat 50 μ M olvanil produces
specific desensitization (Dray et al., 1990c), whereas in
the spinal cord of the adult rat olvanil conce in the tail of the neonatal rat 50 μ M olvanil produces specific desensitization (Dray et al., 1990c), whereas in the spinal cord of the adult rat olvanil concentrations as low as 2 μ M give rise to a nonspecific depr specific desensitization (Dray et a
the spinal cord of the adult rat olv
low as 2 μ M give rise to a non
stimulus-induced peptide release f
minals (Dickenson et al., 1990b).
b. NONSPECIFIC DESENSITIZATIO is expiral cord of the adult rat olvanil concentrations as
w as 2μ M give rise to a nonspecific depression of
imulus-induced peptide release from sensory nerve ter-
inals (Dickenson et al., 1990b).
b. NONSPECIFIC DESENS

Now as 2 μ M give rise to a nonspecific depression of stimulus-induced peptide release from sensory nerve terminals (Dickenson et al., 1990b).
b. NONSPECIFIC DESENSITIZATION. The mechanism of nonspecific desensitization stimulus-induced peptide release from sensory nerve ter-
minals (Dickenson et al., 1990b).
b. NONSPECIFIC DESENSITIZATION. The mechanism of
nonspecific desensitization to capsaicin implies a process
that takes place beyond minals (Dickenson et al., 1990b).
b. NONSPECIFIC DESENSITIZATION. The mechanism of
nonspecific desensitization to capsaicin implies a process
that takes place beyond the level of a specific response
to capsaicin because it b. NONSPECIFIC DESENSITIZATION. The mechanism of nonspecific desensitization to capsaicin implies a process that takes place beyond the level of a specific response to capsaicin because it is associated with the loss of ex that takes place beyond the level of a specific response to capsaicin because it is associated with the loss of excitability and physiological function of sensory neurons. The details of this mechanism are still not understood, but there are a number of possibilities to be

CAPSAICIN 179

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

considered. Many reports concerning capsaicin desensi-CAPSA
considered. Many reports concerning capsaicin desensi-
tization, however, are difficult to assess because neither
the reversibility of the process nor any relationship to CAPSAICIN
considered. Many reports concerning capsaicin desensi-
tization, however, are difficult to assess because neither critic
the reversibility of the process nor any relationship to rem
morphological changes in senso considered. Many reports concerning capsaicin desensitization, however, are difficult to assess because neither
the reversibility of the process nor any relationship to
morphological changes in sensory neurons has been exconsidered. Many reports concerning capsaicin desentization, however, are difficult to assess because neith
the reversibility of the process nor any relationship
morphological changes in sensory neurons has been e
amined. tization, however, are difficult to assess because neith
the reversibility of the process nor any relationship
morphological changes in sensory neurons has been e
amined. Consequently, it is often not possible to diffe
ent the reversibility of the process nor any relationship to rem
morphological changes in sensory neurons has been ex-
amined. Consequently, it is often not possible to differ-
al.,
entiate between temporary defunctionalizati morphological changes in sensory neurons has been ex-
amined. Consequently, it is often not possible to differ-
entiate between temporary defunctionalization or longer-
lasting neurotoxicity. Given the fact that in vitro 0 amined. Consequently, it is often not possible to differentiate between temporary defunctionalization or longer-
lasting neurotoxicity. Given the fact that in vitro 0.5 to
 2μ M capsaicin or 1 to 10 nM resiniferatoxin ca entiate between temporary defunctionalization or longer-
lasting neurotoxicity. Given the fact that in vitro 0.5 to
 2μ M capsaicin or 1 to 10 nM resiniferatoxin can lead to
damage of sensory neurons (Bevan et al., 1987; lasting neurotoxicity. Given the fact that in vitro 0.5 to 2μ M capsaicin or 1 to 10 nM resiniferatoxin can lead to damage of sensory neurons (Bevan et al., 1987; Marsh et al., 1987; Winter, 1987; Wood et al., 1988; Kir 2 μ M capsaicin or 1 to 10 nM resiniferatoxin can lead to Form damage of sensory neurons (Bevan et al., 1987; Marsh et in al., 1987; Winter, 1987; Wood et al., 1988; Király et al., an 1991; Winter et al., 1990) within 5 damage of sensory neurons (Bevan et al., 1987; Marsh et al., 1987; Winter, 1987; Wood et al., 1988; Király et al.
1991; Winter et al., 1990) within 5 min (Marsh et al.
1987), it seems that nonspecific desensitization to th al., 1987; Winter, 1987; Wood et al., 1988; Király et al., an
1991; Winter et al., 1990) within 5 min (Marsh et al., th
1987), it seems that nonspecific desensitization to these
concentrations of the drugs reflects neuroto 1991; Winter et al., 1990) within 5 min (Marsh et al., th. 1987), it seems that nonspecific desensitization to these 19 concentrations of the drugs reflects neurotoxicity. However, because nonspecific desensitization to l concentrations of the drugs reflects neurotoxicity. How-
ever, because nonspecific desensitization to low doses of
is controlled by Ca^{2+} has not yet been elucidated, there
capsaicin can be reversible within a couple of concentrations of the drugs reflects neurotoxicity. However, because nonspecific desensitization to low doses of capsaicin can be reversible within a couple of hours (He et al., 1990; Szolcsányi, 1990), there might be a ra ever, because nonspecific desensitization to low doses of capsaicin can be reversible within a couple of hours (H et al., 1990; Szolcsányi, 1990), there might be a range concentrations that produce nonspecific desensitizat capsaicin can be reversible within a couple of hours (He et al., 1990; Szolcsányi, 1990), there might be a range of concentrations that produce nonspecific desensitization in the absence of neurotoxicity. The width of the et al., 1990; Szolcsányi, 1990), there might be a range of dependent
concentrations that produce nonspecific desensitization specific that
in the absence of neurotoxicity. The width of the tran-
sition zone between concent

concentrations that produce nonspecific desensitization specific in the absence of neurotoxicity. The width of the tran-
sition zone between concentrations of capsaicin that tide
cause specific desensitization only and tho in the absence of neurotoxicity. The width of the transition zone between concentrations of capsaicin that tides cause specific desensitization only and those that give volties to nonspecific desensitization as well appea sition zone between concentrations of capsaicin that cause specific desensitization only and those that give rise to nonspecific desensitization as well appears to depend on the experimental temperature. At 37°C it is dif cause specific desensitization only and those that give
rise to nonspecific desensitization as well appears to
depend on the experimental temperature. At 37°C it is
difficult to demonstrate specific desensitization at cap rise to nonspecific desensitization as well appears to depend on the experimental temperature. At 37°C it is ldifficult to demonstrate specific desensitization at capsicin concentrations $>0.3 \mu$ M (Amann, 1990), whereas a depend on the experimental temperature. At 37°C it is
difficult to demonstrate specific desensitization at cap-
saicin concentrations >0.3 μ M (Amann, 1990), whereas
at 20° to 24°C desensitization is specific for the dr difficult to demonstrate specific desensitization at cap-
saicin concentrations $>0.3 \mu$ M (Amann, 1990), whereas and 20° to 24°C desensitization is specific for the drug at cloncentrations up to 2 μ M (Dray et al., 1989 saicin concentrations $>0.3 \mu$ M (Amann, 1990), wherease that 20° to 24°C desensitization is specific for the drug at concentrations up to 2μ M (Dray et al., 1989a,b, 1990a,b,c Winter et al., 1990). However, a direct com at 20° to 24°C desensitization is specific for the drug at concentrations up to 2μ M (Dray et al., 1989a,b, 1990a,b,c;
Winter et al., 1990). However, a direct comparison of specific and nonspecific desensitization at di meentrations up to 2μ M (Dray et al., 1989a,b, 1990a,b,c; at
inter et al., 1990). However, a direct comparison of (D
ecific and nonspecific desensitization at different tem-
tion
ratures has not yet been made.
Fatigue a

Winter et al., 1990). However, a direct comparison of (specific and nonspecific desensitization at different temperatures has not yet been made.

Fatigue and functional exhaustion of the neurons due to excessive stimulatio specific and nonspecific desensitization at different temperatures has not yet been made.
Fatigue and functional exhaustion of the neurons due
to excessive stimulation are generally dismissed as causes
of desensitization b peratures has not yet been made.
Fatigue and functional exhaustion of the neurons due
to excessive stimulation are generally dismissed as causes
of desensitization because the depolarizing effect of cap-
saicin abates with Fatigue and functional exhaustion of the neurons due
to excessive stimulation are generally dismissed as causes
of desensitization because the depolarizing effect of cap-
saicin abates within a few minutes (Hayes et al., 1 to excessive stimulation are generally dismissed as causes
of desensitization because the depolarizing effect of cap-
saicin abates within a few minutes (Hayes et al., 1984a;
Bevan et al., 1987; Marsh et al., 1987; Winter of desensitization because the depolarizing effect of cap-
saicin abates within a few minutes (Hayes et al., 1984a;
Bevan et al., 1987; Marsh et al., 1987; Winter et al., 1990;
Docherty et al., 1991). This also rules out t saicin abates within a few minutes (Hayes et al., 1984)
Bevan et al., 1987; Marsh et al., 1987; Winter et al., 1984
Docherty et al., 1991). This also rules out that a sustain
depolarization of the neurons accounts for thei Bevan et al., 1987; Marsh et al., 1987; Winter et al., 1990; ob
Docherty et al., 1991). This also rules out that a sustained ob
depolarization of the neurons accounts for their pro-
longed inexcitability. Unlike specific d Docherty et al., 1991). This also rules out that a sustained
depolarization of the neurons accounts for their pro-
longed inexcitability. Unlike specific desensitization,
which can occur in the absence of an excitatory eff depolarization of the neurons accounts for their pro-
longed inexcitability. Unlike specific desensitization,
which can occur in the absence of an excitatory effect of
capsaicin-like drugs (Dray et al., 1990b,c), nonspecif longed inexcitability. Unlike specific desensitization,
which can occur in the absence of an excitatory effect of
capsaicin-like drugs (Dray et al., 1990b,c), nonspecific
desensitization seems to be related to an initial e which can occur in the absence of an excitatory effect of capsaicin-like drugs (Dray et al., 1990b,c), nonspecific level desensitization seems to be related to an initial excitatory in effect (Dray et al., 1990c; He et al desensitization seems to be related to an initial excitatory
effect (Dray et al., 1990c; He et al., 1990). Thus, olvanil
causes nonspecific desensitization of nociceptors in the
tail of newborn rats only at a concentratio desensitization seems to be related to an initial excitatory if effect (Dray et al., 1990c; He et al., 1990). Thus, olvanil causes nonspecific desensitization of nociceptors in the tail of newborn rats only at a concentra effect (Dray et al., 1990c; He et al., 1990). Thus, olvanil 19
causes nonspecific desensitization of nociceptors in the
tail of newborn rats only at a concentration (500 μ M) is
that is sufficient to produce initial exc causes nonspecific desensitization of nociceptors in the tail of newborn rats only at a concentration (500 μ M) is that is sufficient to produce initial excitation (Dray et nal., 1990c). In contrast, 2μ M olvanil, whi tail of newborn rats only at a concentration $(500 \mu M)$
that is sufficient to produce initial excitation (Dray et
al., 1990c). In contrast, $2 \mu M$ olvanil, which is only weakly
active in stimulating peptide release from s that is sufficient to produce initial excitation (Dray et al., 1990c). In contrast, $2 \mu M$ olvanil, which is only weakly active in stimulating peptide release from sensory nerve terminals in the spinal cord of adult rats, al., 1990c). In contrast, $2 \mu M$ olvanil, which is only weakly Leadive in stimulating peptide release from sensory nerve ind terminals in the spinal cord of adult rats, suppresses ind stimulus-evoked peptide release in a active in stimulating peptide release from sensory nerve in
terminals in the spinal cord of adult rats, suppresses in
stimulus-evoked peptide release in a nonspecific manner the
(Dickenson et al., 1990b). Although it remai terminals in the spinal cord of adult rats, suppresses ind
stimulus-evoked peptide release in a nonspecific manner tha
(Dickenson et al., 1990b). Although it remains to be acc
determined whether this peculiarity of olvanil stimulus-evoked peptide release in a nonspecific mann
(Dickenson et al., 1990b). Although it remains to
determined whether this peculiarity of olvanil's action
compatible with a common mechanism of excitation a
nonspecific (Dickenson et al., 1990b). Although it remains to be addetermined whether this peculiarity of olvanil's action is (lompatible with a common mechanism of excitation and L nonspecific desensitization, it may at present be po determined whether this peculiarity of olvanil's action is
compatible with a common mechanism of excitation and
nonspecific desensitization, it may at present be postu-
lated that a component of the initial excitatory acti compatible with a common mechanism of excitation and
nonspecific desensitization, it may at present be postu-
lated that a component of the initial excitatory action of
capsaicin on sensory neurons is a priming event that
 nonspecific desensitization, it may at present be postulated that a component of the initial excitatory action of capsaicin on sensory neurons is a priming event that triggers a functional change that outlasts the initial

(Dray et al., 1990b), nonspecific desensitization depends critically on the availability of extracellular Ca^{2+} because critically on the availability of extracellular Ca²⁺ because
critically on the availability of extracellular Ca²⁺ because
removal of external Ca²⁺ blocks (Santicioli et al., 1987; 179
(Dray et al., 1990b), nonspecific desensitization depends
critically on the availability of extracellular Ca^{2+} because
removal of external Ca^{2+} blocks (Santicioli et al., 1987;
Wood, 1987; James et al., 1988; Ji (Dray et al., 1990b), nonspecific desensitization depends
critically on the availability of extracellular Ca²⁺ because
removal of external Ca²⁺ blocks (Santicioli et al., 1987;
Wood, 1987; James et al., 1988; Jin et al (Dray et al., 1990b), nonspecific desensitization depends
critically on the availability of extracellular Ca^{2+} because
removal of external Ca^{2+} blocks (Santicioli et al., 1987;
Wood, 1987; James et al., 1988; Jin et critically on the availability of extracellular Ca^{2+} because
removal of external Ca^{2+} blocks (Santicioli et al., 1987;
Wood, 1987; James et al., 1988; Jin et al., 1989; Maggi et
al., 1989e; Amann, 1990; Bleakman et removal of external Ca^{2+} blocks (Santicioli et al., 198
Wood, 1987; James et al., 1988; Jin et al., 1989; Maggi
al., 1989e; Amann, 1990; Bleakman et al., 1990), and
increase of the extracellular Ca^{2+} concentration a Wood, 1987; James et al., 1988; Jin et al., 1989; Maggi et
al., 1989e; Amann, 1990; Bleakman et al., 1990), and an
increase of the extracellular Ca²⁺ concentration aug-
ments (Dray et al., 1990b), nonspecific desensitiza al., 1989e; Amann, 1990; Bleakman et al., 1990), and an increase of the extracellular Ca^{2+} concentration augments (Dray et al., 1990b), nonspecific desensitization.
Furthermore, ruthenium red is considerably more poten increase of the extracellular Ca²⁺ concentration aug-
ments (Dray et al., 1990b), nonspecific desensitization.
Furthermore, ruthenium red is considerably more potent
in preventing desensitization than in blocking excitat ments (Dray et al., 1990b), nonspecific desensitization.
Furthermore, ruthenium red is considerably more potent
in preventing desensitization than in blocking excitation,
and protection from desensitization lasts much long 1988b,d, 1989a; Chahl, 1989; Amann et al., 1990b). preventing desensitization than in blocking excitation,
d protection from desensitization lasts much longer
an does antagonism of excitation (Maggi et al.,
88b,d, 1989a; Chahl, 1989; Amann et al., 1990b).
Although the pre and protection from desensitization lasts much longer
than does antagonism of excitation (Maggi et al.,
1988b,d, 1989a; Chahl, 1989; Amann et al., 1990b).
Although the precise desensitization mechanism that
is controlled than does antagonism of excitation (Maggi et al., 1988b,d, 1989a; Chahl, 1989; Amann et al., 1990b).
Although the precise desensitization mechanism that
is controlled by Ca^{2+} has not yet been elucidated, there
are at l 1988b,d, 1989a; Chahl, 1989; Amann et al., 1990b).
Although the precise desensitization mechanism that
is controlled by Ca^{2+} has not yet been elucidated, there
are at least three possibilities to consider, all of which Although the precise desensitization mechanism that
is controlled by Ca^{2+} has not yet been elucidated, there
are at least three possibilities to consider, all of which
depend critically on the influx of Ca^{2+} . First,

are at least three possibilities to consider, all of which
depend critically on the influx of Ca^{2+} . First, it has been
speculated (Amann, 1990; Bevan and Szolcsányi, 1990)
that nonspecific desensitization to capsaicinspeculated (Amann, 1990; Bevan and Szolcsányi, 1990) depend critically on the influx of Ca^{2+} . First, it has been
speculated (Amann, 1990; Bevan and Szolcsányi, 1990)
that nonspecific desensitization to capsaicin-evoked pep-
tide release is caused by the sustained inactiv speculated (Amann, 1990; Bevan and Szolcsányi, 1990)
that nonspecific desensitization to capsaicin-evoked pep-
tide release is caused by the sustained inactivation of
voltage-gated Ca²⁺ channels which results from the c that nonspecific desensitization to capsaicin-evoked pep-
tide release is caused by the sustained inactivation of
voltage-gated Ca²⁺ channels which results from the cap-
saicin-induced influx of Ca²⁺ (Bleakman et al., tide release is caused by the sustained inactivation of voltage-gated Ca^{2+} channels which results from the capsaicin-induced influx of Ca^{2+} (Bleakman et al., 1990; Docherty et al., 1991). This effect is indeed very voltage-gated Ca²⁺ channels which results from the capsaicin-induced influx of Ca²⁺ (Bleakman et al., 1990; Docherty et al., 1991). This effect is indeed very likely to contribute to defunctionalization of sensory neu Docherty et al., 1991). This effect is indeed very likely
to contribute to defunctionalization of sensory neurons,
and the long duration of the block of voltage-gated Ca^{2+}
channels has been suggested to reflect a struc to contribute to defunctionalization of sensory neurons,
and the long duration of the block of voltage-gated Ca^{2+}
channels has been suggested to reflect a structural alter-
ation of the channels induced by proteolytic to contribute to defunctionalization of sensory neumand the long duration of the block of voltage-gated channels has been suggested to reflect a structural a ation of the channels induced by proteolytic enzy (Docherty et a and the long duration of the block of voltage-gated Ca^{2+}
channels has been suggested to reflect a structural alter-
ation of the channels induced by proteolytic enzymes
(Docherty et al., 1991). Second, nonspecific dese channels has been suggested to reflect a structural alteration of the channels induced by proteolytic enzymes (Docherty et al., 1991). Second, nonspecific desensitization may be a direct functional correlate of a mild and, ation of the channels induced by proteolytic enzymes (Docherty et al., 1991). Second, nonspecific desensitization may be a direct functional correlate of a mild and, therefore, reversible form of capsaicin's neurotoxic act (Docherty et al., 1991). Second, nonspecific desensitiation may be a direct functional correlate of a mild a therefore, reversible form of capsaicin's neurotoxic tion on sensory neurons, a contention that receiversion supp tion may be a direct functional correlate of a mild and,
therefore, reversible form of capsaicin's neurotoxic ac-
tion on sensory neurons, a contention that receives
strong support from the similarity in the ionic requiretherefore, reversible form of capsaicin's neurotoxic action on sensory neurons, a contention that receives strong support from the similarity in the ionic requirements of nonspecific desensitization (Dray et al., 1990b) an tion on sensory neurons, a contention that receives
strong support from the similarity in the ionic require-
ments of nonspecific desensitization (Dray et al., 1990b)
and neurotoxicity (Winter et al., 1990). Thus, express strong support from the similarity in the ionic requiments of nonspecific desensitization (Dray et al., 1990) and neurotoxicity (Winter et al., 1990). Thus, expressition of nonspecific desensitization depends on the prese ments of nonspecific desensitization (Dray et al., 1990)
and neurotoxicity (Winter et al., 1990). Thus, expressio
of nonspecific desensitization depends on the presenc
of extracellular Ca²⁺ and Na⁺ and may, like the ne and neurotoxicity (Winter et al., 1990). Thus, expression
of nonspecific desensitization depends on the presence
of extracellular Ca²⁺ and Na⁺ and may, like the neuro-
toxic action of capsaicin, arise from intracellula of nonspecific desensitization depends on the presence
of extracellular Ca²⁺ and Na⁺ and may, like the neuro-
toxic action of capsaicin, arise from intracellular accu-
mulation of calcium and NaCl (Dray et al., 1990b) toxic action of capsaicin, arise from intracellular accumulation of calcium and NaCl (Dray et al., 1990b). The capsaicin/resiniferatoxin-evoked increase in cyclic GMP levels, another consequence of Ca^{2+} entry, is witho mulation of calcium and NaCl (Dray et al., 1990b). The capsaicin/resiniferatoxin-evoked increase in cyclic GMP levels, another consequence of Ca^{2+} entry, is without influence on desensitization to these drugs (Wood et mulation of calcium and Na
capsaicin/resiniferatoxin-ev
levels, another consequenc
influence on desensitization
1989; Winter et al., 1990).
A third aspect arises wher psaicin/resiniferatoxin-evoked increase in cyclic GMP
vels, another consequence of Ca^{2+} entry, is without
fluence on desensitization to these drugs (Wood et al.,
89; Winter et al., 1990).
A third aspect arises when des

levels, another consequence of Ca^{2+} entry, is without influence on desensitization to these drugs (Wood et al., 1989; Winter et al., 1990).
A third aspect arises when desensitization to capsaicin is studied during the influence on desensitization to these drugs (Wood et al., 1989; Winter et al., 1990).
A third aspect arises when desensitization to capsaicin
is studied during the release of peptides from sensory
neurons (Dray et al., 198 1989; Winter et al., 1990).
A third aspect arises when desensitization to capsa
is studied during the release of peptides from sens
neurons (Dray et al., 1989b; Amann, 1990; Amann
Lembeck, 1991). The characteristics of the A third aspect arises when desensitization to capsa
is studied during the release of peptides from sens
neurons (Dray et al., 1989b; Amann, 1990; Amann
Lembeck, 1991). The characteristics of the capsai
induced release of s is studied during the release of peptides from sensory
neurons (Dray et al., 1989b; Amann, 1990; Amann and
Lembeck, 1991). The characteristics of the capsaicin-
induced release of substance P from, and the capsaicin-
induc Lembeck, 1991). The characteristics of the capsaicin-
induced release of substance P from, and the capsaicin-
induced contraction of, the rabbit iris sphincter suggest
that desensitization to capsaicin in this tissue could Lembeck, 1991). The characteristics of the capsaicin-
induced release of substance P from, and the capsaicin-
induced contraction of, the rabbit iris sphincter suggest
that desensitization to capsaicin in this tissue could induced release of substance P from, and the capsaicin-
induced contraction of, the rabbit iris sphincter suggest
that desensitization to capsaicin in this tissue could be
accounted for by depletion of the releasable pepti induced contraction of, the rabbit iris sphincter suggest
that desensitization to capsaicin in this tissue could be
accounted for by depletion of the releasable peptide pool
(Ueda et al., 1984; Håkanson et al., 1987; Amann that desensitization to capsaicin in this tissue could be
accounted for by depletion of the releasable peptide pool
(Ueda et al., 1984; Håkanson et al., 1987; Amann and
Lembeck, 1991). In agreement with this contention, sp accounted for by depletion of the releasable peptide pool
(Ueda et al., 1984; Håkanson et al., 1987; Amann and
Lembeck, 1991). In agreement with this contention, spe-
cific desensitization to capsaicin-induced peptide rele (Ueda et al., 1984; Håkanson et al., 1987; Amann and
Lembeck, 1991). In agreement with this contention, specific desensitization to capsaicin-induced peptide release
does not occur in the rabbit iris sphincter (Amann and
L Lembeck, 1991). In agreement with this contention, specific desensitization to capsaicin-induced peptide release does not occur in the rabbit iris sphincter (Amann and Lembeck, 1991). As neuropeptide release depends on Ca cific desensitization to capsaicin-induced peptide release
does not occur in the rabbit iris sphincter (Amann and
Lembeck, 1991). As neuropeptide release depends on
 Ca^{2+} influx, depletion of the releasable peptide pool

HOM

place. In contrast, desensitization to capsaicin will not take

place. In contrast, desensitization to capsaicin-induced

peptide release in the guinea pig ureter (Dray et al., HOLZ
consequently, desensitization to capsaicin will not take
place. In contrast, desensitization to capsaicin-induced
peptide release in the guinea pig ureter (Dray et al.,
1989b) and rat urinary bladder (Amann, 1990; Ama consequently, desensitization to capsaicin will not take ir place. In contrast, desensitization to capsaicin-induced an peptide release in the guinea pig ureter (Dray et al., ib 1989b) and rat urinary bladder (Amann, 1990; consequently, desensitization to capsaicin will not take irrever
place. In contrast, desensitization to capsaicin-induced and La
peptide release in the guinea pig ureter (Dray et al., ible co
1989b) and rat urinary bladder place. In contrast, desensitization to capsaicin-induced
peptide release in the guinea pig ureter (Dray et al.,
1989b) and rat urinary bladder (Amann, 1990; Amann
and Lembeck, 1991; Maggi et al., 1990a) does not seem
to re peptide release in the guinea pig ureter (Dray et a 1989b) and rat urinary bladder (Amann, 1990; Ama and Lembeck, 1991; Maggi et al., 1990a) does not set to result exclusively from depletion of the releasal peptide pool be 1989b) and rat urinary bladder (Amann, 1990; Amann
and Lembeck, 1991; Maggi et al., 1990a) does not seem
to result exclusively from depletion of the releasable
peptide pool because, with low concentrations of capsai-
cin, and Lembeck, 1991; Maggi et al., 1990a) does not seem in
to result exclusively from depletion of the releasable an
peptide pool because, with low concentrations of capsai-
cin, it is possible to demonstrate specific desens to result exclusively from depletion of the releasable apeptide pool because, with low concentrations of capsai-
cin, it is possible to demonstrate specific desensitization lot
to capsaicin (Dray et al., 1989b; Amann, 1990 peptide pool because, with low concentrations of capsaicin, it is possible to demonstrate specific desensitization
to capsaicin (Dray et al., 1989b; Amann, 1990; Amann
and Lembeck, 1991). Furthermore, the total amount of
p cin, it is possible to demonstrate specific desensitization lor
to capsaicin (Dray et al., 1989b; Amann, 1990; Amann abland Lembeck, 1991). Furthermore, the total amount of sai
peptide released by capsaicin is in the range to capsaicin (Dray et al., 1989b; Amann, 1990; Amann ab
and Lembeck, 1991). Furthermore, the total amount of sail
peptide released by capsaicin is in the range of that ch
released by other nondesensitizing stimuli and has and Lembeck, 1991). Furthermore, the total amount of said peptide released by capsaicin is in the range of that charge released by other nondesensitizing stimuli and has been tion considered to be too small to significant released by other nondesensitizing stimuli and has been tion (Waddell and Lawson, 1989).

considered to be too small to significantly change the The long-lasting inhibition of voltage-gated Ca²⁺ chan-

peptide content o considered to be too small to significantly change the peptide content of sensory nerve endings in the rat and guinea pig (Gamse et al., 1979b; Hua et al. 1986; Dray et al. 1989b; Amann, 1990; Maggi et al., 1990a). In addi peptide content of sensory nerve endings in the rat and guinea pig (Gamse et al., 1979b; Hua et al. 1986; Dray et al. 1989b; Amann, 1990; Maggi et al., 1990a). In addition, the release of peptides induced by capsaicin is not sustained but abates within a matter of 10 to 20 min, al. 1989b; Amann, 1990; Maggi et al., 1990a). In addition, in the conduction block if a similar effect were to be the release of peptides induced by capsaicin is not sus-
tained but abates within a matter of 10 to 20 min, the release of peptides induced by capsaicin is not sustained but abates within a matter of 10 to 20 min, whereas it takes hours until a depletion of peptides from rat sensory neurons becomes appreciable (Lembeck and Donne the release of peptides induced by capsaicin is not sustained but abates within a matter of 10 to 20 min, whereas it takes hours until a depletion of peptides from rat sensory neurons becomes appreciable (Lembeck and Donne tained but abates within a matter of 10 to 20 min, tion
whereas it takes hours until a depletion of peptides from
rat sensory neurons becomes appreciable (Lembeck and
ernomerer, 1981; Bittner and LaHann, 1985; Maggi et al. whereas it takes hours until a depletion of peptides from
rat sensory neurons becomes appreciable (Lembeck and
Donnerer, 1981; Bittner and LaHann, 1985; Maggi et al.,
1987e; Donnerer and Amann, 1990). These latter data
19
 rat sensory neurons becomes appreciable (Lembeck and Donnerer, 1981; Bittner and LaHann, 1985; Maggi et al., 1987e; Donnerer and Amann, 1990). These latter data certainly do not rule out that some exhaustion of the releasa Donnerer, 1981; Bittner and LaHann, 1985; Maggi et al., 1987e; Donnerer and Amann, 1990). These latter data certainly do not rule out that some exhaustion of the releasable peptide pool, the size of which may be small comp 1987e; Donnerer and Amann, 1990). These latter data 198
certainly do not rule out that some exhaustion of the of ϵ
releasable peptide pool, the size of which may be small req
compared to the total peptide content, coul certainly do not rule out that some exhaustion of the of e
releasable peptide pool, the size of which may be small requ
compared to the total peptide content, could occur the
(Amann, 1990). It is unlikely, however, that su releasable peptide pool, the size of which may be small recompared to the total peptide content, could occur the (Amann, 1990). It is unlikely, however, that such a caps mechanism could have any bearing on desensitization compared to the total peptide content, could occur the (Amann, 1990). It is unlikely, however, that such a camechanism could have any bearing on desensitization to fit the depolarizing effect of capsaicin, peptide release (Amann, 1990). It is unlikely, however, that such a mechanism could have any bearing on desensitization to the depolarizing effect of capsaicin, peptide release being a secondary consequence of capsaicin's excitatory acti mechanism could have any bearing on desensitization to
the depolarizing effect of capsaicin, peptide release being
a secondary consequence of capsaicin's excitatory action
on sensory neurons. Peptide release depends on Ca the depolarizing effect of capsaicin, peptide release being et a secondary consequence of capsaicin's excitatory action 19 on sensory neurons. Peptide release depends on Ca^{2+} be entry through voltage-dependent membrane a secondary consequence of capsaicin's excitatory action sensory neurons. Peptide release depends on Caentry through voltage-dependent membrane channel and at present it is most reasonable to assume that the long-lasting i on sensory neurons. Peptide release depends on Ca^{2+}
entry through voltage-dependent membrane channels,
and at present it is most reasonable to assume that the
long-lasting inhibition of voltage-dependent Ca^{2+} chan-
 entry through voltage-dependent membrane channels, seed at present it is most reasonable to assume that the the capsaicin-induced dependent Ca^{2+} channels (Bleakman et al., 1990; Docherty et al., 1991) underlies the cap and at present it is most reasonable to assume that the
long-lasting inhibition of voltage-dependent Ca^{2+} chan-
nels (Bleakman et al., 1990; Docherty et al., 1991) un-
derlies the capsaicin-induced nonspecific inhibiti ng-lasting inhibition of voltage-dependent Ca²⁺ cha
 3. (Bleakman et al., 1990; Docherty et al., 1991) unities the capsaicin-induced nonspecific inhibition

ptide release.
 3. Conduction block. Periaxonal application

nels (Bleakman et al., 1990; Docherty et al., 1991) underlies the capsaicin-induced nonspecific inhibition of (peptide release.

3. Conduction block. Periaxonal application of capsaicin blocks conduction in afferent nerve cin blocks conduction in afferent nerve fibers (Petsche et al., 1983; Lynn et al., 1984), an effect that phenome-
nologically resembles nonspecific desensitization. The note) 19

19

2. Conduction block. Periaxonal application of capsai-

cin blocks conduction in afferent nerve fibers (Petsche

2. et al., 1983; Lynn et al., 1984), an effect that phenome-

a nologically resembles nonspecif 3. Conduction block. Periaxonal application of capsai-
cin blocks conduction in afferent nerve fibers (Petsche A-fi
et al., 1983; Lynn et al., 1984), an effect that phenome- a re
mologically resembles nonspecific desensiti cin blocks conduction in afferent nerve fibers (Petsche A-
et al., 1983; Lynn et al., 1984), an effect that phenome-
mologically resembles nonspecific desensitization. The sa
mechanisms underlying these two effects, howeve et al., 1983; Lynn et al., 1984), an effect that phenome-
nologically resembles nonspecific desensitization. The said
mechanisms underlying these two effects, however, do sep
not seem to be identical. Conduction block ensu nologically resembles nonspecific desensitization. The mechanisms underlying these two effects, however, do not seem to be identical. Conduction block ensues within a few minutes and, in analogy to observations made on dor mechanisms underlying these two effects, however, do separation is not seem to be identical. Conduction block ensues within fibre fibre is flow minutes and, in analogy to observations made on the initial phase of nerve blo not seem to be identical. Conduction block ensues within for a few minutes and, in analogy to observations made on the axons dorsal root ganglia (Williams and Zieglgänsberger, 1982), sit could be argued that the initial ph a few minutes and, in analogy to observations made of dorsal root ganglia (Williams and Zieglgänsberger, 1982).
it could be argued that the initial phase of nerve block due to a still prevailing depolarization of the axor. dorsal root ganglia (Williams and Zieglgänsberger, 1982),
it could be argued that the initial phase of nerve block is
due to a still prevailing depolarization of the axons
(Handwerker et al., 1984; Baranowski et al., 1986) it could be argued that the initial phase of nerve block is
due to a still prevailing depolarization of the axons
(Handwerker et al., 1984; Baranowski et al., 1986). How-
ever, the block of nerve conduction lasts much long due to a still prevailing depolarization of the axons et a

(Handwerker et al., 1984; Baranowski et al., 1986). How-

it vever, the block of nerve conduction lasts much longer C-1

than depolarization (Ault and Evans, 198 (Handwerker et al., 1984; Baranowski et al., 1986). How-
ever, the block of nerve conduction lasts much longer C-fi
than depolarization (Ault and Evans, 1980; Hayes et al., μ M
1984a; Bevan et al., 1987; Marsh et al., 1 ever, the block of nerve conduction lasts much longer C
than depolarization (Ault and Evans, 1980; Hayes et al., μ 1
1984a; Bevan et al., 1987; Marsh et al., 1987) and, with
the isolated to duration, it has actually bee than depolarization (Ault and Evans, 1980; Hayes et al., 1984a; Bevan et al., 1987; Marsh et al., 1987) and, with respect to duration, it has actually been possible to distinguish two components of nerve block in the isol 1984a; Bevan et al., 1987; Marsh et al., 1987) and, with respect to duration, it has actually been possible to distinguish two components of nerve block in the isolated vagus nerve of the rat (Waddell and Lawson, 1989). C respect to duration, it has actually been possible to distinguish two components of nerve block in the isolated vagus nerve of the rat (Waddell and Lawson, 1989). Concentrations of up to $1 \mu M$ capsaicin cause a C-fiber b distinguish two components of nerve block in the isolated Ca^{2+} (Marsh et al., 1987; Winter et al., 1990), the irre-
vagus nerve of the rat (Waddell and Lawson, 1989). versible block of C-fiber conduction is not blocked

180

consequently, desensitization to capsaicin will not take irreversible within the time of the experiment (Waddell

place. In contrast, desensitization to capsaicin-induced and Lawson, 1989). The dose dependency of the irreversible within the time of the experiment (Waddel! ER
irreversible within the time of the experiment (Wadd
and Lawson, 1989). The dose dependency of the reven
ible conduction block in vagal C-fibers (Waddell a ER
irreversible within the time of the experiment (Waddell
and Lawson, 1989). The dose dependency of the revers-
ible conduction block in vagal C-fibers (Waddell and
Lawson, 1989) is similar to that found for the capsaicin Interversible within the time of the experiment (Wad
and Lawson, 1989). The dose dependency of the revible conduction block in vagal C-fibers (Waddell
Lawson, 1989) is similar to that found for the capsai
induced depolariz irreversible within the time of the experiment (Waddell
and Lawson, 1989). The dose dependency of the revers-
ible conduction block in vagal C-fibers (Waddell and
Lawson, 1989) is similar to that found for the capsaicin-
i and Lawson, 1989). The dose dependency of the revers-
ible conduction block in vagal C-fibers (Waddell and
Lawson, 1989) is similar to that found for the capsaicin-
induced depolarization of the vagus (Marsh et al., 1987)
 ible conduction block in vagal C-fibers (Waddell and
Lawson, 1989) is similar to that found for the capsaicin-
induced depolarization of the vagus (Marsh et al., 1987)
and sciatic (Hayes et al. 1984a) nerves. Thus, althoug Lawson, 1989) is similar to that found for the capsaid induced depolarization of the vagus (Marsh et al., 19
and sciatic (Hayes et al. 1984a) nerves. Thus, althou
the transient depolarization does not explain the p
longed induced depolarization of the vagus (Marsh et al., 1987)
and sciatic (Hayes et al. 1984a) nerves. Thus, although
the transient depolarization does not explain the pro-
longed block of C-fiber conduction, it appears conceiv and sciatic (Hayes et al. 1984a) nerves. Thus, although
the transient depolarization does not explain the pro-
longed block of C-fiber conduction, it appears conceiv-
able that a common factor triggers both effects of capthe transient depolarization does not explain the longed block of C-fiber conduction, it appears conceled that a common factor triggers both effects of saicin or that depolarization triggers some function change in the axo longed block of C-fiber conduction
able that a common factor triggers
saicin or that depolarization trigg
change in the axons that outlasts t
tion (Waddell and Lawson, 1989).
The long-lasting inhibition of volt le that a common factor triggers both effects of cajicin or that depolarization triggers some function ange in the axons that outlasts the initial depolarizion (Waddell and Lawson, 1989).
The long-lasting inhibition of vo

saicin or that depolarization triggers some functional
change in the axons that outlasts the initial depolariza-
tion (Waddell and Lawson, 1989).
The long-lasting inhibition of voltage-gated Ca²⁺ chan-
nels that capsaic change in the axons that outlasts the initial depolarization (Waddell and Lawson, 1989).
The long-lasting inhibition of voltage-gated Ca²⁺ channels that capsaicin induces in sensory ganglia (Bleakman et al., 1990; Doche tion (Waddell and Lawson, 1989).
The long-lasting inhibition of voltage-gated Ca²⁺ chan-
nels that capsaicin induces in sensory ganglia (Bleakman
et al., 1990; Docherty et al., 1991) could be a major factor
in the conduc The long-lasting inhibition of voltage-gated Ca^{2+} channels that capsaicin induces in sensory ganglia (Bleakm et al., 1990; Docherty et al., 1991) could be a major fact in the conduction block if a similar effect were t nels that capsaicin induces in sensory ganglia (Bleakmannet al., 1990; Docherty et al., 1991) could be a major factor in the conduction block if a similar effect were to be
voked in afferent axons. However, whereas the inh et al., 1990; Docherty et al., 1991) could be a major fact
in the conduction block if a similar effect were to
evoked in afferent axons. However, whereas the inhit
tion of voltage-gated Ca^{2+} channels depends on the pre in the conduction block if a similar effect were to be
evoked in afferent axons. However, whereas the inhibi-
tion of voltage-gated Ca^{2+} channels depends on the pres-
ence of extracellular Ca^{2+} (Bleakman et al., 199 evoked in afferent axons. However, whereas the inhibition of voltage-gated Ca^{2+} channels depends on the presence of extracellular Ca^{2+} (Bleakman et al., 1990; Docherty et al., 1991), the block of nerve conduction in tion of voltage-gated Ca²⁺ channels depends on the presence of extracellular Ca²⁺ (Bleakman et al., 1990; Docherty et al., 1991), the block of nerve conduction in the vagus nerve is either not changed (Waddell and Law ence of extracellular Ca²⁺ (Bleakman et al., 1990; Docherty et al., 1991), the block of nerve conduction in the vagus nerve is either not changed (Waddell and Lawson, 1989) or even enhanced (Marsh et al., 1987) by remov erty et al., 1991), the block of nerve conduction in the vagus nerve is either not changed (Waddell and Lawson, 1989) or even enhanced (Marsh et al., 1987) by removal of extracellular Ca^{2+} . The presence of Ca^{2+} , how 1989) or even enhanced (Marsh et al., 1987) by removal
of extracellular Ca^{2+} . The presence of Ca^{2+} , however, is
required for the recovery of the reversible component of
the conduction block (Waddell and Lawson, 1989 of extracellular Ca^{2+} . The presence of Ca^{2+} , however, is
required for the recovery of the reversible component of
the conduction block (Waddell and Lawson, 1989). Be-
cause the ionic dependency of the capsaicin-indu the conduction block (Waddell and Lawson, 1989). Be-
cause the ionic dependency of the capsaicin-induced C-
fiber block is similar to that of excitation (Yanagisawa
et al., 1980; Baccaglini and Hogan, 1983; Marsh et al., required for the recovery of the reversible component of
the conduction block (Waddell and Lawson, 1989). Be-
cause the ionic dependency of the capsaicin-induced C-
fiber block is similar to that of excitation (Yanagisawa
 the conduction block (Waddell and Lawson, 1989). Be-
cause the ionic dependency of the capsaicin-induced C-
fiber block is similar to that of excitation (Yanagisawa
et al., 1980; Baccaglini and Hogan, 1983; Marsh et al.,
1 cause the ionic dependency of the capsaicin-induced C-
fiber block is similar to that of excitation (Yanagisawa
et al., 1980; Baccaglini and Hogan, 1983; Marsh et al.,
1987; Bettaney et al., 1988; Amann et al., 1989a), it et al., 1980; Baccaglini and Hogan, 1983; Marsh et al., 1987; Bettaney et al., 1988; Amann et al., 1989a), it could be proposed that opening of the capsaicin-operated non-selective cation channel leads to a temporary chang tentials. be proposed that opening of the capsaicin-operated non-
selective cation channel leads to a temporary change in
the axons which precludes the conduction of action po-
tentials. The dose dependency of the persistent ("irrev

selective cation channel leads to a temporary change in
the axons which precludes the conduction of action po-
tentials.
The dose dependency of the persistent ("irreversible")
C-fiber block in the vagus nerve (Waddell and the axons which precludes the conduction of action po
tentials.
The dose dependency of the persistent ("irreversible"
C-fiber block in the vagus nerve (Waddell and Lawson
1989) is similar to that of the A-fiber block (Bara tentials.
The dose dependency of the persistent ("irreversible")
C-fiber block in the vagus nerve (Waddell and Lawson,
1989) is similar to that of the A-fiber block (Baranowski
et al., 1986; Marsh et al., 1987). The blocka The dose dependency of the persistent ("irreversible")
C-fiber block in the vagus nerve (Waddell and Lawson,
1989) is similar to that of the A-fiber block (Baranowski
et al., 1986; Marsh et al., 1987). The blockade of affe C-fiber block in the vagus nerve (Waddell and Lawson,
1989) is similar to that of the A-fiber block (Baranowski
et al., 1986; Marsh et al., 1987). The blockade of afferent
A-fibers, however, is readily reversible and most 1989) is similar to that of the A-fiber block (Baranowski
et al., 1986; Marsh et al., 1987). The blockade of afferent
A-fibers, however, is readily reversible and most probably
a reflection of the cell-nonselective actions et al., 1986; Marsh et al., 1987). The blockade of afferent A-fibers, however, is readily reversible and most probably a reflection of the cell-nonselective actions which capsaicin exerts on a variety of neurons, as is dis A-fibers, however, is readily reversible and most probably
a reflection of the cell-nonselective actions which cap-
saicin exerts on a variety of neurons, as is discussed in a
separate section, whereas the irreversible blo a reflection of the cell-nonselective actions which capsaicin exerts on a variety of neurons, as is discussed in a separate section, whereas the irreversible block of C-
fiber conduction is a sensory neuron-selective effec saicin exerts on a variety of neurons, as is discussed in a separate section, whereas the irreversible block of C-
fiber conduction is a sensory neuron-selective effect of
the drug. Because perineural application of millim separate section, whereas the irreversible block of C-
fiber conduction is a sensory neuron-selective effect of
the drug. Because perineural application of millimolar
solutions of capsaicin leads to a permanent degeneratio fiber conduction is a sensory neuron-selective effect of the drug. Because perineural application of millimolar solutions of capsaicin leads to a permanent degeneration of unmyelinated (probably afferent) nerve fibers (Lyn the drug. Because perineural application of millimolar solutions of capsaicin leads to a permanent degeneration of unmyelinated (probably afferent) nerve fibers (Lynn et al., 1987; Jancsó and Lawson, 1990; Pini et al., 199 solutions of capsaicin leads to a permanent degeneration
of unmyelinated (probably afferent) nerve fibers (Lynn
et al., 1987; Jancsó and Lawson, 1990; Pini et al., 1990),
it would be logical to infer that the irreversible of unmyelinated (probably afferent) nerve fibers (Lynn
et al., 1987; Jancsó and Lawson, 1990; Pini et al., 1990),
it would be logical to infer that the irreversible block of
C-fiber conduction induced by concentrations of et al., 1987; Jancsó and Lawson, 1990; Pini et al., 1990),
it would be logical to infer that the irreversible block of
C-fiber conduction induced by concentrations of 3 to 50
 μ M (Waddell and Lawson, 1989) reflects neuro it would be logical to infer that the irreversible block of C-fiber conduction induced by concentrations of 3 to 50 μ M (Waddell and Lawson, 1989) reflects neurotoxicity of the drug. However, although the neurotoxic eff C-fiber conduction induced by concentrations of 3 to 50 μ M (Waddell and Lawson, 1989) reflects neurotoxicity of the drug. However, although the neurotoxic effects of capsaicin can be inhibited by the removal of extrace μ M (Waddell and Lawson, 1989) reflects neurotoxicity of
the drug. However, although the neurotoxic effects of
capsaicin can be inhibited by the removal of extracellular
Ca²⁺ (Marsh et al., 1987; Winter et al., 1990), the drug. However, although the neurotoxic effects of capsaicin can be inhibited by the removal of extracellular Ca²⁺ (Marsh et al., 1987; Winter et al., 1990), the irreversible block of C-fiber conduction is not blocked capsaicin can be inhibited by the removal of extracellular Ca²⁺ (Marsh et al., 1987; Winter et al., 1990), the irreversible block of C-fiber conduction is not blocked by this maneuver (Waddell and Lawson, 1989). It follo Ca^{2+} (Marsh et al., 1987; Winter et al., 1990), the irreversible block of C-fiber conduction is not blocked by this maneuver (Waddell and Lawson, 1989). It follows that the persistent C-fiber block, at least in its ini

PHARMACOLOGICAL REVIEWS

CAPSAIC
mulation as is the case for the neurotoxic action of lucapsaicin. In conclusion, the mechanisms of capsaicinmulation as is the case for the neurotoxic action
capsaicin. In conclusion, the mechanisms of capsai
induced blockade of C-fiber conduction remain to CAPSAICII

mulation as is the case for the neurotoxic action of luk

capsaicin. In conclusion, the mechanisms of capsaicin-

induced blockade of C-fiber conduction remain to be

lelucidated.

dif elucidated.

capsaicin. In conclusion, the mechanisms of capsaicin-
induced blockade of C-fiber conduction remain to be
elucidated.
4. Neurotoxicity. a. INTRACELLULAR ACCUMULATION
of CALCIUM AND NACL. From the evidence available it
se induced blockade of C-fiber conduction remain to be
elucidated. (
4. Neurotoxicity. a. INTRACELLULAR ACCUMULATION
of CALCIUM AND NACL. From the evidence available it
seems that the stimulant and initial neurotoxic effects elucidated.
4. Neurotoxicity. a. INTRACELLULAR ACCUMULATION
OF CALCIUM AND NACL. From the evidence available
seems that the stimulant and initial neurotoxic effec
of capsaicin-related compounds arise from similar mec
anism 4. Neurotoxicity. a. INTRACELLULAR ACCUMULATION
OF CALCIUM AND NACL. From the evidence available it
seems that the stimulant and initial neurotoxic effects
of capsaicin-related compounds arise from similar mech-
anisms of OF CALCIUM AND NACL. From the evidence available it reverses that the stimulant and initial neurotoxic effects tion of capsaicin-related compounds arise from similar mechanisms of action. Two pathways leading to neurotoxi seems that the stimulant and initial neurotoxic effects
of capsaicin-related compounds arise from similar mech-
anisms of action. Two pathways leading to neurotoxicity
can be differentiated, one pathway depending on the
i of capsaicin-related compounds arise from similar mech-
anisms of action. Two pathways leading to neurotoxicity
can be differentiated, one pathway depending on the ing
influx of Ca^{2+} and the other involving intracellul anisms of action. Two pathways leading to neurotoxicity relation of the expression of NaCl. The critical involvement of Ca^{2+} in the expression of neurotoxicity is demonstrated by the expression of neurotoxicity is demo can be differentiated, one pathway depending on the ing calcium, temporary nonspecific desensitization will
influx of Ca^{2+} and the other involving intracellular ac-
cumulation of NaCl. The critical involvement of Ca^{2+ influx of Ca²⁺ and the other involving intracellular ac-
cumulation of NaCl. The critical involvement of Ca²⁺ in
the expression of neurotoxicity is demonstrated by the
findings that the neuronal damage caused by capsa cumulation of NaCl. The critical involvement of Ca^{2+} in
the expression of neurotoxicity is demonstrated by the
findings that the neuronal damage caused by capsaicin
and resiniferatoxin is markedly reduced by removal of the expression of neurotoxicity is demonstrated by the findings that the neuronal damage caused by capsaiciand resiniferatoxin is markedly reduced by removal extracellular Ca^{2+} (Marsh et al., 1987; Winter et al., 1990 findings that the neuronal damage caused by capsaicin^{qua}
and resiniferatoxin is markedly reduced by removal of
extracellular Ca²⁺ (Marsh et al., 1987; Winter et al., 1990)
but not by blockade of voltage-dependent calc and resiniferatoxin is markedly reduced by removal of
extracellular Ca^{2+} (Marsh et al., 1987; Winter et al., 1990)
but not by blockade of voltage-dependent calcium chan-
nels (Marsh et al., 1987). These observations ha extracellular Ca²⁺ (Marsh et al., 1987; Winter et al., 1990)
but not by blockade of voltage-dependent calcium chan-
nels (Marsh et al., 1987). These observations have been
taken to infer that entry of Ca²⁺ into the ce but not by blockade of voltage-dependent calcium channels (Marsh et al., 1987). These observations have been taken to infer that entry of Ca^{2+} into the cell is a priming event for the neurotoxic action of capsaicin (Ma event for the neurotoxic action of capsaicin (Marsh et al., 1987). Entry of Ca^{2+} is an early response to capsaicin al., 1987). Entry of Ca²⁺ is an early response to capsaicin
and related compounds and, in line with this, exposure
of isolated nodose ganglion cells to 1 to 10 μ M capsaicin
leads to disruption of the microtubular and and related compounds and, in line with this, exposure of isolated nodose ganglion cells to 1 to 10 μ M capsaicin leads to disruption of the microtubular and neurofilament organization within 5 to 10 min (Marsh et al., leads to disruption of the microtubular and neurofila-
ment organization within 5 to 10 min (Marsh et al., 1987). Cell damage in cultured sensory neurons develops
at a similar speed (Winter et al., 1990), and the ultr ment organization within 5 to 10 min (Marsh et al., 1987). Cell damage in cultured sensory neurons develops at a similar speed (Winter et al., 1990), and the ultra-
structural alterations are paralleled by a quick defunc-
 ment organization within 5 to 10 min (Marsh et al., 1987). Cell damage in cultured sensory neurons develops at a similar speed (Winter et al., 1990), and the ultrastructural alterations are paralleled by a quick defunctio 1987). Cell damage in cultured sensory neurons develops
at a similar speed (Winter et al., 1990), and the ultra-
structural alterations are paralleled by a quick defunc-
tionalization of sensory neurons (Marsh et al., 198 at a similar speed (Winter et al., 1990), and the ultra-
structural alterations are paralleled by a quick defunc-
tionalization of sensory neurons (Marsh et al., 1987;
Winter et al., 1990). The way in which Ca^{2+} influx structural alterations are paralleled by a quick defunctionalization of sensory neurons (Marsh et al., 1987; Winter et al., 1990). The way in which Ca^{2+} influx leads to damage has not yet been studied, but it is likely tionalization of sensory neurons (Marsh et al., 1987;
Winter et al., 1990). The way in which Ca^{2+} influx leads
to damage has not yet been studied, but it is likely that
the massive accumulation of intracellular calcium Winter et al., 1990). The way in which Ca^{2+} influx leads
to damage has not yet been studied, but it is likely that
the massive accumulation of intracellular calcium that
capsaicin and resiniferatoxin bring about in cul to damage has not yet been studied, but it is likely that
the massive accumulation of intracellular calcium that
capsaicin and resiniferatoxin bring about in cultured
the sensory neurons (Wood et al., 1988; Winter et al., the massive accumulation of intracellular calcium that

capsaicin and resiniferatoxin bring about in cultured

sensory neurons (Wood et al., 1988; Winter et al., 1990)

is a key event. This inference is supported by the f sensory neurons (Wood et al., 1988; Winter et al., 1990)

is a key event. This inference is supported by the finding

that 2 μ M capsaicin, which induces maximal calcium

accumulation, causes a similar proportion of cul is a key event. This inference is supported by the finding
that 2 μ M capsaicin, which induces maximal calcium
accumulation, causes a similar proportion of cultured
sensory neurons to degenerate (Wood et al., 1988) as
i that 2 μ M capsaicin, which induces maximal calcium
accumulation, causes a similar proportion of cultured
sensory neurons to degenerate (Wood et al., 1988) as
does systemic treatment of newborn rats with 50 mg/kg
capsai sensory neurons to degenerate (Wood et al., 1988) as in ser-
does systemic treatment of newborn rats with 50 mg/kg 1975,
capsaicin. Furthermore, exposure of B-type sensory neu-
rons to capsaicin or resiniferatoxin in vivo does systemic treatment of newborn rats with 50 mg/kg
capsaicin. Furthermore, exposure of B-type sensory neu-
rons to capsaicin or resiniferatoxin in vivo is followed by
the histochemically demonstrable appearance of calci rons to capsaicin or resiniferatoxin in vivo is followed by
the histochemically demonstrable appearance of calcium
in the cell bodies of these neurons (Szallasi et al., 1989), development of damage is more rapid when both the histochemically demonstrable appearance of calcium e histochemically demonstrable appearance of calcium
the cell bodies of these neurons (Szallasi et al., 1989),
effect that is particularly pronounced when capsaicin
given to newborn rats (Jancsó et al., 1978, 1984).
Excess in the cell bodies of these neurons (Szallasi et al., 1989),
an effect that is particularly pronounced when capsaicin
is given to newborn rats (Jancsó et al., 1978, 1984).
Excessive accumulation of calcium within cells is

an effect that is particularly pronounced when capsaicin
is given to newborn rats (Jancsó et al., 1978, 1984).
Excessive accumulation of calcium within cells is ex-
tremely toxic and appears to be a common final process
in is given to newborn rats (Jancsó et al., 1978, 1984).
Excessive accumulation of calcium within cells is
tremely toxic and appears to be a common final proc
by which toxins cause degeneration and cell de
(Schanne et al., 19 Excessive accumulation of calcium within cells is ex-
tremely toxic and appears to be a common final process
by which toxins cause degeneration and cell death
the
(Schanne et al., 1979; Kamakura et al., 1983). Calcium-
fr tremely toxic and appears to be a common final process ind
by which toxins cause degeneration and cell death the
(Schanne et al., 1979; Kamakura et al., 1983). Calcium-
from
activated proteases and other degradative enzyme by which toxins cause degeneration and cell death the de (Schanne et al., 1979; Kamakura et al., 1983). Calcium-
activated proteases and other degradative enzymes are 1981; thought to destroy the cytoskeletal organization activated proteases and other degradative enzymes a
thought to destroy the cytoskeletal organization as
thereby to interfere, for example, with axoplasmic fle
(Kamakura et al., 1983), a function that is also inhibit
by cap thought to destroy the cytoskeletal organization and
thereby to interfere, for example, with axoplasmic flow
(Kamakura et al., 1983), a function that is also inhibited
by capsaicin (Gamse et al., 1982). In addition, the ca

CIN
lular calcium is apparently lower than that of other
neurons (Jia and Nelson, 1986; Maggi and Meli, 1988). neurons (Jia and Nelson, 1986; Maggi and Meli, 1988).
It could be deduced from these considerations that
It could be deduced from these considerations that

mulation as is the case for the neurotoxic action of lular calcium is apparently lower than that of other capsaicin. In conclusion, the mechanisms of capsaicin-
induced blockade of C-fiber conduction remain to be It could 181
Iar calcium is apparently lower than that of other
urons (Jia and Nelson, 1986; Maggi and Meli, 1988).
It could be deduced from these considerations that
fferent degrees of calcium accumulation, and the rapidlular calcium is apparently lower than that of oth
neurons (Jia and Nelson, 1986; Maggi and Meli, 1988)
It could be deduced from these considerations th
different degrees of calcium accumulation, and the rapi
ity with whic lular calcium is apparently lower than that of other
neurons (Jia and Nelson, 1986; Maggi and Meli, 1988).
It could be deduced from these considerations that
different degrees of calcium accumulation, and the rapid-
ity wi reversed, dia and Nelson, 1986; Maggi and Meli, 1
It could be deduced from these considerations
different degrees of calcium accumulation, and the
ity with which the calcium overloading of the cell
reversed, determine whet It could be deduced from these considerations the different degrees of calcium accumulation, and the rapity with which the calcium overloading of the cell can reversed, determine whether transient defunctionalizion (nonspe different degrees of calcium accumulation, and the rapid-
ity with which the calcium overloading of the cell can be
reversed, determine whether transient defunctionaliza-
tion (nonspecific desensitization) or long-lasting ity with which the calcium overloading of the cell can l
reversed, determine whether transient defunctionaliz
tion (nonspecific desensitization) or long-lasting neur
toxicity ensues. Under circumstances in which the co
rem reversed, determine whether transient defunctionaliza-
tion (nonspecific desensitization) or long-lasting neuro-
toxicity ensues. Under circumstances in which the cell
remains capable of buffering and disposing of the ente tion (nonspecific desensitization) or long-lasting neurotoxicity ensues. Under circumstances in which the cell
remains capable of buffering and disposing of the enter-
ing calcium, temporary nonspecific desensitization wil toxicity ensues. Under circumstances in which the cell
remains capable of buffering and disposing of the enter-
ing calcium, temporary nonspecific desensitization will
be observed. However, when the cellular calcium loadin remains capable of buffering and disposing of the enter-
ing calcium, temporary nonspecific desensitization will
be observed. However, when the cellular calcium loading
in response to high concentrations of capsaicin is in ing calcium, temporary nonspecific desensitization w
be observed. However, when the cellular calcium loadii
in response to high concentrations of capsaicin is
excess of that which can be buffered and disposed
quickly, calc be observed. However, wh
in response to high concexcess of that which can
quickly, calcium accumula
changes and cell damage.
The observation that the response to high concentrations of capsaicin is
cess of that which can be buffered and disposed
ickly, calcium accumulation will lead to ultrastructu
anges and cell damage.
The observation that the neurotoxic effects of ca

taken to infer that entry of Ca^{2+} into the cell is a priming
event for the neurotoxic action of capsaicin (Marsh et
al., 1987). Entry of Ca^{2+} is an early response to capsaicin
and related compounds and, in line with sensory neurons (Wood et al., 1988; Winter et al., 1990)
is (Hogan, 1983; Bevan and Szolcsányi, 1990; Winter
is a key event. This inference is supported by the finding
that 2 μ M capsaicin, which induces maximal calcium sensory neurons to degenerate (Wood et al., 1988) as in sensory neurons (Joó et al., 1969, Szolcsányi et al., does systemic treatment of newborn rats with 50 mg/kg 1975, 1990; Hoyes and Barber, 1981; Hoyes et al., 1981; c excess of that which can be buffered and disposed of quickly, calcium accumulation will lead to ultrastructural changes and cell damage.
The observation that the neurotoxic effects of capsai-
cin and resiniferatoxin on cul quickly, calcium accumulation will lead to ultrastructural
changes and cell damage.
The observation that the neurotoxic effects of capsai-
cin and resiniferatoxin on cultured sensory neurons are
also reduced when NaCl is r changes and cell damage.
The observation that the neurotoxic effects of capsaicin and resiniferatoxin on cultured sensory neurons are also reduced when NaCl is replaced by sucrose, but abolished only when, in addition, ex The observation that the neurotoxic effects of capse
cin and resiniferatoxin on cultured sensory neurons a
also reduced when NaCl is replaced by sucrose, b
abolished only when, in addition, external Ca^{2+} is r
moved as cin and resiniferatoxin on cultured sensory neurons are also reduced when NaCl is replaced by sucrose, but abolished only when, in addition, external Ca^{2+} is removed as well, indicates the existence of a second mechani abolished only when, in addition, external Ca^{2+} is removed as well, indicates the existence of a second mechmoved as well, indicates the existence of a second mechanism of neurotoxicity (Winter et al., 1990). This other pathway requires the availability of permeant monovalent cations and anions and, under physiological conditio anism of neurotoxicity (Winter et al., 1990). This other pathway requires the availability of permeant monovalent cations and anions and, under physiological conditions, appears to involve the influx of $N a^+$ through the pathway requires the availability of permeant monovalent cations and anions and, under physiological conditions, appears to involve the influx of Na⁺ through the capsaicin-operated cation channels; Na⁺ entry is passive lent cations and anions and, under physiological condi-
tions, appears to involve the influx of Na^+ through the
capsaicin-operated cation channels; Na^+ entry is pas-
sively followed by Cl^- through a "resting leakage" capsaicin-operated cation channels; Na⁺ entry is passively followed by Cl⁻ through a "resting leakage" route (Bevan and Szolcsányi, 1990; Winter et al., 1990). This comovement of Na⁺ and Cl⁻ is necessary for neuro permeant ion glutamate abolishes those toxic effects of capsaicin and resiniferatoxin that are seen in the absence (Bevan and Szolcsányi, 1990; Winter et al., 1990). This comovement of Na⁺ and Cl⁻ is necessary for neurotoxicity because replacement of external Cl⁻ with the impermeant ion glutamate abolishes those toxic effects of comovement of Na⁺ and Cl⁻ is necessary for neurotox-
icity because replacement of external Cl⁻ with the im-
permeant ion glutamate abolishes those toxic effects of
capsaicin and resiniferatoxin that are seen in the icity because replacement of external Cl⁻ with the im-
permeant ion glutamate abolishes those toxic effects of
capsaicin and resiniferatoxin that are seen in the absence
of external Ca²⁺ (Winter et al., 1990). The ent permeant ion glutamate abolishes those toxic effects of capsaicin and resiniferatoxin that are seen in the absence of external Ca²⁺ (Winter et al., 1990). The entry of Na⁺ and Cl⁻ will result in a net uptake of NaCl, capsaicin and resiniferatoxin that are seen in the absence
of external Ca²⁺ (Winter et al., 1990). The entry of Na⁺
and Cl⁻ will result in a net uptake of NaCl, which is
thought to be followed by an influx of water a and Cl⁻ will result in a net uptake of NaCl, which is thought to be followed by an influx of water and osmotic thought to be followed by an influx of water and osmotic
lysis (Hogan, 1983; Bevan and Szolcsányi, 1990; Winter
et al., 1990). Fiber enlargement and swelling of mito-
chondria indeed are prominent features of the ultrastru lysis (Hogan, 1983; Bevan and Szolcsányi, 1990; Winter
et al., 1990). Fiber enlargement and swelling of mito-
chondria indeed are prominent features of the ultrastruc-
tural changes produced by capsaicin-related compounds
 et al., 1990). Fiber enlargement and swelling of mito-
chondria indeed are prominent features of the ultrastruc-
tural changes produced by capsaicin-related compounds
in sensory neurons (Joó et al., 1969, Szolcsányi et al. chondria indeed are prominent features of the ultrastructural changes produced by capsaicin-related compounds
in sensory neurons (Joó et al., 1969, Szolcsányi et al.,
1975, 1990; Hoyes and Barber, 1981; Hoyes et al., 1981; tural changes produced by capsaicin-related compounds
in sensory neurons (Joó et al., 1969, Szolcsányi et al.,
1975, 1990; Hoyes and Barber, 1981; Hoyes et al., 1981;
Sikri et al., 1981; Chiba et al., 1986, Marsh et al., 1 in sensory neurons (Joó et al., 1969, Szolcsányi et al., 1975, 1990; Hoyes and Barber, 1981; Hoyes et al., 1981;
Sikri et al., 1981; Chiba et al., 1986, Marsh et al., 1987;
Szallasi et al., 1989). Sensory neurons in cultur 1975, 1990; Hoyes and Barber, 1981; Hoyes et al., 1981;
Sikri et al., 1981; Chiba et al., 1986, Marsh et al., 1987;
Szallasi et al., 1989). Sensory neurons in culture can be
killed by either pathway of neurotoxicity alone, Sikri et al., 1981; Chiba et al., 1986, Marsh et al., 198
Szallasi et al., 1989). Sensory neurons in culture can
killed by either pathway of neurotoxicity alone, but t
development of damage is more rapid when both opera
si killed by either pathway of neurotoxicity alone, but the development of damage is more rapid when both operate simultaneously as is the case under physiological conditions (Bevan and Szolcsányi, 1990; Winter et al., 1990). velopment of damage is more rapid when both openultaneously as is the case under physiological comes (Bevan and Szolcsányi, 1990; Winter et al., 1996). SECONDARY DEPLETION OF PEPTIDES. Capsaiduced cell damage and/or defunc simultaneously as is the case under physiological conditions (Bevan and Szolcsányi, 1990; Winter et al., 1990).
b. SECONDARY DEPLETION OF PEPTIDES. Capsaicin-
induced cell damage and/or defunctionalization precede

