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ACOLOGICAL REVIEWS
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Pharmacological Modulation of Voltage-Gated Na⁺
Channels: A Rational and Ef **COSO CONCREVERS:** CONDUCTION ON THE CHANNEL CONDUCTION ANANONOGICAL REVIEWS CONCRETING IN COLUMITY OF Pharmacology and Experimental Therapeutics
 Channels: A Rational and Effective Strategy Against
 Channels: A Ration ISCONG AND ALEXPETIMENTAL Therapeutics
 **Ischemic Brain Damage

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 ISChemic Brain Damage
 JUTTA URENJAK AND TIHOMIR P. OBRENOVITCH JUTTA URENJAK AND TIHOMIR P. OBRENOVITCH
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Sandwich, UK (J.U.); and Department of Pharmacology, School of Pharmacy, London, UK (T.P.O.)

I. Introduction
Mortality and neurological disabilities due to stroke. I. Introduction
Mortality and neurological disabilities due to stroke,
rdiac arrest, or perinatal asphyxia have an enormous I. Introduction
Mortality and neurological disabilities due to stroke,
cardiac arrest, or perinatal asphyxia have an enormous
impact on public health and resources. Stroke alone is **implementary in the Mortality and neurological disabilities due to stroke.** (K) cardiac arrest, or perinatal asphyxia have an enormous impact on public health and resources. Stroke alone is impact the third most common ca **the third most common cause of death in the United States** (after heart disease and cancer), the leading the United States (after heart disease and cancer), the leading the third most common cause of death in the United S Mortality and neurological disabilities due to stroke, cardiac arrest, or perinatal asphyxia have an enormous impact on public health and resources. Stroke alone is in the third most common cause of death in the United ex cardiac arrest, or perinatal asphyxia have an enormous
impact on public health and resources. Stroke alone is
the third most common cause of death in the United
States (after heart disease and cancer), the leading
cause of impact on public health and resources. Stroke alon
the third most common cause of death in the Uni
States (after heart disease and cancer), the lead
cause of serious disability, and it accounts for an e
mated one-half of a the third most common cause of death in the United
States (after heart disease and cancer), the leading
cause of serious disability, and it accounts for an esti-
mated one-half of all hospitalizations for acute neurolog-
i States (after heart disease and cancer), the leading cause of serious disability, and it accounts for an estimated one-half of all hospitalizations for acute neurological disease (Drug & Market Development, Inc., 1994). Ov cause of serious disability, and it accounts for an esti-
mated one-half of all hospitalizations for acute neurolog-
ical disease (Drug & Market Development, Inc., 1994).
Over the last 10 years, there has been considerable mated one-half of all hospitalizations for acute neurolog-
ical disease (Drug & Market Development, Inc., 1994).
Over the last 10 years, there has been considerable
progress in the understanding of the mechanisms un-
derl ical disease (Drug & Market Development, Inc., 199
Over the last 10 years, there has been consideral
progress in the understanding of the mechanisms at
derlying ischemic brain damage, and a wide range
drugs has been shown Over the last 10 years, there has been considerable progress in the understanding of the mechanisms underlying ischemic brain damage, and a wide range of drugs has been shown to be neuroprotective in experimental models. D progress in the understanding of the mechanisms underlying ischemic brain damage, and a wide range of drugs has been shown to be neuroprotective in experimental models. Despite these advances, a clinically effective drug c derlying ischemic brain damage, and a wide range of drugs has been shown to be neuroprotective in experimental models. Despite these advances, a clinically effective drug capable of protecting neurons against ischemia is s drugs has been shown to be neuroprotective in experimental models. Despite these advances, a clinically ef-
fective drug capable of protecting neurons against isch-
emia is still awaited (Zivin and Choi, 1991; Bullock, fi
 mental models. Despite these advances, a clinically
fective drug capable of protecting neurons against i
emia is still awaited (Zivin and Choi, 1991; Bull
1992; White et al., 1993). The fact that brain tii
damage subsequen

therapeutic strategies currently under investigation

(Kogure et al., 1993; Hallenbeck and Frerichs, 1993). (Kogure et al., 1993; Hallenbeck and Frerichs, 1993).
The most common approaches are: free radical scaveng-The most common approaches are: free radical scave
The most common approaches are: free radical scave
ing (Watson, 1993), prevention of glutamate-media therapeutic strategies currently under investigation
(Kogure et al., 1993; Hallenbeck and Frerichs, 1993)
The most common approaches are: free radical scaveng
ing (Watson, 1993), prevention of glutamate-mediate
excitotoxic therapeutic strategies currently under investigation (Kogure et al., 1993; Hallenbeck and Frerichs, 1993). The most common approaches are: free radical scavenging (Watson, 1993), prevention of glutamate-mediated excitotoxi (Kogure et al., 1993; Hallenbeck and Frerichs, 1993).
The most common approaches are: free radical scaveng-
ing (Watson, 1993), prevention of glutamate-mediated
excitotoxicity (Diemer et al., 1993), preservation of in-
tr The most common approaches are: free radical scaveng-
ing (Watson, 1993), prevention of glutamate-mediated
excitotoxicity (Diemer et al., 1993), preservation of in-
tracellular Ca²⁺-homeostasis (Simon et al., 1984; Choi ing (Watson, 1993), prevention of glutamate-mediate excitotoxicity (Diemer et al., 1993), preservation of in tracellular Ca²⁺-homeostasis (Simon et al., 1984; Choi
1988; Siesjö and Bengtsson, 1989), and improvement o
mi excitotoxicity (Diemer et al., 1993), preservation of intracellular Ca²⁺-homeostasis (Simon et al., 1984; Chan-
1988; Siesjö and Bengtsson, 1989), and improvement
microvascular perfusion (Dirnagl, 1993). In comparison
p tracellular Ca²⁺-homeostasis (Simon et al., 1984; Choi, 1988; Siesjö and Bengtsson, 1989), and improvement of microvascular perfusion (Dirnagl, 1993). In comparison, pharmacological modulation of voltage-gated Na⁺ cha microvascular perfusion (Dirnagl, 1993). In comparison, pharmacological modulation of voltage-gated Na⁺ channels has received very little attention. It seems that this molecular target is restricted to antiarrhythmic dr microvascular perfusion (Dirnagl, 1993). In comparison,
pharmacological modulation of voltage-gated Na⁺ chan-
nels has received very little attention. It seems that this
molecular target is restricted to antiarrhythmic narmacological modulation of voltage-gated Na⁺ channels has received very little attention. It seems that this blecular target is restricted to antiarrhythmic drugs iticonvulsants, and local anesthetics (Catterall, 1987

fective drug capable of protecting neurons against isch-
emia is still awaited (Zivin and Choi, 1991; Bullock, function of nervous system. More precisely, Na⁺ chan-
1992; White et al., 1993). The fact that brain tissue nels has received very little attention. It seems that this molecular target is restricted to antiarrhythmic drugs, anticonvulsants, and local anesthetics (Catterall, 1987). Voltage-gated Na⁺ channels are responsible for molecular target is restricted to antiarrhythmic drugs,
anticonvulsants, and local anesthetics (Catterall, 1987).
Voltage-gated Na⁺ channels are responsible for initi-
ation and conduction of the neuronal action potenti anticonvulsants, and local anesthetics (Catterall, 1987
Voltage-gated Na⁺ channels are responsible for init
ation and conduction of the neuronal action potentia
and therefore play a fundamental role in the norma-
functi Voltage-gated Na⁺ channels are responsible for initiation and conduction of the neuronal action potential and therefore play a fundamental role in the normal function of nervous system. More precisely, Na⁺ channels in ation and conduction of the neuronal action potential
and therefore play a fundamental role in the normal
function of nervous system. More precisely, $Na⁺$ chan-
nels in cell bodies and axon initial segments determine and therefore play a fundamental role in the normal function of nervous system. More precisely, Na^+ channels in cell bodies and axon initial segments determine the threshold for action potential generation and affect th function of nervous system. More precisely, Na⁺ channels in cell bodies and axon initial segments determine
the threshold for action potential generation and affect
the duration and frequency of repetitive neuronal firi nels in cell bodies and axon initial segments determine
the threshold for action potential generation and affect
the duration and frequency of repetitive neuronal firing.
In addition, in nerve terminals, $Na⁺$ channel the threshold for action potential generation and affect
the duration and frequency of repetitive neuronal firing.
In addition, in nerve terminals, Na⁺ channels can po-
tentially influence neurotransmitter release from p

PHARMACOLOGICAL REVIEW!

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MODULATION OF VOLTAGE-GATED NA⁺ CHANNELS 23

onstrate that selective down-modulation of voltage-
gated $Na⁺$ channels is a rational and effective approach
to protect brain tissue in conditions associated with de-MODULATION OF VOLTAGE-

onstrate that selective down-modulation of voltage-

gated Na⁺ channels is a rational and effective approach

to protect brain tissue in conditions associated with de-MODULATION OF VOLTAG
onstrate that selective down-modulation of voltage-
gated Na⁺ channels is a rational and effective approach
to protect brain tissue in conditions associated with de-
fective blood supply, and one tha onstrate that selective down-modulation of voltage-
gated Na⁺ channels is a rational and effective approach
to protect brain tissue in conditions associated with de-
fective blood supply, and one that may still be benef onstrate that selective down-modulation of voltage-
gated Na⁺ channels is a rational and effective approach
to protect brain tissue in conditions associated with de-
fective blood supply, and one that may still be benef gated Na⁺ channels is a rational and effective approacto protect brain tissue in conditions associated with defective blood supply, and one that may still be beneficial when treatment of transient ischemia or stroke is to protect brain tissue in conditions associated with defective blood supply, and one that may still be beneficial and when treatment of transient ischemia or stroke is delayed. The first section (II) is an overview of $\$ fective blood supply, and one that may still be beneficial as
when treatment of transient ischemia or stroke is de-
layed. The first section (II) is an overview of Na⁺ chan-
nels in the central nervous system (CNS).^a when treatment of transient ischemia or stroke is d
layed. The first section (II) is an overview of Na⁺ cha
nels in the central nervous system (CNS).^a By focusion
the molecular determinants of Na⁺ channel function
a layed. The first section (II) is an overview of Na^+ channels in the central nervous system (CNS).^a By focusing on the molecular determinants of Na^+ channel function and pharmacology, this section makes clear nels in the central nervous system (CNS).^a By focusion the molecular determinants of Na^+ channel functional pharmacology, this section makes clear that development of site-directed Na^+ channel modulaters is fesible. on the molecular determinants of Na⁺ channel function
and pharmacology, this section makes clear that devel-
opment of site-directed Na⁺ channel modulaters is fea-
sible. Next (section III), we detail the rationale fo and pharmacology, this section makes clear that devel-
opment of site-directed Na^+ channel modulaters is fea-
sible. Next (section III), we detail the rationale for down-
produlation of Na^+ channels in ischemia, conce opment of site-directed Na⁺ channel modulaters is feasible. Next (section III), we detail the rationale for down-
modulation of Na⁺ channels in ischemia, concentrating
on four major points: (1) Most of the brain's ene sible. Next (section III), we detail the rationale for down-pomodulation of Na⁺ channels in ischemia, concentrating at a on four major points: (1) Most of the brain's energy im consumption is used to maintain Na⁺ and modulation of Na⁺ channels in ischemia, concentrating at on four major points: (1) Most of the brain's energy in consumption is used to maintain Na⁺ and K⁺ gradients the across the cellular membrane, and these gradi on four major points: (1) Most of the brain's energy
consumption is used to maintain Na^+ and K^+ gradients
across the cellular membrane, and these gradients are
vital to electrical activity and transport mechanisms; (consumption is used to maintain Na^+ and K^+ gradients tractors the cellular membrane, and these gradients are movital to electrical activity and transport mechanisms; (2) wis sustained Na^+ influx, such as that occur across the cellular membrane, and these gradients
vital to electrical activity and transport mechanisms;
sustained Na⁺ influx, such as that occurring in is
emia, is neurotoxic both acutely and indirectly; (3)
survival s wital to electrical activity and transport mechanisms; (2) sustained Na⁺ influx, such as that occurring in ischemia, is neurotoxic both acutely and indirectly; (3) the survival strategy of the turtle and immature mammal emia, is neurotoxic both acutely and indirectly; (3) the survival strategy of the turtle and immature mammalian brain to anoxia includes down-regulation of Na⁺ currents; and (4) *post*ischemic down-modulation of Na⁺ c survival strategy of the turtle and immature mamma-
lian brain to anoxia includes down-regulation of Na⁺
currents; and (4) *post*ischemic down-modulation of Na⁺
channels is also beneficial. Section IV provides further lian brain to anoxia includes down-regulation of Na^+
currents; and (4) *postischemic down-modulation* of Na^+
channels is also beneficial. Section IV provides further
supporting evidence for the beneficial effe currents; and (4) *post*ischemic down-modulation of Nat-
channels is also beneficial. Section IV provides furth
supporting evidence for the beneficial effect of Nat-
channel down-modulation, based on in vitro exper-
ments channels is also beneficial. Section IV provides further
supporting evidence for the beneficial effect of Na⁺
channel down-modulation, based on in vitro experi-
ments with Na⁺-free medium, and studies using recog-
niz supporting evidence for the beneficial effect of $Na⁺$
channel down-modulation, based on in vitro experi-
ments with $Na⁺$ -free medium, and studies using recog-
nized $Na⁺$ channel blockers such as tetrodotoxi channel down-modulation, based on in vitro experiments with Na⁺-free medium, and studies using recognized Na⁺ channel blockers such as tetrodotoxin (TTX), local anesthetics and anticonvulsants. Finally, a number of *an* ments with Na^+ -free medium, and studies using recog-
nized Na^+ channel blockers such as tetrodotoxin (TTX),
local anesthetics and anticonvulsants. Finally, a number
of *anti-ischemic* compounds under development are e mized Na⁺ channel blockers such as tetrodotoxin
local anesthetics and anticonvulsants. Finally, a n
of *anti-ischemic* compounds under development a
amined in section V, all of which appear to pri-
target Na⁺ channels **Internal Compounds under development are examined in section V, all of which appear to primarily such an examined in section V, all of which appear to primarily such appear to primarily such appear to primarily and the Ce the Central Occurs of View Allen System**
 the Central Nervous System
 the Central Nervous System
 hannels involved in electrical signaling

rget Na⁺ channels at therapeutic concentrations.
 I. Overview of Voltage-Gated Na⁺ Channels in

the **Central Nervous System**

The ion channels involved in electrical signaling be-

ng to two classes. *Ligand-operate* II. Overview of Voltage-Gated Na⁺ Channels in
the Central Nervous System
The ion channels involved in electrical signaling be-
long to two classes. *Ligand-operated* ion channels (e.g., The ion channels involved in electrical signaling
ng to two classes. *Ligand-operated* ion channels (
**Abbreviations: CNS, central nervous system; DNA, deoxyril
io scid: DNA, complementary DNA, FNA, ribonucleic scid: mi**

glutamate-receptor ionophore complexes) mediate local GATED NA⁺ CHANNELS
glutamate-receptor ionophore complexes) mediate local
increases in ion conductance at chemical synapses, and
thereby depolarize or hyperpolarize the subsynaptic -GATED NA⁺ CHANNELS 23
glutamate-receptor ionophore complexes) mediate local
increases in ion conductance at chemical synapses, and
thereby depolarize or hyperpolarize the subsynaptic
area of the cell. In contrast, *volt* glutamate-receptor ionophore complexes) mediate local
increases in ion conductance at chemical synapses, and
thereby depolarize or hyperpolarize the subsynaptic
area of the cell. In contrast, *voltage-gated* ion channels
m glutamate-receptor ionophore complexes) mediate lo
increases in ion conductance at chemical synapses, a
thereby depolarize or hyperpolarize the subsynap
area of the cell. In contrast, *voltage-gated* ion chann
mediate rapi increases in ion conductance at chemical synapses, and
thereby depolarize or hyperpolarize the subsynaptic
area of the cell. In contrast, *voltage-gated* ion channels
mediate rapid, voltage-dependent changes in ion perme-
 area of the cell. In contrast, *voltage-gated* ion channels
mediate rapid, voltage-dependent changes in ion perme-
ability during action potentials in excitable cells, and
also modulate membrane potential and ion permeabi mediate rapid, voltage-dependent changes in ion permemediate rapid, voltage-dependent changes in ion permeability during action potentials in excitable cells, and
also modulate membrane potential and ion permeability
in many inexcitable cells (e.g., glia) (Hille, 1991). Volt ability during action potentials in excitable cells, and
also modulate membrane potential and ion permeability
in many inexcitable cells (e.g., glia) (Hille, 1991). Volt-
age-gated Na⁺ channels are responsible for the i also modulate membrane potential and ion permeability
in many inexcitable cells (e.g., glia) (Hille, 1991). Volt-
age-gated Na⁺ channels are responsible for the initial
inward current during the depolarization phase of in many inexcitable cells (e.g., glia) (Hille, 1991). Voltage-gated Na⁺ channels are responsible for the initial inward current during the depolarization phase of action potentials, and differences in Na⁺ channel kine age-gated Na⁺ channels are responsible for the initial
inward current during the depolarization phase of action
potentials, and differences in Na⁺ channel kinetics, an-
atomical distribution, and pharmacology have a m inward current during the depolarization phase of action
potentials, and differences in Na^+ channel kinetics, an-
atomical distribution, and pharmacology have a major
impact on cell signaling and information processing. potentials, and differences in Na⁺ channel kinetics, anatomical distribution, and pharmacology have a major impact on cell signaling and information processing. Ion transport, mediated by the Na⁺ channel, is among the atomical distribution, and pharmacology have a major impact on cell signaling and information processing. Io transport, mediated by the $Na⁺$ channel, is among the most rapid of protein-mediated processes, consister w impact on cell signaling and information processing. Ion
transport, mediated by the Na^+ channel, is among the
most rapid of protein-mediated processes, consistent
with the view that ion movement takes place by diffu-
si most rapid of protein-mediated processes, consistent
with the view that ion movement takes plase by diffu-
sion through an aqueous pore rather than by a carrier
mechanism. Na ⁺ channels are also characterized by
high io with the view that ion movement takes place by diffusion through an aqueous pore rather than by a carrier sion through an aqueous pore rather than by a carr
mechanism. Na⁺ channels are also characterized
high ion selectivity, and steep voltage sensitivity of th
ion conductance activity. Several recent reviews ha
covered in mechanism. Na⁺ channels are also characterized by
high ion selectivity, and steep voltage sensitivity of their
ion conductance activity. Several recent reviews have
covered in detail the structure, expression, and molec ion conductance activity. Several recent reviews have
covered in detail the structure, expression, and molecu-
lar determinants of Na⁺ channel functions (Patlak,
1991; Catterall, 1992, 1993a, b; Cohen and Barchi, 1993;
 covered in detail the structure, expression, and molecular determinants of Na⁺ channel functions (Patlak, 1991; Catterall, 1992, 1993a, b; Cohen and Barchi, 1993; Kallen et al., 1994; Kirsch, 1994). The purpose of this section is to focus on features of voltage-gated Na⁺ lar determinants of Na⁺ channel functions (Patlak, 1991; Catterall, 1992, 1993a, b; Cohen and Barchi, 1993; Kallen et al., 1994; Kirsch, 1994). The purpose of this section is to focus on features of voltage-gated Na⁺ 1991; Catterall, 1992, 1993a, b; Cohen and Barchi, 199
Kallen et al., 1994; Kirsch, 1994). The purpose of the
section is to focus on features of voltage-gated Na⁺ chan-
nels that may be relevant to the etiology of ische nel modulators, and to a more selective development of nels that may be relevant to the etiology of ischemic

A. Structure and Classification

Brain Na⁺ channels are heterotrimeric complexes such drugs.
A. Structure and Classification
Brain Na⁺ channels are heterotrimeric complexes
consisting of a highly glycosylated a-subunit (260 kDa),
associated noncovalently with a β_1 -subunit (36 kDA) A. Structure and Classification
Brain Na⁺ channels are heterotrimeric complexes
consisting of a highly glycosylated α -subunit (260 kDa),
associated noncovalently with a β_1 -subunit (36 kDA)
and, via a disulfide-li A. Structure and Classification

Brain Na⁺ channels are heterotrimeric complexes

consisting of a highly glycosylated α -subunit (260 kDa),

associated noncovalently with a β_1 -subunit (36 kDA)

and, via a disulfid Brain Na⁺ channels are heterotrimeric complexes
consisting of a highly glycosylated α -subunit (260 kDa),
associated noncovalently with a β_1 -subunit (36 kDA)
and, via a disulfide-linkage, with a β_2 -subunit (33 consisting of a highly glycosylated α -subunit (260 kDa),
associated noncovalently with a β_1 -subunit (36 kDA)
and, via a disulfide-linkage, with a β_2 -subunit (33 kDA)
(Barchi, 1988; Catterall, 1988a, 1992; Goldi associated noncovalently with a β_1 -subunit (36 kDA
and, via a disulfide-linkage, with a β_2 -subunit (33 kDA
(Barchi, 1988; Catterall, 1988a, 1992; Goldin, 1993)
Analysis of the hydrophobicity of the amino acid se
q and, via a disulfide-linkage, with a β_2 -subunit (33 kDA) (Barchi, 1988; Catterall, 1988a, 1992; Goldin, 1993).
Analysis of the hydrophobicity of the amino acid sequence of α -subunits suggests a membrane-folding to-Analysis of the hydrophobicity of the amino acid sequence of α -subunits suggests a membrane-folding to-
pology consisting of four homologous membrane-bound
repeats (I to IV), each composed of six transmembrane
segments Analysis of the hydrophobicity of the amino acid sequence of α -subunits suggests a membrane-folding to pology consisting of four homologous membrane-boun repeats (I to IV), each composed of six transmembrane segments (quence of α -subunits suggests a membrane-folding to-
pology consisting of four homologous membrane-bound
repeats (I to IV), each composed of six transmembrane
segments (S1 to S6 and additional membrane-associated
seque pology consisting of four homologous membrane-bound
repeats (I to IV), each composed of six transmembrane
segments (S1 to S6 and additional membrane-associated
sequences (fig. 1) (Noda et al., 1984). The N- and C-
termini repeats (I to IV), each composed of six transmembrane segments (S1 to S6 and additional membrane-associated sequences (fig. 1) (Noda et al., 1984). The N- and C-
termini, as well as the linkers between α -subunit repeat segments (S1 to S6 and additional membrane-associa
sequences (fig. 1) (Noda et al., 1984). The N- and
termini, as well as the linkers between α -subunit
peats, are intracellular, whereas the linkers betw
segments altern sequences (fig. 1) (Noda et al., 1984). The N- and C-
termini, as well as the linkers between α -subunit re-
peats, are intracellular, whereas the linkers between
segments alternate between intracellular and extracel-
l termini, as well as the linkers between α -subunit repeats, are intracellular, whereas the linkers between segments alternate between intracellular and extracel-
lular surfaces. Potential glycosylation sites are all in peats, are intracellular, whereas the linkers between
segments alternate between intracellular and extracel-
lular surfaces. Potential glycosylation sites are all in
putative extracellular loops, and phosphorylation sites segments alternate between intracellular and extrace
lular surfaces. Potential glycosylation sites are all i
putative extracellular loops, and phosphorylation site
in intracellular regions (fig. 1). The primary structure lular surfaces. Potential glycosylation sites are all in
putative extracellular loops, and phosphorylation sites
in intracellular regions (fig. 1). The primary structure of
the β_1 -subunit of the rat brain, deduced fro putative extracellular loops, and phosphorylation sites
in intracellular regions (fig. 1). The primary structure of
the β_1 -subunit of the rat brain, deduced from the isola-
tion of complementary DNA (cDNA) clones, ind in intracellular regions (fig. 1). The primary structure of
the β_1 -subunit of the rat brain, deduced from the isola-
tion of complementary DNA (cDNA) clones, indicated
that it contains a single putative transmembrane the β_1 -subunit of the rat it
tion of complementary D
that it contains a single po
and four potential extrace
sites (Isom et al., 1992).
Molecular cloning has on of complementary DNA (cDNA) clones, indicated
at it contains a single putative transmembrane repeat
ind four potential extracellular N-linked glycosylation
ces (Isom et al., 1992).
Molecular cloning has revealed four di

that it contains a single putative transmembrane repeat
and four potential extracellular N-linked glycosylation
sites (Isom et al., 1992).
Molecular cloning has revealed four distinct, but
highly homologous (> 85% sequenc and four potential extracellular N-linked glycosylation
sites (Isom et al., 1992).
Molecular cloning has revealed four distinct, but
highly homologous (> 85% sequence identity), primary
structures of adult rat brain $\$ sites (Isom et al., 1992).

Molecular cloning has revealed four distinct, but

highly homologous (> 85% sequence identity), primary

structures of adult rat brain α -subunits. They are des-

ignated type I, II, IIA and

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long to two classes. *Ligand-operated* ion channels (e.g.,
 a Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid; cDNA, complementary DNA; RNA, ribonucleic acid; mRNA,

messenger RNA; cAMP, cyclic ade ^a Abbreviations: CNS, central nervous system; DNA, deoxyribonucleic acid; cDNA, complementary DNA; RNA, ribonucleic acid; mRNA, messenger RNA; cAMP, cyclic adenosine 3',5'-monophosphate; cA-PK, cAMP-dependent protein kin ^a Abbreviations: CNS, central nervous system; DNA, deoxyribor
cleic acid; cDNA, complementary DNA; RNA, ribonucleic acid; mRN
messenger RNA; cAMP, cyclic adenosine 3',5'-monophosphate; cA-F
cAMP-dependent protein kinase trachotoxinin A 20-a-benzoate; CDNA, complementary DNA; RNA, ribonucleic acid; mRNA, messenger RNA; cAMP, cyclic adenosine 3',5'-monophosphate; cA-PK, cAMP-dependent protein kinase; BTX, batrachotoxin; BTX-B, [³H]batrach protein; D. M. S. AMP, cyclic adenosine 3',5'-monophosphicAMP-dependent protein kinase; BTX, batrachotoxin; BTX
trachotoxinin A 20- α -benzoate; G protein, guanine nucleoti
protein; LDH, lactate dehydrogenase; IFM, isoleu methodoxinine; a mar, when the chinese; BTX, batrachotoxin; BTX-B, [³H]be
trachotoxinin A 20-α-benzoate; G protein, guanine nucleotide bindin
protein; LDH, lactate dehydrogenase; IFM, isoleucine-phenylalanine
methionine; Exactorian A 20-a-benzoate; G protein, guanine nucleotide binding
protein; LDH, lactate dehydrogenase; IFM, isoleucine-phenylalanine-
methionine; CHO, Chinese hamster ovary; PMA, phorbol 12-myristate
13-acetate; ATP, aden protein; LDH, lactate dehydrogenase; IFM, isoleucine-phenylalanine-
methionine; CHO, Chinese hamster ovary; PMA, phorbol 12-myristate
13-acetate; ATP, adenosine triphosphate; CMR, cerebral metabolic rate;
CMR_{gde}, rate of 13-acetate; ATP, adenosine triphosphate; CMR, cerebral n $\mathrm{CMR}_{\mathbf{glc}}$, rate of cerebral glucose utilization; CMRO₂, cerebral glucose utilization; CMRO₂, cerebral glucose utilization; PKC, pro
STX, saxitoxin; TTX, te CMR_{gic}, rate of cerebral glucose utilization; CMRO₂, cerebral rate of oxygen utilization; EEG, electroencephalogram; PKC, protein kinase C; STX, saxitoxin; TTX, tetrodotoxin; AMPA, α -amino-3-hydroxy-5-meth-yl-4-isox Example: The current graduate during the current potential; NMDA, α -amino-3-hydroxy-
STX, saxitoxin; TTX, tetrodotoxin; AMPA, α -amino-3-hydroxy-
yl-4-isoxazolepropionic acid; SD, spreading depression; DC, dirent; DC EXTX, saxitoxin; TTX, tetrodotoxin; AMPA, α -amino-3-hydroxy-5-meth-
yl-4-isoxazolepropionic acid; SD, spreading depression; DC, direct current; DC potential, direct current potential; NMDA, N-methyl-D-aspar-
tate; MCA, **LIP, and Expanditually active terms** component; DC potential, direct current potential; NMDA, N-methyl-D-aspartate; MCA, middle cerebral artery; IC₈₀, concentration that produces 50% of its maximum possible inhibition; Lidocaine ethochlonide; IC₈₀, concentration that the S0% of its maximum possible inhibition; ED₈₀, median effectively for the MFP, long-term potentiation; CAP, compound action potential diocaine ethochloride; KB-2796, (2,3,4-trimethoxybenzyl)piperazine; R56865, **N-[1-[(4-fluorophenoxy)** butyl]-4-piperidinyl]-N-methyl-2-benzothiazolamine; BW1003C87,
5-(2,3,5-trichlorophenyl)-2,4-diaminopyrimidine ethane sulphonate;
BW619C89, 4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophe-
nyl pyrimidine); GABA, 5-(2,3,5-trichlorophenyl)-2,4-diaminopyrimidine ethane sulphonate; **BW619C89,** 4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichiorophetrifluorophenyl)-2,4-diaminopyrimidine ethane sulphonate;
BW619C89, 4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophe-
nyl pyrimidine); GABA, γ-aminobutyric acid; riluzole, 2-amino-6-
trifluoromethoxybenzothiazole, vincours are all and the main observed in the set of the samino-
trifluoromethoxybenzothiazole, PK 26124, RP 54274; PD85,639, N-
(2,6-dimethyl-1-piperidinyl)propyl]- α -phenylbenzeneacetamid
vinpocetine, $[(3\alpha, 16\alpha)$ -ebu

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aspet

FIG. 1. Primary structure of the α -subunit on a Na⁺ channel (rat brain type IIA), illustrated as transmembrane folding diagram, with the major molecular determinants of its function. *Bold lines*, polypeptide chains FIG. 1. Primary structure of the α -subunit on a Na⁺ channel (rat brain type IIA), illustrated as transmembrane folding diagram, with the major molecular determinants of its function. *Bold lines*, polypeptide chains FIG. 1. Primary structure of the α -subunit on a Na⁺ channel (rat brain type IIA), illustrated as transmembrane folding diagram, with the major molecular determinants of its function. *Bold lines*, polypeptide chains major molecular determinants of its function. *Bold lines*, polypeptide chains with length of each segment approximately proportional to its true size in the rat brain Na⁺ channel; *Cylinders*, probable transmembrane $\$ true size in the rat brain Na⁺ channel; *Cylinders*, probable transmembrane α -helices—other segments presumably associated with the membrane (i.e., SS1-SS2) are drawn as loops in extended conformation; *Circled* P_a phosphorylated by cAMP-dependent protein kinase (cA-PK); P^* , this residue (serine⁵⁵⁴) lies within a cA-PK consensus sequence but is not detectably phosphorylated in vitro, suggesting that it is not accessible to cA-P detectably phosphorylated in vitro, suggesting that it is not accessible to cA-PK in the context of the *a*-subunit in vitro, or that it is
quantitatively phosphorylated under basal conditions in vivo (Murphy et al., 1993) quantitatively phosphorylated under basal conditions in vivo (Murphy et al., 1993); P_c *in the diamond symbol in intracellular* $L_{III/IV}$, site phosphorylated under physiological conditions by PKC—further activation of P phosphorylated under physiological conditions by PKC—further activation of PKC, however, also phosphorylates serine₆₁₀; IFM in L_{III/IV},
cluster of three adjacent hydrophic amino acid residues (isoleucine-phenylalaninevoltage sensor for activation; *ScTx*, scorpion toxins receptor sites; *Small circles with* $-$, $+$ or open, amino acid residues required for tetrodotoxin binding (see fig. 2 for details); (ψ), glycosylations sites. M

tetrodotoxin binding (see fig. 2 for details); (ψ), glycosylations sites. Mo
American Physiological Society.
al., 1988; Kayano et al., 1988). The greatest degree of sprimary sequence conservation among isoforms occurs r American Physiological Society.
al., 1988; Kayano et al., 1988). The greatest degree of seque
primary sequence conservation among isoforms occurs many
in repeats I to IV and in the linker between III and IV it is $\overline{\text{L}}$ al., 1988; Kayano et al., 1988). The greatest degree of
primary sequence conservation among isoforms occurs
in repeats I to IV and in the linker between III and IV
(L_{III/IV}), regions of the sequence which presumably subprimary sequence conservation among isoforms occurs
in repeats I to IV and in the linker between III and IV
 $(L_{\text{HII/V}})$, regions of the sequence which presumably sub-
serve conserved functions (see section B.6.) (Cattera primary sequence conservation among isoforms occurs in repeats I to IV and in the linker between III and IV it $(L_{\text{HI/IV}})$, regions of the sequence which presumably sub-
serve conserved functions (see section B.6.) (Catt in repeats I to IV and in the linker between III and IV $(L_{\text{HI/IV}})$, regions of the sequence which presumably subserve conserved functions (see section B.6.) (Catterall, 1992). Type II and IIA subunits are alternatively ($L_{\text{HI/IV}}$), regions of the sequence which presumably subserve conserved functions (see section B.6.) (Catterall, change 1992). Type II and IIA subunits are alternatively spliced gangerorms, differing in only six amino *hypervariable* functions (see section B.6.) (Catterall, 1992). Type II and IIA subunits are alternatively spliced forms, differing in only six amino acids of approximately 2000, and most of these differences are clustered 1992). Type II and II
forms, differing in on
2000, and most of the
hypervariable region
(Auld et al., 1988). One α -subtype from rms, differing in only six amino acids of approximately 00, and most of these differences are clustered in a *pervariable* region in the first homologous repeat uld et al., 1988).
One α -subtype from rat heart (H1) and

2000, and most of these differences are clustered in the first homologous rep (Auld et al., 1988).

One α -subtype from rat heart (H1) and two α -subty from rat skeletal muscle (SkM1 and SkM2; TTX-sensitive and -insen hypervariable region in the first homologous repeated and equals (Auld et al., 1988).