(Schanne et al., 1979; Kamakura et al., 1983). Calcium-
activated proteases and other degradative enzymes are
activated proteases and other degradative enzymes are
1981; Gamse et al., 1982; Bittner and LaHann, 1985;
though simultaneously as is the case under physiological condi-
tions (Bevan and Szolcsányi, 1990; Winter et al., 1990).
b. SECONDARY DEPLETION OF PEPTIDES. Capsaicin-
induced cell damage and/or defunctionalization precede
the de tions (Bevan and Szolcsányi, 1990; Winter et al., 1990).
b. SECONDARY DEPLETION OF PEPTIDES. Capsaicin-
induced cell damage and/or defunctionalization precede
the depletion of peptide markers such as substance P
from senso b. SECONDARY DEPLETION OF PEPTIDES. Capsaicin-
induced cell damage and/or defunctionalization precede
the depletion of peptide markers such as substance P
from sensory neurons in the rat (Lembeck and Donnerer,
1981; Gamse induced cell damage and/or defunctionalization precede
the depletion of peptide markers such as substance P
from sensory neurons in the rat (Lembeck and Donnerer,
1981; Gamse et al., 1982; Bittner and LaHann, 1985;
Maggi e the depletion of peptide markers such as substance P
from sensory neurons in the rat (Lembeck and Donnerer,
1981; Gamse et al., 1982; Bittner and LaHann, 1985;
Maggi et al., 1987d,e) and guinea pig (Miller et al., 1982a;
B from sensory neurons in the rat (Lembeck and Donnerer, 1981; Gamse et al., 1982; Bittner and LaHann, 1985; Maggi et al., 1987d,e) and guinea pig (Miller et al., 1982a; Buck et al., 1983), although there are rapid changes i 1981; Gamse et al., 1982; Bittner and LaHann, 1985;
Maggi et al., 1987d,e) and guinea pig (Miller et al., 1982a;
Buck et al., 1983), although there are rapid changes in
the immunohistochemical appearance of substance P-
co Maggi et al., 1987d,e) and guinea pig (Miller et al., 1982a;
Buck et al., 1983), although there are rapid changes in
the immunohistochemical appearance of substance P-
containing nerve fibers (Papka et al., 1984). It follo

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

182 **HOLZER**
ents is a secondary consequence of the neurotoxic action ferate
of capsaicin on sensory neurons of the rat and guinea endir HOLZE
ents is a secondary consequence of the neurotoxic action
of capsaicin on sensory neurons of the rat and guinea
pig. Consequently, it is not depletion of transmitter p HO
ents is a secondary consequence of the neurotoxic action
of capsaicin on sensory neurons of the rat and guinea
pig. Consequently, it is not depletion of transmitter
substances that leads to a long-lasting defunctionaliz ents is a secondary consequence of the neurotoxic
of capsaicin on sensory neurons of the rat and β
pig. Consequently, it is not depletion of trans
substances that leads to a long-lasting defunction
tion of sensory neuro pig. Consequently, it is not depletion of transmitter pig. Consequently, it is not depletion of transmitter substances that leads to a long-lasting defunctionalization of sensory neurons as was thought in the early phases of research on capsaicin. It may be, however, that und substances that leads to a long-lasting defunctionaliza-calcion of sensory neurons as was thought in the early (An phases of research on capsaicin. It may be, however, that brounder certain circumstances peptide depletion tion of sensory neurons as was thought in the early
phases of research on capsaicin. It may be, however, that
under certain circumstances peptide depletion is a factor
in the later stages of the inhibitory effect of capsai phases of research on capsaicin. It may be, however, the under certain circumstances peptide depletion is a fact
in the later stages of the inhibitory effect of capsaicin esensory neuron functions in the rat (Gamse et al., under certain circumstances peptide depletion is a factor
in the later stages of the inhibitory effect of capsaicin on
sensory neuron functions in the rat (Gamse et al., 1982;
Maggi et al. 1987d). For instance, the onset o in the later stages of the inhibitory effect of capsaicin on sensory neuron functions in the rat (Gamse et al., 1982; Maggi et al. 1987d). For instance, the onset of the inhibitory effect, which perineural capsaicin exerts sensory neuron functions in the rat (Gamse et al., 1982; Maggi et al. 1987d). For instance, the onset of the inhibitory effect, which perineural capsaicin exerts on local effector functions of peripheral sensory nerve endi Maggi et al. 1987d). For instance, the onset of the inhibitory effect, which perineural capsaicin exerts on local effector functions of peripheral sensory nerve endings, parallels that of substance P depletion from afferen itory effect, which perineural capsaicin exerts on local Perfector functions of peripheral sensory nerve endings, diparallels that of substance P depletion from afferent runerve fibers distal to the treatment site (Gamse e effector functions of peripheral sensory nerve endings, disparallels that of substance P depletion from afferent runder of the function causes the functional deficit, but the inevidence for such a relationship is only corr parallels that of substance P depletion from afferent rut
nerve fibers distal to the treatment site (Gamse et al., Cer
1982). It could be inferred, therefore, that in this case
peptide depletion causes the functional defic nerve fibers distal to the treatment site (Gamse et al., 1982). It could be inferred, therefore, that in this case peptide depletion causes the functional deficit, but the evidence for such a relationship is only correlati 1982). It could be inferred, therefore, that in this case
peptide depletion causes the functional deficit, but the
evidence for such a relationship is only correlative and
not causal. There are too few data to decide wheth peptide depletion causes the functional deficit, but the ine evidence for such a relationship is only correlative and observed than in the rat of decide whether defthere is a similar situation in the rabbit, in which capsi evidence for such a relationship is only correlative and
not causal. There are too few data to decide whether
there is a similar situation in the rabbit, in which cap-
saicin is less neurotoxic than in the rat or guinea pi not causal. There are too few data to decide whether
there is a similar situation in the rabbit, in which cap-
saicin is less neurotoxic than in the rat or guinea pig and
in which this drug apparently fails to induce degen there is a similar situation in the rabbit, in which capsaicin is less neurotoxic than in the rat or guinea pig and
in which this drug apparently fails to induce degeneration
or morphological damage of sensory neurons. Cap saicin is less neurotoxic than in the rat or guinea pig and 19
in which this drug apparently fails to induce degeneration Ce
or morphological damage of sensory neurons. Capsaicin, et
however, is capable of stimulating and in which this drug apparently fails to induce degeneration
or morphological damage of sensory neurons. Capsaicin,
however, is capable of stimulating and defunctionalizing
sensory neurons in this species (Szolcsányi, 1987). or morphological damage of sensory neurons. Capsaicin, et however, is capable of stimulating and defunctionalizing lat sensory neurons in this species (Szolcsányi, 1987). It is lat conceivable, therefore, that in the rabbi however, is capable of stimulating and defunctionalizing leasens ory neurons in this species (Szolcsányi, 1987). It is leader conceivable, therefore, that in the rabbit nonspecific probassitization to capsaicin results fro sensory neurons in this species (Szolcsé
conceivable, therefore, that in the ral
desensitization to capsaicin results from
releasable pool of sensory neuropeptide
al., 1987; Amann and Lembeck, 1991).
5. Ruthenium red as a conceivable, therefore, that in the rabbit nonspecific desensitization to capsaicin results from depletion of the releasable pool of sensory neuropeptides (Håkanson et al., 1987; Amann and Lembeck, 1991).
5. *Ruthenium red*

releasable pool of sensory neuropeptides (Håkanson et al., 1987; Amann and Lembeck, 1991).
5. Ruthenium red as a functional antagonist of capsai-
cin. The inorganic dye ruthenium red inhibits the cap-
saicin-induced stimul al., 1987; Amann and Lembeck, 1991).
5. Ruthenium red as a functional antagonist of capsai-
cin. The inorganic dye ruthenium red inhibits the cap-
saicin-induced stimulation of sensory neurons and pre-
vents their desensit 5. Ruthenium red as a functional antagonist of capsaicin. The inorganic dye ruthenium red inhibits the capsaicin-induced stimulation of sensory neurons and prevents their desensitization to capsaicin in rat, guinea pig, l cin. The inorganic dye ruthenium red inhibits the capacion-induced stimulation of sensory neurons and prevents their desensitization to capsaicin in rat, guinea pirabbit, and other species (Amann and Maggi, 1991). Athe co saicin-induced stimulation of sensory neurons and p
vents their desensitization to capsaicin in rat, guinea p
rabbit, and other species (Amann and Maggi, 1991).
the concentration range of 0.03 to 1 μ M, the dye sele
tiv vents their desensitization to capsaicin in rat, guinea pig, rabbit, and other species (Amann and Maggi, 1991). At the concentration range of 0.03 to 1 μ M, the dye selectively blocks capsaicin/resiniferatoxin-induced e rabbit, and other species (Amann and Maggi, 1991). At the concentration range of 0.03 to 1μ M, the dye selectively blocks capsaicin/resiniferatoxin-induced excitation of afferent neurons and leaves responses to other the concentration range of 0.03 to 1 μ M, the dye selectively blocks capsaicin/resiniferatoxin-induced excitation of afferent neurons and leaves responses to other stimuli unaffected. Depending on the tissue under study tively blocks capsaicin/resiniferatoxin-induced excita-
tion of afferent neurons and leaves responses to other The
stimuli unaffected. Depending on the tissue under study, cula
the selectivity for capsaicin-related compou tion of afferent neurons and leaves responses to other "stimuli unaffected. Depending on the tissue under study, che selectivity for capsaicin-related compounds is lost is when concentrations of ruthenium red higher than stimuli unaffected. Depending on the tissue under study, cularities about the selectivity for capsaicin-related compounds is lost intum when concentrations of ruthenium red higher than 1 to when 20μ M are used (Amann an the selectivity for capsaicin-related compounds is lost intr
when concentrations of ruthenium red higher than 1 to whe
 20μ M are used (Amann and Maggi, 1991). The inhibitory met
effect of ruthenium red has been demonstr when concentrations of ruthenium red higher than 1 to
20 μ M are used (Amann and Maggi, 1991). The inhibitory neffect of ruthenium red has been demonstrated on a tvariety of sensory neuron-mediated reflex responses to s 20μ M are used (Amann and Maggi, 1991). The inhibitory effect of ruthenium red has been demonstrated on a variety of sensory neuron-mediated reflex responses to capsaicin including excitation of nociceptors as measured effect of ruthenium red has been demonstrated on a
variety of sensory neuron-mediated reflex responses to
capsaicin including excitation of nociceptors as measured
by depolarization of spinal ventral roots (Dray et al.,
19 variety of sensory neuron-mediated reflex responses to
capsaicin including excitation of nociceptors as measured
by depolarization of spinal ventral roots (Dray et al.,
1990d), cardiovascular reflexes (Amann and Lembeck,
1 capsaicin including excitation of nociceptors as measured
by depolarization of spinal ventral roots (Dray et al., ci
1990d), cardiovascular reflexes (Amann and Lembeck, t
1989; Amann et al., 1989a, 1990a; Maggi et al., 198 by depolarization of spinal ventral roots (Dray et al., 1990d), cardiovascular reflexes (Amann and Lembeck, 1989; Amann et al., 1989a, 1990a; Maggi et al., 1989a, 1990c), the Bezold-Jarisch reflex (Pethö and Szolcsányi, 19 1990d), cardiovascular reflexes (Amann and Lembe
1989; Amann et al., 1989a, 1990a; Maggi et al., 198
1990c), the Bezold-Jarisch reflex (Pethö and Szolcsár
1990), and motor reflexes of the urinary bladder (Ma
et al., 1989a) 1989; Amann et al., 1989a, 1990a; Maggi et al., 1989a, 1990c), the Bezold-Jarisch reflex (Pethö and Szolcsányi, 1990), and motor reflexes of the urinary bladder (Maggi et al., 1989a). Activation of sensory neurons by mecha 1990c), the Bezold-Jarisch reflex (Pethö and Szolcsány
1990), and motor reflexes of the urinary bladder (Mag
et al., 1989a). Activation of sensory neurons by mechai
ical stimuli (Maggi et al., 1989a; Dray et al., 1990d
ace 1990), and motor reflexes of the urinary bladder (Maggi
et al., 1989a). Activation of sensory neurons by mechan-
ical stimuli (Maggi et al., 1989a; Dray et al., 1990d),
acetylcholine, bradykinin, and 5-hydroxytryptamine
(A et al., 1989a). Activation of sensory neurons by mechanical stimuli (Maggi et al., 1989a; Dray et al., 1990d), acetylcholine, bradykinin, and 5-hydroxytryptamine (Amann and Lembeck, 1989; Amann et al., 1989a, 1990a; Dray e ical stimuli (Maggi et al., 1989a; Dray et al., 1990d
acetylcholine, bradykinin, and 5-hydroxytryptamin
(Amann and Lembeck, 1989; Amann et al., 1989a, 1990;
Dray et al., 1990d) is not affected by ruthenium ree
Reflex respo acetylcholine, bradykinin, and 5-hydroxytryptamine (Amann and Lembeck, 1989; Amann et al., 1989a, 1990a; Dray et al., 1990d) is not affected by ruthenium red.
Reflex responses to noxious heat either remain unaffected (Dray (Amann and Lembeck, 1989; Amann et al., 1989a,
Dray et al., 1990d) is not affected by ruthenium
Reflex responses to noxious heat either remain
fected (Dray et al., 1990d) or are reduced (Amann
1990a). Ruthenium red also bl

ents is a secondary consequence of the neurotoxic action feratoxin-induced release of peptides from sensory nerve
of capsaicin on sensory neurons of the rat and guinea endings and the local effects of capsaicin that are du feratoxin-induced release of peptides from sensory nerve ER
feratoxin-induced release of peptides from sensory nerve
endings and the local effects of capsaicin that are due to
peptide release. Thus, the release of substance P and/or ER
feratoxin-induced release of peptides from sensory nerve
endings and the local effects of capsaicin that are due to
peptide release. Thus, the release of substance P and/or
calcitonin gene-related peptide from guinea pi feratoxin-induced release of peptides from sensory nerve
endings and the local effects of capsaicin that are due to
peptide release. Thus, the release of substance P and/or
calcitonin gene-related peptide from guinea pig l feratoxin-induced release of peptides from sensory nerve
endings and the local effects of capsaicin that are due to
peptide release. Thus, the release of substance P and/or
calcitonin gene-related peptide from guinea pig l peptide release. Thus, the release of substance P and/or calcitonin gene-related peptide from guinea pig lung (Amann et al., 1989b; Franco-Cereceda et al., 1990) and bronchi (Maggi et al., 1989c), guinea pig and rat urinar calcitonin gene-related peptide from guinea pig lung (Amann et al., 1989b; Franco-Cereceda et al., 1990) and bronchi (Maggi et al., 1989c), guinea pig and rat urinary bladder (Maggi et al., 1988d; Amann et al., 1990c), gui calcitonin gene-related peptide from guinea pig lung
(Amann et al., 1989b; Franco-Cereceda et al., 1990) and
bronchi (Maggi et al., 1989c), guinea pig and rat urinary
bladder (Maggi et al., 1988d; Amann et al., 1990c), gui (Amann et al., 1989b; Franco-Cereceda et al., 1990) and
bronchi (Maggi et al., 1989c), guinea pig and rat urinary
bladder (Maggi et al., 1988d; Amann et al., 1990c), guinea
pig heart (Franco-Cereceda et al., 1989a; Maggi e bronchi (Maggi et al., 1989c), guinea pig and rat urinary
bladder (Maggi et al., 1988d; Amann et al., 1990c), guinea
pig heart (Franco-Cereceda et al., 1989a; Maggi et al.,
1989c), rat trachea (Ray et al., 1990), and rabbi bladder (Maggi et al., 1988d; Amann et al., 1990c), guis pig heart (Franco-Cereceda et al., 1989a; Maggi et 1989c), rat trachea (Ray et al., 1990), and rabbit (Amann et al., 1989a, 1990a) is inhibited by the dependence evo pig heart (Franco-Cereceda et al., 1989a; Maggi et al., 1989c), rat trachea (Ray et al., 1990), and rabbit ear (Amann et al., 1989a, 1990a) is inhibited by the dye.
Peptide release evoked by bradykinin, nicotine, veratridi 1989c), rat trachea (Ray et al., 1990), and rabbit (Amann et al., 1989a, 1990a) is inhibited by the d
Peptide release evoked by bradykinin, nicotine, veratione, or potassium depolarization remains unaltered
ruthenium red ((Amann et al., 1989a, 1990a) is inhibite
Peptide release evoked by bradykinin, nichine, or potassium depolarization remain
ruthenium red (Amann et al., 1989b, 1
Cereceda et al., 1989a; Ray et al., 1990).
Antagonism of caps pptide release evoked by bradykinin, nicotine, veratione, or potassium depolarization remains unaltered if then
ium red (Amann et al., 1989b, 1990a; France receda et al., 1989a; Ray et al., 1990).
Antagonism of capsaicin-,

dine, or potassium depolarization remains unaltered by
ruthenium red (Amann et al., 1989b, 1990a; Franco-
Cereceda et al., 1989a; Ray et al., 1990).
Antagonism of capsaicin-, resiniferatoxin-, or piper-
ine-evoked motor ef ruthenium red (Amann et al., 1989b, 1990a; Franco-
Cereceda et al., 1989a; Ray et al., 1990).
Antagonism of capsaicin-, resiniferatoxin-, or piper-
ine-evoked motor effects by ruthenium red has been
observed in rat and gui Cereceda et al., 1989a; Ray et al., 1990).

Antagonism of capsaicin-, resiniferatoxin-, or piper-

ine-evoked motor effects by ruthenium red has been

observed in rat and guinea pig urinary bladder, rat vas

deferens (Magg ine-evoked motor effects by ruthenium red has been
observed in rat and guinea pig urinary bladder, rat vas
deferens (Maggi et al., 1988b,d, 1989a, 1990c), guinea pig
ileum (Chahl, 1989; Jin et al., 1989, 1990; Takaki et al ine-evoked motor effects by ruthenium red has b
observed in rat and guinea pig urinary bladder, rat
deferens (Maggi et al., 1988b,d, 1989a, 1990c), guinea
ileum (Chahl, 1989; Jin et al., 1989, 1990; Takaki et
1989, 1990), observed in rat and guinea pig urinary bladder, rat vas
deferens (Maggi et al., 1988b,d, 1989a, 1990c), guinea pig
ileum (Chahl, 1989; Jin et al., 1989, 1990; Takaki et al.,
1989, 1990), and guinea pig bronchus and heart (deferens (Maggi et al., 1988b,d, 1989a, 1990c), guinea pileum (Chahl, 1989; Jin et al., 1989, 1990; Takaki et a
1989, 1990), and guinea pig bronchus and heart (Franc
Cereceda et al., 1989a, 1990; Maggi et al., 1989c; Ama
e ileum (Chahl, 1989; Jin et al., 1989, 1990; Takaki et al., 1989, 1990), and guinea pig bronchus and heart (Franco-Cereceda et al., 1989a, 1990; Maggi et al., 1989c; Amann et al., 1990c). Motor responses to electrical field 1989, 1990), and guinea pig bronchus and heart (Franco-Cereceda et al., 1989a, 1990; Maggi et al., 1989c; Amann
et al., 1990c). Motor responses to electrical field stimu-
lation, substance P, neurokinin A, calcitonin gene-Cereceda et al., 1989a, 1990; Maggi et al., 1989c; Amann
et al., 1990c). Motor responses to electrical field stimu-
lation, substance P, neurokinin A, calcitonin gene-re-
lated peptide, acetylcholine, nicotine, or potassi et al., 1990c). Motor responses to electrical field stinution, substance P, neurokinin A, calcitonin gene-
lated peptide, acetylcholine, nicotine, or potassium
polarization are not inhibited by ruthenium red
concentration lation, substance P, neurokinin A, calcitonin gene
lated peptide, acetylcholine, nicotine, or potassium
polarization are not inhibited by ruthenium red
concentrations of ≤ 0.5 to 1 μ M, whereas higher conc
trations lated peptide, acetylcholine, nicotine, or potassium depolarization are not inhibited by ruthenium red at concentrations of ≤ 0.5 to 1μ M, whereas higher concentrations of the dye depress muscle activity in a nonsel polarization
concentrati
trations of t
tive fashion
al., 1990).
Intraveno ncentrations of ≤ 0.5 to 1 μ M, whereas higher concentrions of the dye depress muscle activity in a nonselec-
ve fashion (Maggi et al., 1988d; Chahl, 1989; Takaki et , 1990).
Intravenous administration of ruthenium

trations of the dye depress muscle activity in a nonselective fashion (Maggi et al., 1988d; Chahl, 1989; Takaki et al., 1990).

Intravenous administration of ruthenium red (0.5 to 2
 $mg/kg = 0.6$ to 2.3 μ mol/kg) to the ra tive fashion (Maggi et al., 1988d; Chahl, 1989; Takaki et al., 1990).

Intravenous administration of ruthenium red (0.5 to 2
 $mg/kg = 0.6$ to 2.3 μ mol/kg) to the rat inhibits the

Bezold-Jarisch reflex response to capsaic al., 1990).
Intravenous administration of ruthenium red (0.5 to mg/kg = 0.6 to 2.3 μ mol/kg) to the rat inhibits the reflex response to capsaicin but does rinhibit the reflex response to veratridine or the bradia caused Intravenous administration of ruthenium red $(0.5 \text{ to } 2 \text{ mg/kg}) = 0.6 \text{ to } 2.3 \mu \text{mol/kg}$) to the rat inhibits the Bezold-Jarisch reflex response to capsaicin but does not inhibit the reflex response to veratridine or the bra mg/kg = 0.6 to 2.3μ mol/kg) to the rat inhibits the Bezold-Jarisch reflex response to capsaicin but does not inhibit the reflex response to veratridine or the brady-cardia caused by electrical stimulation of the perip Bezold-Jarisch reflex response to capsaicin but does not
inhibit the reflex response to veratridine or the brady-
cardia caused by electrical stimulation of the peripheral
stump of the cut vagal nerve (Szolcsányi et al., 1 inhibit the reflex response to veratridine or the brady-
cardia caused by electrical stimulation of the peripheral
stump of the cut vagal nerve (Szolcsányi et al., 1991).
The capsaicin-induced increase in blood flow and va cardia caused by electrical stimulation of the peripheral
stump of the cut vagal nerve (Szolcsányi et al., 1991).
The capsaicin-induced increase in blood flow and vas-
cular permeability in the rabbit skin also is prevente stump of the cut vagal nerve (Szolcsányi et al., 19
The capsaicin-induced increase in blood flow and cular permeability in the rabbit skin also is prevente
intradermal administration of ruthenium red (10 nm
whereas the vas methionyl-leucyl-phenylalanine, platelet-activating faccular permeability in the rabbit skin also is prevented by
intradermal administration of ruthenium red (10 nmol),
whereas the vascular responses to bradykinin, N-formyl-
methionyl-leucyl-phenylalanine, platelet-activating intradermal administration of
whereas the vascular responses
methionyl-leucyl-phenylalanin
tor, histamine, and calcitonin
spared (Buckley et al., 1990).
The potency of ruthenium re nereas the vascular responses to bradykinin, N-formylethionyl-leucyl-phenylalanine, platelet-activating fac-
r, histamine, and calcitonin gene-related peptide are
ared (Buckley et al., 1990).
The potency of ruthenium red i

methionyl-leucyl-phenylalanine, platelet-activating fac-
tor, histamine, and calcitonin gene-related peptide are
spared (Buckley et al., 1990).
The potency of ruthenium red in preventing capsaicin
desensitization is distin tor, histamine, and calcitonin gene-related peptide are
spared (Buckley et al., 1990).
The potency of ruthenium red in preventing capsaicin
desensitization is distinctly higher than that in blocking
the stimulant effect of spared (Buckley et al., 1990).
The potency of ruthenium red in preventing capsaicin
desensitization is distinctly higher than that in blocking
the stimulant effect of capsaicin in isolated tissues
(Maggi et al. 1988b, 1989 The potency of ruthenium red in preventing capsaicin
desensitization is distinctly higher than that in blocking
the stimulant effect of capsaicin in isolated tissues
(Maggi et al. 1988b, 1989a). Furthermore, ruthenium reddesensitization is distinctly higher than that in block
the stimulant effect of capsaicin in isolated tiss
(Maggi et al. 1988b, 1989a). Furthermore, ruthenium r
induced protection from capsaicin desensitization la
much lon the stimulant effect of capsaicin in isolated tissues (Maggi et al. 1988b, 1989a). Furthermore, ruthenium redinduced protection from capsaicin desensitization lasts much longer after washout of the dye than does antagonism (Maggi et al. 1988b, 1989a). Furthermore, ruthenium r
induced protection from capsaicin desensitization la
much longer after washout of the dye than does anta
nism of the stimulant effect of capsaicin (Maggi et
1988b,d; Ch induced protection from capsaicin desensitization lasts
much longer after washout of the dye than does antagonism of the stimulant effect of capsaicin (Maggi et al.,
1988b,d; Chahl, 1989). Although these in vitro observa-
 much longer after washout of the dye than does antagonism of the stimulant effect of capsaicin (Maggi et al., 1988b,d; Chahl, 1989). Although these in vitro observations may have something to do with the fact that rutheniu nism of the stimulant effect of capsaicin (Maggi et al., 1988b,d; Chahl, 1989). Although these in vitro observations may have something to do with the fact that ruthenium red is difficult to wash out from the tissue (Maggi 1988b,d; Chahl, 1989). Although these in vitro observa-
tions may have something to do with the fact that
ruthenium red is difficult to wash out from the tissue
(Maggi et al., 1988d; Chahl, 1989; Takaki et al. 1989;
Bleakm tions may have something to do with the fact that
ruthenium red is difficult to wash out from the tissue
(Maggi et al., 1988d; Chahl, 1989; Takaki et al. 1989;
Bleakman et al., 1990; Maggi 1991), they most likely
reflect a ruthenium red is difficult to wash out from the tissue
(Maggi et al., 1988d; Chahl, 1989; Takaki et al. 1989;
Bleakman et al., 1990; Maggi 1991), they most likely
reflect a certain aspect of ruthenium red's mechanism of
ac

aspet

to block capsaicin's desensitizing and/or neurotoxic ac-CAPSAICIN
to block capsaicin's desensitizing and/or neurotoxic ac-
tion on sensory neurons is also seen when ruthenium red
(4.3 mg/kg = 5 μ mol/kg) is administered subcutaneously T $\begin{array}{c}\n\text{CaPs}\n\text{to block capsaicin's desensitizing and/or neurotoxic action on sensory neurons is also seen when ruthenium red (4.3 mg/kg = 5 μ mol/kg) is administered subcutaneously to rats (Amann et al., 1990b). Thus, systemic ruthenium\n$ to block capsaicin's desensitizing and/or neurotoxic ac-
tion on sensory neurons is also seen when ruthenium red
 $(4.3 \text{ mg/kg} = 5 \mu \text{mol/kg})$ is administered subcutaneously
to rats (Amann et al., 1990b). Thus, systemic rutheni to block capsaich's desensitizing and/or neurotoxic
tion on sensory neurons is also seen when ruthenium
 $(4.3 \text{ mg/kg} = 5 \mu \text{mol/kg})$ is administered subcutaneor
to rats (Amann et al., 1990b). Thus, systemic ruthen
red does not tion on sensory neurons is also seen when ruthenium i($4.3 \text{ mg/kg} = 5 \mu \text{mol/kg}$) is administered subcutaneouto rats (Amann et al., 1990b). Thus, systemic ruthenium red does not impair corneal nociception and cardiov cular re $(4.3 \text{ mg/kg} = 5 \mu \text{mol/kg})$ is administered subcutaneously
to rats (Amann et al., 1990b). Thus, systemic ruthenium
red does not impair corneal nociception and cardiovas-
cular reflexes in response to acute capsaicin but atten to rats (Amann et al., 1990b). Thus, systemic ruthenum c
red does not impair corneal nociception and cardiovas-
cular reflexes in response to acute capsaicin but attenu-
ates the long-term neurotoxic effect of capsaicin a red does not impair corneal nociception and cardiovas-
cular reflexes in response to acute capsaicin but attenu-
ates the long-term neurotoxic effect of capsaicin as de-
termined by depletion of substance P and calcitonin
 cular reflexes in response to acute capsaicin but attenu-
ates the long-term neurotoxic effect of capsaicin as de-
termined by depletion of substance P and calcitonin in
gene-related peptide from peripheral terminals of se ates the long-term neurotoxic effect of capsaicin as determined by depletion of substance P and calcitonin
gene-related peptide from peripheral terminals of sensory neurons in the urinary bladder and heart (Amann
et al., 1 termined by depletion of substance P and calcitonin
gene-related peptide from peripheral terminals of sen-
sory neurons in the urinary bladder and heart (Amann disp
et al., 1990b). The capsaicin-induced defunctionalization gene-related peptide from peripheral terminals of sensory neurons in the urinary bladder and heart (Amann et al., 1990b). The capsaicin-induced defunctionalization of peripheral sensory nerve terminals as assessed by pepti sory neurons in the urinary bladder and heart (Amann
et al., 1990b). The capsaicin-induced defunctionalization
of peripheral sensory nerve terminals as assessed by
peptide release and peptide-mediated plasma protein ex-
t et al., 1990b). The capsaich-induced defunctionalization
of peripheral sensory nerve terminals as assessed by
peptide release and peptide-mediated plasma protein ex-
travasation is likewise inhibited by the dye (Amann et
a of peripheral sensory nerve terminals as assessed by
peptide release and peptide-mediated plasma protein ex-
travasation is likewise inhibited by the dye (Amann et
al., 1990b). Capsaicin-induced peptide depletion from,
and peptide release and peptide-mediated plasma protein ex-

travasation is likewise inhibited by the dye (Amann et atol

al., 1990b). Capsaicin-induced peptide depletion from, tage

and defunctionalization of, the central te

travasation is likewise inhibited by the dye (Amann et al., 1990b). Capsaicin-induced peptide depletion from, the central terminals of sensory neurons, however, does not seem to be prevented by cystemic ruthenium red, whi al., 1990b). Capsaicin-induced peptide depletion from,
and defunctionalization of, the central terminals of sen-
sory neurons, however, does not seem to be prevented by
systemic ruthenium red, which suggests that the dye and defunctionalization of, the central terminals of sensory neurons, however, does not seem to be prevented by Ca^{2+} -bisystemic ruthenium red, which suggests that the dye does neuron not effectively enter the central n sory neurons, however, does not seem to be prevented by
systemic ruthenium red, which suggests that the dye does
not effectively enter the central nervous system (Amann
et al., 1990b). Whether ruthenium red can protect fro systemic ruthenium red, which suggest
not effectively enter the central nervolet al., 1990b). Whether ruthenium red
the ultrastructural changes caused by
sory neurons remains to be examined.
The conclusion to be drawn from t effectively enter the central nervous system (Amann
al., 1990b). Whether ruthenium red can protect from
the ultrastructural changes caused by capsaicin in sen-
the process remains to be examined.
The conclusion to be dra

et al., 1990b). Whether ruthenium red can protect from
the ultrastructural changes caused by capsaicin in se
sory neurons remains to be examined.
The conclusion to be drawn from the available data
that, at submicromolar/mi the ultrastructural changes caused by capsaicin in sensory neurons remains to be examined.
The conclusion to be drawn from the available data is
that, at submicromolar/micromolar concentrations,
ruthenium red acts as a spe sory neurons remains to be examined.

The conclusion to be drawn from the available data is

that, at submicromolar/micromolar concentrations, or

ruthenium red acts as a specific antagonist of capsaicin.

Its site and me The conclusion to be drawn from the available data it that, at submicromolar/micromolar concentration ruthenium red acts as a specific antagonist of capsaicing Its site and mechanism of action, however, have prove difficul that, at submicromolar/micromolar concentrations,
ruthenium red acts as a specific antagonist of capsaicin.
Its site and mechanism of action, however, have proved
difficult to elucidate because of the multiplicity of cellu ruthenium red acts as a specific antagonist of capsaici
Its site and mechanism of action, however, have prove
difficult to elucidate because of the multiplicity of cell
lar actions which the dye can exert (Amann and Mag
1 Its site and mechanism of action, however, have prover difficult to elucidate because of the multiplicity of cellar actions which the dye can exert (Amann and Mag 1991). Because of the dye's inhibitory actions on tran mem difficult to elucidate because of the multiplicity of cellu-
lar actions which the dye can exert (Amann and Maggi, blow
1991). Because of the dye's inhibitory actions on trans-
membrane Ca²⁺ fluxes and mitochondrial Ca lar actions which the dye can exert (Amann and Magg,
1991). Because of the dye's inhibitory actions on trans-
membrane Ca²⁺ fluxes and mitochondrial Ca²⁺ seques-
tration, it was originally suspected that ruthenium red 1991). Because of the dye's inhibitory actions on trans-
membrane Ca^{2+} fluxes and mitochondrial Ca^{2+} seques-
tration, it was originally suspected that ruthenium red
acted by blocking the capsaicin-induced Ca^{2+} up membrane Ca²⁺ fluxes and mitochondrial Ca²⁺ seques-
tration, it was originally suspected that ruthenium red
acted by blocking the capsaicin-induced Ca²⁺ uptake at
a mitochondrial level (Wood et al., 1988). Such a si tration, it was originally suspected that ruthenium red
acted by blocking the capsaicin-induced Ca^{2+} uptake at
a mitochondrial level (Wood et al., 1988). Such a site of
action, however, is unlikely to explain its antag acted by blocking the capsaicin-induced Ca^{2+} uptake at a mitochondrial level (Wood et al., 1988). Such a site of action, however, is unlikely to explain its antagonism of capsaicin for two major reasons. First, rutheni a mitochondrial level (Wood et al., 1988). Such a site of cation, however, is unlikely to explain its antagonism of to capsaicin for two major reasons. First, ruthenium red blocks the capsaicin-evoked opening of a nonsele action, however, is unlikely to explain its antagonism of
capsaicin for two major reasons. First, ruthenium red
blocks the capsaicin-evoked opening of a nonselective
wation conductance in the cell membrane of cultured
den capsaicin for two major reasons. First, ruthenium red
blocks the capsaicin-evoked opening of a nonselective
cation conductance in the cell membrane of cultured
sensory neurons (Dray et al., 1990d) and the resulting
depolar blocks the capsaicin-evoked opening of a nonselective
cation conductance in the cell membrane of cultured
sensory neurons (Dray et al., 1990d) and the resulting
depolarization (Bleakman et al., 1990). Second, the in-
trace cation conductance in the cell membrane of cultured
sensory neurons (Dray et al., 1990d) and the resulting
depolarization (Bleakman et al., 1990). Second, the in-
tracellular penetration of ruthenium red is very poor
in
(sensory neurons (Dray et al., 1990d) and the resulting
depolarization (Bleakman et al., 1990). Second, the in-
tracellular penetration of ruthenium red is very poor
(Maggi et al., 1988d; Chahl, 1989; Maggi, 1991) and there depolarization (Bleakman et al., 1990). Second, the in-
tracellular penetration of ruthenium red is very poor
(Maggi et al., 1988d; Chahl, 1989; Maggi, 1991) and there
is pharmacological evidence that, at concentrations ca tracellular penetration of ruthenium red is very poor
(Maggi et al., 1988d; Chahl, 1989; Maggi, 1991) and there
is pharmacological evidence that, at concentrations
needed to antagonize capsaicin, ruthenium red is devoid
of (Maggi et al., 1988d; Chahl, 1989; Maggi, 1991) and there
is pharmacological evidence that, at concentrations
needed to antagonize capsaicin, ruthenium red is devoid
of intracellular actions (Maggi et al., 1988d, 1989c;
Am is pharmacological evidence that, at concentrations
needed to antagonize capsaicin, ruthenium red is devoid
of intracellular actions (Maggi et al., 1988d, 1989c;
Amann et al., 1989a, 1990c; Franco-Cereceda et al.,
1989a). needed to antagonize capsaicin, ruthenium red is devoid
of intracellular actions (Maggi et al., 1988d, 1989c;
Amann et al., 1989a, 1990c; Franco-Cereceda et al.,
1989a). If ruthenium red were to act by preventing Ca²⁺
b of intracellular actions (Maggi et al., 1988d, 1989c; stitudent and al., 1989a, 1990c; Franco-Cereceda et al., 1989a). If ruthenium red were to act by preventing Ca^{2+} capinding to mitochondria, elevation of intracellul Amann et al., 1989a, 1990c; Franco-Cereceda et al., 1989a). If ruthenium red were to act by preventing Ca^{2+} conding to mitochondria, elevation of intracellular Ca^{2+} travould be expected to interfere nonselectively w 1989a). If ruthenium red were to act by preventing (binding to mitochondria, elevation of intracellular (would be expected to interfere nonselectively with stimulation of sensory neurons. Indeed, uncoupling oxidative phosp binding to mitochondria, elevation of intracellular Ca^{2+} travellular conselectively with the also atimulation of sensory neurons. Indeed, uncoupling of etimidative phosphorylation by cyanide inhibits capsaicinand depol would be expected to interfere nonselectively with the al., 1 stimulation of sensory neurons. Indeed, uncoupling of et all oxidative phosphorylation by cyanide inhibits capsaicin-
and depolarization-evoked peptide release stimulation of sensory neurons. Indeed, uncoupling of et oxidative phosphorylation by cyanide inhibits capsaicin-
and depolarization-evoked peptide release from sensory concrve endings in a nonselective manner, yet ruthen oxidative phosphorylation by cyanide inhibits capsaicin-
and depolarization-evoked peptide release from sensory
nerve endings in a nonselective manner, yet ruthenium
saired antagonizes only the response to capsaicin (Aman and depolarization-evoked peptide release from sensory contrary endings in a nonselective manner, yet ruthenium sted antagonizes only the response to capsaicin (Amann net al., 1990c). Furthermore, Ca^{2+} is not essential

CIN 183
removal of external Ca²⁺ is without effect (Amann et al., 1989a). 1989a).

183
moval of external Ca²⁺ is without effect (Amann et al.,
89a).
The observations that ruthenium red prevents the
psaicin-induced opening of a cation channel in isolated removal of external Ca²⁺ is without effect (Amann et al.,
1989a).
The observations that ruthenium red prevents the
capsaicin-induced opening of a cation channel in isolated
cell membrane patches from dorsal root ganglion removal of external Ca²⁺ is without effect (Amann et al., 1989a).
1989a).
The observations that ruthenium red prevents the
capsaicin-induced opening of a cation channel in isolated
cell membrane patches from dorsal root 1989a).
The observations that ruthenium red prevents
capsaicin-induced opening of a cation channel in isola
cell membrane patches from dorsal root ganglion cultu
(Dray et al., 1990d) and the capsaicin-induced depolarion of The observations that ruthenium red prevents the
capsaicin-induced opening of a cation channel in isolated
cell membrane patches from dorsal root ganglion cultures
(Dray et al., 1990d) and the capsaicin-induced depolari-
z capsaicin-induced opening of a cation channel in isolated
cell membrane patches from dorsal root ganglion cultures
(Dray et al., 1990d) and the capsaicin-induced depolari-
zation of whole ganglion cells (Bleakman et al., 1 cell membrane patches from dorsal root ganglion cultures
(Dray et al., 1990d) and the capsaicin-induced depolari-
zation of whole ganglion cells (Bleakman et al., 1990)
indicate that the primary site of its action is the c (Dray et al., 1990d) and the capsaicin-induced depolar
zation of whole ganglion cells (Bleakman et al., 199
indicate that the primary site of its action is the ce
membrane. However, ruthenium red does not appear is
displac zation of whole ganglion cells (Bleakman et al., 1990)
indicate that the primary site of its action is the cell
membrane. However, ruthenium red does not appear to
displace the binding of [³H] resiniferatoxin from mem-
b indicate that the primary site of its action is the emembrane. However, ruthenium red does not appear displace the binding of $[^3H]$ resiniferatoxin from mehranes of dorsal root ganglia, although capsaicin d (Szallasi and membrane. However, ruthenium red does not appear
displace the binding of [³H] resiniferatoxin from mo
branes of dorsal root ganglia, although capsaicin d
(Szallasi and Blumberg, 1990a). It follows that ruth
ium red is no displace the binding of [³H] resiniferatoxin from mem-
branes of dorsal root ganglia, although capsaicin does
(Szallasi and Blumberg, 1990a). It follows that ruthen-
ium red is not a competitive antagonist at the resinif branes of dorsal roo
(Szallasi and Blumbe)
ium red is not a comp
atoxin/capsaicin reco
tagonist of capsaicin.
In view of the inter zallasi and Blumberg, 1990a). It follows that ruthen-
m red is not a competitive antagonist at the resinifer-
oxin/capsaicin recognition site but is a functional an-
gonist of capsaicin.
In view of the interaction of ruthe

ium red is not a competitive antagonist at the resinifer-
atoxin/capsaicin recognition site but is a functional an-
tagonist of capsaicin.
In view of the interaction of ruthenium red with many
Ca²⁺-binding proteins (Cha atoxin/capsaicin recognition site but is a functional antagonist of capsaicin.
In view of the interaction of ruthenium red with many Ca^{2+} -binding proteins (Charuk et al., 1990), including neuronal Ca^{2+} channels (Tap tagonist of capsaicin.

In view of the interaction of ruthenium red with many
 Ca^{2+} -binding proteins (Charuk et al., 1990), including

neuronal Ca^{2+} channels (Tapia et al., 1985), it could be

inferred that the dye In view of the interaction of ruthenium red with many Ca^{2+} -binding proteins (Charuk et al., 1990), including neuronal Ca^{2+} channels (Tapia et al., 1985), it could be inferred that the dye antagonizes capsaicin by bl neuronal Ca^{2+} channels (Tapia et al., 1985), it could be
inferred that the dye antagonizes capsaicin by blocking
the capsaicin-operated nonselective cation channel. In-
direct support for this argument comes from the f neuronal Ca²⁺ channels (Tapia et al., 1985), it could be
inferred that the dye antagonizes capsaicin by blocking
the capsaicin-operated nonselective cation channel. In-
direct support for this argument comes from the fin inferred that the dye antagonizes capsaicin by blue capsaicin-operated nonselective cation chann
direct support for this argument comes from the f
that the ionic requirements for both the stimulant
of capsaicin on sensory the capsaicin-operated nonselective cation channel. Indirect support for this argument comes from the finding that the ionic requirements for both the stimulant action of capsaicin on sensory neurons and the capsaicin-anta direct support for this argument comes from the finding
that the ionic requirements for both the stimulant action
of capsaicin on sensory neurons and the capsaicin-antag-
onistic action of ruthenium red are similar in that that the ionic requirements for both the stimulant action
of capsaicin on sensory neurons and the capsaicin-antag-
onistic action of ruthenium red are similar in that neither
action requires the presence of external Ca²⁺ of capsaicin on sensory neurons and the capsaicin-antag-
onistic action of ruthenium red are similar in that neither
action requires the presence of external Ca^{2+} (Amann et
al., 1989a). However, the inhibitory action o onistic action of ruthenium red are similar in that neither
action requires the presence of external Ca²⁺ (Amann et
al., 1989a). However, the inhibitory action of ruthenium
red on the capsaicin-induced opening of cation action requires the presence of external Ca²⁺ (Amann et al., 1989a). However, the inhibitory action of ruthenium red on the capsaicin-induced opening of cation channels does not have the characteristics typical of ion ch al., 1989a). However, the inhibitory action of ruthenium
red on the capsaicin-induced opening of cation channels
does not have the characteristics typical of ion channel
blockade (Dray et al., 1990d). Hence, it appears as red on the capsaicin-induced opening of cation channels
does not have the characteristics typical of ion channel
blockade (Dray et al., 1990d). Hence, it appears as if the
dye would either interrupt the coupling between th does not have the characteristics typical of ion channel
blockade (Dray et al., 1990d). Hence, it appears as if the
dye would either interrupt the coupling between the
capsaicin recognition site and the cation channels, b blockade (Dray et al., 1990d). Hence, it appears as if the dye would either interrupt the coupling between the capsaicin recognition site and the cation channels, block the binding of cations to the channels, or interfere dye would either interrupt the coupling between the capsaicin recognition site and the cation channels, block the binding of cations to the channels, or interfere in some other way with the activation or inactivation of th capsaicin recognition site and the cation channels, block
the binding of cations to the channels, or interfere in
some other way with the activation or inactivation of the
channels. In an attempt to explain why a short exp the binding of cations to the channels, or interfere in some other way with the activation or inactivation of the channels. In an attempt to explain why a short exposure to ruthenium red does not prevent capsaicin-induced some other way with the activation or inactivation of the channels. In an attempt to explain why a short exposure to ruthenium red does not prevent capsaicin-induced contractions of the guinea pig isolated ileum 30 min aft channels. In an attempt to explain why a short exposure
to ruthenium red does not prevent capsaicin-induced
contractions of the guinea pig isolated ileum 30 min after
washout of the dye but does protect from capsaicin
dese contractions of the guinea pig isolated ileum 30 min after
washout of the dye but does protect from capsaicin
desensitization, Chahl (1989) has proposed a two-site washout of the dye but does protect from capsaicin desensitization, Chahl (1989) has proposed a two-site model of interaction between the dye and the capsaicin receptor/cation channel complex. In this model ruthen-
ium red washout of the dye but does protect from capsaicin
desensitization, Chahl (1989) has proposed a two-site
model of interaction between the dye and the capsaicin
receptor/cation channel complex. In this model ruthen-
ium red desensitization, Chahl (1989) has proposed a two-site model of interaction between the dye and the capsaicin receptor/cation channel complex. In this model ruthen-
ium red is thought to bind irreversibly to a site of the receptor/cation channel complex. In this model ruthen-
ium red is thought to bind irreversibly to a site of the
complex that accounts for the prolonged protection from
capsaicin desensitization and reversibly to some other receptor/cation channel complex. In this model ruthen-
ium red is thought to bind irreversibly to a site of the
complex that accounts for the prolonged protection from
capsaicin desensitization and reversibly to some other ium red is thought to bind irreversibly to a site of the complex that accounts for the prolonged protection from capsaicin desensitization and reversibly to some other site that causes only a short-lasting suppression of t complex that accounts for the prolonged protection from
capsaicin desensitization and reversibly to some other
site that causes only a short-lasting suppression of the
stimulant action of capsaicin on sensory neurons (Chah capsaicin-desensitization and reversibly to some otlest
site that causes only a short-lasting suppression of intracellular action of capsaicin on sensory neurons (Cha
1989). The inhibitory effects of ruthenium red on a
ca site that causes only a short-lasting suppression of the stimulant action of capsaicin on sensory neurons (Chahl, 1989). The inhibitory effects of ruthenium red on the capsaicin-induced increase in the intracellular conce stimulant action of capsaicin on sensory neurons (Chahl, 1989). The inhibitory effects of ruthenium red on the capsaicin-induced increase in the intracellular concentration of free Ca²⁺ ions (Bleakman et al., 1990; Dray 1989). The inhibitory effects of ruthenium red on the capsaicin-induced increase in the intracellular concertration of free Ca^{2+} ions (Bleakman et al., 1990; Dray (al., 1990d), intracellular accumulation of calcium (Wo capsaicin-induced increase in the intracellular concentration of free Ca²⁺ ions (Bleakman et al., 1990; Dray et al., 1990d), intracellular accumulation of calcium (Wood et al., 1988), and inhibition of voltage-gated Ca tration of free Ca²⁺ ions (Bleakman et al., 1990; Dray et al., 1990d), intracellular accumulation of calcium (Wood
et al., 1988), and inhibition of voltage-gated Ca²⁺ chan-
nels (Bleakman et al., 1990) are by all mean al., 1990d), intracellular accumulation of calcium (Wood
et al., 1988), and inhibition of voltage-gated Ca²⁺ chan-
nels (Bleakman et al., 1990) are by all means secondary
consequences of the dye's inhibitory effect on th membrane. Is (Bleakman et al., 1990) are by all means secondar msequences of the dye's inhibitory effect on the capicin-evoked opening of cation channels in the cembrane.
Taken together, ruthenium red appears to be a func-
palar tog consequences of the dye's inhibitory effect on the capsaicin-evoked opening of cation channels in the cell
membrane.
Taken together, ruthenium red appears to be a functional antagonist of capsaicin's stimulant and desensit

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

ing actions on sensory neurons, although it is not clear HOLZE
ing actions on sensory neurons, although it is not clear
whether these two actions are antagonized via a common
pathway. The structural requirements for ruthenium red HOLZER
ing actions on sensory neurons, although it is not clear
whether these two actions are antagonized via a common
pathway. The structural requirements for ruthenium red
to act as a blocker of capsaicin are also unknow ing actions on sensory neurons, although it is not clear
whether these two actions are antagonized via a common
pathway. The structural requirements for ruthenium red
to act as a blocker of capsaicin are also unknown excep ing actions on sensory neurons, although it is not clear of whether these two actions are antagonized via a common neathway. The structural requirements for ruthenium red to act as a blocker of capsaicin are also unknown whether these two actions are antagonized via a common nepathway. The structural requirements for ruthenium red
to act as a blocker of capsaicin are also unknown except fic
that the entire molecule of ruthenium red is requ pathway. The structural requirem
to act as a blocker of capsaicin ar
that the entire molecule of ruth
(Amann and Maggi, 1991) and
ineffective (Maggi et al., 1988b).
6. Interaction with nerve growth act as a blocker of capsaicin are also unknown except ficution at the entire molecule of ruthenium red is required neu mann and Maggi, 1991) and ruthenium chloride is other effective (Maggi et al., 1988b).
6. Interaction w

that the entire molecule of ruthenium red is required neurons.

(Amann and Maggi, 1991) and ruthenium chloride is oneffective (Maggi et al., 1988b).

6. Interaction with nerve growth factor. NGF is able to oprevent the ne (Amann and Maggi, 1991) and ruthenium chloride is other
ineffective (Maggi et al., 1988b). To consider the neurotoxic effect of capsaicin on B-type
prevent the neurotoxic effect of capsaicin on B-type situs
sensory neuron ineffective (Maggi et al., 1988b).
6. *Interaction with nerve growth factor*. NGF is able to
prevent the neurotoxic effect of capsaicin on B-type
sensory neurons in the rat and guinea pig at all ages. To
explain these obse 6. Interaction with nerve growth factor. NGF is able to of c
prevent the neurotoxic effect of capsaicin on B-type situ
sensory neurons in the rat and guinea pig at all ages. To be
explain these observations one has to tak prevent the neurotoxic effect of capsaicin on B-typsensory neurons in the rat and guinea pig at all ages. Texplain these observations one has to take into accourthat capsaicin disrupts the retrograde transport of NG (Mille sensory neurons in the rat and guinea pig at all ages. To
explain these observations one has to take into account
that capsaicin disrupts the retrograde transport of NGF
(Miller et al., 1985) in the adult guinea pig and ra explain these observations one has to take into account
that capsaicin disrupts the retrograde transport of NGF
(Miller et al., 1982a,b) and horseradish peroxidase (Tay-
lor et al., 1985) in the adult guinea pig and rat a that capsaicin disrupts the retrograde transport of NGF (Miller et al., 1982a,b) and horseradish peroxidase (Taylor et al., 1985) in the adult guinea pig and rat and that inhibition of retrograde transport precedes deplet (Miller et al., 1982a,b) and horseradish peroxidase (Taylor et al., 1985) in the adult guinea pig and rat and that inhibition of retrograde transport precedes depletion of substance P from dorsal root ganglia; the potency 1982b). hibition of retrograde transport precedes depletion of
bstance P from dorsal root ganglia; the potency of
psaicin for these two effects is identical (Miller et al.,
82b).
Systemic administration of NGF protects B-type sen-

substance P from dorsal root ganglia; the potency of rolumes representing the capsaicin-induced degeneration in the say neurons from capsaicin-induced degeneration in the newborn rat (Otten et al., 1983) and counteracts c capsaicin for these two effects is identical (Miller et a
1982b).
Systemic administration of NGF protects B-type se
sory neurons from capsaicin-induced degeneration in t
newborn rat (Otten et al., 1983) and counteracts cap 1982b).
Systemic administration of NGF protects B-type sensory neurons from capsaicin-induced degeneration in the
newborn rat (Otten et al., 1983) and counteracts capsai-
cin-induced depletion of substance P from sensory n Systemic administration of NGF protects B-type sensory neurons from capsaicin-induced degeneration in the newborn rat (Otten et al., 1983) and counteracts capsaicin-induced depletion of substance P from sensory neurons in sory neurons from capsaicin-induced degeneration in the
newborn rat (Otten et al., 1983) and counteracts capsai-
cin-induced depletion of substance P from sensory neu-
rons in the adult guinea pig (Miller et al., 1982b). newborn rat (Otten et al., 1983) and counteracts capsaicin-induced depletion of substance P from sensory neurons in the adult guinea pig (Miller et al., 1982b). The site of interaction, however, between NGF and capsaicin i cin-induced depletion of substance P from sensory neu-
rons in the adult guinea pig (Miller et al., 1982b). The
site of interaction, however, between NGF and capsaicin
is not clear. One possibility is that NGF supplementat rons in the adult guinea pig (Miller et al., 1982b). The
site of interaction, however, between NGF and capsaici
is not clear. One possibility is that NGF supplementatio
circumvents the deleterious effect of capsaicin-induc site of interaction, however, between NGF and capsaicin
is not clear. One possibility is that NGF supplementation
circumvents the deleterious effect of capsaicin-induced
inhibition of NGF transport to the sensory ganglia. is not clear. One possibility is that NGF supplementation (Ju
circumvents the deleterious effect of capsaicin-induced
inhibition of NGF transport to the sensory ganglia. How-
ever, NGF also prevents capsaicin from inhibit circumvents the deleterious effect of capsaicin-induced
inhibition of NGF transport to the sensory ganglia. How-
ever, NGF also prevents capsaicin from inhibiting the
retrograde transport of horseradish peroxidase when
bot inhibition of NGF transport to the sensory ganglia. How-
ever, NGF also prevents capsaicin from inhibiting the
retrograde transport of horseradish peroxidase when
both NGF and capsaicin are administered locally to the
peri ever, NGF also prevents capsaicin from inhibiting the
retrograde transport of horseradish peroxidase when
both NGF and capsaicin are administered locally to the
peripheral endings of sensory neurons (Taylor et al.,
1985). retrograde transport of horseradish peroxidase when
both NGF and capsaicin are administered locally to the
peripheral endings of sensory neurons (Taylor et al.,
1985). This suggests that NGF can antagonize capsaicin
at a both NGF and capsaicin are administered locally to the
peripheral endings of sensory neurons (Taylor et al., erat
1985). This suggests that NGF can antagonize capsaicin age
at a peripheral site of action and argues agains peripheral endings of sensory neurons (Taylor et al., 1985). This suggests that NGF can antagonize capsaicin at a peripheral site of action and argues against the ideas that the neurotoxic action of capsaicin is related to 1985). This suggests that NGF can antagonize capsaicin
at a peripheral site of action and argues against the ideas
that the neurotoxic action of capsaicin is related to NGF
deprivation of the neuronal somata or an interfer at a peripheral site of action and argues against the ideas
that the neurotoxic action of capsaicin is related to NGF
deprivation of the neuronal somata or an interference
with the trophic effects of NGF itself (Taylor et that the neurotoxic action of capsaicin is related to NGF
deprivation of the neuronal somata or an interference
with the trophic effects of NGF itself (Taylor et al.,
1985). Consequently, it has been proposed that capsaic deprivation of the neuronal somata or an interference with the trophic effects of NGF itself (Taylor et al 1985). Consequently, it has been proposed that capsaicin may block the uptake of NGF by the peripheral sensor nerve with the trophic effects of NGF itself (Taylor et 1985). Consequently, it has been proposed that capsain may block the uptake of NGF by the peripheral sen nerve endings and that NGF supplementation may come this action of 85). Consequently, it has been proposed that capsaicin
ay block the uptake of NGF by the peripheral sensory et
rve endings and that NGF supplementation may over-
me this action of capsaicin (Taylor et al., 1985).
The situ may block the uptake of NGF by the peripheral sensory
nerve endings and that NGF supplementation may over-
come this action of capsaicin (Taylor et al., 1985).
The situation is profoundly different in sensory neuron
cultur

nerve endings and that NGF supplementation may over-
come this action of capsaicin (Taylor et al., 1985).
The situation is profoundly different in sensory neuron
cultures derived from dorsal root ganglia of adult rats.
NGF come this action of capsaicin (Taylor et al., 1985).

The situation is profoundly different in sensory neuron

cultures derived from dorsal root ganglia of adult rats.

NGF is not required for the survival of these neuron The situation is profoundly different in sensory neuron
cultures derived from dorsal root ganglia of adult rats.
NGF is not required for the survival of these neurons
self but controls their responsiveness to capsaicin (Wi cultures derived from dorsal root ganglia of adult rats.
NGF is not required for the survival of these neurons state but controls their responsiveness to capsaicin (Winter et al., 1988). Sensitivity to capsaicin, as assess NGF is not required for the survival of these neurons seen but controls their responsiveness to capsaicin (Winter et al., 1988). Sensitivity to capsaicin, as assessed by the seed cobalt uptake stain, is retained for weeks but controls their responsiveness to capsaicin (Winter et al., 1988). Sensitivity to capsaicin, as assessed by the cobalt uptake stain, is retained for weeks in culture if there is an adequate supply of NGF. If, however, N al., 1988). Sensitivity to capsaicin, as assessed by the secondit uptake stain, is retained for weeks in culture if there is an adequate supply of NGF. If, however, NGF is sinemoved, the neurons loose their responsiveness cobalt uptake stain, is retained for weeks in culture if there is an adequate supply of NGF. If, however, NGF is removed, the neurons loose their responsiveness to capsaicin within 3 to 4 days (Winter et al., 1988). This l there is an adequate supply of NGF. If, however, NGF is situation removed, the neurons loose their responsiveness to capsical position within 3 to 4 days (Winter et al., 1988). This loss Beta is reversible because full sen removed, the neurons loose their responsiveness to cap-
saicin within 3 to 4 days (Winter et al., 1988). This loss Be
is reversible because full sensitivity to capsaicin is re-
stored within 4 to 6 days after readdition of saicin within 3 to 4 days (Winter et al., 1988). This loss
is reversible because full sensitivity to capsaicin is re-
stored within 4 to 6 days after readdition of NGF. The
time lag of several days suggests that NGF turns is reversible because full sensitivity to capsaicin is re-
stored within 4 to 6 days after readdition of NGF. The
time lag of several days suggests that NGF turns on the
synthesis of cellular components, e.g., the cation c stored within 4 to 6 days after readdition of NGF. The lag of several days suggests that NGF turns on the synthesis of cellular components, e.g., the cation channel whose presence determines the capsaicin sensitivity of se time lag of several days suggests that NGF turns on
synthesis of cellular components, e.g., the cation char
whose presence determines the capsaicin-sensitivity
sensory neurons (Winter et al., 1988). Alternativ
NGF is invol

ER
operated cation channel or in the modulation of other
neuronal functions (Winter et al., 1988). neuronal functions (Winter et al., 1988).
Although the in vivo observations are at present dif-

Although the in vivo observations of other
though the in vivo observations are at present dif-
although the in vivo observations are at present dif-
tult to reconcile with the data from cultured sensory operated cation channel or in the modulation of other
neuronal functions (Winter et al., 1988).
Although the in vivo observations are at present dif-
ficult to reconcile with the data from cultured sensory
neurons, they ar operated cation channel or in the modulation of other
neuronal functions (Winter et al., 1988).
Although the in vivo observations are at present dif-
ficult to reconcile with the data from cultured sensory
neurons, they ar neuronal functions (Winter et al., 1988).
Although the in vivo observations are at present dif-
ficult to reconcile with the data from cultured sensory
neurons, they are not necessarily contradictory with each
other. The f Although the in vivo observations are at present dif-
ficult to reconcile with the data from cultured sensory
neurons, they are not necessarily contradictory with each
other. The findings obtained from cultured sensory neu ficult to reconcile with the data from cultured sensory
neurons, they are not necessarily contradictory with each
other. The findings obtained from cultured sensory neu-
rons indicate that NGF regulates the cellular expres neurons, they are not necessarily contradictory with each other. The findings obtained from cultured sensory neurons indicate that NGF regulates the cellular expression of capsaicin sensitivity. This also may hold true for other. The findings obtained from cultured sensory neu-
rons indicate that NGF regulates the cellular expression
of capsaicin sensitivity. This also may hold true for the
situation in vivo but has not yet been examined. It rons indicate that NGF regulates the cellular expression
of capsaicin sensitivity. This also may hold true for the
situation in vivo but has not yet been examined. It would
be worth testing whether treatment of adult rats situation in vivo but has not yet been examined. It would
be worth testing whether treatment of adult rats or
guinea pigs with antibodies to NGF can prevent the
deleterious action of capsaicin on sensory neurons. The
prote situation in vivo but has not yet been examined. It would
be worth testing whether treatment of adult rats or
guinea pigs with antibodies to NGF can prevent the
deleterious action of capsaicin on sensory neurons. The
prote be worth testing whether treatment of adult rats or
guinea pigs with antibodies to NGF can prevent the
deleterious action of capsaicin on sensory neurons. The
protective effect of NGF in vivo could be related to the
mainte guinea pigs with antibodies to NGF can prevent the
deleterious action of capsaicin on sensory neurons. The
protective effect of NGF in vivo could be related to the
maintenance of an optimal supply of NGF, which en-
hances deleterious action of c
protective effect of N(
maintenance of an op
hances neuronal resist
ronal repair processes.
7. Peripheral ending otective effect of NGF in vivo could be related to the
aintenance of an optimal supply of NGF, which en-
nces neuronal resistance to damage and promotes neu-
nal repair processes.
7. *Peripheral endings of sensory neurons*

maintenance of an optimal supply of NGF, which en-
hances neuronal resistance to damage and promotes neu-
ronal repair processes.
7. Peripheral endings of sensory neurons as primary
target of capsaicin's action--distal axo *capsaicin in the adult rat.* In view of the inserting the adult rat.
 T. Peripheral endings of sensory neurons as primary target of capsaicin's action—distal axonopathy induced by capsaicin in the adult rat. In view of t ronal repair processes.