One α -subtype from rat heart (H1) and two α -subtype from rat skeletal muscle (SkM1 and SkM2; TTX-sens tive and -insensitive, res (Auld et al., 1988). all and two α -subtypes term rat skeletal muscle (SkM1 and SkM2; TTX-sensing from rat skeletal muscle (SkM1 and SkM2; TTX-sensing interesting and -insensitive, respectively) have also been docu-
men One α -subtype from rat heart (H1) and two α -subtypes tem
from rat skeletal muscle (SkM1 and SkM2; TTX-sensi-
tive and -insensitive, respectively) have also been docu-
mented (Rogart et al., 1989; Trimmer et al., 198 from rat skeletal muscle (SkM1 and SkM2; TTX-sensitive and -insensitive, respectively) have also been docu-
the mented (Rogart et al., 1989; Trimmer et al., 1989; Kallen of
et al., 1990). They have a close structural rela tive and -insensitive, respectively) have also been doc
mented (Rogart et al., 1989; Trimmer et al., 1989; Kalle
t al., 1990). They have a close structural relationship
those in the brain, with the greatest similarity in a mented (Rogart et al., 1989; Trimmer et al., 1989; Kallen
et al., 1990). They have a close structural relationship to
those in the brain, with the greatest similarity in amino
acid sequence in the homologous repeats from t et al., 1990). They have a close structural relationship to
those in the brain, with the greatest similarity in amino
acid sequence in the homologous repeats from trans-
membrane segments S1 to S6, whereas the intracellula those in the brain, with the greatest similarity in amino cells
acid sequence in the homologous repeats from trans-
membrane segments S1 to S6, whereas the intracellular sate
connecting loops are not highly conserved (Tri acid sequence in the homologous repeats from trans-
membrane segments S1 to S6, whereas the intracellular so
connecting loops are not highly conserved (Trimmer et
ind., 1989; Rogart et al., 1989). Finally, it is important membrane segments S1 to S6, whereas the intracellula
connecting loops are not highly conserved (Trimmer eal., 1989; Rogart et al., 1989). Finally, it is important t
mention that two novel Na⁺ channel α -subunits hav
b connecting loops are not highly conserved (Trimmer et in al., 1989; Rogart et al., 1989). Finally, it is important to position that two novel Na⁺ channel α -subunits have lubeen reported recently: (α) Na-g, a disti al., 1989; Rogart et al., 1989). Finally, it is important to pumeration that two novel Na^+ channel α -subunits have lulibeen reported recently: (α) Na-g, a distinctive Na⁺ channel α -subunit cloned from rat ast been reported recently: (a) Na-g, a distinctive Na⁺ chan-Sontheimer et al., 1994).

nel α -subunit cloned from rat astrocytes cDNA (Gautron An Na⁺ channel α -subtype from human brain has

et al., 1992); and (b) Na

odified from Caterall (1992), with permission of the author and the
sequence of Na-g retains the four-repeat structure and
many conserved features of other brain α -subunits, but
it is distinctly more divergent, and has sequence of Na-g retains the four-repeat structure and
many conserved features of other brain α-subunits, but
it is distinctly more divergent, and has, presumably, a
low sensitivity to TTX. In vivo, the mRNA from this gl sequence of Na-g retains the four-repeat structure and
many conserved features of other brain α -subunits, but
it is distinctly more divergent, and has, presumably, a
low sensitivity to TTX. In vivo, the mRNA from this sequence of Na-g retains the four-repeat structure and
many conserved features of other brain α -subunits, but
it is distinctly more divergent, and has, presumably, a
low sensitivity to TTX. In vivo, the mRNA from this many conserved features of other brain α -subunits, but
it is distinctly more divergent, and has, presumably, a
low sensitivity to TTX. In vivo, the mRNA from this glial
channel was detected not only in the brain, dorsa it is distinctly more divergent, and has, presumably, a
low sensitivity to TTX. In vivo, the mRNA from this glial
channel was detected not only in the brain, dorsal root
ganglia and sciatic nerve, but also in tissues outsi low sensitivity to TTX. In vivo, the mRNA from this glial
channel was detected not only in the brain, dorsal root
ganglia and sciatic nerve, but also in tissues outside the
nervous system including heart, skeletal muscle a channel was detected not only in the brain, dorsal root ganglia and sciatic nerve, but also in tissues outside the nervous system including heart, skeletal muscle and lung (Gautron et al., 1992). With regard to NaCh6, its ganglia and sciatic nerve, but also in tissues outside the
nervous system including heart, skeletal muscle and
lung (Gautron et al., 1992). With regard to NaCh6, its
most significant aspects are that it is one of the most nervous system including heart, skeletal muscle and
lung (Gautron et al., 1992). With regard to NaCh6, its
most significant aspects are that it is one of the most
abundant Na⁺ channel α -subtypes in the nervous sys-
t lung (Gautron et al., 1992). With regard to NaCh6, its
most significant aspects are that it is one of the most
abundant Na⁺ channel α -subtypes in the nervous sys-
tem at the RNA level, and that it is expressed in bot most significant aspects are that it is one of the most abundant Na⁺ channel α -subtypes in the nervous system at the RNA level, and that it is expressed in both neurons and glia (Schaller et al., 1995). It is notewor abundant Na⁺ channel α -subtypes in the nervous system at the RNA level, and that it is expressed in both neurons and glia (Schaller et al., 1995). It is noteworthy that glial cells, although nonexcitable, express a w tem at the RNA level, and that it is expressed in both
neurons and glia (Schaller et al., 1995). It is noteworthy
that glial cells, although nonexcitable, express a wealth
of voltage-gated ion channels, including Na^+ an that glial cells, although nonexcitable, express a wealth
of voltage-gated ion channels, including Na^+ and Ca^{2+}
channels that are typically characteristic of excitable
cells (Ritchie, 1992; Sontheimer, 1994; Oh and W that glial cells, although nonexcitable, express a wealth
of voltage-gated ion channels, including Na^+ and Ca^{2+}
channels that are typically characteristic of excitable
cells (Ritchie, 1992; Sontheimer, 1994; Oh and W of voltage-gated ion channels, including Na⁺ and Ca²⁺
channels that are typically characteristic of excitable
cells (Ritchie, 1992; Sontheimer, 1994; Oh and Wax-
mann, 1994). The primary role of Na⁺ channels in these channels that are typically characteristic of excitable
cells (Ritchie, 1992; Sontheimer, 1994; Oh and Wax
mann, 1994). The primary role of Na⁺ channels in thes
satellite cells may be to ensure a controlled leak of Na⁻ cells (Ritchie, 1992; Sontheimer, 1994; Oh and W
mann, 1994). The primary role of Na⁺ channels in th
satellite cells may be to ensure a controlled leak of Γ
into cells, thereby fueling the glial Na⁺/K⁺-ATP
pump, mann, 1994). The primary role of Na⁺ channels in these satellite cells may be to ensure a controlled leak of Na⁺ into cells, thereby fueling the glial Na⁺/K⁺-ATPase pump, which removes local excess of K⁺ in the satellite cells may be to en
into cells, thereby fuelin
pump, which removes loca
lular space (i.e., spatial b
Sontheimer et al., 1994).
An Na⁺ channel α -sub to cells, thereby fueling the glial Na⁺/K⁺-ATPase
ump, which removes local excess of K⁺ in the extracel-
lar space (i.e., spatial buffering) (Sontheimer, 1994;
ntheimer et al., 1994).
An Na⁺ channel α -subtype f pump, which removes local excess of K^+ in the extracel-
lular space (i.e., spatial buffering) (Sontheimer, 1994;
Sontheimer et al., 1994).
An Na⁺ channel α -subtype from human brain has
been identified from a cDNA

lular space (i.e., spatial buffering) (Sontheimer, 1994;
Sontheimer et al., 1994).
An Na⁺ channel α -subtype from human brain has
been identified from a cDNA library derived from hu-
man cerebral cortex, and its expre

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MODULATION OF VOLTA
Na⁺ channels. The predicted structure exhibits greatest
homology (97% sequence identity) and structural simi-MODULATION OF VOLT.
Na⁺ channels. The predicted structure exhibits greates
homology (97% sequence identity) and structural simi-
larities to the rat brain type II Na⁺ channels (Ahmed e MODULATION OF VOLTAGE-

Na⁺ channels. The predicted structure exhibits greatest

homology (97% sequence identity) and structural simi-

larities to the rat brain type II Na⁺ channels (Ahmed et

al., 1992). Other studi Na^+ channels. The predicted structure exhibits greatest for
homology (97% sequence identity) and structural simi-
larities to the rat brain type II Na^+ channels (Ahmed et ity
al., 1992). Other studies aiming t Na⁺ channels. The predicted structure exhibits greate homology (97% sequence identity) and structural sinarities to the rat brain type II Na⁺ channels (Ahmed al., 1992). Other studies aiming to identify human bra Na⁺ larities to the rat brain type II Na⁺ channels (Ahmed et al., 1992). Other studies aiming to identify human brain Na⁺ channel α subtypes have suggested a strong homology between these channels and their rat brain c larities to the rat brain type II Na⁺ channels (Ahmed et ity, and carry out the basic functions of the Na⁺ channel.
al., 1992). Other studies aiming to identify human brain They also contain most of the receptor sites Na⁺ channel α subtypes have suggested a strong homology between these channels and their rat brain counter-
parts (Lu et al., 1992), and the human β_1 -subunit was
found 96% identical to the rat brain subunit at th ogy between these channels and their rat brain counterogy between these channels and their rat brain counter-
parts (Lu et al., 1992), and the human β_1 -subunit was Na⁴
found 96% identical to the rat brain subunit at the of a
amino acid level (McClatchey et al., 1993; M parts (Lu et al., 1992), and the human β_1 -subunit was found 96% identical to the rat brain subunit at the amino acid level (McClatchey et al., 1993; Makita et al., 1994). These structural analogies, supplemented by cl found 96% identical to the rat brain subunit at the of amino acid level (McClatchey et al., 1993; Makita et al., pe 1994). These structural analogies, supplemented by 2b close functional properties between rat and human N amino acid level (McClatchey et al., 1993; Makita et al., pe
1994). These structural analogies, supplemented by 2b
close functional properties between rat and human Na⁺
currents (Cummins et al., 1994), strongly support 1994). These structural analogies, supplemented by
close functional properties between rat and human Na
currents (Cummins et al., 1994), strongly support the
view that rat neurons represent a valid model for the
study of currents (Cummins et al., 1994), strongly support the view that rat neurons represent a valid model for the study of human Na^+ channel expression and function,
B. Molecular Determinants of Na^+ Channel Function, Toxico *The view that rat neurons representy of human Na⁺ channel example the Modecular Determinants of National Pharmacology Most Na⁺ channels are in a*

udy of human Na⁺ channel expression and function.
 $Molecular Determinants of Na⁺ Channel Function,
\nxxicology, and Pharmacology
\nMost Na⁺ channels are in a closed, resting state at
\ngative membrane potentials. During a step depolar-$ B. Molecular Determinants of Na⁺ Channel Function
Toxicology, and Pharmacology
Most Na⁺ channels are in a closed, resting state
negative membrane potentials. During a step depol
ization, the membrane Na⁺ conductance Examples the membrane of Na Channel Function,
 $Toxicology, and Pharmacology$ conductance $\frac{1}{2}$

Most Na⁺ channels are in a closed, resting state at binegative membrane potentials. During a step depolar-

ization, the membrane Na⁺ c due to *voltage-dependent activation*, and *reating* state at negative membrane potentials. During a step depolarization, the membrane Na⁺ conductance rises rapidly due to *voltage-dependent activation* of Na⁺ channels Most Na⁺ channels are in a closed, *resting* state at negative membrane potentials. During a step depolarization, the membrane Na⁺ conductance rises rapidly due to *voltage-dependent activation* of Na⁺ channels, rea negative membrane potentials. During a step depolar-
ization, the membrane Na⁺ conductance rises rapidly of t
due to *voltage-dependent activation* of Na⁺ channels, ide
reaches a peak within a few milliseconds, and the ization, the membrane Na^+ conductance rises rapidly
due to *voltage-dependent activation* of Na^+ channels,
reaches a peak within a few milliseconds, and then de-
clines gradually due to channel *inactivation*. due to *voltage-dependent activation* of $Na⁺$ channels, reaches a peak within a few milliseconds, and then declines gradually due to channel *inactivation*. These two fundamental processes ensure a rapid but transien reaches a peak within a few milliseconds, and then declines gradually due to channel *inactivation*. These two fundamental processes ensure a rapid but transient increase of ion conductance in response to membrane potentia clines gradually due to channel *inactivation*. These two
fundamental processes ensure a rapid but transient in-
crease of ion conductance in response to membrane po-
tential changes. They can be portrayed by an activation fundamental processes ensure a rapid but transient in-
crease of ion conductance in response to membrane po-
tential changes. They can be portrayed by an activation
gate that opens rapidly upon depolarization and closes
t crease of ion conductance in response to membrane po-
tential changes. They can be portrayed by an activation
gate that opens rapidly upon depolarization and closes
rapidly upon repolarization and an inactivation gate
that tential changes. They can be portrayed by an activation gate that opens rapidly upon depolarization and closes rapidly upon repolarization and an inactivation gate that closes slowly upon depolarization and opens upon repo gate that opens rapidly upon depolarization and closes
rapidly upon repolarization and an inactivation gate
that closes slowly upon depolarization and opens upon
repolarization (Hodgkin and Huxley, 1952; Hille, 1991).
Volt rapidly upon repolarization and an inactivation gate
that closes slowly upon depolarization and opens upon
repolarization (Hodgkin and Huxley, 1952; Hille, 1991).
Voltage-dependent activation controls the timing and
voltag that closes slowly upon depolarization and opens upon
repolarization (Hodgkin and Huxley, 1952; Hille, 1991).
Voltage-dependent activation controls the timing and
voltage-dependence of ion channels opening in response
to m Voltage-dependent activation controls the timing and voltage-dependence of ion channels opening in response to membrane potential changes; inactivation controls the rate and extent of ion channel closure during maintained voltage-dependence of ion channels opening in response
to membrane potential changes; inactivation controls
the rate and extent of ion channel closure during main-
tained depolarization. In addition to these very rapid
ch to membrane potential changes; inactivation controls to membrane potential changes; inactivation controls
the rate and extent of ion channel closure during main-
tained depolarization. In addition to these very rapid
changes, the ion conductance activity of voltage-gated
 Na the rate and extent of ion channel closure during main-
tained depolarization. In addition to these very rapid
changes, the ion conductance activity of voltage-gated
 Na^+ channels can be modulated over longer periods tained depolarization. In addition to these very rapidenges, the ion conductance activity of voltage-gate Na⁺ channels can be modulated over longer periods b protein phosphorylation and interaction with guanyl nu cleotid $Na⁺$ channels can be modulated over longer periods by
protein phosphorylation and interaction with guanyl nu-
cleotide binding (G) proteins (see below, section C).
Remarkable progress has been made toward defini-
tio

Na⁺ channels can be modulated over longer periods by
protein phosphorylation and interaction with guanyl nu-
cleotide binding (G) proteins (see below, section C).
The structural elements that are responsible for
the bas protein phosphorylation and interaction with guanyl nucleotide binding (G) proteins (see below, section C). The emarkable progress has been made toward definition of the structural elements that are responsible for the ba cleotide binding (G) proteins (see below, section C).

Remarkable progress has been made toward defini-

tion of the structural elements that are responsible for

the basic functions outlined above, as well as for the

bi Remarkable progress has been made toward definition of the structural elements that are responsible for the basic functions outlined above, as well as for the binding of specific neurotoxins and local anesthetic (Catteral tion of the structural elements that are responsible for the basic functions outlined above, as well as for the binding of specific neurotoxins and local anesthetic (Catterall, 1993a, b). The α -subunit is the principal the basic functions outlined above, as well as for the binding of specific neurotoxins and local anestheti (Catterall, 1993a, b). The α -subunit is the principal conponent of the Na⁺ channel, and it forms functional c binding of specific neurotoxins and local anesthetics (Catterall, 1993a, b). The α -subunit is the principal component of the Na⁺ channel, and it forms functional channels when expressed alone in mammalian cells or *X* (Catterall, 1993a, b). The α -subunit is the principal component of the Na⁺ channel, and it forms functional channels when expressed alone in mammalian cells or *Xenopus* occytes (Goldin et al., 1986; Noda et al., 198 ponent of the Na⁺ channel, and it forms functional channels when expressed alone in mammalian cells or *Xeno-*
pus oocytes (Goldin et al., 1986; Noda et al., 1986;
Scheuer et al., 1990; West et al., 1992b) This feature, nels when expressed alone in mammalian cells or *Xeno*-
pus oocytes (Goldin et al., 1986; Noda et al., 1986; select
Scheuer et al., 1990; West et al., 1992b) This feature, are and the fact that no drug or toxin has so far pus oocytes (Goldin et al., 1986; Noda et al., 1986
Scheuer et al., 1990; West et al., 1992b) This feature
and the fact that no drug or toxin has so far been re
ported to interact with β_1 or β_2 subunits, prompted Scheuer et al., 1990; West et al., 1992b) This feature, and the fact that no drug or toxin has so far been reported to interact with β_1 or β_2 subunits, prompted us to overlook these accessory subunits in this revi and the fact that no drug or toxin has so far been re-
ported to interact with β_1 or β_2 subunits, prompted us to
overlook these accessory subunits in this review. How-
ever, the β_1 subunit may well be a valuab ported to interact with β_1 or β_2 subunits, prompted us to clusted overlook these accessory subunits in this review. How-
ever, the β_1 subunit may well be a valuable target for 19
developing therapeutic Na⁺ c overlook these accessory subunits in this review. However, the β_1 subunit may well be a valuable target for
developing therapeutic Na⁺ channel modulators, be-
cause it appears to modify the inactivation properties o ever, the β_1 subunit may well be a valuable target
developing therapeutic Na⁺ channel modulators,
cause it appears to modify the inactivation properties
Na⁺ channels (Isom et al., 1992; Goldin, 1993), althou
coexp developing therapeutic Na⁺ channel modulators, the cause it appears to modify the inactivation properties Na⁺ channels (Isom et al., 1992; Goldin, 1993), although coexpression of β_1 is required for normal kinetic

 $-$ GATED NA⁺ CHANNELS 25
fore, contain all the necessary structural elements to
form the transmembrane ion pore, ensure ion selectiv- $-$ GATED NA⁺ CHANNELS
fore, contain all the necessary structural elements
form the transmembrane ion pore, ensure ion selectiv, and carry out the basic functions of the Na⁺ chann -GATED NA⁺ CHANNELS 25
fore, contain all the necessary structural elements to
form the transmembrane ion pore, ensure ion selectiv-
ity, and carry out the basic functions of the Na⁺ channel.
They also contain most of fore, contain all the necessary structural elements to
form the transmembrane ion pore, ensure ion selectiv-
ity, and carry out the basic functions of the Na⁺ channel.
They also contain most of the receptor sites for th fore, contain all the necessary structural elements to
form the transmembrane ion pore, ensure ion selectiv-
ity, and carry out the basic functions of the Na⁺ channel.
They also contain most of the receptor sites for th form the transmembrane ion pore, ensure ion selectiv-
ity, and carry out the basic functions of the Na⁺ channel.
They also contain most of the receptor sites for the
toxins and many pharmacological agents that modify
Na ity, and carry out the basic functions of the Na⁺ channel.
They also contain most of the receptor sites for the toxins and many pharmacological agents that modify Na⁺ channel functions. In all models for voltage-gated toxins and many pharmacological agents that modify $Na⁺$ channel functions. In all models for voltage-gated $Na⁺$ channels, the transmembrane pore is at the center of a square array of homologous repeats, with each repeat contributing to a quarter of the channel p Na⁺ channels, the transmembrane pore is at the center ¹ channels, the transmembrane pore is at the center
a square array of homologous repeats, with each re-
at contributing to a quarter of the channel pore (fig.
 1) (Hille, 1991; Catterall, 1993a, b; Heinemann, 1995).
1.

of a square array of homologous repeats, with each repeat contributing to a quarter of the channel pore (fig. 2b) (Hille, 1991; Catterall, 1993a, b; Heinemann, 1995).
 1. Extracellular opening of the pore: tetrodotoxin an peat contributing to a quarter of the channel pore (fig. 2b) (Hille, 1991; Catterall, 1993a, b; Heinemann, 1995).

1. Extracellular opening of the pore: tetrodotoxin and

saxitoxin receptor site. TTX and saxitoxin (STX) ar saxitoxin receptor site. TTX and saxitoxin (STX) are wa-
ter-soluble guanidinium toxins that selectively block
 $Na⁺$ channels by binding, with high affinity, to the ex-
ternal side of the pore (neurotoxin receptor sit 1. Extracellular opening of the pore: tetrodotoxin and saxitoxin receptor site. TTX and saxitoxin (STX) are water-soluble guanidinium toxins that selectively block Na^+ channels by binding, with high affinity, to the ext saxitoxin receptor site. TTX and saxitoxin (STX) are wa-
ter-soluble guanidinium toxins that selectively block
Na⁺ channels by binding, with high affinity, to the ex-
ternal side of the pore (neurotoxin receptor site 1) ter-soluble guanidinium toxins that selectively block Na^+ channels by binding, with high affinity, to the external side of the pore (neurotoxin receptor site 1) (Adams and Olivera, 1994). The fact that protonation or co $Na⁺$ channels by binding, with high affinity, to the external side of the pore (neurotoxin receptor site 1) ($Ad-$ ams and Olivera, 1994). The fact that protonation or covalent modification of carboxyl residues blocks ternal side of the pore (neurotoxin receptor site 1) (Ad-
ams and Olivera, 1994). The fact that protonation or
covalent modification of carboxyl residues blocks their
binding suggests that these cationic toxins may bind to ams and Olivera, 1994). The fact that protonation or covalent modification of carboxyl residues blocks their binding suggests that these cationic toxins may bind to a ring of carboxyl residues at the extracellular opening covalent modification of carboxyl residues blocks their binding suggests that these cationic toxins may bind to a ring of carboxyl residues at the extracellular opening of the pore (Hille, 1991). The first of these sites

FIG. 2. Current model of the extracellular opening of type II rat
brain Na⁺ channel. The transmembrane pore is at the center of a
square array of homologous repeats, with each repeat contributing to
a quarter of the chan brain Na⁺ channel. The transmembrane pore is at the center of a
square array of homologous repeats, with each repeat contributing to
a quarter of the channel pore (b) . a Folding topology of repeat I,
illustrating the Figure array of homologous repeats, with each repeat contributing to a quarter of the channel pore (b) . a Folding topology of repeat illustrating the hairpin-like P-region located in the S5-S6 linker. This segment, pre to quarter of the channel pore (b) . *a* Folding topology of repeat I, illustrating the hairpin-like P-region located in the S5-S6 linker.
This segment, previously called short segments SS1-SS2, contributes to the lining I ustrating the hairpin-like P-region located in the S5-S6 linker.
This segment, previously called short segments SS1-SS2, contributes
to the lining of the pore at its extracellular opening. The P-region is
critical to the This segment, previously called short segments SS1-SS2, contributes
to the lining of the pore at its extracellular opening. The P-region is
critical to the binding of guanidinium toxins (TTX and STX), Na⁺
channel conduct critical to the binding of guanidinium toxins (TTX and STX), Na⁺
channel conductance, and ion selectivity. Amino acids code and po-
sition in the sequence: E, glutamate³⁸⁷; F, tyrosine³⁸⁵; D, aspar-
tate³⁸⁴. *b* S channel conductance, and ion selectivity. Amin acids code and po-
sition in the sequence: E, glutamate³⁸⁷; F, tyrosine³⁸⁵; D, aspar-
tate³⁸⁴. *b* Schematic diagram of the extracellular opening of type II
rat brain N extrained by the sequence: E, glutamate³⁸⁷; F, tyrosine³⁸⁵; D, aspartate³⁸⁴. *b* Schematic diagram of the extracellular opening of type II rat brain Na⁺ channels. The two rings of four amino acid residues that are state³⁸⁴. *b* Schematic diagram of the extracellular opening of type II rat brain Na⁺ channels. The two rings of four amino acid residues that are represented, as well as F^{385} in repeat I, are all essential for TT are at identical position, a wear as it is in testes in a second ductance and selectivity, with the inner ring differentiating Na⁺-selectivity from Ca²⁺-selectivity (see text). Amino acids in each ring are located at i accurive from Ca²⁺-selectivity (see text). Amino acids in each ring
are located at identical position on each P-region of repeat I-IV.
Positive amino acid residues are in black, neutral residues in gray,
and negative res **clockwise, the control of the control of the current experimental data does not expect I-I-Positive amino acid residues are in black, neutral residues in grand negative residues in open circles. Homologous repeats are dra** Positive amino acid residues are in black, neutral residues in gray,
and negative residues in open circles. Homologous repeats are drawn
clockwise, but current experimental data does not exclude a coun-
terclockwise arran Positive amino acid residues are in black, neutral residues in gray,
and negative residues in open circles. Homologous repeats are drawn
clockwise, but current experimental data does not exclude a coun-
terclockwise arrang and negative residues in open circles. Homologous repeats are drawn clockwise, but current experimental data does not exclude a counterclockwise arrangement (Heinemann, 1995; Heinemann et al., 1994). *Repeat I*, outer rin clockwise, but current experimental data does not exclude a couterclockwise arrangement (Heinemann, 1995; Heinemann et a 1994). *Repeat I*, outer ring = E, glutamate³⁴⁵; *Repeat II*, outer ring = E, glutamate³⁴⁵; *in* terclockwise arrangement (Heinemann, 1995; Heinemann et al
1994). Repeat I, outer ring = E, glutamate³⁸⁷, F, tyrosine³⁸⁵; inne
ring: D, aspartate³⁸⁴; Repeat II, outer ring = E, glutamate⁹⁴⁵; inne
ring = E, glutama 1994). Repeat *I*, outer ring = E, glutamate³⁸⁷, F, tyrosine³⁸⁵; inner ring: D, aspartate³⁸⁴; Repeat *II*, outer ring = E, glutamate³⁴⁵; inner ring = E, glutamate³⁴²; Repeat *III*, outer ring: M, methionine¹⁴²⁵ ring = E, glutamate⁹⁴², Repeat III, outer ring: M, methionine¹⁴²⁵, inner ring: K, lysine ¹⁴²²; Repeat IV, outer ring: D, aspartate¹⁷¹⁷; inner ring: A, alanine¹⁷¹⁴. Diagram *b* is reproduced from Heinemann (1995)

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URENJAK AND OBRENOVITCH
located on the S5-S6 linker of repeat I (fig. 2). Mutation an aqueous pore, and the alkali cations permeability
of this residue to glutamine reduces 10,000-fold the af- falls with increasing crysta OF URENJAK AND
located on the S5-S6 linker of repeat I (fig. 2). Mutation
of this residue to glutamine reduces 10,000-fold the af-
finity of TTX for the channel (Noda et al., 1989). The URENJAK AND OBF
located on the S5-S6 linker of repeat I (fig. 2). Mutation
of this residue to glutamine reduces 10,000-fold the af-
finity of TTX for the channel (Noda et al., 1989). The Rh
nearby, negatively charged aspar located on the S5-S6 linker of repeat I (fig. 2). Mutation and of this residue to glutamine reduces 10,000-fold the affinity of TTX for the channel (Noda et al., 1989). The Rb nearby, negatively charged aspartate³⁸⁴ was located on the S5-S6 linker of repeat I (fig. 2). Mutation
of this residue to glutamine reduces 10,000-fold the af-
finity of TTX for the channel (Noda et al., 1989). The
nearby, negatively charged aspartate³⁸⁴ was also of this residue to glutamine reduces 10,000-fold the af-
finity of TTX for the channel (Noda et al., 1989). The Rb⁺
nearby, negatively charged aspartate³⁸⁴ was also found aga:
to be important for guanidinium toxin bloc finity of TTX for the channel (Noda et al., 1989). The
nearby, negatively charged aspartate³⁸⁴ was also found
to be important for guanidinium toxin block. The mutant
D384N (i.e., aspartate replaced by asparagine) was no
 nearby, negatively charged aspartate³⁸⁴ was also found
to be important for guanidinium toxin block. The mutant
D384N (i.e., aspartate replaced by asparagine) was no
longer blocked by TTX and STX and showed an ex-
tremely to be important for guanidinium toxin block. The mutant sur
D384N (i.e., aspartate replaced by asparagine) was no obs
longer blocked by TTX and STX and showed an ex-
tremely low single-channel conductance (Pusch et al., ot D384N (i.e., aspartate replaced by asparagine) was no
longer blocked by TTX and STX and showed an ex-
tremely low single-channel conductance (Pusch et al.,
1991). Subsequent studies have identified amino acid
residues in t longer blocked by TTX and STX and showed an ex-
tremely low single-channel conductance (Pusch et al., otl
1991). Subsequent studies have identified amino acid
residues in the same position as glutamate³⁸⁷ and as-
partate tremely low single-channel conductance (Pusch et al., 1991). Subsequent studies have identified amino acid residues in the same position as glutamate³⁸⁷ and aspartate³⁸⁴ in the S5-S6 linker of the other repeats, which 1991). Subsequent studies have identified amino acid
residues in the same position as glutamate³⁸⁷ and as-
partate³⁸⁴ in the S5-S6 linker of the other repeats, which
are all required for high-affinity TTX binding and partate³⁸⁴ in the S5-S6 linker of the other repeats, which
are all required for high-affinity TTX binding and nor-
mal single-channel conductance (Terlau et al., 1991).
These, and other results obtained from Ca^{2+} and are all required for high-affinity TTX binding and nor-
mal single-channel conductance (Terlau et al., 1991). als
These, and other results obtained from Ca^{2+} and K^+ al.
channel studies, contributed to the current mo mal single-channel conductance (Terlau et al., 1991).
These, and other results obtained from Ca^{2+} and K^{+}
channel studies, contributed to the current model of
voltage-gated ion channels in which a section of the
S5-These, and other results obtained from Ca^{2+} and K^{+}
channel studies, contributed to the current model of
voltage-gated ion channels in which a section of the
S5-S6 linker forms at least part of the actual pore, dipchannel studies, contributed to the current model voltage-gated ion channels in which a section of the S5-S6 linker forms at least part of the actual pore, diping into and out of the membrane as a hairpin-likertucture (fig voltage-gated ion channels in which a section of S5-S6 linker forms at least part of the actual pore, ping into and out of the membrane as a hairpin structure (fig. 2a) (Heinemann et al., 1994; Heinem 1995). This region co S5-S6 linker forms at least part of the actual pore, dipping into and out of the membrane as a hairpin-like structure (fig. 2a) (Heinemann et al., 1994; Heinemann, 1995). This region corresponds to the short membrane-assoc ping into and out of the membrane as a hairpin-like
structure (fig. 2a) (Heinemann et al., 1994; Heinemann,
1995). This region corresponds to the short membrane-
associated segments SS1 and SS2 (now termed P-region,
for po structure (fig. 2a) (Heinemann et al., 1994; Heinemann, 1995). This region corresponds to the short membrane-
associated segments SS1 and SS2 (now termed P-region, r
for pore-region), previously postulated to form the nar-1995). This region corresponds to the short membrane-
associated segments SS1 and SS2 (now termed P-region,
for pore-region), previously postulated to form the nar-
row section of the channel ensuring ionic selectivity
(Gr for pore-region), previously postulated to form the narrow section of the channel ensuring ionic selectivity (Greenblatt et al., 1985; Guy and Seetharamulu, 1986; Guy and Conti, 1990).
Although cardiac Na⁺ channels cont r pore-region), previously postulated to form the nar-
w section of the channel ensuring ionic selectivity
reenblatt et al., 1985; Guy and Seetharamulu, 1986;
uy and Conti, 1990).
Although cardiac Na⁺ channels contain th

row section of the channel ensuring ionic selective
(Greenblatt et al., 1985; Guy and Seetharamulu, 19
Guy and Conti, 1990).
Although cardiac Na⁺ channels contain the eight r
idues described above, which are essential f (Greenblatt et al., 1985; Guy and Seetharamulu, 1986;

Guy and Conti, 1990).

Although cardiac Na⁺ channels contain the eight res-

idues described above, which are essential for high-af-

finity TTX binding, they bind Guy and Conti, 1990).

Although cardiac Na⁺ channels contain the eight residues described above, which are essential for high-af-

finity TTX binding, they bind to TTX with 200 times

lower affinity than brain or skelet Although cardiac Na⁺ channels contain the eight residues described above, which are essential for high-affinity TTX binding, they bind to TTX with 200 times lower affinity than brain or skeletal muscle (SkM1) Na⁺ chan idues described above, which are essential for high-af-
finity TTX binding, they bind to TTX with 200 times
lower affinity than brain or skeletal muscle (SkM1) Na^+
channels. This indicates that other residues must con-
 finity TTX binding, they bind to TTX with 200 times per lower affinity than brain or skeletal muscle (SkM1) Na^+ gather channels. This indicates that other residues must contribute in an essential way to the TTX receptor lower affinity than brain or skeletal muscle (SkM1) Na⁺
channels. This indicates that other residues must con-
tribute in an essential way to the TTX receptor site.
Site-directed mutagenesis and toxin assay have located
 channels. This indicates that other residues must con-
tribute in an essential way to the TTX receptor site. ch
Site-directed mutagenesis and toxin assay have located tio
one such residue at position 385 (fig. 2), i.e., t tribute in an essential way to the TTX receptor site. characteristic-directed mutagenesis and toxin assay have located tion one such residue at position 385 (fig. 2), i.e., two residues guas from glutamate³⁸⁷ toward the Site-directed mutagenesis and toxin assay have loctone such residue at position 385 (fig. 2), i.e., two resider
from glutamate³⁸⁷ toward the amino terminus in repeat I of type IIA brain α -subtype. In the brain skelet one such residue at position 385 (fig. 2), i.e., two residues
from glutamate³⁸⁷ toward the amino terminus in the
repeat I of type IIA brain α -subtype. In the brain and
skeletal muscle, this residue is tyrosine and ph repeat I of type IIA brain α -subtype. In the brain and skeletal muscle, this residue is tyrosine and phenylalanine, respectively, but it is cysteine in the heart Na⁺ channel. Mutation of this residue from cysteine to repeat I of type IIA brain α -subtype. In the brain and skeletal muscle, this residue is tyrosine and phenylala-
nine, respectively, but it is cysteine in the heart Na⁺
channel. Mutation of this residue from cysteine skeletal muscle, this residue is tyrosine and phenylala-
nine, respectively, but it is cysteine in the heart $Na⁺$
channel. Mutation of this residue from cysteine to phe-
nylalanine or tyrosine causes a 200-fold incre mine, respectively, but it is cysteine in the heart Na^+ b;
channel. Mutation of this residue from cysteine to phe- (7)
nylalanine or tyrosine causes a 200-fold increase in af-
whity for TTX in the cardiac Na^+ channel channel. Mutation of this residue from cysteine to phe- (Tay nylalanine or tyrosine causes a 200-fold increase in af-
finity for TTX in the cardiac Na⁺ channel (Heinemann al., et al., 1992a). The converse mutation in th nylalanine or tyrosine causes a 200-fold increase in affinity for TTX in the cardiac Na^+ channel (Heinemann et al., 1992a). The converse mutation in the brain or skeletal muscle channel reduces their affinity for TTX by hity for TTX in the cardiac Na^+ channel (Heinemann al., 1992a). The converse mutation in the brain or eletal muscle channel reduces their affinity for TTX by e same factor (Satin et al., 1992; Backx et al., 1992). T et al., 1992a). The converse mutation in the brain or skeletal muscle channel reduces their affinity for TTX by the same factor (Satin et al., 1992; Backx et al., 1992). The current structural model depicts the external m

skeletal muscle channel reduces their affinity for TTX b
the same factor (Satin et al., 1992; Backx et al., 1992)
The current structural model depicts the externs
mouth of the Na⁺ channel pore as a funnel-shape
space, i the same factor (Satin et al., 1992; Backx et al., 1992).
The current structural model depicts the external
mouth of the Na⁺ channel pore as a funnel-shaped
space, in which TTX and STX occlude the pore by bind-
ing at m The current structural model depicts the external mouth of the $Na⁺$ channel pore as a funnel-shaped space, in which TTX and STX occlude the pore by binding at multiple attachment points constituting the neurotoxin re mouth of the Na⁺ channel pore as a funnel-shaped 194 space, in which TTX and STX occlude the pore by bind-
ing at multiple attachment points constituting the neu-
turboxin receptor site 1. This model conforms to the gen space, in which TTX and STX occlude the pore by bind-
ing at multiple attachment points constituting the neu-
rotoxin receptor site 1. This model conforms to the gen-
eral view of interchangeability between TTX and STX
wit ing at multiple attachment points constituting the ne rotoxin receptor site 1. This model conforms to the geral view of interchangeability between TTX and S' with regard to their binding to the channel. Howev the chemical rotoxin receptor site 1. This model conforms to the general view of interchangeability between TTX and STX with regard to their binding to the channel. However, the chemical structures of these two toxins differ considerab eral view of interchangeability between TTX and STX
with regard to their binding to the channel. However,
the chemical structures of these two toxins differ consid-
erably (Shimizu, 1986) and there is clear indication that with regard to their binding to the channel. Here the chemical structures of these two toxins differerably (Shimizu, 1986) and there is clear indicate the two toxin-receptor interaction at microscopic leverent for the two e chemical structures of these two toxins differ considered about cation charged about cation-receptor interaction at microscopic level is dif-
e toxin-receptor interaction at microscopic level is dif-
to the two toxins (K

the toxin-receptor interaction at microscopic level is different for the two toxins (Kirsch et al., 1994).
2. *Divalent cation-blocking sites: selectivity filter*. The ionic selectivity of $Na⁺$ channels is well defin

are all required for high-affinity TTX binding and nor-
mal single-channel conductance (Terlau et al., 1991). also change the divalent ion blocking affinity (Pusch et
These, and other results obtained from Ca^{2+} and $K^$ an aqueous pore, and the alkali cations permeability FORENOVITCH
an aqueous pore, and the alkali cations permeability
falls with increasing crystal radius $(L_i^+ \sim Na^+ > K^+ > Rb^+ > Cs^+$). Although K^+ and Ca^{2+} ions are selected BRENOVITCH
an aqueous pore, and the alkali cations permeability
falls with increasing crystal radius $(Li^+ \sim Na^+ > K^+ >$
 $Rb^+ > Cs^+$). Although K⁺ and Ca^{2+} ions are selected
against in Na⁺ channels, these ions are stil an aqueous pore, and the alkali cations permeabilit
falls with increasing crystal radius $(Li^+ \sim Na^+ > K^+ > Rh^+ > Cs^+)$. Although K^+ and Ca^{2+} ions are selected
against in Na⁺ channels, these ions are still quite mea
sur an aqueous pore, and the alkali cations permeability
falls with increasing crystal radius $(Li^+ \sim Na^+ > K^+ > Rh^+ > Cs^+$). Although K^+ and Ca^{2+} ions are selected
against in Na⁺ channels, these ions are still quite mea-
s falls with increasing crystal radius $(Li^+ \sim Na^+ > K^+ > Rb^+ > Cs^+$). Although K^+ and Ca^{2+} ions are selected against in Na^+ channels, these ions are still quite measurably permeant (Meves and Vogel, 1973). A number of o $Rb^{+} > Cs^{+}$). Although K^{+} and Ca^{2+} ions are selected against in Na⁺ channels, these ions are still quite measurably permeant (Meves and Vogel, 1973). A number of observations indicate that the divalent ion-block against in Na⁺ channels, these ions are still quite measurably permeant (Meves and Vogel, 1973). A number of observations indicate that the divalent ion-blocking site and the guanidinium toxin receptor site 1 overlap eac surably permeant (Meves and Vogel, 1973). A number of observations indicate that the divalent ion-blocking site and the guanidinium toxin receptor site 1 overlap each other: (a) divalent cations block within the open cha observations indicate that the divalent ion-blocking site
and the guanidinium toxin receptor site 1 overlap each
other: (a) divalent cations block within the open channel
and compete with toxin binding to the channel, wi and the guanidinium toxin receptor site 1 overlap each other: (a) divalent cations block within the open channel and compete with toxin binding to the channel, with isoform-specific differences in the blocking affinity a other: (*a*) divalent cations block within the open channel
and compete with toxin binding to the channel, with
isoform-specific differences in the blocking affinity and
competitive efficacy (Schild and Moczydlowski, 1991; and compete with toxin binding to the channel, with
isoform-specific differences in the blocking affinity and
competitive efficacy (Schild and Moczydlowski, 1991;
Doyle et al., 1993); (b) mutations affecting toxin affinity competitive efficacy (Schild and Moczydlowski, 1991; competitive efficacy (Schild and Moczydlowski, 1991;
Doyle et al., 1993); (b) mutations affecting toxin affinity
also change the divalent ion blocking affinity (Pusch et
al., 1991; Heinemann et al., 1992a; Satin et al., 19 Doyle et al., 1993); (*b*) mutations affecting toxin affinity also change the divalent ion blocking affinity (Pusch et al., 1991; Heinemann et al., 1992a; Satin et al., 1992; Backx et al., 1992); and (*c*) voltage depende also change the divalent ion blocking affinity (Pusch et al., 1991; Heinemann et al., 1992a; Satin et al., 1992; Backx et al., 1992); and (c) voltage dependence analysis of the divalent ions block (Yamamoto et al., 1984; N al., 1991; Heinemann et al., 1992a; Satin et al., 1992;
Backx et al., 1992); and (c) voltage dependence analysis
of the divalent ions block (Yamamoto et al., 1984; Nilius,
1988; Sheets and Hanck, 1992; Sheets et al., 1987; Backx et al., 1992); and (c) voltage dependence analysis
of the divalent ions block (Yamamoto et al., 1984; Nilius,
1988; Sheets and Hanck, 1992; Sheets et al., 1987;
Backx et al., 1992) and that of the guanidinium toxins
 of the divalent ions block (Yamamoto et al., 1984; Nilius, 1988; Sheets and Hanck, 1992; Sheets et al., 1987; Backx et al., 1992) and that of the guanidinium toxins block (Satin et al., 1994) showed that both binding site 1988; Sheets and Hanck, 1992; Sheets et al., 1987;
Backx et al., 1992) and that of the guanidinium toxins
block (Satin et al., 1994) showed that both binding sites
are 15 to 30% into the membrane field. In addition,
mutat Backx et al., 1992) and that of the guanidinium toxins
block (Satin et al., 1994) showed that both binding sites
are 15 to 30% into the membrane field. In addition,
mutation of lysine¹⁴²² and alanine¹⁷¹⁴ (K and A on t block (Satin et al., 1994) showed that both binding sites
are 15 to 30% into the membrane field. In addition,
mutation of lysine¹⁴²² and alanine¹⁷¹⁴ (K and A on the
inner ring in fig. 2b) to negatively charged residue are 15 to 30% into the membrane field. In addition,
mutation of lysine¹⁴²² and alanine¹⁷¹⁴ (K and A on the
inner ring in fig. 2b) to negatively charged residues, not
only alters TTX binding, but also switches the sele inner ring in fig. 2b) to negatively charged residues, not
only alters TTX binding, but also switches the selectivity
of the channel from Na⁺- to Ca²⁺-selectivity (Heine-
mann et al., 1992b). The corresponding mutant only alters TTX binding, but also switches the selectivity
of the channel from Na⁺- to Ca²⁺-selectivity (Heine-
mann et al., 1992b). The corresponding mutant showed
no more selectivity among monovalent cations, strong of the channel from Na⁺- to Ca²⁺-selectivity (Heimann et al., 1992b). The corresponding mutant show
no more selectivity among monovalent cations, stro
block of monovalent current by divalent cations, a
permeation of d mann et al., 1992b). The corresponding mutant showed
no more selectivity among monovalent cations, strong
block of monovalent current by divalent cations, and
permeation of divalent cations, i.e., features of voltage-
gat no more selectivity among monovalent cations, strong
block of monovalent current by divalent cations, and
permeation of divalent cations, i.e., features of voltage-
gated Ca^{2+} channels. These findings strongly suggest
 block of monovalent current by divalent cations, and permeation of divalent cations, i.e., features of voltage-
gated Ca^{2+} channels. These findings strongly suggest that the inner ring constitutes the selectivity filte permeation of divalent cations, i.e., features of voltage-
gated Ca^{2+} channels. These findings strongly suggest
that the inner ring constitutes the selectivity filter of ion
channels (Heinemann et al., 1994). To summar gated Ca^{2+} channels. These findings strongly sugges
that the inner ring constitutes the selectivity filter of ior
channels (Heinemann et al., 1994). To summarize sec
tions 1 and 2, the P-region in each repeat is critic that the inner ring
channels (Heinem:
tions 1 and 2, the
guanidinium toxin
and ion selectivity
3. Ion conductin, tions 1 and 2, the P-region in each repeat is critical to guanidinium toxin binding, $Na⁺$ channel conductance and ion selectivity.
3. Ion conducting pore: local anesthetics receptor site.
Local anesthetics block the

the toxin-receptor interaction at microscopic level is dif-
ferent for the two toxins (Kirsch et al., 1994).
2. *Divalent cation-blocking sites: selectivity filter*. The tives, such as the quaternary analogue of lidocaine tions 1 and 2, the P-region in each repeat is critical to guanidinium toxin binding, $Na⁺$ channel conductance and ion selectivity.
3. Ion conducting pore: local anesthetics receptor site.
Local anesthetics block the guanidinium toxin binding, Na^+ channel conductance
and ion selectivity.
3. Ion conducting pore: local anesthetics receptor site.
Local anesthetics block the propagation of nerve impulse
by preventing the normal function and ion selectivity.

3. Ion conducting pore: local anesthetics receptor site.

Local anesthetics block the propagation of nerve impulse

by preventing the normal function of Na^+ channels

(Taylor, 1959), and they were 3. Ion conducting pore: local anesthetics receptor site.
Local anesthetics block the propagation of nerve impulse
by preventing the normal function of Na^+ channels
(Taylor, 1959), and they were also shown to interact
wi Local anesthetics block the propagation of nerve impulse
by preventing the normal function of Na^+ channels
(Taylor, 1959), and they were also shown to interact
with Na^+ channels of central neurons (Butterworth et
al., by preventing the normal function of $Na⁺$ chanes (Taylor, 1959), and they were also shown to inte with $Na⁺$ channels of central neurons (Butterwort al., 1993; Capek and Esplin, 1994). The action of lanesthetics (Taylor, 1959), and they were also shown to intera
with Na⁺ channels of central neurons (Butterworth
al., 1993; Capek and Esplin, 1994). The action of loo
anesthetics on Na⁺ currents is complex, with use-depe
dent and with Na^+ channels of central neurons (Butterworth et al., 1993; Capek and Esplin, 1994). The action of local anesthetics on Na^+ currents is complex, with use-dependent and frequency-dependent (i.e., inhibition is pote al., 1993; Capek and Esplin, 1994). The action of loca
anesthetics on Na⁺ currents is complex, with use-depen
dent and frequency-dependent (i.e., inhibition is poten
tiated with repetitive stimuli) properties which sugge anesthetics on Na⁺ currents is complex, with use-dependent and frequency-dependent (i.e., inhibition is potentiated with repetitive stimuli) properties which suggest that binding is modulated by channel state (Catterall, dent and frequency-dependent (i.e., inhibition is potentiated with repetitive stimuli) properties which suggest
that binding is modulated by channel state (Catterall,
1987; Butterworth and Strichartz, 1990; Starmer et al., that binding is modulated by channel state (Catterall, 1987; Butterworth and Strichartz, 1990; Starmer et al., 1990). These drugs were initially thought to act by perturbing the properties of the phospholipid phase of biothat binding is modulated by channel state (Catterall, 1987; Butterworth and Strichartz, 1990; Starmer et al., 1990). These drugs were initially thought to act by perturbing the properties of the phospholipid phase of bio 1987; Butterworth and Strichartz, 1990; Starmer et al., 1990). These drugs were initially thought to act by perturbing the properties of the phospholipid phase of biological membranes, because they are effective only at r 1990). These drugs were initially thought to act by per-
turbing the properties of the phospholipid phase of bio-
logical membranes, because they are effective only at
relatively high concentrations $(10^{-6}$ to 10^{-2} M) turbing the properties of the phospholipid phase of bio-
logical membranes, because they are effective only at
relatively high concentrations $(10^{-6}$ to 10^{-2} M), and
their potency is most strongly correlated with thei logical membranes, because they are effective only at relatively high concentrations $(10^{-6}$ to 10^{-2} M), and their potency is most strongly correlated with their lipid solubility. However, experiments with impermeant relatively high concentrations $(10^{-6}$ to 10^{-2} M), and
their potency is most strongly correlated with their lipid
solubility. However, experiments with impermeant de-
rivatives strongly suggested that local anesthetic their potency is most strongly correlated with their lipsolubility. However, experiments with impermeant crivatives strongly suggested that local anesthetics bit of specific receptor sites located on the $Na⁺$ changed solubility. However, experiments with impermeant de-
rivatives strongly suggested that local anesthetics bind
to specific receptor sites located on the $Na⁺$ channel
protein itself. Permanently positively charged deri rivatives strongly suggested that local anesthetics bind
to specific receptor sites located on the Na⁺ channel
protein itself. Permanently positively charged deriva-
tives, such as the quaternary analogue of lidocaine
QX

located in the channel blockade by local
anesthetics. a Two pathways exist for drugs to reach the receptor
located in the channel pore: neutral (hydrophobic) compounds can
bind and unbind even when the inactivation gate is FIG. 3. Molecular mechanism of Na^+ channel blockade by local anesthetics. α Two pathways exist for drugs to reach the receptor located in the channel pore: neutral (hydrophobic) compounds can bind and unbind even enesthetics. a Two pathways exist for drugs to reach the receptor located in the channel pore: neutral (hydrophobic) compounds can bind and unbind even when the inactivation gate is closed, whereas charged hydrophilic drug biocated in the channel pore: neutral (hydrophobic) compounds can
bind and unbind even when the inactivation gate is closed, whereas
charged hydrophilic drugs require the gate to be open to access the
binding site. BTX, ba bind and unbind even when the inactivation gate is closed, whereas charged hydrophilic drugs require the gate to be open to access the binding site. BTX, batrachotoxin receptor site: there is an indirect allosteric couplin charged hydrophilic drugs require the gate to be open to access the binding site. BTX, batrachotoxin receptor site: there is an indirect allosteric coupling between this neurotoxin receptor (site 2) and the receptor site f binding site. BTX, batrachotoxin receptor site: there is an indireallosteric coupling between this neurotoxin receptor (site 2) and treceptor site for local anesthetics. Adapted from Hille (1991) with permission of the aut allosteric coupling between this neurotoxin receptor (site 2) and the receptor site for local anesthetics. Adapted from Hille (1991) with permission of the author and Sinauer Associates. b, Putative orientation of amino a channel) with respect to a quaternary analogue of lidocaine (QX314) bound in the ion-conducting pore. In this model, phenylalanine ¹⁷⁽⁶⁴⁾ and tyrosine¹⁷⁽⁷¹⁾ are both oriented on the same face of the IVS6 helix, facing bound in the ion-conducting pore. In this model, phenylalanine 1 ¹ and tyrosine¹⁷⁽⁷¹⁾ are both oriented on the same face of the Γ helix, facing the pore lumen, because their mutation to alar strongly suggests that xours in the control and tyrosine¹⁷⁽⁷¹⁾ are both oriented on the same face of the IVS6 helix, facing the pore lumen, because their mutation to alanine strongly suggests that these hydrophobic aromatic residues contribut helix, facing the pore lumen, because their mutation to alanine strongly suggests that these hydrophobic aromatic residues contribute to the free energy of drug binding (see text). Binding presumably occurs through hydrop tive local anesthetics are characterized by positively charged and by occurs through hydrophobic of π electron interactions, because effective local anesthetics are characterized by positively charged and hydrophobic m ute to the free energy of drug binding (see text). Binding presumably
occurs through hydrophobic of π electron interactions, because effec-
tive local anesthetics are characterized by positively charged and
hydrophobic occurs through hydrophobic of π electron interactions, because effec-
tive local anesthetics are characterized by positively charged and
hydrophobic moieties at either end of the molecule (Zamponi and
French, 1994a). T are contained to modulate at either end of the molecule (Zamponi and French, 1994a). The bulky isoleucine ¹⁷⁽⁶⁰⁾ is oriented on the same face of the helix as 17(64) and 17(71) residues and is therefore well positioned to French, 1994a). The bulky isoleucine $^{17(60)}$ is oriented on the same
face of the helix as 17(64) and 17(71) residues and is therefore well
positioned to modulate extracellular access to the local anesthetic
binding site permission from the authors and 17(71) residues and is therefore well
positioned to modulate extracellular access to the local anesthetic
binding site. Modified from Ragsdale and coworkers (1994), with
permission from the

Emaing Site. Modified Holm Ragodale and Coworkers (1994), while
permission from the authors and the American Association for the
Advancement of Science.
intracellularly (Frazier et al., 1970; Strichartz, 1973;
Courtney, 19 and

intracellularly (Frazier et al., 1970; Strichartz, 1973; mo

Courtney, 1975; Khodorov et al., 1976). Further experi-

ments confirmed that these drugs act mainly on open (Za

Na⁺ channels, through a cytoplasmic, hyd intracellularly (Frazier et al., 1970; Strichartz, 197
Courtney, 1975; Khodorov et al., 1976). Further experents confirmed that these drugs act mainly on operative and Na^+ channels, through a cytoplasmic, hydrophilic intracellularly (Frazier et al., 1970; Strichartz, 1973;
Courtney, 1975; Khodorov et al., 1976). Further experi-
ments confirmed that these drugs act mainly on open
Na⁺ channels, through a cytoplasmic, hydrophilic path-
 Courtney, 1975; Khodorov et al., 1976). Further experiments confirmed that these drugs act mainly on open $Na⁺$ channels, through a cytoplasmic, hydrophilic path way which is occluded by the activation and inactivatio ments confirmed that these drugs act mainly on $\overline{N}a^+$ channels, through a cytoplasmic, hydrophilic way which is occluded by the activation and inactive gates (Catterall, 1987; Butterworth and Strich. 1990; Ragsdale e a⁺ channels, through a cytoplasmic, hydrophilic path-
ay which is occluded by the activation and inactivation due
tes (Catterall, 1987; Butterworth and Strichartz, or
90; Ragsdale et al., 1991; Hille, 1991) (fig. 3a).
Th way which is occluded by the activation and inactivation du
gates (Catterall, 1987; Butterworth and Strichartz, or
1990; Ragsdale et al., 1991; Hille, 1991) (fig. 3a). the
The S6 segment in repeat IV of Ca^{2+} channels,

gates (Catterall, 1987; Butterworth and Strichartz, or 1990; Ragsdale et al., 1991; Hille, 1991) (fig. 3a). the S6 segment in repeat IV of Ca^{2+} channels, and mathe single S6 segment of K⁺ channels as well, have been 1990; Ragsdale et al., 1991; Hille, 1991) (fig. 3a).
The S6 segment in repeat IV of Ca^{2+} channels, and m
the single S6 segment of K⁺ channels as well, have been
aimplicated in the binding of pore blockers (Catterall The S6 segment in repeat IV of Ca^{2+} channels, as
the single S6 segment of K^+ channels as well, have be
implicated in the binding of pore blockers (Catterall as
Striessnig, 1992). Ragsdale and coworkers (1994) ha
dem the single S6 segment of K⁺ channels as well, have been affect toxin binding to neurotoxin receptor sites 1 (TTX, implicated in the binding of pore blockers (Catterall and STX) or 3 (α -scorpion toxins, see fig. 1), b implicated in the binding of pore blockers (Catterall and STY
Striessnig, 1992). Ragsdale and coworkers (1994) have teri
demonstrated that site-directed mutations in trans- 2 (F
membrane segment S6 of repeat IV of the rat Striessnig, 1992). Ragsdale and coworkers (1994) have
demonstrated that site-directed mutations in trans-
membrane segment S6 of repeat IV of the rat brain
 α -subunit selectively modified the binding of QX314 to
resting demonstrated that site-directed mutations in tra
membrane segment S6 of repeat IV of the rat brace-
a-subunit selectively modified the binding of QX314
resting or to open and inactivated channels when
pressed in *Xenopus* membrane segment S6 of repeat IV of the rat brain α -subunit selectively modified the binding of QX314 to resting or to open and inactivated channels when expressed in *Xenopus* occytes (fig. 3b). Mutation of phenylalan α -subunit selectively modified the binding of QX314 to
resting or to open and inactivated channels when ex-
pressed in *Xenopus* oocytes (fig. 3b). Mutation of phenyl-
alanine¹⁷⁶⁴ near the middle of this segment to a resting or to open and inactivated channels when ex
pressed in *Xenopus* oocytes (fig. 3b). Mutation of phenyl
alanine¹⁷⁶⁴ near the middle of this segment to alanine
decreased the affinity of open and inactivated channe pressed in *Xenopus* oocytes (fig. 3b). Mutation of pher
alanine¹⁷⁶⁴ near the middle of this segment to alani
decreased the affinity of open and inactivated chann
to 1% of the wild-type value, resulting in almost co
ple alanine¹⁷⁶⁴ near the middle of this segment to alanine,
decreased the affinity of open and inactivated channels
to 1% of the wild-type value, resulting in almost com-
plete abolition of both the use-dependence and volta decreased the affinity of open and inactivated channels su
to 1% of the wild-type value, resulting in almost com-
plete abolition of both the use-dependence and voltage-
dependence of drug block. In contrast, mutation of a

MODULATION OF VOLTAGE-GATED NA⁺ CHANNELS 27
 $\bigcap_{k=1}^{\infty}$ ^{1VS6} k resting channel 15-fold. Replacement of the bulky iso- $-$ GATED NA⁺ CHANNELS 27

resting channel 15-fold. Replacement of the bulky iso-

leucine residue at position 1760 with alanine allowed $\frac{1}{4}$

denotes $\frac{1}{4}$

denotes residue at position 1760 with alanine allowed

denotes residue at position 1760 with alanine allowed

denotes at position 1760 with alanine allowed

denotes the site from the extracel -GATED NA⁺ CHANNELS 27

resting channel 15-fold. Replacement of the bulky iso-

leucine residue at position 1760 with alanine allowed
 $QX314$ to reach the site from the extracellular side,

perhaps by passing directly resting channel 15-fold. Replacement of the bulky iso-
leucine residue at position 1760 with alanine allowed
QX314 to reach the site from the extracellular side,
perhaps by passing directly through the pore from the
outsid resting channel 15-101d. Replacement of the bulky is
leucine residue at position 1760 with alanine allow
QX314 to reach the site from the extracellular sid
perhaps by passing directly through the pore from th
outside. Pres QX314 to reach the site from the extracellular side, perhaps by passing directly through the pore from the outside. Presumably, this amino acid residue corresponds to a narrow region in the pore, just to the extra-cellular QX314 to reach the site from the extracellular side perhaps by passing directly through the pore from t outside. Presumably, this amino acid residue corresponds to a narrow region in the pore, just to the extreellular sid perhaps by passing directly through the pore from the outside. Presumably, this amino acid residue corresponds to a narrow region in the pore, just to the extra-
cellular side of the local anesthetic binding site. Muta-
ti outside. Presumably, this amino acid residue corresponds to a narrow region in the pore, just to the extra-
cellular side of the local anesthetic binding site. Muta-
tions of isoleucine¹⁷⁶¹, valine¹⁷⁶⁶ and asparagine¹ sponds to a narrow region in the pore, just to the extra-
cellular side of the local anesthetic binding site. Muta-
tions of isoleucine¹⁷⁶¹, valine¹⁷⁶⁶ and asparagine¹⁷⁶⁹ to
alanine increased QX314 resting block wit cellular side of the local anesthetic binding site. Mutations of isoleucine¹⁷⁶¹, valine¹⁷⁶⁶ and asparagine¹⁷⁶⁹ to alanine increased $QX314$ resting block without altering inactivated state affinity, despite being pr alanine increased QX314 resting block without altering
inactivated state affinity, despite being presumably ori-
ented away from the channel pore, suggesting that these
mutations may increase channel sensitivity to drugs
t alanine increased QX314 resting block without altering
inactivated state affinity, despite being presumably ori-
ented away from the channel pore, suggesting that these
mutations may increase channel sensitivity to drugs
t inactivated state affinity, despite being presumably oriented away from the channel pore, suggesting that these mutations may increase channel sensitivity to drugs through indirect effects on the local anesthetic site. To ented away from the channel pore, suggesting that these mutations may increase channel sensitivity to drugs through indirect effects on the local anesthetic site. Together, these data clearly define the location of the lo mutations may increase channel sensitivity to derive through indirect effects on the local anesthetic site gether, these data clearly define the location of the anesthetic receptor site in the pore of the Na⁺ chand iden through indirect effects on the local anesthetic situation of the anesthetic receptor site in the pore of the Na⁺ chand identify molecular determinants of the state-dent binding of these drugs and related blockers.
4. V ther, these data clearly define the location of the lowesthetic receptor site in the pore of the Na⁺ channent didentify molecular determinants of the state-depent binding of these drugs and related blockers.
4. Veratridi

anesthetic receptor site in the pore of the Na⁺ channel
and identify molecular determinants of the state-depen-
and thinding of these drugs and related blockers.
4. Veratridine and batrachotoxin receptor site. Gray-
ano and identify molecular determinants of the state-dependent binding of these drugs and related blockers.
4. Veratridine and batrachotoxin receptor site. Gray-
anotoxin and the alkaloids veratridine, aconitine and
batrachoto dent binding of these drugs and related blockers.
4. Veratridine and batrachotoxin receptor site. Gray-
anotoxin and the alkaloids veratridine, aconitine and
batrachotoxin (BTX) compete for binding at neurotoxin
receptor s 4. Veratridine and batrachotoxin receptor site. Gra
anotoxin and the alkaloids veratridine, aconitine are
batrachotoxin (BTX) compete for binding at neurotox
receptor site 2 (Catterall, 1980; Catterall et al., 1981
These anotoxin and the alkaloids veratridine, aconitine and
batrachotoxin (BTX) compete for binding at neurotoxin
receptor site 2 (Catterall, 1980; Catterall et al., 1981).
These toxins cause persistent activation of Na⁺ chan batrachotoxin (BTX) compete for binding at neurotor
receptor site 2 (Catterall, 1980; Catterall et al., 198
These toxins cause persistent activation of Na⁺ channels at the resting membrane potential by blocking N
channe These toxins cause persistent activation of $Na⁺$ channels at the resting membrane potential by blocking $Na⁺$ channel inactivation and shifting the voltage dependence of the channel activation to a more negative preferential, high affinity binding of the toxins to the nels at the resting membrane potential by blocking Na^+
channel inactivation and shifting the voltage depen-
dence of the channel activation to a more negative mem-
brane potential. These effects presumably result fr channel inactivation and shifting the voltage depence of the channel activation to a more negative m
brane potential. These effects presumably result f
preferential, high affinity binding of the toxins to
active states of dence of the channel activation to a more negative mem-
brane potential. These effects presumably result from
preferential, high affinity binding of the toxins to the
active states of Na⁺ channels, and consequent stabili brane potential. These effects presumably result from
preferential, high affinity binding of the toxins to the
active states of Na⁺ channels, and consequent stabiliza-
tion of those states (Catterall, 1980; Khodorov, 19 preferential, high affinity binding of the toxins to the active states of Na⁺ channels, and consequent stabilization of those states (Catterall, 1980; Khodorov, 1985; Hille et al., 1987). As the toxins acting at site 2 active states of Na⁺ channels, and consequent stabiliza-
tion of those states (Catterall, 1980; Khodorov, 1985;
Hille et al., 1987). As the toxins acting at site 2 also alter
the ion selectivity of the Na⁺ channel, th tion of those states (Catterall, 1980; Khodorov, 1988)
Hille et al., 1987). As the toxins acting at site 2 also alt
the ion selectivity of the Na⁺ channel, this receptor sit
is presumably in a region of the α subtype Hille et al., 1987). As the toxins acting at site 2 also alter
the ion selectivity of the Na⁺ channel, this receptor site
is presumably in a region of the α subtype that is in-
volved in voltage-dependent activation the ion selectivity of the Na⁺ channel, this receptor site
is presumably in a region of the α subtype that is in-
volved in voltage-dependent activation and inactivation,
and allosterically linked to the transmembran is presumably in a region of the α subtype that is involved in voltage-dependent activation and inactivation,
and allosterically linked to the transmembrane pore of
the channel (Catterall, 1992). As these toxins are la volved in voltage-dependent activation and inactivation,
and allosterically linked to the transmembrane pore of
the channel (Catterall, 1992). As these toxins are large
molecules, their multiple effects might also result f and allosterically linked to the
the channel (Catterall, 1992).
molecules, their multiple effec
an interaction at several micro
(Zamponi and French, 1994).
Due to their lipophilic natu e channel (Catterall, 1992). As these toxins are large
olecules, their multiple effects might also result from
a interaction at several microsites of the Na⁺ channel
amponi and French, 1994).
Due to their lipophilic nat

molecules, their multiple effects might also result from
an interaction at several microsites of the Na⁺ channe
(Zamponi and French, 1994).
Due to their lipophilic nature, these toxins can pro
duce their effects when add an interaction at several microsites of the $Na⁺$ channel (Zamponi and French, 1994).

Due to their lipophilic nature, these toxins can produce their effects when added to either the extracellular or the cytoplasmic s (Zamponi and French, 1994).

Due to their lipophilic nature, these toxins can pro-

duce their effects when added to either the extracellular

or the cytoplasmic side of the membrane. They are

thought to bind to the chan duce their effects when added to either the extracellular
or the cytoplasmic side of the membrane. They are
thought to bind to the channel at sites buried in the
matrix of the lipid bilayer. Local anesthetics do not
affec or the cytoplasmic side of the membrane. They are thought to bind to the channel at sites buried in the matrix of the lipid bilayer. Local anesthetics do not affect toxin binding to neurotoxin receptor sites 1 (TT2 STX) o thought to bind to the channel at sites buried in the matrix of the lipid bilayer. Local anesthetics do not affect toxin binding to neurotoxin receptor sites 1 (TTX, STX) or 3 (α -scorpion toxins, see fig. 1), but they matrix of the lipid bilayer. Local anesthetics do affect toxin binding to neurotoxin receptor sites 1 (T) STX) or 3 (α -scorpion toxins, see fig. 1), but they all terically inhibit BTX binding to neurotoxin receptor s 2 affect toxin binding to neurotoxin receptor sites 1 (TTX, STX) or 3 (α -scorpion toxins, see fig. 1), but they allos-
terically inhibit BTX binding to neurotoxin receptor site
2 (Postma and Catterall, 1984; Catterall, 1 STX) or 3 (α -scorpion toxins, see fig. 1), but they allos-
terically inhibit BTX binding to neurotoxin receptor site
2 (Postma and Catterall, 1984; Catterall, 1987; Crevel-
ing et al., 1983; McNeal et al., 1985). This terically inhibit BTX binding to neurotoxin receptor site 2 (Postma and Catterall, 1984; Catterall, 1987; Creveling et al., 1983; McNeal et al., 1985). This inhibition results from indirect allosteric coupling between the 2 (Postma and Catterall, 1984; Catterall, 1987; Creveling et al., 1983; McNeal et al., 1985). This inhibition results from indirect allosteric coupling between the receptor site for the drugs and neurotoxin receptor site 2 ing et al., 1983; McNeal et al., 1985). This inhibition results from indirect allosteric coupling between the receptor site for the drugs and neurotoxin receptor site 2, rather than from direct steric interaction at a comm results from indirect allosteric coupling between the receptor site 2, rather than from direct steric interaction at a common binding site (fig. 3a). This interaction presumably results from the fact that neurotoxins acti ceptor site for the drugs and neurotoxin receptor site 2, rather than from direct steric interaction at a common binding site (fig. 3a). This interaction presumably results from the fact that neurotoxins acting at site 2 rather than from direct steric interaction at a common
binding site (fig. 3a). This interaction presumably re-
sults from the fact that neurotoxins acting at site 2 bind
with high affinity to active states of $Na⁺$ ch binding site (fig. 3a). This interaction presumably results from the fact that neurotoxins acting at site 2 bind with high affinity to active states of Na⁺ channels, whereas local anesthetics bind with highest affinity sults from the fact that neurotoxins acting at site 2 bind
with high affinity to active states of Na⁺ channels,
whereas local anesthetics bind with highest affinity to
either resting or inactivated states of Na⁺ chann

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the toxins, these drugs therefore stabilize those states of BT

the channel and reduce neurotoxin binding affinity and (Ve

persistent activation of Na⁺ channels. Together, these min 28
the toxins, these drugs therefore stabilize those states of B
the channel and reduce neurotoxin binding affinity and (N
persistent activation of Na^+ channels. Together, these m
findings strongly suggest that the BTX the toxins, these drugs therefore stabilize those states of B?
the channel and reduce neurotoxin binding affinity and (V
persistent activation of Na⁺ channels. Together, these mi
findings strongly suggest that the BTX si the toxins, these drugs therefore stabilize those states of B1
the channel and reduce neurotoxin binding affinity and (V
persistent activation of Na⁺ channels. Together, these mi
findings strongly suggest that the BTX s the channel and red
persistent activation
findings strongly su
proximity to the loc
lumen of the pore.
BTX and veratrid: Framework activation of Na⁺ channels. Together, these modings strongly suggest that the BTX site is in close α oximity to the local anesthetic site and, thus, of the iven of the pore. per and veratridine have become

findings strongly suggest that the BTX site is in close act
proximity to the local anesthetic site and, thus, of the ive
lumen of the pore. pro
BTX and veratridine have become very popular tools pou
for the selection of d proximity to the local anesthetic site and, thus, of the ivera,
lumen of the pore. propri-
BTX and veratridine have become very popular tools pound
for the selection of drugs acting on the Na⁺ channel, and by usi-
for t lumen of the pore.

BTX and veratridine have become very popular tools

for the selection of drugs acting on the Na⁺ channel, and

for the investigation of their mode of action. A BT2

analogue ([³H]batrachotoxinin A BTX and veratridine have become very popular to
for the selection of drugs acting on the Na⁺ channel, a
for the investigation of their mode of action. A B'
analogue ([³H]batrachotoxinin A 20- α -benzoa
(BTX-B) was de for the investigation of their mode of action. A BTX analogue ([³H]batrachotoxinin A 20- α -benzoate) (BTX-B) was developed as a radioligand for the neurotoxin site 2 (Brown et al., 1981; Catterall et al., 1981; Crevel toxin site 2 (Brown et al., 1981; Catterall et al., 1981; Creveling and Daly, 1992). Initially, as local anesthetics were known to displace BTX-B from synaptosomal membranes (Creveling et al., 1983; Postma and Catterall, (BTX-B) was developed as a radioligand for the neuro-(BTX-B) was developed as a radioligand for the neuro-
toxin site 2 (Brown et al., 1981; Catterall et al., 1981;
Creveling and Daly, 1992). Initially, as local anesthetics
were known to displace BTX-B from synaptosomal memtoxin site 2 (Brown et al., 1981; Catterall et al., 1981; ja
Creveling and Daly, 1992). Initially, as local anesthetics (1
were known to displace BTX-B from synaptosomal mem-
branes (Creveling et al., 1983; Postma and Catt Creveling and Daly, 1992). Initially, as local anesthetics (L
were known to displace BTX-B from synaptosomal mem-
branes (Creveling et al., 1983; Postma and Catterall, in:
1984), BTX-B binding was proposed as a rapid assay were known to displace BTX-B from synaptosomal mem-
branes (Creveling et al., 1983; Postma and Catterall, in
1984), BTX-B binding was proposed as a rapid assay for
local anesthetic activity (McNeal et al., 1985), but it is branes (Creveling et al., 1983; Postma and Catterall, in:
1984), BTX-B binding was proposed as a rapid assay for
local anesthetic activity (McNeal et al., 1985), but it is ga
now clear that binding to site 2 is not a uniq

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the toxins, these drugs therefore stabilize those states of BTX site does not imply potent local anesthetic activity
the channel and reduce neurotoxin binding affinity and (Velly et al., 1987; Pauw BRENOVITCH
BTX site does not imply potent local anesthetic activity
(Velly et al., 1987; Pauwels et al., 1986). This is a re-BRENOVITCH
BTX site does not imply potent local anesthetic activity
(Velly et al., 1987; Pauwels et al., 1986). This is a re-
minder that *high-affinity binding and potent functional* BRENOVITCH
BTX site does not imply potent local anesthetic activity
(Velly et al., 1987; Pauwels et al., 1986). This is a re-
minder that *high-affinity binding and potent functional*
activity are not necessarily coinciden BTX site does not imply potent local anesthetic activity (Velly et al., 1987; Pauwels et al., 1986). This is a re-
minder that *high-affinity binding and potent functional*
activity are not necessarily coincident (Adams an BTX site does not imply potent local anesthetic activity (Velly et al., 1987; Pauwels et al., 1986). This is a reminder that *high-affinity binding and potent functional* activity are not necessarily coincident (Adams and (Velly et al., 1987; Pauwels et al., 1986). This is a re
minder that *high-affinity binding and potent functiona*
activity are not necessarily coincident (Adams and Ol
ivera, 1994). Veratridine-induced Na^+ influx is an minder that *high-affinity binding and potent functional* activity are not necessarily coincident (Adams and Olivera, 1994). Veratridine-induced Na⁺ influx is an appropriate functional test to verify whether a given com activity are not necessarily coincident (Adams and Olivera, 1994). Veratridine-induced Na^+ influx is an appropriate functional test to verify whether a given compound inhibits Na^+ currents. Na^+ influx can be assesse ivera, 1994). Veratridine-induced Na⁺ influx is an appropriate functional test to verify whether a given compound inhibits Na⁺ currents. Na⁺ influx can be assessed by using ²²Na (Zimanyi et al., 1989), fluorescent propriate functional test to verify whether a given com-
pound inhibits Na^+ currents. Na^+ influx can be assessed
by using ²²Na (Zimanyi et al., 1989), fluorescent Na^+
indicators (Daniell, 1992; Deri and Adam-Vizi, by using ²²Na (Zimanyi et al., 1989), fluorescent Na⁺
indicators (Daniell, 1992; Deri and Adam-Vizi, 1993),
 $[14C]$ guanidinium ion (Jacques et al., 1980; Reith, 1990),
or indirectly, by monitoring oxygen consumption (indicators (Daniell, 1992; Deri and Adam-Vizi, 1993), $[14C]$ guanidinium ion (Jacques et al., 1980; Reith, 1990), or indirectly, by monitoring oxygen consumption (Uren-
jak et al., 1991) or toxicity [e.g., lactate dehydro $[14C]$ guanidinium ion (Jacques et al., 1980; Reith, 1990), or indirectly, by monitoring oxygen consumption (Urenjak et al., 1991) or toxicity [e.g., lactate dehydrogenase (LDH) release in cultured neurons; Pauwels et al. or indirectly, by monitoring oxygen consumption (Uren-
jak et al., 1991) or toxicity [e.g., lactate dehydrogenase
(LDH) release in cultured neurons; Pauwels et al., 1990].
BTX is also used in voltage-clamp studies to elimi jak et al., 1991) or toxicity [e.g., lactate dehydrogenase *f* and *5. 1991*) or toxicity [e.g., lactate dehydrogen:
 DH) release in cultured neurons; Pauwels et al., 199
 FX is also used in voltage-clamp studies to eliminativation (Keller et al., 1986).
 5. Voltage-dependent

(LDH) release in cultured neurons; Pauwels et al., 199
BTX is also used in voltage-clamp studies to elimini
inactivation (Keller et al., 1986).
5. *Voltage-dependent activation*. Activation of volta
gated ion channels is t BTX is also used in voltage-clamp studies to elimi
inactivation (Keller et al., 1986).
5. Voltage-dependent activation. Activation of volt
gated ion channels is thought to result from a volt
driven conformational change th inactivation (Keller et al., 1986).
5. Voltage-dependent activation. Activation of voltage-
gated ion channels is thought to result from a voltage-
driven conformational change that opens a transmem-
brane pore through the

Xyiocaine

.Prilocain.

Nitrendipi

Nifedioi

brather 1998 Inhibition of veratridine-induced released LDH (IC₅₀, M)
Frain neuronal cultures [assessed by lactate dehydrogenase (LDH) release], and their binding affinity for the [³H]BTX-B binding site in rat
corte FIG. 4. Correlation between the potencies of Ca²⁺ blockers and local anesthetics to prevent neurotoxicity induced by 30 μ M veratridine in brain neuronal cultures [assessed by lactate dehydrogenase (LDH) release], and FIG. 4. Correlation between the potencies of Ca²⁺ blockers and local anesthetics to prevent neurotoxicity induced by 30 μ M veratridine in brain neuronal cultures [assessed by lactate dehydrogenase (LDH) release], and Fig. The correlation neuronal cultures (assessed by lactate dehydrogenase (LDH) release], and their binding affinity for the ^{[3}H]BTX-B binding site in rat cortex synaptosomal preparation. The plotted values are mean IC Figure 1 and the unit of the synaptosomal preparation. The plotted values are mean Γ_{c50} . The correlation between neurotoxicity and binding data was calculated
by linear regression analysis (slope = 0.96; correlation **Wilkens.**

REVIEW

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MODULATION OF VOLTA
triggered by membrane depolarization, exerting an elec-
trical force on gating charges (voltage sensors) located MODULATION OF VOLTAGE-G

triggered by membrane depolarization, exerting an elec-

trical force on gating charges (voltage sensors) located

within the transmembrane electrical field (Catterall, ph MODULATION OF VOLTA
triggered by membrane depolarization, exerting an electrical force on gating charges (voltage sensors) located
within the transmembrane electrical field (Catterall
1993a, b). The movement of the gating triggered by membrane depolarization, exerting an elec-
trical force on gating charges (voltage sensors) located the
within the transmembrane electrical field (Catterall, p
1993a, b). The movement of the gating charges thr triggered by membrane depolarization, exerting an electrical force on gating charges (voltage sensors) located
within the transmembrane electrical field (Catterall,
1993a, b). The movement of the gating charges through
the trical force on gating charges (voltage sensors) located
within the transmembrane electrical field (Catterall,
1993a, b). The movement of the gating charges through
the membrane has been directly measured as an out-
ward within the transmembrane electrical field (Catterall, 1993a, b). The movement of the gating charges through the membrane has been directly measured as an outward gating current (Armstrong, 1981). Na⁺ currents through the 1993a, b). The movement of the gating charges through
the membrane has been directly measured as an out-
ward gating current (Armstrong, 1981). Na⁺ currents
through the channel can be blocked by toxins without
affecting the membrane has been directly measured as are ward gating current (Armstrong, 1981). Na⁺ cure through the channel can be blocked by toxins wis affecting these gating currents, suggesting that ments of the channel protei ward gating current (Armstrong, 1981). Na⁺ currents
through the channel can be blocked by toxins without an
affecting these gating currents, suggesting that ele-
in ments of the channel protein involved in voltage-depen through the channel can be blocked by toxins without amerified and affecting these gating currents, suggesting that ele-
ments of the channel protein involved in voltage-depen-
dent activation are separate from those that affecting these gating currents, suggesting that elements of the channel protein involved in voltage-dependent activation are separate from those that form the pore. Similarly, mutations in the P-region that alter ion pron ments of th
dent activa
pore. Simila
conduction
al., 1991).
The S4 tr nt activation are separate from those that form the
re. Similarly, mutations in the P-region that alter ion
nduction have no effect on gating currents (Pusch et
, 1991).
The S4 transmembrane regions of one or more repeats

pore. Similarly, mutations in the P-region that alter ion pepiconduction have no effect on gating currents (Pusch et fast al., 1991). (Eal., The S4 transmembrane regions of one or more repeats have contain voltage sensing conduction have no effect on gating currents (Pusch et fast
al., 1991). (Ea.
The S4 transmembrane regions of one or more repeats have
contain voltage sensing structures that are critical to cine
activation gating (fig. 1) al., 1991).
The S4 transmembrane regions of one or more repeat
contain voltage sensing structures that are critical i
activation gating (fig. 1). Analogous sequences to S
have been found in Ca^{2+} and K^+ voltage-activ The S4 transmembrane regions of one or more repeats
contain voltage sensing structures that are critical to
activation gating (fig. 1). Analogous sequences to S4
have been found in Ca²⁺ and K⁺ voltage-activated chan-
 contain voltage sensing structures that are critical to activation gating (fig. 1). Analogous sequences to S4 have been found in Ca^{2+} and K^+ voltage-activated channels, and they all share a unique motif composed of activation gating (fig. 1). Analogous sequences to S4
have been found in Ca^{2+} and K^+ voltage-activated chan-
nels, and they all share a unique motif composed of four
to eight positively charged amino acids (arginine have been found in Ca²⁺ and K⁺ voltage-activated chan-
nels, and they all share a unique motif composed of four
to eight positively charged amino acids (arginine or ly-
sine), spaced at three-residue intervals along a nels, and they all share a unique motif composed of four
to eight positively charged amino acids (arginine or ly-
sine), spaced at three-residue intervals along a putative
 α -helical segment. Activation gating is though to eight positively charged amino acids (arginine or ly-
sine), spaced at three-residue intervals along a putative the
 α -helical segment. Activation gating is thought to result bec
from a displacement of these charged sine), spaced at three-residue intervals along a putative α -helical segment. Activation gating is thought to result from a displacement of these charged residues in response to changes in the transmembrane electrical f α -helical segment. Activation gating is thought to result
from a displacement of these charged residues in re-
sponse to changes in the transmembrane electrical field
(Armstrong and Bezanilla, 1973; Catterall, 1993a, b from a displacement of these charged residues in response to changes in the transmembrane electrical field (Armstrong and Bezanilla, 1973; Catterall, 1993a, b).
Site-directed mutagenesis and in vitro expression of rat
bra sponse to changes in the transmembrane electrical field fast (Armstrong and Bezanilla, 1973; Catterall, 1993a, b).