7. Peripheral endings of sensory neurons as primary

target of capsaicin's action—distal axonopathy induced by

capsaicin in the adult rat. In view of the insensitivity of

capsaicin's local excita 7. Peripheral endings of sensory neurons as primar
target of capsaicin's action—distal axonopathy induced b
capsaicin in the adult rat. In view of the insensitivity
capsaicin's local excitatory action to tetrodotoxin and c target of capsaicin's action—distal axonopathy induced by
capsaicin in the adult rat. In view of the insensitivity of
capsaicin's local excitatory action to tetrodotoxin and of
other characteristics of the "dual sensory-ef capsaicin in the adult rat. In view of the insensitivity of capsaicin's local excitatory action to tetrodotoxin and of other characteristics of the "dual sensory-efferent function" of afferent nerve endings, the hypothesis capsaicin's local excitatory action to tetrodotoxin and of
other characteristics of the "dual sensory-efferent func-
tion" of afferent nerve endings, the hypothesis has been
put forward that the very terminal region of sen hances neuronal resistance to damage and promotes neuronal repair processes.
 τ . Peripheral endings of sensory neurons as primary
 z . Peripheral endings of sensory neurons as primary
 $target$ arged of capsaicin is action tion" of afferent nerve endings, the hypothesis has been
put forward that the very terminal region of sensory
nerve fibers is the primary target of capsaicin's action
(Jancsó, 1960, 1968; Szolcsányi, 1984b, 1988; Maggi and put forward that the very terminal region of sensory
nerve fibers is the primary target of capsaicin's action
(Jancsó, 1960, 1968; Szolcsányi, 1984b, 1988; Maggi and
Meli, 1988; Maggi, 1991; Szolcsányi et al., 1991). In th (Jancsó, 1960, 1968; Szolcsányi, 1984b, 1988; Maggi and Meli, 1988; Maggi, 1991; Szolcsányi et al., 1991). In this model, the sensory nerve ending consists of a generator or sensory receptor region, in which stimulation pr (Jancsó, 1960, 1968; Szolcsányi, 1984b, 1988; Maggi a
Meli, 1988; Maggi, 1991; Szolcsányi et al., 1991). In th
model, the sensory nerve ending consists of a generat
or sensory receptor region, in which stimulation produc
a Meli, 1988; Maggi, 1991; Szolcsányi et al., 1991). In this model, the sensory nerve ending consists of a generator or sensory receptor region, in which stimulation produces a tetrodotoxin-resistant generator potential, and model, the sensory nerve ending consists of a generator
or sensory receptor region, in which stimulation produces
a tetrodotoxin-resistant generator potential, and a regen-
erative (preterminal axonal) region which possess or sensory receptor region, in which stimulation produces
a tetrodotoxin-resistant generator potential, and a regen-
erative (preterminal axonal) region which possesses volt-
age-gated Na⁺ channels. Here the generator p a tetrodotoxin-resistant generator potential, and a regenerative (preterminal axonal) region which possesses voltage-gated Na⁺ channels. Here the generator potential gives rise to propagated action potentials that can be erative (preterminal axonal) region which possesses voltage-gated Na⁺ channels. Here the generator potential gives rise to propagated action potentials that can be blocked by tetrodotoxin. The Na⁺ channels also can be age-gated $Na⁺$ channels. Here the generator potential gives rise to propagated action potentials that can be blocked by tetrodotoxin. The $Na⁺$ channels also can be activated by veratridine, and the inability of gives rise to propagated action potentials that can be blocked by tetrodotoxin. The $Na⁺$ channels also can be activated by veratridine, and the inability of ruthenium red to block the excitatory action of veratridine blocked by tetrodotoxin. The Na⁺ channels also can
activated by veratridine, and the inability of ruthenit
red to block the excitatory action of veratridine has be
used to add weight to the above hypothesis (Szolcsán
et activated by veratridine, and the inability of rutheni
red to block the excitatory action of veratridine has b
used to add weight to the above hypothesis (Szolcsá
et al., 1991). These arguments, however, are not conc
sive red to block the excitatory action of veratridine has been
used to add weight to the above hypothesis (Szolcsányi
et al., 1991). These arguments, however, are not conclu-
sive and inconsistent with capsaicin's ability to d used to add weight to the above hypothesis (Szolc et al., 1991). These arguments, however, are not co
sive and inconsistent with capsaicin's ability to dep
ize all parts of sensory neurons, from which it ap
as if capsaicin et al., 1991). These arguments, however, are not conclusive and inconsistent with capsaicin's ability to depolar-
ize all parts of sensory neurons, from which it appears
as if capsaicin recognition sites coupled to tetrodo sive and inconsistent with capsaicin's ability to depolar-
ize all parts of sensory neurons, from which it appears
as if capsaicin recognition sites coupled to tetrodotoxin-
resistant cation channels are present in all par ize all parts of sensory neurons, from which it appeas if capsaicin recognition sites coupled to tetrodoto:
resistant cation channels are present in all parts
sensory neurons. In addition, the above model does
take account as if capsaicin recognition sites coupled to tetrodotoxin-
resistant cation channels are present in all parts of
sensory neurons. In addition, the above model does not
take account of the varicose structure of many capsaic resistant cation channels are present in all parts of sensory neurons. In addition, the above model does not take account of the varicose structure of many capsaicinsensitive peptidergic nerve fibers, peptide release being sensory neurons. In addition, the above model does not
take account of the varicose structure of many capsaicin
sensitive peptidergic nerve fibers, peptide release bein
thought to occur from the varicosities, i.e., from mu take account of the varicose structure of many capsaicinsensitive peptidergic nerve fibers, peptide release being thought to occur from the varicosities, i.e., from multiple sites along the terminal axons of sensory neuron sensitive peptidergic nerve fibers, peptide release beir
thought to occur from the varicosities, i.e., from multip
sites along the terminal axons of sensory neurons (Gil
bins et al., 1987; Lundberg and Saria, 1987; Weihe, thought to occur from the varicosities, i.e., from multiple
sites along the terminal axons of sensory neurons (Gib-
bins et al., 1987; Lundberg and Saria, 1987; Weihe, 1990).
Because peptide release evoked by capsaicin als sites along the terminal axons of sensory neurons (Gibbins et al., 1987; Lundberg and Saria, 1987; Weihe, 1990).
Because peptide release evoked by capsaicin also is tetro-
dotoxin resistant (Saria et al., 1983b; Hua et al. bins et al., 1987; Lundberg and Saria, 1987; Weihe, 1990).
Because peptide release evoked by capsaicin also is tetro-
dotoxin resistant (Saria et al., 1983b; Hua et al., 1986;
Maggi et al., 1989c, 1990b), it is conceivable Because peptide release evoked by capsaicin also is tetro-
dotoxin resistant (Saria et al., 1983b; Hua et al., 1986;
Maggi et al., 1989c, 1990b), it is conceivable that there
are multiple sites on the preterminal axon that dotoxin resistant (Saria et al., 1983b; Hua et al., 1986;
Maggi et al., 1989c, 1990b), it is conceivable that there
are multiple sites on the preterminal axon that are di-
rectly sensitive to capsaicin. From these consider Maggi et al., 1989c, 1990b), it is conceivable that there are multiple sites on the preterminal axon that are directly sensitive to capsaicin. From these considerations it is clear that the issue of the primary site, if an are multiple sites on the preterminal axon that are directly sensitive to capsaicin. From these considerations
it is clear that the issue of the primary site, if any, of
capsaicin's excitatory action will only be resolved

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

PHARM
REV

HARM
REV

PHARMACOLOGICAL REVIEWS

capsaicin receptor/cation
axons of sensory neurons.
In vivo, the route of ad

CAPSAICIN

psaicin receptor/cation channel complexes along the

ons of sensory neurons.

In vivo, the route of administration of capsaicin and (Cle

existence of diffusion barriers for the drug may favour

198 capsaicin receptor/cation channel complexes along the axons of sensory neurons.
In vivo, the route of administration of capsaicin and
the existence of diffusion barriers for the drug may favour
certain sites of action. Thu capsaicin receptor/cation channel complexes along the axions of sensory neurons.
In vivo, the route of administration of capsaicin are the existence of diffusion barriers for the drug may favore certain sites of action. Th axons of sensory neurons.

In vivo, the route of administration of capsaicin and

the existence of diffusion barriers for the drug may favour

certain sites of action. Thus, some neurophysiological

characteristics of the In vivo, the route of administration of capsaicin and
the existence of diffusion barriers for the drug may favour
certain sites of action. Thus, some neurophysiological
characteristics of the stimulant and desensitizing ef the existence of diffusion barriers for the drug may favour
certain sites of action. Thus, some neurophysiological
characteristics of the stimulant and desensitizing effects
and topical capsaicin on cutaneous C-fiber polym certain sites of action. Thus, some neurophysiological
characteristics of the stimulant and desensitizing effects
of topical capsaicin on cutaneous C-fiber polymodal no-
ciceptors have been used to suggest a primary action characteristics of the stimulant and desensitizing effects affects of topical capsaicin on cutaneous C-fiber polymodal no-
ciceptors have been used to suggest a primary action of unnecapsaicin on the peripheral endings of of topical capsaicin on cutaneous C-fiber polymodal no-
ciceptors have been used to suggest a primary action of
capsaicin on the peripheral endings of rat sensory neu-
rons (Kenins, 1982). Support for this reasoning also
c capsaicin on the peripheral endings of rat sensory neurons (Kenins, 1982). Support for this reasoning also comes from the observation that close arterial injection of capsaicin to the rabbit ear can abolish the responsivecapsaicin on the peripheral endings of rat sensory neu-
rons (Kenins, 1982). Support for this reasoning also all
comes from the observation that close arterial injection ((
of capsaicin to the rabbit ear can abolish the re rons (Kenins, 1982). Support for this reasoning also al., comes from the observation that close arterial injection (Ch of capsaicin to the rabbit ear can abolish the responsive- to 9 ness of polymodal nociceptors to certai comes from the observation that close arterial injection (Close of capsaicin to the rabbit ear can abolish the responsive-
ness of polymodal nociceptors to certain, but not all, of cap
its modalities (Szolcsányi, 1987). Th of capsaicin to the rabbit ear can abolish the responsiness of polymodal nociceptors to certain, but not all, its modalities (Szolcsányi, 1987). This finding points a site of action on the sensory receptors themselves a ar ness of polymodal nociceptors to certain, but not all
its modalities (Szolcsányi, 1987). This finding point:
a site of action on the sensory receptors themselves
argues against a site of action on the conducting pre
minal its modalities (Szolcsányi, 1987). This finding points to the a site of action on the sensory receptors themselves and Becargues against a site of action on the conducting preterminal part of sensory fibers (Szolcsányi, 19 a site of action on the sensory receptors themselves and
argues against a site of action on the conducting preter-
minal part of sensory fibers (Szolcsányi, 1987). Further-
more, close arterial administration of capsaicin argues against a site of action on the conducting preter-
minal part of sensory fibers (Szolcsányi, 1987). Further-
more, close arterial administration of capsaicin to a
segment of the rat saphenous nerve cut at both ends, more, close arterial administration of capsaicin to a treatment of adult rats, reflects a regeneration of dam-
segment of the rat saphenous nerve cut at both ends, but aged nerve terminals.
with intact vascular supply, has more, close arterial administration of capsaicin to a
segment of the rat saphenous nerve cut at both ends, but
with intact vascular supply, has been found to be rather
ineffective in producing axonal excitation (G. Pethö a segment of the rat saphenous nerve cut at both ends, but
with intact vascular supply, has been found to be rather
ineffective in producing axonal excitation (G. Pethö and
J. Szolcsányi, personal communication). These findi with intact vascular supply, has been found to be rather
ineffective in producing axonal excitation (G. Pethö and
J. Szolcsányi, personal communication). These findings
suggest that the peripheral nerve endings are the pri J. Szolcsányi, personal communication). These findings suggest that the peripheral nerve endings are the primary site of action of capsaicin when the drug is administered by the topical or close arterial route and thus is J. Szolcsányi, personal communication). These findings
suggest that the peripheral nerve endings are the primary
site of action of capsaicin when the drug is administered
by the topical or close arterial route and thus is

by the topical or close arterial route and thus is preferentially delivered to the axon terminals of sensory neurons.
Although the primary site of capsaicin's excitatory action remains to be elucidated, there is a body of entially delivered to the axon terminals of sensory neu-
rons.
Although the primary site of capsaicin's excitatory
action remains to be elucidated, there is a body of cir-
cumstantial evidence indicating that the periphera 1981

Although the primary site of capsaicin's excitatory

action remains to be elucidated, there is a body of cir-

cumstantial evidence indicating that the peripheral nerve

proterminals are much more vulnerable to the d Although the primary site of capsaicin's excitatory reaction remains to be elucidated, there is a body of circumstantial evidence indicating that the peripheral nerve preminals are much more vulnerable to the drug given ve action remains to be elucidated, there is a body of circumstantial evidence indicating that the peripheral nerve preminals are much more vulnerable to the drug given way stemically to adult rats than are the somata and axo terminals are much more vulnerable to the drug given
systemically to adult rats than are the somata and axons
of sensory neurons (Chung et al., 1985b, 1990). This
segmentally different neurotoxicity could be due to dif-
fe terminals are much more vulnerable to the drug given
systemically to adult rats than are the somata and axons (
of sensory neurons (Chung et al., 1985b, 1990). This (
segmentally different neurotoxicity could be due to dif systemically to adult rats than are the somata and axons
of sensory neurons (Chung et al., 1985b, 1990). This
segmentally different neurotoxicity could be due to dif-
ferences in the access of capsaicin to the different pa of sensory neurons (Chung et al., 1985b, 1990). This (Vertex of segmentally different neurotoxicity could be due to dif-
ferences in the access of capsaicin to the different parts nof sensory neurons. Thus, although capsai segmentally different neurotoxicity could be due to differences in the access of capsaicin to the different parts of sensory neurons. Thus, although capsaicin given parenterally distributes rapidly throughout the body (Sar ferences in the access of capsaicin to the different parts
of sensory neurons. Thus, although capsaicin given par-
enterally distributes rapidly throughout the body (Saria
et al., 1982), the Schwann cell sheath (perineuriu of sensory neurons. Thus, although capsaicin given p
enterally distributes rapidly throughout the body (Sa
et al., 1982), the Schwann cell sheath (perineuriu
around bundles of unmyelinated afferent nerve fib
may represent enterally distributes rapidly throughout the body (Saria vet al., 1982), the Schwann cell sheath (perineurium) around bundles of unmyelinated afferent nerve fibers (may represent a barrier that prevents neurotoxic concentr et al., 1982), the Schwann cell sheath (perineurium
around bundles of unmyelinated afferent nerve fibe
may represent a barrier that prevents neurotoxic conce
trations of capsaicin from reaching the axons (Chung
al., 1990). around bundles of unmyelinated afferent nerve fibmay represent a barrier that prevents neurotoxic concentrations of capsaicin from reaching the axons (Chung al., 1990). This assumption is in keeping with the necesity of us may represent a barrier that prevents neurotoxic concentrations of capsaicin from reaching the axons (Chung et al., 1990). This assumption is in keeping with the necessity of using high (millimolar) concentrations of peria trations of capsaicin from reaching the axons (Chung et al., 1990). This assumption is in keeping with the necessity of using high (millimolar) concentrations of periax-
onal capsaicin to induce ablation of afferent neuron al., 1990). This assumption is in keeping with the netty of using high (millimolar) concentrations of peonal capsaicin to induce ablation of afferent neu (Gamse et al., 1982; Jancsó et al., 1987a,b; Lynn e 1987; Jancsó and by of using high (millimolar) concentrations of periax-
al capsaicin to induce ablation of afferent neurons
lamse et al., 1982; Jancsó et al., 1987a,b; Lynn et al.,
87; Jancsó and Lawson, 1990; Pini et al., 1990).
Alternat

onal capsaicin to induce ablation of afferent neuro
(Gamse et al., 1982; Jancsó et al., 1987a,b; Lynn et a
1987; Jancsó and Lawson, 1990; Pini et al., 1990).
Alternatively, the segmentally different neurotoxic
of capsaicin (Gamse et al., 1982; Jancsó et al., 1987a,b; Lynn et al., 1987; Jancsó and Lawson, 1990; Pini et al., 1990).
Alternatively, the segmentally different neurotoxicity
of capsaicin may be due to segmentally different capaci-
t 1987; Jancsó and Lawson, 1990; Pini et al., 1990).
Alternatively, the segmentally different neurotoxicity
of capsaicin may be due to segmentally different capaci-
ties of resistance and repair in sensory neurons. Thus,
onl Alternatively, the segmentally different neurotoxicity
of capsaicin may be due to segmentally different capaci-
ties of resistance and repair in sensory neurons. Thus,
only a few, if any, B-type neurons degenerate after sy of capsaicin may be due to segmentally different capacies of resistance and repair in sensory neurons. Thus only a few, if any, B-type neurons degenerate after sy temic capsaicin treatment of adult rats (Jancsó et a 1985b) ties of resistance and repair in sensory neurons. Thus,

only a few, if any, B-type neurons degenerate after sys-

temic capsaicin treatment of adult rats (Jancsó et al., 1

1985b), although many somata display ultrastruct only a few, if any, B-type neurons degenerate after sys-
temic capsaicin treatment of adult rats (Jancsó et al., 198
1985b), although many somata display ultrastructural their
changes for several weeks (Joó et al., 1969; S temic capsaicin treatment of adult rats (Jancsó et al., 1985b), although many somata display ultrastructural the changes for several weeks (Joó et al., 1969; Szolcsányi et 1
al., 1975; Chiba et al., 1986); neuropeptides, a 1985b), although many somata display ultrastructural their s
changes for several weeks (Joó et al., 1969; Szolcsányi et 1982; C
al., 1975; Chiba et al., 1986); neuropeptides, after an of thes
initial increase (Lembeck and

capsaicin receptor/cation channel complexes along the dorsal root ganglia (Jessell et al., 1978; Gamse et al., axons of sensory neurons.

In vivo, the route of administration of capsaicin and (Chung et al., 1985b, 1990), o cin
dorsal root ganglia (Jessell et al., 1978; Gamse et al.,
1981b; Gamse, 1982; Geppetti et al., 1988a). Likewise, no 1981
1981b; Gamse, 1982; Gessell et al., 1978; Gamse et al.,
1981b; Gamse, 1982; Geppetti et al., 1988a). Likewise, no
(Chung et al., 1985b, 1990), or minor (Jancsó et al., 185
dorsal root ganglia (Jessell et al., 1978; Gamse et al.,
1981b; Gamse, 1982; Geppetti et al., 1988a). Likewise, no
(Chung et al., 1985b, 1990), or minor (Jancsó et al.,
1985b), degeneration of axons in afferent nerves dorsal root ganglia (Jessell et al., 1978; Gamse et al., 1981b; Gamse, 1982; Geppetti et al., 1988a). Likewise, no (Chung et al., 1985b, 1990), or minor (Jancsó et al., 1985b), degeneration of axons in afferent nerves or d dorsal root ganglia (Jessell et al., 1978; Gamse et al., 1981b; Gamse, 1982; Geppetti et al., 1988a). Likewise, no (Chung et al., 1985b, 1990), or minor (Jancsó et al., 1985b), degeneration of axons in afferent nerves or d 1981b; Gamse, 1982; Geppetti et al., 1988a). Likewise, no
(Chung et al., 1985b, 1990), or minor (Jancsó et al.,
1985b), degeneration of axons in afferent nerves or dorsal
roots is noted. This indicates that somata and axon (Chung et al., 1985b, 1990), or minor (Jancsó et al., 1985b), degeneration of axons in afferent nerves or dorsal roots is noted. This indicates that somata and axons of afferent neurons in the adult rat are fairly resistan 1985b), degeneration of axons in afferent nerves or dorsal
roots is noted. This indicates that somata and axons of
afferent neurons in the adult rat are fairly resistant to
the neurodegenerative action of capsaicin. In con roots is noted. This indicates that somata and axons of afferent neurons in the adult rat are fairly resistant to the neurodegenerative action of capsaicin. In contrast, unmyelinated sensory nerve terminals in the peripher afferent neurons in the adult rat are fairly resistant to
the neurodegenerative action of capsaicin. In contrast,
unmyelinated sensory nerve terminals in the periphery
(Hoyes and Barber, 1981; Hoyes et al., 1981; Chung et
 the neurodegenerative action of capsaicin. In contrast, unmyelinated sensory nerve terminals in the periphery (Hoyes and Barber, 1981; Hoyes et al., 1981; Chung et al., 1985b, 1990) show extensive degeneration. In skin (Ch unmyelinated sensory nerve terminals in the periphery
(Hoyes and Barber, 1981; Hoyes et al., 1981; Chung et
al., 1985b, 1990) show extensive degeneration. In skin
(Chung et al., 1990) and ureter (Chung et al., 1985b) 50
to (Hoyes and Barber, 1981; Hoyes et al., 1981; Chung et al., 1985b, 1990) show extensive degeneration. In skin (Chung et al., 1990) and ureter (Chung et al., 1985b) 50 to 90% of all axon terminals degenerate. The result of c al., 1985b, 1990) show extensive degeneration. In skin (Chung et al., 1990) and ureter (Chung et al., 1985b) 50 to 90% of all axon terminals degenerate. The result of capsaicin treatment of adult rats has been described, t (Chung et al., 1990) and ureter (Chung et al., 1985b) 50
to 90% of all axon terminals degenerate. The result of
capsaicin treatment of adult rats has been described,
therefore, as "distal axonopathy" (Chung et al., 1990). to 90% of all axon terminals degenerate. The result of capsaicin treatment of adult rats has been described, therefore, as "distal axonopathy" (Chung et al., 1990). Because the somata and axons do not degenerate, it seems capsaicin treatment of adult rats has been described, therefore, as "distal axonopathy" (Chung et al., 1990). Because the somata and axons do not degenerate, it seems likely that the slow neurochemical and functional recov therefore, as "distal axonopathy" (Chung et al., 1990)
Because the somata and axons do not degenerate, is
seems likely that the slow neurochemical and functions
recovery of sensory neurons, which is seen after capsaici
tre Because the somata
seems likely that the
recovery of sensory no
treatment of adult ra
aged nerve terminals
There are addition ems likely that the slow neurochemical and functional
covery of sensory neurons, which is seen after capsaicin
eatment of adult rats, reflects a regeneration of dam-
ed nerve terminals.
There are additional data to suggest treatment of adult rats, reflects a regeneration of dam-

treatment of adult rats, reflects a regeneration of damaged nerve terminals.
There are additional data to suggest that the primary
target of capsaicin's neurotoxic action on sensory neu-
rons of the adult rat is the periph aged nerve terminals.

There are additional data to suggest that the primary

target of capsaicin's neurotoxic action on sensory neu-

rons of the adult rat is the peripheral nerve terminal or

a site distal to the cell b There are additional data to suggest that the primary
target of capsaicin's neurotoxic action on sensory neu-
rons of the adult rat is the peripheral nerve terminal on
a site distal to the cell body. For instance, substanc target of capsaicin's neurotoxic action on sensory nons of the adult rat is the peripheral nerve terminal
a site distal to the cell body. For instance, substance
depletion from the peripheral processes of sensory no
rons p rons of the adult rat is the peripheral nerve terminal or
a site distal to the cell body. For instance, substance P
depletion from the peripheral processes of sensory neu-
rons proceeds considerably faster after systemic c a site distal to the cell body. For instance, substance P
depletion from the peripheral processes of sensory neu-
rons proceeds considerably faster after systemic capsai-
cin administration than after nerve section (Maggi depletion from the peripheral processes of sensory neurons proceeds considerably faster after systemic capsaicin administration than after nerve section (Maggi et al., 1987e). Furthermore, NGF appears to antagonize the neu rons proceeds considerably faster after systemic capsaicin administration than after nerve section (Maggi et al., 1987e). Furthermore, NGF appears to antagonize the neurotoxic action of capsaicin at a site distal to the ce cin administration than after nerve section (Maggi et al., 1987e). Furthermore, NGF appears to antagonize the neurotoxic action of capsaicin at a site distal to the cell body (Miller et al., 1982a), if not at the periphera neurotoxic action of capsaicin at a site distal to the cell
body (Miller et al., 1982a), if not at the peripheral nerve
process itself (Taylor et al., 1985). In addition, studies
with sensory neuron cultures from the embry neurotoxic action of capsaicin at a site distal to the cell
body (Miller et al., 1982a), if not at the peripheral nerve
process itself (Taylor et al., 1985). In addition, studies
with sensory neuron cultures from the embry body (Miller et al., 1982a), if not at the peripheral nerve
process itself (Taylor et al., 1985). In addition, studies
with sensory neuron cultures from the embryonic chick
(Hiura and Sakamoto, 1987a) and newborn and adult with sensory neuron cultures from the embryonic chick
(Hiura and Sakamoto, 1987a) and newborn and adult rat
(Winter et al., 1988, 1990) have shown that neurites
rather than somata are the preferential target of the
neuroto with sensory neuron cultures i
(Hiura and Sakamoto, 1987a) a
(Winter et al., 1988, 1990) h
rather than somata are the p
neurotoxic action of capsaicin.
It is at present not possib Is iura and Sakamoto, 1987a) and newborn and adult rat
Vinter et al., 1988, 1990) have shown that neurites
ther than somata are the preferential target of the
urotoxic action of capsaicin.
It is at present not possible to

(Winter et al., 1988, 1990) have shown that neurites rather than somata are the preferential target of the neurotoxic action of capsaicin.
It is at present not possible to decide conclusively whether the distal axonopathy rather than somata are the preferential target of the
neurotoxic action of capsaicin.
It is at present not possible to decide conclusively
whether the distal axonopathy caused by systemic cap-
saicin treatment of adult rat neurotoxic action of capsaicin.
It is at present not possible to decide conclusively
whether the distal axonopathy caused by systemic cap-
saicin treatment of adult rats arises from segmental
differences in the accessibili It is at present not possible to decide conclusively
whether the distal axonopathy caused by systemic cap-
saicin treatment of adult rats arises from segmental
differences in the accessibility of the drug and/or seg-
menta whether the distal axonopathy caused by systemic cap-
saicin treatment of adult rats arises from segmental
differences in the accessibility of the drug and/or seg-
mental differences in the vulnerability to the drug. Ad-
d saicin treatment of adult rats arises from segmental
differences in the accessibility of the drug and/or seg-
mental differences in the vulnerability to the drug. Ad-
ditional factors may have a differential bearing on the differences in the accessibility of the drug and/or seg-
mental differences in the vulnerability to the drug. Ad-
ditional factors may have a differential bearing on the
neurotoxicity of capsaicin, depending on whether the mental differences in the vulnerability to the drug. Additional factors may have a differential bearing on the neurotoxicity of capsaicin, depending on whether the drug is administered systemically or applied locally to ax ditional factors may have a differential bearing on the
neurotoxicity of capsaicin, depending on whether the
drug is administered systemically or applied locally to
axons or nerve terminals of sensory neurons or to cul-
tu neurotoxicity of capsaicin, depending on whether the
drug is administered systemically or applied locally to
axons or nerve terminals of sensory neurons or to cul-
tured sensory neurons. Thus, periaxonal capsaicin is
effec drug is administered systemically or applied locally to
axons or nerve terminals of sensory neurons or to cul-
tured sensory neurons. Thus, periaxonal capsaicin is
effective in causing substantial degeneration of all seg-
 axons or nerve terminals of sensory neurons or to cultured sensory neurons. Thus, periaxonal capsaicin is
effective in causing substantial degeneration of all seg-
ments of unmyelinated afferent neurons (Jancsó and
Lawson, tured sensory neurons. Thus, periaxonal capsaicin is
effective in causing substantial degeneration of all seg-
ments of unmyelinated afferent neurons (Jancsó and
Lawson, 1990), whereas local administration of capsaicin
to effective in causing substantial degeneration of all segments of unmyelinated afferent neurons (Jancsó and Lawson, 1990), whereas local administration of capsaicin
to the spinal cord produces extensive damage of the
centra ments of unmyelinated afferent neurons (Jancsó and Lawson, 1990), whereas local administration of capsaicin
to the spinal cord produces extensive damage of the
central terminals of sensory neurons (Palermo et al.,
1981; Ri Lawson, 1990), whereas local administration of capsaicin
to the spinal cord produces extensive damage of the
central terminals of sensory neurons (Palermo et al.,
1981; Ribeiro-da-Silva and Coimbra, 1984) but not to
their to the spinal cord produces extensive damage of the central terminals of sensory neurons (Palermo et al., 1981; Ribeiro-da-Silva and Coimbra, 1984) but not to their somata and distal axons (Jancsó, 1981; Gamse, 1982; Gamse central terminals of sensory neurons (Palermo et al., 1981; Ribeiro-da-Silva and Coimbra, 1984) but not to their somata and distal axons (Jancsó, 1981; Gamse, 1982; Gamse et al., 1984, 1986). A better understanding of thes 1981; Ribeiro-da-Silva and Coimbra, 1984) but not to
their somata and distal axons (Jancsó, 1981; Gamse,
1982; Gamse et al., 1984, 1986). A better understanding
of these phenomena will require investigation of the
segmenta their somata and distal axons (Jancsó, 1981; Gamse, 1982; Gamse et al., 1984, 1986). A better understanding of these phenomena will require investigation of the segmental distribution of the capsaicin receptor/cation chann

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

PHARM
REV

PHARMACOLOGICAL REVIEWS

segments of sensory neurons, being especially high in axonal terminal regions (Kostyuk, 1989).
8. Ontogenetic shift in the neurotoxicity of capsaicin in
the rat. The somata of B-type sensory neurons in the
newborn rat are axonal terminal regions (Kostyuk, 1989). This
 8. Ontogenetic shift in the neurotoxicity of capsaicin in
 the rat. The somata of B-type sensory neurons in the capsaich

mewborn rat are considerably more sensitive to t 8. Ontogenetic shift in the neurotoxicity of capsaicin in a the rat. The somata of B-type sensory neurons in the consumborn rat are considerably more sensitive to the neurodegenerative action of systemic capsaicin than ar the rat. The somata of B-type sensory neurons in the character found the new-
newborn rat are considerably more sensitive to the neu-
rodegenerative action of systemic capsaicin than are s
those in the adult rat. The neuro newborn rat are considerably more sensitive to the neu-
rodegenerative action of systemic capsaicin than are
those in the adult rat. The neurotoxic action of capsaicin
has been found to be expressed at 16 days of gestation rodegenerative action of systemic capsaicin than are
those in the adult rat. The neurotoxic action of capsaicin
has been found to be expressed at 16 days of gestation
in the rat (Kirby et al., 1982) and at 15 days of gesta those in the adult rat. The neurotoxic action of capsaicin
has been found to be expressed at 16 days of gestation
in the rat (Kirby et al., 1982) and at 15 days of gestation
in the mouse (Atkinson and Chaggar, 1983). In th has been found to be expressed at 16 days of gestation Him the rat (Kirby et al., 1982) and at 15 days of gestation the in the mouse (Atkinson and Chaggar, 1983). In the adult cine only the peripheral axon terminals of unm in the rat (Kirby et al., 1982) and at 15 days of gestation
in the mouse (Atkinson and Chaggar, 1983). In the adult
rat only the peripheral axon terminals of unmyelinated
afferent fibers seem to be as vulnerable to capsaic in the mouse (Atkinson and Chaggar, 1983). In the adult
rat only the peripheral axon terminals of unmyelinated
afferent fibers seem to be as vulnerable to capsaicin as
those in the newborn rat (Chung et al., 1985b, 1990).
 rat only the peripheral axon terminals of unmyelinated hafferent fibers seem to be as vulnerable to capsaicin as m
those in the newborn rat (Chung et al., 1985b, 1990). the
This ontogenetic loss of capsaicin vulnerability afferent fibers seem to be as vulnerable to capsaicin as those in the newborn rat (Chung et al., 1985b, 1990). This ontogenetic loss of capsaicin vulnerability does not appear to be due to a change in the number or affinit those in the newborn rat (Chung et al., 1985b, 1
This ontogenetic loss of capsaicin vulnerability doe
appear to be due to a change in the number or af
of the capsaicin recognition sites in dorsal root ga
as estimated by th This ontogenetic loss of capsaicin vulnerability does not
appear to be due to a change in the number or affinity
of the capsaicin recognition sites in dorsal root ganglia,
as estimated by the specific binding of $[^{3}H]$ r appear to be due to a change in the number or affinity
of the capsaicin recognition sites in dorsal root ganglia,
as estimated by the specific binding of [³H] resinifera-
toxin (Szallasi and Blumberg, 1990b). Consequentl of the capsaicin recognition sites in dorsal root ganges as estimated by the specific binding of [³H] resinife toxin (Szallasi and Blumberg, 1990b). Consequently must be other determinants of capsaicin's neurotos action as estimated by the specific binding of $[^{3}H]$ resinifera-
toxin (Szallasi and Blumberg, 1990b). Consequently, it fu
must be other determinants of capsaicin's neurotoxic ni
action that change with age. Although these det toxin (Szallasi and Blumberg, 1990b). Consequently, it funtat be other determinants of capsaicin's neurotoxic nection that change with age. Although these determinants have not yet been elucidated, it could be argued that must be other determinants of capsaicin's neurotoxic action that change with age. Although these determinants have not yet been elucidated, it could be argued that there is an ontogenetic change in the expression or activi action that change with age. Although these determents have not yet been elucidated, it could be arguest that there is an ontogenetic change in the expression activity of the capsaicin-operated membrane channel that prime nants have not yet been elucidated, it could be argued
that there is an ontogenetic change in the expression or tic
activity of the capsaicin-operated membrane channels in
that prime the intracellular admission of toxic co that there is an ontogenetic change in the expression or activity of the capsaicin-operated membrane channels that prime the intracellular admission of toxic concentrations of cations. This speculation is based on the fin activity of the capsaicin-operated membrane channe
that prime the intracellular admission of toxic concertrations of cations. This speculation is based on the
findings that the expression of a certain voltage-gate
Ca²⁺ that prime the intracellular admission of toxic concentrations of cations. This speculation is based on the findings that the expression of a certain voltage-gated Ca^{2+} channel and of a tetrodotoxin-resistant Na^+ cha trations of cations. This speculation is based on the indings that the expression of a certain voltage-gated Ca^{2+} channel and of a tetrodotoxin-resistant Na⁺ channel in sensory neurons has been found to vary with age findings that the expression of a certain voltage-gated Ca^{2+} channel and of a tetrodotoxin-resistant Na^+ channel in sensory neurons has been found to vary with age, being typical of developing nerve cells only (Fedul Ca^{2+} channel and of a tetrodotoxin-resistant Na⁺ channel in sensory neurons has been found to vary with age, being typical of developing nerve cells only (Fedulova et al., 1986; Kostyuk et al., 1986; Petersen et al., nel in sensory neurons has been found to vary with age,
being typical of developing nerve cells only (Fedulova et
al., 1986; Kostyuk et al., 1986; Petersen et al., 1987;
Kostyuk, 1989). It is possible, therefore, that affe being typical of developing nerve cells only (Fedulova et iones). The neurodegenerative at al., 1986; Petersen et al., 1987; enters Kostyuk, 1989). It is possible, therefore, that afferent ious neurons in the developing ra al., 1986; Kostyuk et al., 1986; Petersen et al., 1987; ent Kostyuk, 1989). It is possible, therefore, that afferent ious neurons in the developing rat are particularly susceptible ruth to the neurodegenerative action of c Kostyuk, 1989). It is possible, therefore, that afferent iounivers in the developing rat are particularly susceptible rut to the neurodegenerative action of capsaicin because they dyerossess more capsaicin-operated cation neurons in the developing rat are particularly susceptible rub to the neurodegenerative action of capsaicin because they dypossess more capsaicin-operated cation channels than do safferent neurons in the adult animal in wh channels. ssess more capsaicin-operated cation channels than offerent neurons in the adult animal in which only axeminals remain endowed with a high density of the annels.
Because the expression of functional capsaicin recep-
poster

afferent neurons in the adult animal in which only axon
terminals remain endowed with a high density of these va
channels.
Because the expression of functional capsaicin recep-
tor/cation channel complexes appears to be un terminals remain endowed with a high density of these vachannels.

Secause the expression of functional capsaicin recep-

tor/cation channel complexes appears to be under the the

control of NGF (Winter et al., 1988), and channels.

Because the expression of functional capsaicin rector/cation channel complexes appears to be under vontrol of NGF (Winter et al., 1988), and possibly

other trophic factors, it could be inferred that down

gulat Because the expression of functional capsaicin receptor/cation channel complexes appears to be under the control of NGF (Winter et al., 1988), and possibly of other trophic factors, it could be inferred that downregulation tor/cation channel complexes appears to be under the the control of NGF (Winter et al., 1988), and possibly of wother trophic factors, it could be inferred that downre-ungulation of the receptor/channel complexes in the ad control of NGF (Winter et al., 1988), and possibly of where trophic factors, it could be inferred that downre-
gulation of the receptor/channel complexes in the adult phanimal is due to the fact that the NGF requirements o other trophic factors, it could be inferred that downre-
gulation of the receptor/channel complexes in the adult
animal is due to the fact that the NGF requirements of
sensory neurons decrease during ontogeny (Buck and
Bur gulation of the receptor/channel complexes in the adult ph
animal is due to the fact that the NGF requirements of Lu
sensory neurons decrease during ontogeny (Buck and sul
Burks, 1986). Alternatively, it could be speculate animal is due to the fact that the NGF requirements of sensory neurons decrease during ontogeny (Buck and Burks, 1986). Alternatively, it could be speculated that the immature sensory neurons in the newborn rat are particu sensory neurons decrease during ontogeny (Buck and
Burks, 1986). Alternatively, it could be speculated that
the immature sensory neurons in the newborn rat are
particularly susceptible to the secondary, intracellular
conse In 1986). Alternatively, it could be speculated that
 9. immature sensory neurons in the newborn rat are

inticularly susceptible to the secondary, intracellular
 9. *Endogenous capsaicin-like substances*. The presence

the immature sensory neurons in the newborn rat are particularly susceptible to the secondary, intracellular consequences of capsaicin's action on the cell membrane.
9. Endogenous capsaicin-like substances. The presence of consequences of capsaicin's action on the cell membrane.
9. Endogenous capsaicin-like substances. The presence
of a specific recognition site for capsaicin-like substances
coupled to nonselective cation channels on sensory consequences of capsaicin's action on the cell membrane.
9. Endogenous capsaicin-like substances. The presence
of a specific recognition site for capsaicin-like substances
coupled to nonselective cation channels on sensory 9. Endogenous capsaicin-like substances. The presence of a specific recognition site for capsaicin-like substances hypoupled to nonselective cation channels on sensory neu-
comparison realises the question as to whether ce

segments of sensory neurons, being especially high in 1990a), the discovery of a competitive capsaicin antago-
axonal terminal regions (Kostyuk, 1989).
8. Ontogenetic shift in the neurotoxicity of capsaicin in and the es ER
structures. The development of a radioimmunoassay for
capsaicin (Wood et al., 1990), the availability of a [³H] ER
structures. The development of a radioimmunoassay for
capsaicin (Wood et al., 1990), the availability of a [³H]
resiniferatoxin-binding assay (Szallasi and Blumberg, ER
structures. The development of a radioimmunoassay for
capsaicin (Wood et al., 1990), the availability of a [³H]
resiniferatoxin-binding assay (Szallasi and Blumberg,
1990a), the discovery of a competitive capsaicin an structures. The development of a radioimmunoassay
capsaicin (Wood et al., 1990), the availability of a [³
resiniferatoxin-binding assay (Szallasi and Blumbe
1990a), the discovery of a competitive capsaicin anta
nist, cap capsaicin (Wood et al., 1990), the availability of a $[{}^3H]$ resiniferatoxin-binding assay (Szallasi and Blumberg, resiniferatoxin-binding assay (Szallasi and Blumberg, 1990a), the discovery of a competitive capsaicin antagonist, capsazepine (Bevan et al., 1991; Dray et al., 1991), and the establishment of ruthenium red as a functional 1990a), the discovery of a competitive capsaicin antagonist, capsazepine (Bevan et al., 1991; Dray et al., 1991), and the establishment of ruthenium red as a functional capsaicin antagonist (Amann and Maggi, 1991) have mad nist, capsazepine (Bevan et al., 1991; Dray et al., 1991),
and the establishment of ruthenium red as a functional
capsaicin antagonist (Amann and Maggi, 1991) have
made it possible to search for the existence of endogenous and the establishment of ruthenium red as a functional capsaicin antagonist (Amann and Maggi, 1991) have made it possible to search for the existence of endogenous substances that are structurally related to capsaicin or u capsaicin antagonist (Amann and Maggi, 1991) have
made it possible to search for the existence of endogenous
substances that are structurally related to capsaicin or
use the same transduction mechanisms as capsaicin.
Howev made it possible to search for the existence of endogenosubstances that are structurally related to capsaicin
use the same transduction mechanisms as capsaic
However, studies in which a sensitive radioimmunoass
that grossl substances that are structurally related to capsaicin or
use the same transduction mechanisms as capsaicin.
However, studies in which a sensitive radioimmunoassay
that grossly recognizes the structural features of capsai-
 use the same transduction mechanisms as capsaicin.
However, studies in which a sensitive radioimmunoassay
that grossly recognizes the structural features of capsai-
cin required for stimulation of sensory neurons was used
 However, studies in which a sensitive radioimmunoassay
that grossly recognizes the structural features of capsai-
cin required for stimulation of sensory neurons was used
have failed to detect any endogenous capsaicin-like that grossly recognizes the structural features of capsaicin required for stimulation of sensory neurons was used
have failed to detect any endogenous capsaicin-like im-
munoreactive material in normal and inflamed tissues cin required for stimulation of sensory neurons was used
have failed to detect any endogenous capsaicin-like im-
munoreactive material in normal and inflamed tissues of
the rat (Wood et al., 1990). It would appear, therefo have failed to detect any endogenous capsaicin-like im-
munoreactive material in normal and inflamed tissues of
the rat (Wood et al., 1990). It would appear, therefore,
that there is no endogenous substance that fulfills t munoreactive material in normal and inflamed tissues of
the rat (Wood et al., 1990). It would appear, therefore,
that there is no endogenous substance that fulfills the
structural requirements that a compound has to meet i the rat (Wood et al., 1990). It would appear, therefore, that there is no endogenous substance that fulfills the structural requirements that a compound has to meet in order to interact with the capsaicin recognition site that there is no endogenous substance that fulfills structural requirements that a compound has to meet order to interact with the capsaicin recognition site sensory neurons. This contention, however, ought to further str structural requirements that a compound has to meet in order to interact with the capsaicin recognition site on sensory neurons. This contention, however, ought to be further strengthened by experiments using the $[^{3}H]$ r order to interact with the case
sensory neurons. This conten
further strengthened by expeniferatoxin assay and the co
sazepine, as screening tools.
Given that at submicromo msory neurons. This contention, however, ought t
rther strengthened by experiments using the [³H]
feratoxin assay and the competitive antagonist,
zepine, as screening tools.
Given that at submicromolar/micromolar concer

further strengthened by experiments using the [³H] resi-
niferatoxin assay and the competitive antagonist, cap-
sazepine, as screening tools.
Given that at submicromolar/micromolar concentra-
tions ruthenium red antagoni niferatoxin assay and the competitive antagonist, cs
sazepine, as screening tools.
Given that at submicromolar/micromolar concentr
tions ruthenium red antagonizes the action of capsaid
in a specific fashion, it would seem sazepine, as screening tools.

Given that at submicromolar/micromolar concentra-

tions ruthenium red antagonizes the action of capsaicin

in a specific fashion, it would seem that there are endog-

enous and exogenous su Given that at submicromolar/micromolar concentra-
tions ruthenium red antagonizes the action of capsaicin
in a specific fashion, it would seem that there are endog-
enous and exogenous substances that utilize a ruthenium
r tions ruthenium red antagonizes the action of capsai
in a specific fashion, it would seem that there are end
enous and exogenous substances that utilize a rutheni
red-blockable transduction pathway, even though th
are not in a specific fashion, it would seem that there are endogenous and exogenous substances that utilize a ruthenium
red-blockable transduction pathway, even though they
are not structurally related to capsaicin. Thus, ruthenenous and exogenous substances that utilize a ruthenium
red-blockable transduction pathway, even though they
are not structurally related to capsaicin. Thus, ruthen-
ium red has been found to reduce the stimulant actions
o red-blockable transduction pathway, even though there not structurally related to capsaicin. Thus, ruthe ium red has been found to reduce the stimulant action of toluene disocyanate (Mapp et al., 1990) and hydrog ions (Gep are not structurally related to capsaicin. Thus, ruthen-
ium red has been found to reduce the stimulant actions
of toluene diisocyanate (Mapp et al., 1990) and hydroger
ions (Geppetti et al., 1991) on capsaicin-sensitive a ium red has been found to reduce the stimulant actions
of toluene diisocyanate (Mapp et al., 1990) and hydrogen
ions (Geppetti et al., 1991) on capsaicin-sensitive affer-
ent neurons. Similarly, nociceptor stimulation by n of toluene diisocyanate (Mapp et al., 1990) and hydrogen
ions (Geppetti et al., 1991) on capsaicin-sensitive affer-
ent neurons. Similarly, nociceptor stimulation by nox-
ious heat applied to the rabbit ear is also inhibit ions (Geppetti et al., 1991) on capsaicin-sensitive afferent neurons. Similarly, nociceptor stimulation by noxious heat applied to the rabbit ear is also inhibited by ruthenium red (Amann et al., 1990a). In addition, the d ent neurons. Similarly, nociceptor stimulation by noxious heat applied to the rabbit ear is also inhibited by ruthenium red (Amann et al., 1990a). In addition, the dye is able to antagonize sodium deoxycholate, a bile salt ious heat applied to the rabbit ear is also inhibited l
ruthenium red (Amann et al., 1990a). In addition, t
dye is able to antagonize sodium deoxycholate, a b
salt, in facilitating capsaicin's excitatory effect on se
sory ruthenium red (Amann et al., 1990a). In addition, the dye is able to antagonize sodium deoxycholate, a bile salt, in facilitating capsaicin's excitatory effect on sensory neurons (Jin and Nakayama, 1990). These observation dye is able to antagonize sodium deoxycholate, a bile
salt, in facilitating capsaicin's excitatory effect on sen-
sory neurons (Jin and Nakayama, 1990). These obser-
vations suggest that the aforementioned stimuli activate salt, in facilitating capsaicin's excitatory effect on sensory neurons (Jin and Nakayama, 1990). These observations suggest that the aforementioned stimuli activate sensory neurons by a transduction mechanism similar to th sory neurons (Jin and Nakayama, 1990). These observations suggest that the aforementioned stimuli activate sensory neurons by a transduction mechanism similar to that of capsaicin or can release an endogenous compound that vations suggest that the aforementioned stimuli activat
sensory neurons by a transduction mechanism similar t
that of capsaicin or can release an endogenous compoun
that acts like capsaicin. It remains to be examine
whethe sensory neurons by a transduction mechanism similar to
that of capsaicin or can release an endogenous compound
that acts like capsaicin. It remains to be examined
whether other factors such as mechanical noxious stim-
uli, that acts like capsaicin. It remains to be examined
whether other factors such as mechanical noxious stim-
uli, ischemia (Franco-Cereceda et al., 1989b), the vapour
phase of tobacco smoke (Lundberg and Saria, 1983, 1987; that acts like capsaicin. It remains to be examined
whether other factors such as mechanical noxious stim-
uli, ischemia (Franco-Cereceda et al., 1989b), the vapour
phase of tobacco smoke (Lundberg and Saria, 1983, 1987;
L whether other factors such as mechanical noxious stim-
uli, ischemia (Franco-Cereceda et al., 1989b), the vapour
phase of tobacco smoke (Lundberg and Saria, 1983, 1987;
Lundblad, 1984), xylene (Abelli et al., 1988), or hyd Lundblad, 1984), xylene (Abelli et al., 1988), or hydrogen
sulphide (Prior et al., 1990), all of which stimulate, and
acrylamide (Abelli et al., 1991), which defunctionalizes phase of tobacco smoke (Lundberg and Saria, 1983, 1987;
Lundblad, 1984), xylene (Abelli et al., 1988), or hydrogen
sulphide (Prior et al., 1990), all of which stimulate, and
acrylamide (Abelli et al., 1991), which defuncti Lundblad, 1984), xylene (Abelli et al., 1
sulphide (Prior et al., 1990), all of whi
acrylamide (Abelli et al., 1991), which
capsaicin-sensitive afferent neurons
transduction pathways with capsaicin.
An aspect of capsaicin-

transduction pathways with capsaicin.
An aspect of capsaicin-sensitive neurons that may be
of pathophysiological significance is their sensitivity to capsaicin-sensitive afferent neurons, share common
transduction pathways with capsaicin.
An aspect of capsaicin-sensitive neurons that may be
of pathophysiological significance is their sensitivity to
hydrogen ions, a prop capsaicin-sensitive afferent neurons, share common
transduction pathways with capsaicin.
An aspect of capsaicin-sensitive neurons that may be
of pathophysiological significance is their sensitivity to
hydrogen ions, a prop transduction pathways with capsaicin.

An aspect of capsaicin-sensitive neurons that may be

of pathophysiological significance is their sensitivity to

hydrogen ions, a property for which there is both indirect

(Clarke a An aspect of capsaicin-sensitive neurons that may be
of pathophysiological significance is their sensitivity to
hydrogen ions, a property for which there is both indirect
(Clarke and Davison, 1978; Cervero and McRitchie, 1 of pathophysiological significance is their sensitivity to
hydrogen ions, a property for which there is both indirect
(Clarke and Davison, 1978; Cervero and McRitchie, 1982;
Martling and Lundberg, 1988; Geppetti et al., 19

CAPSAICIN 187

(Bevan and Yeats, 1989) evidence. Studies of rat dorsal CAPSAIC
(Bevan and Yeats, 1989) evidence. Studies of rat dorsal 19
root ganglion cultures have demonstrated that lowering in
the pH to <6.4 activates a long-lasting inward current re CAPS
(Bevan and Yeats, 1989) evidence. Studies of rat dorsal
root ganglion cultures have demonstrated that lowering
the pH to <6.4 activates a long-lasting inward current
in about 30 to 50% of the neurons. This proton-evok (Bevan and Yeats, 1989) evidence. Studies of rat dorsal root ganglion cultures have demonstrated that lowering the pH to ≤ 6.4 activates a long-lasting inward current in about 30 to 50% of the neurons. This proton-evo (Bevan and Yeats, 1989) evidence. Studies of rat dorsal 1987).

root ganglion cultures have demonstrated that lowering inhibit

the pH to $\lt 6.4$ activates a long-lasting inward current rent as

in about 30 to 50% of the root ganglion cultures have demonstrated that lowes
the pH to ≤ 6.4 activates a long-lasting inward currel
in about 30 to 50% of the neurons. This proton-evo
current has a reversal potential of approximately 0
which i the pH to <6.4 activates a long-lasting inward current
in about 30 to 50% of the neurons. This proton-evoked
current has a reversal potential of approximately 0 mV
which is indistinguishable from that of the capsaicin-
evo in about 30 to 50% of the neurons. This proton-evoked (left current has a reversal potential of approximately 0 mV S
which is indistinguishable from that of the capsaicin-
evoked inward current (Bevan and Yeats, 1989). Fu current has a reversal potential of approximately 0 mV
which is indistinguishable from that of the capsaicin-
evoked inward current (Bevan and Yeats, 1989). Fur-
thermore, the neurons that respond to hydrogen ions
with a l which is indistinguishable from that of the capsaicinevoked inward current (Bevan and Yeats, 1989). Furthermore, the neurons that respond to hydrogen ions with a long-lasting inward current appear to be identical with tho evoked inward current (Bevan and Yeats, 1989). Fur-
thermore, the neurons that respond to hydrogen ions
with a long-lasting inward current appear to be identical
inh
with those neurons that are killed by prolonged exposure thermore, the neurons that respond to hydrogen ions cert
with a long-lasting inward current appear to be identical
with those neurons that are killed by prolonged exposure
to micromolar concentrations of capsaicin (Bevan a with a long-lasting inward current appear to be identical
with those neurons that are killed by prolonged exposure
to micromolar concentrations of capsaicin (Bevan and
Yeats, 1989). In addition, protons have been found to
 with those neurons that are killed by prolonged exposure
to micromolar concentrations of capsaicin (Bevan and
Yeats, 1989). In addition, protons have been found to
activate a short-lasting Na⁺ conductance in isolated se to micromolar concentrations of capsaicin (Bevan and 1982). This inhibition of membrane currents is likely to
Yeats, 1989). In addition, protons have been found to
account for a capsaicin-induced transient blockade of
act Yeats, 1989). In addition, protons have been found to activate a short-lasting Na⁺ conductance in isolated sensory neurons (Krishtal and Pidoplichko, 1980, 1981), which most probably represents a Ca^{2+} channel that is activate a short-lasting Na⁺ conductance in isolated
sory neurons (Krishtal and Pidoplichko, 1980, 19
which most probably represents a Ca^{2+} channel this
transformed to a Na⁺ channel in the presence of pro
(Konnerth sory neurons (Krishtal and Pidoplichko, 1980, 1980, 1980)
which most probably represents a Ca^{2+} channel that
transformed to a Na⁺ channel in the presence of prot
(Konnerth et al., 1987; Kostyuk, 1989). This short-la
 which most probably represents a Ca^{2+} channel that
transformed to a Na⁺ channel in the presence of proto
(Konnerth et al., 1987; Kostyuk, 1989). This short-la
ing inward current evoked by hydrogen ions predon
nates i transformed to a Na⁺ channel in the presence of protons

(Konnerth et al., 1987; Kostyuk, 1989). This short-last-

ing inward current evoked by hydrogen ions predomi-

nates in the smaller trigeminal ganglion neurons (K (Konnerth et al., 1987; Kostyuk, 1989). This short-last-
ing inward current evoked by hydrogen ions predominates in the smaller trigeminal ganglion neurons (Krish-
tal and Pidoplichko, 1981) but is not confined to the
pop ing inward current evoked by hydrogen ions predominates in the smaller trigeminal ganglion neurons (Krishtal and Pidoplichko, 1981) but is not confined to the propulation of capsaicin-sensitive neurons cultured from dorsa mates in the smaller trigeminal ganglion neurons (Krishtal and Pidoplichko, 1981) but is not confined to the population of capsaicin-sensitive neurons cultured from spotter dorsal root ganglia (Bevan and Yeats, 1989). Futu tal and Pidoplichko, 1981) but is not confined to the population of capsaicin-sensitive neurons cultured from dorsal root ganglia (Bevan and Yeats, 1989). Future work will have to reveal the exact relationships between the population of capsaicin-sensitive neurons cultured from
dorsal root ganglia (Bevan and Yeats, 1989). Future work
will have to reveal the exact relationships between the
inward currents induced by hydrogen ions and those
i will have to reveal the exact relationship
inward currents induced by hydrogen is
induced by capsaicin. A close examination
transitions between known cation conce
those evoked by capsaicin also is needed.
C. Mechanisms of *C. Mechanisms of the Cell-nonselective Effects*
C. Mechanisms of the Cell-nonselective Effects
Apart from the activation of a cation conduction

those evoked by capsaicin also is needed.

C. Mechanisms of the Cell-nonselective Effects

Apart from the activation of a cation conductance in

certain sensory neurons, capsaicin exerts other actions

on sensory as well a C. Mechanisms of the Cell-nonselective Effects
Apart from the activation of a cation conductance
certain sensory neurons, capsaicin exerts other action
sensory as well as nonsensory neurons and nonn
ronal cells, which seem C. Mechanisms of the Cell-nonselective Effects

Apart from the activation of a cation conductance in

certain sensory neurons, capsaicin exerts other actions

on sensory as well as nonsensory neurons and nonneu-

ronal ce Apart from the activation of a cation conductance in care
certain sensory neurons, capsaicin exerts other actions of
on sensory as well as nonsensory neurons and nonneu-
ronal cells, which seem to be unrelated to its selec certain sensory neurons, capsaicin exerts other actions
on sensory as well as nonsensory neurons and nonneu-
ronal cells, which seem to be unrelated to its selective
stimulant, desensitizing, and neurotoxic effects on thin on sensory as well as nonsensory neurons and non
ronal cells, which seem to be unrelated to its selec
stimulant, desensitizing, and neurotoxic effects on
sensory neurons. Although these cell-nonselective
tions of capsaicin ronal cells, which seem to be unrelated to its selective
stimulant, desensitizing, and neurotoxic effects on thin
sensory neurons. Although these cell-nonselective ac-
tions of capsaicin have not been investigated systema stimulant, desensitizing, and neurotoxic effects on thin
sensory neurons. Although these cell-nonselective ac-
tions of capsaicin have not been investigated systemati-
cally, it is possible to identify some common traits s sensory neurons. Although these cell-nonselective actions of capsaicin have not been investigated systematically, it is possible to identify some common traits shared by them. Thus, the nonselective effects of capsaicin ca tions of capsaicin have not been investigated systemati-
cally, it is possible to identify some common traits shared
by them. Thus, the nonselective effects of capsaicin can
in the shown repetitively and do not exhibit de cally, it is possible to identify some common traits shared
by them. Thus, the nonselective effects of capsaicin can
be shown repetitively and do not exhibit desensitization
and are not related to cell toxicity. Whereas t by them. Thus, the nonselective effects of capsaicin can
be shown repetitively and do not exhibit desensitization
and are not related to cell toxicity. Whereas the sensory
neuron-selective effects are produced by nanomola be shown repetitively and do not exhibit desensitization
and are not related to cell toxicity. Whereas the sensory
neuron-selective effects are produced by nanomolar $(>10$
nM) concentrations of capsaicin (EC₅₀ approxim and are not related to cell toxicity. Whereas the sensory
neuron-selective effects are produced by nanomolar (>10
nM) concentrations of capsaicin (EC₅₀ approximately 0.2
 μ M; Marsh et al., 1987; Wood et al., 1988; Ama neuron-selective effects are produced by nanomolar (>10

nM) concentrations of capsaicin (EC₅₀ approximately 0.2
 μ M; Marsh et al., 1987; Wood et al., 1988; Amann, 1990;

Winter et al., 1990), it is typically micromo nM) concentrations of capsaicin (EC₅₀ approximately 0.2 μ M; Marsh et al., 1987; Wood et al., 1988; Amann, 1990; Winter et al., 1990), it is typically micromolar ($>3 \mu$ M) concentrations of capsaicin that are required μ M; Marsh et al., 1987; Wood et al., 1988; Amann, 1990;
Winter et al., 1990), it is typically micromolar (>3 μ M)
concentrations of capsaicin that are required to cause its
cell-nonselective effects (Bevan and Szol Winter et al., 1990), it is
concentrations of capsaic
cell-nonselective effects
Precise estimations of th
respect are not available.
With respect to membi mcentrations of capsaicin that are required to cause its

Il-nonselective effects (Bevan and Szolcsányi, 1990). (I

recise estimations of the potency of capsaicin in this

spect are not available.

With respect to membran

cell-nonselective effects (Bevan and Szolcsányi, 1990).

Precise estimations of the potency of capsaicin in this

respect are not available.

With respect to membrane mechanisms, inhibition of (1

voltage-gated Na⁺ and Precise estimations of the potency of capsaicin in this to
respect are not available.
With respect to membrane mechanisms, inhibition of $\rm (E$
voltage-gated Na⁺ and K⁺ channels is the most common
component in the non respect are not available.

With respect to membrane mechanisms, inhibition of σ

voltage-gated Na⁺ and K⁺ channels is the most common

component in the nonselective actions of capsaicin. The

drug is able to influ With respect to membrane mechanisms, inhibition of
voltage-gated Na⁺ and K⁺ channels is the most common
component in the nonselective actions of capsaicin. The
drug is able to influence the action potential in all sen voltage-gated Na⁺ and K⁺ channels is the most common component in the nonselective actions of capsaicin. The drug is able to influence the action potential in all sensory neurons of the rat, guinea pig, and chick (Godf component in the nonselective actions of capsaicin. The tive drug is able to influence the action potential in all sensory thes neurons of the rat, guinea pig, and chick (Godfraind et stab) al., 1981; Petersen et al., 1987 drug is able to influence the action potential in all sensory
neurons of the rat, guinea pig, and chick (Godfraind et
al., 1981; Petersen et al., 1987; Szolcsányi, 1990). Cap-
saicin prolongs the duration of the action pot neurons of the rat, guinea pig, and chick (Godfraind et al., 1981; Petersen et al., 1987; Szolcsányi, 1990). Capsaicin prolongs the duration of the action potential in sensory neurons of the rat and chick (Godfraind et al.