Site-directed mutagenesis and in vitro expression of rat cal brain II Na⁺ channels have strongly support (Armstrong and Bezanilla, 1973; Catterall, 1993a, b).
Site-directed mutagenesis and in vitro expression of rat
brain II Na⁺ channels have strongly supported this con-
cept: (α) replacement of positively charged amino Site-directed mutagenesis and in vitro expression of rat
brain II Na⁺ channels have strongly supported this con-
cept: (a) replacement of positively charged amino acid
residues in S4 of repeat I, by neutral or negative brain II Na⁺ channels have strongly supported this concept: (α) replacement of positively charged amino acid deresidues in S4 of repeat I, by neutral or negatively appeared residues, reduced the steepness of the pote cept: (*a*) replacement of positively charged amino acid diversidues in S4 of repeat I, by neutral or negatively a charged residues, reduced the steepness of the potential a dependence of activation, indicating a decrease residues in S4 of repeat I, by neutral or negatively a
charged residues, reduced the steepness of the potential
dependence of activation, indicating a decrease in the
apparent gating charges (Stühmer et al., 1989); and $(b$ charged residues, reduced the steepness of the potential amino
dependence of activation, indicating a decrease in the consist
apparent gating charges (Stühmer et al., 1989); and (b) dues in
alteration of a single neutral dependence of activation, indicating a decrease in the apparent gating charges (Stühmer et al., 1989); and (*b*) alteration of a single neutral residue in the S4 sequence of repeat II shifted the I-V relationship by 20 to apparent gating charges (Stühmer et al., 1989);
alteration of a single neutral residue in the S4 se
of repeat II shifted the I-V relationship by 20 to
toward more positive potentials, reflecting a dr
change in gating behav **Example 1.5. Fast increase in the S4 sequence repeat II shifted the I-V relationship by 20 to 25 m's ward more positive potentials, reflecting a dramation ange in gating behaviour (Auld et al., 1990).
6.** *Fast inactivat*

for repeat II shifted the I-V relationship by 20 to 25 mV toward more positive potentials, reflecting a dramatic change in gating behaviour (Auld et al., 1990).
6. Fast inactivation. A wide range of experimental evidence toward more positive potentials, reflecting a dramatic change in gating behaviour (Auld et al., 1990). C .
6. Fast inactivation. A wide range of experimental evidence indicates that activated channels become non-
conduct change in gating behaviour (Auld et al., 1990).
6. Fast inactivation. A wide range of experimental
evidence indicates that activated channels become non-
conducting when a blocking site at the inner side of the
membrane is 6. Fast inactivation. A wide range of experimental evidence indicates that activated channels become non-conducting when a blocking site at the inner side of the membrane is physically occupied by an *inactivation particl* evidence indicates that activated channels become non-
conducting when a blocking site at the inner side of the
membrane is physically occupied by an *inactivation par-*
ticle, presumably located in the cytoplasmic linker conducting when a blocking site at the inner side of t
membrane is physically occupied by an *inactivation po
ticle*, presumably located in the cytoplasmic linker co
necting repeats III and IV ($L_{\text{II/IVV}}$) (fig. 1): (*a* membrane is physically occupied by an *inactivation particle*, presumably located in the cytoplasmic linker connecting repeats III and IV $(L_{\text{H}1\text{V}1\text{V}})$ (fig. 1): (*a*) perfusion of the intracellular surface of Na Figure 1, the system of the external inker connecting repeats III and IV (L_{HLY}) (fig. 1): (*a*) perfusion exported of the intracellular surface of Na⁺ channels with proteo-
lytic enzymes prevented inactivation (Ar necting repeats III and IV $(L_{\text{H}1/\text{IV}})$ (fig. 1): (*a*) perfusion ev
of the intracellular surface of Na⁺ channels with proteo-
lytic enzymes prevented inactivation (Armstrong et al., ar
1973; Rojas and Rudy, 1976); of the intracellular surface of Na⁺ channels with proteo-
lytic enzymes prevented inactivation (Armstrong et al.,
1973; Rojas and Rudy, 1976); (b) antibody directed y
against a peptide sequence of $L_{\text{H}1/\text{IV}}$ marked lytic enzymes prevented inactivation (Armstrong et 1973; Rojas and Rudy, 1976); (b) antibody directiong against a peptide sequence of L_{HLY} markedly slovinactivation, and the intracellular sequence recogniply the ant 1973; Rojas and Rudy, 1976); (b) antibody directed against a peptide sequence of L_{HLYV} markedly slowed inactivation, and the intracellular sequence recognized by the antibody was rendered inaccessible by inactivatio against a peptide sequence of $L_{\text{H}17V}$ markedly slowed inactivation, and the intracellular sequence recognized
by the antibody was rendered inaccessible by inactiva-
tion, suggesting a conformational change of this s inactivation, and the intracellular sequence recognized 1. Phosphorylation by adenosine $3',5'$ -cyclic mono-
by the antibody was rendered inaccessible by inactiva-
tion, suggesting a conformational change of this se-
quenc quence during inactivation (Vassilev et al., 1988, 1989); monophosphate (cAMP)-dependent protein kinase (cA-

(c) mutational cleavage of the linkage between repeats PK) in purified preparations (Costa and Catterall, 1982), tion, suggesting a conformational change of this sequence during inactivation (Vassilev et al., 1988, 1989);
(c) mutational cleavage of the linkage between repeats III and IV of the rat brain type II Na⁺ channel caused quence during inactivation (Vassilev et al., 1988, 1989);
(c) mutational cleavage of the linkage between repeats
III and IV of the rat brain type II Na⁺ channel caused a
imarked reduction in the rate of inactivation (Stü (c) mutational cleavage of the linkage between repeats
III and IV of the rat brain type II Na⁺ channel caused a
marked reduction in the rate of inactivation (Stühmer et
al., 1989); and (d) deletions of some residues (Pa III and IV of the rat brain type II Na⁺ channel caused a marked reduction in the rate of inactivation (Stühmer et al., 1989); and (d) deletions of some residues (Patton et al., 1992), or mutation of three contiguous hy marked reduction in the rate of inactivation (Stühmer et end., 1989); and (d) deletions of some residues (Patton et c. ed., 1992), or mutation of three contiguous hydrophobic 13 residues [isoleucine-phenylalanine-methioni al., 1992), or mutation of three contiguous hydrophobic 1987). The fact that the same residues were phosphory-
residues [isoleucine-phenylalanine-methionine (IFM); lated in vitro, and following activation of cA-PK in vivo

-GATED NA⁺ CHANNELS 29
1992a). The phenylalanine¹⁴⁸⁹ residue at the centre of
the IFM cluster seems critical for the presumed hydro--GATED NA⁺ CHANNELS
1992a). The phenylalanine¹⁴⁸⁹ residue at the centre
the IFM cluster seems critical for the presumed hydr
phobic interaction, because its conversion to glutami -GATED NA⁺ CHANNELS 29
1992a). The phenylalanine¹⁴⁸⁹ residue at the centre of
the IFM cluster seems critical for the presumed hydro-
phobic interaction, because its conversion to glutamine
is sufficient, by itself, to 1992a). The phenylalanine¹⁴⁸⁹ residue at the centre of the IFM cluster seems critical for the presumed hydro-
phobic interaction, because its conversion to glutamine
is sufficient, by itself, to almost completely preven the IFM cluster seems critical for the presumed hydro-
phobic interaction, because its conversion to glutamine
is sufficient, by itself, to almost completely prevent fast
channel inactivation.
The cluster of residues IFM e IFM cluster seems critical for the presumed hydro-
nobic interaction, because its conversion to glutamine
sufficient, by itself, to almost completely prevent fast
annel inactivation.
The cluster of residues IFM in L_{\text

phobic interaction, because its conversion to glutamine
is sufficient, by itself, to almost completely prevent fast
channel inactivation.
The cluster of residues IFM in $L_{\text{H}1\text{H}V}$ is conserved
among α subtype is is sufficient, by itself, to almost completely prevent fast
channel inactivation.
The cluster of residues IFM in L_{HLYV} is conserved
among α subtype isoforms, and it performs a similar role
in heart (Hartmann et a channel inactivation.

The cluster of residues IFM in $L_{\text{H}1/\text{IV}}$ is conserved

among α subtype isoforms, and it performs a similar role

in heart (Hartmann et al., 1994) and skeletal muscle

channels (Orias et al. The cluster of residues IFM in $L_{\text{H}11/\text{IV}}$ is conserved
among α subtype isoforms, and it performs a similar role
in heart (Hartmann et al., 1994) and skeletal muscle
channels (Orias et al., 1994). In addition, thi among α subtype isoforms, and it performs a similar role
in heart (Hartmann et al., 1994) and skeletal muscle
channels (Orias et al., 1994). In addition, this cluster has
affinity for a receptor in the pore, inasmuch a in heart (Hartmann et al., 1994) and skeletal muscle
channels (Orias et al., 1994). In addition, this cluster has
affinity for a receptor in the pore, inasmuch as small
peptides containing the motif IFM are able to restore affinity for a receptor in the pore, inasmuch as small
peptides containing the motif IFM are able to restore
fast inactivation to channels mutated in this region
(Eaholtz et al., 1994). McPhee and coworkers (1994)
have ide affinity for a receptor in the pore, inasmuch as a peptides containing the motif IFM are able to refast inactivation to channels mutated in this r (Eaholtz et al., 1994). McPhee and coworkers (have identified three adjace peptides containing the motif IFM are able to restore fast inactivation to channels mutated in this region (Eaholtz et al., 1994). McPhee and coworkers (1994) have identified three adjacent residues (valine-isoleucine-leuc fast inactivation to channels mutated in this region (Eaholtz et al., 1994). McPhee and coworkers (1994) have identified three adjacent residues (valine-isoleucine-leucine) at the intracellular end of segment IVS6, which m (Eaholtz et al., 1994). McPhee and coworkers (199
have identified three adjacent residues (valine-isole
cine-leucine) at the intracellular end of segment IVS
which may be part of the hydrophobic receptor site
the fast inac have identified three adjacent residues (valine-isolet cine-leucine) at the intracellular end of segment IVS6 which may be part of the hydrophobic receptor site for the fast inactivation gate (fig. 1) because their convers which may be part of the hydrophobic receptor site for
the fast inactivation gate (fig. 1) because their conver-
sion to alanine markedly disrupted fast inactivation.
Interactions between cluster IFM and the receptor for
t the fast inactivation gate $($ fig. 1 $)$ because their converthe inactivation particle are likely to be hydrophobic, because there is a close correlation between hydropho-
bicity of the residue at that position and the extent of fast $Na⁺$ channel inactivation (Scheuer et al., bicity of the residue at that position and the extent of Interactions between cluster IFM and the receptor for the inactivation particle are likely to be hydrophobibecause there is a close correlation between hydrophobicity of the residue at that position and the extent (fast N e inactivation particle are likely to be hydrophobic
cause there is a close correlation between hydropho
city of the residue at that position and the extent of
st Na⁺ channel inactivation (Scheuer et al., 1993).
Althoug

because there is a close correlation between hydrophobicity of the residue at that position and the extent of fast Na⁺ channel inactivation (Scheuer et al., 1993). Although the charged residues of L_{HUV} are not cri bicity of the residue at that position and the extent
fast Na⁺ channel inactivation (Scheuer et al., 1993).
Although the charged residues of L_{III/IV} are not cr
cal for fast inactivation (Moorman et al., 1990; Pattor
al fast Na⁺ channel inactivation (Scheuer et al., 1993).
Although the charged residues of $L_{\text{TI/IV}}$ are not critical for fast inactivation (Moorman et al., 1990; Patton et al., 1992), mutations altering them shifted the Although the charged residues of L_{HUV} are not critical for fast inactivation (Moorman et al., 1990; Patton e al., 1992), mutations altering them shifted the voltage dependent properties of the channel, and these shi cal for fast inactivation (Moorman et al., 1990; Patton et al., 1992), mutations altering them shifted the voltage-
dependent properties of the channel, and these shifts
appeared to correlate with the charge of the replace al., 1992), mutations altering them shifted the voltage
dependent properties of the channel, and these shifts
appeared to correlate with the charge of the replacement
amino acids (Patton et al., 1992). This observation is
 dependent properties of the channel, and these shifts
appeared to correlate with the charge of the replacement
amino acids (Patton et al., 1992). This observation is
consistent with the hypothesis that these charge resi-
d appeared to correlate with the charge of the replacement
amino acids (Patton et al., 1992). This observation is
consistent with the hypothesis that these charge resi-
dues interact electrostatically from the cytoplasmic si amino acids (Patton et al., 1992). Th
consistent with the hypothesis that the
dues interact electrostatically from the
with a voltage sensor of the channel, p
S4 segments (Moorman et al., 1990). dues interact electrostatically from the cytoplasmic side
with a voltage sensor of the channel, possibly one of the
S4 segments (Moorman et al., 1990).
C. Physiological Modulation of Na⁺ Channels
Voltage-gated Na⁺ ch

ith a voltage sensor of the channel, possibly one of the
 $\frac{1}{2}$ segments (Moorman et al., 1990).
 Physiological Modulation of Na⁺ Channels

Voltage-gated Na⁺ channels are not only responsible

r initiation and c S4 segments (Moorman et al., 1990).

C. Physiological Modulation of Na⁺ Channels

Voltage-gated Na⁺ channels are not only responsit

for initiation and conduction of neuronal action pote

tials, but can also influence C. Physiological Modulation of Na⁺ Channels
Voltage-gated Na⁺ channels are not only responsible
for initiation and conduction of neuronal action poten-
tials, but can also influence neurotransmitter release
from presy C. Physiological modulation of Na Channels
Voltage-gated Na⁺ channels are not only responsible
for initiation and conduction of neuronal action poten-
tials, but can also influence neurotransmitter release
from presynap Voltage-gated $Na⁺$ channels are not only responsible
for initiation and conduction of neuronal action poten-
tials, but can also influence neurotransmitter release
from presynaptic vesicles (Krueger et al., 1980; Abi for initiation and conduction of neuronal action potentials, but can also influence neurotransmitter release
from presynaptic vesicles (Krueger et al., 1980; Abita et
al., 1977; see also section III. B.5.). There is strong tials, but can also influence neurotransmitter releation presynaptic vesicles (Krueger et al., 1980; Abita al., 1977; see also section III. B.5.). There is stro evidence indicating that these integrative functions Na⁺ ch from presynaptic vesicles (Krueger et al., 1980; Abit al., 1977; see also section III. B.5.). There is strevidence indicating that these integrative function Na^+ channels are subject to neuromodulation by sectary messen al., 1977; see also section III. B.5.). There is strong
evidence indicating that these integrative functions of
Na⁺ channels are subject to neuromodulation by second-
ary messenger systems, especially by protein phosphor evidence indicating that these integrative functions ary messenger systems, especially by protein photogram properties (Levitan, 1988).

1. Phosphorylation by adenosine 3',5'-cyclic is also been been been been been been be ary messenger systems, especially by protein phosphorylation, a fundamental regulatory mechanism in the control of membrane properties (Levitan, 1988).
 1. Phosphorylation by adenosine 3',5'-cyclic mono-

ary messenger systems, especially by protein phosphorylation, a fundamental regulatory mechanism in the control of membrane properties (Levitan, 1988).
 1. Phosphorylation by adenosine $3', 5'$ -cyclic mono-
 phosphate-de ylation, a fundamental regulatory mechanism in the
control of membrane properties (Levitan, 1988).
1. *Phosphorylation by adenosine* 3',5'-cyclic mono-
phosphate-dependent protein kinase. Rat brain Na⁺
channels are readi control of membrane properties (Levitan, 1988).

1. Phosphorylation by adenosine $3', 5'$ -cyclic mono-

phosphate-dependent protein kinase. Rat brain Na^+

channels are readily phosphorylated by $3', 5'$ -cyclic

monophosph 1. Phosphorylation by adenosine $3',5'$ -cyclic mono-
phosphate-dependent protein kinase. Rat brain Na⁺
channels are readily phosphorylated by $3',5'$ -cyclic
monophosphate (cAMP)-dependent protein kinase (cA-
PK) in purifi phosphate-dependent protein kinase. Rat brain Na⁺
channels are readily phosphorylated by 3',5'-cyclic
monophosphate (cAMP)-dependent protein kinase (cA-
PK) in purified preparations (Costa and Catterall, 1982)
isolated n channels are readily phosphorylated by 3',5'-cyclic monophosphate (cAMP)-dependent protein kinase (cAPK) in purified preparations (Costa and Catterall, 1982)
isolated nerve endings (synaptosomes) (Costa and Caterall, 1984a monophosphate (cAMP)-dependent protein kinase (cA-PK) in purified preparations (Costa and Catterall, 1982)
isolated nerve endings (synaptosomes) (Costa and Caterall, 1984a), and following elevation of intracellular
cAMP in PK) in purified preparations (Costa and Catterall, 19
isolated nerve endings (synaptosomes) (Costa and
erall, 1984a), and following elevation of intracell
cAMP in intact rat brain neurons (Rossie and Catte
1987). The fact isolated nerve endings (synaptosomes) (Costa and Caterall, 1984a), and following elevation of intracellular cAMP in intact rat brain neurons (Rossie and Catterall, 1987). The fact that the same residues were phosphory-late erall, 1984a), and following elevation of intracellul
cAMP in intact rat brain neurons (Rossie and Catters
1987). The fact that the same residues were phosphor
lated in vitro, and following activation of cA-PK in vir
sugge cAMP in intact rat brain neurons (Rossie and Catterall, 1987). The fact that the same residues were phosphory-
lated in vitro, and following activation of cA-PK in vivo, suggested a physiological role for this covalent mod

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Four serine residues have been identified as sites of Na⁺ currents

selective cA-PK phosphorylation and dephosphoryla- cylglycerol sig So
Four serine residues have been identified as si
selective cA-PK phosphorylation and dephosph
tion. They are all clustered within the intracellula The series residues have been identified as sites of selective cA-PK phosphorylation and dephosphorylation. They are all clustered within the intracellular segment linking homologous repeats 1 and 2 (L_{LII}) of the Four serine residues have been identified as sites of Na
selective cA-PK phosphorylation and dephosphoryla-
tion. They are all clustered within the intracellular seg-
ment linking homologous repeats 1 and 2 (L_{III}) of th Four serine residues have been identified as sites
selective cA-PK phosphorylation and dephosphory
tion. They are all clustered within the intracellular s
ment linking homologous repeats 1 and 2 ($L_{I/II}$) of α -subunit selective cA-PK phosphorylation and dephosphorylation. They are all clustered within the intracellular segment linking homologous repeats 1 and 2 (L_{LTI}) of the α -subunit (fig. 1) (Rossie et al., 1987; Rossie and tion. They are all clustered within the intracellular segment linking homologous repeats 1 and 2 $(L_{I/II})$ of the α -subunit (fig. 1) (Rossie et al., 1987; Rossie and Catterall, 1989; Murphy et al., 1993), and antibodies ment linking homologous repeats 1 and 2 ($L_{\text{I/II}}$) of the α -subunit (fig. 1) (Rossie et al., 1987; Rossie and Catter-
all, 1989; Murphy et al., 1993), and antibodies against
this region partially block phosphorylati α -subunit (fig. 1) (Rossie et al., 1987; Rossie and Catter-
all, 1989; Murphy et al., 1993), and antibodies against
this region partially block phosphorylation (Nakayama
et al., 1992). Because $L_{\text{I/II}}$ is highly con all, 1989; Murphy et al., 1993), and antibodies agains
this region partially block phosphorylation (Nakayam
et al., 1992). Because $L_{I/II}$ is highly conserved among re
brain α subtypes (Noda et al., 1986; Kayano et al this region partially block phosphorylation (Nakayama et al., 1992). Because $L_{I/II}$ is highly conserved among rat brain α subtypes (Noda et al., 1986; Kayano et al., 1988; Auld et al., 1988), modulation by cAMP-depen et al., 1992). Because
brain α subtypes (No
Auld et al., 1988), mo
phorylation is presu
brain Na⁺ channels.
A number of findi ain α subtypes (Noda et al., 1986; Kayano et al., 1
ild et al., 1988), modulation by cAMP-dependent porylation is presumably a mechanism common to
ain Na⁺ channels.
A number of findings suggest that cA-PK down-reg Na

Auld et al., 1988), modulation by cAMP-dependent phorphorylation is presumably a mechanism common to brain Na⁺ channels.
A number of findings suggest that cA-PK down-reglates Na⁺ channel activity in neurons. Increased phorylation is presumably a mechanism common to all Kream Na⁺ channels. 1993

A number of findings suggest that cA-PK down-regu-

lates Na⁺ channel activity in neurons. Increased cytoso-

lic cAMP reduced neurotoxin-a brain Na⁺ channels.

A number of findings suggest that cA-PK down-regulates Na⁺ channel activity in neurons. Increased cytoso-

lic cAMP reduced neurotoxin-activated 22 Na influx into

rat brain synaptosomes (Costa A number of findings suggest that cA-PK down-regulates Na^+ channel activity in neurons. Increased cytosolic cAMP reduced neurotoxin-activated ²²Na influx interat brain synaptosomes (Costa and Catterall, 1984a) Na^+ c lates Na⁺ channel activity in neurons. Increased cytoso-
lic cAMP reduced neurotoxin-activated ²²Na influx into
rat brain synaptosomes (Costa and Catterall, 1984a).
Na⁺ currents in acutely dissociated striatonigral lic cAMP reduced neurotoxin-activated ²²Na influx into
rat brain synaptosomes (Costa and Catterall, 1984a).
Na⁺ currents in acutely dissociated striatonigral neu-
rons were reduced by agonists acting at D_1 dopamine rat brain synaptosomes (Costa and Catterall, 1984a). phy and Catterall, 1992).

Na⁺ currents in acutely dissociated striatonigral neu-

PKC activation by arachidonic acid and other cis-

rons were reduced by agonists ac Na⁺ currents in acutely dissociated striatonigral neurons were reduced by agonists acting at D_1 dopamine receptors that activate adenylate cyclase, whereas agonists acting at D_2 receptors, which inhibit adenylate rons were reduced by agonists acting at D_1 dopamine
receptors that activate adenylate cyclase, whereas ago-
nists acting at D_2 receptors, which inhibit adenylate
cyclase, had no action or increased the evoked curren cyclase, had no action or increased the evoked currents m
(Surmeier and Kitai, 1993). The most convincing evi-
dence was obtained by purified cA-PK acting directly on G
Na⁺ channels in excised membrane patches (Gershon e (Surmeier and Kitai, 1993). The most convincing evidence was obtained by purified cA-PK acting directly on Ga^+ channels in excised membrane patches (Gershon et Sal., 1992; Li et al., 1992). cA-PK phosphorylation of a in dence was obtained by purified cA-PK acting directly on Na^+ channels in excised membrane patches (Gershon et al., 1992; Li et al., 1992). cA-PK phosphorylation of inside-out membrane patches from rat brain neurons, or C Na⁺ channels in excised membrane patches (Gershon et Sch
al., 1992; Li et al., 1992). cA-PK phosphorylation of and
inside-out membrane patches from rat brain neurons, or pro
Chinese hamster ovary (CHO) fibroblasts expre al., 1992; Li et al., 1992). cA-PK phosphorylation
inside-out membrane patches from rat brain neurons,
Chinese hamster ovary (CHO) fibroblasts expressi
type IIA Na⁺ channels, reduced peak Na⁺ current by
to 50%, without inside-out membrane patches from rat brain neurons, or
Chinese hamster ovary (CHO) fibroblasts expressing
type IIA Na⁺ channels, reduced peak Na⁺ current by up
to 50%, without change in the kinetics or voltage depen-Chinese hamster ovary (CHO) fibroblasts expressing P
type IIA Na⁺ channels, reduced peak Na⁺ current by up
to 50%, without change in the kinetics or voltage depen-
dence of activation or inactivation of the channel, t type IIA Na⁺ channels, reduced peak Na⁺ current by up Na⁺ ch
to 50%, without change in the kinetics or voltage depen-rents (*dence of activation or inactivation of the channel*, thus cal and
suggesting a decrease in dence of activation or inactivation of the channel, thus
suggesting a decrease in the open probability of single
Na⁺ channels during depolarization (Li et al., 1992). A
significant reduction in Na⁺ channel number and dence of activation or inactivation of the channel, thus cal an suggesting a decrease in the open probability of single phory Na^+ channels during depolarization (Li et al., 1992). A slow is significant reduction in Na^+ suggesting a decrease in the open probability of single ph
Na⁺ channels during depolarization (Li et al., 1992). A skignificant reduction in Na⁺ channel number and activity was caused by the basal activity of $CA-PK$ in significant reduction in Na⁺ channel number and activity was caused by the basal activity of cA-PK in CHO cells, indicating that the activity of Na⁺ channels is dynamically modulated by fluctuations in cAMP concentrat significant reduction in Na⁺ channel number and activity was caused by the basal activity of cA-PK in CHO cells, indicating that the activity of Na⁺ channels is dynamically modulated by fluctuations in cAMP concentrat ity was caused by the basal activity of cA-PK in CHO
cells, indicating that the activity of Na⁺ channels is
dynamically modulated by fluctuations in cAMP concen-
tration at or above the resting level in cells (Li et al., cells, indicating that the activity of Na⁺ channels dynamically modulated by fluctuations in cAMP conce tration at or above the resting level in cells (Li et a 1992). Thus, both basal and stimulated levels of cA-Pias wel dynamically modulated by fluctuations in cAMP concentration at or above the resting level in cells (Li et al., 1992). Thus, both basal and stimulated levels of cA-PK, as well as the activity of phosphoprotein phosphatases, tration at or above the resting level in cells (Li et al., 1992). Thus, both basal and stimulated levels of cA-PK, as well as the activity of phosphoprotein phosphatases, are likely to play important roles in controlling 1992). Thus, both basal and stimulated levels of cA-PK,
as well as the activity of phosphoprotein phosphatases,
are likely to play important roles in controlling the dy-
namic state of α -subunit phosphorylation and, th as well as the activity of phosphoprotein phosphatases, sare likely to play important roles in controlling the dy-
namic state of α -subunit phosphorylation and, thereby, a
the regulation of channel function. This furth are likely to play important roles in controlling the dynamic state of α -subunit phosphorylation and, thereby, the regulation of channel function. This further implies that a wide range of neurotransmitters acting thro namic state of α -subunit phosphorylation and, thereby,
the regulation of channel function. This further implies
that a wide range of neurotransmitters acting through
cAMP as a second messenger can modulate neuronal
Na currents. that a wide range of neurotransmitters acting through cAMP as a second messenger can modulate neuronal $Na⁺$ channels, with increased cAMP attenuating $Na⁺$ currents.
2. *Phosphorylation by protein kinase C*. Prot

cAMP as a second messenger can modulate neuronal
Na⁺ channels, with increased cAMP attenuating Na⁺
currents.
2. *Phosphorylation by protein kinase C*. Protein kinase
C (PKC) is a Ca²⁺/phospholipid-dependent regulato Na⁺ channels, with increased cAMP attenuating Na⁺
currents.
2. *Phosphorylation by protein kinase* C. Protein kinase
C (PKC) is a $Ca^{2+}/phospholipid-dependent regulatory$
enzyme activated by diacylglycerol. Its activation is be-
lieved to invo currents.

2. Phosphorylation by protein kinase C. Protein kinase

C (PKC) is a Ca²⁺/phospholipid-dependent regulatory

enzyme activated by diacylglycerol. Its activation is be-

lieved to involve a translocation to cell 2. Phosphorylation by protein kinase C. Protein kinds C (PKC) is a $Ca^{2+}/phospholipid-dependent regular$ regulaenzyme activated by diacylglycerol. Its activation is lieved to involve a translocation to cell membranes lowed by activation, after C (PKC) is a $Ca^{2+}/phospholipid-dependent regulatory$ et enzyme activated by diacylglycerol. Its activation is believed to involve a translocation to cell membranes, followed by activation, after which substrate phosphorylation takes place. PKC is lieved to involve a translocation to cell membranes, followed by activation, after which substrate phosphorylation takes place. PKC is highly concentrated in the brain and exists in several different isoforms that are diff tion takes place. PKC is highly concentrated in the brain
and exists in several different isoforms that are differ-
entially distributed and differentially activated by sec-
ondary messengers (Nishizuka, 1988, 1992). The lowed by activation, after which substrate phosphorylation takes place. PKC is highly concentrated in the brain and exists in several different isoforms that are differentially distributed and differentially activated by tion takes place. PKC is highly concentrated in the brain
and exists in several different isoforms that are differ-
entially distributed and differentially activated by sec-
ondary messengers (Nishizuka, 1988, 1992). The and exists in several different isoforms that are differentially distributed and differentially activated by secondary messengers (Nishizuka, 1988, 1992). The finding that α -subunits of purified Na⁺ channels from rat

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Na⁺ currents may also be modulated by the Ca²⁺-cylglycerol signaling pathway (Costa and Catte EXENOVITCH
Na⁺ currents may also be modulated by the Ca²⁺-dia-
cylglycerol signaling pathway (Costa and Catterall,
1984b). Under physiological conditions, PKC phosphory BRENOVITCH
Na⁺ currents may also be modulated by the Ca²⁺.
cylglycerol signaling pathway (Costa and Catte
1984b). Under physiological conditions, PKC phosph
lates a single serine residue (serine¹⁵⁰⁶) of rat b Na⁺ currents may also be modulated by the Ca²⁺-dia-
cylglycerol signaling pathway (Costa and Catterall,
1984b). Under physiological conditions, PKC phosphory-
lates a single serine residue (serine¹⁵⁰⁶) of rat brain
 cylglycerol signaling pathway (Costa and Catterall, 1984b). Under physiological conditions, PKC phosphory-
lates a single serine residue (serine¹⁵⁰⁶) of rat brain α -subunits, located in the inactivation gate formed b 1984b). Under physiological conditions, PKC phosphory-
lates a single serine residue (serine¹⁵⁰⁶) of rat brain α -subunits, located in the inactivation gate formed by
the short intracellular loop between repeats III a lates a single serine residue (serine¹⁵⁰⁶) of rat brain α -subunits, located in the inactivation gate formed by the short intracellular loop between repeats III and IV ($L_{\text{H}UV}$) (fig. 1) (West et al., 1991). The s α -subunits, located in the inactivation gate formed by α -subunits, located in the inactivation gate formed b
the short intracellular loop between repeats III and I
($L_{\text{HII/IV}}$) (fig. 1) (West et al., 1991). The sequence sur
rounding serine¹⁵⁰⁶ (lysine-lysine-leucine-gl $(L_{\text{HII/IV}})$ (fig. 1) (West et al., 1991). The sequence surrounding serine¹⁵⁰⁶ (lysine-lysine-leucine-glycine-
serine-lysine-lysine; Auld et al., 1988) favours its phos-
phorylation by PKC, but not by cA-PK (Kennelly a rounding serine¹⁵⁰⁶ (lysine-lysine-leucine-glycine serine-lysine; Auld et al., 1988) favours its photophorylation by PKC, but not by cA-PK (Kennelly an Krebs, 1991; Kemp and Pearson, 1990; West et al. 1991). Further act serine-lysine-lysine; Auld et al., 1988) favours its phos-
phorylation by PKC, but not by cA-PK (Kennelly and
Krebs, 1991; Kemp and Pearson, 1990; West et al.,
1991). Further activation of PKC, however, also phos-
phorylat phorylation by PKC, but not by cA-PK (Kennelly and Krebs, 1991; Kemp and Pearson, 1990; West et al., 1991). Further activation of PKC, however, also phosphorylates serine⁶¹⁰ in L_{I/II} (Numann et al., 1992), thus implyin Krebs, 1991; Kemp and Pearson, 1990; West et al
1991). Further activation of PKC, however, also phos
phorylates serine⁶¹⁰ in L_{VII} (Numann et al., 1992), thu
implying that this residue may be a phosphorylation sit
com 1991). Further activation ophorylates serine⁶¹⁰ in L_{UII} implying that this residue rommon to cA-PK and PK(
phy and Catterall, 1992). PKC activation by aractive implying that this residue may be a phosphorylation site
common to cA-PK and PKC (see above, section 1.; Mur-
phy and Catterall, 1992).
PKC activation by arachidonic acid and other *cis-*

nists acting at D_2 receptors, which inhibit adenylate toma cells, rat brain neurons and *Xenopus* occytes and cyclase, had no action or increased the evoked currents mammalian cells expressing rat brain Na⁺ channels cyclase, had no action or increased the evoked currents mammalian cells expressing rat brain Na⁺ channels or (Surmeier and Kitai, 1993). The most convincing evi-
dence was obtained by purified cA-PK acting directly on G implying that this residue may be a phosphorylation
common to cA-PK and PKC (see above, section 1.;
phy and Catterall, 1992).
PKC activation by arachidonic acid and other
unsaturated fatty acids, phorbol esters or diacylg common to cA-PK and PKC (see above, section 1.; N
phy and Catterall, 1992).
PKC activation by arachidonic acid and other
unsaturated fatty acids, phorbol esters or diacylglyce
like compounds modulates Na^+ currents in ne phy and Catterall, 1992).