CIN 1987). This effect of capsaicin may be related to an inhibition of both the Na⁺ inward and K^+ outward cur-FIGIN 187
1987). This effect of capsaicin may be related to an
inhibition of both the Na⁺ inward and K⁺ outward cur-
rent as seen in guinea pig and chick sensory neurons 187
1987). This effect of capsaicin may be related to an
inhibition of both the Na⁺ inward and K⁺ outward cur-
rent as seen in guinea pig and chick sensory neurons
(Petersen et al., 1987; Bevan and Forbes, 1988; 1987). This effect of capsaicin may be related to an inhibition of both the Na⁺ inward and K^+ outward current as seen in guinea pig and chick sensory neurons (Petersen et al., 1987; Bevan and Forbes, 1988; Szolcsányi 1987). This effect of capsaicin may be related to an inhibition of both the Na⁺ inward and K⁺ outward current as seen in guinea pig and chick sensory neurons (Petersen et al., 1987; Bevan and Forbes, 1988; Szolcsányi, rent as seen in guinea pig and chick sensory neurons (Petersen et al., 1987; Bevan and Forbes, 1988; Szolcsányi, 1990), rat sympathetic neurons (Bevan et al., 1987), snail neurons (Erdélyi et al., 1987), and crayfish giant rent as seen in guinea pig and chick sensory neurons
(Petersen et al., 1987; Bevan and Forbes, 1988;
Szolcsányi, 1990), rat sympathetic neurons (Bevan et al.,
1987), snail neurons (Erdélyi et al., 1987), and crayfish
giant (Petersen et al., 1987; Bevan and Forbes, 1988;
Szolcsányi, 1990), rat sympathetic neurons (Bevan et al., 1987), snail neurons (Erdélyi et al., 1987), and crayfish
giant axons (Yamanaka et al., 1984). Blockade of a
certai Szolcsányi, 1990), rat sympathetic neurons (Bevan et al., 1987), snail neurons (Erdélyi et al., 1987), and crayfish giant axons (Yamanaka et al., 1984). Blockade of a certain component of the outward K^+ current, with s 1987), snail neurons (Erdélyi et al., 1987), and crayfish giant axons (Yamanaka et al., 1984). Blockade of a certain component of the outward K^+ current, with some inhibition of the Na⁺ inward current, also is observ giant axons (Yamanaka et al., 1984). Blockade of a
certain component of the outward K^+ current, with some
inhibition of the Na⁺ inward current, also is observed in
myelinated nerve fibers of the frog sciatic nerve (D inhibition of the Na⁺ inward current, also is observed in myelinated nerve fibers of the frog sciatic nerve (Dubois, inhibition of the Na⁺ inward current, also is observed in myelinated nerve fibers of the frog sciatic nerve (Duboid 1982). This inhibition of membrane currents is likely t account for a capsaicin-induced transient blocka myelinated nerve fibers of the frog sciatic nerve (Dubois, 1982). This inhibition of membrane currents is likely to account for a capsaicin-induced transient blockade of nerve conduction as has been shown in rat A-fiber af 1982). This inhibition of membrane currents is likely to
account for a capsaicin-induced transient blockade of
nerve conduction as has been shown in rat A-fiber affer-
ent neurons (Baranowski et al., 1986; Marsh et al., 19 account for a capsaicin-induced transient blockadenerve conduction as has been shown in rat A-fiber and the ent neurons (Baranowski et al., 1986; Marsh et al., 1
cat sympathetic nerve fibers (Such and Jancsó, 1
and crayfis rve conduction as has been shown in rat A-fiber affer
t neurons (Baranowski et al., 1986; Marsh et al., 1987)
t sympathetic nerve fibers (Such and Jancsó, 1986)
d crayfish giant axons (Yamanaka et al., 1984).
Although the

For all membrane. Rat and chick sensory
dorsal root ganglia (Bevan and Yeats, 1989). Future work
will have to reveal the exact relationships between the
inward currents induced by hydrogen ions and those
induced by removal C. Mechanisms of the Cell-nonselective Effects
ance of the membrane (Foster et al. 1981). In contrast,
Apart from the activation of a cation conductance in capsaicin has been reported to depolarize giant neurons ent neurons (Baranowski et al., 1986; Marsh et al., 1987),
cat sympathetic nerve fibers (Such and Jancsó, 1986),
and crayfish giant axons (Yamanaka et al., 1984).
Although the nonselective effects of capsaicin on volt-
age cat sympathetic nerve fibers (Such and Jancso, 1986), and crayfish giant axons (Yamanaka et al., 1984).
Although the nonselective effects of capsaicin on voltage-dependent ion conductances in the cell membrane
are fairly c and crayfish giant axons (Yamanaka et al., 1984).
Although the nonselective effects of capsaicin on volt-
age-dependent ion conductances in the cell membrane
are fairly consistent in vertebrate and nonvertebrate
species, t Although the nonselective effects of capsaicin on volt-
age-dependent ion conductances in the cell membrane
are fairly consistent in vertebrate and nonvertebrate
species, there is much variation in the effect of capsaicin
 age-dependent ion conductances in the cell membrane
are fairly consistent in vertebrate and nonvertebrate
species, there is much variation in the effect of capsaicin
on the resting cell membrane. Rat and chick sensory
neur are fairly consistent in vertebrate and nonvertebrate
species, there is much variation in the effect of capsaicin
on the resting cell membrane. Rat and chick sensory
neurons respond to capsaicin with a hyperpolarization
th species, there is much variation in the effect of capsaicin
on the resting cell membrane. Rat and chick sensory
neurons respond to capsaicin with a hyperpolarization
that is blocked by removal of extracellular Cl⁻ (Godfr on the resting cell membrane. Rat and chick sensory
neurons respond to capsaicin with a hyperpolarization
that is blocked by removal of extracellular Cl⁻ (Godfraind
et al., 1981). In the crayfish giant axon (Yamanaka et
 neurons respond to capsaicin with a hyperpolarization
that is blocked by removal of extracellular Cl⁻ (Godfraind
et al., 1981). In the crayfish giant axon (Yamanaka et
al., 1984) and in the giant amoeba (Foster et al., 1 that is blocked by removal of extracellular CI⁻ (Godfrain
et al., 1981). In the crayfish giant axon (Yamanaka
al., 1984) and in the giant amoeba (Foster et al., 198
capsaicin is without effect on the resting potential, i al., 1984) and in the giant amoeba (Foster et al., 1981). al., 1984) and in the giant amoeba (Foster et al., 1981)
capsaicin is without effect on the resting potential, al-
though in the amoeba capsaicin reduces the input resist-
ance of the membrane (Foster et al. 1981). In con capsaicin is without effect on the resting potential, although in the amoeba capsaicin reduces the input resistance of the membrane (Foster et al. 1981). In contrast, capsaicin has been reported to depolarize giant neurons capsaicin has been reported to depolarize giant neurons
of the snail and to inhibit voltage-gated Ca^{2+} inward
currents in these neurons (Erdélyi et al., 1987).
It is conceivable that the inhibitory effect of capsaicin

on the neuronal Ca^{2+} conductance bears a relation to the capsaicin has been reported to depolarize giant neurons
of the snail and to inhibit voltage-gated Ca^{2+} inward
currents in these neurons (Erdélyi et al., 1987).
It is conceivable that the inhibitory effect of capsaicin
 of the snail and to inhibit voltage-gated Ca^{2+} inward
currents in these neurons (Erdélyi et al., 1987).
It is conceivable that the inhibitory effect of capsaicin
on the neuronal Ca^{2+} conductance bears a relation to currents in these neurons (Erdélyi et al., 1987).
It is conceivable that the inhibitory effect of capsaicin
on the neuronal Ca²⁺ conductance bears a relation to the
capsaicin-induced inhibition of Ca²⁺ uptake in mouse It is conceivable that the inhibitory effect of capsaicin
on the neuronal Ca^{2+} conductance bears a relation to the
capsaicin-induced inhibition of Ca^{2+} uptake in mouse
neuroblastoma cells and rat aortic smooth muscl on the neuronal Ca²⁺ conductance bears a relation to the capsaicin-induced inhibition of Ca^{2+} uptake in mouse neuroblastoma cells and rat aortic smooth muscle cells (Monsereenusorn and Kongsamut, 1985). Whether the i capsaicin-induced inhibition of Ca⁴⁺ uptake in moundle neuroblastoma cells and rat aortic smooth muscle ce (Monsereenusorn and Kongsamut, 1985). Whether timhibitory effects of capsaicin and piperine on cardimuscle (Zerni neuroblastoma cells and rat aortic smooth muscle cells
(Monsereenusorn and Kongsamut, 1985). Whether the
inhibitory effects of capsaicin and piperine on cardiac
muscle (Zernig et al., 1984; Franco-Cereceda and Lund-
berg, (Monsereenusorn and Kongsamut, 1985). Whether the
inhibitory effects of capsaicin and piperine on cardiac
muscle (Zernig et al., 1984; Franco-Cereceda and Lund-
berg, 1988) and visceral smooth muscle (Holzer and
Lembeck, 1 inhibitory effects of capsaicin and piperine on cardiac
muscle (Zernig et al., 1984; Franco-Cereceda and Lund-
berg, 1988) and visceral smooth muscle (Holzer and
Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al.,
198 muscle (Zernig et al., 1984; Franco-Cereceda and Lund-
berg, 1988) and visceral smooth muscle (Holzer and
Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al.
1987c, 1989b; Takaki et al., 1990) arise from a similar
acti berg, 1988) and visceral smooth muscle (Holzer and Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, 1989b; Takaki et al., 1990) arise from a similar action has not yet been examined. In contrast, the contrac Lembeck, 1979; Barthó et al., 1982b, 1987; Maggi et al., 1987c, 1989b; Takaki et al., 1990) arise from a similar action has not yet been examined. In contrast, the contractile effect of capsaicin on vascular smooth muscle 1987c, 1989b; Takaki et al., 1990) arise from a similar action has not yet been examined. In contrast, the contractile effect of capsaicin on vascular smooth muscle (Donnerer and Lembeck, 1982; Duckles, 1986; Saito et al. action has not yet been examined. In contrast, the contractile effect of capsaicin on vascular smooth muscle (Donnerer and Lembeck, 1982; Duckles, 1986; Saito et al., 1988; Bény et al., 1989; Holzer et al., 1990b) seems t tractile effect of capsaici
(Donnerer and Lembeck,
al., 1988; Bény et al., 198
to be associated with an
(Edvinsson et al., 1990).
The molecular mechanis onnerer and Lembeck, 1982; Duckles, 1986; Sai, 1988; Bény et al., 1989; Holzer et al., 1990b) s
be associated with an influx of extracellular
dvinsson et al., 1990).
The molecular mechanism of capsaicin's cell-nons
re effe

al., 1988; Bény et al., 1989; Holzer et al., 1990b) seems
to be associated with an influx of extracellular Ca^{2+}
(Edvinsson et al., 1990).
The molecular mechanism of capsaicin's cell-nonselec-
tive effects remains to be to be associated with an influx of extracellular Ca^{2+}
(Edvinsson et al., 1990).
The molecular mechanism of capsaicin's cell-nonselec-
tive effects remains to be disclosed. Because many of
these actions manifest themsel (Edvinsson et al., 1990).
The molecular mechanism of capsaicin's cell-nonselective effects remains to be disclosed. Because many of
these actions manifest themselves in a kind of membrane
stabilization, it is conceivable t The molecular mechanism of capsaicin's cell-nonselective effects remains to be disclosed. Because many of these actions manifest themselves in a kind of membrane stabilization, it is conceivable that they are related to th tive effects remains to be disclosed. Because many of
these actions manifest themselves in a kind of membrane
stabilization, it is conceivable that they are related to the
lipophilicity of the drug. Owing to this chemical these actions manifest themselves in a kind of membra
stabilization, it is conceivable that they are related to t
lipophilicity of the drug. Owing to this chemical proper
capsaicin could interact directly with the cell mem ability.

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

- ¹⁸⁸ **HOLZER** TABLE 3 *Characteristics and mechanisms of capsaicin 's actions on excitable cells* **A. Cell-nonselective effects of capsaicin** 1. TABLE 3
 1. Targets: excitable cells of capsaicin

1. Targets: excitable cells of vertebrate and invertebrate species (myelinated and unmyelinated sensory neurons, sympathetic neurons,

2. Targets: excitable cells of Characteristics and mechanisms of capsaic
 onselective effects of capsaicin

tets: excitable cells of vertebrate and invertebrate species (myeline

cardiac muscle, vascular smooth muscle, visceral smooth muscle)

nomenol **2. Phenomenology of acts of capsaicin**
 2. Phenomenology of action
 2. Phenomenology of action
 2. Phenomenology of action
 3. Typically depression of excitability (except in vascular smooth muscle)
 **2. Phenomeno Targets: excitable cells of vertebrate and invertebrate species (myelinated and unmyelinated sensory neuro cardiac muscle, vascular smooth muscle, visceral smooth muscle)
Phenomenology of action
a. Typically depression** Targets: excitable cells of vertebrate and invertebra
cardiac muscle, vascular smooth muscle, visceral
Phenomenology of action
a. Typically depression of excitability (except in vasc
b. Effect to be shown repetitively (n cardiac muscle,
Phenomenology of a
a. Typically depres
b. Effect to be show
c. Nonneurotoxic
d. Unaffected by p!
	-
- Phenomenology of action

a. Typically depression of excitability (except in vasce

b. Effect to be shown repetitively (not desensitizing)

c. Nonneurotoxic

d. Unaffected by prior ablation of sensory neurons

Potency: spec
	-
	-
	-
	-
- 2. Typically diploes
b. Effect to be shown repetitively (not desensitizing)
c. Nonneurotoxic
d. Unaffected by prior ablation of sensory neurons
3. Potency: species and tissue differences; in many cases EC_{50} probably >1 d. Unaffected by prior ablation of sensory neurons
3. Potency: species and tissue differences; in many cases EC_{50} probably >10 μ M
4. Mechanisms of action: in most instances (except vascular smooth muscle) stab
potas d. Unaffected by prior ablation of sensory neurons
3. Potency: species and tissue differences; in many case
4. Mechanisms of action: in most instances (except vasc
potassium conductance and the inward current
B. Sensory n

- *3. Potency:* species and tissue differences; in many cases EC_{50} probably >10 μ M
 4. Mechanisms of action: in most instances (except vascular smooth muscle) stabilization of the cell membrane: reduction of both t potassium conductance and
 3. Targets: primary afferent net

(Ab-) fibers

2. Phenomenology of action

Sequence of effects consisting **nsory neuron-selective effects of**

Targets: primary afferent neurons $(A\delta-)$ fibers
 Phenomenology of action

Sequence of effects consisting of:
 a. Dose-dependent excitation **(Aδ-)** fibers
 Phenomenology of action

Sequence of effects consisting of:
 a. Dose-dependent excitation

b. Capsaicin-specific (low doses) or capsaicin-nonspecific (moderate to high doses) desensitization

c. Blocka
-
-
-
- **3.** Dose-dependent excitation
 3. Capsaicin-specific (low doses) or capsaicin-nonspecific (moderate to high dos
 3. Potency: species differences; in the rat EC_{50} in the range of 0.1-0.3 μ M
 4. Mechanisms of a
	-
- Phenomenology of action
Sequence of effects consisting of:
a. Dose-dependent excitation
b. Capsaicin-specific (low doses) or
c. Blockade of nerve conduction
d. Neurotoxic alterations (moderate
- Sequence of effects consisting of:

a. Dose-dependent excitation

b. Capsaicin-specific (low doses) or capsaicin-nonspec

c. Blockade of nerve conduction

d. Neurotoxic alterations (moderate to high doses)
 Potency: spe
-
- 1. Blockade of nerve conduction
 4. Neurotoxic alterations (moderate to high doses)

3. Potency: species differences; in the rat EC_{50} in the range of 0.1–0.3 μ M

4. Mechanisms of action
 a. Occupation of a speci
	- c. Blockade of nerve conduction
d. Neurotoxic alterations (moderate to high doses)
Potency: species differences; in the rat EC_{50} in the range of 0.1–0.3 μ M
Mechanisms of action
a. Occupation of a specific recogn d. Neurotoxic alterations (moderate to high doses)
 Potency: species differences; in the rat EC₅₀ in the range of 0.1–0.3 μ M
 Mechanisms of action

	a. Occupation of a specific recognition site ("receptor") on the : species differences; in the rat EC_{50} in the issues of action
upation of a specific recognition site ("recording of nonselective cation channels (insection cate Ca²⁺, and other cations, depolarization
ease in the in Mechanisms of action
a. Occupation of a specific recognition site ("receptor") on the c
b. Opening of nonselective cation channels (insensitive to tetro
Ca²⁺, and other cations, depolarization
c. Increase in the intracel a. Occupation of a spe
b. Opening of nonsele
Ca²⁺, and other
c. Increase in the intr.
d. Peptide release
e. Activation of a Ca²⁺ b. Opening of nonselective cation channels (insensitive to tetrodotoxin and blockers of voltage-dependent Ca²⁺ Ca²⁺, and other cations, depolarization
c. Increase in the intracellular concentration of Ca²⁺ and Na⁺
	- f. Increase in the intracellular concentration.

	H. Peptide release

	F. Activation of a Ca²⁺-dependent outward

	f. Desensitization (functional refractorines

	Specific desensitization due to inhibiti
	-
	-
	-
	- Specific release
Specific release
Specific desensitization due to inhibition of transduction mechanisms utilized by capsaicin only
Specific desensitization due to inhibition of transduction mechanisms utilized by capsaicin Pura Formation of a Ca²⁺-dependent outward current and long-lasting inhibition of voltage-gated Ca²⁺ channels
beensitization (functional refractoriness)
Specific desensitization due to inhibition of transduction mechan icity g. Desensitization (functional refractoriness)
Specific desensitization due to inhibition of transduction mechanisms utilized by capsaicin only
Nonspecific desensitization due to general neuronal defunctionalization, proba
- some discussion and the to general neuronal defunctionalization, probably reflecting a mild and reversible form of neurotomorphic of reversible (degeneration) or irreversible (degeneration of neuronal soma), associated wit g. Neurotoxicity (ultrastructural damage of alowly reversible (no somatic degene

zation and delayed depletion of cellu
 D. Summary: Mechanisms of Action
 1. Sensory neuron-selective actions. It on) due to intracellular accumulation of calcium and NaCl, either
generation of neuronal soma), associated with quick defunctionali-
ide transmitters
Further, although indirect, support for the presence of
ch a recognition

²²¹ *1. Sensory neuron-selective actions.* It is now possible statements and performulate an overall hypothesis explaining the prin-1. Summary: Mechanisms of Action
1. Sensory neuron-selective actions. It is now possible
to formulate an overall hypothesis explaining the prin-
cipal features of the effects of capsaicin on thin sensor D. Summary: Mechanisms of Action
1. Sensory neuron-selective actions. It is now possible
to formulate an overall hypothesis explaining the prin-
cipal features of the effects of capsaicin on thin sensory
neurons: excitatio D. Summary: Mechanisms of Action
1. Sensory neuron-selective actions. It is now possible suc-
to formulate an overall hypothesis explaining the prin-
cipal features of the effects of capsaicin on thin sensory act
neurons: 1. Sensory neuron-selective actions. It is now possible to formulate an overall hypothesis explaining the principal features of the effects of capsaicin on thin sensory neurons: excitation, desensitization, neurotoxicity, their cell membrane or to their possession of free nerve neurons: excitation, desensitization, neurotoxicity, and Siselectivity (table 3). It has previously been speculated be
that the unique sensitivity of certain afferent neurons to recapsaicin is due to a particular functiona selectivity (table 3). It has previously been speculated that the unique sensitivity of certain afferent neurons to capsaicin is due to a particular functional makeup of their cell membrane or to their possession of free n that the unique sensitivity of certain afferent neurons to capsaicin is due to a particular functional makeup of their cell membrane or to their possession of free nerve endings (Buck and Burks, 1986). These well-taken arg capsaicin is due to a particular functional makeup of
their cell membrane or to their possession of free nerve
endings (Buck and Burks, 1986). These well-taken ar-
guments, however, have been superseded by a concept
that e their cell membrane or to their possession of free nerve
endings (Buck and Burks, 1986). These well-taken ar-
guments, however, have been superseded by a concept
that explains the sensory neuron-selective effects of cap-
s endings (Buck and Burks, 1986). These well-taken ar-
guments, however, have been superseded by a concept
that explains the sensory neuron-selective effects of cap-
saicin, i.e., by the identification of a specific membran guments, however, have been superseded by a concept
that explains the sensory neuron-selective effects of cap-
saicin, i.e., by the identification of a specific membrane
recognition site that is coupled to cation channels at explains the sensory neuron-selective effects of capicin, i.e., by the identification of a specific membrane
cognition site that is coupled to cation channels in the
ll membrane (table 3).
Direct evidence for a capsaici

saicin, i.e., by the identification of a specific membrane
recognition site that is coupled to cation channels in the
cell membrane (table 3).
Direct evidence for a capsaicin or "vanilloid" (Szallasi
and Blumberg, 1990b) recognition site that is coupled to cation channels in cell membrane (table 3).

Direct evidence for a capsaicin or "vanilloid" (Szall

and Blumberg, 1990b) recognition site on thin sense

neurons comes from binding studie cell membrane (table 3).

Direct evidence for a capsaicin or "vanilloid" (Szalla

and Blumberg, 1990b) recognition site on thin senso

neurons comes from binding studies in which [³H] re

niferatoxin is used as the test Direct evidence for a capsaicin or "vanilloid" (Szallasi
and Blumberg, 1990b) recognition site on thin sensory
neurons comes from binding studies in which $[^{3}H]$ resi-
niferatoxin is used as the test ligand (Szallasi an and Blumberg, 1990b) recognition site on thin sensory
neurons comes from binding studies in which $[^{3}H]$ resi-
niferatoxin is used as the test ligand (Szallasi and Blum-
berg, 1990a) and from the development of a specifi neurons comes from binding studies in which [³H]resiniferatoxin is used as the test ligand (Szallasi and Blumberg, 1990a) and from the development of a specific and competitive receptor antagonist, capsazepine (Bevan et niferatoxin is used as the test ligand (Szallasi and Blum-
berg, 1990a) and from the development of a specific and
competitive receptor antagonist, capsazepine (Bevan et and
al., 1991; Dray et al., 1991). The molecular str berg, 1990a) and from the development of a specific and competitive receptor antagonist, capsazepine (Bevan et al., 1991; Dray et al., 1991). The molecular structure of the capsaicin/vanilloid receptor and its orientation

to formulate an overall hypothesis explaining the prin-
cipal features of the effects of capsaicin on thin sensory
civity (Szolcsányi and Jancsó-Gábor, 1975, 1976;
neurons: excitation, desensitization, neurotoxicity, and (degeneration of neuronal soma), associated with quick defunctional-
pride transmitters
Further, although indirect, support for the presence of
such a recognition site is provided by *(a)* the existence
of a structure-acti Further, although indirect, support for the presence of
such a recognition site is provided by (*a*) the existence
of a structure-activity relationship for capsaicin-like
activity (Szolcsányi and Jancsó-Gábor, 1975, 1976; Further, although indirect, support for the presence of such a recognition site is provided by (*a*) the existence of a structure-activity relationship for capsaicin-like activity (Szolcsányi and Jancsó-Gábor, 1975, 1976; Further, although indirect, support for the presence
such a recognition site is provided by (*a*) the existen
of a structure-activity relationship for capsaicin-li
activity (Szolcsányi and Jancsó-Gábor, 1975, 19⁷
Szolcsá such a recognition site is provided by (*a*) the existence
of a structure-activity relationship for capsaicin-like
activity (Szolcsányi and Jancsó-Gábor, 1975, 1976;
Szolcsányi, 1982; Hayes et al., 1984b; Szallasi and Blum of a structure-activity relationship for capsaicin-like
activity (Szolcsányi and Jancsó-Gábor, 1975, 1976;
Szolcsányi, 1982; Hayes et al., 1984b; Szallasi and Blum-
berg, 1990b), (b) the ability to label the putative capsa activity (Szolcsányi and Jancsó-Gábor, 1975, 19
Szolcsányi, 1982; Hayes et al., 1984b; Szallasi and Blu
berg, 1990b), *(b)* the ability to label the putative capsai
recognition site with structurally related and long-act
p Szolcsányi, 1982; Hayes et al., 1984b; Szallasi and Blum-
berg, 1990b), (*b*) the ability to label the putative capsaicin
recognition site with structurally related and long-acting
photoaffinity probes (James et al., 1988) berg, 1990b), (*b*) the ability to label the putative capsaicin recognition site with structurally related and long-acting photoaffinity probes (James et al., 1988), (*c*) the remark-able cell selectivity of capsaicin's ac recognition site with structurally related and long-acting
photoaffinity probes (James et al., 1988), (c) the remark-
able cell selectivity of capsaicin's actions on thin sensory
neurons, (d) the ability of capsaicin to photoaffinity probes (James et al., 1988), (c) the remark-
able cell selectivity of capsaicin's actions on thin sensory
neurons, (d) the ability of capsaicin to activate single
cation channels in membrane patches from dors te to high doses) desensitization $\frac{1}{2}$
 $\frac{1}{2}$ $\frac{1}{$ neurons, (*d*) the ability of
cation channels in membrar
ganglion neurons (Forbes an
cellular regulation of the res
NGF (Winter et al., 1988).
Occupation of the capsaic tion channels in membrane patches from dorsal root
nglion neurons (Forbes and Bevan, 1988), and (e) the
llular regulation of the responsiveness to capsaicin by
GF (Winter et al., 1988).
Occupation of the capsaicin recogn

ganglion neurons (Forbes and Bevan, 1988), and (e) the cellular regulation of the responsiveness to capsaicin by NGF (Winter et al., 1988).
Occupation of the capsaicin recognition site leads to the opening of nonselectiv cellular regulation of the responsiveness to capsaicin by
NGF (Winter et al., 1988).
Occupation of the capsaicin recognition site leads to
the opening of nonselective cation channels in the cell
membrane that are unique i NGF (Winter et al., 1988).
Occupation of the capsaicin recognition site leads to
the opening of nonselective cation channels in the cell
membrane that are unique in that they are not affected
by tetrodotoxin or blockers o Occupation of the capsaicin recognition site leads to
the opening of nonselective cation channels in the cell
membrane that are unique in that they are not affected
by tetrodotoxin or blockers of voltage-dependent Ca^{2+} the opening of nonselective cation channels in the membrane that are unique in that they are not affect by tetrodotoxin or blockers of voltage-dependent C channels. Opening of these channels admits Na^+ , C and other cati membrane that are unique in that they are not affer by tetrodotoxin or blockers of voltage-dependent (channels. Opening of these channels admits Na^+ , (and other cations to the cytoplasm and causes depozation. The increa by tetrodotoxin or blockers of voltage-dependent Ca²⁻
channels. Opening of these channels admits Na⁺, Ca²⁺
and other cations to the cytoplasm and causes depolari-
zation. The increase in the intracellular Ca²⁺ con channels. Opening of these channels admits Na⁺, Ca
and other cations to the cytoplasm and causes depola
zation. The increase in the intracellular Ca²⁺ concenti
tion inhibits voltage-dependent Ca²⁺ channels and ac
va

aspet

CAPSAICIN 189

CAPSAIC
intracellular enzymes (table 3). All of these effects of
capsaicin depend on the applied concentration of the CAPSAICI
intracellular enzymes (table 3). All of these effects of acc
capsaicin depend on the applied concentration of the cap
drug, and it appears that the magnitude of the primary sel CAPSAIC
intracellular enzymes (table 3). All of these effects of a
capsaicin depend on the applied concentration of the ca
drug, and it appears that the magnitude of the primary se
action on the cell membrane determines th intracellular enzymes (table 3). All of these effects of acquision depend on the applied concentration of the carding, and it appears that the magnitude of the primary sequence of or some secondary effects such as nonspeci intracellular enzymes (table 3). All of these effect
capsaicin depend on the applied concentration of
drug, and it appears that the magnitude of the prin
action on the cell membrane determines the sequene
some secondary ef capsaicin depend on the applied concentration of
drug, and it appears that the magnitude of the prin
action on the cell membrane determines the sequene
some secondary effects such as nonspecific desensi
tion and neurotoxic drug, and it appears that the magnitude of the primary
action on the cell membrane determines the sequence of
some secondary effects such as nonspecific desensitiza-
tion and neurotoxicity. In contrast, specific desensitiz action on the cell membrane determines the sequence
some secondary effects such as nonspecific desensiti:
tion and neurotoxicity. In contrast, specific desensiti:
tion to capsaicin, which implies inactivation of the ce
ula some secondary effects such as nonspecific desensitiza-
tion and neurotoxicity. In contrast, specific desensitiza-
tion to capsaicin, which implies inactivation of the cell-
this drugs only, may occur in the absence of an
 tion and neurotoxicity. In contrast, specific desensitization to capsaicin, which implies inactivation of the cell-
ular transduction mechanism that is utilized by capsai-
cin-like drugs only, may occur in the absence of a tion to capsaicin, which implies inactivation of the cell-
ular transduction mechanism that is utilized by capsai-
cin-like drugs only, may occur in the absence of an
accitatory action on sensory nerve endings (Dray et al. ular transduction mechanism that is utilized by capsaicin-like drugs only, may occur in the absence of an nexcitatory action on sensory nerve endings (Dray et al., of 1990b,c). Nonspecific desensitization reflects a genera cin-like drugs only, may occur in the absence of an neu excitatory action on sensory nerve endings (Dray et al., of a 1990b,c). Nonspecific desensitization reflects a general to impairment of sensory neuron function and, excitatory action on sensory nerve endings (Dray et 1990b,c). Nonspecific desensitization reflects a gerempairment of sensory neuron function and, as just by its ionic requirements, is probably the result reversible neurot 90b,c). Nonspecific desensitization reflects a general pairment of sensory neuron function and, as judged its ionic requirements, is probably the result of a versible neurotoxic action of the drug (table 3). The neurotoxic

impairment of sensory neuron function and, as judy its ionic requirements, is probably the result of reversible neurotoxic action of the drug (table 3). The neurotoxic action of high concentrations of considering appears t by its ionic requirements, is probably the result of a
reversible neurotoxic action of the drug (table 3).
The neurotoxic action of high concentrations of cap-
saicin appears to arise from the intracellular accumula-
tion reversible neurotoxic action of the drug (table 3).
The neurotoxic action of high concentrations of cap-
saicin appears to arise from the intracellular accumula-
tion of calcium and NaCl and, in this respect, resembles
neu The neurotoxic action of high concentrations of capsaicin appears to arise from the intracellular accumulation of calcium and NaCl and, in this respect, resembles neurotoxicity induced by activation of, for example, excita saicin appears to arise from the intracellular accumu
tion of calcium and NaCl and, in this respect, resemb
neurotoxicity induced by activation of, for example,
citatory amino acid receptors (Garthwaite et al., 19
Choi, 19 tion of calcium and NaCl and, in this respect, resembles
neurotoxicity induced by activation of, for example, ex-
citatory amino acid receptors (Garthwaite et al., 1986;
Choi, 1987). This process gives rise not only to def neurotoxicity induced by activation of, for example, excitatory amino acid receptors (Garthwaite et al., 1986; the Choi, 1987). This process gives rise not only to defunctionalization but also to ultrastructural and degene citatory amino acid receptors (Garthwaite et al., 1986; the sensory neuron-selective actions of capsaicin because
Choi, 1987). This process gives rise not only to defunction alization for the nonselective effects can be sh Choi, 1987). This process gives rise not only to defunctionalization but also to ultrastructural and degenerative $\frac{1}{\sqrt{2}}$ changes of sensory neurons which, in turn, explain the tiolong duration of capsaicin's neuroto tionalization but also to ultrastructural and degenerative
changes of sensory neurons which, in turn, explain the
long duration of capsaicin's neurotoxic action. Depletion
of peptides and other constituents of sensory neur changes of sensory neurons which, in turn, explain the
long duration of capsaicin's neurotoxic action. Depletion
of peptides and other constituents of sensory neurons is
probably a consequence of the neurotoxic action of c long duration of capsaicin's neurotoxic action. Depletic of peptides and other constituents of sensory neurons
probably a consequence of the neurotoxic action of capsicin but is not the cause of defunctionalization. If the of peptides and other constituents of sensory neurons is
probably a consequence of the neurotoxic action of cap-
saicin but is not the cause of defunctionalization. If the
somata of sensory neurons do not degenerate, the m probably a consequence of the neurotoxic action of capsaicin but is not the cause of defunctionalization. If the somata of sensory neurons do not degenerate, the manifestations of neurotoxicity may be slowly reversible whe saicin but is not the cause of defunct
somata of sensory neurons do not deg
festations of neurotoxicity may be
whereas degeneration of the somata
versible neurotoxic effect (table 3).
2. Cell-nonselective actions. It is in mata of sensory neurons do not degenerate, the mani-

istations of neurotoxicity may be slowly reversible,

nereas degeneration of the somata results in an irre-

rsible neurotoxic effect (table 3).

2. Cell-nonselective a

festations of neurotoxicity may be slowly reversible,
whereas degeneration of the somata results in an irre-
versible neurotoxic effect (table 3).
2. Cell-nonselective actions. It is important to realize
that, apart from i whereas degeneration of the somata results in an irre-
versible neurotoxic effect (table 3).
2. Cell-nonselective actions. It is important to realize
that, apart from its sensory neuron-selective effects,
capsaicin also e versible neurotoxic effect (table 3). applies

2. Cell-nonselective actions. It is important to realize which

that, apart from its sensory neuron-selective effects, lized by

capsaicin also exerts cell-nonselective effec 2. Cell-nonselective actions. It is important to realize
that, apart from its sensory neuron-selective effects,
capsaicin also exerts cell-nonselective effects on a variety
of excitable cells. These nonselective effects d that, apart from its sensory neuron-selective effects,
capsaicin also exerts cell-nonselective effects on a variety
of excitable cells. These nonselective effects do not seem
to be mediated by a specific recognition site b capsaicin also exerts cell-nonselective effects on a variety
of excitable cells. These nonselective effects do not seem
to be mediated by a specific recognition site but may be
due to physicochemical interactions of the l of excitable cells. These nonselective effects do not seem
to be mediated by a specific recognition site but may be
due to physicochemical interactions of the lipophilic
capsaicin molecule with the cell membrane, especial to be mediated by a specific recognition site but may be due to physicochemical interactions of the lipophilic capsaicin molecule with the cell membrane, especially when high concentrations of the drug are used. Unlike the due to physicochemical interactions of the lipophilic capsaicin molecule with the cell membrane, especially tem
when high concentrations of the drug are used. Unlike the
sensory neuron-selective effects, the cell-nonselec capsaicin molecule with the cell mem
when high concentrations of the drug
the sensory neuron-selective effects, the
effects of capsaicin do not show desen
not result in neurotoxicity (table 3). the sensory neuron-selective effects, the cell-nonselective
effects of capsaicin do not show desensitization and do
not result in neurotoxicity (table 3).
IV. Capsaicin as a Pharmacological Tool
A. Caveats to Be Considered enects of capsatch do not show
not result in neurotoxicity (tab.
IV. Capsaicin as a Phair
A. Caveats to Be Considered
The sensory neuron-selective

IV. Capsaicin as a Pharmacological Tool
Caveats to Be Considered
The sensory neuron-selective effects of capsaicin ex-
bit a high degree of selectivity for a group of primary IV. Capsaicin as a Pharmacological Tool it

A. Caveats to Be Considered contract the considered contract of capsaicing ex-

The sensory neuron-selective effects of capsaicing ex-

hibit a high degree of selectivity for a A. Caveats to Be Considered
The sensory neuron-selective effects of capsaicin e
hibit a high degree of selectivity for a group of prima
afferent neurons with unmyelinated and thinly mye
nated nerve fibers. This observation The sensory neuron-selective effects of capsaicin ex-
hibit a high degree of selectivity for a group of primary
afferent neurons with unmyelinated and thinly myeli-
nated nerve fibers. This observation has made capsaicin
 The sensory neuron-selective effects of capsaicin ex-
hibit a high degree of selectivity for a group of primary
afferent neurons with unmyelinated and thinly myeli-
toxi
nated nerve fibers. This observation has made capsai hibit a high degree of selectivity for a group of primary planet afferent neurons with unmyelinated and thinly myeli-
nated nerve fibers. This observation has made capsaicin sim
an important, if not indispensable, tool wit afferent neurons with unmyelinated and thinly myeli-
nated nerve fibers. This observation has made capsaicin
an important, if not indispensable, tool with which to
investigate the neuroanatomical, neurochemical, and
functi nated nerve fibers. This observation has made capsaic
an important, if not indispensable, tool with which
investigate the neuroanatomical, neurochemical, an
functional characteristics of afferent neurons. It is we
ranted t an important, if not indispensable, tool with which to all
investigate the neuroanatomical, neurochemical, and
functional characteristics of afferent neurons. It is war-
ranted that further elucidation of its targets and m investigate the neuroanatomical, neurochemical, a
functional characteristics of afferent neurons. It is we
ranted that further elucidation of its targets and meanisms of action will further improve the potential
capsaicin functional characteristics of afferent neurons. It is war-
ranted that further elucidation of its targets and mech-
systemisms of action will further improve the potential of 5.
capsaicin as a selective probe for establish ranted that further elucidation of its targets and mech-
anisms of action will further improve the potential of
capsaicin as a selective probe for establishing the partic-
soipation of sensory neurons in physiological proc

acute excitatory and the long-term neurotoxic actions of capsaic in the long-term neurotoxic actions of
acute excitatory and the long-term neurotoxic actions of
capsaicin have been, and can be, made use of. The
selectivity of capsaicin for sensory neurons, however, is 189
acute excitatory and the long-term neurotoxic actions of
capsaicin have been, and can be, made use of. The
selectivity of capsaicin for sensory neurons, however, is
only relative and there are a number of limitations t acute excitatory and the long-term neurotoxic actions of capsaicin have been, and can be, made use of. The selectivity of capsaicin for sensory neurons, however, is only relative and there are a number of limitations to be acute excitatory and the long-term neurotoxic actions
capsaicin have been, and can be, made use of. T
selectivity of capsaicin for sensory neurons, however,
only relative and there are a number of limitations to
considere selectivity of capsaicin for sensory neurons, however, is only relative and there are a number of limitations to be considered when capsaicin is used as a pharmacological tool. The major caveats that have to be considered selectivity of capsaicin for sensory
only relative and there are a numbe
considered when capsaicin is used
tool. The major caveats that have
this respect are listed in table 4.
1. The group of capsaicin-sensit ly relative and there are a number of limitations to be nsidered when capsaicin is used as a pharmacological
pl. The major caveats that have to be considered in
is respect are listed in table 4.
1. The group of capsaicin-s

considered when capsaicin is used as a pharmacological
tool. The major caveats that have to be considered in
this respect are listed in table 4.
1. The group of capsaicin-sensitive primary afferent
neurons is not identical tool. The major caveats that have to be considered in
this respect are listed in table 4.
1. The group of capsaicin-sensitive primary afferent
neurons is not identical with any particular population
of afferent neurons tha this respect are listed in table 4.
1. The group of capsaicin-sensitive primary afferent
neurons is not identical with any particular population
of afferent neurons that have been classified according
to morphological, neu 1. The group of capsaicin-sensitive primary afferent
urons is not identical with any particular population
afferent neurons that have been classified according
morphological, neurochemical, or functional criteria.
2. The d

neurons is not identical with any particular population
of afferent neurons that have been classified according
to morphological, neurochemical, or functional criteria.
2. The degree of selectivity differs considerably for of afferent neurons that have been classified according
to morphological, neurochemical, or functional criteria.
2. The degree of selectivity differs considerably for the
acute and long-term actions of capsaicin. This is b to morphological, neurochemical, or functional criteria.
2. The degree of selectivity differs considerably for the
acute and long-term actions of capsaicin. This is because,
when acutely administered, the drug exerts both acute and long-term actions of capsaicin. This is because, when acutely administered, the drug exerts both sensory neuron-selective and cell-nonselective effects; the acute effects of capsaicin display the least selectivit acute and long-term actions of capsaicin. This is because,
when acutely administered, the drug exerts both sensory
neuron-selective and cell-nonselective effects; the acute
effects of capsaicin display the least selectivit when acutely administered, the drug exerts both sensory
neuron-selective and cell-nonselective effects; the acute
effects of capsaicin display the least selectivity for sen-
sory neurons (table 4). In many instances, howe neuron-selective and cell-nonselective effects; the acute
effects of capsaicin display the least selectivity for sen-
sory neurons (table 4). In many instances, however, the
cell-nonselective effects can easily be differen effects of capsaicin display the least selectivity for sensory neurons (table 4). In many instances, however, the cell-nonselective effects can easily be differentiated from the sensory neuron-selective actions of capsaici sory neurons (table 4). In many instances, however, the cell-nonselective effects can easily be differentiated from
the sensory neuron-selective actions of capsaicin becaus
the nonselective effects can be shown repetitivel the nonselective effects can be shown repetitively, do not

3. Another limitation has to do with the acute excitatory effect of capsaicin on sensory neurons. Depending on their magnitude, the manifestations of sensory neuron exhibit desensitization, and remain unaltered after abla-
tion of capsaicin-sensitive neurons.
3. Another limitation has to do with the acute excita-
tory effect of capsaicin on sensory neurons. Depending
on their magnitud tion of capsaicin-sensitive neurons.
3. Another limitation has to do with the acute excite
tory effect of capsaicin on sensory neurons. Dependin
on their magnitude, the manifestations of sensory neuro
stimulation can tempo 3. Another limitation has to do with the acute excita-
tory effect of capsaicin on sensory neurons. Depending
on their magnitude, the manifestations of sensory neuron
stimulation can temporarily override or obscure the fun for an involvement on sensory neurons. Depending
on their magnitude, the manifestations of sensory neuror
stimulation can temporarily override or obscure the func-
tion of other systems such that false-positive evidence
fo on their magnitude, the manifestations of sensory neuron
stimulation can temporarily override or obscure the func-
tion of other systems such that false-positive evidence
for an involvement of capsaicin-sensitive sensory stimulation can temporarily override or obscure the function of other systems such that false-positive evidence
for an involvement of capsaicin-sensitive sensory neurons in these systems may be obtained. This problem
appli tion of other systems such that false-positive evidence
for an involvement of capsaicin-sensitive sensory neu-
rons in these systems may be obtained. This problem
applies particularly to the gastrointestinal system in
whic for an involvement of capsaicin-sensitive sensory neurons in these systems may be obtained. This problem
applies particularly to the gastrointestinal system in
which peptide transmitters such as substance P are uti-
lized rons in these systems may be obtained. This problem
applies particularly to the gastrointestinal system in
which peptide transmitters such as substance P are uti-
lized by both primary afferent and enteric neurons. After
h applies particularly to the gastrointestinal system in
which peptide transmitters such as substance P are uti-
lized by both primary afferent and enteric neurons. After
having been released by capsaicin from sensory nerve
 lized by both primary afferent and enteric neurons. After having been released by capsaicin from sensory nerve endings in the gut, these peptides may also activate and desensitize receptors that are the physiological targe having been released by capsaicin from sensory nerve having been released by capsaicin from sensory nerve
endings in the gut, these peptides may also activate and
desensitize receptors that are the physiological targets of
peptides released from enteric neurons and, thereby, endings in the gut, these peptides may also activelesensitize receptors that are the physiological to peptides released from enteric neurons and, temporarily interrupt enteric reflex pathways (B al., 1982a; Holzer et al., sensitize receptors that are the physiological targets of
ptides released from enteric neurons and, thereby,
mporarily interrupt enteric reflex pathways (Barthó et
, 1982a; Holzer et al., 1989; Jin et al., 1990).
4. There

peptides released from enteric neurons and, thereby,
temporarily interrupt enteric reflex pathways (Barthó et
al., 1982a; Holzer et al., 1989; Jin et al., 1990).
4. There are also restrictions in the sensory neuron
selecti temporarily interrupt enteric reflex pathways (Barthó et al., 1982a; Holzer et al., 1989; Jin et al., 1990).
4. There are also restrictions in the sensory neuror selectivity of the long-term neurotoxic effect of capsaicinal., 1982a; Holzer et al., 1989; Jin et al., 1990).

4. There are also restrictions in the sensory neuron selectivity of the long-term neurotoxic effect of capsaicin

because the capsaicin-induced ablation of C-fiber neur 4. There are also restrictions in the sensory neuron selectivity of the long-term neurotoxic effect of capsaicin because the capsaicin-induced ablation of C-fiber neurons results in changes in the afferent neuron system it selectivity of the long-term neurotoxic effect of capsaicin
because the capsaicin-induced ablation of C-fiber neu-
rons results in changes in the afferent neuron system
itself and in the cellular systems that are functiona because the capsaicin-induced ablation of C-fiber neu-
rons results in changes in the afferent neuron system
itself and in the cellular systems that are functionally
connected to these neurons. Complete reorganization of
s rons results in changes in the afferent neuron syste
itself and in the cellular systems that are functiona
connected to these neurons. Complete reorganization
sensory pathways and associated systems appears to ta
place fol itself and in the cellular systems that are functionally
connected to these neurons. Complete reorganization of
sensory pathways and associated systems appears to take
place following treatment of newborn rats with a neuro connected to these neurons. Complete reorganization of
sensory pathways and associated systems appears to take
place following treatment of newborn rats with a neuro-
toxic dose of capsaicin. It is not yet clear whether a
 sensory pathways and associated systems appears to take
place following treatment of newborn rats with a neuro-
toxic dose of capsaicin. It is not yet clear whether a
similar extent of reorganization occurs when adult rats place following treatment of newborn rats with a neurotoxic dose of capsaicin. It is not yet clear whether a similar extent of reorganization occurs when adult rats are treated with systemic capsaicin or whether the neuron toxic dose of capsaicin. It is not yet clear whether a similar extent of reorganization occurs when adult rats are treated with systemic capsaicin or whether the neuronal reorganization seen in rats treated as neonates is system. e treated with systemic capsaicin or whether the n
nal reorganization seen in rats treated as neonates
lated to the plasticity of the still immature nerve
stem.
5. Certain long-term actions of capsaicin on nons
ry neural s

ronal reorganization seen in rats treated as neonates is
related to the plasticity of the still immature nervous
system.
5. Certain long-term actions of capsaicin on nonsen-
sory neural systems, such as thermosensitive neu related to the plasticity of the still immature nervous
system.
5. Certain long-term actions of capsaicin on nonsen-
sory neural systems, such as thermosensitive neurons in
the hypothalamus, some neurons in other brain are system.
5. Certain long-term actions of capsaicin on nonsensory neural systems, such as thermosensitive neurons in
the hypothalamus, some neurons in other brain areas,
and some neurons of the enteric nervous system, cannot

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

190 **HOLZER**

TABLE 4
Capsaicin as a pharmacological tool: Caveats to be considered

Capsaicin as a pharmacological tooL Caveats to be considered **A. Limitations in the classification of capsaicin-sensitive afferent neurons**

-
- 1. *Capsaicin as a pharmacological tool: Caveats to be considered*

1. *Not all* unmyelinated (C-fiber) or thinly myelinated (A δ -fiber) afferent neurons are capsaicin sensitive

2. *Not all* afferent neurons containing 2. *Capsaicin as a pharmacological tool: Caveats to be considered*

2. *Not all* unmyelinated (C-fiber) or thinly myelinated (A δ -fiber) afferent neurons

2. *Not all* afferent neurons containing substance P, CGRP, and o
-
- 3. Capsaicin-sensitive afferent neurons are heterogeneous in terms of their sensory modality
4. The group of capsaicin-sensitive afferent neurons are not identical with any group of afferent neurons defined according to mo
-
- 2. Not all afferent neurons containing substance P, CGRP, and other peptide markers are capsaicin sensitive
3. Capsaicin-sensitive afferent neurons are heterogeneous in terms of their sensory modality
4. The group of capsa **B.** Acute effects of capsaicin are less selective for thin sensory neurons than its long-term effects 1. Sensory neuron-selective effects of capsaicin may be obecured by its cell-nonselective effects 2. Sensory neuron-sel **E.** Acute effects of capsaicin are less selective for thin sensory neurons than its long-term effects
1. Sensory neuron-selective effects of capsaicin may be obecured by its cell-nonselective effects
2. Sensory neuron-sel
	-
	-
	- 1. Sensory neuron-selective effects of capsaicin can temporarily override the function of other systems, which may give rise to false positive evidence for an involvement of thin afferent neurons in the function under stud 1. Secondary alterations in the afferent system itself and in the cellular systems that are functionally connected to capsaicin-sensitive afferent neurons
- system may be susceptible to the neurotoxic effect of capsaicin
D. Age-dependent differences in sensory neuron sensitivity to capsaicin 2. Certain neurons of the central nervous system (preoptic region of the hypothalamus and other nuclei) and perhaps of the enteric nervous
	-
- 1. Certain neurons of the central nervous system (preoptic region of the hypothalamus and other nuclei) and perhaps of the enteric nervous
system may be susceptible to the neurotoxic effect of capsaicin
Age-dependent diffe intain neurons of the central nervous system (preoptic region of the hypothalamus and other nucleystem may be susceptible to the neurotoxic effect of capsaicin
dependent differences in sensory neuron sensitivity to capsaic
- 2. Treatment of adult rats with a neurotoxic effect of capsaicin

2. Treatment of newborn rats with a neurotoxic dose of capsaicin leads to degeneration of the majority of thin afferent neurons, but in the

2. Treatment of 2. Treatment of adult rats with systemic capsaicin is neurotoxic to the majority of thin afferent neurons but does not necessarily cause degeneration of the whole neuron. Certain receptor types, such as polymodal nocicepto **E. Strain and species differences in the sensory neuron sensitivity to capsaic in leads to degeneration of animals grown to adulthood there is no change in the different types of afferent ner 2. Treatment of adult rats wi** numals grown to adulthood there is no change in the different types of afferent nerve fibers
2. Treatment of adult rats with systemic capsaicin is neurotoxic to the majority of thin afferent neurons but does not necessaril 2. Treatment of adult rats with systemic capsaicin is neurotoxic to the majority of thin afferent neurons but does not necessarily cause degeneration of the whole neuron. Certain receptor types, such as polymodal nocicepto
	- -
- Strain and species differences in the sensory neuron sensitivity to capsaicin
1. There are subtle quantitative differences in the manifestations of the neurotoxic effect of capsaicin among differences.
2. There are pronoun be explained as being consequences of sensory neuron used when examining the anatomical, neurochemical, and guinear proposed used when examining the anatomical, neurochemical, and guinear analogue of sensory neuron selecti
	-

mote, and guinea pigs are very sensitive, whereas the rabbit and hal
3. Nonmammalian species appear to be essentially unresponsive to the s
be explained as being consequences of sensory neuron use
ablation. Confirmation an 3. Nonmammalian species appear to be essentially unresponsive to the
be explained as being consequences of sensory neuron
ablation. Confirmation and clarification of this issue is
of particular importance for the future v be explained as being consequences of sensory neuron
ablation. Confirmation and clarification of this issue is
of particular importance for the future value of capsaicin
as a research tool and for the validity of the concl be explained as being consequences of sensory neuron
ablation. Confirmation and clarification of this issue is
of particular importance for the future value of capsaicin
as a research tool and for the validity of the concl ablation. Confirmatiof particular important as a research tool and that have been dragation.
actions of capsaicin.
6. Special attention of particular importance for the future value of capsaicin
as a research tool and for the validity of the conclusions
that have been drawn from the long-term neurotoxic
actions of capsaicin.
6. Special attention needs to b as a research tool and for the validity of the conclusions
that have been drawn from the long-term neurotoxic continues of capsaicin.
6. Special attention needs to be given to age, strain,
and species differences in the s

that have been drawn from the long-term neurotoxic
actions of capsaicin.
6. Special attention needs to be given to age, strain,
and species differences in the sensory neuron sensitivity
to capsaicin that may be related in actions of capsaicin.

6. Special attention needs to be given to age, strain,

and species differences in the sensory neuron sensitivity

to capsaicin that may be related in part to different

degrees of sensory neuron sel 6. Special attention needs to be given to age, strain, to and species differences in the sensory neuron sensitivity add to capsaicin that may be related in part to different abegrees of sensory neuron selectivity of the d and species differences in the sensory neuron sensitivity
to capsaicin that may be related in part to different
degrees of sensory neuron selectivity of the drug. In the
rat, there are obvious differences in the neurotoxi to capsaicin that may be related in part to different allegrees of sensory neuron selectivity of the drug. In the trat, there are obvious differences in the neurotoxic action as of capsaicin, depending upon whether the dr degrees of sensory neuron selectivity of the drug. In the rat, there are obvious differences in the neurotoxic action of capsaicin, depending upon whether the drug is given to newborn or adult animals. Whereas there is a l rat, there are obvious differences in the neurotoxic action of capsaicin, depending upon whether the drug is given to newborn or adult animals. Whereas there is a loss of polymodal nociceptors after treatment of adult rats of capsaicin, depending upon whether the drug is given
to newborn or adult animals. Whereas there is a loss of
polymodal nociceptors after treatment of adult rats,
there is apparently no change in the types of nociceptors
 to newborn or adult animals. Whereas there is a loss of polymodal nociceptors after treatment of adult rats, there is apparently no change in the types of nociceptors after treatment of newborn rats, although most unmyelin polymodal nociceptors after treatment of adult rats,
there is apparently no change in the types of nociceptors
after treatment of newborn rats, although most unmye-
linated afferent nerve fibers have degenerated. The dis-
 there is apparently no change in the types of nociceptors
after treatment of newborn rats, although most unmye-
linated afferent nerve fibers have degenerated. The dis-
parity of these observations is not understood but th after treatment of newborn rats, although most unmye-
linated afferent nerve fibers have degenerated. The dis-
parity of these observations is not understood but throws
some doubt on the value of neonatal capsaicin treatme linated afferent nerve fibers have degenerated. The dis-
parity of these observations is not understood but throws
some doubt on the value of neonatal capsaicin treatment
in the functional investigation of sensory neurons. parity of these observations is not understood but through
some doubt on the value of neonatal capsaicin treatment
in the functional investigation of sensory neurons. T
profound alterations in sensory pathways may be anot
 me doubt on the value of neonatal capsaicin treatment
the functional investigation of sensory neurons. The
ofound alterations in sensory pathways may be another
favourable feature of neonatal capsaicin treatment.
Taken tog

in the functional investigation of sensory neurons. The and
profound alterations in sensory pathways may be another after
unfavourable feature of neonatal capsaicin treatment.
Taken together, there are a number of factors profound alterations in sensory pathways may be another unfavourable feature of neonatal capsaicin treatment.
Taken together, there are a number of factors that
limit the selectivity and usefulness of capsaicin as a
resear research tool for the investigation of sensory neurons limit the selectivity and usefulness of capsaicin a
research tool for the investigation of sensory neur
(table 4). Many of these restrictions, however, can
overcome by the use of appropriate controls and b
careful consider research tool for the investigation of sensory neurons perfections, however, can be view overcome by the use of appropriate controls and by a weareful consideration of the advantages and disadvantages associated with the d capsaicin. *B. Routes by the use of app*
 B. Routes of Administration
 B. Routes of Administration
 By Systemic treatment of small **Systemic and Systemic treatment of small rodents with neurotoxic Systemic treatment of small rodents with neurotoxic ses of capsaicin has been the most frequent method**

unfavourable feature of neonatal capsaicin treatment. al., 1982; Lynn and Shakhanbeh, 1988); systemic capsai-
Taken together, there are a number of factors that cin administration is less effective in this respect (Tervo,
 hamster are clearly less sensitive
hamster are clearly less sensitive
ne sensory neuron selective effects of capsaicin-
used when examining the anatomical, neurochemical
and functional alterations induced in capsaicin-sens as sensory neuron selective effects of capsaicin
used when examining the anatomical, neurochemical,
and functional alterations induced in capsaicin-sensitive
afferent neurons. This approach ablates all neurons sen-
sitive and functional alterations induced in capsaicin-sensitive afferent neurons. This approach ablates all neurons sensitive and accessible to the drug. Alternative routes of considerable potential are *periaxonal* treatment of used when examining the anatomical, neurochemica
and functional alterations induced in capsaicin-sensitive
afferent neurons. This approach ablates all neurons ser
sitive and accessible to the drug. Alternative routes of
co and functional alterations induced in capsaicin-sensitive
afferent neurons. This approach ablates all neurons sen-
sitive and accessible to the drug. Alternative routes of
considerable potential are *periaxonal* treatment afferent neurons. This approach ablates all neurons sensitive and accessible to the drug. Alternative routes of considerable potential are *periaxonal* treatment of afferent nerve fibers and *local (topical)* application o sitive and accessible to the drug. Alternative routes of considerable potential are *periaxonal* treatment of afferent nerve fibers and *local (topical)* application of the drug to the receptive fields under study. These r considerable potential are *periaxonal* treatment of afferent nerve fibers and *local (topical)* application of the drug to the receptive fields under study. These routes of administration enable the investigator to select ent nerve fibers and *local (topical)* application of the drug
to the receptive fields under study. These routes of
administration enable the investigator to selectively
ablate the sensory projections under study and, ther to the receptive fields under study. These routes of administration enable the investigator to selectively ablate the sensory projections under study and, thereby, to avoid the selectivity problems associated with systemic administration enable the investigator to selectively
ablate the sensory projections under study and, thereby,
to avoid the selectivity problems associated with systemic
administration of capsaicin. In the adult rat, peria ablate the sensory projections under study and, thereby,
to avoid the selectivity problems associated with systemic
administration of capsaicin. In the adult rat, periaxonal
application of capsaicin causes substantial deg to avoid the selectivity problems associated with systemic
administration of capsaicin. In the adult rat, periaxonal
application of capsaicin causes substantial degeneration
of C-fiber afferent neurons (Lynn et al., 1987; administration of capsaicin. In the adult rat, periaxonal
application of capsaicin causes substantial degeneration
of C-fiber afferent neurons (Lynn et al., 1987; Jancsó
and Lawson, 1990) and, in this respect, is considera application of capsaicin causes substantial degeneration
of C-fiber afferent neurons (Lynn et al., 1987; Jancsó
and Lawson, 1990) and, in this respect, is considerably
more effective than is systemic administration (Chung
 of C-fiber afferent neurons (Lynn et al., 1987; Jancsó
and Lawson, 1990) and, in this respect, is considerably
more effective than is systemic administration (Chung
et al., 1985b, 1990; Jancsó et al., 1985b). Even in a spe and Lawson, 1990) and, in this respect, is considerably
more effective than is systemic administration (Chung
et al., 1985b, 1990; Jancsó et al., 1985b). Even in a species
such as the rabbit which is comparatively resistan more effective than is systemic administration (Chung
et al., 1985b, 1990; Jancsó et al., 1985b). Even in a species
such as the rabbit which is comparatively resistant to
the drug, it is possible to both induce loss of fun et al., 1985b, 1990; Jancsó et al., 1985b). Even in a species
such as the rabbit which is comparatively resistant to
the drug, it is possible to both induce loss of function
and cause depletion of peptides from sensory neu such as the rabbit which is comparatively resistant
the drug, it is possible to both induce loss of functi
and cause depletion of peptides from sensory neuro
after their exposure to periaxonal capsaicin (Gamse
al., 1982; L the drug, it is possible to both induce loss of function and cause depletion of peptides from sensory neurons after their exposure to periaxonal capsaicin (Gamse et al., 1982; Lynn and Shakhanbeh, 1988); systemic capsaicin and cause depletion of peptides from sensory neurons
after their exposure to periaxonal capsaicin (Gamse et
al., 1982; Lynn and Shakhanbeh, 1988); systemic capsai-
cin administration is less effective in this respect (Terv after their exposure to periaxonal capsaicin (Gamse et al., 1982; Lynn and Shakhanbeh, 1988); systemic capsaicin administration is less effective in this respect (Tervo, 1981; Lynn et al., 1984; Maggi et al., 1987b). Thus, al., 1982; Lynn and Shakhanbeh, 1988); systemic capsaicin administration is less effective in this respect (Tervo, 1981; Lynn et al., 1984; Maggi et al., 1987b). Thus, periaxonal administration of capsaicin combines the ad cin administration is less effective in this respect (T
1981; Lynn et al., 1984; Maggi et al., 1987b). T
periaxonal administration of capsaicin combines the
vantage of producing an effective ablation of neu
with a high deg

B. Routes of Administration
Imgard Th. Lippe, Josef Donnerer, and Ulrike Holzer-Petsche for
doses of capsaicin has been the most frequent method manuscript. Dr. Ulrike Holzer-Petsche prepared the graph. th a high degree of topical and C-fiber selectivity.
Acknowledgments. The author is indebted to Drs. János Szolcsányi,
bor Jancsó, Carlo A. Maggi, Robert E. Stitzel, Rainer Amann, Acknowledgments. The author is indebted to Drs. János Szolcsányi,
Gábor Jancsó, Carlo A. Maggi, Robert E. Stitzel, Rainer Amann,
Irmgard Th. Lippe, Josef Donnerer, and Ulrike Holzer-Petsche for
their critical reading of, a Gábor Jancsó, Carlo A. Maggi, Robert E. Stitzel, Rainer Amann,

- REFERENCES ABELLI, L., CONTE, B., SOMMA, V., MAGGI, C. A., GIULIANI, S., GEPPETTI, P.,
 ALESSANDRI, M., THEODORSSON, E., AND MELI, A.: The contribution of capacicin-sensitive sensory nerves to xylene-induced visceral pain CAL SET CAPS ALESSANDRI, M., THEODORSSON, E., AND MELI, A.: The contribution of capeaicin-sensitive sensory nerves to xylene-induced viscera FREERENCES
RELLI, L., CONTE, B., SOMMA, V., MAGGI, C. A., GIULIANI, S., GEPPETTI, P.,
ALESSANDRI, M., THEODORSSON, E., AND MELI, A.: The contribution of
capeaicin-sensitive sensory nerves to xylene-induced visceral pai 1988.
Abelli, L., Ferri, G.-L., Astolfi, M., Conte, B., Geppetti, P., Parlani, M., ABELLI, L., CONTE, B., SOMMA, V., MAGGI, C. A., GIULIANI, S., GEPPETTI, P.,
ALESSANDRI, M., THEODORSSON, E., AND MELI, A.: The contribution of
capacitin-sensitive sensory nerves to xylene-induced visceral pain in conscious
- really moving rats. Naunyn Schmiedebergs Arch. Pharmacol. 337: 545-551,

1988.