PKC activation by arachidonic acid and other *cis*-

unsaturated fatty acids, phorbol esters or diacylglycerol-

like compounds modulates Na⁺ currents in neuroblas-

toma cells, rat brain neuro PKC activation by arachidonic acid and other *cis*-
unsaturated fatty acids, phorbol esters or diacylglycerol-
like compounds modulates Na^+ currents in neuroblas-
toma cells, rat brain neurons and *Xenopus* occytes and
 unsaturated fatty acids, phorbol esters or diacylglycerol-
like compounds modulates Na^+ currents in neuroblas-
toma cells, rat brain neurons and *Xenopus* oocytes and
mammalian cells expressing rat brain Na^+ channels like compounds modulates Na⁺ currents in neuroblastoma cells, rat brain neurons and *Xenopus* oocytes and mammalian cells expressing rat brain Na⁺ channels or type IIA α -subunits (Linden and Routtenberg, 1989; Godo toma cells, rat brain neurons and *Xenopus* oocytes and
mammalian cells expressing rat brain Na⁺ channels or
type IIA α -subunits (Linden and Routtenberg, 1989;
Godoy and Cukierman, 1994; Numann et al., 1991, 1992;
Sc type IIA α -subunits (Linden and Routtenberg, 1989; Godoy and Cukierman, 1994; Numann et al., 1991, 1992; Schreibmayer et al., 1991; Dascal and Lotan, 1991; Sigel and Baur, 1988). Although there are some discrepancies, type IIA α -subunits (Linden and Routtenberg, 1989;
Godoy and Cukierman, 1994; Numann et al., 1991, 1992;
Schreibmayer et al., 1991; Dascal and Lotan, 1991; Sigel
and Baur, 1988). Although there are some discrepancies,
 Godoy and Cukierman, 1994; Numann et al., 1991, 1992;
Schreibmayer et al., 1991; Dascal and Lotan, 1991; Sigel
and Baur, 1988). Although there are some discrepancies,
probably arising from differences in preparations and
 Schreibmayer et al., 1991; Dascal and Lotan, 1991; Sigel
and Baur, 1988). Although there are some discrepancies,
probably arising from differences in preparations and
PKC activators, overall, phosphorylation by PKC slows
N and Baur, 1988). Although there are some discrepancies
probably arising from differences in preparations and
PKC activators, overall, phosphorylation by PKC slows
 Na^+ channel inactivation and reduces peak Na^+ cur
rent probably arising from differences in preparations an
PKC activators, overall, phosphorylation by PKC slow
Na⁺ channel inactivation and reduces peak Na⁺ cu
rents (West et al., 1991; Schreibmayer et al., 1991; Da
cal and PKC activators, overall, phosphorylation by PKC slows
Na⁺ channel inactivation and reduces peak Na⁺ currents (West et al., 1991; Schreibmayer et al., 1991; Das-
cal and Lotan, 1991; Murphy and Catterall, 1992). Phos-
 Na⁺ channel inactivation and reduces peak Na⁺ cur-
rents (West et al., 1991; Schreibmayer et al., 1991; Das-
cal and Lotan, 1991; Murphy and Catterall, 1992). Phos-
phorylation by PKC of serine¹⁵⁰⁶, alone, is suffici rents (West et al., 1991; Schreibmayer et al., 1991; Das-
cal and Lotan, 1991; Murphy and Catterall, 1992). Phos-
phorylation by PKC of serine¹⁵⁰⁶, alone, is sufficient to
slow inactivation (West et al., 1991), which is cal and Lotan, 1991; Murphy and Catterall, 1992). Phos-
phorylation by PKC of serine¹⁵⁰⁶, alone, is sufficient to
slow inactivation (West et al., 1991), which is consistent
with the location of this residue in a protein phorylation by PKC of serine¹⁵⁰⁶, alone, is sufficient to slow inactivation (West et al., 1991), which is consistent with the location of this residue in a protein segment essential to inactivation gating. However, the slow inactivation (West et al., 1991), which is consistent
with the location of this residue in a protein segment
essential to inactivation gating. However, the reduction
of peak Na⁺ currents required PKC phosphorylatio with the location of this residue in a protein segment
essential to inactivation gating. However, the reduction
of peak Na⁺ currents required PKC phosphorylation of
both serine¹⁵⁰⁶ in $L_{\text{HII/V}}$ and serine⁶¹⁰ in L essential to inactivation gating. However, the reduction
of peak Na⁺ currents required PKC phosphorylation of
both serine¹⁵⁰⁶ in L_{HUV} and serine⁶¹⁰ in L_{VII} (West et
al., 1991). Li and coworkers (1993) sh of peak Na⁺ currents required PKC phosphorylation of both serine¹⁵⁰⁶ in $L_{\text{HII/V}}$ and serine⁶¹⁰ in L_{VII} (West et al., 1991). Li and coworkers (1993) showed that the reduction of peak Na⁺ currents by cA-PK both serine¹⁵⁰⁶ in $L_{\text{HII/V}}$ and serine⁶¹⁰ in $L_{\text{L/II}}$ (West et al., 1991). Li and coworkers (1993) showed that the reduction of peak Na⁺ currents by cA-PK (see above, section 1.) only occurs when serine¹⁵⁰⁶ al., 1991). Li and coworkers (1993) showed that the reduction of peak Na^+ currents by cA-PK (see above, section 1.) only occurs when serine¹⁵⁰⁶ is phosphorylated by PKC, or substituted with a negatively charged amino reduction of peak Na⁺ currents by cA-PK (see above section 1.) only occurs when serine¹⁵⁰⁶ is phosphorylate by PKC, or substituted with a negatively charged aminetid. This strongly suggests that the effect of cA-PK of section 1.) only occurs when serine¹⁵⁰⁶ is phosphoryl
by PKC, or substituted with a negatively charged a
acid. This strongly suggests that the effect of cA-P!
peak Na⁺ current is conditional, dependent on p
phorylatio PKC, or substituted with a negatively charged amino
id. This strongly suggests that the effect of cA-PK on
ak Na⁺ current is conditional, dependent on phos-
orylation of serine¹⁵⁰⁶ by PKC (Li et al., 1993).
Serine¹⁵⁰

peak Na⁺ current is conditional, dependent on phos-
phorylation of serine¹⁵⁰⁶ by PKC (Li et al., 1993).
Serine¹⁵⁰⁶ and the adjacent amino acids of the PKC
phosphorylation site are conserved in Na⁺ channel
 α -sub phorylation of serine¹⁵⁰⁶ by PKC (Li et al., 1993).

Serine¹⁵⁰⁶ and the adjacent amino acids of the PKC

phosphorylation site are conserved in Na⁺ channel
 α -subunits from brain, heart and skeletal muscle (Noda
 Serine¹⁵⁰⁶ and the adjacent amino acids of the PKC
phosphorylation site are conserved in Na⁺ channel
 α -subunits from brain, heart and skeletal muscle (Noda
et al., 1984; Auld et al., 1988; Kayano et al., 1988; Kall phosphorylation site are conserved in Na⁺ channel α -subunits from brain, heart and skeletal muscle (No et al., 1984; Auld et al., 1988; Kayano et al., 1988; Kall et al., 1990; Rogart et al., 1989; Trimmer et al., 198 α -subunits from brain, heart and skeletal muscle (Noda et al., 1984; Auld et al., 1988; Kayano et al., 1988; Kallen et al., 1990; Rogart et al., 1989; Trimmer et al., 1989), suggesting that Na⁺ channel function may b tissues. al., 1990; Rogart et al., 1989; Trimmer et al., 1989
ggesting that Na⁺ channel function may be modu
ted by activation of PKC in a wide range of excitabl
sues.
It is relevant to mention here that, although TTX
nsitive Na suggesting that Na^+ channel function may be mod
lated by activation of PKC in a wide range of excitab
tissues.
It is relevant to mention here that, although TT.
sensitive Na^+ channels expressed in neurons and astr
cyt

lated by activation of PKC in a wide range of excitable
tissues.
It is relevant to mention here that, although TTX
sensitive Na^+ channels expressed in neurons and astro
cytes exhibit reduced Na^+ currents with PKC acti tissues.
It is relevant to mention here that, although TTX-
sensitive Na⁺ channels expressed in neurons and astro-
cytes exhibit reduced Na⁺ currents with PKC activation,
the distinct TTX-resistant Na⁺ channel expre It is relevant to mention here that, although TTX-
sensitive Na^+ channels expressed in neurons and astro-
cytes exhibit reduced Na^+ currents with PKC activation,
the distinct TTX-resistant Na^+ channel expressed in
a sensitive Na⁺ channels expressed in neurons and astrocytes exhibit reduced Na⁺ currents with PKC activation, the distinct TTX-resistant Na⁺ channel expressed in astrocytes showed a strong potentiation of currents fo

Morphologically distinguishable subtypes of astrocytes Morphologically distinguishable subtypes of astrocytes
cultured from neonatal rat spinal cord, expressed dis-
tinct Na⁺ current types that differed by up to 1000-fold MODULATION OF VOLTAGE-G

Morphologically distinguishable subtypes of astrocytes (C

cultured from neonatal rat spinal cord, expressed dis-

1993. Itinct Na⁺ current types that differed by up to 1000-fold

in their TTX se Morphologically distinguishable subtypes of astrocytes cultured from neonatal rat spinal cord, expressed distinct Na⁺ current types that differed by up to 1000-fold in their TTX sensitivity (Thio and Sontheimer, 1993). A Morphologically distinguishable subtypes of astrocytes
cultured from neonatal rat spinal cord, expressed dis-
tinct Na⁺ current types that differed by up to 1000-fold
in their TTX sensitivity (Thio and Sontheimer, 1993) cultured from neonatal rat spinal cord, expressed dis-
tinct Na^+ current types that differed by up to 1000-fold
prot
in their TTX sensitivity (Thio and Sontheimer, 1993). tion
Activation of PKC by phorbol 12-myristate 1 tinct Na⁺ current types that differed by up to 1000-fol
in their TTX sensitivity (Thio and Sontheimer, 1993
Activation of PKC by phorbol 12-myristate 13-acetat
(PMA) reduced peak TTX-sensitive Na⁺ currents by 2
to 60% in their TTX sensitivity (Thio and Sontheimer, 1993
Activation of PKC by phorbol 12-myristate 13-aceta
(PMA) reduced peak TTX-sensitive Na⁺ currents by 5
to 60%, whereas PMA potentiated peak TTX-resista
Na⁺ currents b (PMA) reduced peak TTX-sensitive Na⁺ currents by 20 demand, because a large part of the energy consumed by to 60%, whereas PMA potentiated peak TTX-resistant the brain is used for maintenance of ionic gradients Na⁺ cu (PMA) reduced peak TTX-sensitive Na⁺ currents by 20
to 60%, whereas PMA potentiated peak TTX-resistant
Na⁺ currents by 60 to 150%. PMA-induced effects devel-
oped within minutes and were typically not reversible
(Thio to 60%, whereas PMA potentiated peak TTX-resistan Na⁺ currents by 60 to 150%. PMA-induced effects deverspoted within minutes and were typically not reversib.
(Thio and Sontheimer, 1993). The functional importance of thi Na⁺ currents by 60 to 150
oped within minutes and
(Thio and Sontheimer, 19
of this up-regulation of ϵ
nels by PKC is unknown.
3. Modulation of Na⁺ c red within minutes and were typically not reversible
hio and Sontheimer, 1993). The functional importance
this up-regulation of glial TTX-resistant Na⁺ chan-
ls by PKC is unknown.
3. *Modulation of Na⁺ channels by guan*

binding proteins $(G$ proteins). In addition to protein nels by PKC is unknown.
3. Modulation of Na^+ channels by guanine nucleotion
binding proteins (G proteins). In addition to prote
phosphorylation, there is evidence suggesting that ac
vation of G proteins in response to n 3. Modulation of Na^+ channels by guanine nucleotide
binding proteins (G proteins). In addition to protein
phosphorylation, there is evidence suggesting that acti-
vation of G proteins in response to neurotransmitters
ca binding proteins (G proteins). In addition to protein
phosphorylation, there is evidence suggesting that activation of G proteins in response to neurotransmitter
can modulate $N a^+$ channel function. $N a^+$ current
throug phosphorylation, there is evidence suggesting that act
vation of G proteins in response to neurotransmitter
can modulate Na^+ channel function. Na^+ current
through brain Na^+ channels expressed in *Xenopus* oc
cytes w vation of G proteins in response to neurotransmitt
can modulate Na^+ channel function. Na^+ curre
through brain Na^+ channels expressed in *Xenopus*
cytes were reduced by guanosine 5'-[gamma-th
triphosphate, a nonhydro can modulate Na^+ channel function. Na^+ currents act
through brain Na^+ channels expressed in *Xenopus* oobel
cytes were reduced by guanosine 5'-[gamma-thio]-
the
triphosphate, a nonhydrolyzable guanosine triphos-
act through brain Na⁺ channels expressed in *Xenopus* oobecytes were reduced by guanosine 5'-[gamma-thio]-
triphosphate, a nonhydrolyzable guanosine triphos-acephate analogue (Cohen-Armon et al., 1989). Ma and
coworkers (19 cytes were reduced by guanosine $5'$ -[gamma-thio]-
triphosphate, a nonhydrolyzable guanosine triphos-
phate analogue (Cohen-Armon et al., 1989). Ma and
coworkers (1994) have shown that activation of brain
Na⁺ channels w triphosphate, a nonhydrolyzable guanosine triph
phate analogue (Cohen-Armon et al., 1989). Ma a
coworkers (1994) have shown that activation of br
Na⁺ channels was enhanced by activation of G prote
in both hippocampal ne phate analogue (Cohen-Armon et al., 1989). Ma coworkers (1994) have shown that activation of b
Na⁺ channels was enhanced by activation of G prote
in both hippocampal neurons and in CHO cells expre-
ing the α -subunit coworkers (1994) have shown that activation of brain carriers (1994) have shanced by activation of G proteins for in both hippocampal neurons and in CHO cells expressing the α -subunit of the type IIA Na⁺ channel. Fur Na⁺ channels was enhanced by activation of G proteins for the hippocampal neurons and in CHO cells expressing the α -subunit of the type IIA Na⁺ channel. Further-
more, basal activation of G proteins (i.e., in absen in both hippocampal neurons and in CHO cells express-
ing the α -subunit of the type IIA Na⁺ channel. Further-
more, basal activation of G proteins (i.e., in absence of fu
agonist) was sufficient to shift significantl ing the α -subunit of the type IIA Na⁺ channel. Further-
more, basal activation of G proteins (i.e., in absence of fun
agonist) was sufficient to shift significantly the voltage lin
dependence of both activation and i more, basal activation of G proteins (i.e., in absence of fund
agonist) was sufficient to shift significantly the voltage link
dependence of both activation and inactivation toward redu
more negative potentials. As G prot agonist) was sufficient to shift significantly the voltage
dependence of both activation and inactivation toward
more negative potentials. As G proteins were also found
to mediate the regulation of cardiac Na⁺ channels dependence of both activation and inactivation toward reduces
more negative potentials. As G proteins were also found local Cl
to mediate the regulation of cardiac Na⁺ channels by vation :
 β -adrenergic receptors (Sch more negative potentials. As G proteins were also found lot mediate the regulation of cardiac Na⁺ channels by β -adrenergic receptors (Schubert et al., 1990; Matsuda is et al., 1992), modulation of Na⁺ channel activ to mediate the regulat β -adrenergic receptors
et al., 1992), modulatio
proteins may be a wide
of electrical excitability

be a widespread mechanism for xxcitability.
 Na for Pharmacological Modu Na ⁺ Channels in Ischemia
 Na ⁺ Channels in Ischemia
 Lular Ionic Homeostasis and Energy **A. Brationale for Pharmacological Modulation

Na⁺ Channels in Ischemia
** *A. Brain Cellular Ionic Homeostasis and Energy***
** *Requirement*

Requirement

A. Brain Cellular Ionic Homeostasis and Energy
Requirement
Although the precise meaning of ischemia is interrup-
tion or reduction of blood flow, it is more pertinent to
consider ischemia as an imbalance between energy sup A. Brain Cellular Ionic Homeostasis and Energy

Requirement
 R^+ :

Although the precise meaning of ischemia is interrup-
 R^+ :

Although the precise meaning of ischemia is interrup-

consider ischemia as an imbalance A. Brain Cettutar fontc Homeostasts and Energy
Requirement
Although the precise meaning of ischemia is interrup-
tion or reduction of blood flow, it is more pertinent to
consider ischemia as an imbalance between energy sup Requirement
Although the precise meaning of ischemia is interr
tion or reduction of blood flow, it is more pertinent
consider ischemia as an imbalance between energy s
ply and demand when considering cerebroprotecti
This e Although the precise meaning of ischemia is interruption or reduction of blood flow, it is more pertinent t
consider ischemia as an imbalance between energy sup
ply and demand when considering cerebroprotection
This extend tion or reduction of blood flow, it is more pertinent to deconsider ischemia as an imbalance between energy sup-
ply and demand when considering cerebroprotection. is
This extended definition encompasses situations with-
b consider ischemia as an imbalance between energy sup-
ply and demand when considering cerebroprotection. is
This extended definition encompasses situations with-
bout occlusive impairment of blood flow but where energy
dem ply and demand when considering cerebroprotection.
This extended definition encompasses situations with-
out occlusive impairment of blood flow but where energy
demand exceeds supply, such as hypoglycemia (Astrup
and Norbe This extended definition encompasses situations with-
out occlusive impairment of blood flow but where energy
demand exceeds supply, such as hypoglycemia (Astrup
and Norberg, 1976; Pelligrino et al., 1982; Harris et al.,
1 out occlusive impairment of blood flow but where energ
demand exceeds supply, such as hypoglycemia (Astru
and Norberg, 1976; Pelligrino et al., 1982; Harris et al
1984), hypotension superimposed upon sustained se
zures (As demand exceeds supply, such as hypoglycemia (Astrup 1993).

and Norberg, 1976; Pelligrino et al., 1982; Harris et al., 2. Barbiturate inhibition of functional activity and

1984), hypotension superimposed upon sustained se and Norberg, 1976; Pelligrino et al., 1982; Harris et al., 2
1984), hypotension superimposed upon sustained sei-
zures (Astrup et al., 1979), and deficient mitochondrial ban
ATP synthesis (Beal, 1992; Sparaco et al., 1993) 1984), hypotension superimposed upon sustained sei
zures (Astrup et al., 1979), and deficient mitochondria
ATP synthesis (Beal, 1992; Sparaco et al., 1993). Above
all, this concept illustrates that protection may be
achiev zures (Astrup et al., 1979), and deficient mitochondrial ATP synthesis (Beal, 1992; Sparaco et al., 1993). Above all, this concept illustrates that protection may be achieved, not only by improving local perfusion in ische ATP synthesis (Beal, 1992; Sparaco et al., 1993). Above
all, this concept illustrates that protection may be
achieved, not only by improving local perfusion in isch-
emic territories, but also by decreasing their metabolic all, this concept illustrates that protection may b
achieved, not only by improving local perfusion in ischemic territories, but also by decreasing their metaboli
demand (Obrenovitch, 1995a). Reduction of cerebra
metabolic achieved, not only by improving local perfusion in ischemic territories, but also by decreasing their metabolic
demand (Obrenovitch, 1995a). Reduction of cerebral
metabolic rate by barbiturates (Bendo et al., 1987; Spet-
z

**MODULATION OF VOLTAGE-GATED NA⁺ CHANNELS 31

subtypes of astrocytes (Ginsberg et al., 1992; Dietrich, 1992; Dietrich et al.,** 1993) is probably responsible, at least partly, for their 1992; GATED NA⁺ CHANNELS

1993) is probably responsible, at least partly, for their

1993) is probably responsible, at least partly, for their

1996 protective effects in cerebral ischemia (see below, sec--GATED NA⁺ CHANNELS 31
(Ginsberg et al., 1992; Dietrich, 1992; Dietrich et al., 1993) is probably responsible, at least partly, for their
protective effects in cerebral ischemia (see below, sec-
tions 2. and 3.). Down-m (Ginsberg et al., 1992; Dietrich, 1992; Dietrich et al., 1993) is probably responsible, at least partly, for their protective effects in cerebral ischemia (see below, sections 2. and 3.). Down-modulation of voltage-gated N (Ginsberg et al., 1992; Dietrich, 1992; Dietrich et al., 1993) is probably responsible, at least partly, for their protective effects in cerebral ischemia (see below, sections 2. and 3.). Down-modulation of voltage-gated 1993) is probably responsible, at least partly, for their protective effects in cerebral ischemia (see below, sections 2. and 3.). Down-modulation of voltage-gated Na⁺ channels is another effective way of reducing energ protective effects in cerebral ischemia (see below, sections 2. and 3.). Down-modulation of voltage-gated Na⁺ channels is another effective way of reducing energy demand, because a large part of the energy consumed by th tions 2. and 3.). Down-modulation of voltage-gated Na⁺
channels is another effective way of reducing energy
demand, because a large part of the energy consumed by
the brain is used for maintenance of ionic gradients
acro demand, because a large part of the energy consumed by
the brain is used for maintenance of ionic gradients
across the cellular membrane (Erecinska and Silver,
1989), even when synaptic activity is abolished (e.g.,
barbitu barbiturate coma) (Astrup, 1982).

rels by PKC is unknown.
 binding proteins (G proteins). In addition to protein sum of activation metabolism, and residual or basal

phosphorylation, there is evidence suggesting that acti-

vation (Michenfelder, 1974; A as cerebral metabolic rate (CMR) of either oxygen across the cellular membrane (Erecinska and Silver, 1989), even when synaptic activity is abolished (e.g., barbiturate coma) (Astrup, 1982).
The total energy consumption of the brain, expressed as cerebral metabolic rate 1989), even when synaptic activity is abolished (e.g., barbiturate coma) (Astrup, 1982).
The total energy consumption of the brain, expressed
as cerebral metabolic rate (CMR) of either oxygen
(CMRO₂) or glucose (CMR_{glc} barbiturate coma) (Astrup, 1982).
The total energy consumption of the brain, expressed
as cerebral metabolic rate (CMR) of either oxygen
(CMRO₂) or glucose (CMR_{glc}), can be considered as the
sum of activation metaboli The total energy consumption of the brain, express
as cerebral metabolic rate (CMR) of either oxyg
(CMRO₂) or glucose (CMR_{glc}), can be considered as t
sum of activation metabolism, and residual or ba
metabolism (Michen as cerebral metabolic rate (CMR) of either oxygen

(CMRO₂) or glucose (CMR_{glc}), can be considered as the

sum of activation metabolism, and residual or basal

metabolism (Michenfelder, 1974; Astrup, 1982). *Activa-*
 (CMRO₂) or glucose (CMR_{glc}), can be considered as the sum of activation metabolism, and residual or basal metabolism (Michenfelder, 1974; Astrup, 1982). *Activation metabolism*, which supports electrical and synaptic metabolism (Michenfelder, 1974; Astrup, 1982). *Activa-*
tion metabolism, which supports electrical and synaptic
activity, varies with the functional state of the brain (see
below, sections 1. and 2.). *Residual metabolism* tion metabolism, which supports electrical and synaptic tion metabolism, which supports electrical and synap activity, varies with the functional state of the brain (below, sections 1. and 2.). Residual metabolism support the basal cellular processes that persist after function *is* ivity, varies with the functional state of the brain (s low, sections 1. and 2.). *Residual metabolism* suppore basal cellular processes that persist after function is ivity has been abolished (see below, section 3.).

below, sections 1. and 2.). Residual metabolism supports
the basal cellular processes that persist after functional
activity has been abolished (see below, section 3.).
1. Functional activity and energy metabolism. Appli-
 the basal cellular processes that persist after functional
activity has been abolished (see below, section 3.).
1. Functional activity and energy metabolism. Appli-
cation of the autoradiographic 2-deoxy-D-glucose method
 activity has been abolished (see below, section 3.)
1. Functional activity and energy metabolism.
cation of the autoradiographic 2-deoxy-D-glucose m
for measurement of local CMR_{glc}, and of its extens
positron emission t 1. Functional activity and energy metabolism. Application of the autoradiographic 2-deoxy-D-glucose method for measurement of local CMR_{glc}, and of its extension to positron emission tomography with $2-[^{18}F]$ fluoro-2-de cation of the autoradiographic 2-deoxy-D-glucose method
for measurement of local CMR_{glc} , and of its extension to
positron emission tomography with 2- [^18F] fluoro-2-de-
oxy-D-glucose in man, have clearly establ for measurement of local CMR_{glc}, and of its extension to
positron emission tomography with $2\cdot1^{18}F$ fluoro-2-de-
oxy-D-glucose in man, have clearly established that local
functional activity and activation metabolism positron emission tomography with 2-^{[18}F]fluoro-2-de-
oxy-D-glucose in man, have clearly established that local
functional activity and activation metabolism are closely
linked in nervous tissues. Decreased functional ac oxy-D-glucose in man, have clearly established that local
functional activity and activation metabolism are closely
linked in nervous tissues. Decreased functional activity
reduces local CMR_{glc}, whereas increased activi functional activity and activation metabolism are closely
linked in nervous tissues. Decreased functional activity
reduces local CMR_{glc}, whereas increased activity raises
local CMR_{glc} (Sokoloff, 1993). The highest lev linked in nervous tissues. Decreased functional activity
reduces local CMR_{glc} , whereas increased activity raises
local CMR_{glc} (Sokoloff, 1993). The highest levels of acti-
vation metabolism are reached dur local CMR_{gle} (Sokoloff, 1993). The highest levels of activation metabolism are reached during the synchronous neuronal firing in epileptic seizures; CMRO₂ was increased three-fold in the rat brain during bicuculline-i local CMR_{glc} (Sokoloff, 1993). The highest levels vation metabolism are reached during the synch neuronal firing in epileptic seizures; CMRO₂ v creased three-fold in the rat brain during bicuc induced seizures (Meldru tion metabolism are reached during the synchronous
uronal firing in epileptic seizures; CMRO₂ was in-
eased three-fold in the rat brain during bicuculline-
duced seizures (Meldrum and Nilsson, 1976).
It is also well docu

et al., 1992), modulation of Na⁺ channel activity by G creased three-fold in the rat brain during bicuculline-
proteins may be a widespread mechanism for regulation induced seizures (Meldrum and Nilsson, 1976).
It is als neuronal firing in epileptic seizures; $CMRO_2$ was in-
creased three-fold in the rat brain during bicuculline-
induced seizures (Meldrum and Nilsson, 1976).
It is also well documented that most of the energy
demand couple creased three-fold in the rat brain during bicuculline-
induced seizures (Meldrum and Nilsson, 1976).
It is also well documented that most of the energy
demand coupled to brain functional activity is used for
ion transport induced seizures (Meldrum and Nilsson, 1976).
It is also well documented that most of the ener
demand coupled to brain functional activity is used i
ion transport. The main function of the CNS is t
generation, processing a It is also well documented that most of the energy
demand coupled to brain functional activity is used for
ion transport. The main function of the CNS is the
generation, processing and transmission of action poten-
tials. ion transport. The main function of the CNS is the generation, processing and transmission of action potentials. These do not consume energy by themselves; they are passive electrical consequences of the movement of K^+ ion transport. The main function of the CNS is the generation, processing and transmission of action potentials. These do not consume energy by themselves; they are passive electrical consequences of the movement of K^+ generation, processing and transmission of action potentials. These do not consume energy by themselves; they are passive electrical consequences of the movement of K^+ from inside the cell to the extracellular space, a tials. These do not consume energy by themselves; they are passive electrical consequences of the movement of K^+ from inside the cell to the extracellular space, and of Na^+ in the reverse direction, when the cell mem are passive electrical consequences of the movement of K^+ from inside the cell to the extracellular space, and of Na^+ in the reverse direction, when the cell membrane is depolarized. Instead, energy metabolism associ K^+ from inside the cell to the extracellular space, and Na^+ in the reverse direction, when the cell membrane depolarized. Instead, energy metabolism associated with the electrical and functional activities of nervous $Na⁺$ in the reverse direction, when the cell membrane is depolarized. Instead, energy metabolism associated with the electrical and functional activities of nervous tissue is used to restore the ionic gradients and r depolarized. Instead, energy metabolism associated with
the electrical and functional activities of nervous tissue
is used to restore the ionic gradients and resting mem-
brane potentials that were partly degraded during t **1993).** used to restore the ionic gradients and resting memane potentials that were partly degraded during the citation phase (Erecinska and Silver, 1989; Sokoloff, 93).
2. *Barbiturate inhibition of functional activity and* rebro

brane potentials that were partly degraded during the excitation phase (Erecinska and Silver, 1989; Sokoloff, 1993).

2. *Barbiturate inhibition of functional activity and* cerebroprotection. The primary protective mechani excitation phase (Erecinska and Silver, 1989; Sokoloff, 1993).

2. Barbiturate inhibition of functional activity and

cerebroprotection. The primary protective mechanism of

barbiturates is generally attributed to their ab 1993).

2. Barbiturate inhibition of functional activity and

cerebroprotection. The primary protective mechanism of

barbiturates is generally attributed to their ability to

decrease the cerebral metabolic rate, thus imp 2. Barbiturate inhibition of functional activity and cerebroprotection. The primary protective mechanism of barbiturates is generally attributed to their ability to decrease the cerebral metabolic rate, thus improving the cerebroprotection. The primary protective mechanism
barbiturates is generally attributed to their ability
decrease the cerebral metabolic rate, thus improving th
ratio of energy supply to energy demand. Barbiturat
depress barbiturates is generally attributed to their ability to decrease the cerebral metabolic rate, thus improving the ratio of energy supply to energy demand. Barbiturates depress carbohydrate metabolism (Strang and Bachelard, decrease the cerebral metabolic rate, thus improving the ratio of energy supply to energy demand. Barbiturates
depress carbohydrate metabolism (Strang and Bach-
elard, 1973; Nilsson and Siesjö, 1975; Sokoloff et al.,
1977) ratio of energy supply to energy demand. Barbiturat depress carbohydrate metabolism (Strang and Baelard, 1973; Nilsson and Siesjö, 1975; Sokoloff et and 1977) and increase brain energy reserves (Gatfield et and 1966), but depress carbohydrate metabolism (Strang and Bach-
elard, 1973; Nilsson and Siesjö, 1975; Sokoloff et al.,
1977) and increase brain energy reserves (Gatfield et al.,
1966), but these actions result from inhibition of synap-

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energy metabolism. Barbiturates dose-dependently reduce glucose consumption, only as long as some EEG URENJAK AND OBRENCE

energy metabolism. Barbiturates dose-dependently re-

duce glucose consumption, only as long as some EEG port N

activity remains (Michenfelder and Milde, 1975; Astrup thus 1 URENJAK AND OB.

energy metabolism. Barbiturates dose-dependently re-

duce glucose consumption, only as long as some EEG po

activity remains (Michenfelder and Milde, 1975; Astrup th

et al., 1981a, b). This feature may e energy metabolism. Barbiturates dose-dependently
duce glucose consumption, only as long as some E
activity remains (Michenfelder and Milde, 1975; Ast
et al., 1981a, b). This feature may explain why barbi
rates are benefici energy metabolism. Barbiturates dose-dependently iduce glucose consumption, only as long as some EB activity remains (Michenfelder and Milde, 1975; Astret al., 1981a, b). This feature may explain why barbit rates are benef duce glucose consumption, only as long as some EEG
activity remains (Michenfelder and Milde, 1975; Astrup
et al., 1981a, b). This feature may explain why barbitu-
rates are beneficial against focal ischemia and incom-
plet activity remains (Michenfelder and Milde, 1975; Astrup et al., 1981a, b). This feature may explain why barbitu-
rates are beneficial against focal ischemia and incom-
plete global ischemia, especially when administered beet al., 1981a, b). This feature may explain why barbitu-
rates are beneficial against focal ischemia and incom-
plete global ischemia, especially when administered be-
fore the ischemia onset (Spetzler and Hadley, 1989; Ha rates are beneficial against focal ischemia and incomplete global ischemia, especially when administered before the ischemia onset (Spetzler and Hadley, 1989; Hall fand Murdoch, 1990). In these conditions, they selectively plete global ischemia, especially when administered to
fore the ischemia onset (Spetzler and Hadley, 1989; Ha
and Murdoch, 1990). In these conditions, they selective
reduce the energy expenditure required for synapt
transm fore the ischemia onset (Spetzler and Hadley, 1989; H
and Murdoch, 1990). In these conditions, they selective
reduce the energy expenditure required for synaptransmission while maintaining the component nec
sary for basic and Murdoch, 1990). In these conditions, they selectively reduce the energy expenditure required for synaptic transmission while maintaining the component necessary for basic cellular functions (Steen and Michenfelder, 198 reduce the energy expenditure required for synaptic transmission while maintaining the component necessary for basic cellular functions (Steen and Michenfelder, 1980), thus favouring a redistribution of cerebral $\frac{2}{1000$ transmission while maintaining the component necessary for basic cellular functions (Steen and Michenfelder, 1980), thus favouring a redistribution of cerebral blood flow to ischemic tissue in focal ischemia (Branston et a sary for basic cellular functions (Steen and Michenfelder, 1980), thus favouring a redistribution of cerebral 2
blood flow to ischemic tissue in focal ischemia (Branston
et al., 1979; Feustel et al., 1981). In contrast, ba felder, 1980), thus favouring a redistribution of cerebs blood flow to ischemic tissue in focal ischemia (Branst et al., 1979; Feustel et al., 1981). In contrast, barbiture therapy is of no benefit during instances of comp blood flow to ischemic tissue in focal ischemia (Branston are al., 1979; Feustel et al., 1981). In contrast, barbiturate io therapy is of no benefit during instances of complete naglobal ischemia, including cardiac arrest et al., 1979; Feustel et al., 1981). In contrast, barbiturate ion
therapy is of no benefit during instances of complete na
global ischemia, including cardiac arrest (Brain Resus-
firitation Clinical Trial I Study Group, 19 global ischemia, including cardiac arrest (Brain Resuscitation Clinical Trial I Study Group, 1986), during which EEG silence occurs within seconds, and rapid depletion of brain energy stores is little altered by bar-
bitur depletion of brain energy stores is little altered by bar-
biturate (Steen et al., 1978; Mrsulja et al., 1984).
3. *Brain utilization of residual energy metabolism*.
Basal energy metabolism (i.e., residual metabolism after

which EEG silence occurs within seconds, and rapid
depletion of brain energy stores is little altered by bar-
biturate (Steen et al., 1978; Mrsulja et al., 1984).
3. *Brain utilization of residual energy metabolism*.
Basal biturate (Steen et al., 1978; Mrsulja et al., 1984).

3. Brain utilization of residual energy metabolism.

Basal energy metabolism (i.e., residual metabolism after

inhibition of synaptic transmission) is especially rele-
 inhibition of synaptic transmission) is especially relevant to protection against cerebral ischemia, because it corresponds to the level of energy necessary for preservation of nonfunctional, but still viable, ischemic bra Basal energy metabolism (i.e., residual metabolism after
inhibition of synaptic transmission) is especially rele-
vant to protection against cerebral ischemia, because it
theorresponds to the level of energy necessary for inhibition of synaptic transmission) is especially rele-
vant to protection against cerebral ischemia, because it
corresponds to the level of energy necessary for preser-
vation of nonfunctional, but still viable, ischemic vant to protection against cerebral ischemia, because it the corresponds to the level of energy necessary for preservation of nonfunctional, but still viable, ischemic brain vergions. Residual energy metabolism is a featur corresponds to the level of energy necessary for pres
vation of nonfunctional, but still viable, ischemic br
regions. Residual energy metabolism is a feature of
ischemic penumbra, regions where neuronal function
lost but c vation of nonfunctional, but still viable, ischemic brain regions. Residual energy metabolism is a feature of the ischemic penumbra, regions where neuronal function is lost but cellular ionic gradients are maintained (Obre regions. Residual energy metabolism is a feature of the
ischemic penumbra, regions where neuronal function is
lost but cellular ionic gradients are maintained (Obreno-
vitch, 1995a). By superimposing ouabain, a specific i ischemic penumbra, regions where neuronal function is
lost but cellular ionic gradients are maintained (Obreno
vitch, 1995a). By superimposing ouabain, a specific in
hibitor of Na⁺/K⁺-ATPase, onto barbiturate inhibiti lost but cellular ionic gradients are maintained (Obreno-
vitch, 1995a). By superimposing ouabain, a specific in-
hibitor of Na⁺/K⁺-ATPase, onto barbiturate inhibition
of electrical activity, Astrup and coworkers (1981 vitch, 1995a). By superimposing ouabain, a specific in-
hibitor of Na⁺/K⁺-ATPase, onto barbiturate inhibition 199
of electrical activity, Astrup and coworkers (1981b) dem-
may
onstrated that 40 to 50% of residual meta hibitor of Na⁺/K⁺-ATPase, onto barbiturate inhibition
of electrical activity, Astrup and coworkers (1981b) den
onstrated that 40 to 50% of residual metabolism in th
dog brain was still linked to Na⁺/K⁺-ATPase acti of electrical activity, Astrup and coworkers (1981b) den
onstrated that 40 to 50% of residual metabolism in th
dog brain was still linked to Na⁺/K⁺-ATPase activity i
compensate for Na⁺-K⁺ leakage across cellular m onstrated that 40 to 50% of residual metabolism in the cell
dog brain was still linked to Na⁺/K⁺-ATPase activity to cell
compensate for Na⁺-K⁺ leakage across cellular mem-
branes. The same investigators showed tha dog brain was still linked to Na⁺/K⁺-ATPase activity to compensate for Na⁺-K⁺ leakage across cellular men branes. The same investigators showed that these resional ion transports were also markedly inhibited by hi compensate for Na⁺-K⁺ leakage across cellular mem-
branes. The same investigators showed that these resid-
ignificantly to regional energy demand associated with
ual ion transports were also markedly inhibited by high branes. The same investigators showed that these residual ion transports were also markedly inhibited by high doses of lidocaine, a local anesthetic blocking Na⁺ channels, or hypothermia. This action was referred to as ual ion transports
doses of lidocaine,
nels, or hypothern
membrane stabiliz
b; Astrup, 1982).
In vitro studies ses of lidocaine, a local anesthetic blocking Na⁺ chan-
Is, or hypothermia. This action was referred to as
embrane stabilization or sealing (Astrup et al., 1981a,
Astrup, 1982).
In vitro studies are consistent with the

mentally half or hypothermia. This action was referred to as all membrane stabilization or sealing (Astrup et al., 1981a, to b; Astrup, 1982). an an inviro studies are consistent with the notion that glue approximately ha membrane stabilization or sealing (Astrup et al., 1981a,
b; Astrup, 1982).
In vitro studies are consistent with the notion that
approximately half of the residual energy expenditure is
used for ion transport. Specific inhi b; Astrup, 1982).
In vitro studies are consistent with the notion that
approximately half of the residual energy expenditure is
used for ion transport. Specific inhibition of Na⁺/K⁺-
ATPase by ouabain, or incubation i approximately half of the residual energy expenditure is from transport. Specific inhibition of Na^+/K^+ - in ATPase by ouabain, or incubation in Na^+ -free medium, followered the energy consumption of brain slices by $40\$ used for ion transport. Specific inhibition of Na⁺/K⁺- in
ATPase by ouabain, or incubation in Na⁺-free medium, for
lowered the energy consumption of brain slices by 40% F
(Whittam, 1962). Simultaneous measurement of ATPase by ouabain, or incubation in Na^+ -free medium, followered the energy consumption of brain slices by 40% Five (Whittam, 1962). Simultaneous measurement of oxygen extransport by consumption and lactate production lowered the energy consumption of brain slices by 40% 1
(Whittam, 1962). Simultaneous measurement of oxygen
consumption and lactate production of a rabbit retina
preparation in darkness indicated that Na⁺ transport b consumption and lactate production of a rabbit retina
preparation in darkness indicated that Na^+ transport by
 Na^+/K^+ -ATPase accounted for approximately half of all
energy expenditure (Ames et al., 1992). Marked reducconsumption and lactate production of a rabbit retipreparation in darkness indicated that Na⁺ transport Na⁺/K⁺-ATPase accounted for approximately half of energy expenditure (Ames et al., 1992). Marked reducions in ox preparation in darkness indicated that $Na⁺$ transport by $Na⁺/K⁺$ -ATPase accounted for approximately half of all energy expenditure (Ames et al., 1992). Marked reductions in oxidative activity were also obser Na^+/K^+ -ATPase
energy expenditutions in oxidative
elinated nerves e
(Ritchie, 1967).
4. Mechanism *4. Mechanism coupling energy metabolism to trans- membrane ion transport.* The key component linking lenergy metabolism to trans- *membrane ion transport.* The key component linking lenergy metabolism to transmembr

elinated nerves exposed to ouabain or with reduced Na⁺ in (Ritchie, 1967).