ABELLI, L., FERRI, G.-L., ASTOLFI, M., CONTE, B., GEPPETTI, P., PARLANI, M.,

CALI, D., POLAK, J. M., AND MAGGI, C. A.: Acrylamide-induced vis uglil, L., FERRI, G.-L., ASTOLFI, M., CONTE, B., GEPPETTI, P., PARLANI, M.,
DAHL, D., POLAK, J. M., AND MAGGI, C. A.: Acrylamide-induced visceral
neuropathy: evidence for the involvement of capsaicin-sensitive nerves of th
- DAHL, D., POLAK, J. M., AND MAGGI, C. A.: Acrylamide-induced visceral
neuropathy: evidence for the involvement of capeaicin-sensitive nerves of the
naruhary bladder. Neuroscience, 41: 311-321, 1991.
NEWER, J., CORR, L., MI neuropathy: evidence for
rat urinary bladder. Neuropathy
ERDERN, J., CoRR, L., Mincreases in calcitonin general
rat following long-term strategy
Marwark, R. C., AND BHID
Menesioin) in Syrian such
measion) in Syrian such rat urinary bladder. Neuroscience, 41: 311-321, 1991.
ABERDEEN, J., CORR, L., MILNER, P., LINCOLN, J., AND BURNSTOCK, G.: Marked
increases in calcitonin gene-related peptide-containing nerves in the developing
rat followin ABERDEEN, J., CORR, L., MILNER, P., LINCOLN, J., AND BURNSTOCK, G.: Marked
increases in calcitonin gene-related peptide-containing nerves in the developing
rat following long-term sympathectomy with guanethidine. Neuroscie
-
- 175–184, 1990.
MARWAL, R. C., AND BHIDE, S. V.: Histopathological studies on toxic
(capsaicin) in Syrian golden hamsters. Ind. J. Exp. Biol. 26: 377–39
ILSTEDT, S., ALVING, K., HESSELMAR, B., AND OLAISSON, E.: Enl
of the b
- AGARWAL, R. C., AND BHIDE, S. V.: Histopathological studies on toxicity of chilli
(capeaicin) in Syrian golden hamsters. Ind. J. Exp. Biol. 26: 377-382, 1988.
AHLSTEDT, S., ALVING, K., HESSELMAR, B., AND OLAISSON, E.: Enha capeaicin. Int. Arch. Allergy Appl. Imm
NSWORTH, A., HALL, P., WALL, P. D.,
S., AND POLAK, J. M.: Effects of capes
nerve. II. Anatomy and energine and peg
spinal cord. Pain 11: 379-388, 1981.
KAGI, H., OTSUKA, M., AND YANA **AKAGI,** H., HALL, P., WALL, P. D., ALLT, G., MACKENZIE, M. L., GIBSON,

S., AND POLAK, J. M.: Effects of capacicn applied locally to adult peripheral

nerve. II. Anatomy and engryme and peptide chemistry of peripheral ner
-
- nerve. II. Anatomy and enzyme and peptide chemistry of peripheral nerve and
spinal cord. Pain 11: 379-388, 1981.
AKAGI, H., OTSUKA, M., AND YANAGISAWA, M.: Identification by high-perform-
ance liquid chromatography of immu AKAGI, H., OTSUKA, M., AND YANAGISAWA, M.: Identification by high-performance liquid chromatography of immunoreactive substance P released from
isolated rat spinal cord. Neurosci. Lett. 20: 259-263, 1980.
ALBER, G., SCHEUB ALBER, G., SCHEUBER, P. H., RECK, B., SAILER-KRAMER, B., HARTMANN, A.,
AND HAMMER, D. K.: Role of substance P in immediate-type skin reactions
induced by staphylococcal enterotorin B in unsensitized monkeys. J. Allergy
Cli
- Naunyn Schmiedebergs Arch. Pharmacol. Sin unsensitized monitological pharmacol. S4: 880–885, 1989.
NAUNG, K., MATRAN, R., AND LUNDBERG, J. M.: Capsaicin-inducedebergs Arch. AND LUNDBERG, J. M.: Capsaicin-inducedebergs Arch induced by staphylococcal enterotoxin B in unsensitized monkeys. J. Allergy
Clin. Immunol. 84: 880–885, 1989.
ALVING, K., MATRAN, R., AND LUNDERG, J. M.: Capsaicin-induced local effector
responses, autonomic reflexes and s Clin. Immunol. 84: 880–885, 1989.

VING, K., MATRAN, R., AND LUNDBERG, J. M.: Capsaicin-induced local effector

responses, autonomic reflexes and sensory neuropeptide depletion in the pig.

Naunyn Schmiedebergs Arch. Pharm
- responses, and
Naunyn Sch
AANN, R.: Dof Ca²⁺ and
676, 1990.
AANN, R., Do **AMANN, R.: Desensitization of capsaicin-evoked neuropeptide depletion in the pig.

AMANN, R.: Desensitization of capsaicin-evoked neuropeptide release—influence
** α^2 **Ca²⁺ and temperature. Naunyn Schmiedebergs Arch. P** MANN, R.: Desensitization of capeaicin-evoked neuropeptide release—influence
of Ca²⁺ and temperature. Naunyn Schmiedebergs Arch. Pharmacol. 342: 671-
676, 1990.
MANN, R., DONNERER, J., AND LEMBECK, F.: Capeaicin-induced
- of Ca²⁺ and temperature. Naunyn Schmiedebergs Arch. Pharmacol. 342: 671–
676, 1990.
AMANN, R., DONNERER, J., AND LEMBECK, F.: Capsaicin-induced stimulation of
polymodal nociceptors is antagonized by ruthenium red indepen
-
- 676, 1990.

AMANN, R., DONNERER, J., AND LEMBECK, F.: Capaaicin-induced stimulation of

polymodal nociceptors is antagonized by ruthenium red independently of

extracellular calcium. Neuroscience 32: 255–259, 1989a.

AMAN capasicin-induced release of calcitonin gene-related perfused from the isolated perfused guinea pig lung. Neurosci. Lett. 101: 311-315, 1989b.
AMANN, R., DONNERER, J., AND LEMBECK, F.: Activation of primary afferent neuron perfused guinea pig lung. Neurosci. Lett. 101: 311-315, 1989b.
AMANN, R., DONNERER, J., AND LEMBECK, F.: Activation of primary afferent
neurons by thermal stimulation. Influence of ruthenium red. Naunyn Schmie-
debergs Arc perfused guinea pig lung. Neurosci. Lett. 101: 311-315, 1989b.
MANN, R., DONNERER, J., AND LEMBECK, F.: Activation of primary afferent
neurons by thermal stimulation. Influence of ruthenium red. Naunyn Schmie-
debergs Arch
-
- neurons by thermacol. 341: 108-113, 1990a.
AMANN, R., DONNERER, J., MAGGI, C. A., GIULIANI, S., DELBIANCO, E., WEIH
E., AND LEMBECK, F.: Capsaicin sesensitization *in uiuo* is inhibited by rut
enium red. Eur. J. Pharmacol. E., AND LEMBECK, F.: Capsaicin desensitization *in vivo* is inhibited enium red. Eur. J. Pharmacol. 186: 169–175, 1990b.
ARNN, R., AND LEMBECK, F.: Capsaicin sensitive afferent neurons from ARN, R., AND LEMBECK, F.: Capsai **R., AND LEMBECK, F.: Capsaicin desensitization in vivo is inhibited by ruthemium red. Eur. J. Pharmacol. 186: 169-175, 1990b.

AMANN, R., AND LEMBECK, F.: Capsaicin sensitive afferent neurons from peripheral glucose rece** enium red. Eur. J. Pharmacol. 186: 169–175, 1990b.
AMANN, R., AND LEMBECK, F.: Capsaicin sensitive afferent neurons from peripheral glucose receptors mediate the insulin-induced increase in adrenaline secretion. Naunyn Sch AMANN, R., AND LEMBECK, F.: Capsaicin sensitive afferent neurons from peripheral glucose receptors mediate the insulin-induced increase in adrenaline secretion. Naunyn Schmiedebergs Arch. Pharmacol. 334: 71–76, 1986.
AMANN
-
-
-
-
- induced nociceptor stimulation. Eur. J. Pharmacol. 161: 227-229, 1989.
AMANN, R., AND LEMBECK, F.: Capsaicin-induced desensitization in rat and
rabbit. Ann. NY Acad. Sci., in press, 1991.
AMANN, R., AND MAGGI, C. A.: Ruthe MANN, R., AND LEMBECK, F.: Capasicin-induced desensitization in rat and
rabbit. Ann. NY Acad. Sci., in press, 1991.
MANN, R., AND MAGGI, C. A.: Ruthenium red as a capasicin antagonist. Life
Sci., in press, 1991.
MANN, R., Sci., in press, 1991.

Sci., in press, 1991.

Effects of carbonyl cyanide pa

Effects of carbonium red on cepesiciterminals of primary afferent n

macol. 341: 534-537, 1990c.

SANN, R., SKOPTTSCH, G., AND I. Effects of carbonyl cyanide para-trichloromethoxyphenylhydrazone (CCCP)

and of ruthenium red on capsaicin-svoked neuropeptide release from peripheral

terminals of primary afferent neurones. Naunyn Schmiedebergs Arch. Pha
- terminals of primary afferent neurones. Naunyn Schmiedebergs Arch. Ph
macol. 341: 534-537, 1990c.
AMANN, R., SKOFITSCH, G., AND LEMBECK, F.: Species-related differences in
capsaicin-sensitive innervation of the rat and g macol. 341: 534-537, 1990c.

AMANN, R., SKOFTTSCH, G., AND LEMBECK, F.: Species-related differences in the

capeaicin-sensitive innervation of the rat and guinea-pig ureter. Naunyn

Schmiedebergs Arch. Pharmacol. 338: 407
-
- AMANN, R., SKOFITSCH, G., AND LEMBECK, F.: Species-related differences in the
capsaicin-sensitive innervation of the rat and guinea-pig ureter. Naunyn
Schmeidebergs Arch. Pharmacol. 338: 407–410, 1988.
ANAND, P., BLOOM, S ANAND, P., GIBSON, S. J., SCARAVILLI, F., BLANK, M. A., MCGREGOR, G. F
APPENZELLER, O., DHITAL, K., POLAK, J. M., AND BLOOM, S. R.: Studies
vasoactive intestinal polypeptide expression in injured peripheral neurons usin
ca tiatmg **effects of** prostsglandin B, **on** bradykinin and capsaicin responses in medial thalamic nociceptive **neurons. Jpn.** J. Pharinacol. 32: 81-89, 1982.
- capsaicin, sympathectomy and mf mutant rats. Neurosci. Lett. 118: 61-66,
1990.
ANDOH, R., SAKURADA, S., SATO, T., TAKAHASHI, M., AND KISARA, K.: Poten-
Batting effects of prostaglandin E₂ on bradykinin and capsaicin resp
-
- kvinsson, J., AND Yoog, J.: A quantitative study of the effects of neonatal capsaicin treatment and of subsequent peripheral nerve transection in the adult rat. Brain Res. 397: 130-136, 1986.
THE TRAINSON, M. E., AND CHAGG

- (CIN
1914)

AULT, B., AND EVANS, H.: Depolarizing action of capasicin on isolated dorsal

root fibres of the rat. J. Physiol. (Lond.) 3068: 22P-23P, 1980.

BACCAGLINI, P. I., AND HOGAN, P. G.: Some rat sensory neurons in c AULT, B., AND EVANS, H.: Depolarizing action of capacicin on isolated dorsal
root fibres of the rat. J. Physiol. (Lond.) 306: 22P-23P, 1980.
BACCAGLINI, P. I., AND HOGAN, P. G.: Some rat sensory neurons in culture
express
- express characteristics of differentiated pain sensory cells. Proc. Natl. Acad.
Sci. USA 80: 594-598, 1983.
BARANOWSKI, R., LYNN, B., AND PINI, A.: The effects of locally applied capaaicin
on conduction in cutaneous nerves
-
- macol. 89: 267-276, 1986.
macol. 89: 267-276, 1986.
matrió, L., AND HOLZER, P.: Search for a physiological role of substance P in
gastrointestinal motility. Neuroscience 16: 1-32, 1985.
contractile response of the guinea-p
- BARTHO, L., AND HOLZER, P.: Search for a physiological role of substance P in gastrointestinal motility. Neuroscience 16: 1-32, 1985.
BARTHO, L., HOLZER, P., LEMBECK, F., AND SZOLCSÁNYI, J.: Evidence that the contractile r IRTHO, L., HOLZER, P., LEMBECK, F., AND SZOLCSÁNYI, J.: Evidence that the contractile response of the guinea-pig ileum to capsaicin is due to release of substance P. J. Physiol. (Lond.) 3321: 157-167, 1982a.
RRTHO, L., PET contractile response of the guinea-pig ileum to capaaicin is due to release of
substance P. J. Physiol. (Lond.) 332: 157-167, 1982a.
BARTHÓ, L., PETHÓ, G., ANTAL, A., HOLEER, P., AND SZOLCSÁNYI, J.: Two types
of relaxation
-
- of relaxation due to capsaicin in the guinea-pig isolated ileum. Neurosci. Lett.

81: 146-150, 1987.

BARTHÓ, L., SEBÖK, B., AND SZOLCSÁNYI, J.: Indirect evidence for the inhibition

of enteric substance P neurones by opia of enteric substance P neurones by opiate agonists but not by capsaicin. Eu

J. Pharmacol. 77: 273-279, 1982b.

BARTHO, L., STEIN, C., AND HERE, A.: Involvement of capsaicin-sensitive news

rones in hyperalgesia and enhanc RTHO, L., STEIN, C., AND HERZ, A.: Involvement of capsaicin-sensitive neurones in hyperalgesia and enhanced opioid antinociception in inflammation. Naunyn Schmiedebergs Arch. Pharmacol. 342: 666-670, 1990.
RTHO, L., AND SZ

- From the mechanism of the motor response to periodic lieum. Next periodic stimulation in the small intestine of the motor response to periodic lieum. Next BARTHO, L., AND SZOLCSÁNYI, J.: The site of action of capsaicin on the guinea-
pig isolated ileum. Naunyn Schmiedebergs Arch. Pharmacol. 305: 75–31, 1978.
BARTHO, L., AND SZOLCSÁNYI, J.: The mechanism of the motor response
- periarterial nerve stimulation in the small intestine of the rabbit. Br. J.
BENNETT, T., AND GARDINER, S. M.: Neonatal capsaicin treatment impairs
vasopressin-mediated blood pressure recovery following acute hypotension. B BENNETT, T., AND GARDINER, S. M.: Neonatal capsaicin treatment impairs
vasopressin-mediated blood pressure recovery following acute hypotension. Br.
J. Pharmacol. 81: 341-345, 1984.
BENNETT, T., AND GARDINER, S. M.: Neonat
-
-
- gene-related peptide and capsaicin on tension and membrane potential of pig
coronary artery in vitro. Regul. Pept. 25: 25-36, 1989.
BERGSTROM, L., HAMMOND, D. L., Go, V. L. W., AND YAKSH, T. L.: Concurrent
measurement of 1983.
- coronary artery in vitro. Regul. Pept. 25: 25-36, 1989.
BERGSTROM, L., HAMMOND, D. L., GO, V. L. W., AND YAKSH, T. L.: Concurrent
measurement of substance P and serotonin in spinal superfusates: failure of
capsaicin and p-BERKENBOSCH, F., SCHIPPER, J., AND TILDERS, F. J. H.: Corticotropin-releasing
factor immunostaining in the rat spinal cord and medulla oblongata: an
mexpected form of cross-reactivity with substance P. Brain Ree. 399: 87-9 factor immunostaining in the rat spinal cord and medulla oblongata: an unexpected form of cross-reactivity with substance P. Brain Res. 399: 87-96, 1986.
BERNSTEIN, J. E., BICKERS, D. R., DAHL, M. V., AND ROSHAL, J. Y.: Tr
- unexpected form of cross-reactivity with substance P. Brain Res. 399: 87-96,
1986.
BERNSTEIN, J. E., BICKERS, D. R., DAHL, M. V., AND ROSHAL, J. Y.: Treatment
of chronic postherpetic neuralgia with topical capasicin: a pre BERNSTEIN, J. E., BICKERS, D. R., DAHL, M. V., AND ROSHAL, J. Y.: Treatment
of chronic postherpetic neuralgia with topical capsaicin: a preliminary study.
J. Am. Acad. Dermatol. 17: 93-96, 1987.
BERNSTEIN, J. E., PARISH, R
-
- J. Am. Acad. Dermatol. 17: 93–96, 1987.
RNSTEIN, J. E., PARISH, R. C., RAPAPORT, M., ROSENBAUM, M. M., AND
ROENIGK, H. H.: Effect of topically applied capsaicin on moderate and severe
peoriasis vulgaris. J. Am. Acad. Derma ROENIGK, H. H.: Effect of topically applied capsaicin on moderate and severe
peorasis vulgaris. J. Am. Acad. Dermatol. 15: 504–507, 1986.
BERNSTEIN, J. E., SWIFT, R. M., SOLTANI, K., AND LOENICAT. A. L.: Inhibition
of axon
- rats. Br. J. Pharmacol. 90: 727-731, 1987.

AMANN, R., AND LEMBECK, F.: Ruthenium red selectively prevents capsaicin-

induced nociceptor stimulation. Eur. J. Pharmacol. 191: 227-229, 1989.

AMANN, R., AND LEMBECK, F.: Cap 76: 394-395, 1981.

BETTANEY, J., DRAY, A., AND FORSTER, P.: Calcium and the effects of capaaicin

on afferent fibres in a neonatal rat isolated spinal cord-tail preparation. J.

BEVAN, S. J., AND FORBES, C. A.: Membrane e
	-
	- on afferent fibres in a neonatal rat isolated spinal cord-tail preparation. J.
Physiol. (Lond.) 406: 37P, 1988.
VAN, S. J., AND FORBES, C. A.: Membrane effects of capaaicin on rat dorsal
root ganglion neurones in cell cult
	- BEVAN, S. J., AND FORBES, C. A.: Membrane effects of capsaicin on rat dorsal
root ganglion neurones in cell culture. J. Physiol. (Lond.) 398: 28P, 1988.
BEVAN, S., HOTHI, S., HUGHES, G. A., JAMES, I. F., RANG, H. P., SHAH, Free Maximus, **I.** F., RANG, I. F., Thermacol., 3102: 77P, 1999. BEVAN, S. J., JAMES, I. F., RANG, H. P., WINTER, J., AND WOOD, J. N.: The Their Pharmacological Implications. ed. by P. Jenner, pp. 261–277, Rave Press, New
	-
	- Their Pharmacological Implications, ed. by P. Jenner, pp. 261–277, Raven
Press, New York, 1987.
BEVAN, S., AND SZOLCSÁNYI, J.: Sensory neuron-specific actions of capaaicin-
mechanisms and applications. Trends Pharmacol. Sc
	- BryAN, S., AND SZOLCSANYI, J.: Sensory neuron-specific actions of capsaicin-mechanisms and applications. Trends Pharmacol. Sci. 11: 330–333, 1990.
BrVAN, S., AND YEATS, J. C.: Protons activate a sustained inward current in (Lond.) 417: 81P, 1989.
BrrTNER, M. A., AND LAHANN, T. R.: Biphasic time-course of capsaicin-induced
substance P depletion: failure to correlate with thermal analgesia in the rat.
Brain Res. 322: 305-309, 1985.
BBERNING, P (Lond.) 417: 81P, 1989.
TTNER, M. A., AND LAHANN, T. R.: Biphasic time-course of capasicin-induced
substance P depletion: failure to correlate with thermal analgesia in the rat.
Brain Res. 323: 305-309, 1985.
ERRING, P., A
	-
	- substance P depletion: failure to correlate with thermal analgesia in the rat.
Brann Res. 322: 305-309, 1985.
BJERRING, P., ARD SODERBERG, U.: Argon laser induced
cutaneous sensory and pain thresholds in post-herpetic neur ERRING, P., ARENDT-NIELSEN, L., AND SODERBERG, U.: Argon laser induced cutaneous sensory and pain thresholds in post-herpetic neuralgia. Quantitative modulation by topical capsacic. Acta Dermatol. Venereol. 70: 121-125, 19 **BODINAR,** D., BRORSON, J. R., AND MILLER, R. J.: The effect of capasicin on voltage-gated calcium currents and calcium signals in cultured dorsal root ganglion cells. Br. J. Pharmacol. 101: 423–431, 1990.
BODNAR, R. J., K
	- voltage-gated calcium currents and calcium signals in cultured dorsal root ganglion cells. Br. J. Pharmacol. 101: 423-431, 1990.
BODNAR, R. J., KIRCHGESSNER, A., NILAVER, G., MULHERN, J., AND ZIMMER-MAN, E. A.: Intraventri
	-

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

ARMACOLOGI

spet

 $\overline{\mathbb{O}}$

PHARM
REV

REVIEW ARMACOLOGIO

spet

 $\overline{0}$

- BRAGA, P. C., **BIELLA, G., AND TIENGO, M.: Effects of capsaicin peripherally** proposed activity of thalamic nociceptive neurons in applied on spontaneous and evoked activity of thalamic nociceptive neurons in Bin rat. Med. applied on spontaneous and evoked activity of thalamic nociceptive neurons in
rat. Med. Sci. Res. 15: 1511-1512, 1987.
BRAND, L. M., SKARE, K. L., LOOMANS, M. E., RELLER, H. H., SCHWEN, R. J.,
LADE, D. A., BOHNE, R. L., MA
- **EXAGA, P. C., BIELLA, G., AND TIENGO, M.: Effects of capsaicin peripherally**
applied on spontaneous and evoked activity of thalamic nociceptive neurons in
rat. Med. Sci. Res. 15: 1511-1512, 1987.
BRAND, L. M., SKARE, K. L **EXECUTE TO AND TAINT OF THE CONSUMER AND SET AND SET AND SET AND SET AND LEAD SET AND, L. M., SEARE, K. L., LOOMANS, M. E., RELLER, H. H., SCHWEN, R. LADE, D. A., BOHNE, D. P., FANELLI, R. L., LOOMAND, C., CASTELLI, M. G.** macology and mechanism of the orally active capsaicin analogy and mechanism CHI

BRAND, L. M., SKARE, K. L., LOOMANS, M. E., RELLER, H. H., SCHWEN, R. J.,

LADE, D. A., BOHNE, R. L., MADDIN, C. S., MOOREHEAD, D. P., FANELL
- CHIABRANDO, C., CASTELLI, M. G., AND TAI, H. H.: Anti-inflammatory phar-
macology and mechanism of the orally active capsaicin analogs, NE-19550 and
NE-28345. Agents Actions 31: 329-340, 1990. (1)
exponses, F., Evans, R. H NE-28345. Agents Actions 31: 329-340, 1990.

BRUGGER, F., EVANS, R. H., AND HAWKINS, N. S.: Effects of N-methyl-D-

aspartate antagonists and spantide on spinal reflexes and responses to sub-

stance P and capacicin in iso NE-28345. Agents Actions 31: 329-340, 1990. (Lond.) 284: 55-67, 1978. (Lond.) 284: 55-67, 1978.

BRUGGER, F., EVANS, R. H., AND HAWKINS, N. S.: Effects of N-methyl-D-CODERRE, T. J., ABSOTT, F. V., AND MELZACK, R.: Behavior
-
- stance P and capsaicin in isolated spinal cord preparations from mouse and
rat. Neuroscience 36: 611-622, 1990.
UCK, S. H., AND BURKS, T. F.: The neuropharmacology of capsaicin—review
of some recent observations. Pharmacol BUCK, S. H., AND BURKS, T. F.: The neuropharmacology of capaaicin—review of some recent observations. Pharmacol Rev 38: 179–226, 1986.

BUCK, S. H., MILLER, M. S., AND BURKS, T. F.: Depletion of primary afferent Computerin
-
- XAID BURKS, T. F.: Characterization of the peffects of capsaicin in the guinea pig. J. Neuron CKLEY, T. L., BRAIN, S. D., AND WILLIAMS, The rabitit section formation and increased blooms.
Trabbit skin. Br. J. Pharmacol. 99 effects of capsaicin in the guinea pig. J. Neurosci. 3: 2064-2074, 1983.
BUCKLEY, T. L., BRAIN, S. D., AND WILLIAMS, T. J.: Ruthenium red selectively
inhibits oedema formation and increased blood flow induced by capsaicin
-
- BUCKLEY, T. L., BRAIN, S. D., AND WILLIAMS, T. J.: Ruthenium red selectively
inhibits oedema formation and increased blood flow induced by capacicin in
rabbit skin. Br. J. Pharmacol. 99: 7-8, 1990.
BUCSICS, A., AND LEMBECK rabbit skin. Br. J. Pharmacol. 99: 7-8, 1990.
BUCSICS, A., AND LEMBECK, F.: In vitro release of substance P from spinal cord
Bucsics, A., AND LEMBECK, F.: In vitro release of substance P from spinal cord
alces by capacitin BUCSICS, A., MAYER, N., PABST, M. A., AND LEMBECK, F.: Distribution of spinal
- DCSICS, A., SUTTER, D., JANCSO, G., AND LEMBECK, F.: Quantitative assay capsaicin-sensitive thiamine monophosphatase and β -glycerophosphatase ativity in rodent spinal cord. J. Neurosci. Meth. 24: 155-162, 1988.
TNKE, G.
- BYNKE, G.: Capsaicin pretreatment prevents disruption of the blood-aqueous
barrier in the rabbit eye. Invest. Ophthalmol. Vis. Sci. 24: 744-748, 1983.
- capacicin-sensitive thiamine monophosphatase and β -glycerophosphatase activity in rodent spinal cord. J. Neurosci. Meth. 24: 155-162, 1988.
BYNKE, G.: Capacicin pretreatment prevents diaruption of the blood-aqueous Der CAMRAS, C. B., AND Brro, L. Z.: The pathophysiological effects of nitrogen mustard on the rabbit eye. II. The inhibition of the initial hypertensive phase by capsaicin and the apparent role of substance P. Invest. Ophthalm **to mild injury** after topical treatment with capsaical effects of nitrogen mustard on the rabbit eye. II. The inhibition of the initial hypertensive phase by capsaicin and the apparent role of substance P. Invest. Ophthal
-
- by capsaicin and the apparent role of substance P. Invest. Ophthalmol. Vis.

Sci. 19: 423-428, 1960.

CARPENTER, S. E., AND LYNN, B.: Vascular and sensory responses of human skin

to mild injury after topical treatment wit to mild injury after topical treatment with capacicin. Br. J. Pharmacol. 73:
755-758, 1981.
CARR, P. A., YAMAMOTO, T., AND NAGY, J. I.: Calcitonin gene-related peptide in
primary afferent neurons of rat: co-existence with **CERVERO, F., AND MCRITCHIE, H. A.: Neonatal capsaicin and thermal points of the CERVERO, F., AND MCRITCHIE, H. A.: Neonatal capsaicin and thermal nocice tion: a paradox. Brain Res. 215: 414–418, 1981.

CERVERO, F., AND MC** primary afferent neurons of rat: co-existence with fluoride-resistant acid phos-
phatase and depletion by neonatal capsaicin. Neuroscience 36: 751-760, 1990.
CERVERO, F., AND MCRITCHIE, H. A.: Neonatal capsaicin and therma
-
- ERVERO, F., AND MCRITCHI
tion: a paradox. Brain Res.
ERVERO, F., AND MCRITCHI
linated efferent fibers of the
Brain Res. 239: 283-288, 1
ERVERO, F., AND PLENDER cion: a paradox. Brain Res. 215: 414–418, 1981.
CERVERO, F., AND MCRITCHIE, H. A.: Neonatal capacicin does not affect unmy-
linated efferent fibers of the autonomic nervous system: functional evidence.
Brain Res. 239: 283-
-
- neous increases in adult rats treated at birth with
CERVERO, F., AND PLENDERLEITH, M. B.: Spinal cord sensory systems after
neonatal capsaicin. Acta Physiol. Hung. 69: 393-401, 1987.
CERVERO, F., SCHOUENBORG, J., SJOLUND, neonatal capsaicin. Acta Physiol. Hung. 69: 393-401, 1987. DE V.
CERVERO, F., SCHOUENBORG, J., SJOLUND, B. H., AND WADDELL, P. J.: Cutaneous inputs to dorsal horn neurones in adult rats treated at birth with DIB, capsaicin
-
- capasicin. Brain Res. 301: 47-57, 1984.
CERVERO, F., AND SHARKEY, K. A.: An electrophysiological and anatomical study
of intestinal afferent fibres in the rat. J. Physiol. (Lond.) 401: 381-397, 1988.
CHAHL, L. A.: Evidenc CHAHL, L. A.: Ann SHARKEY, K. A.: An electrophysiological and anatomical study of intestinal afferent fibres in the rat. J. Physiol. (Lond.) 401: 381-397, 1986
CHAHL, L. A.: Evidence that the contractile response of the gu of intestinal afferent fibres in the rat. J. Physiol. (Lond.) $401:381-397, 1988$. Antim
CHAHL, L. A.: Evidence that the contractile response of the guinea-pig ileum to J. Pha
capsaicin is due to substance P release. Naun
-
-
- macol. 319: 212-215, 1982.
CHAHL, L. A.: Antidromic vasodilatation and neurogenic inflammation. Pharmacol. Ther. 37: 275-300, 1983.
CHAHL, L. A.: The effects of ruthenium red on the response of guinea-pig ileum
to capasici
- CHARUK, J. H. M., PIRRAGLIA, C. A., AND RETTHMEIER, R. A. F.: Interaction of ruthenium red with Ca²⁺-binding proteins. Anal. Biochem. 188: 123-131, 1990.
CHERY-CROZE, S., BOSSHARD, A., MARTIN, H., CUBER, J. C., CHARNAY,
- ruthenium red with Ca²⁺-binding proteins. Anal. Biochem. 188: 123-131, 1990.
CHÉRY-CROZE, S., BO88HARD, A., MARTIN, H., CUBER, J. C., CHARNAY, Y., AND
CHAYVIALLE, J. A.: Peptide immunocytochemistry in afferent neurons fr CHERY-CROZE, S., GODINOT, F., JOURDAN, G., BERNARD, C., AND CHAYVIALLE, J. A.: Capasicin in adult frogs: effects on nociceptive responses to cutaneous Istimuli and on nervous tissue concentrations of immunoreactive substan
- attimuli and on nervous tissue concentrations of immunoreactive substance **P**, and solid and cholecystokinin. Naunyn Schmiedebergs Arch. Pharmacol.

331: 159–165, 1986.

47., MASUKO, S., AND KAWANO, H.: Correlation of mito CHBA, T., MASUKO, S., AND KAWANO, H.: Correlation of mitochondrial swelling
after capsaicin treatment and substance P and somatostatin immunoresctivity
in small neurons of dorsal root ganglion in the rat. Neurosci. Lett. 6 after capaaicin treatment and substance P and somatostatin immunoresctivity
in small neurons of dorsal root ganglion in the rat. Neurosci. Lett. 64: 311-
316, 1986.
CHOI, D. W.: Ionic dependence of glutamate neurotoxicity.
-
- 316, 1986.

316, 1986.

301, D. W.: Ionic dependence of glutamate neurotoxicity. J. Neurosci. 7: 362

379, 1987.

STORICAL AND JANTHASOOT, W.: Mechanism of the inhibitory action

of capasicin on energy metabolism by rat li CHUNG, D. W.: Ionic dependence of glutamate neurotoxicity. J. Neurosci. 7: 369-
379, 1987.
CHUDAPOROSE, P., AND JANTHASOOT, W.: Mechanism of the inhibitory action
of capsaicin on energy metabolism by rat liver mitochondria
- CHUDAPONGSE, P., AND JANTHASOOT, W.: Mechanism of the inhibitory action
of capsaich on energy metabolism by rat liver mitochondria. Biochem. Phar-
macol. 30: 735-740, 1981.
CHUNG, J. M., LEE, K. H., HORI, Y., AND WILLIS, W
-

primary afferent axon is most vulnerable **to systemic capsaicin in adult rats.** Brain Rae. **511: 222-226, 1990.**

- ER

primary afferent axon is most vulnerable to systemic capsaicin in adult rats.

Brain Res. 511: 222–226, 1990.

CHUNG, K., SCHWEN, R. J., AND COGGESHALL, R. E.: Ureteral axon damage

following subcutaneous administratio primary afferent axon is most vulnerable to systemic capsaicin in adult rats.
Brain Res. 511: 222-226, 1990.
CHUNG, K., SCHWEN, R. J., AND COGGESHALL, R. E.: Ureteral axon damage
following subcutaneous administration of c
-
- (Lond.) 284: 55-67, 1978.

CLARKE, G. D., AND DAVISON, J. S.: Mucosal receptors in the gastric antrum and

small intestine of the rat with afferent fibres in the cervical vagus. J. Physiol.

(Lond.) 284: 55-67, 1978.

CODE function. Neurosci. Lett. 47: 113-118, 1984.
CODERRE, T. J., ABBOTT, F. V., AND MELZACK, R.: Behavioral evidence in rats
for a peptidergic-noradrenergic interaction in cutaneous sensory and vascular
function. Neurosci. Let DERRE, T. J., ABBOTT, F. V., AND MELZACK, R.: Behavioral evidence in rats
for a peptidergic-noradrenergic interaction in cutaneous sensory and vascular
function. Neurosci. Lett. 47: 113-118, 1984.
DLERIDOR, H. M., AND COLE
-
- for a peptidergic-noradrenergic interaction in cutaneous sensory and vascular
function. Neurosci. Lett. 47: 113-118, 1984.
COLERIDGE, H. M., AND COLERIDGE, J. C. G.: Impulse activity in afferent vagal
29: 125-142, 1977.
20 **Pharmacol. 99: 125-142, 1977.**
 Pharmacol. 99: 125-142, 1977.
 Pharmacol. 9. C. G., AND COLERIDGE, H. M.: Afferent vagal C fibre innervation of the lung and airways and its functional significance. Rev. Physiol. Bioch of the lung and airways and its functional significance. Rev. Physiol. Biochem.

COLLER, J. G., AND FULLER, R. W.: Capsaicin inhalation in man and the effects

of sodium cromoglycate. Br. J. Pharmacol. 81: 113-117, 1984.
 COLERIDGE, J. C. G., AND COLERIDGE, H. M.: Afferent vagal C fibre innervation of the lung and airways and its functional significance. Rev. Physiol. Biocher Pharmacol. 99: 1-110, 1964.

COLLER, J. G., AND FULLER, R. W.: Ca
-
-
- Pharmacol. 99: 1-110, 1984.
COLLIER, J. G., AND FULLER, R. W.: Capsaicin inhalation in man and the effects
of sodium cromoglycate. Br. J. Pharmacol. 81: 113-117, 1984.
COSTA, M., FURNESS, J. B., AND GIBSINS, I. L.: Coexist gers: a new principle in chemical transmission: chemical coding of enteric
neurons. Prog. Brain Res. 68: 217–239, 1966.
CRAYTON, S. C., MITCHELL, J. H., AND PAYNE, F. C.: Reflex cardiovascular
response during injection of
- response during injection of capsaicin into skeletal muscle. Am. J. Physiol.
240: H315-H319, 1981.
UI, J., ZAROR-BEHRENS, G., AND HIMMS-HAGEN, J.: Capsaicin desensitization
induces atrophy of brown adipose tissue in rats. CUI, J., ZAROR-BEHRENS, G., AND HIMMS-HAGEN, J.: Capsaicin desensitization
induces atrophy of brown adipose tissue in rats. Am. J. Physiol. 259: R324-
R332, 1990.
CULP, W. J., OCHOA, J., CLINE, M., AND DOTSON, R.: Mechanic induces atrophy of brown adipose tissue in rats. Am. J. Physiol. 259: R324-
-
- DANIEL, E. E., NAGAHMA, M., SATO, H., JURY, J., AND BOWKER, P.: Immuno-chemical studies on substance P release from muscularis mucosa of opossum induces atrophy of brown adipose tissue in rats. Am. J. Physiol. 259: R324-
R332, 1990.
CULP, W. J., OCHOA, J., CLINE, M., AND DOTSON, R.: Mechanical hyperalgesia
induced by capsaicin—cross modality threshold modulation in Mociceptors. Brain 112: 1317-1331, 1989.

ANIEL, E. E., NAGAHMA, M., SATO, H., JURY, J., AND BOWKER, P.: Immuno-

chemical studies on substance P release from muscularis mucosa of oposum

sesophagus. In Substance P and Neu DANIEL, E. E., NAGAHMA, M., SATO, H., JURY, J., AND BOWKER, P.: Immuno-
chemical studies on substance P release from muscularis mucosa of oposaum
esophagus. In Substance P and Neurokinins, ed. by J. L. Henry, R. Couture,
A
- A. C. Cuello, G. Pelletier, R. Quirion, and D. Regoli, pp. 266-269, Springer, New York, 1987.
DAWBARN, D., HARMAR, A. J., AND PYCOCK, C. J.: Intranigral injection of capaaicin enhances motor activity and depletes nigral 5-
- **DE, A. K., AND GHOSH,** J. J.: Short- and D. Regoli, pp. 266-269, Springer, New York, 1987.
DAWBARN, D., HARMAR, A. J., AND PYCOCK, C. J.: Intranigral injection of capsaicin enhances motor activity and depletes nigral 5-hy
- DECKER, M. W., TOWLE, A. C., BISSETTE, G., MUELLER, R. A., LAUDER, J. M., 1981.
DECKER, M. W., TOWLE, A. C., BISSETTE, G., MUELLER, R. A., LAUDER, J. M., 1989.
DECKER, M. W., TOWLE, A. C., BISSETTE, G., MUELLER, R. A., LAU 1989.
DECKER, M. W., TOWLE, A. C., BISSETTE, G., MUELLER, R. A., LAUDER, J. M., AND NEMEROPP, C. B.: Bombesin-like immunoreactivity in the central nervous system of capsaicin-treated rats: a radioimmunoessay and immunohist **ISBO.**

DECKER, M. W., TOWLE, A. C., BISSETTE, G., MUELLER, R. A., LAUDER, J. M.,

AND NEMEROFF, C. B.: Bombesin-like immunoreactivity in the central nervous

state at study. Brain Res. 342: 1-8, 1985.

DELLA, N. G., PAPK
- system of capacitin-treated rats: a radioimmunosasay and immunohistochemical study. Brain Res. 342: 1-8, 1985.
DELLA, N. G., PAPKA, R. E., FURNESS, J. B., AND COSTA, M.: Vasoactive intestinal peptide-like immunoreactivity intestinal peptide-like immunoreactivity in nerves associated with the cardio-
vascular system of guinea pigs. Neuroscience 9: 605–619, 1983.
DE VRES, D. J., AND BLUMBERG, P. M.: Thermoregulatory effects of resinifer-
aton
- induced by neonatal capsaic neonato and the system of guinea pigs. Neuroscience 9: 805-619, 1983.
I VRIES, D. J., AND BLUMBERG, P. M.: Thermoregulatory effects of ratoxin in the mouse: comparison with capsaicin. Life Sci.
-
- Antinociception produced by capsaicin: spinal or peripheral mechanism? Eur.
J. Pharmacol. 187: 225–233, 1990a.
DICKENSON, A., HUGHES, C., RUEFF, A., AND DRAY, A.: A spinal mechanism of atoxin in the mouse: comparison with a
B. B.: Dissociation between peripher
induced by neonatal capacitin. Behav.
CKENSON, A., ASHWOOD, N., SULLIV.
Antinociception produced by capacicin
J. Pharmacol. 187: 225-233, 1990a.
C
- DICKENSON, A., ASHWOOD, N., SULLIVAN, A. F., JAMES, I., AND DRAY, A.:
DICKENSON, A., ASHWOOD, N., SULLIVAN, A. F., JAMES, I., AND DRAY, A.:
J. Pharmacol. 187: 225-233, 1990a.
D. Pharmacol. 187: 225-233, 1990a.
DICKENSON, A Antinocicoption produced by capsaicin: spinal or peripheral mechanism? Eur.

J. Pharmacol. 187: 225-233, 1990a.

DICKENSON, A., HUGHES, C., RUEFF, A., AND DRAY, A.: A spinal mechanism of

action is involved in the antinoc
-
- DIEZ GUERRA, F. J., ZAIDI, M., BEVIS, P., MACINTYRE, I., AND EMSON, P. C.: Evidence for release of calcitonin gene-related peptide and neurokinin A from sensory nerve endings in nino. Neuroscience 25: 839-846, 1987.
DOCHER
- DINH, T. T., AND RITTER, S.: Capasicin induces neuronal degeneration in midbrain and forebrain structures in neonatally treated rats. Soc. Neurosci.
Abstr. 13: 1684, 1987.
DOCHERTY, R. J., ROBERTSON, B., AND BEVAN, S.: Cap midbrain and forebrain structures in neonatally treated rats. Soc. Neurosci.
Abstr. 13: 1684, 1987.
OCHERTY, R. J., ROBERTSON, B., AND BEVAN, S.: Capsaicin causes prolonged
inhibition of voltage-activated calcium currents
-
- DONNERER, J., AND AMANN, R.: Capsaicin-evoked neuropeptide release is not dependent on membrane potential changes. Neurosci. Lett. 117: 331-334, 1990. inhibition of voltage-activated calcium currents in adult rat dorsal root ganglion
neurons in culture. Neuroscience 40: 513–521, 1991.
DON, P. C.: Topical capsaicin for treatment of neuralgia associated with herpes
orter i
-
- dependent on membrane potential changes. Neurosci. Lett. 117: 331-334,
1990.
DONNERER, J., BARTHÓ, L., HOLZER, P., AND LEMBECK, F.: Intestinal peristalsis
associated with release of immunoreactive substance P. Neuroscience function in the capsaicin-treated rat: evidence for afferent neural modulation in vivo. In The Neuroendocrine-Immune Network, ed. by S. Freier, pp. 69–83, CRC Press, Boca Raton, FL, 1990.
DONNERER, J., AND LEMBECK, F.: An
- 1982. in vivo. In The Neuroendocrine-Immune Network, ed. by S. Freier, pp. 69–83,
CRC Press, Boca Raton, FL, 1990.
DONNERER, J., AND LEMBECK, F.: Analysis of the effects of intravenously injected
apasicin in the rat. Naunyn Schm CRC Press, Boca Raton, FL, 1990.
ONNERER, J., AND LEMBECK, F.: Analyais of the effects of intravence
capsaicin in the rat. Naunyn Schmiedebergs Arch. Pharmacol.
1982.
ONNERER, J., AND LEMBECK, F.: Heat loss reaction to cap
-

CA

DONNERER, J., AND LEMBECK, F.: Different control of the adrenocorticotropin-

corticosterone response and of prolactin secretion during cold stress, ane

thesia, surgery, and nicotine injection in the rat: involvement CAPS
conticosterone response and of prolactin secretion during cold stress, anes-
thesia, surgery, and nicotine injection in the rat: involvement of capsaicin-
sensitive sensory neurons. Endocrinology 126: 921-926, 1990.
O **DONNERER, J., AND LEMBECK, F.: Different control of the adrenocorticotropin-corticosterone response and of prolactin secretion during cold stress, anestesiative sensory neurons. Endocrinology 126: 921-926, 1990.

DONNERE** corticosterone response and of prolactin secretion during cold stress, anes-
thesia, surgery, and nicotine injection in the rat: involvement of capacicin-
sensitive sensory neurons. Endocrinology 126: 921-926, 1990.
DONNER

- SCHERG, J., SCHULIGOI, R., AND LEMBECK, F.: Influence of capsaicin-induced
denervation on neurogenic and humoral control of arterial pressure. Naunyn
Schmiedebergs Arch. Pharmacol. 340: 740-743, 1989.
DOUCETTE, R., THERIAU
- **tion of cutation of periphermal nociception in rate of capsaicin. J. Comp.** Schmiedebergs Arch. Pharmacol. 340: 740-743, 1989.
 DOUCETTE, R., THERIAULT, E., AND DIAMOND, J.: Regionally selective elimination of cutaneous OUCETTE, R., THERIAULT, E., AND DIAMOND, J.: Regionally selective elimination of cutaneous thermal nociception in rats by neonatal capsaicin. J. Comp.
Neurol. 261: 583-591, 1987.
RAY, A., BETTANEY, J., AND FORSTER, P.: Cap
- Neurol. 261: 583-591, 1987.
DRAY, A., BETTANEY, J., AND FORSTER, P.: Capacicin desensitization of periodic of the solution of the solution of periodic Meurosci. Lett. 99: 50-54, 1989a.
DRAY, A., BETTANEY, J., AND FORSTER,
- DRAY, A., BETTANEY, J., AND FORSTER, P.: Capsaicin desensitization of peripheral nociceptive fibers does not impair sensitivity to other noxious stimuli.
Neurosci. Lett. 99: 50-54, 1989a.
DRAY, A., BETTANEY, J., AND FORSTE
- NOCICE TO DETANEY, J., AND FORSTER, P.: Resiniferatoxin, a potent capacicilike stimulator of peripheral nociceptors in the neonatal rat tail *in vitro*. Br. Pharmacol. 99: 323-326, 1990a.

RAY, A., BETTANEY, J., AND FORSTE **charms** is the stimulator of peripheral nociceptors in the neonatal rat tail in vitro. Br. J.
Pharmacol. 99: 323-326, 1990a.
RAY, A., BETTANEY, J., AND FORBTER, P.: Actions of capasicin on peripheral
nociceptors of the ne max summacol. 99: 3
RAY, A., BETTANE
nociceptors of the
cellular ions and
727-733, 1990b.
RAY, A., BETTANE
- nociceptors of the neonatal rat spinal cord-tail in vitro: dependence of extra-
cellular ions and independence of second messengers. Br. J. Pharmacol. 101:
727–733, 1990b.
DRAY, A., BETTANEY, J., RUEFF, A., WALPOLE, C., AN cellular ions and independence of second messengers. Br. J. Pharmacol. 101:
727–733, 1990b.
RAY, A., BETTANEY, J., RUEFF, A., WALPOLE, C., AND WRIGGLESWORTH, R.:
NE. 19550 and NE-21610, antiocciceptive capaciton analogues: DRAY, A., BETTANEY, J., RUEFF, A., WALPOLE, C., AND WRIGGLESWORTH, R.:
NE-19550 and NE-21610, antinociceptive capasicin analogues: studies on no-
ciceptive fibres of the neonatal rat tail in vitro. Eur. J. Pharmacol. 181:
- 293, 1990c.

DRAY, A., CAMPBELL, E. A., HUGHES, G. A., PATEL, I. A., PERKINS, M. N.,

RANG, H. P., RUEFF, A., SENO, N., URBAN, L., AND WALPOLE, C. S. J.:

Antagonism of capazini-induced activation of C-fibres by a selectiv
- RANG, H. P., RUEFF, A., SENO, N., URBAN, L., AND WALPOLE, C. S. J.:
Antagonism of capsaicin-induced activation of C-fibres by a selective capsaicin
antagonist, capsazepine. Br. J. Pharmacol., 102: 78P, 1991.
RAY, A., FORBE antagonist, capsazepine. Br. J. Pharmacol., 102: 78P, 1991.
DRAY, A., FORBES, C. A., AND BURGESS, G. M.: Ruthenium red blocks the
capsacin-induced increase in intracellular calcium and activation of membrane
currents in se DRAY, A., FORBES, C. A., AND BURGESS, G. M.: Ruthenium red blocks the capsaicin-induced increase in intracellular calcium and activation of membrane currents in sensory neurones as well as the activation of peripheral noci
- induced release of substance P-like immunoreactivity from guinea-pig ureter in vitro. Neuroscience $31:479-483$, 1989b.
DUBOIS, J. M.: Capsaicin blocks one class of K^+ channels in the frog node of currents in sensory neurones as well as the activation of peripheral nociceptors in vitro. Neurosci. Lett. 110: 52-59, 1990d.

RAY, A., HANKINS, M. W., AND YEATS, J. C.: Desensitization and capasicin-

induced release of s induced release of substance P-like immunoreactivity from guinea-pig ure

in vitro. Neuroacience 31: 479–483, 1989b.

DUBOIS, J. M.: Capsaicin blocks one class of K⁺ channels in the frog node

Ranvier. Brain Res. 245: 37
-
-
- in vitro. Neuroscience 31: 479-483, 1989b.
DUBOIS, J. M.: Capsaicin blocks one class of K⁺ channels in the frog node of
Ranvier. Brain Res. 245: 372-375, 1982.
DUCKLES, S. P.: Effects of capsaicin causes release of a sub **Ranvier. Brain Res. 245:** 372-375, 1982.

UCKLES, S. P.: Effects of capsaicin on vascular smooth muscle. Naunyn Schmie-

debergs Arch. Pharmacol. 333: 59-64, 1986.

UN, N. J., AND KIRALY, M.: Capsaicin causes release of a **120,** 1983.
- debergs Arch. Pharmacol. 333: 59-64, 1986.

DUN, N. J., AND KIRALY, M.: Capsaicin causes release of a substance P-like

peptide in guinea-pig inferior mesenteric ganglia. J. Physiol. (Lond.) 340: 107-

120, 1983.

EDVNSSON **EDVINSSON, L., JANSEN, I., KINGMAN, T. A., AND MCCULLOCH, J.: Cerebrovas-cular responses to capaaicin in vitro and in situ. Br. J. Pharmacol. 100: 312-318, 1990.

EIMERI, D., AND PAPIR-KRICHELI, D.: Epidural capaaicin pr**
-
- acetylcholine receptor activation, desensitization, and resensitization. J. Neurochem. 34: 1288–1295, 1980. 318, 1990.

EIMERL, D., AND PAPIR-KRICHELI, D.: Epidural capsaicin produces prolonged

segmental analgesis in the rat. Exp. Neurol. 97: 169-178, 1987.

EL-FAKAHANY, E., AND RICHELSON, E.: Temperature dependence of muscarin
- of capsaicin induced effects on a sensory neuron model. Acta Physiol. Hung.

The capsaicin induced effects on a sensory neuron model. Acts Physiol. Hung.

2016. Hung. S. Hung. G., AND JANCSÓ, G.: Intracellular and voltage acetylcholine receptor activation, desensitization, and resensitization. J. Neu-
rochem. 34: 1288-1295, 1980.
ERDEX.Y. L., SUCH, G., AND JANCSÓ, G.: Intracellular and voltage clamp studies
of capsaicin induced effects on a
-
- spilliouss, J. V., RAMOS, E. G., Gri., L., AND ESPLUGUES, J.: Influence of capsaicin-sensitive afferent neurones on the acid secretory responses of the rat stomach *in vivo*. Br. J. Pharmacol. 100: 491-496, 1989.
BPLUGUES, **EXAMGELISTA, S., MAGGI, C. A., AND MONCADA, S.:** Local opioid-sensitive afferent sensory neurones in the modulation of gastric damage induced by Paf.
Br. J. Pharmacol. 97: 579-585, 1989.
Br. J. Pharmacol. 97: 579-585, 198 ESPLUGUES, J. V., WHITTLE, B. J. R., AND MONCADA, S.: Local opioid-sensitive afferent sensory neurones in the modulation of gastric damage induced by Paf. Br. J. Pharmacol. 97: 579-585, 1989. EVANGELISTA, S., MAGGI, C. A.,
-
- VANGELISTA, S., MAGGI, C. A., AND MELI, A.: Evidence for a role of adrenals
in the capasicin-sensitive "gastric defence mechanism" in rats. Proc. Soc. Exp.
Biol. Med. 183: 568-659, 1986.
ULKNER, D. C., AND GROWCOTT, J. W.:
- Biol. Med. 182: 568-569, 1986.

FAULKNER, D. C., AND GROWCOTT, J. W.: Effects of neonatal capaaicin administration on the nociceptive response of the rat to mechanical and chemical

stration on the nociceptive response of FEDULOVA, S. A., KOSTYUK, P. G., AND VESELOVSKY, N. S.: Changes in ionic mechanisms of electrical excitability of the somatic membrane of rat's dorsal root ganglion neurons during ontogenesis. Correlation between inward cu incolarisms of electrical excitability of the somatic membrane mechanisms of electrical excitability of the somatic membrane root ganglion neurons during ontogenesis. Correlation between these, E., AND VAJDA, J.: Effect of
-
- root ganglion neurons during ontogenesis. Correlation between inward currents
densities. Neurophysiology (Kiev) 18: 820-827, 1986.
FEHER, E., AND VAJDA, J.: Effect of capacicin on the nerve elements of the small
intestine. intestine. Acta Morphol. Acad. Sci. Hung. 30: 57-63, 1982.
 **EANSE, R., MOLNAR, A., AND LEMBECK, F.: Substance P release from spinal

FERRI, G. L., SABANI, A., ABELLI, L., POLAK, J. M., DAHL, D., AND PORTIER,

M. M.: Neuro** M. M.: Neuronal intermediate filaments in rat dorsal root ganglia—differential distribution of peripherin and neurofilament protein immunoreactivity and effect of capsaicin. Brain Res. 515: 331–335, 1990.
TEGERALD, M.: Alt
- effect of capsaicin. Brain Res. 515: 331-335, 1990.

FITZGERALD, M.: Alterations in the ipsi- and contralateral afferent inputs of dorsal horn cells produced by capsaicin treatment of one sciatic nerve in the rat. Brain R **FITZGERALD, M.: Alterations in the ipsi-** and contralateral afferent inputs of dorsal horn cells produced by capsaicin treatment of one sciatic nerve in the rat. Brain Res. 248: 92-107, 1982.
FITZGERALD, M.: Capsaicin and dorsal horn cells produced by capsaicin treatment of one sciatic nerve in the
rat. Brain Res. 248: 92-107, 1982.
FITZGERALD, M.: Capsaicin and sensory neurones—a review. Pain 15: 109-130,
1983.
FITZGERALD, M., AND WOOLF, C
-
- rat. Brain Res. 248: 92-107, 1982.

rzGERALD, M.: Capsaicin and sensory neurones—a review. Pain 15: 109-130,

1983.

changes in the behavioural and dorsal horn cell responses to noxious stimuli

changes in the behavioural **FITZGERALD, M., AND WOOLF, C. J.: The time course and specificity of the changes in the behavioural and dorsal horn cell responses to noxious stimuli Glassifical following peripheral nerve capsaicin treatment in the rat.**
-

neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capsaicin and re-lated pungent compounds. Prostaglandins Leuk. Med. 24: 195-198, 1986. IN
neutrophil 5-lipoxygenase activity by gingerdione, shogaol, capaaicin
lated pungent compounds. Prostaglandins Leuk. Med. 24: 195–198, 19
PRBES, C. A., AND BEVAN, S. J.: Properties of single capaaicin-activate

-
- nels. Soc. Neurosci. Abstr. 14: 642, 1988.
FORSTER, E. R., GREEN, T., ELLIOT, M., BREMNER, A., AND DOCKRAY, G. J.:
Gastric emptying in rata—role of afferent neurons and cholecystokinin. Am. J.
Physiol. 258: G552-G556, 1990 PRBES, C. A., AND BEVAN, S. J.: P.
nels. Soc. Neuroaci. Abstr. 14: 642
PRSTER, E. R., GREEN, T., ELLIOT
Gastric emptying in rata—role of a
Physiol. 258: G552-G556, 1990.
PSTER, R. W., AND RAMAGE, A. G RSTER, E. R., GREEN, T., ELLIOT, M., BREMNER, A., AND DOCKRAY, G. J. Gastric emptying in rats—role of afferent neurons and cholecystokinin. Am. J
Physiol. 258: G552-G556, 1990.
STER, R. W., AND RAMAGE, A. G.: The action of
- **FOSTER, R. W., AND RAMAGE, A. G.: The action of some chemical** irritants on
- Gastric emptying in rata—role of afferent neurons and cholecystokinin. Am. J.
Physiol. 258: G552-G556, 1990.
FOSTER, R. W., AND RAMAGE, A. G.: The action of some chemical irritants on
somatoeensory receptors of the cat. Ne
- STER, R. W., WESTON, A. H., AND WESTON, K. M.: Some effects of chemical irritants on the membrane of the giant amoeba. Br. J. Pharmacol. 74: 333-339, 1981.
239, 1981.
LANCO-CERECEDA, A., BENGTSSON, L., AND LUNDBERG, J. M.: Irritants on the membrane of the giant amoeba. Br. J. Pharmacol. 74: 333-
339, 1981.
AANCO-CERECEDA, A., BENGTSSON, L., AND LUNDBERG, J. M.: Inotropic effects
AANCO-CERECEDA, A., BENGTSSON, I., AND LUNDBERG, J. Pharmacol. **FRANCO-CERECEDA, A., BENGTSSON, L., AND LUNDBERG, J. M.: Inotropic effects** of calcitonin gene-related peptide, vasoactive intestinal polypeptide and sometotestin on the human right atrium in vitro. Eur. J. Pharmacol. 134
- matoritation of the human right atrium in vitro. Eur. J. Pharmacol. 134: 69-76, 1987a.
TRANCO-CERECEDA, A., HENKE, H., LUNDBERG, J. M., PETERMANN, J. B., HOKFELT, T., AND FISCHER, J. A.: Calcitonin gene-related peptide (CG HOKFELT, T., AND FISCHER, J. A.: Calcitonin gene-related peptide (CGRP) in
capsaicin-sensitive substance P-immunoreactive sensory neurons in animals
and man: distribution and release by capsaicin. Peptides 8: 399-410, 1987
-
- differentiates between capeaicin and nicotine effects on cardiac sensory
Acta Physiol. Scand. 137: 457–458, 1989a.
KANCO-CERECEDA, A., LOU, Y.-P., AND LUNDBERG, J. M.: Resiniference
Moved CGRP release and bronchoconstricti Acta Physiol. Scand. 137: 457-458, 1989a.
 FRANCO-CERECEDA, A., LOU, Y.-P., AND LUNDBERG, J. M.: Resiniferatoxin-

evoked CGRP release and bronchoconstriction in the guinea-pig lung are

inhibited by ruthenium red. Eur.
- RANCO-CERECEDA, A., LOU, Y.-P., AND LUNDBERG, J. M.: Resiniferatoxinevoked CGRP release and bronchoconstriction in the guinea-pig lung are inhibited by ruthenium red. Eur. J. Pharmacol. 187: 291–292, 1990.
RANCO-CERECEDA, evoked CGRP release and bronchoconstriction in the guinea-pig lung are inhibited by ruthenium red. Eur. J. Pharmacol. 187: 291-292, 1990.
RANCO-CERECEDA, A., AND LUNDBERG, J. M.: Actions of calcitonin gene-related
peptide FRANCO-CERECEDA, A., AND LUNDBERG, J. M.: Actions of calcitonin gene-relat peptide and tachykinins in relation to the contractile effects of capasicin the guinea-pig and rat heart *in vitro*. Naunyn Schmiedebergs Arch. Pha peptide and tachykinins in relation to the contractile effects of capsaid
the guinea-pig and rat heart in vitro. Naunyn Schmiedebergs Arch. Pharm
337: 649–655, 1988.
AA, AND LUNDBERG, J. M.: Post-occlusive reactive haemia
- the guinea-pig and rat heart in vitro. Naunyn Schmiedebergs Arch. Pharmaco 337: 649-655, 1988.
FRANCO-CERECEDA, A., AND LUNDBERG, J. M.: Post-occlusive reactive hyperemia in the heart, skeletal muscle and six of control an RANCO-CERECEDA, A., AND LUNDBERG, J. M.: Post-occlusive reactive hyperaemia in the heart, skeletal muscle and skin of control and capsaicin-pre-
treated pigs. Acta Physiol. Scand. 137: 271-277, 1989.
RANCO-CERECEDA, A., RU
-
- **DUCKLES, S. P.: Effects of capsaicin on vascular smooth muscle. Naunyn Schmie**
DUCKLES, S. P.: Effects of capsaicin on vascular smooth muscle. Naunyn Schmie-FRANCO-CERECEDA, A., RUDEHILL, A., AND LUNDBERG, J. M.: Calcitonin gene-related peptide but not substance P mimics capasicin-induced coronary vaso-
dilatation in the pig. Eur. J. Pharmacol. 142: 235-243, 1987c.
dilatation related peptide but not substance P mimics capsaicin-induced coronary vaso-
dilatation in the pig. Eur. J. Pharmacol. 142: 235-243, 1987c.
FRANCo-CERECEDA, A., SARIA, A., AND LUNDEBRA, J. M.: Differential release of
calcit calcitonin gene-related peptide and neuropeptide Y from the isolated heart b capsaicin, ischaemia, nicotine, bradykinin and ouabain. Acta Physiol. Scannel 135: 173–188, 1989b.
185: 173–188, 1989b.
1810, K., ALDSKOGIUS, H.,
	- capsaicin, ischaemia, nicotine, bradykinin and ouabain. Acta Physiol. Scand.
135: 173-188, 1989b.
FRIED, K., ALDSKOGIUS, H., AND HILDEBRAND, C.: Proportion of unmyelinated
axons in rat molar and incisor tooth pulps followi
	- N.ED, K., ALDSKOGIUS, H., AND HILDEBRAND, C.: Proportion of unmyelinated axons in rat molar and incisor tooth pulps following neonatal capsaicin treatment and/or sympathectomy. Brain Res. 463: 118-123, 1988.
JJTRA, S., SHI
	- FURNESS, SHIMIZU, T., IZUMI, K., FUKUDA, T., SAMESHIMA, M., AND OHBA, N.: Capsaicin-induced neuroparalytic keratitis-like corneal changes in the mouse. Erp. Eye Res. 38: 185-175, 1984.

	FURNESS, J. B., PAPKA, R. E., DELLA, N.: Capsaicin-induced neuroparalytic keratitis-like comouse. Exp. Eye Res. 38: 165-175, 1984.
mRNESS, J. B., PAFKA, R. E., DELLA, N. G., COSTA, MRNESS, J. B., PAFKA, R. E., DELLA, N. G., COSTA, M
Substance P-like immunorea mouse. Exp. Eye Res. 38: 165-175, 1984.
FURNESS, J. B., PAPKA, R. E., DELLA, N. G., COSTA, M., AND ESKAY, R. L.:
Substance P-like immunoreactivity in nerves associated with the vascular
system of guinea-pigs. Neuroscience
	-
	- system of guinea-pigs. Neuroscience 7: 447-459, 1982.
MSS, R.: Capsaicin and nociception in the rat and mouse. Possible role of
substance P. Naunyn Schmiedebergs Arch. Pharmacol. 320: 205-216, 1982.
MSS, R., HOLZER, P., AN system of guinea-pigs. Neuroscience 7: 447-459, 1982.
GAMSE, R.: Capsaicin and nociception in the rat and mouse. Possible role of substance P. Naunyn Schmiedebergs Arch. Pharmacol. 320: 205-216, 1982.
GAMSE, R., HOLZER, P. substance P. Naunyn Schmiedebergs Arch. Pharmacol. 320: 205-216, 1982.
GAMSE, R., HOLZER, P., AND LEMBECK, F.: Decrease of substance P in primary
sensory neurones and impairment of neurogenic plasma extravasation by
capasi
	- Sensory neurones and impairment of neurogenic plasma extra
capsaicin. Br. J. Pharmacol. 38: 207-213, 1980.
MASE, R., HOLZER, P., AND LEMBECK, F.: Indirect evidence for
location of opiate receptors on chemosensitive primary capsaicin. Br. J. Pharmacol. 68: 207-213, 1980.
GAMSE, R., HOLZER, P., AND LEMBECK, F.: Indirect evidence for presynaptic location of opiate receptors on chemosenaitive primary sensory neurones.
Naunyn Schmiedebergs Arch.
	- amples R., HOLZER, P., AND LEMBECK, F.: Indirect evidence for presynal location of opiate receptors on chemosensitive primary sensory neuron
Naunyn Schmiedebergs Arch. Pharmacol. 308: 281–285, 1979a.
AMBE, R., JANCSÓ, G., location of opiate receptors on chemosensitive primary sensory neurones.
Naunyn Schmiedebergs Arch. Pharmacol. 308: 281–285, 1979e.
MSE, R., JANCSO, G., AND KIRÁLY, E.: Intracisternal capsaicin: a novel
approach for studyi Naunyn Schmiedebergs Arch. Pharmacol. 308: 281-285, 1979a.
GAMSE, R., JANCSÓ, G., AND KIRÁLY, E.: Intracisternal capsaicin: a novel
approach for studying nociceptive sensory neurons. In Antidromic Vasodila-
tation and Neur
	- approach for studying nociceptive sensory neurons. *In* Antidromic Vasodila-Leinbeck, pp. 93-106, Akadémiai Kiadó, Budapest, 1984.
Lembeck, pp. 93-106, Akadémiai Kiadó, Budapest, 1984.
MSE, R., LACKNER, D., GAMSE, G., AND GAMSE, R., LACKNER, D., GAMSE, G., AND LEEMAN, S. E.: Effect of capsaicin pretreatment on capsaicin-evoked release of immunoreactive somatostatin and substance P. from primary sensory neurons. Naunyn Schmiedebergs Arch. Ph
	- substance P from primary sensory neurons. Naunyn Schmiedebergs Arch.
Pharmacol. 316: 38–41, 1981a.
MMSE, R., LEEMAN, S. E., HOLZEER, P., AND LEMBECK, F.: Differential effects
of capsaicin on the content of somatostatin, su Pharmacol. 316: 38-41, 1981a.

	GAMSE, R., LEEMAN, S. E., HOLZER, P., AND LEMBECK, F.: Differential effects

	of capacicin on the content of somatostatin, substance P, and neurotensin in

	the nervous system of the rat. Nauny cord scientin. The content of somatostatin, substance
the nervous system of the rat. Naunyn Schmiedebergs 1
140–148, 1981b.
MMSE, R., MOLNAR, A., AND LEMBECK, F.: Substance
cord alices by capsaicin. Life Sci. 25: 629–636, the nervous system of the rat. Naunyn Schmiedebergs Arch. Pharmacol. 317:
140–148, 1981b.
GAMSE, R., MOLNAR, A., AND LEMBECK, F.: Substance P release from spinal
cord slices by capsaicin. Life Sci. 25: 629–636, 1979b.
GAMS
	-
	- **peripheral nerve inhibits axoplasmic framework** of substance P release from spinal
cord alices by capasicin. Life Sci. 25: 629-636, 1979b.
MSB, R., PETSCHE, U., LEMBECK, F., AND JANCSÓ, G.: Capasicin applied to
peripheral CAMSE, R., PETSCHE, U., LEMBECK, F., AND JANCSÓ, G.: Capsaicin applied to peripheral nerve inhibits aroplasmic transport of substance P and somatostani. Brain Res. 239: 447-462, 1982.
GAMSE, R., SARIA, A., LUNDBERG, J. M.,
	- peripheral nerve inhibits axoplasmic transport of sultain. Brain Res. 239: 447-462, 1982.
statin. Brain Res. 239: 447-462, 1982.
MASE, R., SARIA, A., LUNDBERG, J. M., AND THEOD
Behavioral and neurochemical changes after in GAMSE, R., SARIA, A., LUNDESRO, J. M., AND THEODORSSON-NORHEIM, E.: Behavioral and neurochemical changes after intractisternal capacitin treatment of the guines pig. Neurosci. Lett. $64:287-292$, 1986.
GAMSE, R., WAX, A.,
	- substance P in sympathetic ganglia: distribution and sensitivity E.:
Behavioral and neurochemical changes after intracisternal capacicin treatment
of the guinea pig. Neurosci. Lett. 64: 287-292, 1986.
MMSE, R., WAX, A., Zi
	- of the guinea pig. Neuroeci. Lett. 64: 287–292, 1986.
GAMSE, R., WAX, A., ZIGMOND, R. E., AND LEEMAN, S. E.: Immunoreactive
substance P in sympathetic ganglia: distribution and sensitivity towards cap-
saicin. Neuroscience substance P in sympathetic ganglia: distribution and sensitivity towards cap-
saicin. Neuroscience 6: 437-441, 1981c.
GANNETT, P. M., NAGEL, D. L., REILLY, P. J., LAWSON, T., SHARPE, J., AND
TOTH, P.: The capsaicinoids: th
	-

ARMACOLOGI

193

-
- HOLZER

reversibly impairs vasopressin-mediated blood pressure recovery. Am. J. Physiol. 257: R1429-R1435, 1969.

GARTHWATTE, G., HAJOS, F., AND GARTHWATTE, J.: Ionic requirements for HAMPORIC effects of excitatory amino a **nourotoxic effects of excitatory amino acid analogues in rat cerebellar slices.**
Neuroscience 18: 437–447, 1986.
AZELIUS, B., BRODIN, E., KAHAN, T., PANOPOULOS, P., AND OLGART, L.: Local Happlication of capasicin to a per XELIUS, B., BRODIN, E., KAHAN, T., PANOPOULO
application of capasicin to a peripheral nerve:
noradrenaline levels in peripheral nerve ending
nerve stimulation. In Substance P—Dublin 1983.
Powell, pp. 241-242, Boole Press, application of capsaicin to a peripheral nerve: effects on substance P an noradrenaline levels in peripheral nerve endings and vascular responses there we stimulation. In Substance P—Dublin 1983, ed. by P. Skrabanek and E
- noradrenaline levels in peripheral nerve endings and vascular responses to nerve stimulation. In Substance P—Dublin 1983, ed. by P. Skrabanek and D. Powell, pp. 241–242, Boole Press, Dublin, 1983.
EUSTHOVEL, E., LUDWIG, O.
- Powell, pp. 241-242, Boole Press, Dublin, 1983.

GEISTHOVEL, E., LUDWIG, O., AND SIMON, E.: Capsaicin fails to produce disturbances of autonomic heat and cold defence in an avian species (Anas IMA)

platyrhynchos). Pflüger platyrhynchos). Pflügers Arch. 406: 343-350, 1986.

EPPETTI, P., FRILLI, S., RENZI, D., SANTICIOLI, P., MAGGI, C. A., THEODORS-SON, E., AND FANCIULLACCI, M.: Distribution of calcitonin gene-related pepteriods.

and other t SON, E., AND FANCIULLACCI, M.: Distribution of calcitonin gene-related peptide-like immunoreactivity in various rat tissues: correlation with substance P and other tachykinins and sensitivity to capsaicin. Regul. Pept. 23:
- and other tachykinins and sensitivity to capaaicin. Regul. Pept. 23: 289–298,

1988a.

GEPPETTI, P., FUSCO, B., MARABINI, S., MAGGI, C. A., FANCIULLACCI, M., AND

SICUTERI, F.: Secretion, pain and sneezing induced by the a
- SICUTERI, F.: Secretion, pain and sneezing induced by the application of capsaicin to the nasal mucosa in man. Br. J. Pharmacol. 93: 509-514, 1988b.
RPPETTI, P., MAGGI, C. A., PERRETTI, F., FRILLI, S., AND MANZINI, S.:
Sim capasicin to the nasal mucosa in man. Br. J. Pharmacol. 93: 509-514, 1988b.
 EPPETTI, P., MAGGI, C. A., PERRETTI, F., FRILLI, S., AND MANZINI, S.:

Simultaneous release by bradykinin of substance P- and calcitonin gene-r GEPPETTI, P., MAGGI, C. A., PERRETTI, F., FRILLI, S., AND MANZINI, S.:
Simultaneous release by bradykinin of substance P- and calcitonin gene-related
peptide immunoreactivities from capacicin-sensitive structures in guinea
- Simultaneous release by bradykinin of substance P- and calcitonin gene-related
peptide immunoreactivities from capasicin-sensitive structures in guinea-pig
heart. Br. J. Pharmacol. 94: 288-290, 1988c.
GEPPETTI, P., TRAMONT **PUSCO, B. M., AND DEL BIANCO, E.: Differential effect on neuropeptide release** of different concentrations of thydrogenions on afferent and intrinsic neurons of the rat stomach. Gastroenterology, in press, 1991.
 REPETTI
- of different concentrations of hydrogenions on afferent and intrinsic neurons
of the rat stomach. Gastroenterology, in press, 1991.
 EPPETIT, P., TRAMONTANA, M., PATACCHINI, R., DEL BIANCO, E., SANTICIOLI,
 P., AND MAGG of the rat stomach. Gastroenterology, in press, 1991.
 gPETTI, P., TRAMONTANA, M., PATACCHINI, R., DEL BIANCO, E.,

P., AND MAGGI, C. A.: Neurochemical evidence for the active

"efferent" function of capsaicin-sensitive GEPPETTI, P., TRAMONTANA, M., PATACCHINI, R., DEL BIANCO, E., SANTICIOLI,
P., AND MAGGI, C. A.: Neurochemical evidence for the activation of the
"efferent" function of capacicin-sensitive nerves by lowering of the pH in th
- P., AND MAGGI, C. A.: Neurochemical evidence for the activation of the 'efferent' function of capeaicin-sensitive nerves by lowering of the pH in the guinea-pig urinary bladder. Neuroaci. Lett. 114: 101–106, 1990.
BBINS, I guinea-pig urinary bladder. Neuroaci. Lett. 114: 101-106, 1990.
GIBBINS, I. L., FURNESS, J. B., AND COSTA, M.: Pathway-specific patterns of the co-existence of substance P, calcitonin gene-related peptide, cholecystokinin
- **AND GIRGIST GIRGIST CONSTRAND GIRGIST CONSTRAND GIRGIST CONSTRANDING THE SAMPLE THEOUS Res. 248: 417-437, 1987.**
 THEOUS Res. 248: 417-437, 1987.
 NADD GIRGIS, S.: Lo. FURNESS, J. B., COSTA, M., MACINTYRE, I., HILLYARD GIBBINS, I. L., FURNESS, J. B., COSTA, M., MACINTYRE, I., HILLYARD, C. J., HE,
AND GIRGIS, S.: Co-localization of calcitonin gene-related peptide-like immu-
noreactivity with substance P in cutaneous, vascular and visceral
- **neurons of** guinea **pigs.** Neurosci. Lett. **57: 125-130, 1985.** Local application of capsaicin to one sciatic nerve of the adult rat induces a
marked depletion in the peptide content of the lumbat dorsal horn. Neurosci-
ence 7: 3153-3162, 1982.
GLINSUKON, T., STITMUNNAITHUM, V., TOSKUL
- A. M. W., T., STITHUNNARTHUM, V., TOSKULKAO, C., BARANAWUTI, T., AND
 ANGKRISANAVINONT, V.: Acute toxicity of capsaicin in several animal species.
 A. W., AND YAMAMOTO, M.: Capsaicin prolongs action potential duration i
- Toxicon 18: 215-220, 1980.
GODFRAIND, J. M., JESSELL, T. M., KELLY, J. S., MCBURNEY, R. N., MUDGE,
A. W., AND YAMAMOTO, M.: Capsaicin prolongs action potential duration in
cultured sensory neurones. J. Physiol. (Lond.) 312 A. W., AND YAMAMOTO, M.: Capsaicin prolongs action potential duration in cultured sensory neurones. J. Physiol. (Lond.) 312: 32P-33P, 1981.
GREEN, B. G.: Sensory interactions between capacicin and temperature in the oral c
-
- cultured sensory neurones. J. Physiol. (Lond.) 312: 32P-33P, 1981.
REEN, B. G.: Sensory interactions between capasicin and temperature in the
oral cavity. Chem. Senses 11: 371-382, 1986.
REEN, B. G.: Capasicine sensitizati
- GREEN, B. G.: Sensory interactions between capacitin and temperature in the oral cavity. Chem. Senses 11: 371–382, 1986.
GREEN, B. G.: Capacitin sensitization and desensitization on the tongue produced
by brief exposures t GREEN, B. G.: Capacicin sensitization and desensitization on the tongue produced
by brief exposures to a low concentration. Neurosci. Lett. 107: 173-178, 1989.
GREEN, T., AND DOCKRAY, G. J.: Characterization of the peptide REEN, T., AND DOCKRAY, G. J.: Characterization of the peptidergic afferent innervation of the stomach in the rat, mouse and guinea-pig. Neuroscience 25:
181-183, 1988.
RELER, H.-J., JÄNIG, W., AND KOLTZENBURG, M.: Activati innervation of the stomach in the rat, m
181-193, 1988.
KBLER, H.-J., JÄNIG, W., AND KOLTZEN
afferents by mechanical stimuli and inferents by mechanical stimuli and in
Physiol. (Lond.) 425: 545-563, 1990.
Mós, M., ENGRERG,
-
- HABLER, H.-J., JÄNIG, W., AND KOLTZENBURG, M.: Activation of unmyelinated
HABLER, H.-J., JÄNIG, W., AND KOLTZENBURG, M.: Activation of unmyelinated
afferents by mechanical stimuli and inflammation of the urinary bladder. J HAJÓS, M., ENGEREG, G., AND ELAM, M.: Reduced responsiveness of locus roundeus neurons to cutaneous thermal stimuli in capsaicin-treated rats. 20
Neurosci. Lett. 70: 382–387, 1986a.
HAJÓS, M., OBÁL, F., JANCSO, G., AND OBÁ
- rats **pretreated as adults** Naunyn Schmiedebergs Arch. Pharmacol. **324: 219-** 222, 1983. HAJOS, M., OBÁL, F., JANCSO, G., AND OBÁL, F.: The capsaicin sensitivity of the preoptic region is preserved in adult rats pretreated as neonates, but lost in rats pretreated as adults. Naunyn Schmiedebergs Arch. Pharmacol
- **SUNDLER, F.: MULTIPLE TACH SUNDER, F.: AND CARLSSON, A.:**
HAJÓS, M., SVENSSON, K., NISSBRANDT, H., OBÁL, F., AND CARLSSON, A.:
SEffects of capeaicin on central monoaminergic mechanisms in the rat. J. Neural
Transm. 6
- HAKANSON, **R., BEDING, B., EKMAN, R., HEILIG, M., WAHLESTEDT,** C., **AND** Effects of capacicin on central monoaminergic mechanisms in the rat. J. Neural
Transm. 66: 221-242, 1966b.
HÄKANSON, R., BEDING, B., EKMAN, R., HEILIG, M., WAHLESTEDT, C., AND
SUNDLER, F.: Multiple tachykinin pools in sens
- SUNDLER, F.: Multiple tachykinin pools in sensory nerve fibres in the rabbit Hiris. Neuroacience 21: 943-950, 1987.

NAMOND, D. L., AND RUDA, M. A.: Developmental alterations in thermal nonciceptive threshold and the dist The Ration Control of the *RATHONDID, D. L.*, AND RUDA, M. A.: Developmental alterations in thermal
mociceptive threshold and the distribution of immunoreactive calcitonin generated periods and substance P after neonatal a mocic prive threshold and the distribution of immunoreactive calcitonin generals are related peptide and substance P after neonatal administration of capsaicin in in the rat. Neuroaci. Lett. 97: 57-62, 1989.

MAON, M., GAL
- **HAMON, M., GALLISSOT, M. C., MENARD, F., GOZLAN, H., BOURGOIN, S., AND VERGE, D.: 5-HT, receptor binding sites are on capsacion-sensitive fibres in the rat spinal cord. Eur. J. Pharmacol. 164: 315-322, 1989.
HANDWERKER, H** HAMON, M., GALLISSOT, M. C., MENARD, F., GOZLAN, H., BOURGOIN, S., AND VERGE, D.: 5-HT₃ receptor binding sites are on capsaicin-sensitive fibres in the rat spinal cord. Eur. J. Pharmacol. 164: 315-322, 1989. HANDWERKE, H
-

Inflammation, ed. by L. A. Chahl, J. Szolcsányi, and F. Lembeck, pp. 57-78, Akadémiai Kiadó. Budapest. 1984. **Akadémiai Kiadó, Budapest, 1984.**
Akadémiai Kiadó, Budapest, 1984.
HARMAR, A., SCHOFIELD, J. G., AND KEEN, P.: Substance P biosynthesis in
dorsal root ganglia: an immunohistochemical study of [³⁶S]methionine and

- The means of the M. A. Chahl, J. Szolcsányi, and F. Lembeck, pp. 57–78,
Akadémiai Kiadó, Budapest, 1984.
ARMAR, A., SCHOFIELD, J. G., AND KEEN, P.: Substance P biosynthesis in
dorsal root ganglia: an immunohistochemical st Inflammation, ed. by L. A. Chahl, J. Szolcsányi, and F. Lembeck, pp. 57-
Akadémiai Kiadó, Budapest, 1984.
HARMAR, A., SCHOFIELD, J. G., AND KEEN, P.: Substance P biosynthesis
dorsal root ganglia: an immunohistochemical stu REMAR, A., SCHOFIELD, J. G., AND KEEN, P.: Substance P biosynthesis in dorsal root ganglia: an immunohistochemical study of [⁹⁶S]methionine and [⁹¹H]proline incorporation *in uitro*. Neuroscience 6: 1917-1922, 1981.
AR
-
- [¹H]proline incorporation in vitro. Neuroscience 6: 1917-1922, 1981.
HARPER, A. A., AND LAWSON, S. N.: Conduction velocity is related to morphological cell type in rat dorsal root ganglion neurones. J. Physiol. (Lond.) 3
- RRTI, G.: Wirkung von Capsaicin auf afferente peptiderge Nervenfasern: Immunohistochemische Untersuchungen an Ratten, Meerschweinchen und Tauben. Dr. rer. nat. thesis, University of Giessen, 1988.
NRTI, G.: SHARKEY, K. A.,
- munohistochemische Untersuchungen an Ratter
ben. Dr. rer. nat. thesis, University of Giessen, 1
RRTI, G., SHARKEY, K. A., AND PIERAU, F.-K.: 1
pigeon on peripheral neves containing substance
peptide. Cell Tissue Res. 256: **HARTI, G., SHARKEY, K. A., AND PIERAU, F.-K.: Effects of capsaicin in rat and pigeon on peripheral nerves containing substance P and calcitonin gene-related peptide. Cell Tissue Res. 2566: 465-474, 1989.
HARTI, G., SHARKE**
- SON, E., AND FANCIULLACCI, M.: Distribution of calcitonin gene-related pep-

Since it issues: correlation with substance P pigeon on peripheral nerves containing substance P and calcitonin gene-related

and other tachykini pigeon on peripheral nerves containing substance P and calcitonin gene-related peptide. Cell Tissue Res. 256: 465-474, 1989.
RRTI, G., SHARKEY, K. A., ROSSLER, W., AND PIERAU, F.-K.: Distribution of substance P (SP) and ca peptide. Cell
ARTI, G., SHA
substance P (
of capsaicin i
S322, 1987.
ARTUNG, M., HARTI, G., SHARKEY, K. A., ROSSLER, W., AND PIERAU, F.-K.: Distribution of substance P (SP) and calcitonin gene-related peptide (CGRP) and the effect of capacicin in sensory neurones of rat and pigeon. Neuroscience 22 (sup
	-
	-
	- S322, 1987.

	HARTUNG, M., LEAH, J., AND ZIMMERMANN, M.: The excitation of cutaneous

	nerve endings in a neuroma by capsaicin. Brain Res. 499: 363-366, 1989.

	HAYES, A. G., HAWCOCK, A. B., AND HILL, R. G.: The depolarising merve endings in a neuroma by capsaicin. Brain Res. 499: 363–366, 1989.
NYES, A. G., HAWCOCK, A. B., AND HILL, R. G.: The depolarising action of capsaicin on rat isolated sciatic nerve. Life Sci. 35: 1561-1568, 1984a.
NYES **AYES, A. G., HAWCOCK, A. B., AND HILL, R. G.: The depolarising action of capsaicin on rat isolated sciatic nerve. Life Sci. 35: 1561-1568, 1984a.

	AYES, A. G., OXFORD, A., REYNOLDS, M., SHINGLER, A. H., SKINGLE, M., SHIN**
	- capsaicin on rat isolated sciatic nerve. Life Sci. 35: 1561-1568, 1984a.
HAYES, A. G., OXFORD, A., REYNOLDS, M., SHINGLER, A. H., SKINGLE, M.,
SMITH, C., AND TYERS, M. B.: The effects of a series of capsaicin analogues
on on nociception and body temperature in the rat. Life Sci. 34: 1241-1248, 1984b.
HAYES, A. G., SCADDING, J. W., SKINGLE, M., AND TYERS, M. B.: Effects of
neonatal administration of capacicin on nociceptive thresholds in the
	- HAYES, A. G., SCADDING, J. W., SKINGLE, M., AND TYERS, M. B.: Effects of
neonatal administration of capsaicin on nociceptive thresholds in the mouse
and rat. J. Pharm. Pharmacol. 33: 183-185, 1981a.
HAYES, A. G., SKINGLE,
	- on nociceptive thresholds in the rodent. Neuropharmacology 20: 505-511, 1981b.
HAYES, A. G., AND TYERS, M. B.: Effects of capsaicin on nociceptive heat, pressure and chemical thresholds and on substance P levels in the rat
	- HE, X., SCHEPELMANN, K., SCHAIBLE, H.-G., AND SCHMIDT, R. F.: Capsaicin inhibits responses of fine afferents from the knee joint of the cat to mechanical and chemical stimuli. Brain Res. 530: 147-150, 1990.
HE, X., SCHMITT
	- HE, X., SCHMIDT, R. F., AND SCHMITTNER, H.: Effects of capsaicin on articular afferents of the cat's knee joint. Agents Actions 25: 222-224, 1988.
	- inhibits responses of fine afferents from the knee joint of the cat to mechanical
and chemical stimuli. Brain Res. 530: 147-150, 1990.
HE, X., SCHMIDT, R. F., AND SCHMITTNER, H.: Effects of capsaicin on articular
afferents **HELKE, C. J., DIMICCO, J. A., JACOBOWITZ, D. M., AND KOPIN, I. J.: Effect of**
 HELKE, C. J., DIMICCO, J. A., JACOBOWITZ, D. M., AND KOPIN, I. J.: Effect of
 CNS regions. Brain Res. 222: 4234, 1981a.
 HELKE, C. J., JA ELKE, C. J., DIMICCO, J. A., JACOBOWITZ, D. M., AND KOPIN, I. J.: Effect of capeaicin administration to neonatal rats on the substance P content of discrete CNS regions. Brain Res. 222: 428-431, 1981a.
ELKE, C. J., JACOBOW
	-
	- capsaicin administration to neonatal rats on the substance P content of discrete
CNS regions. Brain Res. 222: 428-431, 1981a.
HELKE, C. J., JACOBOWITZ, D. M., AND THOA, N. B.: Capsaicin and potassium
evoked substance P rel **and the stimulation in capsaicin-pretreated ration** is and spinal trigeminal nucleus *in vitro*. Life Sci. 29: 1779–1785, 1981b.
ELME, R. D., EGLEZOS, A., DANDIE, G. W., ANDREWS, P. V., AND BOYD, R. L. The effect of s HELME, R. D., EGLEZOS, A., DANDIE, G. W., ANDREWS, P. V., AND BOYD, R.
L.: The effect of substance P on the regional lymph node antibody response to
antigenic stimulation in capacicin-pretreated rats. J. Immunol. 139: 3470
	-
	- antigenic stimulation in capsaicin-pretreated rats. J. Immunol. 139: 3470-HEYMAN, I., AND RANG, H. P.: Depolarizing responses to capsaicin in a subpopulation of rat dorsal root ganglion cells. Neurosci. Lett. 56: 69–75, 19
	-
	- HIURA, A., AND ISHIZUKA, H.: Changes in features of degenerating primary
sensory neurons with time after capsaicin treatment. Acta Neuropathol. 78:
35–46, 1989.
HIURA, A., ISHIZUKA, H., AND SAKAMOTO, Y.: Electron microscop HIURA, A., AND SAKAMOTO, Y.: Effect of capsaicin on neurites of cultured dorsal
root ganglia and isolated neurons of chick embryos. Neurosci. Lett. 73: 237-
241, 1987a.
HIURA, A., AND SAKAMOTO, Y.: Quantitative estimation
	-
	- root ganglia and isolated neurons of chick embryos. Neurosci. Lett. 73: 237-
241, 1987a.
HIURA, A., AND SAKAMOTO, Y.: Quantitative estimation of the effect of capsaicin
on the mouse primary sensory neurons. Neurosci. Lett. FIR, 2001.

	THA, A., AND SAKAMOTO, Y.: Quantitative estimon the mouse primary sensory neurons. Neuroscours, Histol. Cytol. 53: 455-466, 1990b.

	primary afferent central terminals in the supernor primary afferent central te on the mouse primary sensory neurons. Neurosci. Lett. 76: 101-106, 1987b.
HIURA, A., VILLALOBOS, E. L., AND ISHIZUKA, H.: The action of capasicin on
primary afferent central terminals in the superficial dorsal horn of newb
	-
	- HOGAN, P.: Expression of markers for pain sensory neurones in cell culture. Ph.
D. thesis, Harvard University, Boston, 1983.
HOGYES, A.: Beiträge zur physiologiachen Wirkung der Bestandteile des Capsiculars, A.: Beiträge z
	- **Propose The smallest dorsal root ganglion cells downsal root ganglion cells downsal root ganglion cells do not originate Holders in the cat. Neurosci. Holders and MENSE, S.: Non-myelinated afferent fibres do not originate**
	- HOHEISEL, U., AND MENSE, S.: Non-myelinated afferent fibres do not originate
exclusively from the smallest dorsal root ganglion cells in the cat. Neurosci.
Lett. 72: 153-157, 1986.
HOLJE, H., HILDEBRAND, C., AND FRIED, K.: administration of capsaicin. Brain Res. 266: 133-136, 1983.
	- HOLJE, H., HILDEBRAND, C., AND FRIED, K.: Proportion of unmyelinated axons
in the rat inferior alveolar nerve and mandibular molar pulps after neonatal
administration of capaaicin. Brain Res. 266: 133-136, 1983.
HOLZ, G. G in the rat inferior alveolar nerve and mandibular molar pulps after neonatal
administration of capasicin. Brain Res. 266: 133-136, 1983.
HOLZ, G. G., DUNLAP, K., AND KREAM, R. M.: Characterization of the electrically
evoke
	- **HOLZ, G. G., DUNLAP, K., AND KREAM, R. M.: Characterization of the electrically**
 HOLZ, G. G., DUNLAP, K., AND KREAM, R. M.: Characterization of the electrically
 evoked release of substance P from dorsal root ganglion

REVIEW

 $\, \mathbb G \,$

- CAPS

HOLZER, P.: Capsaicin-sensitive afferent neurones and gastrointestinal propul-

sion in the rat. Naunyn Schmiedebergs Arch. Pharmacol. 332: 62–65, 1986.

HOLZER, P.: Local effector functions of capsaicin-sensitive se **pLEER, P.: Capeaicin-sensitive afferent neuron**
sion in the rat. Naunyn Schmiedebergs Arch
**pLEER, P.: Local effector functions of capeaicinvolvement of tachykining, calcitoning generopy
peptides. Neuroscience 24: 739–768** sion in the rat. Naunyn Schmiedebergs Arch. Pharmacol. 332: 62-65, 1986.
HOLZER, P.: Local effector functions of capacicin-sensitive sensory nerve endings:
involvement of tachykinins, calcitonin gene-related peptides. Neur
- publication on intestinal circular muscle. Am. J. Physiol. 256: G546-G552, 1989.
involvement of tachykinina, calcitonin gene-related peptide and other neuro-
peptides. Neuroscience 24: 739-768, 1988.
DLEER, P., BARTHÓ, L., **HOLZER, P., BARTHÓ, L., MATUSÁK, O., AND BAUER, V.: Calcitonin gene-related peptide action on intestinal circular muscle. Am. J. Physiol. 256: G546-G552, 1869.
HOLZER, P., BUCSICS, A., AND LEMBECK, F.: Distribution of cap** DLEER, P., BARTHO, L., MATUSAK, O., AND BAUER, V.: Calcitonin gene-related peptide action on intestinal circular muscle. Am. J. Physiol. 256: G546-G552, 1989.
1989.
DEER, P., BUCSICS, A., AND LEMBECK, F.: Distribution of c
- peptide action on intestinal circular muscle. Am. J. Ph.
1989.
DLEER, P., BUCSICS, A., AND LEMBECK, F.: Distributionerve fibres containing immunoreactive substance P in
tissues of the rat. Neurosci. Lett. 31: 253-257, 1982
- 1989.
HOLEER, P., Bucsics, A., AND LEMBECK, F.: Distribution of capeaicin-senative
nerve fibres containing immunoresctive substance P in cutaneous and visceral
lissues of the rat. Neurosci. Lett. 31: 253-257, 1982.
HOLEER,
-
- rat gastrointestinal tract—lack of effect of capsaicin pretreatment. Eur. J.
Pharmacol. 61: 303-307, 1980.
HOLZER, P., JURNA, I., GAMSE, R., AND LEMBECK, F.: Nociceptive threshold
after neonatal capsaicin treatment. Eur. J Fharmacol. 31: 303-307, 1980.

HOLZER, P., JURNA, I., GAMSE, R., AND LEMBECK, F.: Nociceptive threshold

after neonatal capsaicin treatment. Eur. J. Pharmacol. 58: 511-514, 1979.

HOLZER, P., AND LEMBECK, F.: Longitudinal DLZER, P., AND LEMBECK, F.: Longitudinal contraction of isolated guinea-pig ileum induced by rapid cooling. Naunyn Schmiedebergs Arch. Pharmacol. 310:
169-174, 1979. L. TH., AND HOLZER-PETSCHE, U.: Inhibition of gastrointe
- capsaic indiced by rapid cooling. Naunyn Schmiedebergs Arch. 189-174, 1979.
189-174, 1979.
CLEER, P., LIPPE, I. TH., AND HOLZER-PETSCHE, U.: Inhibitionial transit due to surgical trauma or peritoneal irritation
capsaicin-t **HOLZER, P., LIPPE, I. TH., AND HOLZER-PETSCHE, U.: Inhibition of gastrointes-

HOLZER, P., LIPPE, I. TH., AND HOLZER-PETSCHE, U.: Inhibition of gastrointes-

capsaicin-treated rate. Gastronetrology 91:360-363, 1986.

HOLZ**
- an increase in rat gastric mucosal blood flow in the face of pending tensor increased in capeacin-treated rats. Gastroenterology 91: 360-363, 1986.
any size in the face of pending acid in the face of pending acid injury.
B tinal transit due to surgical trau
capsaicin-treated rats. Gastroenter
DLZER, P., LIVINGSTON, E. H., AN
an increase in rat gastric mucosal bastroenterology, in press, 1991.
DLZER, P., PABST. M. A., LIPPE,
- capsaicin-treated rats. Gastroenterology 91: 360-363, 1986.
HOLZER, P., LIVINGSTON, E. H., AND GUTH, P. H.: Sensory neurons signal for
casatroenterology, in press, 1991.
Gastroenterology, in press, 1991.
HOLZER, P., PABST, an increase in rat gastric mucosal blood flow in the face of pending acid injury.
Gastroenterology, in press, 1991.
HOLEER, P., PABST, M. A., LIPPE, I. TH., PESKAR, B. M., PESKAR, B. A., LIVINGSTON, E. H., AND GUTH, P. H.: HOLIER, P., PABST, M. A., LIPPE, I. TH., PESKAR, B. M., PESKAR, B. A., LIVINGSTON, E. H., AND GUTH, P. H.: Afferent nerve-mediated protection against deep mucosal damage in the rat stomach. Gastroenterology 98: 838-848, 19
-
- calcitonin gene-related peptide induced by capaaicin in the vascularly perfused
rat stomach. Neurosci. Lett. 108: 195-200, 1990b.
HOLZER, P., AND SAMETZ, W.: Gastric mucosal protection against ulcerogenic
factors in the ra factors in the rat mediated by capsaicin-sensitive afferent neurons. Gastroen-
- terology 91: 975-981, 1986.
HOLZER, P., SARIA, A., SKOFITSCH, G., AND LEMBECK, F.: Increase in tissue
concentrations of histamic and 5-hydroxytryptamine following capsaicin
treatment of newborn rata. Life Sci. 29: 1099-110 DLEER, P., SARIA, A., SKOFITSCH, G., AND LEMBECK, F.: Increase in concentrations of histamine and 5-hydroxytryptamine following capternent of newborn rate. Life Sci. 299: 1005-1006. 1981.
Uteratment of newborn rat. Life Sc
-
- concentrations of histamine and 5-hydroxytryptamine following capsaicin
treatment of newborn rats. Life Sci. 29: 1099-1105, 1981.
HOLEER-PETSCHE, U., AND LEMBECK, F.: Systemic capsaicin treatment impairs
the micturition re DLEER-PETSCHE, U., RINNER, I., AND LEMBECK, F.: Distribution accetyltransferase activity in rat spinal cord—influence of primary aff Neural Transm. 66: 85-92, 1986.
Neural Transm. 66: 85-92, 1986.
the capsaicin-desensitize **Hornes and central control of the matter of primary afferents? J.
Neural Transm. 66: 85-92, 1986.
Horn, T.: Thermorensitivity of preoptic and anterior hypothalamic neurons in
the capsaicin-desensitized rat. Pflügers Arch.**
-
- Neural Transm. 66: 85-92, 1986.
 26: 38-92, 1986.
 26: 297-299, 1981.
 26: 297-299, 1981.
 26: 297-299, 1981.
 26: 298-416, 1984.
 26: 389-416, 1984.
 26: 389-416, 1984.
 26: 389-416, 1984.
 26: 389-416, 1 one, and according the capsaicin desensitized rat. Pflugers Arch. 389: 297-299, 1981.
26: 389-416, 1984.
26: 389-416, 1984.
treated with capasicin as neonates. Pflugers Arch. 390: 219-223, 1
port, T., AND TSUZUKI, S.: Ther
-
- the capsaicin activation of adenylate cyclase in rat brain. Brain Res. 179: 401-403, 1979.
HOTTENSTEIN, O. D., PAWLIK, W. W., REMAK, G., AND JACOBSON, E. D.: DRI, T., ANI
treated with
DRVATH, K.
the capaaici
403, 1979.
OTTENSTEIN HORVATH, K. J., JANCSO, G., AND WOLLEMANN, M.: The effect of calcium on the capsaicin activation of adenylate cyclase in rat brain. Brain Res. 179: 401-403.
HORVATH, K. J., JANCSO, G., AND WOLLEMANN, M.: The effect of calc
- **rat gut. IT and the capacities archivation of adenyiate cyclase in rat brain. Brain Res. 179: 401-403, 1979.**
Horreswsrexive, O. D., PAWLIK, W. W., REMAK, G., AND JACOBSON, E. D.: Capacities nensitive nerves modulate rest
- OTTENSTEIN, O. D., PAWLIK, W. W., REMAK, G., AND JACOBSON, E. D.:
Capsaicin-sensitive nerves modulate resting blood flow and vascular tone in
rat gut. Naunyn Schmiedebergs Arch. Pharmacol. 343: 179-184, 1991.
duodenal nerv rat gut. Naunyn Schmiedebergs Arch. Pharmacol. 343: 179-184, 1991.
HovEs, A. D., AND BARBER, P.: Degeneration of axons in the ureteric and
duodenal nerve plexuese of the adult rat following in vivo treatment with
capsaicin
-
- duodenal nerve plexuses of the adult rat following in vivo treatment with capsaicin. Neurosci. Lett. 25: 19-24, 1981.
HOYES, A. D., BARBER, P., AND JAGESSAR, H.: Effect of capsaicin on the intraperioneal axons of the rat t HOYES, A. D., BARBER, P., AND JAGESSAR, H.: Effect of capsaicin on the intraperitoneal axons of the rat trachea. Neuroaci. Lett. 26: 329-334, 1981.
HUA, X.-Y., AND LUNDERG, J. M.: Dual capsaicin effects on ureteric motilit
- HUA, X.-Y., AND LUNDBERG, J. M.: Dual capsaicin effects on ureteric motility:

low dose inhibition mediated by calcitonin gene-related peptide and high dose

stimulation by tachykinins? Acta Physiol. Scand. 128: 453-465, 1
- (substance P, neurokinin A and eledoisin-like material) from guinea-pig spinal
cord and ureter. Neuroscience 19: 313-319, 1986.
HUA, X.-Y., THEODORSSON-NORHEIM, E., BRODIN, E., LUNDBERG, J. M., AND
HOKFELT, T.: Multiple t Monter. T.: Multiple tachykinina (neurokinin A, neuropeptide K and substance P) in capasicin-sensitive sensory neurons in the guinea-pig. Regul. Pept.
13: 1-19, 1985.
INOMATA, K., AND NASU, F.: Effects of neonatal capsaici
- monophosphatase (TMPase) activity in the substantia gelatinosa of the spinal cord. Int. J. Dev. Neurosci. 2: 307–311, 1984. COMATA, K., AND NASU, F.: Effects of neonatal capsaicin treatment on thiamine
monophosphatase (TMPase) activity in the substantia gelatinosa of the spinal
cord. Int. J. Dev. Neuroaci. 2: 307-311, 1984.
MES, I. F., WALPOLE,
- cord. Int. J. Dev. Neurosci. 2: 307-311, 1984.
JAMES, I. F., WALPOLE, C. S. J., HIXON, J., WOOD, J. N., AND WRIGGLESWORTH,
R.: Long-lasting agonist activity produced by a capaaicin-like photoaffinity
probe. Mol. Pharmacol. MES, I. F., WALFOLE, C. S. J., HIXON, J., WOOD, J. N., AND WRIGGLESWORT R.: Long-lasting agonist activity produced by a capsaicin-like photoaffin probe. Mol. Pharmacol. 33: 643-649, 1988.
probe. Mol. Pharmacol. 33: 643-649 R.: Long-lasting agonist activity produced by a capsaicin-like photoaffinity probe. Mol. Pharmacol. 33: 643-649, 1988.
JANCSO, G.: Selective degeneration of chemosensitive primary sensory neurones induced by capsaicin: gli
-
-
- JANCSO, G.: Selective degeneration of chemosensitive primary sensory neurones induced by capsaicin: gial changes. Cell Tissue Res. 195: 145-152, 1978.
JANCSO, G.: Intracisternal capsaicin: selective degeneration of chemose NCSÔ, G.: Intracisternal capsaicin: selective degeneration of chemosensitive primary sensory afferents in the adult rat. Neurosci. Lett. 27: 41-45, 1981.
NCSÔ, G.: Sensory nerves as modulators of inflammatory reactions. In primary sensory afferents in the adult rat. Neurosci. Lett. 27: 41-45, 1981.
JANCSO, G.: Sensory nerves as modulators of inflammatory reactions. In Anti-
dromic Vasodilatation and Neurogenic Inflammation, ed. by L. A. Chah
-

M.: Morphological effects of capsaicin and its analogues in newborn and adult mammals. *In* Tachykinin Antagonists, ed. by R. Håkanson and F. Sundler, pp. 35–44, Eleevier, Amsterdam, 1985a. 35-44, Electrical effects of capaaicin and its analogues in newborn and adult mammals. In Tachykinin Antagonists, ed. by R. Håkanson and F. Sundler, pp 35-44, Electric, Amsterdam, 1985a.
JANCS6, G., HOKFELT, T., LUNDBERG,

- M.: Morphological effects of capsaicin and its analogues in newborn and adult
mammals. In Tachykinin Antagonists, ed. by R. Håkanson and F. Sundler, pp.
35–44, Elesvier, Amsterdam, 1985a.
NCSO, G., Hökrekr, T., LUNDBERG, J mammals. In Tachykinin Antagonists, ed. by R. Häkanson and F. Sundler, pp.
35–44, Eleevier, Amsterdam, 1985a.
NCSO, G., HOKFELT, T., LUNDBERG, J. M., KIRALY, E., HALASZ, N., NILSSON,
G., TERENIUS, L., REHFELD, J., STEINBUS NCSÓ, G., HÖKFELT, T., LUNDBERG, J. M., KIRÁLY, E., HALÁSZ, N., NILSSO
G., TERENIUS, L., REHFELD, J., STEINBUSCH, H., VERHOFSTAD, A. E. I
SAID, S., AND BROWN, M.: Immunohistochemical studies on the effect
capsaciin on spin G., TERENIUS, L., REHFELD, J., STEINBUSCH, H., VERHOFSTAD, A
SAID, S., AND BROWN, M.: Immunohistochemical studies on the capsaciin on spinal and medullary peptide and monoamine neurocytol.
antisera to substance P., gastrin SAID, S., AND BROWN, M.: Immunohistochemical studies on the effect of capsaicin on spinal and medullary peptide and monoamine neurons using tensin and 5-hydroxytrytamine. J. Neurocytol. 10: 963-980, 1981.
JANCSO, G., AND J
- antisera to substance P, gastrin/C
tensin and 5-hydroxytryptamine. J
NC80, G, AND JANC80-GABOR, A.:
possible involvement of hypothalam
Pharmacol. 311: 285-288, 1980.
NC80, G., KARC80, S., KIRÁLY, E., tensin and 5-hydroxytryptamine. J. Neurocytol. 10: 963–980, 1981.
JANCSO, G., AND JANCSO-GÁBOR, A.: Effect of capasicin on morphine analgesia—
possible involvement of hypothalamic structures. Naunyn Schmiedeberga Arch.
Pha ANC BO, G., AND JANCSO-GABOR, A.: Effect of capaaicin on morphine analgesia—possible involvement of hypothalamic structures. Naunyn Schmiedebergs Arch.
Pharmacol. 311: 285–288, 1980.
ANC 86, G., KARCSO, S., KIRÁLY, E., SZE
- Pharmacol. 311: 285-288, 1980.
JANCSÓ, G., KARCSÚ, S., KIRÁLY, E., SZEBENI, A., TÓTH, L., BÁCSY, E., JOÓ, F.,
AND PARDUCZ, A.: Neurotoxin induced nerve cell degeneration: possible in-
JANCSÓ, G., AND KIRÁLY, E.: Distributi
- NCSO, G., KARCSU, S., KIRÁLY, E., SZEBENI, A., TÓTH, L., BÁCSY, E., JOÓ, F., AND PÁRDUCZ, A.: Neurotoxin induced nerve cell degeneration: possible in-
volvement of calcium. Brain Res. 295: 211-216, 1984.
NCSO, G., AND KIRÁ 792, 1980. AND PARDUCZ, A.: Neurotoxin induced nerve cell degeneration: possible in-
volvement of calcium. Brain Res. 295: 211-216, 1984.
JANCSO, G., AND KIRALY, E.: Distribution of chemosenative primary sensory
afferents in the cent JANCSO, G., AND KIRALY, E.: Distribution of chemosensitive primary sensory afferents in the central nervous system of the rat. J. Comp. Neurol. 190: 781–792, 1980.
JANCSO, G., AND KIRALY, E.: Sensory neurotoxins: chemicall
-
-
- **792, 1980.**

JANCSÓ, G., AND KIRÁLY, E.: Sensory neurotoxins: chemically induced selective

destruction of primary sensory neurons. Brain Res. 210: 83-89, 1981.

JANCSÓ, G., AND KIRÁLY, E.: Regneration of peptidergic sens destruction of primary sensory neurons. Brain Res. 210: 83-89, 1981.
NCSO, G., AND KIRÁLY, E.: Regeneration of peptidergic sensory nerves in the
rat skin. Acta Physiol. Acad. Sci. Hung. 63: 239-240, 1964.
NCSO, G., KIRÁLY, JANCSO, G., AND KIRALY, E.: Regeneration of peptidergic sensory nerves in the rat skin. Acta Physiol. Acad. Sci. Hung. 63: 239-240, 1964.
JANCSO, G., KIRALY, E., AND JANCSO-GABOR, A.: Pharmacologically induced selective de
-
- JANCSÓ, G., KIRÁLY, E., AND JANCSÓ-GÁBOR, A.: Pharmacologically induced
selective degeneration of chemosensitive primary sensory neurones. Nature
270: 741-743, 1977.
JANCSÓ, G., KIRÁLY, E., AND JANCSÓ-GÁBOR, A.: Chemosensi JANCSO, G., KIRALY, E., AND JANCSO-GÁBOR, A.: Chemosensitive pain fibres
and inflammation. Int. J. Tissue React. 2: 57-66, 1980a.
JANCSO, G., KIRALY, E., AND JANCSO-GÁBOR, A.: Direct evidence for an axonal
site of action o
- by capsaicin of a subpopulation of primary sensory neurons in the adult rat.
site of action of capsaicin. Naunyn Schmiedebergs Arch. Pharmacol. 313: 91-
94, 1980b.
No. KIRÁLY, E., Joó, F., Such, G., AND NAGY, A.: Selective **JANCSO, G., KIRALY, E., JOO, F., SUCH, G., AND NAGY, A.: Selective degeneration**
by capsaicin of a subpopulation of primary sensory neurons in the adult rat.
Neurosci. Lett. 59: 209-214, 1985b.
JANGSO, G., KIRÁLY, E., SUC
-
- COLER, P., AND SAMETZ, W.: Gastric mucosal protection against ulcerogenic
factors in the rat mediated by capsaicin-sensitive afferent neurons. Gastroen-
following capsaicin in mammals. Acta Physiol. Hung. 69: 295-313, 1987 by capsaicin of a subpopulation of primary sensory neurons in the adult rat.
Neurosci. Lett. 59: 209-214, 1985b.
JANCSO, G., KIRÁLY, E., SUCH, G., JOO, F., AND NAGY, A.: Neurotoxic effect of
capsaicin in mammals. Acta Phys capsaicin in mammals. Acta Physiol. Hung. 69: 295-313, 1987a.
JANCSÓ, G., AND KNYIHÁR, E.: Functional linkage between nociception are fluoride-resistant acid phosphatase activity in the Rolando substance. Neuro biology 5:
	- fluoride-resistant acid phosphatase activity in the Rolando substance. Neuro-
biology 5: 42-43, 1975.
JANCSO, G., AND LAWSON, S. N.: Ganglionic changes associated with transgan-
glionic degeneration of capsaicin-sensitive sensory afferents: a quantitative morphometric and immunohistochemical study. Regul. Pept. 22: 97, 1988.
JANCSO, G., AND LAWSON, S. N.: Transganglionic degeneration of capsaicin-sensitive C-fiber primary afferent terminals
	- 1988.

	NC80, G., AND LAWSON, S. N.: Transganglionic degeneration of capasitive C-fiber primary afferent terminals. Neuroacience 39: 501-511, 1

	NC80, G., AND MAGGI, C. A.: Distribution of capasicin-sensitive uritude

	bladd
	-
- the capasicin-desensitized rat. Pflügers Arch. 389: 297-299, 1981.

HORI, T.: Capasicin and central control of thermoregulation. Pharmacol. Ther.

26: 389-416, 1984.

26: 389-416, 1984.

26: 389-416, 1984.

26: 389-416, 19 JANCSO, G., AND LAWSON, S. N.: Transganglionic degeneration of capsaicin-
sensitive C-fiber primary afferent terminals. Neuroscience 39: 501-511, 1990.
JANCSO, G., AND MAGGI, C. A.: Distribution of capsaicin-sensitive urin
	- JANCSO, G., AND MAGGI, C. A.: Distribution of capsaicin-sensitive urinary
bladder afferents in the rat spinal cord. Brain Res. 418: 371-376, 1987.
JANCSO, G., SAVAY, G., AND KIRÁLY, E.: Appearance of biochemically detectab ionic calcium in degenerating primary sensory neurons. Acta Histochem. 6
165-169, 1978.
JANCSO, G., AND SUCH, G.: Effects of capsaicin applied perineurally to the vag
nerve on cardiovascular and respiratory functions in th
	- NCSO, G., AND SUCH, G.: Effects of capsaicin applied perineurally to the value of the value of the value of the cat. J. Physiol. (Lot 341: 359–370, 1983.)
341: 359–370, 1983.
Anison of the cat. Naunyn Schmanian in the vent merve on cardiovascular and respiratory functio
341: 359-370, 1983.
NCSO, G., AND SUCH, G.: Evidence for a capacitie anism in the ventral mediulary chemosensitive
debergs Arch. Pharmacol. 329: 56-62, 1985.
NCSO, G., SUCH, 341: 359-370, 1983.
JANCSO, G., AND SUCH, G.: Evidence for a capaaicin-sensitive vasomotor mechanism in the ventral medullary chemosensitive area of the cat. Naunyn Schmis-
debergs Arch. Pharmacol. 329: 56-62, 1985.
JANCSO
	- NCSO, G., AND SUCH, G.: Evidence for a capaaicin-sensitive vasomotor mechanism in the ventral medullary chemosensitive area of the cat. Naunyn Schmie-
debergs Arch. Pharmacol. 329: 56-62, 1985.
RCSO, G., SUCH, G., AND RODE mism in the ventral medullary chemosensitive area of the cat. Naunyn Schmie-
debergs Arch. Pharmacol. 329: 56-62, 1985.
JANCSO, G., SUCH, G., AND RODEL, C.: A new approach to selective regional
analgesia. In Trends in Clus
	-
	- analgesia. In Trends in Cluster Headache, ed. by F. Sicuteri, L. Vecchiet, and
M. Fanciullacci, pp. 59–68, Elsevier, Amsterdam, 1987b.
JANCSÓ, N.: Role of the nerve terminals in the mechanism of inflammatory
reactions. Bul **FREE ASSESS THE INSTERNATION CONSUMING THE INCREDIBLE INCREDIBLE SET ALL DESCRIPTIONS ON A JANCSO, N., JANCSO-GABOR, A., AND SZOLCSANYI, J.: Direct evidence for neu-rogenic inflammation and its prevention by denervation a** ROGENIC IN: Desensitization with capsaicin and related acylamides as a tool for studying the function of pain receptors. In Pharmacology of Pain, ed. by R. K. S. Lim, pp. 33-55, Oxford, Pergamon Press, 1968.
NCS6, N., JANC
	-
	- S. Lim, pp. 33-55, Oxford, Pergamon Press, 1988.
JANCSÓ, N., JANCSÓ-GÁBOR, A., AND SZOLCSÁNYI, J.: Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment
with capsaicin. Br. J. Ph
	- vith capsaicin. Br. J. Pharmacol. 31: 138-151, 1967.
JANCSO, N., JANCSO-GÁBOR, A., AND SZOLCSÁNYI, J.: The role of sensory nerve
endings in neurogenic inflammation induced in human skin and in the eye and
paw of the rat. B
	- ration. Acts Physiol. (Load.) 206; 495-607, 1970.

	The stances Acts bital sleep produced by pungent agents in normal and capasicin-desensitized
rats. Acta Physiol. Acad. Sci. Hung. 55: 57-62, 1980.
JANCSÓ-GÁBOR, A., SZOLCSÁNYI, J., AND JANCSÓ, N.: Irreversible impairment
of thermoregulatio NCSO-GABOR, A., SZOLCSANYI, J., AND JANCSO, N.: Irreversible impairment
of thermoregulation induced by capasicin and similar pungent substances. J.
Physiol. (Lond.) 206: 495-507, 1970.
SSELL, T. M., IVERSEN, L. L., AND CUE
	-
	- of thermoregulation induced by capaaicin and similar pungent substances. J.
Physiol. (Lond.) 206: 495-507, 1970.
JESSELL, T. M., IVERSEN, L. L., AND CUELLO, A. C.: Capaaicin-induced depletion
of substance P from primary se JESSELL, T. M., IVERSEN, L. L., AND CUELLO, A. C.: Capsaicin-induced depletion of substance P from primary sensory neurones. Brain Res. 152: 183-188, 1978.
JHAMANDAS, K., YAKSH, T. L., HARTY, G., SZOLCSÁNYI, J., AND GO, V. Action of intrathecal capsaicin and its structural analogues on the content and
release of spinal substance P: selective action and relationship to analgesia.
Brain Res. 306: 215-225, 1984.
JIA, AN, AND NELSON, P. G.: Calc
	-

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

Downloaded from pharmrev aspetjournals org at Thammasart University on December 8, 2012

ARMACOLO

spet

 $\overline{\mathbb{O}}$

**JIN, J.-G., AND NAKAYAMA, S.: Bile salt potentiates the action of capsaicin on LA
JIN, J.-G., AND NAKAYAMA, S.: Bile salt potentiates the action of capsaicin on LA**
• **sensory neurones of guinea-pig ileum. Neurosci. Lett** 96
N, J.-G., AND NAKAYAMA, S.: Bile salt potentiates the action of capsaicir
sensory neurones of guinea-pig ileum. Neurosci. Lett. 109: 88–91, 1990.
N, J.-G., ТАКАКІ, M., AND NAKAYAMA, S.: Ruthenium red prevents capsai

- **JIN, J.-G., AND NAKAYAMA, S.: Bile salt potentiates the action of capsaicines**
 SERVIS TO SERVIS ENDING SERVIS CAPT SERVIS CAPT SERVIS CAPS
 JIN, J.-G., TAKAKI, M., AND NAKAYAMA, S.: Ruthenium red prevents capsainduced induced neurotoxic action on sensory fibers of the action of capsaicin on sensory neurones of guinea-pig ileum. Neurosci. Lett. 106: 88–91, 1990.
 N. J.-G., TAKAKI, M., AND NAKAYAMA, S.: Ruthenium red prevents capsaicin JIN, J.-G., TAKAKI, M., AND NAKAYAMA, S.: Ruthenium red prevents capsaicin-
JIN, J.-G., TAKAKI, M., AND NAKAYAMA, S.: Ruthenium red prevents capsaicin-
induced neurotoxic action on sensory fibers of the guinea pig ileum.
- JIN, J.-G., TAKAKI, M., AND NAKAYAMA, S.: Ruthenium red prevents capacicin-
induced neurotoxic action on sensory fibers of the guinea pig ileum. Neurosci.
Lett. 106: 152-156, 1989.
JIN, J.-G., TAKAKI, M., AND NAKAYAMA, S.:
- N. J.-G., TAKAKI, M., AND NAKAYAMA, S.: Inhibitory effect of capsaicin on the ascending pathway of the guinea-pig ileum and antagonism of this effect by ruthenium red. Eur. J. Pharmacol. 180: 13-19, 1990.

16, F., SZOLCSÁN
- IU, G., HOKFELT, J., AND JANCSO-GÁBOR, A.: Mitochondrial alterations in the spinal ganglion cells of the rat accompanying the long-lasting sensory disturbance induced by capaciteit. Life Sci. 8: 621-626, 1969.

JU, G., HOK neuroscient calcitonin generation colls of the relation calculation colls of the relation calculation. Letter
disturbance induced by capacicin. Life Sci. 8: 621-626, 1969.

, G., HOKFELT, T., FISCHER, J. A., FREY, P., REHF **310,** 1986. JU, G., HOKFELT, T., FISCHER, J. A., FREY, P., REHFELD, J. F., AND DOCKRAY, G. J.: Does cholecystokinin-like immunoreactivity in rat primary sensory neurons represent calcitonin gene-related peptide? Neurosci. Lett. 68: 30 39. J.: Does cholecystokinin-like immunoreactivity in rat primary sensory
neurons represent calcitonin gene-related peptide? Neurosci. Lett. 68: 305-
310, 1986.
A.H., LEMBECK, F., SEEWANN, S., AND HACK, U.: Nociceptor stim
- 110, 1986.

1310, 1986.

1390. H. A., LEMBECK, F., SEEWANN, S., AND HACK, U.: Nociceptor stimulation

139-143, 1980.

139-143, 1980.

143-143, 1980.

KAI-KAI, M. A., ANDERTON, B. H., AND KEEN, P.: A quantitative analysis o
- JAN, H., LEMBECK, F., SEEWANN, S., AND HACK, U.: Nociceptor stimulation
and PGE release by capsaicin. Naunyn Schmiedebergs Arch. Pharmacol. 312:
139–143, 1980.
AI-KAI, M. A., ANDERTON, B. H., AND KEEN, P.: A quantitative a AI-KAI, M. A
interrelation
arginine vas
resistant aci
486, 1986.
AMAKURA, K interrelationships between subpopulations of rat sensory neurons containing
arginine vasopressin or oxytocin and those containing substance P, fluoride-
resistant acid phosphatase or neurofilament protein. Neuroscience 18:
- KAMAKURA, K., ISHIURA, S., SUGITA, H., AND TOYOKURA, Y.: Identification of
Ca²⁺-activated neutral protease in the peripheral nerve and its effect on
neurofilament degeneration. J. Neurochem. 40: 908-913, 1983.
IXANURI, T
-
-
- ing splanchnic and cutaneous dorsal root ganglion neurons following
neonatal capeaicin treatment in the rat. Peptides 11: 491–496, 1990a.
neonatal capeaicin treatment in the rat. Peptides 11: 491–496, 1990a.
newspape. H., meonatal capeaicin treatment in the rat. Peptides 11: 491-496, 1990a.
 **KABHIBA, H., SENBA, E., UEDA, Y., AND TOHYAMA, M.: Calbindin D28k-contain-

ing splachnic and cutaneous dorsal root ganglion neurons of the rat. Brain**
- muscle. Circ. Res. 50: 133-139, 1982.
- muscle. Circ. Res. 50: 133-139, 1982.

KERN, P., TULLO, A. B., BLYTH, W. A., AND HILL, T. J.: Substance P in the

mouse cornea: effects of chemical and surgical denervation. Neurosci. Lett. 29:

231-235, 1982.

KENINS, P.: mouse cornea: effects of chemical and surgical denervation. Neurosci. Lett. 29:

231-235, 1982.
 KENINS, P.: Responses of single nerve fibres to capsaicin applied to the skin.

Neurosci. Lett. 29: 83-88, 1982.
 KENINS,
-
- Neurosci. Lett. 29: 83-88, 1982.
KENINS, P., HURLEY, J. V., AND BELL, C.: The role of substance P in the axon reflex in the rat. Br. J. Dermatol. 111: 551-559, 1984.
- KENINS, P.: Responses of single nerve fibres to capasicin applied to the skin.
Neurosci. Lett. 29: 83–88, 1982.
KENINS, P., HURLEY, J. V., AND BELL, C.: The role of substance P in the axon
reflex in the rat. Br. J. Dermato Neurosci. Lett. 29: 83-88, 1982.
RNINS, P., HURLEY, J. V., AND BELL, C.: The role of substance P in the axon
reflex in the rat. Br. J. Dermatol. 111: 551-559, 1984.
P., P., NEGULESCO, J. A., AND MURNANE, M.: Decreased tota refler in the rat. Br. J. Dermatol. 111: 551-559, 1984.

KI, P., NEGULESCO, J. A., AND MURNANE, M.: Decreased total serum, myocardial

KI, P., NEGULESCO, J. A., AND MURNANE, M.: Decreased total serum, myocardial

and aorti
-
- 10: 446-447, 1982.

10: 446-447, 1982.

RÁLY, E., JANCSÓ, G., AND HAJÓS, M.: Possible morphological correlates of

capsaciin desensitization. Brain Res. 540: 279-282, 1991.

IREN, M. L., GALE, T. F., AND MATTIO, T. G.: Eff capacicin desensitization. Brain Res. 540: 279-282, 1991.

KIRBY, M. L., GALE, T. F., AND MATTIO, T. G.: Effects of prenatal capacicin

treatment on fetal spontaneous activity, opiate receptor binding, and acid

phosphatas RBY, M. L., GALE, T. F., AND MATTIO, T. G.: Effects of prenatal captreatment on fetal spontaneous activity, opiate receptor binding, and phosphatase in the spinal cord. Exp. Neurol. 76: 298-308, 1982. DRCHGESNER, A. L., DO
-
- treatment on fetal spontaneous activity, opiate receptor binding, and acid
phosphatase in the spinal cord. Exp. Neurol. 76: 298-308, 1982.
KIRCHGESSNER, A. L., DODD, J., AND GERSHON, M. D.: Markers ahared between
dorsal ro KIRCHGESSNER, A. L., DODD, J., AND GERSHON, M. D.: Markers shared between dorsal root and enteric ganglia. J. Comp. Neurol. 276: 607-621, 1988.

KJARTANSSON, J., DALSGAARD, C. J., AND JONSSON, C. E.: Decreased survival of
-
- of experimental critical flaps in rats after sensory denervation with capsaicin.

Plast. Reconstr. Surg. 79: 218–221, 1987.

KNYAZEV, G. G., KNYAZEVA, G. B., AND NIKIFOROV, A. F.: Neuroparalytic

kerattist and capsaicin. A
- Keratitis and capasicin. Acta Physiol. Hung. 75: 29-34, 1990.
KONIETZNY, F., AND HENSEL, H.: The effect of capasicin on the response
characteristics of human C-polymodal nociceptors. J. Therm. Biol. 8: 213-215,
1983.
1983: KONIETZNY, F., AND HENSEL, H.: The effect of capacicin on the response
characteristics of human C-polymodal nociceptors. J. Therm. Biol. 8: 213-215,
1983.
KONNERTH, A., LUX, H. D., AND MORAD, M.: Proton-induced transformat KONNERTH, A., LUX, H. D., AND MORAD, M.: Proton-induced transformation of calcium channel in chick dorsal root ganglion cells. J. Physiol. (Lond.) 386: 603-633, 1987.
KOSTYUK, P. G.: Diversity of calcium ion channels in ce
-
- ensus of electrical excitation of electrical excitations of rates and the somewhere and the somewhere and the somewhere are the somewhere the somewhere the somewhere the somewhere $\frac{1}{\sqrt{2}}$ and $\frac{1}{\sqrt{2}}$ and $\frac{1}{\sqrt$ Neuroscience 28: 253-261, 1989.