The Chanism coupling energy metabolism to transmembrane ion transport. The key component linking less

energy metabolism to transmembrane ion tr

EXEMPLE THE SET OF SET AT THE NAST SET AT AT PASS ATP AT AT PASSALLY AT PASSALLY AT A SET AT AT A
Fig. 1 and K⁺ back out of the cell and K⁺ back into the ce between the Na⁺/K⁺-ATPase, an enzyme that uses ATP to transport Na⁺ back out of the cell and K⁺ back into the cell, thus restoring the ionic gradients across the cellular BRENOVITCH
the Na⁺/K⁺-ATPase, an enzyme that uses ATP to trans-
port Na⁺ back out of the cell and K⁺ back into the cell,
thus restoring the ionic gradients across the cellular
membrane. For example, electrical sti the Na⁺/K⁺-ATPase, an enzyme that uses ATP to transport Na⁺ back out of the cell and K⁺ back into the cell, thus restoring the ionic gradients across the cellular membrane. For example, electrical stimulation of r port $Na⁺$ back out of the cell and $K⁺$ back into the cell, thus restoring the ionic gradients across the cellular membrane. For example, electrical stimulation of rat posterior pituitary glands in vitro increas thus restoring the ionic gradients across the cellular
membrane. For example, electrical stimulation of rat
posterior pituitary glands in vitro increased 2-deoxy-D-
glucose uptake in almost direct proportion to the spike
f membrane. For example, electrical stimulation of rat the inhibition of $\text{Na}^+\text{/K}^+$ -ATPase with ouabain (Mata et posterior pituitary glands in vitro increased 2-deoxy-p-
glucose uptake in almost direct proportion to the spike
frequency, indicating increased glucose utilization, and
the enhancement of uptake was completely blocked by glucose uptake in almost direct proportion to the spike
frequency, indicating increased glucose utilization, and
the enhancement of uptake was completely blocked by
the inhibition of Na⁺/K⁺-ATPase with ouabain (Mata e frequency, indicating increased glucose utilization, and
the enhancement of uptake was completely blocked by
the inhibition of Na^+/K^+ -ATPase with ouabain (Mata et
al., 1980). The K_m of the Na^+/K^+ -ATPase from neurons the enhancement of uptake was completely blocked by
the inhibition of Na^+/K^+ -ATPase with ouabain (Mata et
al., 1980). The K_m of the Na^+/K^+ -ATPase from neurons
and synaptosomes is approximately 80 mM for Na^+ and
2 the inhibition of Na⁺/K⁺-ATPase with ouabain (Mata et al., 1980). The K_m of the Na⁺/K⁺-ATPase from neurons and synaptosomes is approximately 80 mM for Na⁺ and 2 to 3 mM for K⁺ (Logan, 1980; reviewed by Ereci and synaptosomes is approximately 80 mm for Na⁺ and 2 to 3 mm for K⁺ (Logan, 1980; reviewed by Erecinska and Silver, 1989), which implies that, with regard to ions, the activity of this enzyme in neurons is predominan and synaptosomes is approximately 80 mM for Na^+ and 2 to 3 mM for K^+ (Logan, 1980; reviewed by Erecinska and Silver, 1989), which implies that, with regard to ions, the activity of this enzyme in neurons is predomina 2 to 3 mM for K^+ (Logan, 1980; reviewed by Erecinska and Silver, 1989), which implies that, with regard to ions, the activity of this enzyme in neurons is predominantly controlled by intracellular Na^+ . This was confi ions, the activity of this enzyme in neurons is predon
nantly controlled by intracellular Na^+ . This was consumented by experimental procedures that induce Na^+ is
flux. The basal consumption of oxygen by rat brain syna nantly controlled by intracellular Na^+ . This was confirmed by experimental procedures that induce Na^+ in-
flux.
The basal consumption of oxygen by rat brain synap-
tosomes was increased 2.5-fold by veratridine, and th

firmed by experimental procedures that induce Na^+ in-
flux.
The basal consumption of oxygen by rat brain synap-
tosomes was increased 2.5-fold by veratridine, and this
effect was blocked by TTX or ouabain, indicatin flux.
The basal consumption of oxygen by rat brain synaptosomes was increased 2.5-fold by veratridine, and this
effect was blocked by TTX or ouabain, indicating that
the stimulation of respiration was directly linked to N The basal consumption of oxygen by rat brain synaptosomes was increased 2.5-fold by veratridine, and this effect was blocked by TTX or ouabain, indicating that the stimulation of respiration was directly linked to Na^+ in tosomes was increased 2.5-fold by veratridine, and this effect was blocked by TTX or ouabain, indicating that the stimulation of respiration was directly linked to Na⁺ influx (Erecinska and Dagani, 1990; Urenjak et al., the stimulation of respiration was directly linked to Na⁺
influx (Erecinska and Dagani, 1990; Urenjak et al.,
1991). In the same preparation, veratridine increased
the calculated turnover of ATP in oxygenated synapto-
so the stimulation of respiration was directly linked to Na⁺
influx (Erecinska and Dagani, 1990; Urenjak et al.,
1991). In the same preparation, veratridine increased
the calculated turnover of ATP in oxygenated synapto-
s influx (Erecinska and Dagani, 1990; Urenjak et al., 1991). In the same preparation, veratridine increased the calculated turnover of ATP in oxygenated synaptosomes five-fold (Gleitz et al., 1993). In cultured neurons, ver 1991). In the same preparation, veratridine increased
the calculated turnover of ATP in oxygenated synapto-
somes five-fold (Gleitz et al., 1993). In cultured neurons,
veratridine increased CO_2 production three times (P the calculated turnover of ATP in oxygenated synapto-
somes five-fold (Gleitz et al., 1993). In cultured neurons,
veratridine increased CO_2 production three times (Peng
and Hertz, 1994). Monensin (an antibiotic that med somes five-fold (Gleitz et al., 1993). In cultured neurons,
veratridine increased CO_2 production three times (Peng
and Hertz, 1994). Monensin (an antibiotic that mediates
electroneutral exchange of external Na^+ for in veratridine increased CO_2 production three times (Peng
and Hertz, 1994). Monensin (an antibiotic that mediates
electroneutral exchange of external Na^+ for internal
 H^+) also increased energy consumption in both neur and Hertz, 1994). Monensin (an antibiotic that mediates electroneutral exchange of external Na⁺ for internal H⁺) also increased energy consumption in both neurons and glial cells (Yarowski et al., 1986; Erecinska et al electroneutral exchange of external $Na⁺$ for internal $H⁺$) also increased energy consumption in both neuror and glial cells (Yarowski et al., 1986; Erecinska et al. 1991). Although part of the monensin effect i H^+) also increased energy consumption in both neurons
and glial cells (Yarowski et al., 1986; Erecinska et al.,
1991). Although part of the monensin effect in the glia
may be due to direct stimulation of glycolysis by and glial cells (Yarowski et al., 1986; Erecinska et al., 1991). Although part of the monensin effect in the glia may be due to direct stimulation of glycolysis by intracellular alkalinization (Erecinska et al., 1991), th 1991). Although part of the monensin effect in the glia may be due to direct stimulation of glycolysis by intra-
cellular alkalinization (Erecinska et al., 1991), these
cells contain high levels of Na⁺/K⁺-ATPase activ may be due to direct stimulation of glycolysis by intra-
cellular alkalinization (Erecinska et al., 1991), these
cells contain high levels of Na^+/K^+ -ATPase activity (At-
terwill et al., 1984), and they may therefore con cellular alkalinization (Erecinsk
cells contain high levels of Na⁺/K
terwill et al., 1984), and they mainlificantly to regional energy d
functional activity in the brain.
The high energy requirement of lls contain high levels of Na⁺/K⁺-ATPase activity (At-
rwill et al., 1984), and they may therefore contribute
gnificantly to regional energy demand associated with
nctional activity in the brain.
The high energy requi

approximately half of the residual energy expenditure is from the blood and local utilization, were significantly used for ion transport. Specific inhibition of Na^+/K^+ - increased in the presence of TTX and decreased sha terwill et al., 1984), and they may therefore contribute
significantly to regional energy demand associated with
functional activity in the brain.
The high energy requirement of $Na⁺$ homeostasis was
also confirmed in significantly to regional energy demand associated with
functional activity in the brain.
The high energy requirement of $Na⁺$ homeostasis was
also confirmed in freely moving rats, using microdialysis
to measure local functional activity in the brain.
The high energy requirement of $Na⁺$ homeostasis was
also confirmed in freely moving rats, using microdialysis
to measure local changes in brain extracellular glucose
and lactate (Fel The high energy requirement of Na⁺ homeostasis was
also confirmed in freely moving rats, using microdialysis
to measure local changes in brain extracellular glucose
and lactate (Fellows et al., 1992, 1993). Extracellula also confirmed in freely moving rats, using microdialysis
to measure local changes in brain extracellular glucose
and lactate (Fellows et al., 1992, 1993). Extracellular
glucose levels, which reflect the balance between su to measure local changes in brain extracellular glucose
and lactate (Fellows et al., 1992, 1993). Extracellular
glucose levels, which reflect the balance between supply
from the blood and local utilization, were significan and lactate (Fellows et al., 1992, 1993). Extracellular glucose levels, which reflect the balance between supply from the blood and local utilization, were significantly increased in the presence of TTX and decreased sharp from the blood and local utilization, were significantly increased in the presence of TTX and decreased sharply
following veratridine application (Fellows et al., 1992).
Five minutes of tail pinch-induced stress nearly doubled
extracellular lactate concentration, indicating incr increased in the presence of TTX and decreased sharply
following veratridine application (Fellows et al., 1992).
Five minutes of tail pinch-induced stress nearly doubled
extracellular lactate concentration, indicating incr following veratridine application (Fello
Five minutes of tail pinch-induced stress
extracellular lactate concentration, indi
nonoxidative glucose metabolism, and
blocked by TTX (Fellows et al., 1993).
The elements outlined we minutes of tail pinch-induced stress nearly doubled
tracellular lactate concentration, indicating increased
noxidative glucose metabolism, and this effect was
ocked by TTX (Fellows et al., 1993).
The elements outlined a

extracellular lactate concentration, indicating increased
nonoxidative glucose metabolism, and this effect was
blocked by TTX (Fellows et al., 1993).
The elements outlined above support the rationale
of pharmacological dow nonoxidative glucose metabolism, and this effect was
blocked by TTX (Fellows et al., 1993).
The elements outlined above support the rationale
of pharmacological down-regulating voltage-gated
Na⁺ channels in ischemia: i. blocked by TTX (Fellows et al., 1993).
The elements outlined above support the rational of pharmacological down-regulating voltage-gate Na⁺ channels in ischemia: i.e., reduction of Na⁺ influstion brain cells, with sub The elements outlined above support the rationale
of pharmacological down-regulating voltage-gated
Na⁺ channels in ischemia: i.e., reduction of Na⁺ influx
into brain cells, with subsequent energy preservation.
The rec of pharmacological down-regulating voltage-gated $Na⁺$ channels in ischemia: i.e., reduction of $Na⁺$ influx into brain cells, with subsequent energy preservation.
The recent study of Xie and coworkers (1995) clea Na⁺ channels in ischemia: i.e., reduction of Na⁺ influx
into brain cells, with subsequent energy preservation.
The recent study of Xie and coworkers (1995) clearly
illustrates this concept: among several compounds seinto brain cells, with subsequent energy press
The recent study of Xie and coworkers (1995
illustrates this concept: among several compo
lected for their selective actions on ion chann
those modulating α -amino-3-hydrox

MODULATION OF VOLTAGE-GATED NA CHANNELS ³³

MODULATION OF VOLTAGE
azolepropionic acid (AMPA)-operated or voltage-gated
Na⁺ channels delayed anoxic depolarization produced in MODULATION OF VOLTAGE-GAT
azolepropionic acid (AMPA)-operated or voltage-gated tole
Na⁺ channels delayed anoxic depolarization produced in (Rot
the rat cortex by circulatory arrest. The data reviewed so Pau MODULATION OF VOLTAGE-GA1
azolepropionic acid (AMPA)-operated or voltage-gated tole
Na⁺ channels delayed anoxic depolarization produced in (Rot
the rat cortex by circulatory arrest. The data reviewed so Pau
far might sug azole
propionic acid (AMPA)-operated or voltage-gated that channels delayed a
noxic depolarization produced in (the rat cortex by circulatory arrest. The data reviewed so I
far might suggest that cerebroprotection may req azolepropionic acid (AMPA)-operated or voltage-gated Na⁺ channels delayed anoxic depolarization produced in the rat cortex by circulatory arrest. The data reviewed so far might suggest that cerebroprotection may require $Na⁺$ channels delayed anoxic depolarization produced in (1)
the rat cortex by circulatory arrest. The data reviewed so P
far might suggest that cerebroprotection may require a
drastic down-modulation of $Na⁺$ cha the rat cortex by circulatory arrest. The data reviewed so far might suggest that cerebroprotection may require drastic down-modulation of Na^+ channels, such as that produced by lidocaine coma, profound hypothermia far might suggest that cerebroprotection may require
drastic down-modulation of Na^+ channels, such as that
produced by lidocaine coma, profound hypothermia or
TTX application; all associated with severe side-effects
(Ar drastic down-modulation of Na⁺ channels, such as that
produced by lidocaine coma, profound hypothermia or
TTX application; all associated with severe side-effects
c(Artru et al., 1991; Ginsberg et al., 1992; Mosher et a produced by lidocaine coma, profound hypothermia or den
TTX application; all associated with severe side-effects com
(Artru et al., 1991; Ginsberg et al., 1992; Mosher et al., (Pat
1964). However, it seems possible to int TTX application; all associated with severe side-effects conductively in the neuroprotection with specific Na⁺ channels, or Na⁺ channel states, to diprovide neuroprotection without complete blockade of to neuronal fun (Artru et al., 1991; Ginsberg et al., 1992; Mosher et al., 1964). However, it seems possible to interact selectively with specific Na⁺ channels, or Na⁺ channel states, to provide neuroprotection without complete block 1964). However, it seems possible to interact selectively intervit specific Na⁺ channels, or Na⁺ channel states, to dinoprovide neuroprotection without complete blockade of toxineuronal function. As detailed below (in provide neuroprotection without complete blockade of
neuronal function. As detailed below (in section C.), $Na⁺$
channels may be inherently down-regulated during $O₂$
deprivation or metabolic inhibition, and the provide neuroprotection without complete blockade of to:
neuronal function. As detailed below (in section C.), Na⁺
channels may be inherently down-regulated during O_2 maintend and the remarkable of
tolerance of the i neuronal function. As detailed below (in section C.), Na⁺
channels may be inherently down-regulated during O_2 m
deprivation or metabolic inhibition, and the remarkable of
tolerance of the immature brain, as well as t channels may be inherently down-regulated during O_2 may j
deprivation or metabolic inhibition, and the remarkable old. It
tolerance of the immature brain, as well as that of the cacy c
turtle brain, does not result fro tolerance of the immature brain, as well as that of the turtle brain, does not result from complete blockade of $Na⁺$ channels. Some of the data presented in section IV and V also suggests that moderate or selective d tolerance of the immature brain, as well as that of the turtle brain, does not result from complete blockade o Na^+ channels. Some of the data presented in section IV and V also suggests that moderate or selective down m $Na⁺$ channels. Some of the data presented in section IV In hippocampal slices from guinea pigs, veratridine and V also suggests that moderate or selective down-blocked synaptic transmission in CA1 subfield and in-
mo Na⁺ channels. Some of the data presented in section IV and V also suggests that moderate or selective down-modulation of Na⁺ channels is sufficient to confer cere-
broprotection, and that this strategy may be effectiv and V also suggests that mod
modulation of Na⁺ channels is
broprotection, and that this st
even when treatment is initiat
isode (see below, section D.).
 B_1 Sustained N_1 ⁺ I_2 Sun Inte λ broprotection, and that this strategy may be effective
even when treatment is initiated after the ischemic ep-
isode (see below, section D.).
B. Sustained Na⁺ Influx Into Neurons: Acute and
Indirect Neurotoxicity even when treatment is initiated after the ischemic ep-

Ale (see below, section D.).
 *1. Sustained Na⁺ Influx Into Neurons: Acute and

<i>direct Neurotoxicity*
 1. Intrinsic neurotoxicity of acute Na⁺ influx. Vera
 ne, by blocking Na⁺ channel inactivation and shift B. Sustained Na⁺ Influx Into Neurons: Acute and lample indirect Neurotoxicity

Indirect Neurotoxicity

1. Intrinsic neurotoxicity of acute Na⁺ influx. Veratri-

idine, by blocking Na⁺ channel inactivation and shifti B. Sasialned Na n m μ x m ν vearboxs: Active and μ
 Indirect Neurotoxicity

1. Intrinsic neurotoxicity of acute Na^+ influx. Veratri

dine, by blocking Na^+ channel inactivation and shifting

activati 1. Intrinsic neurotoxicity of acute Na^+ influx. Veratri-
dine, by blocking Na^+ channel inactivation and shifting
activation to more negative membrane potentials (Cat-
terall, 1980), causes Na^+ influx and a persisten 1. Intrinsic neurotoxicity of acute Na^+ influx. Veratridine, by blocking Na^+ channel inactivation and shifting activation to more negative membrane potentials (Catterall, 1980), causes Na^+ influx and a persistent te dine, by blocking Na⁺ channel inactivation and shifting stactivation to more negative membrane potentials (Catterall, 1980), causes Na⁺ influx and a persistent tendency for depolarization (Deri and Adam-Vizi, 1993). W activation to more negative membrane potentials (Cat-
terall, 1980), causes Na^+ influx and a persistent ten-
dency for depolarization (Deri and Adam-Vizi, 1993). with
with energy depletion, extracellular concentrations terall, 1980), causes Na^+ influx and a persistent tendency for depolarization (Deri and Adam-Vizi, 1993).
With energy depletion, extracellular concentrations of lNa⁺ are maintained within the normal range as long as i dency for depolarization (Deri and Adam-Vizi, 1993). With energy depletion, extracellular concentrations of HNa⁺ are maintained within the normal range as long as in anoxic depolarization does not occur, but then decrea With energy depletion, extracellular concentrations of Na⁺ are maintained within the normal range as long as anoxic depolarization does not occur, but then decrease abruptly, reflecting sudden Na⁺ influx into the cell $Na⁺$ are maintained within the normal range as long as anoxic depolarization does not occur, but then decrease abruptly, reflecting sudden $Na⁺$ influx into the cells (Harris et al., 1984; Hansen and Nedergaard, anoxic depolarization does not occur, but then decrease neu
abruptly, reflecting sudden Na⁺ influx into the cells move
(Harris et al., 1984; Hansen and Nedergaard, 1988; Obbor
renovitch et al., 1990a). With anoxia or ve (Harris et al., 1984; Hansen and Nedergaard, 1988; Obrenovitch et al., 1990a). With anoxia or veratridine, excessive Na⁺ entry into neurons is clearly hazardous to their survival. For example, in the rat four-vessel occ renovitch et al., 1990a). With anoxia or veratridine, excessive Na⁺ entry into neurons is clearly hazardous to their survival. For example, in the rat four-vessel occlusion model, EEG recovery from 5 to 20 min transient cessive $Na⁺$ entry into neurons is clearly hazardous to cessive Na⁺ entry into neurons is clearly hazardous to
their survival. For example, in the rat four-vessel occlu-
sion model, EEG recovery from 5 to 20 min transient
ischemia was considerably slower when anoxic depolar-
 their survival. For example, in the rat four-vessel occlusion model, EEG recovery from 5 to 20 min transient dischemia was considerably slower when anoxic depolarization occurred during the insult, and even a short a perio sion model, EEG recovery from 5 to 20 min transient
ischemia was considerably slower when anoxic depolar-
ization occurred during the insult, and even a short
period of depolarization was sufficient to produce this
effect ischemia was considerably slower when anoxic depolarization occurred during the insult, and even a short period of depolarization was sufficient to produce this effect (Ueda et al., 1992a; Obrenovitch et al., 1993). Anoxic ization occurred during the insult, and even a shoperiod of depolarization was sufficient to produce the
fefect (Ueda et al., 1992a; Obrenovitch et al., 1993
Anoxic depolarization was also deleterious to neuron
recovery in period of depolarization was sufficient to produce this leffect (Ueda et al., 1992a; Obrenovitch et al., 1993). the Anoxic depolarization was also deleterious to neuronal lifecovery in vitro (Jiang and Haddad, 1992), and p effect (Ueda et al., 1992a; Obrenovitch et al., 1993). th
Anoxic depolarization was also deleterious to neuronal N:
recovery in vitro (Jiang and Haddad, 1992), and previ-
cous studies had shown that the severity of ischemi Anoxic depolarization was also deleterious to neuronal N
recovery in vitro (Jiang and Haddad, 1992), and previ-
cous studies had shown that the severity of ischemic a
injury to neurons correlated with the length of time e recovery in vitro (Jiang and Haddad, 1992), a
ous studies had shown that the severity of
injury to neurons correlated with the length
during which the preparation was in a depolari
(Balestrino et al., 1989; Somjen et al., is studies had shown that the severity of ischemic a
jury to neurons correlated with the length of time
ering which the preparation was in a depolarized state
alestrino et al., 1989; Somjen et al., 1990).
Cultured hippoca

injury to neurons correlated with the length of time et a
during which the preparation was in a depolarized state Ir
(Balestrino et al., 1989; Somjen et al., 1990). acut
cultured hippocampal neurons from 18-day-old rats c during which the preparation was in a depolarized state (Balestrino et al., 1989; Somjen et al., 1990).

Cultured hippocampal neurons from 18-day-old rats convere all destroyed within 30 min when treated with 50 e:
 μ M (Balestrino et al., 1989; Somjen et al., 1990). as

Cultured hippocampal neurons from 18-day-old rats

were all destroyed within 30 min when treated with 50
 μ M veratridine, even when the incubating medium was

Ca²⁺-Cultured hippocampal neurons from 18-day-old rats ce
were all destroyed within 30 min when treated with 50 ex
 μ M veratridine, even when the incubating medium was at
Ca²⁺-deficient (Rothman, 1985). Only replacement of were all destroyed within 30 min when treated with 50 μ M veratridine, even when the incubating medium was Ca^{2+} -deficient (Rothman, 1985). Only replacement of Na⁺ by benzoylcholine, or that of Cl⁻ by SO₄², bl μ M veratridine, even when the incubating medium was

Ca²⁺-deficient (Rothman, 1985). Only replacement of

Na⁺ by benzoylcholine, or that of Cl⁻ by SO₄²⁻, blocked T

veratridine toxicity. Elimination of Na⁺

GATED NA⁺ CHANNELS
tolerate depolarization without excessive osmotic load
(Rothman, 1985). Similar observations were made by (FROTR) NA⁺ CHANNELS
(Rothman, 1985). Similar observations were made by
(Rothman, 1985). Similar observations were made by
Pauwels and coworkers (1989) in the same preparation, -GATED NA⁺ CHANNELS

tolerate depolarization without excessive osmotic loa

(Rothman, 1985). Similar observations were made b

Pauwels and coworkers (1989) in the same preparation

and by Lysko and coworkers (1994) in cu tolerate depolarization without excessive osmotic load (Rothman, 1985). Similar observations were made by Pauwels and coworkers (1989) in the same preparation, and by Lysko and coworkers (1994) in cultured rat cer-ebellar (Rothman, 1985). Similar observations were made by Pauwels and coworkers (1989) in the same preparation, and by Lysko and coworkers (1994) in cultured rat cerebellar granule cells, but toxicity was $25\% \text{ Ca}^{2+}$ -depende (Rothman, 1985). Similar observations were made by
Pauwels and coworkers (1989) in the same preparation,
and by Lysko and coworkers (1994) in cultured rat cer-
ebellar granule cells, but toxicity was $25\% \text{ Ca}^{2+}\text{-dependent}$
d Pauwels and coworkers (1989) in the same preparation,
and by Lysko and coworkers (1994) in cultured rat cer-
ebellar granule cells, but toxicity was $25\% \text{ Ca}^{2+}$ -depen-
dent with 40 μ M veratridine (Lysko et al., 199 and by Lysko and coworkers (1994) in cultured rat cer-
ebellar granule cells, but toxicity was $25\% \text{ Ca}^{2+}$ -depen-
dent with 40 μ M veratridine (Lysko et al., 1994) and
completely Ca^{2+} -dependent with 30 μ M ebellar granule cells, but toxicity was 25% Ca²⁺-dep dent with 40 μ M veratridine (Lysko et al., 1994) a completely Ca²⁺-dependent with 30 μ M of the to (Pauwels et al., 1989). From these three studies, it inte dent with 40 μ M veratridine (Lysko et al., 1994) and
completely Ca²⁺-dependent with 30 μ M of the toxin
(Pauwels et al., 1989). From these three studies, it is
interesting to note that the Ca²⁺ dependency of vera completely Ca²⁺-dependent with 30 μ M of the toxin (Pauwels et al., 1989). From these three studies, it is interesting to note that the Ca²⁺ dependency of veratridine toxicity appears to decrease inversely with the (Pauwels et al., 1989). From these three studies, it is
interesting to note that the Ca^{2+} dependency of veratri-
dine toxicity appears to decrease inversely with the
toxin concentration applied to neurons. This suggest dine toxicity appears to decrease inversely with the toxin concentration applied to neurons. This suggests that direct, acute neurotoxicity of sustained $Na⁺$ influx may predominate only when it exceeds a given thresh dine toxicity appears to decrease inversely with the toxin concentration applied to neurons. This suggests that direct, acute neurotoxicity of sustained Na^+ influx may predominate only when it exceeds a given threshold. toxin concentration applied to neurons. This sugges
that direct, acute neurotoxicity of sustained Na⁺ influ
may predominate only when it exceeds a given thres
old. It is likely that this threshold varies with the efi
ca ability. ay predominate only when it exceeds a given thresh-
d. It is likely that this threshold varies with the effi-
cy of the Na^+/K^+ -ATPase and thus with energy avail-
ility.
In hippocampal slices from guinea pigs, veratridin

old. It is likely that this threshold varies with the efficacy of the Na^+/K^+ -ATPase and thus with energy availability.
In hippocampal slices from guinea pigs, veratridine blocked synaptic transmission in CA1 subfield an In hippocampal slices from guinea pigs, veratridine
blocked synaptic transmission in CA1 subfield and in-
duced several episodes of spreading depression (SD) folability.

In hippocampal slices from guinea pigs, veratridine

blocked synaptic transmission in CA1 subfield and in-

duced several episodes of spreading depression (SD) fol-

lowed by persistent loss of ionic homeostasis In hippocampal slices from guinea pigs, veratrid
blocked synaptic transmission in CA1 subfield and
duced several episodes of spreading depression (SD)
lowed by persistent loss of ionic homeostasis (Ashtor
al., 1990). In vi blocked synaptic transmission in CA1 subfield and i
duced several episodes of spreading depression (SD) f
lowed by persistent loss of ionic homeostasis (Ashton
al., 1990). In vivo, microdialysis application of verat
dine t duced several episodes of spreading depression (SD)
lowed by persistent loss of ionic homeostasis (Ashtc
al., 1990). In vivo, microdialysis application of ver-
dine to the rat striatum produced recurrent SD su
imposed on p lowed by persistent loss of ionic homeostasis (Ashton et al., 1990). In vivo, microdialysis application of veratridine to the rat striatum produced recurrent SD superimposed on persistent negative shifts of the extracellul al., 1990). In vivo, microdialysis application of veraline to the rat striatum produced recurrent SD su
imposed on persistent negative shifts of the extract
lar direct current (DC) potential (Obrenovitch T.P.
Urenjak J., u dine to the rat striatum produced recurrent SD super-
imposed on persistent negative shifts of the extracellu-
lar direct current (DC) potential (Obrenovitch T.P. and
Urenjak J., unpublished observation), and a TTX-sensi-
 imposed on persistent negative shifts of the extracellu-
lar direct current (DC) potential (Obrenovitch T.P. and
Urenjak J., unpublished observation), and a TTX-sensi-
tive efflux of amino acid neurotransmitters in the rat lar direct current (DC) potential (Obrenovitch
Urenjak J., unpublished observation), and a T
tive efflux of amino acid neurotransmitters i
striatum (Butcher and Hamberger, 1987; You
1990) and spinal cord (Skilling et al., renjak J., unpublished observation), and a TTX-sensi-
re efflux of amino acid neurotransmitters in the rat
riatum (Butcher and Hamberger, 1987; Young et al.,
90) and spinal cord (Skilling et al., 1988).
Intrinsic neurotoxi

tive efflux of amino acid neurotransmitters in the rat
striatum (Butcher and Hamberger, 1987; Young et al.,
1990) and spinal cord (Skilling et al., 1988).
Intrinsic neurotoxicity of intracellular Na⁺ loading
was also doc striatum (Butcher and Hamberger, 1987; Young et al., 1990) and spinal cord (Skilling et al., 1988).

Intrinsic neurotoxicity of intracellular Na⁺ loading

was also documented in anoxic neurons (Friedman and

Haddad, 199 1990) and spinal cord (Skilling et al., 1988).
Intrinsic neurotoxicity of intracellular Na⁺ loadin
was also documented in anoxic neurons (Friedman and
Haddad, 1993, 1994a, b). Severe anoxia caused a rapid
increase of $[$ Intrinsic neurotoxicity of intracellular Na⁺ loading
was also documented in anoxic neurons (Friedman and
Haddad, 1993, 1994a, b). Severe anoxia caused a rapid
increase of $[Ca^{2+}]$ _i and $[Na^+]$ _i in adult CA1 hippocamp was also documented in anoxic neurons (Friedman and
Haddad, 1993, 1994a, b). Severe anoxia caused a rapid
increase of $[Ca^{2+}]_i$ and $[Na^+]_i$ in adult CA1 hippocampal
neurons, followed by swelling and bleb formation. Re-
 Haddad, 1993, 1994a, b). Severe anoxia caused a rapid
increase of $[Ca^{2+}]_i$ and $[Na^+]_i$ in adult CA1 hippocampal
neurons, followed by swelling and bleb formation. Re-
moval of extracellular Ca^{2+} and addition of Co^{2+ increase of $[Ca^{2+}]_i$ and $[Na^+]_i$ in adult CA1 hippocampal
neurons, followed by swelling and bleb formation. Re-
moval of extracellular Ca^{2+} and addition of Co^{2+} to
block Ca^{2+} channels markedly attenuated the i neurons, followed by swelling and bleb formation. Re
moval of extracellular Ca^{2+} and addition of Co^{2+} to
block Ca^{2+} channels markedly attenuated the increase
in $[Ca^{2+}]_i$ in response to anoxia, but did not preve moval of extracellular Ca^{2+} and addition of Co^{2+} to block Ca^{2+} channels markedly attenuated the increase in $[Ca^{2+}]_i$ in response to anoxia, but did not prevent cell swelling and injury. Antagonists of glutamate block Ca^{2+} channels markedly attenuated the increase
in $[Ca^{2+}]_i$ in response to anoxia, but did not prevent cell
swelling and injury. Antagonists of glutamate-operated
ion channels did not affect the increase in $[Ca^{$ swelling and injury. Antagonists of glutamate-operated
ion channels did not affect the increase in $[Ca^{2+}]_i$ in-
duced by anoxia. Only replacement of extracellular Na⁺
with the impermeant N-methyl-D-glucamine prevented swelling and injury. Antagonists of glutamate-operated
ion channels did not affect the increase in $[Ca^{2+}]_i$ in-
duced by anoxia. Only replacement of extracellular Na⁺
with the impermeant N-methyl-D-glucamine prevented ion channels did not affect the increase in $[Ca^{2+}]_i$ induced by anoxia. Only replacement of extracellular Na⁺ with the impermeant N-methyl-D-glucamine prevented anoxia-induced neuronal injury (Friedman and Haddad, 199 duced by anoxia. Only replacement of extracellular Na⁺
with the impermeant N-methyl-D-glucamine prevented
anoxia-induced neuronal injury (Friedman and Haddad
1993, 1994b). In addition, $[Ca^{2+}]$ _i levels dropped, rathe with the impermeant *N*-methyl-D-glucamine prevented
anoxia-induced neuronal injury (Friedman and Haddad,
1993, 1994b). In addition, $[Ca^{2+}]_i$ levels dropped, rather
than increased, during anoxia without extracellular
Na anoxia-induced neuronal injury (Friedman and Haddad, 1993, 1994b). In addition, $[Ca^{2+}]$, levels dropped, rather than increased, during anoxia without extracellular Na^+ (Friedman and Haddad, 1993). Influx of Na^+ also 1993, 1994b). In addition, $[Ca^{2+1}]$, levels dropped, rather than increased, during anoxia without extracellular Na⁺ (Friedman and Haddad, 1993). Influx of Na⁺ also contributed to neuronal damage produced by anoxia/ag than increase
Na⁺ (Friedma
contributed to
aglycemia in c
et al., 1986).
In addition a^+ (Friedman and Haddad, 1993). Influx of Na⁺ also
ntributed to neuronal damage produced by anoxia/
lycemia in cultures of rat basal ganglia cells (Goldberg
al., 1986).
In addition to the potential intrinsic neurotox

contributed to neuronal damage produced by anoxia/
aglycemia in cultures of rat basal ganglia cells (Goldberg
et al., 1986).
In addition to the potential intrinsic neurotoxicity of
acute Na^+ influx, the inward gradient aglycemia in cultures of rat basal ganglia cells (Goldberg
et al., 1986).
In addition to the potential intrinsic neurotoxicity of
acute Na^+ influx, the inward gradient of Na^+ across the
cellular membrane is re et al., 1986).
In addition to the potential intrinsic neurotoxicity (acute Na⁺ influx, the inward gradient of Na⁺ across the cellular membrane is required to drive a number (exchange/transport mechanisms and, therefore In addition to the potential intrinsic neurotoxicity of
acute Na⁺ influx, the inward gradient of Na⁺ across the
cellular membrane is required to drive a number of
exchange/transport mechanisms and, therefore, alter-
a ute Na⁺ influx, the inward gradient of Na⁺ across th

llular membrane is required to drive a number c

change/transport mechanisms and, therefore, alter

ion of this gradient threatens several vital processes

2. *Int* cellular membrane is required to drive a number of exchange/transport mechanisms and, therefore, alteration of this gradient threatens several vital processes.
2. *Intracellular Na*⁺ loading and Ca^{2+} homeostasis.
The

Na⁺ by benzoylcholine, or that of Cl⁻ by SO₄², blocked The so-called Ca^{2+} -overload hypothesis (i.e., increase of veratridine toxicity. Elimination of Na⁺ presumably intracellular free Ca²⁺, triggering a cas exchange/transport mechanisms and, therefore, alter-
ation of this gradient threatens several vital processes.
2. Intracellular Na^+ loading and Ca^{2+} homeostasis.
The so-called Ca^{2+} -overload hypothesis (i.e., incre ation of this gradient threatens several vital processes.