KOSTYUK, P. G., FEDULOVA, S. A., AND VESELOVSKY, N. S.: Changes in ionic

mechanisms of electrical excitability of the somatic membrane of rat dorsal

inward current. Neurophysiology (Kiev) mechanisms of electrical excitability of the somatic membrane of rat dorsal
root ganglion neurons during ontogenesis. Distribution of ionic channels of
inward current. Neurophysiology (Kiev) 18: 813-820, 1986.
KRISHTAL,
-
- neward current. Neurophysiology (Kiev) 18: 813-820, 1986.
RESHTAL, O. A., AND PIDOPLICHKO, V. I.: A receptor for protons in the nerve
cell membrane. Neuroscience 5: 2325-2327, 1980.
neurons of trigeminal ganglia: possible Cell membrane. Neuroscience 5: 2325-2327, 1980.

KRISHTAL, O. A., AND PIDOPLICHKO, V. I.: A 'receptor' for protons in small

neurons of trigeminal ganglia: possible role in nociception. Neurosci. Lett. 24:

LADENHEIM, E. E
- RISHTAL, O. A., AND PIDOPLICHKO, V. 1.: A receptor for protons in small neurons of trigeminal ganglia: possible role in nociception. Neurosci. Lett. 24: 24: 24: DENHEIM, E. E., SPETH, R. C., AND RITTER, R. C.: Reduction of 243-246, 1961.

LADENHEIM, E. E., SPETH, R. C., AND RITTER, R. C.: Reduction of CCK-8

binding in the nucleus of the solitary tract of capsaicin-pretreated rats. Soc.

Neuronei. Abstr. 12: 828, 1986.

LADURON, P. M.: Axona **IDENHEIM, E. E., SPETH, R. C., AND RITT**
binding in the nucleus of the solitary tract
Neurosci. Abstr. 12: 828, 1986.
nourone, P. M.: Axonal transport of opiat.
nourones. Brain Res. 294: 157-160, 1984.
MOTTE, R. H., SIMON binding in the nucleus of the solitary tract of capsaicin pretreated rats. Soc.

LADURON, P. M.: Axonal transport of opiate receptors in capsaicin-sensitive

neurones. Brain Res. 294: 157-160, 1984.

LAMOTTE, R. H., SIMONE
-
- Neurosci. Abstr. 12: 828, 1986.

hDURON, P. M.: Axonal transport of opiate receptors in capsaicin-sensitive

neurones. Brain Res. 294: 157-160, 1984.

MOTTE, R. H., SIMONE, D. A., BAUMANN, T. K., SHAIN, C. N., AND ALREJA,

- **LANG, E., NOVAK, A., REEH, P. W., AND HANDWERKER, H.** 0.: Chemosensitivity of fine afferents from rat skin *in vitro.* J. Neurophysiol. 63: 887-901, 1990.
- ER

LANG, E., NOVAK, A., REEH, P. W., AND HANDWERKER, H. O.: Chemosensitivity

of fine afferents from rat skin in vitro. J. Neurophysiol. 63: 887–901, 1990.

LAWSON, S. N., AND HARPER, A. A.: A Neonatal capsaicin is not a of fine afferents from rat skin *in vitro*. J. Neurophysiol. 63: 887-901, 1990.
LAWSON, S. N., AND HARPER, A. A.: A Neonatal capsaicin is not a specific
neurotoxin for sensory C-fibres or small dark cells of rat dorsal ro pest, 1984. Chahl, J. Szolcsányi, and F. Lembeck, pp. 111-116, Akadémiai Kiadó, Buda-
- monoclonal antibody against neurofilament protein specifically labels a sub-
population of rat sensory neurones. J. Comp. Neurol. 228: 262-272, 1984.
LAWSON, S. N., AND NICKELS, S. M.: The use of morphometric techniques to **LAWSON, S. N., HARPER, A. A., GARSON, J. A., AND ANDERTON, B. H.: A monoclonal antibody against neurofilament protein specifically labels a sub-
population of rat sensory neurones. J. Comp. Neurol. 228: 262-272, 1984.
LAW**
- www. S. N., HARPER, A. A., GARSON, J. A., AND ANDERTON, B. H.: A monoclonal antibody against neurofilament protein specifically labels a sub-
population of rat sensory neurones. J. Comp. Neurol. 228: 262–272, 1984.
www. N. monoclonal antibody against neurofilament protein specifically labels a population of rat sensory neurones. J. Comp. Neurol. 228: 262-272, 1984. LAWSON, S. N., AND NICKELS, S. M.: The use of morphometric technique analyse SWESON, S. N., AND NICKELS, S. M.: The use of mornalyse the effects of neonatal capsaicin treatment of and dorsal roots. J. Physiol. (Lond.) 303: 12P, 1980.
and dorsal roots. J. Physiol. (Lond.) 303: 12P, 1980.
WWSON, T.,
-
- analyse the effects of neonatal capsaicin treatment on rat dorsal root ganglia
and dorsal roots. J. Physiol. (Lond.) 303: 12P, 1980.
LAWSON, T., AND GANNETT, P.: The mutagenicity of capsaicin and dihydrocap-
saich in V79 c and dorsal roots. J. Physiol. (Lond.) 303: 12P, 1980.
LAWSON, T., AND GANNETT, P.: The mutagenicity of capsaicin and dihydrocapsaicin in V79 cells. Cancer Lett. 48: 109-113, 1989.
LEMBECK, F.: A network of defense. In Subs W80N, T., AND GANNETT, P.: The musicin in V79 cells. Cancer Lett. 48: 10
saicin in V79 cells. Cancer Lett. 48: 10
MMBCK, F.: A network of defense. In S.
L. Henry, R. Coture, A. C. Could, G.
380–387, Springer, New York, 198 saicin in V79 cells. Cancer Lett. 48: 109-113, 1989.
LEMBECK, F.: A network of defense. In Substance P and Neurokinins, ed. by J.
L. Henry, R. Couture, A. C. Cuello, G. Pelletier, R. Quirion, and D. Regoli, pp.
380-387, Sp L. Henry, R. Couture, A. C. Cuello, G. Pelletier, R. Quirion, and D. Regoli, pp. 380–387, Springer, New York, 1987a.
LEMBECK, F.: Columbus, Capeicum and capsaicin: past, present and future. Acta Physiol. Hung. 69: 265–273,
- 380–387, Springer, New York, 1987a.
RMBECK, F.: Columbus, Capeicum and capsaicin: past, pr
Physiol. Hung. 69: 265–273, 1987b.
RMBECK, F.: The 1988 Ulf von Euler lecture. Substant
excitement. Acta Physiol. Scand. 133: 435–4
- Physiol. Hung. 69: 265-273, 1987b.
EMBECK, F.: The 1988 Ulf von Euler lecture. Substantine excitement. Acta Physiol. Scand. 133: 435-454, 1988.
- LEMBECK, F.: Columbus, Capsicum and capsaicin: past, present and future. Acta

Physiol. Hung. 69: 265-273, 1987b.

LEMBECK, F.: The 1988 Ulf von Euler lecture. Substance P: from extract to

excitement. Acta Physiol. Scand. FINSIOI. Hung. 09: 265-273, 19870.

EMBECK, F.: The 1988 Ulf von Euler lecture. Substance P: from extract to

excitement. Acta Physiol. Scand. 133: 435-454, 1988.

EMBECK, F., AND DONNERER, J.: Time course of capsaicin-ind
- excitement. Acta Physiol. Scand. 133: 435-454, 1988.
LEMBECK, F., AND DONNERER, J.: Time course of capsaicin-induced functional
impairments in comparison with changes in neuronal substance P content.
Naunyn Schmiedebergs A impairments in comparison with change
Naunyn Schmiedebergs Arch. Pharmaco
NABECK, F., AND HOLZER, P.: Substance F
Nasodilation and neurogenic plasma ex
Arch. Pharmacol. 310: 175-183, 1979.
SMBECK, F., AND SKOFITSCH, G.: Vi Naunyn Schmiedebergs Arch. Pharmacol. 316: 240–243, 1981.
LEMBECK, F., AND HOLZER, P.: Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn Schmiedebergs
Arch. Pharmacol
- EMBECK, F., AND HOLZER, P.: Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn Schmiedebergs Arch. Pharmacol. 310: 175-183, 1979.
EMBECK, F., AND SKOFITSCH, G.: Viscer Arch. Pharmacol. 310: 175-183, 1979.
LEMBECK, F., AND SKOFITSCH, G.: Visceral pain reflex after pretreatment with
capsaicin and morphine. Naunyn Schmiedebergs Arch. Pharmacol. 321: 116-
122, 1982.
LONGHURST, J. C., ASHTON,
- EMBECK, F., AND SKOFITSCH, G.: Visceral pain reflex after pretreatment with
capsaicin and morphine. Naunyn Schmiedebergs Arch. Pharmacol. 321: 116-
122, 1982.
NGHURST, J. C., ASHTON, J. H., AND IWAMOTO, G. A.: Cardiovascul LEMBECK, F., AND SKOFITSCH, G.: Visceral pain reflex after pretreatment with
capsaicin and morphine. Naunyn Schmiedebergs Arch. Pharmacol. 321: 116-
122, 1982.
LONGHURST, J. C., ASHTON, J. H., AND IWAMOTO, G. A.: Cardiovas 122, 1982.

LONGHURST, J. C., ASHTON, J. H., AND IWAMOTO, G. A.: Cardiovascular reflexes

resulting from capasicin-stimulated gastric receptors in anesthetized dogs. Circ.

Res. 46: 780–788, 1980.

LONGHURST, J. C., KAUFMA
- KAUFMAN, M. P., IWAMOTO, G. A., LONGHURST, J. C., AND MITCHELL, J. H.:

Effects of capasicin and bradykinin on afferent fibers with endings in skeletal

muscle. Circ. Res. 50: 133-139, 1982.

KERN, P., TULLO, A. B., BLYTHA
- LONGHURST, J. C., KAUFMAN, M. P., ORDWAY, G. A., AND MUSCH, T. I.: Effects of brackykinin and capsaicin on endings of afferent fibers from abdominal bisceral organs. Am. J. Physiol. 247: R552-R559, 1984.
LOREZ, H. P., HAEU of bradykinin and capasicin on endings of afferent fibers from abdominal visceral organs. Am. J. Physiol. 247: R552-R559, 1984.
DREZ, H. P., HAEUSLER, G., AND AEPPLI, L.: Substance P neurones in medullary baroreflex areas LOREZ, H. P., HAEUSLER, G., AND AEPPLI, L.: Substance P neurones in medullary baroreflex areas and baroreflex areas and baroreflex function of capsaicintreated rata. Comparison with other primary afferent systems. Neurosci
	-
	- treated rats. Comparison with other primary afferent systems. Neuroscience
8: 507-523, 1983.
LOU, Y. P., FRANCO-CERECEDA, A., AND LUNDBERG, J. M.: Omega-conotoxin
inhibits CGRP release and bronchoconstriction evoked by a l musical and calcitonin gene-related peptide
immunoreactivities in sensory nerves in relation to cardiovascular and bron-
choconstrictor effects of capasicin. Eur. J. Pharmacol. 108: 315–319, 1985.
INDEREG, J. M., AND SARIA
	- 251-253, 1983. LUNDBERG, J. M., AND SARIA, A.: Capsaicin induced desensitization of the airway

	LUNDBERG, J. M., AND SARIA, A.: Capsaicin induced desensitization of the airway

	mucosa to cigarette smoke, mechanical and chemical irritants mucosa to cigarette smoke, mechanical and chemical irritants. Nature 302:
251-253, 1983.
LUNDBERG, J. M., AND SARIA, A.: Polypeptide-containing neurons in airway
smooth muscle. Annu. Rev. Physiol. 49: 557-572, 1987.
LUNDBL
	-
	- 251–253, 1983.

	251–253, 1983.

	INDBERG, J. M., AND SARIA, A.: Polypeptide-containing neurons in airway

	smooth muscle. Annu. Rev. Physiol. 49: 557–572, 1987.

	elicited by activation of capsaicin-sensitive substance P-immu
	- smooth muscle. Annu. Rev. Physiol. 49: 557-572, 1987.
LUNDBLAD, L.: Protective reflexes and vascular effects in the nasal mucosa
elicited by activation of capacitin-sensitive substance P-immunoreactive tri-
geminal neurons LUNDBLAD, L., LUNDBERG, J. M., ANGGARD, A., AND ZETTERSTRÖM, D.: Capsaicin-sensitive nerves and the cutaneous allergy reaction in man. Possible involvement of sensory neuropeptides in the flare reaction. Allergy 42: 20–25,
	- involvement of sensory neuropeptides in the flare reaction. Allergy 42: 20-25, 1987.
UTHMAN, J., STROMBERG, I., BRODIN, E., AND JONSSON, G.: Capsaicin treatment to developing rats induces increase of noradrenaline levels i LUTHMAN, J., STROMBERG, I., BRODIN, E., AND JONSSON, G.: Capsaicin treatment to developing rats induces increase of noradrenaline levels in the iris without affecting the adrenergic terminal density. Int. J. Dev. Neurosci.
	- OSTYUK, P. G.: Diversity of calcium ion channels in cellular membranes. LYNN, B.: Effect of neonatal treatment with capsaicin on the numbers and
Neuroscience 28: 253–261, 1989.
OSTYUK, P. G., FEDULOVA, S. A., AND VESELOVSK properties of cutaneous afferent units from the hairy skin of the rat. Brain
		- LYNN, B.: Capsaicin: actions on nociceptive C-fibres and therapeutical potential.
Pain 41: 61-69, 1990.
LYNN, B., CARPENTER, S. E., AND PINI, A.: Capsaicin and cutaneous afferents.
		- INTER, B., Caparities of cutaneous afferent units from the hairy skin of the rat. Brain
Res. 322: 255-260, 1984.
LYNN, B.: Capsaicin: actions on nociceptive C-fibres and therapeutical potential.
Pain 41: 61-69, 1990.
The A LYNN, B.: Capsaicin: actions on nociceptive C-fibres and therapeutical potential.

		Pain 41: 61-69, 1990.

		LYNN, B., CARPENTER, S. E., AND PINI, A.: Capsaicin and cutaneous afferents.
 In Antidromic Vasodilatation and Neu In Antidromic Vasodilatation and Neurogenic Inflammation, ed. by L. A.
Chahl, J. Szolcsányi, and F. Lembeck, pp. 83–92, Akadémiai Kiadó, Budapest,
1984.
LYNN, B., AND PINI, A.: Long-term block of afferent C-fibres followin
		-
		- capsaicin: selectivity and *s* regenerate. The regenerate consisteners in the rat. J. Physiol. (Lond.) 362: 198, 1985.
 Institute and in the rat. J. Physiol. (Lond.) 362: 198, 1985.
 Institute is a properate. In Effects LYNN, B., AND PINI, A.: Long-term block of afferent C-fibres following capsaicin
treatment in the rat. J. Physiol. (Lond.) 362: 198, 1985.
LYNN, B., PINI, A., AND BARANOWSKI, R.: Injury of somatosensory afferents by
capsai
		-
		-

REVIEW

ARMACOLOGI

spet

 $\overline{\mathbb{O}}$

spet

 $\overline{\mathbb{O}}$

CAPSA
MAGGI, C. A.: Capsaicin-sensitive nerves in the gastrointestinal tract. Arch. Int.
Pharmacodyn. Ther. 303: 157–166, 1990. AGGI, C. A.: Capsaicin-sensitive nerves in the
Pharmacodyn. Ther. 303: 157–166, 1990.
AGGI, C. A.: Capsaicin and primary afferen CAPSAIC

MAGGI, C. A.: Capsaicin-sensitive nerves in the gastrointestinal tract. Arch. Int. M

MaGGI, C. A.: Capsaicin and primary afferent neurons: from basic science to MaGGI, C. A.: Capsaicin and primary afferent neuron

-
- Pharmacodyn. Ther. 303: 157-166, 1990.
AGGI, C. A.: Capsaicin and primary afferent neurons: from basic science to
human therapy? J. Auton. Nerv. Syst., in press, 1991.
AGGI, C. A., ASTOLFI, M., DONNERER, J., AND AMANN, R.: **MAGGI, C. A., ASTOLFI, M., DONNERER, J., AND AMANN, R.: Which mechanis account for the sensory neuron blocking action of capsaicin on primary affects ents in the rat urinary bladder? Neurosci. Lett. 110: 267-272, 1990a.
**
- **LISTA,** S., **MANzINI,** S., **THEODORSSON-NORHEIM,** E., **SOMMA,** V., **AMENTA,** account for the sensory neuron blocking action of capsaicin on primary afferents in the rat urinary bladder? Neurosci. Lett. 110: 267-272, 1990a.
MAGGI, C. A., BORSINI, F., SANTICIOLI, P., GEPPETTI, P., ABELLI, L., EVANGEL ents in the rat urinary biacider? Neurosci. Lett. 110: 267–272, 1990a.
AGGI, C. A., BORSINI, F., SANTICIOLI, P., GEPPETTI, P., ABELLI, L., EVANGE
LISTA, S., MANZINI, S., THEODORSSON-NORHEIM, E., SOMMA, V., AMENTA
F., BACCI LISTA, S., MANZINI, S., THEODORSSON-NORHEIM, E., SOMMA, V., AMENTA, F., BACCIARELLI, C., AND MELI, A.: Cutaneous lesions in capsaicin-pretreated rats. A trophic role of capasicin-sensitive afferents? Naunyn Schmiedebergs A
-
- F., BACCIARELLI, C., AND MELI, A.: Cutaneous lesions in capsaicin-pretreated
rats. A trophic role of capsaicin-sensitive afferents? Naunyn Schmiedebergs
Arch. Pharmacol. 336: 538-545, 1987a.
MAGGI, C. A., GIULIANI, S., AND mediated by activation of capsaicin-sensitive nerves of the rat urinary bladder.
Naunyn Schmiedebergs Arch. Pharmacol. 340: 541-546, 1989a.
MAGGI, C. A., GIULIANI, S., SANTICIOLI, P., ABELLI, L., GEPPETTI, P., SOMMA,
V., R AGGI, C. A.,
V., RENZI,
capsaicin on
P-like immu
555, 1987b.
AGGI, C. A., W., RENZI, D., AND MELI, A.: Species-related variations in the effects of capsaicin on urinary bladder functions: relation to bladder content of substance P-like immunoreactivity. Naunyn Schmiedebergs Arch. Pharmacol. 336: ¹, cancer on urinary bladder functions: relation to bladder content of substance
P-like immunoreactivity. Naunyn Schmiedebergs Arch. Pharmacol. 336: 546-555, 1987b.
AGGI, C. A., GIULIANI, S., SANTICIOLI, P., TRAMONTANA,
- P-like immunoreactivity. Naunyn Schmiedebergs Arch. Pharmacol. 336: 546-
MAGGI, 1987b.
MAGGI, C. A., GIULIANI, S., SANTICIOLI, P., TRAMONTANA, M., AND MELI, A.:
Effect of omega conotoxin on reflex responses mediated by act
- Effect of omega conotoxin on reflex responses mediated by activation of capsaicin-sensitive nerves of the rat urinary bladder and peptide release from AGGI, C. A., LIPPE, I. TH., GIULIANI, S., ABELLI, L., SOMMA, V., GEPPET the rat spinal cord. Neuroscience 34: 243-250, 1990b.
MAGGI, C. A., LIPPE, I. TH., GIULIANI, S., ABELLI, L., SOMMA, V., GEPPETTI,
P., JANCSÓ, G., SANTICIOLI, P., AND MELI, A.: Topical versus systemic cap-
saicin desensitiz
- relation of relationing perific and unspecific effects as indicated by modification of reflex micturition in rats. Neuroscience 31: 745-756, 1989b.
AGGI, C. A., MANZINI, S., GIULIANI, S., SANTICIOLI, S., AND MELI, A.: Extr AGGI, C. A., MANZINI, S., GIULIANI, S., SANTICIOLI, S., AND MELI, A.: E. origin of the capeaicin-sensitive innervation of rat duodenum: possible in
ment of calcitoning generative innervation of rat duodenum: possible in
me origin of the capacicin-sensitive innervation of rat duodenum: possible involvement of calcitonin gene-related peptide (CGRP) in the capacicin-induced
activation of intramural non-adrenergic non-cholinergic ('purinergic'?)
- rons. Naunyn Schmiedebergs Arch. Pharmacol. 334: 172-180, 1986.

MAGGI, C. A., AND MELI, A.: The role of neuropeptides in the regulation of the

micturition reflex. J. Auton. Pharmacol. 6: 133-162, 1986.

MAGGI, C. A., AND
-
-
- micturition reflex. J. Auton. Pharmacol. 6: 133-162, 1986.
MAGGI, C. A., AND MELI, A.: The sensory-efferent function of capsaicin-sensitive
sensory neurons. Gen. Pharmacol. 19: 1-43, 1988.
MAGGI, C. A., MELI, A., AND SANTI AGGI, C. A., MELI, A., AND SANTICIOLI, P.: Four motor effects of capsumea-pig distal colon. Br. J. Pharmacol. 90: 651-660, 1987c.
AGGI, C. A., PATACCHINI, R., GIULIANI, S., SANTICIOLI, P., AND M.
GGI, C. A., PATACCHINI, R. guinea-pig distal colon. Br. J. Pharmacol. 90: 651–660, 1987c.
MAGGI, C. A., PATACCHINI, R., GIULIANI, S., SANTICIOLI, P., AND MELI, A.:
Evidence for two independent modes of activation of the 'efferent' function of
capasi
- AGGI, C. A., PATACCHINI, R., GIULIANI, S., SANTICIOLI, P., AND MELI, A.: Evidence for two independent modes of activation of the 'efferent' function of capsaicin-sensitive nerves. Eur. J. Pharmacol. 156: 367-374, 1988a.
AG MAGGI, C. A., PATACCHINI, R., SANTICIOLI, P., GIULIANI, S., DEL BIANCO, E.,

GEPPETTI, P., AND MELI, A.: The efferent function of capsaicin-sensitive

vation. Eur. J. Pharmacel. 170: 167-177, 1880c.

MaGGI, C. A., PATACCHI
- nerves—ruthenium red discriminates between different mechanisms of activation. Eur. J. Pharmacol. 170: 167-177, 1989c.
MAGGI, C. A., PATACCHINI, R., SANTICIOLI, P., GIULIANI, S., GEPPETTI, P., AND
MELI, A.: Protective acti
- MAGGI, C. A., PATACCHINI, R., SANTICIOLI, P., GIULIANI, S., GEPPETTI, P., AND MATSUMIYA, T., SAWA, A., AND OKA, T.: The effect of capasicin on C-fiber reflex
MELI, A.: Protective action of ruthenium red toward capasicin de calcium channels, on motor responses produced by activation of eensely fibers. Neurosci. Lett. 88: 201-205, 1988b.
AGGI, C. A., PATACCHINI, R., SANTICIOLI, P., LIPPE, I. TH., GIULIANI, S., MGEPPETTI, P., DEL BIANCO, E., SE AGGI, C. A., PATACCHINI, R., SANTICIOLI, P., LIPPE, I. TH., GIULIANI, S., GEPPETTI, P., DEL BIANCO, E., SELLERI, S., AND MELI, A.: The effect of omege conotoxine GVIA, a poptide modulator of the N-type voltage sensitive ca **MAGGI, C. A., PATACCHINI, R., TRAMONTANA, M., AMANN, R., GIULIANI, S., AND SANTICIOLI, P.: Similarities and differences in the action of efferent and sensory nerves in mammalian smooth muscle. Naunyn Schmiedebergs Arch.
P**
- calcium channels, on motor responses produced by activation of efferent and sensory nerves in mammalian smooth muscle. Naunyn Schmiedebergs Arch. Pharmacol. 338: 107-113, 1988c.
LaGGI, C. A., PATACCHINI, R., TRAMONTANA, M. sensory nerves in mammalian smooth muscle. Naunyn Schmiedebergs Arch.

MAGGI, C. A., PATACCHINI, R., TRAMONTANA, M., AMANN, R., GIULIANI, S.,

AND SANTICIOLI, P.: Similarities and differences in the action of resiniferator NOUT OF THE SIMILATION AND BANTICIOLI, P.: Similarities and differences in the action of resiniferated and capasicin on central and peripheral endings of primary sensory neu
Neuroscience 37: 531-539, 1990c.
AGOI, C. A., SA
- and capsaicin on central and peripheral endings of primary sensory neurons.
Neuroscience 37: 531–539, 1990c.
AGGI, C. A., SANTICILI, P., DEL BIANCO, E., GEPPETTI, P., BARBANTI, G.,
TURINI, D., AND MELI, A.: Release of VIP-Neuroscience 37: 531-539, 1990c.

MAGGI, C. A., SANTICIOLI, P., DEL BIANCO, E., GEPPETTI, P., BARBANTI, G.,

TURINI, D., AND MELI, A.: Release of VIP- but not CGRP-like immunoreactivity by capasicin from the human isolated TURINI, D., AND MELI, A.: Release of VIP- but not CGRP-like immunoreactivity by capsaicin from the human isolated small intestine. Neurosci. Lett.
98: 317–320, 1989d.
MAGGI, C. A., SANTICIOLI, P., GEPPETTI, P., FURIO, M.
- stivity by capasicin from the human isolated small intestine. Neurosci. Lett.

98: 317–320, 1989d.

AGGI, C. A., SANTICIOLI, P., GEPPETTI, P., FURIO, M., FRILLI, S., CONTE, B.,

FANCIULLACCI, M., GIULANI, S., AND MELL, A.: AGGI, C. A., SANTICIOLI, P., GEPPETTI, P., FURIO, M., FRILLI, S., CONTE, B., FANCIULLACCI, M., GIULIANI, S., AND MELI, A.: The contribution of capsaicin-
sensitive innervation to activation of the spinal vesicovesical refl **MAGGI,** C. A., SANTICIOLI, P., GEPPETTI, P., GIULIANI, S., PATACCHINI, R., 1987, 1987, C. A., SANTICIOLI, P., GEPPETTI, P., GIULIANI, S., PATACCHINI, R., 1987, 1987, C. A., SANTICIOLI, P., GEPPETTI, P., GIULIANI, S., PATA
- **in the early phase of neurons.** Brain Res. 415: 1-
13, 1987d.
MAGGI, C. A., SANTICIOLI, P., GEPPETTI, P., GIULIANI, S., PATACCHINI, R., MCC
FRILLI, S., GRASSI, J., AND MELI, A.: Involvement of a peripheral site of action
 BRILLI, S., GRASSI, J., AND MELI, A.: Involvement of a peripheral site of action
in the early phase of neuropeptide depletion following capaaicin desensitization. foll
Brain Res. 436: 402-406, 1987e.
AGOI, C. A., SANTICC
- Free medium and nifedipine of substance P-like immunoreactivity and night has a 486: 402-406, 1987e.

AGGI, C. A., SANTICIOLI, P., GEPPETTI, P., PARLANI, M., ASTOLFI, M., DEL

BIANCO, E., PATACCHINI, R., GIULIANI, S., AND
- BIANCO, E., PATACCHINI, R., GIULIANI, S., AND MELI, A.: The errect of calcium
free medium and infedigine on the release of substance P-like immunoreactivity
and contractions induced by capsaicin in the isolated guinea pig Gen. Pharmacol. 20: 445-456, 1989e.

AGGI, C. A., SANTICIOLI, P., GEPPETTI, P., PARLANI, M., ASTO

DELLES, P., PATACCHINI, R., AND MELI, A.: The antagonian

ruthenium red of the actions of capasicino on the peripheral term MAGGI, C. A., SANTICIOLI, P., GEPPETTI, P., PARLANI, M., ASTOLFI, M., PRADELLES, P., PATACCHINI, R., AND MELI, A.: The antagonism induced by ruthenium red of the actions of capasicin on the peripheral terminals of sensory **DELLES, P., PATACCHINI, R., AND MELI, A.: The antagonism induced by** ruthenium red of the actions of capacicin on the peripheral terminals of sensory neurons: turther studies. Eur. J. Pharmacol. 154: 1-10, 1988d.
MAGGI, C
- AND MELI, A.: Calcium and capsaicin-induced substance P release from pe-
- 197
Maggi, C. A., Santicioli, P., and Meli, A.: The effects of capsaicin on rat
minary bladder motility in wivo. Eur. J. Pharmacol. 103: 41–50, 1984.
Maggi, C. A., Santicioli, P., Patacchini, R., Geppetti, P., Giuliani, S.
- **ASTOLFI,** M., **BALDI,** E., **PARLANI,** M., **THEODORSSON,** E., **FUSCO,** B., **AND** AGGI, C. A., SANTICIOLI, P., AND MELI, A.: The effects of capasicin on urinary bladder motility *in vivo.* Eur. J. Pharmacol. 103: 41-50, 1984.
AGGI, C. A., SANTICIOLI, P., PATACCHINI, R., GEPPETTI, P., GIULIANI,
ASTOLFI, urinary bladder: relative role. Eur. J. Frammacol. 103: 41-00, 1964.
AGGI, C. A., SANTICIOLI, P., PATACCHINI, R., GEPPETTI, P., GIULIANI, S.,
ASTOLIT, M., BALDI, E., PARLANI, M., THEODRESSON, E., FUSCO, B., AND
MELI, A.: R MAGGIO, M., BALDI, E., PARLANI, M., THEODORSSON, E., PUSCO, B., AND
MELI, A.: Regional differences in the motor response to capasicin in the guinea-
pig urinary bladder: relative role of pre- and postituctional factors rel MELI, A.: Regional differences in the motor response to capsaicin in the guinea-
pig urinary bladder: relative role of pre- and postjunctional factors related to
neuropeptide-containing sensory nerves. Neuroscience 27: 675
- pig urinary bladder: relative role of p
neuropeptide-containing sensory nerve
AGGIO, J. E., AND HUNTER, J. C.:
immunoreactivity in rat central and pe
cin. Brain Res. 307: 370-373, 1984.
ANZINI, S., MAGGI, C. A., GEPPETTI reuropeptide-containing sensory nerves. Neuroscience 27: 675-688, 1988f.
MAGGIO, J. E., AND HUNTER, J. C.: Regional distribution of kassinin-like
immunoreactivity in rat central and peripheral tissues and the effect of cap
- AGGIO, J. E., AND HUNTER, J. C.: Regional distribution or Kassimin-like
immunoreactivity in rat central and peripheral tissues and the effect of capsai-
cin. Brain Res. 307: 370-373, 1984.
ANZINI, S., MAGGI, C. A., GEPPETT
- cin. Brain Res. 307: 370-373, 1984.

MANZINI, S., MAGGI, C. A., GEPPETTI, P., AND BACCIARELLI, C.: Capsaicin

desensitization protects from antigen-induced bronchospasm in conscious

guinea-pigs. Eur. J. Pharmacol. 138: 30 guinea-pigs. Eur. J. Pharmacol. 138: 307-308, 1987.
MANZINI, S., TRAMONTANA, M., PAGE, C. P., AND PERRETTI, F.: Motor effects
of capsaicin-sensitive nerves in rabbit isolated bronchus. Eur. J. Pharmacol.
183: 1696, 1990.
M
- of capsaicin-sensitive nerves in rabbit isolated bronchus. Eur. J. Pharmacol.
183: 1696, 1990.
MAPP, C. E., CHITANO, P., FABBRI, L. M., PATACCHINI, R., AND MAGGI, C. A.:
Pharmacological modulation of the contractile respon
- Pharmacological modulation of the contractile response to toluene disocyanate
in the rat isolated urinary bladder. Br. J. Pharmacol. 100: 886-888, 1990.
MARABINI, S., CIABATTI, G., POLLI, G., FUSCO, B. M., GEPPETTI, P., MA ARABINI, S., CIABATTI, G., POLLI, G., FUSCO, B. M.,
A., FANCIULLACCI, M., AND SICUTERI, F.: Effect of
with capeaicin in vasomotor rhinits. Regul. Pept. 22
ARLEY, P., AND LIVETT, B. G.: Neuropeptides in the
CRC Crit. Rev. C
- MARLEY, P., AND LIVETT, B. G.: Neuropeptides in the autonomic nervous system.
- A., FANCIULLACCI, M., AND SICUTERI, F.: Effect of topical nasal treatment with capsaicin in vasomotor rhinitis. Regul. Pept. 22: 121, 1988.
MARLEY, P., AND LIVETT, B. G.: Neuropeptides in the autonomic nervous system.
CRC
-
- CRC Crit. Rev. Clin. Neurobiol. 1: 201-283, 1985.
MARLIER, L., RAJAOFETRA, N., POULAT, P., AND PRIVAT, A.: Modification of
escotonergic innervation of the rat spinal cord dorsal horn after neonatal
capacicin tractment. J. axons in vitro. Neuroscience 23: 275-290, 1987.

MARTIN, H. A., BASBAUM, A. I., KWIAT, G. C., GOETZL, E. J., AND LEVINE, J.

D.: Leukotriene and prostaglandin sensitization of cutaneous high threshold

C- and A-delta mecha D.: Leukotriene and prostaglandin sensitization of cutaneous high threshold C- and A-delta mechanonociceptors in the hairy skin of rat hindlimbs. Neuroscience 22: 651-659, 1987.
ARTLING, C.-R., AND LUNDBERG, J. M.: Capsaic
- C- and A-delta mechanonociceptors in the hairy akin of rat hindlimbs. Neuroscience 22: 651-659, 1987.
MARTLING, C.-R., AND LUNDBRRG, J. M.: Capasicin sensitive afferents contribute to acute airway edema following trachesio
- MARTLING, C.-R., AND LUNDBERG, J. M.: Capsaicin sensitive afferents contribute
to acute airway edema following trachesl instillation of hydrochloric acid or
gastric juice in the rat. Anesthesiology 68: 360-366, 1988.
MASON MASON, R. J., AND MARUNIAK, J. A.: Bahavioral and physiological effects of capsaicin in red-winged blackbirds. Pharmacol. Biochem. Behav. 19: 857-862, 1983.
MATRAN, R., ALVING, K., AND LUNDBERG, J. M.: Cigarette smoke, nic
-
- capsaicin in red-winged blackbirds. Pharmacol. Biochem. Behav. 19: 857-862, 1983.
MATRAN, R., ALVING, K., AND LUNDBERG, J. M.: Cigarette smoke, nicotine and capsaicin aerosol-induced vasodilatation in pig respiratory mucos capsaicin aerosol-induced vasodilatation in pig re
Pharmacol. 100: 535-541, 1990.
ATRAN, R., ALVING, K., MARTLING, C.-R., LACROIX.
Effects of neuropeptides and capsaicin on track
the pig. Acta Physiol. Scand. 135: 335-342, **MATRAN, R., ALVING, K., MARTLING, C.-R., LACROX, J. S., AND LUNDBERG, J.**
M.: Effects of neuropeptides and capsaicin on tracheobronchial blood flow of
the pig. Acta Physiol. Scand. 135: 335-342, 1989.
MarsuMIYA, T., SAWA,
- ATRAN, R., ALVING, K., MARTLING, C.-R., LACROIX, J. S., AND LUNDBERG, J.
M.: Effects of neuropeptides and capeaicin on tracheobronchial blood flow of
the pig. Acta Physiol. Scand. 135: 335-342, 1989.
ATSUMIYA, T., SAWA, A. M.: Effects of neuropeptides and capaaicin on tracheobronchial blood flow of
the pig. Acta Physiol. Scand. 135: 335-342, 1989.
MATSUMIYA, T., SAWA, A., AND OKA, T.: The effect of capaaicin on C-fiber reflex
and heat evoked
- **branches of sensory neurons innervate guinea-pig sympathetic neurons. Proc.**
- and heat evoked discharge in the acute spinal cat. Tokai J. Exp. Clin. Med. 8:
325-332, 1983.
MATTHEWS, M. R., AND CUELLO, A. C.: Substance P-immunoreactive peripheral
branches of sensory neurons innervate guinea-pig sympa ATUCCI-CERINIC, M., MARABINI, S., JANTSCH, S., CAGNONI, M., AND PARTSCH, G.: Effects of capsaicin on the metabolism of rheumatoid arthritis synoviccytes in vitro. Ann. Rheum. Dis. 49: 598-602, 1990.

attenuates multiple re
-
- **23: Effects of capsaicin on the metabolism of rheumatoid arthritis synoviccytes**
 in vitro. Ann. Rheum. Dis. 49: 598-602, 1990.

MCCANN, M. J., VERBALIS, J. G., AND STRICKER, E. M.: Capsaicin pretreatment

attenuates mu
- stemuates multiple responses to cholecystokinin in rats. J. Auton. Nerv. Syst.
23: 265-271, 1988.
MCCUSKER, M. T., CHUNG, K. F., ROBERTS, N. M., AND BARNES, P. J.: Effect
of topical capsaicin on the cutaneous responses to contrast of topical capacicin on the cutaneous responses to inflammatory mediators and to antigen in man. J. Allergy Clin. Immunol. 83: 1118-1123, 1989.
MCDOUGAL, D. B., YUAN, M. J. C., DARGAR, R. V., AND JOHNSON, E. M.: N Neonatal capsaicin and guanethidine and axonally transported organelle-specific enzymes in sciatic nerve and in sympathetic and dorsal root ganglia. J. Neurosci. 3: 124–132, 1983.
CDOUGAL, D. B., YUAN, M. J. C., AND JOHNSO
- cific enzymes in sciatic nerve and in sympathetic and dorsal root ganglia. J. Neurosci. 3: 124-132, 1983.
CDOUGAL, D. B., YUAN, M. J. C., AND JOHNSON, E. M.: Effect of capasicin
upon fluoride sensitive acid phosphatases in 63-70, 1985. MCDOUGAL, D. B., YUAN, M. J. C., AND JOHNSON, E. M.: Effect of capsaicin upon fluoride sensitive acid phosphatases in selected ganglia and spinal cord and upon neuronal size and number in dorsal root ganglion. Brain Res. 3
- upon fluoride sensitive acid phosphatases in selected ganglia and spinal cord
and upon neuronal size and number in dorsal root ganglion. Brain Ree. 331:
6GREGOR, G. P., AND CONLON, J. M.: Regulatory peptide and serotonin
c ers. Regul. Pept. 32: 109-119, 1991.

MCGREGOR, G. P., AND CONLON, J. M.: Regulatory peptide and serotonin

content and brush-border enzyme activity in the rat gastrointestinal tract

following neonatal treatment with capa content and brush-border enzyme activity in the rat gastrointestinal tract
following neonatal treatment with capasicin: lack of effect on epithelial mark-
ers. Regul. Pept. 32: 109-119, 1991.
MCMAHON, S., AND KOLTZENBURG,
-
-
- neurones in pain. Pain 43: 269-272, 1990.
McMAHON, S. B., WALL, P. D., GRANUM, S. L., AND WEBSTER, K. E.: The effect
of capacicin applied to peripheral nerves on responses of a group of lamina I
cells in adult rats. J. Com cells in adul

CNEILL, D.

E.: Denerva

peptide con

268, 1990.

ICEVYCH, P. MCNEILL, D. L., CARLTON, S. M., COGGESHALL, R. E., AND HULSEBOSCH, C.
E.: Denervation-induced intraspinal synaptogenesis of calcitonin gene-related
peptide containing primary afferent terminals. J. Comp. Neurol. 296: 263-

- peptide containing primary afferent terminals. J. Comp. Neurol. 296: 263-268, 1990.
MICEVVCH, P. E., YAKSH, T. L., AND SZOLCSÁNYI, J.: Effect of intrathecal capeacion analogues on the immunofluorescence of peptides and ser
- **MILLER,** M. S., **BRENDEL,** K., BURKS, T. F., **AND SIPES,** I. G.: Interaction of capsaicinoids with drug-metabolizing systems-relationship **to toxicity.** HO
MILLER, M. S., BRENDEL, K., BURKS, T. F., AND SIPES, I. G.: Interaction of
capsaicinoids with drug-metabolising systems—relationship to toxicity.
Biochem. Pharmacol. 32: 547-551, 1983.
MILLER, M. S., BUCK, S. H., SIPES,
- capasicinoids with drug-metabolizing systems—relationship to toxicity.
Biochem. Pharmacol. 32: 547-551, 1983.
MILLER, M. S., BUCK, S. H., SIPES, I. G., AND BURKS, T. F.: Capasicinoid-
induced local and systemic antinocicep
- MILLER, M. S., BUCK, S. H., SIPES, I. G., AND BURKS, T. F.: Capsaicinoid-
induced local and systemic antinociception without substance P depletion.
Brain Res. 254: 193-197, 1982a.
MILLER, M. S., BUCK, S. H., SHPES, I. G.,
- **MIXAUCHI,** M.S., BUCK, S. H., SIPES, I. G., YAMAMURA, H. I., AND BURKS, T. F.: Regulation of substance P by nerve growth factor: disruption by capaaicin.
Brain Res. 250: 193-196, 1982b.
MIXAUCHI, T., IsHIKAWA, T., SQISHIT **tropic effects of substance P** by nerve growth factor: diaruption by capaaicin.
 Brain Res. 250: 193-196, 1982b.
 piperine and development of cross-tachyphylaxis between

ment of calcitonin gene-related peptide in the Brain Res. 250: 193-196, 1982b.
MIYAUCHI, T., ISHIKAWA, T., SGISHITA, Y., SAITO, A., AND GOTO, K.: Involvement of calcitonin gene-related peptide in the positive chronotropic and inotropic effects of piperine and developme ment of calcitonin gene-related peptide in the positive chronotropic and inotropic effects of piperine and development of cross-tachyphylaxis between of piperine and capsaicin in the isolated rat atria. J. Pharmacol. Exp.
- **BIGKERS,** D. R.: Capsaicin in the isolated rat atria. J. Pharmacol. Exp. Ther. 248: p

BIG-824, 1969.

BIG-824, 1969.

DICKERS, D. As, M., DON, P. S. C., MARCELO, C. L., MUKHTAR, H., AND

DICKERS, D. R.: Capsaicin as an
- capsaicin. Rea. Commun. Chem. PathoL Pharmacol. 47: 453-456, 1985.
- **MOODY,** T. W., **THOA,** N. B., O'DONOHUE, T. L., **AND JACOBOWITZ,** D. M.: Bombesin-like peptides in rat spinal cord. biochemical characterization, local-MONSEREENUSORN, Y., AND KONGSAMUT, S.: Inhibition of calcium uptake by
capsaicin. Res. Commun. Chem. Pathol. Pharmacol. 47: 453-456, 1985.
MOODY, T. W., THOA, N. B., O'DONOHUE, T. L., AND JACOBOWITZ, D. M.:
combesin-like p
- responses of the rabbit **examples of the rabbit stimulation**, T. L., AND JACOBOWITZ, D. M.:
Bombesin-like peptides in rat spinal cord: biochemical characterization, localization, and mechanism of release. Life Sci. 29: 227 EXERISEN, M., PIERAU, F.-K., AND WEYRICH, M.: The influence of capsaicin on
MORTOKI, H., TAKASE, H., AND TANIOKA, A.: Dual effects of capsaicin on
152–156, 1990.
152–166, A.: Dual effects of capsaicin on
152–166, 1990.
152
- ORITOKI, H., TAKASE, H., AND TANIOKA, A.: Dual effects of capsaicin on
responses of the rabbit ear artery to field stimulation. Br. J. Pharmacol. 99:
152–156, 1980.
ORTON, C. R., AND CHAHL, L. A.: Pharmacology of the neuro **MORTON, C. R., AND CHAHL, L. A.: Pharmacology of the neurogenic oedema**
response to electrical stimulation of the saphenous nerve in the rat. Naunyn
Schmiedebergs Arch. Pharmacol. 314: 271-276, 1980.
MUELLER, G. P.: Beta-**MUNTENER, G. P.: Beta-endorphin immunoreactivity in rat plasma: variations in COMURALIDHARA, M.: Meta-endorphin immunoreactivity in rat plasma: variations in response to different physical stimuli. Life Sci. 29: 1669-1674**
-
-
- MUELLER, G. P.: Beta-endorphin immunoreactivity in rat plasma: variations in response to different physical stimuli. Life Sci. 29: 1669–1674, 1981.
MUNTENER, M.: Muscle fiber transformation in capsaicin-treated rats. Exp.

- MUNTENER, M.: Muscle fiber transformation in capsaicin-treated rats. Exp.
MURALIDHARA, N., AND NARASIMHAMURTHY, K.: Non-mutagenicity of capsaicin
MURALIDHARA, N., AND NARASIMHAMURTHY, K.: Non-mutagenicity of capsaicin
in a Neurol. 88: 205-214, 1985.

MURALIDHARA, N., AND NARASIMHAMURTHY, K.: Non-mutagenicity of capasicin

in albino mice. Food Chem. Toxicol. 26: 955-958, 1988.

MUSSAP, C. J., LEW, R., AND BURCHER, E.: The autoradiographic dis MUSSAP, C. J., LEW, R., AND BURCHER, E.: The autoradiographic distribution of substance P binding sites in guinea-pig vas deferens is altered by capsaicing retreatment. Eur. J. Pharmacol. 168: 337-345, 1989.
NAGABHUSHAN, M
-
- AGABHUSHAN, M., AND BHIDE, S. V.: Mutagenicity of chili ext
in short-term tests. Environ. Mutagen. 7: 881–888, 1985.
NGV, J. I.: Capsaicin: a chemical probe for sensory neuron. S.
Handbook of Psychopharmacology, ed. by L. in short-term tests. Environ. Mutagen. 7: 881-888, 1985.

NAGY, J. I.: Capsaicin: a chemical probe for sensory neuron mochanisms. In

H. Snyder, vol. 16, pp. 186-235, Plenum, New York, 1982.

H. Snyder, vol. 16, pp. 186-23
- and a containing problem and a containing problem of the research of Psychopharmacology, ed. by L. L. Iversen, S. D. Iversen, and H. Snyder, vol. 15, pp. 185-235, Plenum, New York, 1982.
AGY, J. I., AND DADDONA, P. E.: Ana Handbook of Psychopharma
H. Snyder, vol. 15, pp. 185–2
AGY, J. I., AND DADDONA, P.
acience 15: 799–813, 1985.
acience 15: 799–813, 1985.
AGY, J. I., EMSON, P. C., AN H. Snyder, vol. 15, pp. 185-235, Plenum, New York, 1982.
NAGY, J. I., AND DADDONA, P. E.: Anatomical and cytochemical relationships of
adenosine deaminase-containing primary afferent neurons in the rat. Neuro-
science 15:
- adenosine deaminase-containing primary afferent neurons in the rat. Neuro-
science 15: 799-613, 1985.
NAGY, J. I., EMSON, P. C., AND IVERSEN, L. L.: A re-evaluation of the neuro-
chemical and antinociceptive effects of in SCHER CHER STAND IN THE SCHER STATE IN SCHER SCHER IN THE SCHER SCHER PASS NAGY, J. I., **EMSON**, P. C., AND IVERSEN, L. L.: A re-evaluation of the neuro-

Res. 211: 497-502, 1981a.

NAGY, J. I., 4ND HUNT, S. P.: The termin
- EXAND TO THE DORSAL HORN: EVIDENCE FOR REARRAGED AND INCREDIBLE THE REAL BRAIN REAL BRAIN REAL BRAIN REAL BRAIN REAL BRAIN REARRANGLE THAT don't J. The Lemmination of primary afferents within the next dorsal horn: within c Res. 211: 497-502, 1981s.

Res. 211: 497-502, 1981s.

NAGY, J. I., AND HUNT, S. P.: The termination of primary afferents within the

rat dorsal horn: evidence for rearrangement following capsaicin treatment. J.

Comp. Neur
-
- Comp. Neurol. 218: 145-158, 1983.

NAGY, J. I., HUNT, S. P., IVERSEN, L. L., AND EMSON, P. C.: Biochemical and

anatomical observations on the degeneration of peptide-containing primary

afferent neurons after neonatal cap afferent neurons after neonatal capaaicin. Neuroscience 6: 1923-1934, 1981b.
AGY, J. I., IVERSEN, L. L., GOEDERT, M., CHAPMAN, D., AND HUNT, S. P.:
Dose-dependent effects of capaaicin on primary sensory neurons in the neon national capacitics. NAGY, J. I., **IVERSEN, L. L., GOEDERT, M., CHAPMAN, D., AND HUNT, S. P.:**

Doe-dependent effects of capacition on primary sensory neurons in the neonatal

rat. J. Neurosci. 3: 399-408, 1983.

NAGY, J.
-
- NAGY, J. I., AND VAN DER KOY, D.: Effects of neonatal capasicin treatment on rat. J. Neurosci. 3: 399-406, 1983.

NAGY, J. I., AND VAN DER KOY, D.: Effects of neonatal capasicin treatment on incorperive thresholds in the r neurons. Brain Res. 186: 435-444, 1980.

RGY, J. I., AND VAN DER KOY, D.: Effects and YAMANURA, H. I.; Neurons. 35-444, 1980.

AND YAMANURA, H. I.: Neurotoxic action

meurons. Brain Res. 186: 435-444, 1980.

EGULESCO, J. A NEGULESCO, J. A., YINCENT, S. R., STAINES, W. M. A., FIBIOER, H. C., REISINE, T. IAND YAMAMURA, H. I.: Neurotoxic action of capaaicin on spinal substance neurons. Brain Res. 186: 435-444, 1980.
NEGULESCO, J. A., YUNCENT, S
-
- **NIELSCH,** U., **AND KEEN,** P.: Effects of neonatal 6-hydroxydopamine administra-tion on different substance P-containing sensory neurones. Eur. J. Pharmacol. 138: 193-197, 1987. terol and triglycerides of lagomorphs. Artery 12: 301-311, 1983.

NIELSCH, U., AND KEEN, P.: Effects of neonnatal 6-hydroxydopamine administration on different substance P-containing sensory neurones. Eur. J. Pharmacol.

1
-
- ISB: 193-197, 1987.

NILSSON, G.: Modulation of the immune response in rat by utilizing the neuro-

toxin capacicin. Acta Universitatis Upsaliensis, Uppsala, 1989.

NORTHAM, W. J., AND JONES, D. J.: Comparison of capacicin DRTHAM, W. J., AND JONES, D. J.: Comparison of capsaicin and substance induced cyclic AMP accumulation in spinal cord tissue slices. Life Sci. 3
293-302, 1984.
5ÅI, F.: JANCSÓ. G., JANCSÓ-GÁBOR, A., AND OBÁL, F.: Vasodilat induced cyclic AMP accumulation in spinal cord tissue slices. Life Sci. 35:
293-302, 1984.
OBAL, F., JANCSÓ, G., JANCSÓ-GÁBOR, A., AND OBÁL, F.: Vasodilatation on
proportic heating in capasicin-treated rats. Experientia 39
-
- sensory fibers in rats treated at birth with capacities 3. Pays 1984.

SAL, F., JANCSÓ, G., JANCSÓ-GÁBOR, A., AND OBÁL, F.: Vasodilatation on

prooptic heating in capsaicin. Invest. Experientia 39: 221-223, 1983.

Discussi SAL, F., JANCSO, G., JAI
preoptic heating in capeainLVY, C. S., SILVERBERG
BILVY, C. S., SILVERBERG
Sci. 32: 112-121, 1991.
RDWAY, G. A., AND LONGI
- prooptic heating in capacicin-treated rats. Experientia 39: 221-223, 1983.
OGILVY, C. S., SILVERBERG, K. R., AND BORGES, L. F.: Sprouting of corneal
eensory fibers in rats treated at birth with capacicin. Invest. Ophthalmo
- study of the splanchnic innervation, J.C.: Cardiovascular reflexes arising from the gallbladder of the cat. Effects of capsaicin, bradykinin, and distension. Circ.
Res. 52: 26–35, 1983.
BORNE, P., AND CAMPBELL, G.: A pharm **gallbladder of the cat. Effects of capsaicin, bradykinin, and distension. Circ.**
Res. 52: 26-35, 1983.
OSBORNE, P., AND CAMPBELL, G.: A pharmacological and immunohistochemical
study of the splanchaic innervation of ileal
-

- ER
the neurotoxic action of capsaicin on primary sensory neurones. Nature 301:
515-517, 1983.
PALERMO, N. N., BROWN, H. K., AND SMITH, D. L.: Selective neurotoxic action
of capsaicin on glomerular C-type terminals in rat S the neurotoxic action of capaaicin on primary sensory neurones. Nature 301:
515-517, 1983.
PALERMO, N. N., BROWN, H. K., AND SMITH, D. L.: Selective neurotoxic action
of capsaicin on glomerular C-type terminals in rat SG.
- LERMO, N. N., BROWN, H. K., AND SMITH, D. L.: Selective neurotoxic action
of capeaicin on glomerular C-type terminals in rat SG. Brain Res. 207: 506-510, 1981.
NRERAI, A. E., MARTINI, A., LOCATELLI, V., AND MANTEGAZZA, P.: of capeaicin on glomerular C-type te
510, 1981.
1881. A. E., MARTINI, A., LOCATE
decreases b-endorphin hypothalami
Res. Commun. 15: 825-832, 1983.
PKA, R. E., FURNESS, J. B., DELL.
- PANERAI, A. E., MARTINI, A., LOCATELLI, V., AND MANTEGAZZA, P.: Capsaicin
decreases b-endorphin hypothalamic concentrations in the rat. Pharmacol.
Res. Commun. 15: 825-832, 1983.
PAPKA, R. E., FURNESS, J. B., DELLA, N. G., decreases b-endorphin hypothalamic concentrations in the rat. Pharmacol.
Res. Commun. 15: 825-832, 1983.
NPKA, R. E., FURNESS, J. B., DELLA, N. G., MURPHY, R., AND COSTA, M.:
Time course of effect of capacito on ultrastruc Res. Commun. 10: 826-832, 1983.

PAPKA, R. E., FURNESS, J. B., DELLA, N. G., MURPHY, R., AND COSTA, M.:

Time course of effect of capacicine and histochemistry of

substance P-immunoreactive nerves associated with the card
- substance P-immunoreactive nerves associated with the cardio of the guinea-pig. Neuroacience 12: 1277-1292, 1984.
TACCHINI, R., MAGGI, C. A., AND MELI, A.: Capaaicin-like anatural pungent substances on peripheral endings o
- 14: 413-416, 1989.

MODLY, C. B., DAS, M., DON, P. S. C., MARCELO, C. L., MUKHTAR, H., AND

BICKERS, D. R.: Capesicin as an in vitro inhibitor of benso(a)pyrene metabolism

BICKERS, D. R.: Capesicin as an in vitro inhibito of the guinea-pig. Neuroscience 12: 1277-1292, 1984.
PATACCHINI, R., MAGGI, C. A., AND MELI, A.: Capsaicin-like activity of some
natural pungent substances on peripheral endings of visceral primary afferents.
Naunyn Schmie Cadmium chloride induces contractions of the rat isolated urinary bladder by PATACCHINI, R., SANTICIOLI, P., GIULIANI, S., MAGGI, C. A., AND MELI, A.: Cadmium chloride induces contractions of the rat isolated urinary bladder by activation of capsaicin-sensitive sensory nerves. Eur. J. Pharmacol. 14
	- 452, 1988.
PERTOVAARA, A.: Collateral sprouting of nociceptive C-fibers after cut or capsaicin treatment of the sciatic nerve in adult rata. Neurosci. Lett. 90: 248–253,
1988.
PETERSEN, M., PIERAU, F.-K., AND WEYRICH, M.:
	- ERTOVAARA, A.: Collateral sprouting of nociceptive C-fibers after cut or capsaicin treatment of the sciatic nerve in adult rats. Neurosci. Lett. 90: 248–253, 1988.
PFRERSEN, M., PIERAU, F.-K., AND WEYRICH, M.: The influenc PETERSEN, M., PIERAU, F.-K., AND WEYRICH, M.: The influence of capsaicin on membrane currents in dorsal root ganglion neurones of guinea-pig and chicken.
Philgers Arch. 409: 403-410, 1987.
PETERSEN, M., WAGNER, G., AND PIE
	- membrane currents in dorsal root ganglion neurones of g
Pflügers Arch. 409: 403-410, 1987.
FTRESEN, M., WAGNER, G., AND PIERAU, F.-K.: Modulation
by capacicin in a subpopulation of sensory neurones of
Schmiedebergs Arch. P PHügers Arch. 409: 403-410, 1987.

	PETERSEN, M., WAGNER, G., AND PIERAU, F.-K.: Modulation of calcium-currents

	by capasicin in a subpopulation of sensory neurones of guinea pig. Naunyn

	Schmiedergs Arch. Pharmacol. 339: 1
	- **ETERSEN, M., WAGNER, G., AND PIERAU, F.-K.: Modulation of calcium-currents**
by capsaicin in a subpopulation of sensory neurones of guinea pig. Naunyn
Schmiedebergs Arch. Pharmacol. 339: 184–191, 1989.
strind, G., AND SZO Schmiedebergs Arch. Pharmacol. 339: 184-191, 1989.

	PETHO, G., AND SZOLCSÁNYI, J.: Systemically applied ruthenium red inhibits the

	stimulation of sensory receptors by capsaicin. Acta. Physiol. Hung. 75 (Suppl.):

	235-236,
	-
	- Schmiedebergs Arch. Pharmacol. 339: 184-191, 1989.

	PETHO, G., AND SZOLCSÁNYI, J.: Systemically applied ruthenium red inhibits the stimulation of eensory receptors by capaaicin. Acta. Physiol. Hung. 75 (Suppl.):

	235-236, functionally identified afferent nerve fibres. Brain Res. 265: 233-240, 1983.
PFEIFFER, C. J., AND EVANGELISTA, S.: Gastric and jejunal ultrastructure in capasicin-treated rats with and without experimental ulcer. In Senso
	- and Neuropeptides in Gastroenterology: From Basic Science to Clinical Perspectives, ed. by M. Costa, C. Surrenti, S. Gorini, C. A. Maggi, and A. Meli, in press, Plenum, London, 1991.
ERAU, F.-K., SANN, H., HARTI, G., AND G Press, Plenum, London, 1991.

	RRAU, F.-K., SANN, H., HARTI, G., AND GAM

	neurones of pigeons and the insensitivity of a

	fibres and pain, ed. by R. F. Schmidt, H.-G.

	213-223, VHC, Weinheim, Germany, 1987.

	RRAU, F.-K., AN **PIERAU, F.-K., SANN, H., HARTI, G., AND GAMSE, R.: Neuropeptides in sensory**
neurones of pigeons and the insensitivity of avians to capasicin. In Fine nerve
fibres and pain, ed. by R. F. Schmidt, H.-G. Schaible, and C. Va neurones of pigeons and the insensitivity of avians to capsaicin. In Fine nerve fibres and pain, ed. by R. F. Schmidt, H.-G. Schaible, and C. Vahle-Hinz, pp. 213-223, VHC, Weinheim, Germany, 1987.
PIERAU, F.-K., AND SZOLCS
	-
	- 213–223, VHC, Weinheim, Germany, 1987.

	PIERAU, F.-K., AND SZOLCSÁNYI, J.: Neurogenic inflammation: axon reflex in

	pigs. Agents Actions 26: 231–232, 1989.

	PINI, A.: Effects of capsaicin on conduction in a cutaneous nerve
	- **PIERAU, F.-K., AND SZOLCSANYI, J.: Neurogenic inflammation: axon reflex in pigs. Agents Actions 26: 231-232, 1989.

	PINI, A.: Effects of capsaicin on conduction in a cutaneous nerve of the rat. J. Physiol. (Lond.) 338: 60** PH, A.: Effects of capsaicin on conduction in
Physiol. (Lond.) 338: 60P-61P, 1983.
NI, A., BARANOWSKI, R., AND LYNN, B.: Lond.
Of C-fibre nociceptors following capsaicin treadult rats. Eur. J. Neurosci. 2: 89-97, 1990.
NHL **Physiol.** (Lond.) 338: 60P-61P, 1983.

	PINI, A., BARANOWSKI, R., AND LYNN, B.: Long-term reduction in the number

	of C-fibre nociceptors following capacicin treatment of a cutaneous nerve in

	adult rats. Eur. J. Jeuneoci.
	- TAQUET, BARANOWSKI, R., AND LYNN, B.: Long-term reduction in the number of C-fibre nociceptors following capsaicin treatment of a cutaneous nerve in adult rats. Eur. J. Neuroeci. 2: 89-97, 1990.
 PHAMON, M.: BENOLIEE, J. adult rats. Eur. J. Neurosci. 2: 89-97, 1990.

	Adult rats. Eur. J. Neurosci. 2: 89-97, 1990.

	TAQUET, H., CARAYON, A., BESSON, J. M., CESSELIN, F., AND HAMON, M

	Regional distribution of calcitonin gene-related peptide-lik PHL, M., BENOLIEL, J. J., BOURGOIN, S., LOMBARD, M. C., MAUBORGNE, A., TAQUET, H., CARAYON, A., BESSON, J. M., CESSELIN, F., AND HAMON, M.:
Regional distribution of calcitonin gene-related peptide-like, substance P-like,
c TAQUET, H., CARAYON, A., BESSON, J. M., CESSELIN, F., AND HAMON,
Regional distribution of calcitonin gene-related peptide-like, substance P-
cholecystokinin-like, Met¹-enkephalin-like, and dynorphin A (1–8)-like n
rais i Portugal distribution of calcitonin gene-related peptide-like, substance P-like, cholecystokinin-like, Met⁴-enkephalin-like, and dynorphin A (1-8)-like materials in the spinal cord and dorsal root ganglia of adult rats—e
	- cholecystokinin-like, Met⁻-enkephalin-like, and dynorphin A (1-8)-like mate-
rials in the spinal cord and dorsal root ganglia of adult rats—effects of dorsal
chicatomy and neonatal capsaicin. J. Neurochem. 55: 1122-1130,
	- PRIEST. J., AND JANCSO, N.: Studies on the action potentials of sensory nerves in animals desensitized with capsaicin. Acta Physiol. Acad. Sci. Hung. 16:
299-306, 1969.
ERESTLEY, J. V., BRAMWELL, S., BUTCHER, L. L., AND CU in animals desensitized with capsaicin. Acta Physiol. Acad. Sci. Hung. 16:
299-306, 1969.
PRIESTLEY, J. V., BRAMWELL, S., BUTCHER, L. L., AND CUELLO, A. C.: Effect
of capaaicin on neuropeptides in areas of termination of p 299-306, 1959.

	PRIESTLEY, J. V., BRAMWELL, S., BUTCHER, L. L., AND CUELLO, A. C.: Effect

	of capsaicin on neuropeptides in areas of termination of primary sensory

	neurons. Neurochem. Int. 4: 57-65, 1982.

	PRIOR, M., GREE
	-
	- of capacitin on neuropeptides in areas of termination of primary sensory
neurons. Neurochem. Int. 4: 57-65, 1982.
PRIOR, M., GREEN, F., LOPES, A., BALU, A., DE SANCTIS, G. T., AND FICK, G.:
Capacicin pretreatment modifies
	- in rats. Toxicol. Pathol. 18: 279–288, 1990.

	RABE, L. S., BUCK, S. H., MORENO, L., BURKS, T. F., AND DAFNY, N.: Neuro-

	physiological and thermoregulatory effects of capsaicin. Brain. Res. Bull. 5:

	755–758, 1980.

	RAY, N
	- T65-758, 1980.

	RAY, N. J., JONES, A. J., AND KEEN, P.: Ruthenium red: selective, reversible

	inhibition of capasicin-stimulated substance P release from primary afferent

	neurons in rat trachea. Br. J. Pharmacol. 99: 186P inhibition of capsaicin-stimulated substance P release from primary afferent neurons in rat traches. Br. J. Pharmacol. 99: 186P, 1990.
NYBOULD, H. E., EYSSELEIN, V. E., STERNINI, C., AND HOLZER, P.: Spinal
afferent neurons neurons in rat trachea. Br. J. Pharmacol. 99: 186P, 1990.
RAYBOULD, H. E., EvssELENN, V. E., Sminal
afferent neurons to the upper gastrointestinal tract: selective ablation by
perineural capasicin attenuates gastric mucosa
	- STIMULATION OF GASTRICHTS. THE GASTRICHT OF GASTRIC MONDING THE SECRETION OF GASTRICHTS CALL GASTRICHTS. GASTRICHTS. GASTRICHTS. EUR. J. Physiol. 255.
G242-G246, 1988. AND TACHE, Y.: Capsaicin-sensitive vagal afferent fibe
	- emptying via a capaaicin-senaitive vagal pathway in rats. Am. J. Physiol. 255:

	G242-G246, 1988.

	RAYBOULD, H. E., AND TACHÉ, Y.: Capaaicin-senaitive vagal afferent fibers and

	stimulation of gastric acid secretion in anes RAYBOULD, H. E., AND TACHÉ, Y.: Capsaicin-sensitive vagal afferent fibers and stimulation of gastric acid secretion in anesthetized rats. Eur. J. Pharmacol. 167: 237-243, 1989.
RAYNER, H. C., ATKINS, R. C., AND WESTERMAN,
	-
	- **RETHELYI,** M., **SALIM,** M. Z., **AND JANCSO,** G.: Altered distribution of dorsal root

REVIEW

ARMACOLOGI

spet

 $\overline{\mathbb{O}}$

- **CAPSAIC**

T61, 1986.

RIBEIRO-DA-SILVA, A., AND COIMBRA, A.: Capsaicin causes selective damage to

type I synaptic glomeruli in rat substantia gelatinosa. Brain Res. 290: 380-

383, 1984.
- 583, 1986.

RIBEIRO-DA-SILVA, A., AND COIMBRA, A.: Capsaicin causes selective damage to

tree I synaptic glomeruli in rat substantia gelatinosa. Brain Res. 290: 380-

383, 1984.

RITTER, S., AND DINH, T. T.: Capsaicin-indu type I synaptic glomeruli in rat substantia gelatinosa. Brain Res. 290: 380-383, 1984.

RITTER, S., AND DINH, T. T.: Capsaicin-induced neuronal degeneration: silver

impregnation of cell bodies, axons, and terminals in the FITER, S., AND DINH, T. T.: Capsaicin-induced neuronal degeneration: silver impregnation of cell bodies, axons, and terminals in the central nervous system of the adult rat. J. Comp. NeuroL. 29–90, 1988.
TTER, S., AND DINH **EXECUTE CONSUMEDIATE CONSUMPTED AND SET OF SIGNAL STATES,** S., AND DINH, T. T.: Capsaicin-induced neuronal degeneration in the central nervous system and retiring rate. J. Comp. Neurol. 271: 79-90, 1988.
 RITTER, S., AN
-
- of the adult rat. J. Comp. Neurol. 271: 79-90, 1988.

TTER, S., AND DINH, T. T.: Capsaicin-induced neuronal degeneration in the

brain and retina of preweanling rats. J. Comp. Neurol. 296: 447-461, 1990.

D. M.: Abolition RODRIGUEZ-SIERRA, J. E., SKOPTTSCH, G., KOMISARUK, B. R., AND JACOBOWITZ
D. M.: Abolition of vagino-cervical stimulation-induced analgesia by capsaicin
administration to neonatal, but not adult rats. Physiol. Behav. 44: 26 **ROSS,** 1988.

ROGERS, L. R.: Reactions of free-ranging black bears to capsaicin spray repellent.

ROGERS, L. R.: Reactions of free-ranging black bears to capsaicin spray repellent.

Wild. Soc. Bull. 12: 59-61, 1984.

ROGS
-
-
- 1988.

ROGERS, L. R.: Reactions of free-ranging black bears to capsaicin spray repellent.

Wildl. Soc. Bull. 12: 59-61, 1984.

ROSS, D. R., AND VARIPAPA, R. J.: Treatment of painful diabetic neuropathy

with topical capsai Wildl. Soc. Bull. 12: 59-61, 1984.

Wildl. Soc. Bull. 12: 59-61, 1984.

With topical capacition. N. Engl. J. Med. 321: 474-475, 1989.

with topical capacition and preference. Chem. Senses 6: 23-31, 1981.

In chili pepper
- ROSS, D. R., AND VARIPAPA, R. J.: Treatment of painful diabetic neuropathy with topical capsaicin. N. Engl. J. Med. 321: 474–475, 1989.

ROZIN, P., MARK, M., AND SCHILLER, D.: The role of desensitization to capsaicin

in c
- ROZIN, P., MARK, M., AND SCHILLER, D.: The role of desensitization to capsaicin
in chili pepper ingestion and preference. Chem. Senses 6: 23-31, 1981.
ROZSA, Z., AND JACOBSON, E. D.: Capsaicin-sensitive nerves are involved in chili pepper ingestion and preference. Chem. Senses 6: 23-31, 1981.
RÓZSA, Z., AND JACOBSON, E. D.: Capsaicin-sensitive nerves are involved in bile-
oleate induced intestinal hyperemia. Am. J. Physiol. 256: G476-G481, 1
- ROZSA, Z., AND JACOBSON, E. D.: Capsaicin-sensitive nerves are involved in bile-
cleate induced intestinal hyperemia. Am. J. Physiol. 256: G476-G481, 1989.
RUSSELL, L. C., AND BURCHIEL, K. J.: Neurophysiological effects of
- Brain Res. Rev. 8: 165-176, 1984.

SATTO, A., MASAKI, T., LEE, T. J.-F., AND GOTO, T.: Effects of capsaicin on the

contractility and peptide-containing nerves of large cerebral arteries of the cat.

SATTO, A., MASAKI, T., SALT, T. E., AND HILL, R. G.: The effect of microiontophoretically applied
SALT, T. E., AND HILL, R. G.: The effect of microiontophoretically applied
1982.
SALT, T. E., AND HILL, R. G.: The effect of microiontophoretically
- nucleus caudalis of the rat: evidence against a role for substance P as the neurotransmitter serving thermal nociception. Neuroscience 7: 1141-1148
1982.
LF, T. E., AND HILL, R. G.: The effect of microiontophoretically app **SALT, T. E., AND HILL, R. G.: The effect of microiontophoretically applied capsaicin and substance P on single neurones in the rat and cat brain. Neurosci.
Lett. 20: 329–334, 1980.
SALT, T. E., AND HILL, R. G.: Neurotrans** LT, T. E., AND HILL, R. G.: The effect of microiontophocapsaicin and substance P on single neurones in the rat and cately. T. E., AND HILL, R. G.: Neurotransmitter candidates of primary afferent fibres. Neuroscience 10: 10
-
- capsaicin and substance P on single neurones in the rat and cat brain. Neurosci.
Lett. 20: 329-334, 1980.
SALT, T. E., AND HILL, R. G.: Neurotransmitter candidates of somatosensory
primary afferent fibres. Neuroscience 10:
- Frimary afferent fibres. Neuroscience 10: 1083-1103, 1983.
SANN, H., HARTI, G., PIERAU, F.-K., AND SIMON, E.: Effect of capsaicin upon
afferent and efferent mechanisms of nociception and temperature regulation
in birds. Ca In birds. Can. J. Physiol. Pharmacol. 65: 1347-1354, 1987.

SANTICIOLI, P., MAGGI, C. A., AND MELI, A.: The effect of capsaicin pretreatment

on the cystometrograms of urethane anesthetized rats. J. Urol. 133: 700-703,

SA
- ron the cystometrograms of ureth
1985.
NATICOLI, P., PATACCHINI, R.,
calcium-free medium protects sea
rosci. Lett. 80: 167-172, 1987.
PORTA, S.: Loss of spinothalami
-
- of rats with the neurotoxin capsaicin. Somatosens. Res. 4: 153-173, 1986.
SARIA, A.: Substance P in sensory nerve fibres contributes to the development of oedena in the rat hind paw after thermal injury. Br. J. Pharmacol.
- and calcitonin gene-related peptide from rat spinal corders. Pharmacol. 82: 217-222, 1984.
RRIA, A., GAMSE, R., PETERMANN, J., FISCHER, J. A., THEODORSSON-NOR-REIA, A., GAMSE, R., PETERMANN, J., FISCHER, J. A., THEODORSSON **63: 310-314, 1986.**
 63. SARIA, A., GAMSE, R., PETERMANN, J., FISCHER, J. A., THEODORSSON-NOR-HEIM, E., AND LUNDBERG, J. M.: Simultaneous release of several tachykinins and calcitoning gene-related peptide from rat spina HEIM, E., AND LUNDBERG, J. M.: Simultaneous release of several tachykin and calcitonin gene-related peptide from rat spinal cord slices. Neurosci. L63: 310-314, 1986.
63: 310-314, 1986.
RRA, A., LUNDBERG, J. M., HUA, X.-Y.
- and calcitonin gene-related peptide from rat spin 63: 310–314, 1986.

RRIA, A., LUNDBERG, J. M., HUA, X.-Y., AND LE

substance Prelease and sensory control of vasculation

pig ureter. Neurosci. Lett. 41: 167–172, 1983a.

R
- SARIA, A., LUNDBERG, J. M., HUA, X.-Y., AND LEMBECK, F.: Capsaicin-induced substance P release and sensory control of vascular permeability in the guineer protein play ureter. Neverosci. Lett. 41: 167-172, 1983a.
Page in v substance P release and sensory control of vascular permeability in the guinea-
pig ureter. Neurosci. Lett. 41: 167-172, 1983a.
RRIA, A., LUNDBERG, J. M., SKOFITSCH, G., AND LEMBECK, F.: Vascular protein
leakage in various SARIA, A., LUNDBERG, J. M., SKOFITSCH, G., AND LEMBECK, F.: Vascular protein
leakage in various tissues induced by substance P, capsaicin, bradykinin,
serotonin, histamine and by antigen challenge. Naunyn Schmiedebergs Arc
- **Heakage** in various tissues induced by substance P, capsaicin, brady
serotonin, histamine and by antigen challenge. Naunyn Schmiedebergs
Pharmacol. 324: 212-218, 1983b.
RRIA, A., MARTLING, C.-R., YAN, Z., THEODORSSON-NORH **tive serotonin, histamine and by antigen challenge. Naunyn Schmiedebergs Archamacol. 324: 212-218, 1983b.**
Pharmacol. 324: 212-218, 1983b.
RRA, A., MARTLING, C.-R., YAN, Z., THEODORSSON-NORHEIM, E., GAMSE, RAD
LUNDBERG, J Pharmacol. 324: 212-218, 1983b.

RIA, A., MARTLING, C.-R., YAN, Z., THEODORSSON-NORHEIM, E., GAMSE, R., AND LUNDBERG, J. M.: Release of multiple tachykining from capsaicin-sensitive sensory nerves in the lung by bradykinin SARIA, A., MARTLING, C.-R., YAN, Z., THEODORSSON-NORHEIM, E., GAMSE, R., AND LUNDBERG, J. M.: Release of multiple tachykinins from capsaicin-sensitive sensory nerves in the lung by bradykinin, histamine, dimethylphenyl pip
- The sensory nerves in the lung by bradykinin, histamine, dimethylphenyl
piperazinium, and vagal nerve stimulation. Am. Rev. Respir. Dis. 137: 1330-
1335, 1988.
SARIA, A., SKOFTSCH, G., AND LEMBECK, F.: Distribution of caps SARIA, A., SKOFITSCH, G., AND LEMBECK, F.: Distribution of capsaicin in rattissues after systemic administration. J. Pharm. Pharmacol. 34: 273-275, 1982.
SARIA, A., AND WOLF, G.: Beneficial effect of topically applied caps utawise after systemic administration. J. Pharm. Pharmacol. 34: 273-1814, A., AND WOLF, G.: Beneficial effect of topically applied capasitive attention of hyperreactive rhinopathy. Regul. Pept. 22: 167, 1988. 1010. 1011. 1
-
- SARIA, A., AND WOLF, G.: Beneficial effect of topically applied capsaicin in the treatment of hyperreactive rhinopathy. Regul. Pept. 22: 167, 1988.
SAUMET, J.-L., AND DUCLAUX, R.: Analgesia induced by neonatal capsaicin tr UMET, J.-L
treatment ir
treatment ir
calmodulin-
585, 1990.
:ADDING, J. **SCADDING, G., PANCHANATHAN, S., AND SALIMATH, B. P.: Capsaicin inhibits**

SAVITHA, G., PANCHANATHAN, S., AND SALIMATH, B. P.: Capsaicin inhibits

calmodulin-mediated oxidative burst in rat macrophages. Cell. Signal. 2: 57 SAVITHA, G., PANCHANATHAN, S., AND SALIMATH, B. P.: Capsaicin inhibits calmodulin-mediated oxidative burst in rat macrophages. Cell. Signal. 2: 577-585, 1990.
SCADDING, J. W.: The permanent anatomical effects of neonatal c
-
-
- b36, 1990.

SCADDING, J. W.: The permanent anatomical effects of neonatal capsaicin on

somatosensory nerves. J. Anat. 131: 473-484, 1980.

SCHAIBLE, H.-G., AND SCHMIDT, R. F.: Time course of mechanosensitivity students

c changes in articular afferents during a developing arthritis. J. Neurophysiol.
60: 2180-2195, 1988.
SCHANNE, F. A. X., KANE, A. B., YOUNG, E. E., AND FARBER, J. L.: Calcium
dependence of toxic cell death: a final common pa 80: 2180-2195, 1988.

SCHANNE, F. A. X., KANE, A. B., YOUNG, E. E., AND FARBER, J. L.: Calcium

SCHANNE, F. A. X., KANE, A. B., YOUNG, E. E., AND FARBER, J. L.: Calcium

dependence 30: 515-520, 1989.

702, 1979.

702, 1979
-

IN
innervation of the stomach and pancreas. Demonstration of capsaicin-sensiti
sensory neurons in the rat by combined immunohistochemistry and retrogra Sensory neurons in the rat by combined immunohistochemistry and retrograde

sensory neurons in the rat by combined immunohistochemistry and retrograde

tracing. Gastroenterology 87: 914–921, 1984.

MRKEY, K. A., WILLIAMS, innervation of the stomach and pancreas. Demonstration of capasicin-sensitive
sensory neurons in the rat by combined immunohistochemistry and retrograde
tracing. Gastroenterology 87: 914–921, 1984.
SHARKEY, K. A., WILLIAMS

-
- tracing. Gastroenterology 87: 914–921, 1984.
SHARKEY, K. A., WILLIAMS, R. G., SCHULTZBERG, M., AND DOCKRAY, G. J.:
Sensory substance P innervation of the urinary bladder: possible site of action
of capsaicin in causing uri Sensory substance P innervation of the urinary bladder: possible site of actor of capasicin in causing urine retention in rats. Neuroscience 10: 861-868, 19
IMIZU, T., FUJITA, S., IZUMI, K., KOJA, T., OHBA, N., FUKUDA, T.:
- of capacicin in causing urine retention in rats. Neuroacience 10: 861-868, 1983.
SHIMIZU, T., FUJITA, S., IZUMI, K., KOJA, T., OHBA, N., FUKUDA, T.: Corneal
lesions induced by the systemic administration of capacicin in ne and rats. Naunyn Schmiedebergs Arch. Pharmacol. 326: 347-351, 1984.
SHIMIZU, T., IZUMI, K., FUJITA, S., KOJA, T., SORIMACHI, M., OHBA, N., AND FUKUDA, T.: Capsaicin-induced corneal lesions in mice and the effects of chemic
- FUKUDA, T.: Capasicin-induced corneal lesions in mice and the effects of chemical sympathectomy. J. Pharmacol. Exp. Ther. 243: 690–695, 1987.
10RTLAND, P., MOLANDER, C., WOOLF, C. J., AND FITZGERALD, M.: Neonatal experient chemical sympathectomy. J. Pharmacol. Exp. Ther. 243: 690-695, 1987.
SHORTLAND, P., MOLANDER, C., WOOLF, C. J., AND FITZGERALD, M.: Neonatal
capeaicin treatment induces invasion of the substantia gelatinosa by the
terminal capaaicin treatment induces invasion of the substantia gelatinosa by the
terminal arborizations of hair follicle afferents in the rat dorsal horn. J. Comp.
Neurol. 296: 23-31, 1990.
SICUTERI, F., AUGO, B. M., MARABINI, S., terminal arborizations of hair follicle afferents in the rat dorsal horn. J. Comp.
- **SICUTERI,** F., **FUSCO,** B. M., MARABINI, S., **CAMPAGNOLO,** V., **MAGGI,** C. A.,
- AND FISCHER, J. A.: Specific receptor and cardiovascular effects of calcitonin **CUTERI, F., FUSCO, B. M., MARABINI, S., CAMPAGNOLO, V., MAGGI, C. A., GEPPETTI, P., AND FANCIULLACCI, M.: Beneficial effect of capasicin application** to the nasal mucosa in cluster headache. Clin. J. Pain 5: 49-53, 1989.
 GEPPETTI, P., AND FANCIULLACCI, M.: Beneficial effect of capaaicin application
to the nasal mucosa in cluster headache. Clin. J. Pain 5: 49-53, 1989.
SIGRIST, S., FRANCO-CERECEDA, A., MUFF, R., HENKE, H., LUNDBERG, J. M.,
 GRIST, S., FRANCO-CERECEDA, A., MUFF, R., HENKE, H., LUNDBERG, J. M., AND FISCHER, J. A.: Specific receptor and cardiovascular effects of calcitonin gene-related peptide. Endocrinology 119: 381-389, 1986.
RRI, K. L., Hovre
- AND FISCHER, J. A.: Specific receptor and cardiovascular effects of calcitonin gene-related peptide. Endocrinology 119: 381-389, 1986.
SIKRI, K. L., HOYES, A. D., BARBER, P., AND JAGESSAR, H.: Substance P-like immunoreacci
- KRI, K. L., HOYES, A. D., BARBER, P., AND JAGESSAR, H.: Substance P-limmunoreactivity in the intramural nerve plexuses of the guinea-pig ureter light and electron microscopical study. J. Anat. 133: 425-442, 1981.
MONE, D. immunoreactivity in the intra
light and electron microacopic
MONE, D. A., BAUMANN, T. 1
and mechanical hyperalgesis
cin. Pain 38: 99-107, 1989.
MONE, D. A., NOEOW, J. Y. light and electron microscopical study. J. Anat. 133: 425-442, 1981.
SIMONE, D. A., BAUMANN, T. K., AND LAMOTTE, R. H.: Dose-dependent pain
and mechanical hyperalgesia in humans after intradermal injection of capsai-
cin. MONE, D. A., BAUMANN, T. K., AND LAMOTTE, R. H.: Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. Pain 38: 99-107, 1989.
cin. Pain 38: 99-107, 1989.
MONE, D. A., NOEOW, J. SIMONE, D. A., BAUMANN, T. K., AND LAMOTTE, R. H.: Does-dependent pain
and mechanical hyperalgesia in humans after intradermal injection of capaai-
cin. Pain 38: 99-107, 1989.
SIMONE, D. A., NGEOW, J. Y. F., PUTTERMAN, G.
- cin. Pain 38: 99-107, 1989.

SIMONE, D. A., NGEOW, J. Y. F., PUTTERMAN, G. J., AND LAMOTTE, R. H.:

Hyperalgesia to heat after intradermal injection of capeaicin. Brain Res. 418:

201-203, 1987.

SIMORE, E. A., AND PLACHET rat dorsal spinal cord after intradermal injection of capsaicin. Brain Res. 418:
Hyperalgesia to heat after intradermal injection of capsaicin. Brain Res. 418:
201-203, 1987.
RGER, E. A., AND PLACHETA, P.: Reduction of ³
- **SINGER, E. A., AND PLACHETA, P.: Reduction of ³H-muscimol binding sites in rat dorsal spinal cord after neonatal capsaicin treatment. Brain Ree. 202: 484-4871980.
SINGER, E. A., SPERK, G., AND SCHMID, R.: Capsaicin does**
- rat dorsal spinal cord after necessary, 1980.
187, 1980.
NGER, E. A., SPERK, G., AND
Jevels of glutamic acid, its up
them. 38: 1383-1386, 1982.
ZER, F., AND HARRIS, N.: The **SINGER, E. A., SPERK, G., AND SCHMID, R.: Capacicin does not change tis levels of glutanic acid, its uptake, or release in the rat spinal cord. J. Neu chem. 38: 1383-1386, 1982.
SINGER, F., AND HARRIS, N.: The influence o** NGRR, E. A., SPERK, G., AND SCHMID, R.: Capsaicin does not change tissue levels of glutamic acid, its uptake, or release in the rat spinal cord. J. Neuro-chem. 38: 1383-1386, 1982.
ZER, F., AND HARRIS, N.: The influence of
-
- levels of glutamic acid, its uptake, or release in the rat spinal cord. J. Neuro-
chem. 38: 1383-1386, 1982.
SIZER, F., AND HARRIS, N.: The influence of common food additives and temper-
ature on threshold perception of ca ature on threshold perception of capasicin. Chem. Senses 10: 279-286, 1985.
SKOFITSCH, G., DONNERER, J., PETRONLIEVIC, S., SARIA, A., AND LEMBECK, F.:
Release of historine by neuropeptides from the perfused rat hindquarter
- corrisch, G., DONNERER, J., PETRONIJEVIC, S., SARIA, A., AND LEMBECK, F.:
Release of histamine by neuropeptides from the perfused rat hindquarter.
Naunyn Schmiedebergs Arch. Pharmacol. 322: 153-157, 1983.
COTTSCH, G., AND Naunyn Schmiedebergs Arch. Pharmacol. 322: 153-157, 1983.
SKOFITSCH, G., AND JACOBOWITZ, D. M.: Galanin-like immunoreactivity in capsaicin-sensitive sensory neurons and ganglia. Brain Res. Bull. 15: 191-195, 1986a.
SKOFITS
- 1985a.
KOFITSCH, G., AND JACOBOWITZ, D. M.: Calcitonin gene-related peptide coexists
with substance P in capaaicin sensitive neurons and sensory ganglia of the rat.
Peptides 6: 747-754, 1985b.
KOFITSCH, G., ZAMIR, N., HELK
- on the cystometrograms of urethane anesthetized rate. J. Urol. 133: 700–703,

1846.

1846. Sammen Schwarzer (1., AND MELI, A.: Exposure to

1846.

1847. Sammen Schwarzer (1., AND MELI, A.: Exposure to

1847. Sammen and gan 1985a.
SKOFITSCH, G., AND JACOBOWITZ, D. M.: Calcitonin gene-related peptide coexists
with substance P in capsaicin sensitive neurons and sensory ganglia of the rat.
Peptides 6: 747–754, 1985b.
SKOFITSCH, G., ZAMIR, N., HE with substance P in capsaicin sensitive neurons and sensory ganglia of the rat.
Peptides 6: 747–754, 1985b.
KOFFISCH, G., ZAMIR, N., HELKE, C. J., SAVITT, J. M., AND JACOBOWITE, D.
M.: Corticotropin releasing factor-like i Peptides 6: 747-754, 1985b.
Peptides 6: 747-754, 1985b.
COFITSCH, G., ZAMIR, N., HELKE, C. J., SAVITT, J. M.
M.: Corticotropin releasing factor-like immunoreactive
with other neuropeptides. Peptides 6: 307-318, 1985.
DUKUP SKOPTTSCH, G., ZAMIR, N., HELKE, C. J., SAVITT, J. M., AND JACOBOWITZ, D.
M.: Corticotropin releasing factor-like immunoreactivity in sensory ganglia
and capsaicin sensitive neurons of the rat central nervous system: coloc M.: Corticotropin releasing factor-like immunoveactivity in sensory ganglia
and capsaicin sensitive neurons of the rat central nervous system: colocalization
with other neuropeptides. Peptides 6: 307-318, 1985.
DUKUP, T.,
	- with other neuropeptides. Peptides 6: 307-318, 1985.
SOUKUP, T., AND JANCSÓ, G.: Development of muscle stretch receptors in the
rat is not affected by neonatal capsaicin treatment. Acta Physiol. Hung. 69:
527-532, 1987.
SO DUKUP, T., AND JANCSO, G.: Development of muscle stretch receptors in the rat is not affected by neonatal capsaicin treatment. Acta Physiol. Hung. 69: 527–532, 1987.
527–532, 1987.
UUTH, E. H., AND RITTER, R. C.: Overconsu
	- 527-532, 1987.

	SOUTH, E. H., AND RITTER, R. C.: Overconsumption of preferred foods following

	capacitin pretreatment of the area postrema and adjacent nucleus of the solitary

	tract. Brain Res. 288: 243-251, 1983.

	SOUTH,
	-
	- tract. Brain Res. 288: 243-251, 1983.

	UUTH, E. H., AND RITTER, R. C.: Capsaicin application to central or peripheral

	vagal fibers attenuates CCK satiety. Peptides 9: 601-612, 1988.

	EXPLYWASAN, M. R., AND SATYANARAYANA, tract. Brain Res. 288: 243-251, 1983.
SOUTH, E. H., AND RITTER, R. C.: Capsaicin application to central or peripheral
vagal fibers attenuates CCK satiety. Peptides 9: 601-612, 1988.
SRINIVASAN, M. R., AND SATYANARAYANA, M. **STEIN, R. D., GENOVESI, S., DEMAREST, K. T., AND WEAVER, L. C.: Capsaicin on akeletal
SRINIVASAN, M. R., AND SATYANARAYANA, M. N.: Effect of capsaicin on akeletal
muscle lipoprotein lipase in rats fed high fat diet. India**
	- UNIVASAN, M. R., AND SATYANARAYANA, M. N.: Effect of capsaicin on skeletal muscle lipoprotein lipsse in rats fed high fat diet. Indian J. Exp. Biol. 27: 910–912, 1989.
912, 1989.
1989. D., GENOVESI, S., DEMAREST, K. T., AN chemical stimulation of intestinal afferent nerves. Brain Res. 397: 310-312, 1989.
STEIN, R. D., GENOVESI, S., DEMAREST, K. T., AND WEAVER, L. C.: Capsaicin
treatment attenuates the reflex excitation of sympathetic activit
	- chemical stimulation of intestinal afferent nerves. Brain Res. 397: 145-151,
1986.
STJARNE, P., LUNDBLAD, L., LUNDBERG, J. M., AND ANGGARD, A.: Capsaicin
and nicotine-sensitive afferent neurones and nasal secretion in heal volunted stimulation of intestinal afferent nerves. Brain Res. 397: 145-151,
1986.
STJÄRNE, P., LUNDBLAD, L., LUNDBRRG, J. M., AND ANGGARD, A.: Capsaicin
and nicotine-sensitive afferent neurones and nasal secretion in heal of and nicotine-sensitive afferent neurones and nasal secretion in healthy human
volunteers and in patients with vasomotor rhinitis. Br. J. Pharmacol. 96: 693-701, 1989.
TERNIN, C., REEVE, J. R., AND BRECHA, N.: Distributi
	- of calcitonin gene-related peptide immunore activity in the digestive system of normal and capsaicin-treated rats. Gastroenterology 93: 852-862, 1987.
Su, H. C., BISHOP, A. E., POWER, R. F., HAMADA, Y., AND POLAK, J. M.: D 701, 1989.

	TERNINI, C., REEVE, J. R., AND BRECHA, N.: Distribution and characterization

	of calcitonin gene-related peptide immunoreactivity in the digestive system of

	normal and capacicin-treated rats. Gastroenterology
	- normal and capaaicin-treated rats. Gastroenterology 93: 852-862, 1987.
Su, H. C., BisHoP, A. E., Power, R. F., HAMADA, Y., AND POLAK, J. M.: Dual
intrinsic and extrinsic origins of CGRP- and NPY-immunoreactive nerves of
ra
	- rat gut and pancreas. J. Neurosci. 7: 2674–2687, 1987.
UCH, G., AND JANCSÓ, G.: Axonal effects of capsaicin:
study. Acta Physiol. Hung. 67: 53–63, 1986.
	- SZALLASI, A., AND BLUMBERG, P. M.: Resiniferatoxin, a phorbol-related diter-
	- EALLASI, A., AND BLUMBERG, P. M.: Resiniferatorin, a phorbol-related diterpene, acts as an ultrapotent analog of capsaicin, the irritant constituent in red pepper. Neuroacience 30: 515-520, 1989.
KALLASI, A., AND BLUMBERG, pene, acts as an ultrapotent ail pepper. Neuroscience 30: 515
AALLASI, A., AND BLUMBERG,
ultrapotent capasicin analog,
ultrapotent capasicin analog,
524: 106-111, 1990a.

spet

 \mathbb{O}

REV

- LALLASI, A., AND BLUMBERG, P. M.: Resiniferatorin and its analogs prover locities into the pharmacology of the vanilloid (capsaicin) receptor.
Sci. 47: 1399-1406, 1990b.
LALLASI, A., Joo, F., AND BLUMBERG, P. M.: Duration Sci. 47: 1399-1408, 1990b.

SEALLASI, A., Joo, F., AND BLUMBERG, P. M.: Duration of desensitization and

ultrastructural changes in dorsal root ganglia in rate treated with resinifera-

toxin, an ultrapotent capsaicin anal
-
- local glucose utilization in the rat. Neuroscience 25: 917-923, 1989.

SZALLASI, A., SZALLASI, Z., AND BLUMBERG, P. M.: Permanent effects of neonately administered resiniferatorin in the rat. Brain Res. 537: 182–186, 1990. natally administered resiniferatorin in the rat. Brain Res. 537: 182-186, 1990.
SEIKSZAY, M., AND LONDON, E. D.: Effects of subacute capsaicin treatment on
local cerebral glucose utilization in the rat. Neuroscience 25: 91 **SZIKSZAY, M., OBAL, F., AND OBAL, F.: Dose-response relationships in the thermoregulatory effects of capsaicin. Naunyn Schmiedebergs Arch. Pharmacological approach to elucidation of the role of different col. 330: S7-100,**
- thermoregulatory effects of capsaicin. Naunyn Schmiedebergs Arch. Pharmacol. 320: 97-100, 1982.
SZOLCSANYI, J.: A pharmacological approach to elucidation of the role of different nerve fibres and receptor endings in mediat colorsAny, J.: A pharmacological approach to elucidation of the role of different nerve fibres and receptor endings in mediation of pain. J. Physiol. (Paris) 73: 251-259, 1977.
261-259, 1977.
colorsAny, J.: Capasicin type
- 251–259, 1977.

SzoLcsANYI, J.: Capasicin type pungent agents producing pyrexia. In Pyretics

and Antipyretics, Handbook of Experimental Pharmacology, ed. by A. S.

Milton, vol. 60, pp. 437–478, Springer, Berlin, 1982.

Sz SZOLCSANYI, J.: Capsaicin type pungent agents producing pyrexia. In Pyretics
and Antipyretics, Handbook of Experimental Pharmacology, ed. by A. S.
Milton, vol. 60, pp. 437–478, Springer, Berlin, 1982.
SZOLCSANYI, J.: Distu
-
- Milton, vol. 60, pp. 437–478, Springer, Berlin, 1982.
COLCSÁNYI, J.: Disturbances of thermoregulation induced by capsaicin. J.
Therm. Biol. 8: 207–212, 1983a.
COLCSÁNYI, J.: Tetrodotoxin-resistant non-cholinergic neurogeni COLCSANYI, J.: District Colcs
Therm. Biol. 8: 207
COLCSANYI, J.: Tetrevoked by capaaicin
42: 83–88, 1983b.
COLCSANYI, J.: Capa
- Therm. Biol. 8: 207-212, 1983a.

SzoLcSANYI, J.: Tetrodotoxin-resistant non-cholinergic neurogenic contraction

evoked by capsaicinoids and piperine on the guinea-pig trachea. Neurosci. Lett.

42: 83-201CSANYI, J.: Capsaic evoked by capsaicinoids and piperine on the guinea-pig trachea. Neurosci. Lett.
42: 83-88, 1983b.
Szolcsányi, J.: Capsaicin and neurogenic inflammation: history and early find-
ings. In Antidromic Vasodilatation and Neurog SzoLcsánvi, J.: Capsaicin-and neurogenic inflammation: history and early findings. In Antidromic Vasodilatation and Neurogenic Inflammation, ed. by L. A. Chahl, J. Szolcsányi, and F. Lembeck, pp. 7-25, Akadémiai Kiadó, Bud
- inga. *In* Antidromic Vasodilatation and Neurogenic Inflammation, ed. by L. A.

Chahl, J. Szolcsányi, and F. Lembeck, pp. 7–25, Akadémiai Kiadó, Budapest,

1984a.

1984a.

1994 A. Chahl, J. Szolcsányi, and F. Lembeck, pp 1984a.
1984a.
10LCSÁNYI, J.: Capsaicin-1
2007-efferent function. In mation, ed. by L. A. Chahl,
Kiadó, Budapest, 1984b.
20LCSÁNYI, J.: Sensory resp. SEOLCSANYI, J.: Capaaicin-sensitive chemoceptive neural system with dual sensory-efferent function. In Antidromic Vasodilatation and Neurogenic Inflammation, ed. by L. A. Chahl, J. Szolcsányi, and F. Lembeck, pp. 27-52, A
-
- exaction, all Sensory receptors and the antinociceptive effects of capsaicin.

In Tachykinin Antagonists, ed. by R. Hakanson and F. Sundler, pp. 45–54,
 Elsevier, Amsterdam, 1985.
 ear to capsaicin, bradykinin and ultra *In* Tachykinin Ant
Elsevier, Amsterda
Elsevier, Amsterda
colcsányr, J.: Sele
888: 9–23, 1987.
colcsányr, J.: Antie Elsevier, Amsterdam, 1985.

SZOLCSÁNYI, J.: Selective responsiveness of polymodal nociceptors of the rabbit

ear to capeaicin, bradykinin and ultra-violet irradiation. J. Physiol. (Lond.)

888: 9–23, 1987.

SZOLCSÁNYI, J.: **Actions 23: 4-11, 1988.** SzolcsANYI, J.: Capsaicin, bradykinin and ultra-violet irradiation. J. Physiol. (Lone 388: 9-23, 1987.
 Actions 23: 4-11, 1988.
 Actions 23: 4-11, 1988.

SzOLC8ÁNYI, J.: Capsaicin, irritation,
-
- 888: 9-23, 1987.
COLCSÁNYI, J.: Antidromic vasodilatation and neurogenic inflammation. Agents
Actions 23: 4-11, 1988.
COLCSÁNYI, J.: Capsaicin, irritation, and desensitization. Neurophysiological
Dasis and future perspecti GLCSANYI, J.: Antidromic vasodilatation and neurogenic inflammation. Agents Schemens 23: 4-11, 1988.
Actions 23: 4-11, 1988.
COLCSANYI, J.: Capeaicin, irritation, and desensitization. Neurophysiological transportations and Actions 23: 4–11, 1988.
Actions 23: 4–11, 1988.
basis and future perspected
Green, J. R. Mason, and
York and Basel, 1990.
OLCSÁNYI, J., ANTON, 1
- York and Basel, 1990.
SzoLCSÁNYI, J., ANTON, F., REEH, P. W., AND HANDWERKER, H. O.: Selective
excitation by capsaicin of mechano-heat sensitive nociceptors in rat skin. Brain
Res. 446: 262-268, 1988. **chano-heat skinner by capsaic and M. R. Kare, vol. 2, pp. 141–168, Marcel Dekker, New United Basel, 1990.**
 Excitation by capsaicin of mechano-heat sensitive nociceptors in rat skin. Brain

Res. 446: 262–268, 1988.
 Re York and Basel, 1990.

SZOLCSÁNYI, J., ANTON, F., REEH, P. W., AND HANDWERKER, H. O.: Selective

excitation by capasicin of mechano-heat sensitive nociceptors in rat skin. Brain

Res. 446: 262-268, 1988.

SZOLCSÁNYI, J., A
-
- colors ANY J., AND BARTHÓ, L.: New type of nerve-mediated cholinergic
contractions of the guinea-pig small intestine and its selective blockade by
capacicin. Naunyn Schmiedebergs Arch. Pharmacol. 305: 83-90, 1978.
colors A
- SZOLCSANYI, J., AND BARTHO, L.: Impaired detense mechanism to peptic ulcer
in the capsaicin-desensitized rat. In Gastrointestinal Defense Mechanisms, ed.
by G. Mózsik, O. Hänninen, and T. Jávor, Akadémiai Kiadó, Budapest, by G. Móssik, O. Hár
vol. 15, pp. 39–51, Pe
colcsányr, J., and B.
innervation of the gu
34: 247–252, 1982.
colcsányr, J., Barre vol. 15, pp. 39-51, Pergamon Press, Oxford; Akadémiai Kiadó, Budapest, 1981.
SZOLCSÁNYI, J., AND BARTHÓ, L.: Capsaicin-sensitive non-cholinergic excitatory
innervation of the guinea-pig tracheobronchial smooth muscle. Neur
- sameronic and the guines-pig tracheobronchial smooth muscle. Neurosci. Lett.
34: 247-252, 1982.
SzoLcSÁNVI, J., BARTHÓ, L., AND PETHÓ, G.: Capsaicin-sensitive bronchopul-
monary receptors with dual sensory-effects of capsa
- COLCSÁNYI, J., BARTHÓ, L., AND PETHÒ, G.: Capsaicin-sensitive bronchopulmonary receptors with dual sensory-efferent function: mode of action of capsaicin antagonists. Acta Physiol. Hung., in press, 1991.
COLCSÁNYI, J., AND SZOLCSÁNYI, J., BARTHÓ, L., AND PETHÓ, G.: Capsaicin-sensitive bronchopulmonary receptors with dual sensory-efferent function: mode of action of capsaicin antagonists. Acta Physiol. Hung., in press, 1991.

SZOLCSÁNYI, J., saicin antagonists. Acta Physiol. Hung., in press, 1991.

SzoLcSÁNYI, J., AND JANCSO-GÁBOR, A.: Sensory effects of capsaicin congeners.

I. Relationship between chemical structure and pain-producing potency of

pungent age
- L. Relationship between chemical structure and pain-
pungent agents. Drug Res. 25: 1877–1881, 1975.
COLCSÁNYI, J., AND JANCSÓ-GÁBOR, A.: Sensory effects of
II. Importance of chemical structure and pungency in de-
capsaicin
- SzoLcsANVI, J., JANCSO-GABOR, A., AND JOO, F.: Functional and fine structural with the rat on primary afferent depolarization. J. Physiol. (Lond.) 329: 21-35,
SzoLCSANVI, J., JANCSO-GABOR, A., AND JOO, F.: Functional and f Schmiedebergs Arch. PharmacoL 287: 157-169, 1975. **SZOLCSANYI, J., JANCSO-GABOR, A., AND JOO, F.: Functional and fine structural**

SAOLCSANYI, J., JANCSO-GABOR, A., AND JOO, F.: Functional and fine structural

characteristics of the sensory neuron blocking effect of capaa colocsánvn, J., Jancso-Gánda, A., AND Joo, F.: Functional and fine structucharacteristics of the sensory neuron blocking effect of capsaicin. Naur Schmiedebergs Arch. Pharmacol. 287: 157-169, 1975.
colocsánvn, J., Joo, F.,
- Schmiedebergs Arch. Pharmacol. 287: 157-169, 1975.
SZOLCSÁNYI, J., JOÓ, F., AND JANCSÓ-GÁBOR, A.: Mitochondrial changes in
proptic neurones after capsaicin desensitization of the hypothalamic thermo-
detectors in rats. Nat
-
- prooptic neurones after capaaicin desensitization of the hypothalamic thermodetectors in rata. Nature 229: 116-117, 1971.
SzoLcsANYI, J., SANN, H., AND PIERAU, F.-K.: Nociception in pigeons is not impaired by capaaicin. Pa detectors in rats. Nature 229: 116-117, 1971.
SZOLCSÁNYI, J., SANN, H., AND PIERAU, F.-K.: Nociception in pigeons is not
impaired by capeaicin. Pain 27: 247-260, 1986.
SZOLCSÁNYI, J., SZALLASI, A., SZALLASI, Z., JOO, F., A Impaired by capaaicin. Pain 27: 247-260, 1986.

SEOLCSÁNYI, J., SZALLASI, A., SZALLASI, Z., JOO, F., AND BLUMBERG, P. M.:

Resiniferatorin: an ultrapotent selective modulator of capaaicin-sensitive primary afferent neurons SEOLCSANYI, J., SEALLASI, A., SEALLASI, Z., JOO, F., AND BLUMBERG, P. M.:
Resiniferatorin: an ultrapotent selective modulator of capsaicin-sensitive pri-
mary afferent neurons. J. Pharmacol. Exp. Ther. 255: 923-928, 1990.

-
- FAKAKI, M., JIN, J.-G., LU, Y.-F., AND NAKAYAMA, S.: Effects of piperine on the WANG, J.-P., HSU, M.-F., HSU, T.-P., AND TENG, C.-M.: Antihemostatic and
motility of the isolated guinea-pig ileum: comparison with capsaicin.
- TAKAKI, M., AND NAKAYAMA, S.: Effects of capsaicin on myenteric neurons of
- novel insights into the pharmacology of the vanilloid (capsaicin) receptor. Life maintained reflex responses of sympathetic nerve activity to stimulation of
Sci. 47: 1399-1408, 1990b.
SZALLASI, A., Joo, F., AND BLUMBERG, P HOLZER
wide Takano, Y., Nagashima, A., Kamiya, H., Kurosawa, M., and Sato, A.: Well-ER

TAKANO, Y., NAGASHIMA, A., KAMIYA, H., KUROSAWA, M., AND SATO, A.: Well-

maintained reflex responses of sympathetic nerve activity to stimulation of

beroreceptor, chemoreceptor and cutaneous mechanoreceptors in neona
	-
	- enium red to synaptosomes and its effects on neurotransmitter release. J. Neurochem. 45: 1464-1470, 1985.
TAYLOR, D. C. M., PIERAU, F.-K., AND SZOLCSÁNYI, J.: Long lasting inhibition of horseradish peroxidase (HRP) transpo Neurochem. 45: 1464-1470, 1985.

	TAYLOR, D. C. M., PIERAU, F.-K., AND SZOLCSÁNYI, J.: Long lasting inhibition

	of horseradish peroxidase (HRP) transport is ensory nerves induced by

	capsaicin pretreatment of the receptive
	- The Conservatish peroxidase (HRP)
capsaicin pretreatment of the reception
NYLOR, D. C. M., PIERAU, F.-K..
inhibition of axoplasmic transport
Tissue Res. 240: 569-573, 1985.
ERENGHI, G., ZHANG, S. Q., UNGEI capsaicin pretreatment of the receptive field. Brain Res. 298: 45–49, 1984.
TAYLOR, D. C. M., PIERAU, F.-K., AND SZOLCSÁNYI, J.: Capsaicin-induces
inhibition of axoplasmic transport is prevented by nerve growth factor. Cel
	-
	- inhibition of axoplasmic transport is prevented by nerve growth factor. Cell
Tissue Res. 240: 569-573, 1985.
TERROGHI, G., ZHANG, S. Q., UNGER, W. G., AND POLAK, J. M.: Morphological
changes of sensory CGRP-immunoreactive changes of sensory CGRP-immunoreactive and sympathetic nerves in peripheral tissues following chronic denervation. Histochemistry 86: 89-95, 1986.
TERVO, K.: Effect of prolonged and neonatal capsaicin treatments on the sub eral tissues following chronic denervation. Histochemistry 86: 89-95, 1986.
TERVO, K.: Effect of prolonged and neonatal capsaicin treatments on the sub-
stance P immunoreactive nerves in the rabbit eye and spinal cord. Act
	-
	-
	- THERIAULT, E., OTSUKA, M., AND JESSELL, T.: Capsaicin-evoked release of substance P from primary sensory neurons. Brain Res. 170: 209-213, 1979. TODA, N., USUI, H., NISHINO, N., AND FUJIWARA, M.: Cardiovascular effects of
	- TODA, N., USUI, H., NISHINO, N., AND FUJIWARA, M.: Cardiovascular effects of
capsaicin in dogs and rabbits. J. Pharmacol. Exp. Ther. 181: 512-519, 1972.
TÓTH-KÁSA, I., JANCSÓ, G., BOGNÁR, A., HUSZ, S., AND OBÁL, F.: Capsai 34-36, 1983. TÓTH-KÁSA, I., JANCSÓ, G., OBÁL, F., HUSZ, S., AND SIMON, N.: Involvement
of sensory nerve endings in cold and heat urticaria. J. Invest. Dermatol. 80:
34–36, 1983.
TRAD, K. S., HARMON, J. W., FERNICOLA, M. T., HAKKI, F. Z
	- **ATH-KASA, I., JANCSÓ, G., OBAL, F., HUSZ, S., AND SIMON, N.: Involvement** of sensory nerve endings in cold and heat urticaria. J. Invest. Dermatol. 80: 34–36, 1983.
24–36, 1983.
RAD, K. S., HARMON, J. W., FERNICOLA, M. T. afferent nerve endings in cold and heat urticaria. J. Invest. Dermatol. 8
34–36, 1983.
RAD, K. S., HARMON, J. W., FERNICOLA, M. T., HAKKI, F. Z., RAO, J. S., DzIA.
A. J., AND BASS, B. L.: Evidence for a role of capacitin-e TRAD, K.S., HARMON, J. W., FERNICOLA, M. T., HAKKI, F. Z., RAO, J. S., DZIKI, A. J., AND BASS, B. L.: Evidence for a role of capaaicin-sensitive mucosal afferent nerves in the regulation of esophageal blood flow in rabbits
	- on lactstine in the regulation of esophageal blood flow in rabbits. Gastro-
enterology 98: A139, 1990.
TRAURIG, H., PAPKA, R. E., SARIA, A., AND LEMBECK, F.: Substance P immu-
norsactivity in the rat mammary nipple and the RAURIG, H., PAPKA, R. E., SARIA, A., AND LEMBECK, F.: Substance P immu-
noreactivity in the rat mammary nipple and the effects of capsaicin treatment
on lactation. Naunyn Schmiedebergs Arch. Pharmacol. 328: 1-8, 1984a.
RAU
	- noreactivity in the rat mammary nipple and the effects oon lactation. Naunyn Schmiedebergs Arch. Pharmacol. 3
avanto, H., SARIA, A., AND LEMBECK, F.: The effects of
treatment on growth and subsequent reproductive functions
	- on lactation. Naunyn Schmiedebergs Arch. Pharmacol. 328: 1-8, 1984a.
TRAURIG, H., SARIA, A., AND LEMBECK, F.: The effects of neonatal capsaicin
treatment on growth and subsequent reproductive function in the rat. Naunyn
Sc treatment on growth and subsequent reproductive function in the rat. Naunyn
Schmiedebergs Arch. Pharmacol. 327: 254-259, 1984b.
TSUNOO, A., KONISHI, S., AND OTSUKA, M.: Substance P as an excitatory
transmitter of primary a Schmiedebergs Arch. Pharmacol. 327: 254–259, 1984b.

	TSUNOO, A., KONISHI, S., AND OTSUKA, M.: Substance P as an excitatory

	rennoncience 7: 2025–2037, 1982.

	Neuroacience 7: 2025–2037, 1982.

	UEDA, N., MURAMATSU, I., AND F
	- I. Pharmacol. Exp. 230: 469-473, 1984. URBAN, N., MURAMATSU, I., AND FUJIWARA, M.: Capsaicin and bradykinin-
induced substance P-ergic responses in the iris sphincter muscle of the rabbit.
J. Pharmacol. Exp. Ther. 230: 469
	- J. Pharmacol. Exp. Ther. 230: 469-473, 1984.
RBÁN, L., WILLETTS, J., RANDIC, M., AND PAPKA, R. E.: The acute and chronic
effects of capsaicin on slow excitatory transmission in rat dorsal horn. Brain
Res. 330: 390-396, 198 **VARRO, A., WILLETTS, J., RANDIC, M., AND PAPKA, R. E.: The acute and chronic effects of capasicin on slow excitatory transmission in rat dorsal horn. Brain Res. 330. 396, 1986.

	VARRO, A., GREEN, T., HOLMES, S., AND DOCK**
- excitation by capasicin of mechano-heat sensitive nociceptors in rat skin. Brain URBÁN, L., WILLETTS, J., RANDIC, M., AND PAPKA, R. E.: The acute and chronic
Res. 446: 262-268, 1968.
SZOLCSÁNYI, J., AND BARTHÓ, L.: New typ related peptide in visceral afferent nerve fibres: quantification by radioimmuno-
Read, 3.30: 390-396, 1985.
Rea. 3.30: 390-396, 1985.
Rea. 3.30: 390-396, 1985.
The municipal afferent nerve fibres: quantification by radioi
	- VARRO, A., GREEN, T., HOLMES, S., AND DOCKRAY, G. J.: Calcitonin gene-
related peptide in visceral afferent nerve fibres: quantification by radioimmuno-
assay and determination of axonal transport rates. Neuroscience 26: 9 VIRUS, R. M., KNUEPFER, M. M., MCMANUS, D. Q., BRODY, M. J., AND GEBHART, G. F.: Capsaicin treatment in adult Wistar-Kyoto and spontaneously hypertensive rats: effects on nociceptive behavior and cardiovascular regulation.
	- hypertensive rats: effects on nociceptive behavior and cardiovascular regulation. Eur. J. Pharmacol. 72: 209-217, 1981.
VIRUS, R. M., MCMANUS, D. Q., AND GEBHART, G. F.: Capeaicin treatment in adult Wistar-Kyoto and sponta VIRUS, R. M., MCMANUS, D. Q., AND GEBHART, G. F.: Capsaicin treatment in adult Wistar-Kyoto and spontaneously hypertensive rats: effects on substance P contents of peripheral and central nervous system. Eur. J. Pharmacol. adult Wistar-Kyoto and spontaneously hypertensive rats: effects on substance P contents of peripheral and central nervous system. Eur. J. Pharmacol. 81:
67-73, 1982.
67-73, 1982.
adult Wistar-Kyoto and spontaneously hypert
	- **Prontents of peripheral and central nervous system.**
67-73, 1982.
RUS, R. M., McMANUS, D. Q., AND GEBHART, G. F.:
adult Wistar-Kyoto and spontaneously hypertensive ratio
in the spinal cord. Eur. J. Pharmacol. 92: 1-8, 198 WHERE, R. M., MCMANUS, D. Q., AND GEBHART, G. F.: Capsaicin treatment in adult Wister-Kyoto and spontaneously hypertensive rate: neurochemical effects in the spinal cord. Eur. J. Pharmacol. 92: 1-8, 1983.
WADDELL, P. J., A
	-
	- capsaicin on rat vagus **nerve** *in vitro.* Pain 39: 237-242, 1989. Matter-Kyoto and spontaneously hypertensive rats: neurochemical effects
in the spinal cord. Eur. J. Pharmacol. 92: 1-8, 1983.
WADDELL, P. J., AND LAWSON, S. N.: The C-fibre conduction block caused by
capsaicin on rat vagus **Capsaicin on rat vagus nerve in vitro. Pain 39: 237-242, 1989.**
WALL, P. D.: The effect of peripheral nerve lesions and of neonatal capsaicin in
the rat on primary afferent depolarization. J. Physiol. (Lond.) 329: 21-35,

	- **PERIPHERAL ALL, P. D.: The effect of peripheral nerve lesions and of neonatal capsaicin in the rat on primary afferent depolarization. J. Physiol. (Lond.) 329: 21-35, 1982.

	ALL, P. D., AND FITZGERALD, M.: Effects of cap WALL, P. D., AND FITZGERALD, M.; Effects of capaaicin applied locally to adult peripheral nerve. I. Physiology of peripheral nerve and spinal cord. Pain 11:
363-377, 1961.
WALL, P. D., FITZGERALD, M., NUSSBAUMER, J. C., V** WALL, P. D., AND FITZGERALD, M.: Effects of capsaicin applied locally to adult
peripheral nerve. I. Physiology of peripheral nerve and spinal cord. Pain 11:
363-377, 1981.
M. W.S. E., VAN DER LOOS, H., AND
MALL, P. D., FIT
	-
	- matally with capasicin. Nature 295: 691-693, 1982a.
WALL, P. D., FITZGERALD, M., AND WOOLF, C. J.: Effects of capasicin on
receptive fields and on inhibitions in rat spinal cord. Exp. Neurol. 78: 425-436, 1982a.
WANG, J.-P natally with capsaicin. Nature 295: 691-693, 1982a.
WALL, P. D., FITZGERALD, M., AND WOOLF, C. J.: Effects of capsaicin on
receptive fields and on inhibitions in rat spinal cord. Exp. Neurol. 78: 425-436, 1982b.
WANG, J.-P
	- receptive fields and on inhibitions in rat spinal cord. Exp. Neurol. 78: 425-436, 1982b.
WANG, J.-P., HSU, M.-F., HSU, T.-P., AND TENG, C.-M.: Antihemostatic and antithrombotic effects of capsaicin in comparison with aspir WANG, J.-P., HSU, M.-F., HSU, T.-P., AND TENG, C.-M.: Antihemostatic and
antithrombotic effects of capsaicin in comparison with aspirin and indometh-
acin. Thromb. Res. 37: 669-679, 1985.
WANG, J.-P., HSU, M.-F., AND TENG,
	-
	- acin. Thromb. Res. 37: 669-679, 1985.

	AnG, J.-P., Hsu, M.-F., AND TENG, C.-M.: Antiplatelet effect of capsaicin.

	Thromb. Res. 36: 497-507, 1984.

	ATANABE, T., KAWADA, T., AND IWAI, K.: Effect of capsaicin pretreatment on

REVIEW

ARMACOLOGI

spet

 $\overline{0}$

- capsaicin in rats. Am. J. Physiol. 255: E23-E27, 1988b.
ATSON, C. P. N., EVANS, R. J., AND WATT, V. R.: Post-herpetic neuralg
topical capsaicin. Pain 33: 333-340, 1988.
ATSON, C. P. N., EVANS, R. J., AND WATT, V. R.: The p
-
- WATSON, C. P. N., EVANS, R. J., AND WATT, V. R.: Post-herpetic neuralgia and
topical capeaicin. Pain 33: 333-340, 1988.
WATSON, C. P. N., EVANS, R. J., AND WATT, V. R.: The post-mastectomy pain
syndrome and the effect of t topical capsaicin. Pain 33: 333–340, 1988.
ATSON, C. P. N., EVANS, R. J., AND WATT, V. R.: The post-mastectomy pain
syndrome and the effect of topical capsaicin. Pain 38: 177–186, 1989.
EHE, E.: Neuropeptides in prinary af ATSON, C. P. N., E
syndrome and the exhire, E.: Neuropep
Neuron, ed. by W.
New York, 1990.
ELK, E., FLEISCHE syndrome and the effect of topical capsaicin. Pain 38: 177-186, 1989.
WEIHE, E.: Neuropeptides in primary afferent neurons. In The Primary Afferent
Neuron, ed. by W. Zenker and W. L. Neuhuber, pp. 127-159, Plenum Press,
Ne
- Fibres in rats after neonatal capsaicin treatment. Pflügers Arch. 400: 66-71, 1984.
WELK, E., FLEISCHER, E., PETSCHE, U., AND HANDWERKER, H. O.: Afferent C-fibres in rats after neonatal capsaicin treatment. Pflügers Arch. New York, 1990.
WELK, E., FLEISCHER, E., PETSCHE, U., AND HANDWERKER, H. O.: Afferent C.
fibres in rats after neonatal capsaicin treatment. Pflügers Arch. 400: 66–71,
1984.
WELK, E., PETSCHE, U., FLEISCHER, E., AND HANDWER
- ELK, E., FLEISCHER, E., PETSCHE, U., AND HANDWERKER, H. O.: Afferent C-
fibres in rats after neonatal capsaicin treatment. Pflügers Arch. 400: 66-71,
1964.
E.K., E., PETSCHE, U., FLEISCHER, E., AND HANDWERKER, H. O.: Alter fibres in rats after neonatal capsaicin treatment. Pflügers Arch. 400: 66-71,

1984.

WELK, E., PETSCHE, U., FLEISCHER, E., AND HANDWERKER, H. O.: Altered

excitability of afferent C-fibres of the rat distal to a nerve sit ELK, E., PETSCHE, U., FLEISCHER, E., AND HANDWERKER, H. O.: Alter
excitability of afferent C-fibres of the rat distal to a nerve site exposed
capsacien. Neuronsci. Lett. 38: 245-250, 1983.
ILLIAMS, J. T., AND ZIEGLGÄNSBERG excitability of afferent C-fibres of the rat distal to a nerve site exposed to capsaicin. Neurosci. Lett. 38: 245-250, 1983.
WILLIAMS, J. T., AND ZIEGLOÄNSBERGER, W.: The acute effects of capsaicin on rat primary afferents
-
- capsaicin. Neurosci. Lett. 38: 245–250, 1983.
ILLIAMS, J. T., AND ZIEGLGÄNSBERGER, W.: The acute effect primary afferents and spinal neurons. Brain Res. 253: 1
INTER, J.: Characterization of capsaicin-sensitive neurones
ro
- WILLIAMS, J. T., AND ZIEGLOÄNSBERGER, W.: The acute effects of capacition or rat primary afferents and spinal neurons. Brain Res. 253: 125-131, 1982.
WINTER, J.: Characterization of capacitin-sensitive neurones in adult ra root ganglion cultures. Neurosci. Lett. 80: 134–140, 1987.

WINTER, J., DRAY, A., WOOD, J. N., YEATS, J. C., AND BEVAN, S.: Cellular

mechanism of action of resiniferatoxin: a potent sensory neuron excitotoxin.

ERRIR, J. INTER, J., DRAY, A., WOOD, J. N., YEATS, J. C., AND BEVAN, S.: Cellular mechanism of action of resiniferatorin: a potent sensory neuron excitotorin.
Brain Res. 520: 131-140, 1990.
INTER, J., FORBES, C. A., STERNBERG, J., A
- **to the excitotoxin capsaicin.** The excitor of the excitors of the excitor (NGF) regulates adult rat cultured dorsal root ganglion neuron responses
to the exc factor (NGF) regulates adult rat cultured dorsal root ganglion neuron responses
to the excitotoxin capsaicin. Neuron 1: 973–981, 1988.
WOOD, J. N.: Reversible desensitization to capsaicin induced calcium uptake in
cultured
- WOOD, J. N.: Reversible desensitization to capacicin induced calcium uptake in cultured rat sensory neurones. Neuroscience 22: S247, 1987.
WOOD, J. N., COOTE, P. R., MINHAS, A., MULLANEY, I., MCNEILL, M., AND BURGESS, G. M
-

cyclic AMP levels in rat sensory neurones in culture. J. Neurochem. 53: 1203- IN
cyclic AMP levels in
1211, 1989.
00D, J. N., WALPO

-
- 201
cyclic AMP levels in rat sensory neurones in culture. J. Neurochem. 53: 1203–1211, 1989.
WOOD, J. N., WALPOLE, C., JAMES, I. F., DRAY, A., AND COOTE, P. R.: Immu-
nochemical detection of photoaffinity-labelled capasici sensory neurons. FEBS Lett. 269: 381-385, 1990.
Woon, J. N., Whyrax, J., AMES, I. F., RANG, H. P., YEATS, J., AND BEVAN, S.:
Capasicin-induced ion fluxes in dorsal root ganglion cells in culture. J. Neurosci.
8: 3208-3220,
-
- of concernent of NADH-quinone oxidoreductase is correlated
with the presence of energy-coupling site-1 in various organisms. Arch.
Biochem. Biophys. 281: 305-311, 1990.
MSH, T. L., ABAY, E. O., AND Go, V. L. W.: Studies on YAKSH, T. L., ABAY, E. O., AND GO, V. L. W.: Studies on the location and release
of cholecystokinin and vasoactive intestinal peptide in rat and cat spinal cord.
Brain Res. 242: 279-290, 1982.
YAKSH, T. L., FARA, D. H., LE
- TANSH, 1. L., ARAT, E., U., ARU GU, V. L. W.: SUGLES OF Cholecystokinin and vasoective intestinal peptide in rat and cat spinal cord.
Brain Res. 242: 279-290, 1982.
YAKSH, T. L., FARB, D. H., LEEMAN, S. E., AND JESSELL, T.
- **in vivo.** 1. L., rann, D. 11., Lesman, v. experience P in the
capeaicin depletes substance P in the
thermal analgesia. Science 206: 481–4
KSH, T. L., JESSELL, T. M., GAMSE, intrathecal morphine inhibits substance
in vivo. capsacin depretes substance P in the rat spinal cord and produces prolonged
thermal analgesia. Science 206: 481-483, 1979.
YAKSH, T. L., JESSELL, T. M., GAMSE, R., MUDGE, A. W., AND LEEMAN, S. E.:
Intrathecal morphine inhi
- in vivo. Nature 286: 155-157, 1980.

YAMANAKA, K., KIGOSHI, S., AND MURAMATSU, I.: Conduction-block induced by

capeaicin in crayfish giant axon. Brain Res. 300: 113-119, 1984.

YANAGISAWA, M., NAKANO, S., AND OTSUKA, M.:
- rat spinal cord. Biomed. Res. 1 (suppl.): 88-90, 1980. YANAGISAWA, M., NAKANO, S., AND *OTSUKA*, M.: Capsaicin-induced depolarization of primary afferent fibers and the release of substance P from isolated rat spinal cord. Biomed. Res. 1 (suppl).: 88-90, 1980.
 YANAGISAWA, M.
-
- XAGAMI, A. NAMP, A. S., AND UNION, C. A. S. AND UNION CORPORATION and the release of substance P from isolated
rat spinal cord. Biomed. Res. 1 (suppl.): 88-90, 1980.
YOX, D. P., AND RITTER, R. C.: Capsaicin attenuates supp 190, 1991.
ZERNIG, G., HOLZER, P., AND LEMBECK, F.: A study of the mode and site of YOX, D.P., AND RITTEN, R.C.: C., HOLZER, A., D. LAMBERT, G. A.: Craniovascular application of capsaicin activates nociceptive thalamic neurones in the cat. Neurosci. Lett. 121: 187-190, 1991.
ZERNIG, G., HOLZER, P., AND LE
-

201

REV

HARMACOLOGI