2. Intracellular Na^+ loading and Ca^{2+} homeostasis.

The so-called Ca^{2+} -overload hypothesis (i.e., increase of

intracellular free Ca^{2+} , triggering a ca 2. Intracellular Na^{+} loading and Ca^{2+} homeostasis.
The so-called Ca^{2+} -overload hypothesis (i.e., increase of intracellular free Ca^{2+} , triggering a cascade of harmful events via activation of proteases, phospho

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the leading hypothesis of ischemia-induced neuronal ability ratios
death (Choi, 1995). Neurotoxicity of excessive $Na⁺$ in- and a TTXdeath (Choi, 1995). Neurotoxicity of excessive Na⁺ in-
death (Choi, 1995). Neurotoxicity of excessive Na⁺ in-
flux, such as those provoked by severe energy depletion **flux, such as those provides is the set of schemia-induced neuronal as death (Choi, 1995). Neurotoxicity of excessive Na⁺ in-
flux, such as those provoked by severe energy depletion in or veratridine, may include a Ca^{** the leading hypothesis of ischemia-induced neuronal a
death (Choi, 1995). Neurotoxicity of excessive Na⁺ in-
flux, such as those provoked by severe energy depletion
or veratridine, may include a Ca^{2+} component, becau or veratridine, may include a Ca^{2+} component, because
these conditions are associated with an influx of extra-
cellular Ca^{2+} (Blaustein and Oborn, 1975; Hansen, death (Choi, 1995). Neurotoxicity of excessive Na⁺ in-
flux, such as those provoked by severe energy depletion
or veratridine, may include a Ca^{2+} component, because
these conditions are associated with an influx of e flux, such as those provoked by severe energy depletion mor veratridine, may include a Ca^{2+} component, because ce these conditions are associated with an influx of extractillar Ca^{2+} (Blaustein and Oborn, 1975; Hanse or veratridine, may include a Ca^{2+} component, because these conditions are associated with an influx of extreellular Ca^{2+} (Blaustein and Oborn, 1975; Hanse 1985; Uematsu et al., 1988; Jacques et al., 1981; Gibse et ment. Ilular Ca²⁺ (Blaustein and Oborn, 1975; Hansen, p
85; Uematsu et al., 1988; Jacques et al., 1981; Gibson of al., 1991), which may partly result from Na⁺ movetient.
Voltage-gated Ca²⁺ channels are obvious routes for

1985; Uematsu et al., 1988; Jacques et al., 1981; Gibse
et al., 1991), which may partly result from Na⁺ mov
ment.
Voltage-gated Ca²⁺ channels are obvious routes f
Ca²⁺ entry under these circumstances, because exce
s et al., 1991), which may partly result from Na⁺ move-
ment.
Voltage-gated Ca²⁺ channels are obvious routes for
Ca²⁺ entry under these circumstances, because exces-
sive Na⁺ influx depolarizes the cellular membrane ment. et

Voltage-gated Ca²⁺ channels are obvious routes for mediations Ca²⁺ entry under these circumstances, because excessive Na⁺ influx depolarizes the cellular membrane (1986). Unexpectedly, Ca²⁺ influx respe Voltage-gated Ca^{2+} channels are obvious routes for mer
 Ca^{2+} entry under these circumstances, because exces-

sive Na⁺ influx depolarizes the cellular membrane (199

(Adam-Vizi and Ligeti, 1986). Unexpectedly, $Ca^{$ Ca^{2+} entry under these circumstances, because excessive Na⁺ influx depolarizes the cellular membrane (Adam-Vizi and Ligeti, 1986). Unexpectedly, Ca^{2+} influx into hypoxic neurons was only partially dependent on the sive Na⁺ influx depolarizes the cellular membrane (Adam-Vizi and Ligeti, 1986). Unexpectedly, Ca²⁺ influx into hypoxic neurons was only partially dependent on the activity of L-type Ca²⁺ channels (Wauquier et al., 1 (Adam-Vizi and Ligeti, 1986). Unexpectedly, Ca^{2+} influx
into hypoxic neurons was only partially dependent on
the activity of L-type Ca^{2+} channels (Wauquier et al.,
1988; Marcoux et al., 1989) or N-type Ca^{2+} chann into hypoxic neurons was only partially dependent
the activity of L-type Ca^{2+} channels (Wauquier et a
1988; Marcoux et al., 1989) or N-type Ca^{2+} channel
(Madden et al., 1990), and that produced by veratridi
was even the activity of L-type Ca²⁺ channels (Wauquier et al., 1988; Marcoux et al., 1989) or N-type Ca²⁺ channels la (Madden et al., 1990), and that produced by veratridine en was even less sensitive to Ca²⁺ channel blocke 1988; Marcoux et al., 1989) or N-type Ca^{2+} channels
(Madden et al., 1990), and that produced by veratridine
was even less sensitive to Ca^{2+} channel blockers (Adam-
Vizi and Ligeti, 1986). Furthermore, the efficacy o (Madden et al., 1990), and that produced by veratridine energy was even less sensitive to Ca^{2+} channel blockers (Adam-cientizi and Ligeti, 1986). Furthermore, the efficacy of considering that reduce Ca^{2+} influx thro was even less sensitive to Ca^{2+} channel blockers (Adam-
Vizi and Ligeti, 1986). Furthermore, the efficacy of
drugs that reduce Ca^{2+} influx through voltage-gated
 Ca^{2+} channels to protect against cerebral ischemia Vizi and Ligeti, 1986). Furthermore, the efficacy of drugs that reduce Ca^{2+} influx through voltage-gated Ca^{2+} channels to protect against cerebral ischemia is, on the whole, negative (Ginsberg, 1988). These findings drugs that reduce Ca^{2+} in Ca^{2+} channels to protect age the whole, negative (Ginst strongly suggest that Ca^{2+} means during such insults. Under normal conditions μ^{2+} channels to protect against cerebral ischemia is, on
e whole, negative (Ginsberg, 1988). These findings
rongly suggest that Ca²⁺ penetrates the cell by other
eans during such insults.
Under normal conditions, t

the whole, negative (Ginsberg, 1988). These findint strongly suggest that Ca^{2+} penetrates the cell by oth means during such insults.
Under normal conditions, the Na⁺/Ca²⁺ exchang contributes to the maintenance of l strongly suggest that Ca^{2+} penetrates the cell by other homeans during such insults. exchanger Na^+/Ca^{2+} exchanger N contributes to the maintenance of low $[Ca^{2+}]_i$ by extruding one Ca^{2+} in exchange for three means during such insults.

Under normal conditions, the Na⁺/Ca²⁺ exchanger

contributes to the maintenance of low $[Ca^{2+}]_i$ by extrud-

ing one Ca²⁺ in exchange for three Na⁺, a process driven

by the large tran Under normal conditions, the Na^+/Ca^{2+} exchanger N
contributes to the maintenance of low $[Ca^{2+}]_i$ by extrud-
ling one Ca^{2+} in exchange for three Na⁺, a process driven b
by the large transmembrane gradient of Na⁺ contributes to the maintenance of low $[Ca^{2+}]_i$ by extruding one Ca^{2+} in exchange for three Na⁺, a process driven
by the large transmembrane gradient of Na⁺ (Carafoli,
1987). Because this mechanism is electrogenic ing one Ca²⁺ in exchange for three Na⁺, a process driven
by the large transmembrane gradient of Na⁺ (Carafoli,
1987). Because this mechanism is electrogenic, elevation
of [Na⁺]_i and depolarization can reverse it by the large transmembrane gradient of Na⁺ (Caraform 1987). Because this mechanism is electrogenic, elevation of [Na⁺]_i and depolarization can reverse its operation i.e., Na⁺ is transported out of the cell and Ca 1987). Because this mechanism is electrogenic, elevation
of [Na⁺]_i and depolarization can reverse its operation,
i.e., Na⁺ is transported out of the cell and Ca^{2+} enters
(Blaustein, 1988). Intracellular Ca^{2+} l of $[Na^+]$, and depolarization can reverse its operation,
i.e., Na^+ is transported out of the cell and Ca^{2+} enters
(Blaustein, 1988). Intracellular Ca^{2+} loading subse-
quent to reversal of the Na^+/Ca^{2+} exchanger i.e., Na⁺ is transported out of the cell and Ca^{2+} enters (Blaustein, 1988). Intracellular Ca^{2+} loading subsequent to reversal of the Na⁺/Ca²⁺ exchanger is well documented in the anoxic heart (Haigney et al., 1 (Blaustein, 1988). Intracellular Ca^{2+} loading subsequent to reversal of the Na⁺/Ca²⁺ exchanger is well 1 documented in the anoxic heart (Haigney et al., 1992) b and optic nerve (Stys et al., 1992b; see section IV.A quent to reversal of the Na⁺/Ca²⁺ exchanger is documented in the anoxic heart (Haigney et al., and optic nerve (Stys et al., 1992b; see section IN With regard to brain cells, the favoured explanate/ Ca^{2+} entry durin documented in the anoxic heart (Haigney et al., 1992)
and optic nerve (Stys et al., 1992b; see section IV.A.1.)
With regard to brain cells, the favoured explanation for
Ca²⁺ entry during ischemia remains glutamate/excit and optic nerve (Stys et al., 1992b; see section IV.A
With regard to brain cells, the favoured explanation
Ca²⁺ entry during ischemia remains glutamate/ex
toxin-gated Ca²⁺ channels (Meldrum et al., 1993; drum, 1994). With regard to brain cells, the favoured explanation for Ca^{2+} entry during ischemia remains glutamate/excitotoxin-gated Ca^{2+} channels (Meldrum et al., 1993; Meldrum, 1994). It is interesting to note that N -methyl- Ca^{2+} entry during ischemia remains glutamate/excito-
toxin-gated Ca^{2+} channels (Meldrum et al., 1993; Mel-
drum, 1994). It is interesting to note that N-methyl-D-
aspartate (NMDA)-receptor channels played a critical toxin-gated Ca²⁺ channels (Meldrum et al., 1993; M
drum, 1994). It is interesting to note that N-methy
aspartate (NMDA)-receptor channels played a crit
part in membrane depolarization-induced death of tured embryonic sp drum, 1994). It is interesting to note that *N*-methyl-D-
aspartate (NMDA)-receptor channels played a critical
part in membrane depolarization-induced death of cul-
tured embryonic spinal neurons and that the contribu-
ti aspartate (NMDA)-receptor channels played a critical
part in membrane depolarization-induced death of cul-
tured embryonic spinal neurons and that the contribu-
tion of these channels to neurotoxicity was apparently
not r part in membrane depolarization-induced death of cultured embryonic spinal neurons and that the contribu-
tion of these channels to neurotoxicity was apparently level their ability to trigger large Ca^{2+} influx, every s tured embryonic spinal neurons and that the contribution of these channels to neurotoxicity was apparently
not related to their ability to trigger large Ca^{2+} influx
suggesting the involvement of other properties of the tion of these channels to neurotoxicity was apparen
not related to their ability to trigger large Ca^{2+} influ
suggesting the involvement of other properties of the
ligand-operated channels (Tymianski et al., 1993). Ne
e not related to their ability to trigger large Ca^{2+} infl
suggesting the involvement of other properties of th
ligand-operated channels (Tymianski et al., 1993). N
ertheless, reversal of Na⁺/Ca²⁺ exchange was dem
str suggesting the involvement of other properties of these ligand-operated channels (Tymianski et al., 1993). Nevertheless, reversal of Na⁺/Ca²⁺ exchange was demonstrated in neurons (Wakade et al., 1993) and synaptosomes ligand-operated channels (Tymianski et al., 1993). Nevertheless, reversal of Na⁺/Ca²⁺ exchange was demon-
strated in neurons (Wakade et al., 1993) and synapto-
somes (Nachshen and Kongsamut, 1989; Taglialatela et dal. strated in neurons (Wakade et al., 1993) and synapto-
somes (Nachshen and Kongsamut, 1989; Taglialatela et
al., 1990; Dagani et al., 1990) in situations that mimic
hypoxia or energy depletion.
Another possible link betwee rated in neurons (Wakade et al., 1993) and synaptomes (Nachshen and Kongsamut, 1989; Taglialatela et , 1990; Dagani et al., 1990) in situations that mimic poxia or energy depletion.
Another possible link between excessive somes (Nachshen and Kongsamut, 1989; Taglialatela
al., 1990; Dagani et al., 1990) in situations that mim
hypoxia or energy depletion.
Another possible link between excessive influx of Na
and Ca²⁺ may be the voltage-gate

al., 1990; Dagani et al., 1990) in situations that mimic a component of the selection. Can consider their ion selectivity is not perfect. The Na⁺:Ca²⁺ permeability ratio has been estimated to be more perfect. hypoxia or energy depletion. cat

Another possible link between excessive influx of Na⁺

and Ca²⁺ may be the voltage-gated Na⁺ channels them-

selves, because their ion selectivity is not perfect. The

Na⁺:Ca²⁺ Another possible link between excessive influx of Na⁺
and Ca²⁺ may be the voltage-gated Na⁺ channels them-
selves, because their ion selectivity is not perfect. The
Na⁺:Ca²⁺ permeability ratio has been estimated and Ca^{2+} may be the voltage-gated Na^+ channels the selves, because their ion selectivity is not perfect. T Na^+ : Ca^{2+} permeability ratio has been estimated to approximately 10:1 under normal conditions (Hil 1991;

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ability ratios have been suggested; Lederer et al., 1991),
and a TTX-sensitive transient Ca²⁺ current has been BRENOVITCH
ability ratios have been suggested; Lederer et al., 1991),
and a TTX-sensitive transient Ca²⁺ current has been
measured in isolated rat hippocampal CA1 pyramidal BRENOVITCH
ability ratios have been suggested; Lederer et al., 1991),
and a TTX-sensitive transient Ca^{2+} current has been
measured in isolated rat hippocampal CA1 pyramidal
cells (Takahashi et al., 1989). Permeation of ability ratios have been suggested; Lederer et al., 1991), and a TTX-sensitive transient Ca^{2+} current has been measured in isolated rat hippocampal CA1 pyramidal cells (Takahashi et al., 1989). Permeation of Ca^{2+} th and a TTX-sensitive transient Ca^{2+} current has been
measured in isolated rat hippocampal CA1 pyramidal
cells (Takahashi et al., 1989). Permeation of Ca^{2+}
through voltage-gated Na⁺ channels may be more imand a TTX-sensitive transient Ca^{2+} current has been
measured in isolated rat hippocampal CA1 pyramidal
cells (Takahashi et al., 1989). Permeation of Ca^{2+}
through voltage-gated Na⁺ channels may be more im-
portant measured in isolated rat hippocampal CA1 pyramidal
cells (Takahashi et al., 1989). Permeation of Ca²⁺
through voltage-gated Na⁺ channels may be more im-
portant when Na⁺ influx is provoked by veratridine or
other to cells (Takahashi et al., 1989). Permeation of Ca^{2+}
through voltage-gated Na⁺ channels may be more im-
portant when Na⁺ influx is provoked by veratridine or
other toxins acting at Na⁺ channel site 2, because these through voltage-gated Na⁺ channels may be more im-
portant when Na⁺ influx is provoked by veratridine or
other toxins acting at Na⁺ channel site 2, because these
toxins alter the ion selectivity of Na⁺ channels (J other toxins acting at Na⁺ channel site 2, because these toxins alter the ion selectivity of Na⁺ channels (Jacques et al., 1981; Adam-Vizi and Ligeti, 1986). It is relevant to mention that alteration of Na⁺ channels other toxins acting at Na⁺ channel site 2, because these toxins alter the ion selectivity of Na⁺ channels (Jacques et al., 1981; Adam-Vizi and Ligeti, 1986). It is relevant to mention that alteration of Na⁺ channels toxins alter the ion selectivity of Na⁺ channels (Jacques et al., 1981; Adam-Vizi and Ligeti, 1986). It is relevant to mention that alteration of Na⁺ channels selectivity is not exclusive to toxins. For example, Sorbe et al., 1981; Adam-Vizi and Ligeti, 1986). It is relevant to
mention that alteration of Na⁺ channels selectivity is
not exclusive to toxins. For example, Sorbera and Morad
(1990) found that atrionatriuretic peptide rapi mention that alterate
not exclusive to toxin
(1990) found that at
reversibly transform
conducting channels.
3. Collapse of acid *3.* Collapse to toxins. For example, Sorbera and Mora

3. *Solomb* that atrionatriuretic peptide rapidly and
 *S. Collapse of acid-base regulation with anoxic depo-

<i>A. Collapse of acid-base regulation with anoxic depo-
*

(1990) found that atrionatriuretic peptide rapidly and
reversibly transforms cardiac Na^+ channels into Ca^{2+}
conducting channels.
3. Collapse of acid-base regulation with anoxic depo-
larization. As oxygen is reversibly transforms cardiac Na^+ channels into Ca^{2+}
conducting channels.
3. Collapse of acid-base regulation with anoxic depo-
larization. As oxygen is the limiting substrate of brain
energy production in no conducting channels.

3. Collapse of acid-base regulation with anoxic depo-

larization. As oxygen is the limiting substrate of brain

energy production in normoglycemic conditions, defi-

cient oxygen supply implies anae 3. Collapse of acid-base regulation with anoxic depo-
larging substration. As oxygen is the limiting substrate of brain
energy production in normoglycemic conditions, defi-
cient oxygen supply implies anaerobic metabolism energy production in normoglycemic conditions, deficient oxygen supply implies anaerobic metabolism and consequent tissue acidosis. Cytosolic pH (pH_i) is a key regulator of numerous cellular processes (Roos and Bo-ron, 1 energy production in normoglycemic conditions, deficient oxygen supply implies anaerobic metabolism and consequent tissue acidosis. Cytosolic pH (pH_i) is a key regulator of numerous cellular processes (Roos and Bo ron, 1 cient oxygen supply implies anaerobic metabolism and
consequent tissue acidosis. Cytosolic pH (pH_i) is a key
regulator of numerous cellular processes (Roos and Bo-
ron, 1981), and tissue acidosis clearly promotes isch-
e regulator of numerous cellular processes (Roos and Boron, 1981), and tissue acidosis clearly promotes ischemia-induced tissue damage (Siesjö et al., 1993; see, however, Tombaugh and Sapolsky, 1993), even though extracellul ron, 1981), and tissue acidosis clearly promotes ischron, 1981), and tissue acidosis clearly promotes ischemia-induced tissue damage (Siesjö et al., 1993; see, however, Tombaugh and Sapolsky, 1993), even though extracellular acidosis protects cultured neurons against NMDA-re emia-induced tissue damage (Siesjö et al., 1993; showever, Tombaugh and Sapolsky, 1993), even thou
extracellular acidosis protects cultured neurons again
NMDA-receptor mediated injury (Kaku et al., 199
Ischemia-induced aci however, Tombaugh and Sapolsky, 1993), even though
extracellular acidosis protects cultured neurons against
NMDA-receptor mediated injury (Kaku et al., 1993).
Ischemia-induced acidosis is initiated intracellularly,
but ex extracellular acidosis protects cultured neurons against
NMDA-receptor mediated injury (Kaku et al., 1993).
Ischemia-induced acidosis is initiated intracellularly,
but extends to the extracellular space within seconds of
 NMDA-receptor mediated injury (Kaku et al., 1993).
Ischemia-induced acidosis is initiated intracellularly,
but extends to the extracellular space within seconds of
ischemia onset, reflecting increased CO_2 that diffuses
 Ischemia-induced acidosis is initiated intracellularly
but extends to the extracellular space within seconds is
chemia onset, reflecting increased CO_2 that diffuse
freely through all brain tissue compartments and act
va but extends to the extracellular space within seconds of ischemia onset, reflecting increased CO_2 that diffuses freely through all brain tissue compartments and activation of a variety of mechanisms involved in the regu ischemia onset, reflecting increased CO_2 that diffuses
freely through all brain tissue compartments and acti-
vation of a variety of mechanisms involved in the regu-
lation of pH_i. These include: (a) facilitated efflu freely through all brain tissue compartments and activation of a variety of mechanisms involved in the regulation of pH_i. These include: (*a*) facilitated efflux of intracellular lactic acid (Symon et al., 1994; Taylor vation of a variety of mechanisms involved in the lation of pH_i. These include: (*a*) facilitated efflux (tracellular lactic acid (Symon et al., 1994; Taylor (1994); (*b*) extrusion of H⁺ by Na⁺/H⁺ antiporter th b lation of pH_i. These include: (*a*) facilitated efflux of in-
tracellular lactic acid (Symon et al., 1994; Taylor et al.,
1994); (*b*) extrusion of H⁺ by Na⁺/H⁺ antiporter that is
blocked by amiloride and its more tracellular lactic acid (Symon et al., 1994; Taylor et al., 1994); (b) extrusion of H^+ by Na^+/H^+ antiporter that is blocked by amiloride and its more potent N-5-disubstituted derivatives (Sánchez-Armass et al., 1994) 1994); (b) extrusion of H^+ by Na^+/H^+ antiporter that is
blocked by amiloride and its more potent N-5-disubstituted derivatives (Sánchez-Armass et al., 1994); and (c)
exchanges of HCO_3^- with Cl^- via Na^+ -dependent blocked by amiloride and its more potent *N*-5-disubstituted derivatives (Sánchez-Armass et al., 1994); and (*c* exchanges of HCO_3^- with Cl^- via Na⁺-dependent or in dependent HCO^{3-}/Cl^- antiporters that are sensitive tuted derivatives (Sánchez-Armass et al., 1994); and (c) exchanges of HCO_3^- with Cl^- via Na⁺-dependent or in-
dependent HCO^{3-}/Cl^- antiporters that are sensitive to
stilbene derivatives (Schlue and Dorner, 1992; Mel exchanges of HCO_3^- with Cl^- via Na⁺-dependent or dependent HCO^{3-}/Cl^- antiporters that are sensitive stilbene derivatives (Schlue and Dorner, 1992; Mergård et al., 1994). All these mechanisms are activa and retain th dependent HCO^{3-}/Cl^- antiporters that are sensitive
stilbene derivatives (Schlue and Dorner, 1992; Me
lergård et al., 1994). All these mechanisms are activated
and retain their efficacy for as long as anoxic depola
izatio stilbene derivatives (Schlue and Dorner, 1992; Mellergård et al., 1994). All these mechanisms are activated and retain their efficacy for as long as anoxic depolarization does not occur, to such an extent that the extralergård et al., 1994). All these mechanisms are activate
and retain their efficacy for as long as anoxic depolarization does not occur, to such an extent that the extra
cellular space becomes more acid than the cytosol ($\$ and retain their efficacy for as long as anoxic depolarization does not occur, to such an extent that the extra-
cellular space becomes more acid than the cytosol (at
least for some cells) (Obrenovitch et al., 1990b). Howpolarization. least for some cells) (Obrenovitch et al., 1990b). How-
ever, pH_i regulation collapses abruptly with anoxic de-
polarization.
Continuous monitoring of extracellular lactate con-

ever, pH_i regulation collapses abruptly with anoxic de-
polarization.
Continuous monitoring of extracellular lactate con-
centration in the striatum of rat showed that K^+ -in-
duced depolarization (Taylor et al., 1994 ever, pH_i regulation collapses abruptly with anoxic de-
polarization.
Continuous monitoring of extracellular lactate con-
centration in the striatum of rat showed that K^+ -in-
duced depolarization (Taylor et al., 1996 polarization.
Continuous monitoring of extracellular lactate concentration in the striatum of rat showed that K⁺-in-
duced depolarization (Taylor et al., 1994) and anoxic
depolarization (Taylor et al., 1996) were associa Continuous monitoring of extracellular lactate concentration in the striatum of rat showed that K^+ -in duced depolarization (Taylor et al., 1994) and anoxidepolarization (Taylor et al., 1996) were associated with a decr duced depolarization (Taylor et al., 1994) and anoxic depolarization (Taylor et al., 1996) were associated with a decrease in extracellular lactate. These findings indicate that lactate transport out of the cells is impair duced depolarization (Taylor et al., 1994) and anoxic
depolarization (Taylor et al., 1996) were associated with
a decrease in extracellular lactate. These findings indi-
cate that lactate transport out of the cells is impa depolarization (Taylor et al., 1996) were associated with
a decrease in extracellular lactate. These findings indicate that lactate transport out of the cells is impaired
and/or its rate of production reduced (see below, decrease in extracellular lactate. These findings indi-
te that lactate transport out of the cells is impaired,
d/or its rate of production reduced (see below, section
), when transmembrane ionic gradients are disrupted.

cate that lactate transport out of the cells is impaired,
and/or its rate of production reduced (see below, section
6.), when transmembrane ionic gradients are disrupted.
Under physiological conditions, Na^+/H^+ exchanger and/or its rate of production reduced (see below, section 6.), when transmembrane ionic gradients are disrupted.
Under physiological conditions, Na^+/H^+ exchangers mediate the uphill extrusion of H^+ coupled to, and dr 6.), when transmembrane ionic gradients are disrupted
Under physiological conditions, Na^+/H^+ exchangers
mediate the uphill extrusion of H^+ coupled to, and
driven by, the downhill flow of Na^+ into the cell. It is th

PHARMACOLOGICAL REVIEWS

PHARMACOLOGICAL REVIEW

aspet

MODULATION OF VOLTAGE-
acidification in neurons and synaptosomes (Tolkovsky
and Richards, 1987; Schlue and Dorner, 1992; Sánchez-MODULATION OF VO
acidification in neurons and synaptosomes (Tolkov
and Richards, 1987; Schlue and Dorner, 1992; Sánch
Armass et al., 1994). This antiporter system is elec MODULATION OF VOI
acidification in neurons and synaptosomes (Tolkovs
and Richards, 1987; Schlue and Dorner, 1992; Sánch
Armass et al., 1994). This antiporter system is elect
neutral (1:1 stoichiometry) and, therefore, inse acidification in neurons and synaptosomes (Tolkovsky
and Richards, 1987; Schlue and Dorner, 1992; Sánchez-
Armass et al., 1994). This antiporter system is electro-
neutral (1:1 stoichiometry) and, therefore, insensitive to acidification in neurons and synaptosomes (Tolkovsky
and Richards, 1987; Schlue and Dorner, 1992; Sánchez-
Armass et al., 1994). This antiporter system is electro-
neutral (1:1 stoichiometry) and, therefore, insensitive to and Richards, 1987; Schlue and Dorner, 1992; Sánchez-
Armass et al., 1994). This antiporter system is electro-
neutral (1:1 stoichiometry) and, therefore, insensitive to
changes in the membrane potential. Furthermore, a
nu Armass et al., 1994). This antiporter system is electro-
neutral (1:1 stoichiometry) and, therefore, insensitive to
changes in the membrane potential. Furthermore, a
number of studies with vertebrate cells have shown that neutral (1:1 stoichiometry) and, therefore, insensitive to changes in the membrane potential. Furthermore, a number of studies with vertebrate cells have shown that acid extrusion is not blocked by ouabain, even though $[N$ changes in the membrane potential. Furthermore, a
number of studies with vertebrate cells have shown that
acid extrusion is not blocked by ouabain, even though
 $[Na⁺]$ _i was markedly raised (reviewed by Roos and Bo-
r number of studies with vertebrate cells have shown that
acid extrusion is not blocked by ouabain, even though
 $[Na⁺]$ _i was markedly raised (reviewed by Roos and Bo-
ron, 1981), possibly because of the relatively low acid extrusion is not blocked by ouabain, even though $[Na^+]$; was markedly raised (reviewed by Roos and Boron, 1981), possibly because of the relatively low K_m of the Na⁺/H⁺ exchanger for external Na⁺ (3 to 50 mM [Na⁻]_i was markedly raised (reviewed by Roos and Bo-
ron, 1981), possibly because of the relatively low K_m of
the Na⁺/H⁺ exchanger for external Na⁺ (3 to 50 mm at
physiological external pH; Aronson, 1985). Des the Na⁺/H⁺ exchanger for external Na⁺ (3 to 50 mM at
physiological external pH; Aronson, 1985). Despite this
apparent resistance to changes in the transmembrane
gradient of Na⁺, the efficacy of the Na⁺/H⁺ exch the Na⁺/H⁺ exchanger for external Na⁺ (3 to 50 mM
physiological external pH; Aronson, 1985). Despite t
apparent resistance to changes in the transmembre
gradient of Na⁺, the efficacy of the Na⁺/H⁺ exchange
ext physiological external pH; Aronson, 1985). Despite this
apparent resistance to changes in the transmembrane
gradient of Na⁺, the efficacy of the Na⁺/H⁺ exchanger in
extruding H⁺ may still be reduced with anoxic de apparent resistance to changes in the transmembrane
gradient of Na⁺, the efficacy of the Na⁺/H⁺ exchanger in
extruding H⁺ may still be reduced with anoxic depolar-
ization, because of the sudden fall in the ratio gradient of Na⁺, the efficacy of the Na⁺/H⁺ exchanger in extruding H⁺ may still be reduced with anoxic depolarization, because of the sudden fall in the ratio $[Na^+]$, $[Na^+]$, associated with this event (Aronson, 1 extruding H⁺ may still be reduced with anoxization, because of the sudden fall in the rat [Na⁺]_i associated with this event (Aronson, perimposed on extracellular acidosis that als the rate of H⁺ extrusion (Jean et ation, because of the sudden fall in the ratio $[Na^+]_o$
 $[a^+]_i$ associated with this event (Aronson, 1985), su-

rimposed on extracellular acidosis that also reduces

e rate of H⁺ extrusion (Jean et al., 1986).

The dr [Na⁺]_i associated with this event (Aronson, 1985), superimposed on extracellular acidosis that also reduces the rate of H⁺ extrusion (Jean et al., 1986). The driving forces for HCO₃/Cl⁻ exchanges are less obviou perimposed on extracellular acidosis that also reduces
the rate of H^+ extrusion (Jean et al., 1986).
The driving forces for HCO_3^-/Cl^- exchanges are less
obvious. Astrocytes apparently express a HCO_3^-/Cl^- ex-
changer

the rate of H^+ extrusion (Jean et al., 1986).

The driving forces for HCO_3^-/Cl^- exchanges are less

obvious. Astrocytes apparently express a HCO_3^-/Cl^- ex-

changer driven by the Na⁺ gradient, translocating
 HCO_3^- The driving forces for HCO_3^-/Cl^- exchanges are less
obvious. Astrocytes apparently express a HCO_3^-/Cl^- ex-
changer driven by the Na⁺ gradient, translocating
 HCO_3^- inward in response to intracellular acid loading
(Me obvious. Astrocytes apparently express a HCO_3^-/Cl^- ex-
changer driven by the Na⁺ gradient, translocating
 HCO_3^- inward in response to intracellular acid loading
(Mellergård et al., 1994). As with the Na⁺/H⁺ ex-
ch changer driven by the Na⁺ gradient, translocating HCO_3^- inward in response to intracellular acid loading (Mellergård et al., 1994). As with the Na⁺/H⁺ exchanger, this mechanism is presumably altered by anoxic depo HCO_3^- inward in response to intracellular acid loading (Mellergård et al., 1994). As with the Na⁺/H⁺ exchanger, this mechanism is presumably altered by anoxic depolarization. The other HCO_3^-/Cl^- antiporter may not (Mellergård et al., 1994). As with the Na⁺/H⁺ ex-
changer, this mechanism is presumably altered by an-
oxic depolarization. The other HCO_3/Cl^- antiporter
may not be relevant to hypoxic/ischemic conditions be-
cause i changer, this mechanism is presumably altered by an-
oxic depolarization. The other HCO_3^-/Cl^- antiporter
may not be relevant to hypoxic/ischemic conditions be-
cause it is Na^+ -independent, and its function may be to
tr oxic depolarization. The other HCO₃/Cl⁻
may not be relevant to hypoxic/ischemic cor
cause it is Na⁺-independent, and its functior
translocate HCO₃⁻ outward and Cl⁻ inward
kaline transients (Mellergård et al., ay not be relevant to hypoxic/ischemic conditions be-
use it is Na⁺-independent, and its function may be to
anslocate HCO_3^- outward and Cl^- inward during al-
line transients (Mellergård et al., 1993).
Whatever the re

cause it is Na⁺-independent, and its function may be
translocate HCO_3^- outward and Cl^- inward during a
kaline transients (Mellergård et al., 1993).
Whatever the residual efficacy of ion exchangers
control intracellul translocate HCO_3^- outward and Cl^- inward during a kaline transients (Mellergård et al., 1993).
Whatever the residual efficacy of ion exchangers control intracellular acidosis after anoxic depolarization their actions a kaline transients (Mellergård et al., 1993).

Whatever the residual efficacy of ion exchangers to

control intracellular acidosis after anoxic depolarization,

their actions are nullified, because this event is associ-

a Whatever the residual efficacy of ion exchangers to
control intracellular acidosis after anoxic depolarization,
their actions are nullified, because this event is associ-
ated with a sudden increase in cellular permeabili control intracellular acidosis after anoxic depolarization
their actions are nullified, because this event is assoc
ated with a sudden increase in cellular permeability t
 H^+ and pH-changing anions, which may be linked their actions are nullified, because this event is associated with a sudden increase in cellular permeability to H^+ and pH-changing anions, which may be linked to the opening of voltage-gated or ligand-operated ions ch ated with a sudden increase in cellular permeability to H^+ and pH-changing anions, which may be linked to the opening of voltage-gated or ligand-operated ions channels (Obrenovitch et al., 1990b; Symon et al., 1994). P H^+ and pH-changing anions, which may be linked to the opening of voltage-gated or ligand-operated ions channels (Obrenovitch et al., 1990b; Symon et al., 1994). permeation of H^+ through voltage-gated Na⁺ channels Permeation of H⁺ through voltage-gated Na⁺ channels
would be a possibility, particularly as H⁺ are the ions
most permeant through these channels (Hille, 1991), but
this is very unlikely because the amplitude of the Permeation of H^+ through voltage-gated Na⁺ channels fluored would be a possibility, particularly as H^+ are the ions termeant through these channels (Hille, 1991), but this is very unlikely because the amplitude of would be a possibility, particularly as H^+ are the ions tament premeant through these channels (Hille, 1991), but this is very unlikely because the amplitude of the extracellular pH (pH_e) alkalotic shift occurring wi this is very unlikely because the amplitude of the extra-
cellular pH (pH_e) alkalotic shift occurring with anoxic
depolarization, as with the abrupt drop in $[Na⁺]_0$, was
not altered by TTX (Xie et al., 1994b) (fig *cellular pH* (pH_a) alkalotic shift occurring with anoxic cellular pH (pH_e) alkalotic shift occurring with anoxic depolarization, as with the abrupt drop in $[Na^+]$ _o, was not altered by TTX (Xie et al., 1994b) (fig. 5).
4. *Intracellular Na*⁺ *loading and cell swelling*. Ce

depolarization, as with the abrupt drop in $[Na^+]_o$, was
not altered by TTX (Xie et al., 1994b) (fig. 5).
4. Intracellular Na^+ loading and cell swelling. Cellu-
lar swelling (i.e., cytotoxic edema) is another important
 not altered by TTX (Xie et al., 1994b) (fig. 5).
4. *Intracellular Na*⁺ *loading and cell swelling*. Cellu-
lar swelling (i.e., cytotoxic edema) is another important
component of the pathophysiology of cerebral ischemia 4. Intracellular Na^{+} loading and cell swelling. Cellu-
lar swelling (i.e., cytotoxic edema) is another important
component of the pathophysiology of cerebral ischemia
and other conditions characterized by an imbalance lar swelling (i.e., cytotoxic edema) is another important component of the pathophysiology of cerebral ischemia
and other conditions characterized by an imbalance be-
tween energy supply and demand, and/or acidosis
(Kimel component of the pathophysiology of cerebral ischemia stand other conditions characterized by an imbalance be-
tween energy supply and demand, and/or acidosis H
(Kimelberg et al., 1989). Acidosis, high extracellular K⁺, and other conditions characterized by an imbalance be-
tween energy supply and demand, and/or acidosis
(Kimelberg et al., 1989). Acidosis, high extracellular K^+ ,
excitotoxins and free fatty acids initiate cellular swel Example is al., 1989). Acidosis, high extracellular K^+ , effectotoxins and free fatty acids initiate cellular swelling Narough various mechanisms, but all have one impor-sector of the incubation medium below pH 6.8 abou

tant element in common: downhill entry of $Na⁺$.
Acidification of the incubation medium below pH 6.8
immediately induced swelling of cultured glial cells, and excitotoxins and free fatty acids initiate cellular swelling Na
through various mechanisms, but all have one impor-
sectant element in common: downhill entry of Na⁺. AT
Acidification of the incubation medium below pH 6. through various mechanisms, but all have one impor-
tant element in common: downhill entry of Na⁺. A¹
Acidification of the incubation medium below pH 6.8 ab
immediately induced swelling of cultured glial cells, and
th tant element in common: downhill entry of Na⁺.
Acidification of the incubation medium below pH 6.8
immediately induced swelling of cultured glial cells, and
this effect was significantly reduced by amiloride or the
remo Acidification of the incubation medium below pH 6.8 immediately induced swelling of cultured glial cells, and 1
this effect was significantly reduced by amiloride or the semoval of HCO_3^- and Na^+ from the medium (Kemps

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nels (Obrenovitch et al., 1990b; Symon et al., 1994).

Permeation of H⁺ through voltage-gated Na⁺ channels fluorocarbon medium of the isolated rat brain. These data were

would be a possibility, particularly as H⁺ a ⁴ ⁻² ⁰ ² ⁴ ⁶ ⁸ ¹⁰

Time (min)

FIG. 5. Effects of TTX on ischemia-induced changes in extrace

lular Na⁺ (*top panel*); [Na⁺_e] and acidosis (*bottom panel*; pH_e). Cor

plete ischemia was produced by FIG. 5. Effects of TTX on ischemia-induced changes in extracel-
lular Na⁺ (*top panel*); [Na⁺_s] and acidosis (*bottom panel*; pH_s). Com-
plete ischemia was produced by stopping perfusion with oxygenated
fluorocarbo FIG. 5. Effects of TTX on ischemia-induced changes in extracel-
lular Na⁺ (*top panel*); [Na⁺_e] and acidosis (*bottom panel*; pH_e). Com-
plete ischemia was produced by stopping perfusion with oxygenated
fluorocarb taken from X_i and acidosis (*bottom panel*; pH₄). Complete ischemia was produced by stopping perfusion with oxygenated fluorocarbon medium of the isolated rat brain. These data were taken from Xie and coworkers (1994b) plete ischemia was produced by stopping perfusion with oxygenated duced a gradual swelling followed by slow normalization from Xie and coworkers (1994b), with permission from authors and Elsevier Science Publishers BV.
duced a gradual swelling followed by slow normalion, an action blocke

taken from Xie and coworkers (1994b), with permission from the
authors and Elsevier Science Publishers BV.
duced a gradual swelling followed by slow normaliza-
tion, an action blocked by ouabain or iodoacetate and
reduced authors and Elsevier Science Publishers BV.
duced a gradual swelling followed by slow norm
tion, an action blocked by ouabain or iodoacetat
reduced by amiloride, suggesting that both Na⁺/K⁺
ase and Na⁺/H⁺ exchange duced a gradual swelling followed by slow normaliza-
tion, an action blocked by ouabain or iodoacetate and
reduced by amiloride, suggesting that both Na^+/K^+ -ATP-
ase and Na^+/H^+ exchange contributed to K^+ -induced
sw duced a gradual swelling followed by slow normalization, an action blocked by ouabain or iodoacetate and reduced by amiloride, suggesting that both Na^+/K^+ -ATP-
ase and Na^+/H^+ exchange contributed to K^+ -induced
swel tion, an action blocked by ouabain or iodoacetate and
reduced by amiloride, suggesting that both Na⁺/K⁺-ATP-
ase and Na⁺/H⁺ exchange contributed to K⁺-induced
swelling (Kempski et al., 1991). Glutamate-induced
s reduced by amiloride, suggesting that both Na⁺/K⁺-ATP-
ase and Na⁺/H⁺ exchange contributed to K⁺-induced
swelling (Kempski et al., 1991). Glutamate-induced
swelling of rat brain cortical slices was dependent upo ase and Na^+/H^+ exchange contributed to K^+ -induced
swelling (Kempski et al., 1991). Glutamate-induced
swelling of rat brain cortical slices was dependent upon
the presence of Na^+ in the medium (Lund-Andersen and
Her swelling (Kempski et al., 1991). Glutamate-induced
swelling of rat brain cortical slices was dependent upon
the presence of Na⁺ in the medium (Lund-Andersen and
Hertz, 1970), and more recent work suggests that this
effec swelling of rat brain cortical slices was dependent upon
the presence of Na⁺ in the medium (Lund-Andersen and
Hertz, 1970), and more recent work suggests that this
effect involves Na⁺ entry subsequent to stimulation o the presence of Na⁺ in the medium (Lund-Andersen and Hertz, 1970), and more recent work suggests that this effect involves Na⁺ entry subsequent to stimulation of Na⁺-dependent acidic amino acid uptake (see below, se Hertz, 1970), and more recent work suggests that this
effect involves Na⁺ entry subsequent to stimulation of
Na⁺-dependent acidic amino acid uptake (see below,
section 5.), with subsequent activation of Na⁺/K⁺-
AT effect involves Na⁺ entry subsequent to stimulation of Na⁺-dependent acidic amino acid uptake (see below, section 5.), with subsequent activation of Na⁺/K⁺-ATPase and ion exchanges ensuring pH_i control (see abov Na⁺-dependent acidic amino acid uptake (see below,
section 5.), with subsequent activation of Na⁺/K⁺-
ATPase and ion exchanges ensuring pH_i control (see
above, section 3.) (Kimelberg et al., 1989; Hansson et al.,
 section 5.), with subsequent activation of Na^+/K^+ -
ATPase and ion exchanges ensuring pH_i control (see
above, section 3.) (Kimelberg et al., 1989; Hansson et al.,
1994). Finally, replacement of Na⁺ by choline ATPase and ion exchanges ensuring pH_i control (see
above, section 3.) (Kimelberg et al., 1989; Hansson et al.,
1994). Finally, replacement of Na⁺ by choline in the
suspension medium completely abolished the swelling o above, section 3.) (Kimelberg et al., 1989; Hansson et al., 1994). Finally, replacement of Na⁺ by choline in the suspension medium completely abolished the swelling of cultured glial cells produced by arachidonic acid, s

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acids leads to increased $Na⁺$ permeability with subse-
quent influx of water into the cells (Staub et al., 1994 $\begin{array}{ll}\n & \text{URENJAK AND} \\
 \text{acids leads to increased Na}^+ \text{ permeability with subsequent influx of water into the cells (Staub et al., 1994).} \\
 \text{Although anoxia, iodoacetate glycolysis inhibition and}\n \end{array}$

URENJAK AND OBRI

ids leads to increased Na^+ permeability with subse-

repent influx of water into the cells (Staub et al., 1994). Ca

Although anoxia, iodoacetate glycolysis inhibition and

abain Na^+/K^+ -ATPase inhibi acids leads to increased Na^+ permeability with subsequent influx of water into the cells (Staub et al., 1994).
Although anoxia, iodoacetate glycolysis inhibition and couabain Na^+/K^+ -ATPase inhibition failed to increas quent influx of water into the cells (Staub et al., 1994). C
Although anoxia, iodoacetate glycolysis inhibition and
ouabain Na⁺/K⁺-ATPase inhibition failed to increase in
the volume of cultured glioma cells (Kempski et Although anoxia, iodoacetate glycolysis inhibition and

cuabain Na⁺/K⁺-ATPase inhibition failed to increase

the volume of cultured glioma cells (Kempski et al., In

1988), this does not apply in vivo (Cornog et al., ouabain Na⁺/K⁺-ATPase inhibition failed to increase incomposite that cellular swelling (Kempski et al., In 1988), this does not apply in vivo (Cornog et al., 1967) or sympthis in the sum that cellular swelling occurs the volume of cultured glioma cells (Kempski et al., Ir 1988), this does not apply in vivo (Cornog et al., 1967) or sy
in tissue slices (Okamoto and Quastel, 1970). There is m
convincing evidence that cellular swelling occ 1988), this does not apply in vivo (Cornog et al., 1967) or
in tissue slices (Okamoto and Quastel, 1970). There is
convincing evidence that cellular swelling occurs in the
intact brain whenever there is a sudden breakdown in tissue slices (Okamoto and Quastel, 1970). There is medium
convincing evidence that cellular swelling occurs in the ization
intact brain whenever there is a sudden breakdown of (Tibbs
ionic gradients across the cellula convincing evidence that cellular swelling occurs in
intact brain whenever there is a sudden breakdown
ionic gradients across the cellular membrane (Lux et
1986). For example, both anoxic depolarization and
are associated intact brain whenever there is a sudden breakdown of (Tib
ionic gradients across the cellular membrane (Lux et al., chair
1986). For example, both anoxic depolarization and SD pote
are associated with a sudden shrinking o ionic gradients across the cellular membrane (Lux et al., 1986). For example, both anoxic depolarization and SD are associated with a sudden shrinking of the extracel-
lular compartment, reflecting cellular swelling due to 1986). For example, both and
are associated with a sudde
lular compartment, reflection
influx of Na⁺ and Cl⁻ (PH
Hansen and Olsen, 1980).
5. Cellular membrane a

It is compartment, reflecting cellular swelling due to

influx of Na⁺ and Cl⁻ (Phillips and Nicholson 1979;
 Hansen and Olsen, 1980).

5. Cellular membrane depolarization, intracellular
 Na⁺ loading and glutamat influx of Na⁺ and Cl⁻ (Phillips and Nicholson 1979)
Hansen and Olsen, 1980).
5. Cellular membrane depolarization, intracellula
Na⁺ loading and glutamate efflux. It is now accepte
that excessive opening of glutamate-Hansen and Olsen, 1980).
5. Cellular membrane depolarization, intracellular
Na⁺ loading and glutamate efflux. It is now accepted
that excessive opening of glutamate-operated ion chan-
nels plays a major role in ischemia 5. Cellular membrane depolarization, intracellular Na^+ loading and glutamate efflux. It is now accepted that excessive opening of glutamate-operated ion channels plays a major role in ischemia-induced neuronal death, an $Na⁺ loading and glutamate efflux.$ It is now accepte that excessive opening of glutamate-operated ion channels plays a major role in ischemia-induced neuronaleath, and one possible triggering factor may be increased extracellular concentra that excessive opening of glutamate-operated ion channels plays a major role in ischemia-induced neuronal death, and one possible triggering factor may be increased extracellular concentration of glutamate (Meldrum et al., nels plays a major role in ischemia-induced neuronal
death, and one possible triggering factor may be in-
creased extracellular concentration of glutamate (Mel-
drum et al., 1993; Obrenovitch and Richards, 1995).
Under re death, and one possible triggering factor may be increased extracellular concentration of glutamate (Meldrum et al., 1993; Obrenovitch and Richards, 1995).
Under resting conditions, the level of glutamate in the cytoplasm creased extracellular concentration of glutamate (Meldrum et al., 1993; Obrenovitch and Richards, 1995).
Under resting conditions, the level of glutamate in the cytoplasm of brain cells is approximately 10,000 times
higher drum et al., 1993; Obrenovitch and Richards, 1995). The Under resting conditions, the level of glutamate in the cytoplasm of brain cells is approximately 10,000 times dependent han that in the extracellular space, a gradi Under resting conditions, the level of glutamate in the cytoplasm of brain cells is approximately 10,000 times dependent his higher than that in the extracellular space, a gradient his maintained by acidic amino acid carr cytoplasm of brain cells is approximately 10,000 times
higher than that in the extracellular space, a gradient
maintained by acidic amino acid carriers present in both
presynaptic and glial plasma membranes (Nicholls and
 higher than that in the extracellular space, a gradient maintained by acidic amino acid carriers present in both presynaptic and glial plasma membranes (Nicholls and Atwell, 1990). These carriers, which are essential for maintained by acidic amino acid carriers present in both
presynaptic and glial plasma membranes (Nicholls and
Atwell, 1990). These carriers, which are essential for
terminating the postsynaptic action of neurotransmitter
 presynaptic and glial plasma membranes (Nicholls and
Atwell, 1990). These carriers, which are essential for
terminating the postsynaptic action of neurotransmitter
glutamate, are characterized by a high (20 to 50 μ M)
a Atwell, 1990). These carriers, which are essential for
terminating the postsynaptic action of neurotransmitter
glutamate, are characterized by a high (20 to 50 μ M)
affinity for glutamate, and a unique coupling to Na⁺ terminating the postsynaptic action of neurotransmitt
glutamate, are characterized by a high (20 to 50 μ
affinity for glutamate, and a unique coupling to Na⁺ a
K⁺ (Kanai et al., 1993). The transport of glutamate in glutamate, are characterized by a high (20 to 50 μ M)
affinity for glutamate, and a unique coupling to Na⁺ and
 K^+ (Kanai et al., 1993). The transport of glutamate into
presynaptic terminals or neuroglia requires th affinity for glutamate, and a unique coupling to Na⁺ and K^+ (Kanai et al., 1993). The transport of glutamate into presynaptic terminals or neuroglia requires the simultaneous presence of external Na⁺ and internal K K^+ (Kanai et al., 1993). The transport of glutamate into
presynaptic terminals or neuroglia requires the simul-
taneous presence of external Na⁺ and internal K^+ , and
its efficacy is dependent on the Na⁺/ K^+ gr presynaptic terminals or neuroglia requires the simu
taneous presence of external Na^+ and internal K^+ , an
its efficacy is dependent on the Na^+/K^+ gradient acros
the plasma membrane (Kanner and Bendahan, 1982
Any re taneous presence of external Na⁺ and internal K⁺, and
its efficacy is dependent on the Na⁺/K⁺ gradient across
the plasma membrane (Kanner and Bendahan, 1982).
Any reduction of this gradient, resulting from an alte its efficacy is dependent on the Na⁺/K⁺ gradient acros
the plasma membrane (Kanner and Bendahan, 1982
Any reduction of this gradient, resulting from an alte
ation of the Na⁺/K⁺-ATPase (i.e., energy supply) or
sudd the plasma membrane (Kanner and Bendahan, 1982).

Any reduction of this gradient, resulting from an alter-

ation of the Na⁺/K⁺-ATPase (i.e., energy supply) or a

sudden change in the permeability of the cellular mem-Any reduction of this gradient, resulting from an alteration of the Na⁺/K⁺-ATPase (i.e., energy supply) or a sudden change in the permeability of the cellular membrane to Na⁺ or K⁺, reduces and possibly reverses t ation of the Na⁺/K⁺-ATPase (i.e., energy supply) or a sudden change in the permeability of the cellular mem-
brane to Na⁺ or K⁺, reduces and possibly reverses the Ir
action of glutamate transporters (Szatkowski et sudden change in the permeability of the cellular mem-
brane to Na⁺ or K⁺, reduces and possibly reverses the
action of glutamate transporters (Szatkowski et al., waa
1990). Thus, moderate ischemic insults are likely t brane to Na⁺ or K⁺, reduces and possibly reverses the action of glutamate transporters (Szatkowski et al., W₉₉₀). Thus, moderate ischemic insults are likely to supproduce an imbalance between glutamate efflux and au action of glutamate transporters (Szatkowski et al. 1990). Thus, moderate ischemic insults are likely to produce an imbalance between glutamate efflux and uptake (Bradford et al., 1987), whereas more severe insults may rev 1990). Thus, moderate ischemic insults are likely to supproduce an imbalance between glutamate efflux and allem uptake (Bradford et al., 1987), whereas more severe infinsults may reverse glutamate uptake processes complet produce an imbalance between glutamate efflux and uptake (Bradford et al., 1987), whereas more severe insults may reverse glutamate uptake processes completely (Szatkowski et al., 1990). This mechanism, which has yet to be insults may reverse glutamate uptake processes completely (Szatkowski et al., 1990). This mechanism, which
has yet to be demonstrated in vivo (Obrenovitch, 1995b)
very likely applies to a wide range of uptake mechanisms d has yet to be demonstrated in vivo (Obrenovitch, 1995b),
very likely applies to a wide range of uptake mecha-
nisms driven by the Na^+/K^+ transmembrane gradient.
In addition, repetitive action potentials (i.e., Na^+ -inhas yet to be demonstrated in vivo (Obrenovitch, 1995b
very likely applies to a wide range of uptake mechanisms driven by the Na^+/K^+ transmembrane gradient
In addition, repetitive action potentials (i.e., Na^+ -in
flux

very likely applies to a wide range of uptake n
nisms driven by the Na^+/K^+ transmembrane gra
In addition, repetitive action potentials (i.e., N
flux through voltage-gated Na^+ channels) are the
iological trigger for ve misms driven by the Na⁺/K⁺ transmembrane gradient. sect
In addition, repetitive action potentials (i.e., Na⁺-in-
flux through voltage-gated Na⁺ channels) are the phys-
sub-
iological trigger for vesicular release In addition, repetitive action potentials (i.e., Na⁺-in-
flux through voltage-gated Na⁺ channels) are the phys-
iological trigger for vesicular release of neurotransmit-
ter glutamate (exocytosis). Glutamate release e flux through voltage-gated Na⁺ channels) are the phys-
iological trigger for vesicular release of neurotransmit-
ter glutamate (exocytosis). Glutamate release elicited by
short repetitive electrical pulses applied to ce iological trigger for vesicular release of neurotransmitter glutamate (exocytosis). Glutamate release elicited by short repetitive electrical pulses applied to cerebellar slices was TTX- and Ca^{2+} -dependent (De Barry et ter glutamate (exocytosis). Glutamate release elicited by
short repetitive electrical pulses applied to cerebellar
slices was TTX- and Ca^{2+} -dependent (De Barry et al.,
1989). Exposure of synaptosomes to 4-aminopyridine

acids leads to increased Na⁺ permeability with subse-
quent influx of water into the cells (Staub et al., 1994). Ca^{2+} ([Ca²⁺]_c) and glutamate release that was almost
Although anoxia, iodoacetate glycolysis inhibi BRENOVITCH
repetitive firing, induced an increase in cytosolic free
Ca²⁺ ([Ca²⁺]_c) and glutamate release that was almost BRENOVITCH
repetitive firing, induced an increase in cytosolic free
Ca²⁺ ([Ca²⁺]_c) and glutamate release that was almost
entirely blocked by TTX, and 4-aminopyridine failed to EXENOVITCH
repetitive firing, induced an increase in cytosolic free
 Ca^{2+} ([Ca²⁺]_c) and glutamate release that was almost
entirely blocked by TTX, and 4-aminopyridine failed to
increase [Ca²⁺]_c in low-Na⁺ medi repetitive firing, induced an increase in cytosolic free Ca^{2+} ([Ca²⁺]_c) and glutamate release that was almost entirely blocked by TTX, and 4-aminopyridine failed to increase $[Ca^{2+}]_c$ in low-Na⁺ media (Tibbs et repetitive firing, induced an increase in cytosolic free Ca^{2+} ([Ca²⁺]_c) and glutamate release that was almost entirely blocked by TTX, and 4-aminopyridine failed to increase $[Ca^{2+}]_c$ in low-Na⁺ media (Tibbs et Ca^{2+} ([Ca²⁺]_c) and glutamate release that was almost
entirely blocked by TTX, and 4-aminopyridine failed to
increase $[Ca^{2+}]_c$ in low-Na⁺ media (Tibbs et al., 1989).
Increase in $[Ca^{2+}]_c$ and glutamate release entirely blocked by TTX, and 4-aminopyridine failed
increase $[Ca^{2+}]_c$ in low-Na⁺ media (Tibbs et al., 198
Increase in $[Ca^{2+}]_c$ and glutamate release produced
synaptosomes by KCl is insensitive to TTX and low-N
mediu Increase in $[Ca^{2+}]_c$ and glutamate release produced in synaptosomes by KCl is insensitive to TTX and low-Na⁺ medium, but this stimulus provokes a clamped depolarization of the plasma membrane that is not physiological Increase in $[Ca^{2+}]_c$ and glutamate release produced in synaptosomes by KCl is insensitive to TTX and low-Na⁺ medium, but this stimulus provokes a clamped depolarization of the plasma membrane that is not physiological synaptosomes by KCl is insensitive to TTX and low-Na⁺
medium, but this stimulus provokes a clamped depolar-
ization of the plasma membrane that is not physiological
(Tibbs et al., 1989). Therefore, down-modulation of Na medium, but this stimulus provokes a clamped depolization of the plasma membrane that is not physiologic
(Tibbs et al., 1989). Therefore, down-modulation of N
channels reduces vesicular glutamate release, with t
potential ization of the plasma membrane that is not physiological
(Tibbs et al., 1989). Therefore, down-modulation of Na⁺
channels reduces vesicular glutamate release, with two
potential benefits: (*a*) decreased excitotoxic mech (Tibbs et al., 1989). Therefore, down-modulation of Na⁺
channels reduces vesicular glutamate release, with two
potential benefits: (a) decreased excitotoxic mecha-
nisms; and (b) reduced energy-demand, because all exo channels reduces vesicular glutamate release, with two
potential benefits: (a) decreased excitotoxic mecha-
nisms; and (b) reduced energy-demand, because all exo-
cytotic processes require ATP hydrolysis (Söllner and
Ro potential benefits: (a) decreased excitotoxic mechanisms; and (b) reduced energy-demand, because all exo-cytotic processes require ATP hydrolysis (Söllner and Rothman, 1994). One must emphasizes that the latter benefit misms; and (b) reduced energy
cytotic processes require A
Rothman, 1994). One must
benefit is not exclusive to gl
cytosis of all neurotransmit
6. Inhibition of anaerobic totic processes require ATP hydrolysis (Söllner and
thman, 1994). One must emphasizes that the latter
nefit is not exclusive to glutamate but applies to exo-
tosis of all neurotransmitters.
6. Inhibition of anaerobic metab

benefit is not exclusive to glutamate but applies to exocytosis of all neurotransmitters.
6. *Inhibition of anaerobic metabolism with anoxic de- polarization and* Na^+ *influx*. Na⁺ influx stimulates res- piration an polarization and Na^+ influx. Na⁺ influx stimulates respiration and ATP turnover in normoxia (see section III.A.), and anaerobic metabolism as long as physiological conditions are maintained (Fellows et al., 1993). Paradoxically, during anoxia, excessive intracellular polarization and Na^+ influx. Na⁺ influx stimulates respiration and ATP turnover in normoxia (see section III.A.), and anaerobic metabolism as long as physiological conditions are maintained (Fellows et al., 1993) Para piration and ATP turnover in normoxia (see section III.A.), and anaerobic metabolism as long as physiological conditions are maintained (Fellows et al., 1993). Paradoxically, during anoxia, excessive intracellular Na⁺ lo III.A.), and anaerobic metabolism as long as physiolog-
ical conditions are maintained (Fellows et al., 1993).
Paradoxically, during anoxia, excessive intracellular
Na⁺ loading (i.e., intensive electrical stimulation, a ical conditions are maintained (Fellows et al., 1993).
Paradoxically, during anoxia, excessive intracellular Na⁺ loading (i.e., intensive electrical stimulation, anoxic depolarization or treatment with veratridine) can Paradoxically, during anoxia, excessive intracellular Na⁺ loading (i.e., intensive electrical stimulation, anoxic depolarization or treatment with veratridine) can inhibit anaerobic glycolysis. In Ca^{2+} -free medium (i Na⁺ loading (i.e., intensive electrical stimulation, anoxic depolarization or treatment with veratridine) can inhibit anaerobic glycolysis. In Ca^{2+} -free medium (i.e., increased membrane permeability to ions), TTX, at depolarization or treatment with veratridine) can in-
hibit anaerobic glycolysis. In Ca²⁺-free medium (i.e.,
increased membrane permeability to ions), TTX, at con-
centrations that block action potentials, enhanced the
 increased membrane permeability to ions), TTX, at concentrations that block action potentials, enhanced the rate of anaerobic glycolysis of brain cortex slices from rats and guinea pigs (by approximately 300%). A similar e increased membrane permeability to ions), TTX, at c
centrations that block action potentials, enhanced
rate of anaerobic glycolysis of brain cortex slices fi
rats and guinea pigs (by approximately 300%). A sime
ffect was o centrations that block action potentials, enhanced
rate of anaerobic glycolysis of brain cortex slices f
rats and guinea pigs (by approximately 300%). A sime
ffect was observed with local anaesthetics at phar
cologically a rate of anaerobic glycolysis of brain cortex slices from

rats and guinea pigs (by approximately 300%). A similar

effect was observed with local anaesthetics at pharma-

cologically active concentrations, whereas protove effect was observed with local anaesthetics at pharma-
cologically active concentrations, whereas protovera-
trine diminished the glycolytic stimulation of TTX
(Shankar and Quastel, 1972). These findings indicate
that the effect was observed with local anaesthetics at pharma-
cologically active concentrations, whereas protovera-
trine diminished the glycolytic stimulation of TTX
(Shankar and Quastel, 1972). These findings indicate
that the cologically active concentrations, whereas protovera-
trine diminished the glycolytic stimulation of TTX
(Shankar and Quastel, 1972). These findings indicate
that the influx of Na⁺ and efflux of K⁺ under these
conditi trine diminished the glycolytic stimulation of TTX
(Shankar and Quastel, 1972). These findings indicate
that the influx of Na⁺ and efflux of K⁺ under these
conditions blocked anaerobic metabolism, possibly at the
leve (Shankar and Quastel, 1972). These findings indicate
that the influx of Na⁺ and efflux of K⁺ under these
conditions blocked anaerobic metabolism, possibly at the
level of pyruvate kinase. This enzyme, a regulatory ste that the influx of Na^+ and efflux of K
conditions blocked anaerobic metabolism,
level of pyruvate kinase. This enzyme, a r
in glycolysis, is activated by K^+ and inh
(Takagaki, 1968; Rose and Rose, 1969).
Inhibition o nditions blocked anaerobic metabolism, possibly at the
vel of pyruvate kinase. This enzyme, a regulatory step
glycolysis, is activated by K^+ and inhibited by Na^+
akagaki, 1968; Rose and Rose, 1969).
Inhibition of ana

level of pyruvate kinase. This enzyme, a regulatory step
in glycolysis, is activated by K^+ and inhibited by Na^+
(Takagaki, 1968; Rose and Rose, 1969).
Inhibition of anaerobic metabolism by Na^+ loading
was recently in glycolysis, is activated by K^+ and inhibited by Na^+
(Takagaki, 1968; Rose and Rose, 1969).
Inhibition of anaerobic metabolism by Na^+ loading
was recently confirmed in synaptosomes. Veratridine
superimposed onto (Takagaki, 1968; Rose and Rose, 1969).

Inhibition of anaerobic metabolism by Na⁺ loading

was recently confirmed in synaptosomes. Veratridine

superimposed onto anoxia dose-dependently reduced an-

aerobic ATP synthesi Inhibition of anaerobic metabolism by $Na⁺$ loading
was recently confirmed in synaptosomes. Veratridine
superimposed onto anoxia dose-dependently reduced an-
aerobic ATP synthesis. This effect was linked to $Na⁺$
 was recently confirmed in synaptosomes. Veratridine
superimposed onto anoxia dose-dependently reduced an-
aerobic ATP synthesis. This effect was linked to Na⁺
influx as it was blocked by TTX (Gleitz et al., 1993).
Micro superimposed onto anoxia dose-dependently reduced an
aerobic ATP synthesis. This effect was linked to Na
influx as it was blocked by TTX (Gleitz et al., 1993)
Microdialysis studies of extracellular lactate in the stri
atum aerobic ATP synthesis. This effect was linked to Na⁺
influx as it was blocked by TTX (Gleitz et al., 1993).
Microdialysis studies of extracellular lactate in the stri-
atum of rats are also consistent with this hypothesi influx as it was blocked by TTX (Gleitz et al., 1993).
Microdialysis studies of extracellular lactate in the stri-
atum of rats are also consistent with this hypothesis,
although the following observation might also reflec atum of rats are also consistent with this hypothesis, although the following observation might also reflect altered efflux of lactate with depolarization (see above, section 3.). Dialysate lactate decreased during transie atum of rats are also consistent with this hypothesis,
although the following observation might also reflect
altered efflux of lactate with depolarization (see above,
section 3.). Dialysate lactate decreased during transie although the following observation might also reflect
altered efflux of lactate with depolarization (see above,
section 3.). Dialysate lactate decreased during transient
depolarization, increasing markedly only during the
 altered efflux of lactate with depolarization (see absection 3.). Dialysate lactate decreased during trans
depolarization, increasing markedly only during
subsequent repolarization phase (Taylor et al., 19
Similar observat section 3.). Dialysate lactate decreased during transient
depolarization, increasing markedly only during the
subsequent repolarization phase (Taylor et al., 1994).
Similar observations were made with anoxic depolariza-
ti Similar observations were made with anoxic depolariza-
tion provoked by transient ischemia (Taylor et al., 1996).
This inhibitory effect of intracellular $Na⁺$ loading on
anaerobic metabolism is seldom discussed, desp subsequent repolarization phase (Taylor et al., 1994).
Similar observations were made with anoxic depolariza-
tion provoked by transient ischemia (Taylor et al., 1996).
This inhibitory effect of intracellular Na⁺ loading Similar observations were made with anoxic depolarization provoked by transient ischemia (Taylor et al., 1996).
This inhibitory effect of intracellular Na⁺ loading on anaerobic metabolism is seldom discussed, despite the tion provoked by
This inhibitory
anaerobic metab
potential signific
source of ATP.

PHARMACOLOGICAL REVIEWS

MODULATION OF VOLTAGENT AND MODULATION OF VOLTAGENT AND SECTION CHERITY SHOWS that anoxic depolarization detrimental to neuronal survival and that strategies MODULATION OF VOLTAGENTING SECTOR UP AT THE SECTOR CHERAL THIS SECTION IS detrimental to neuronal survival and that strategies
for suppressing or delaying it are bound to be potentially MODULATION OF VOLTAGE-
This section clearly shows that anoxic depolarization
is detrimental to neuronal survival and that strategies
for suppressing or delaying it are bound to be potentially
cerebroprotective. The delay f This section clearly shows that anoxic depolarization
is detrimental to neuronal survival and that strategies Na
for suppressing or delaying it are bound to be potentially to
cerebroprotective. The delay from ischemia onse is detrimental to neuronal survival and that strategies
for suppressing or delaying it are bound to be potentially
cerebroprotective. The delay from ischemia onset to oc-
currence of anoxic depolarization, and its cerebral tor suppressing or delaying it are bound to be potentially
cerebroprotective. The delay from ischemia onset to oc-
currence of anoxic depolarization, and its cerebral blood
flow threshold (Obrenovitch, 1995a), depend on tw cerebroprotective. The delay from ischemia onset to oc-
currence of anoxic depolarization, and its cerebral blood
flow threshold (Obrenovitch, 1995a), depend on two fac-
tors: local rate of energy metabolism (Astrup et al. currence of anoxic depolarization, and its cerebral blood
flow threshold (Obrenovitch, 1995a), depend on two fac-
tors: local rate of energy metabolism (Astrup et al., 1980)
and stores of energy-rich substrates, notably gl flow threshold (Obrenovitch, 1995a), depend on two factors: local rate of energy metabolism (Astrup et al., 1980) cread stores of energy-rich substrates, notably glucose comparison (Bures and Buresova, 1957; Siemkowicz and tors: local rate of energy metabolism (Astrup et al., 1980) cand stores of energy-rich substrates, notably glucose condity (Bures and Buresova, 1957; Siemkowicz and Hansen, diversity of the threshold for anoxic phigh and/o and stores of energy-rich
(Bures and Buresova, 194
1981; Kristián et al., 199
high and/or glucose stores
depolarization is reduced.
Na⁺ channel blockade ures and Buresova, 1957; Siemkowicz and Hansen,
81; Kristián et al., 1994). When energy demand is comparization is reduced.
polarization is reduced.
Na⁺ channel blockade and down-modulation delays soxic depolarization.

1981; Kristián et al., 1994). When energy demand is
high and/or glucose stores low, the threshold for anoxic
depolarization is reduced.
Na⁺ channel blockade and down-modulation delays
anoxic depolarization. This action, high and/or glucose stores low, the threshold for anoxic pot
depolarization is reduced. isol
Na⁺ channel blockade and down-modulation delays stra
anoxic depolarization. This action, clearly demonstrated volt
with TTX bot depolarization is reduced.

Na⁺ channel blockade and down-modulation delays stanoxic depolarization. This action, clearly demonstrated vo

with TTX both in vitro (Rosen et al., 1994) and in vivo m

(Prenen et al., 1988; Na⁺ channel blockade and down-modulation delays
anoxic depolarization. This action, clearly demonstrated
with TTX both in vitro (Rosen et al., 1994) and in vivo
(Prenen et al., 1988; Xie et al., 1994b, 1995) (see section anoxic depolarization. This action, clearly demonstrated with TTX both in vitro (Rosen et al., 1994) and in vivo m
(Prenen et al., 1988; Xie et al., 1994b, 1995) (see section w
IV. B.), has two important benefits: (*a*) e with TTX both in vitro (Rosen et al., 1994) and in vivo
(Prenen et al., 1988; Xie et al., 1994b, 1995) (see section
IV. B.), has two important benefits: (*a*) exposure to neu-
rotoxic intracellular Na⁺ and Ca⁺ loading (Prenen et al., 1988; Xie et al., 1994b, 1995) (see section v
IV. B.), has two important benefits: (*a*) exposure to neu-
rotoxic intracellular Na⁺ and Ca⁺ loading is avoided or g
delayed, and (*b*) vital processes su IV. B.), has two important \vert
rotoxic intracellular Na⁺ a
delayed, and (b) vital pro
acid-base balance, cell vol
mechanisms are preserved delayed, and (*O*) vital processes such as intracentual
acid-base balance, cell volume regulation, and uptake
mechanisms are preserved.
C. Increased Tolerance to Ischemia by Down-Regulation
of Na⁺ Channels

of the base balance,
 mechanisms are pr
 C. Increased Tolera
 of Na⁺ Channels
 1. Inherent down

m
 Increased Tolerance to Ischemia by Down-Regulation

Na⁺ Channels

1. Inherent down-regulation of Na⁺ currents during

oxia and metabolic inhibition. The fact that functional

H *C. Increased Tolerance to Ischemia by Down-Regulation*
of Na⁺ Channels
1. Inherent down-regulation of Na⁺ currents during
anoxia and metabolic inhibition. The fact that functional
loss (i.e., EEG silence) occurs withi Loss (i.e., Increased Tolerance to Ischemia by Down-Regulation

of Na^+ Channels

1. Inherent down-regulation of Na^+ currents during

anoxia and metabolic inhibition. The fact that functional

loss (i.e., EEG silence) of Na⁺ currents during
1. Inherent down-regulation of Na ⁺ currents during
anoxia and metabolic inhibition. The fact that functional
loss (i.e., EEG silence) occurs within seconds of ischemia
onset, whereas energy lev 1. Inherent down-regulation of Na^+ currents durinanoxia and metabolic inhibition. The fact that function loss (i.e., EEG silence) occurs within seconds of ischem onset, whereas energy levels are not depleted for sever m loss (i.e., EEG silence) occurs within seconds of ischemia portant for neuronal tolerance to energy depletion.

onset, whereas energy levels are not depleted for several The apparent sensitivity of Na⁺ channel conductan loss (i.e., EEG silence) occurs within seconds of ischemia

onset, whereas energy levels are not depleted for several

minutes, strongly suggests that anoxia-induced block-

ade of neuronal function may be an adaptive proc onset, whereas energy levels are not depleted for several
minutes, strongly suggests that anoxia-induced block-
ade of neuronal function may be an adaptive process and
not a consequence of energy substrate limitation
(Neub minutes, strongly suggests that anoxia-induced block-
ade of neuronal function may be an adaptive process and
not a consequence of energy substrate limitation
(Neubauer, 1993). As already explained, reducing neu-
ronal met ade of neuronal function may be an adaptive process and
not a consequence of energy substrate limitation
(Neubauer, 1993). As already explained, reducing neu-
ronal metabolism by stabilizing membrane potential
and decreasi not a consequence of energy substrate limitation restricts (Neubauer, 1993). As already explained, reducing neu-
ronal metabolism by stabilizing membrane potential creasing the production of action potentials po-
tentially (Neubauer, 1993). As already explained, reducing neu-
ronal metabolism by stabilizing membrane potential creament and decreasing the production of action potentials po-
tiontially restricts the use of metabolic substrates ronal metabolism by stabilizing membrane potential
and decreasing the production of action potentials po-
tentially restricts the use of metabolic substrates to the
maintenance of cellular integrity, thus extending the
tim and decreasing the premision of cellular damage.

time to which neuror

out cellular damage.

Changes in neuror ntially restricts the use of metabolic substrates to the by
aintenance of cellular integrity, thus extending the exi-
ne to which neurons can be exposed to hypoxia with-
t cellular damage.
Changes in neuronal membrane ion

maintenance of cellular integrity, thus extending the
time to which neurons can be exposed to hypoxia with
out cellular damage.
Changes in neuronal membrane ion conductance are
clearly involved in this survival strategy. I time to which neurons can be exposed to hypoxia with
out cellular damage.
Changes in neuronal membrane ion conductance are
clearly involved in this survival strategy. In vitro elec
trophysiological studies of hypoxia and m out cellular damage.
Changes in neuronal membrane ion conductance a
clearly involved in this survival strategy. In vitro ele
trophysiological studies of hypoxia and metabolic in
bition have shown that early functional loss Changes in neuronal membrane ion conductance are 196
clearly involved in this survival strategy. In vitro elec-
trophysiological studies of hypoxia and metabolic inhi-
mec
bition have shown that early functional loss is a clearly involved in this survival strategy. In vitro electrophysiological studies of hypoxia and metabolic inhibition have shown that early functional loss is associated with hyperpolarization of neurons, and a rise in ex trophysiological studies of hypoxia and metabolic inhibition have shown that early functional loss is associated with hyperpolarization of neurons, and a rise in extracellular K⁺ (Hansen et al., 1982; Fujiwara et al., 19 bition have shown that early functional loss is associated with hyperpolarization of neurons, and a rise in extracellular K^+ (Hansen et al., 1982; Fujiwara et al., or 1987; Leblond and Krnjevic, 1989). This initial inc ated with hyperpolarization of neurons, and a rise in Eextracellular K^+ (Hansen et al., 1982; Fujiwara et al., ods 1987; Leblond and Krnjevic, 1989). This initial increase excitin K^+ conductance presumably involves extracellular K⁺ (Hansen et al., 1982; Fujiwara et al., od
1987; Leblond and Krnjevic, 1989). This initial increase ex
in K⁺ conductance presumably involves the opening of m
Ca²⁺-dependent K⁺ channels subsequent t 1987; Leblond and Krnjevic, 1989). This initial increase
in K^+ conductance presumably involves the opening of mo
Ca²⁺-dependent K^+ channels subsequent to a rise in ad
intracellular free Ca²⁺ (Duchen, 1990), and in K⁺ conductance presumably involves the opening of r Ca²⁺-dependent K⁺ channels subsequent to a rise in sintracellular free Ca²⁺ (Duchen, 1990), and possibly belowing of voltage-independent K⁺ channels such as intracellular free Ca^{2+} (Duchen, 1990), and possibly
opening of voltage-independent K^+ channels such as
ATP-dependent K^+ channels (Mourre et al., 1989; Xie et
al., 1995) (for review, see Obrenovitch et al., 1990a opening of voltage-independent K^+ channels such as
ATP-dependent K^+ channels (Mourre et al., 1989; Xie et
al., 1995) (for review, see Obrenovitch et al., 1990a).
Other conductances also appear to be altered, includi ATP-dependent K⁺ channels (Mourre et al., 1989; Xie et *ti* al., 1995) (for review, see Obrenovitch et al., 1990a). p
Other conductances also appear to be altered, including ca
ca²⁺-dependent Cl⁻ current that may in al., 1995) (for review, see Obrenovitch et al., 1990a).
Other conductances also appear to be altered, including
a Ca^{2+} -dependent Cl^- current that may increase
(Duchen, 1990) and a blockade of Ca^{2+} current (L-type
1989).

Recent findings strongly suggest that reduction in $Na⁺$ conductance may also be an important contributor to decreasing neuronal excitability during anoxia and -GATED NA⁺ CHANNELS 37

Recent findings strongly suggest that reduction in

Na⁺ conductance may also be an important contributor

to decreasing neuronal excitability during anoxia and -GATED NA⁺ CHANNELS 37

Recent findings strongly suggest that reduction in

Na⁺ conductance may also be an important contributor

to decreasing neuronal excitability during anoxia and

metabolic inhibition (Cummins et Recent findings strongly suggest that reduction Na⁺ conductance may also be an important contribute decreasing neuronal excitability during anoxia metabolic inhibition (Cummins et al., 1993). Intracellar recordings of ne Recent indings strongly suggest that reduction in Na⁺ conductance may also be an important contributor to decreasing neuronal excitability during anoxia and metabolic inhibition (Cummins et al., 1993). Intracellular rec Na' conductance may also be an important contributor
to decreasing neuronal excitability during anoxia and
metabolic inhibition (Cummins et al., 1993). Intracellu-
lar recordings of neocortical neurons in human brain
slice to decreasing neuronal excitability during anoxia and
metabolic inhibition (Cummins et al., 1993). Intracellu-
lar recordings of neocortical neurons in human brain
slices showed that their excitability was markedly de-
cr metabolic inhibition (Cummins et al., 1993). Intracellu-
lar recordings of neocortical neurons in human brain
slices showed that their excitability was markedly de-
creased within the first 5 min of anoxia, and this effec lar recordings of neocortical neurons in human brain
slices showed that their excitability was markedly de-
creased within the first 5 min of anoxia, and this effect
could not be explained adequately by increased K^+ co slices showed that their excitability was markedly decreased within the first 5 min of anoxia, and this effect could not be explained adequately by increased K^+ conductance, because it was associated with little or no creased within the first 5 min of anoxia, and this effect
could not be explained adequately by increased K^+ con-
ductance, because it was associated with little or no
change in membrane input resistance and membrane
po could not be explained adequately by increased K^+ conductance, because it was associated with little or change in membrane input resistance and membra potential. Whole-cell voltage-clamp studies of acut isolated human ductance, because it was associated with little or no
change in membrane input resistance and membrane
potential. Whole-cell voltage-clamp studies of acutely
isolated human neocortical pyramidal neurons demon-
strated that potential. Whole-cell voltage-clamp studies of acutely isolated human neocortical pyramidal neurons demonstrated that anoxia and cyanide rapidly decreased a voltage-dependent, TTX-sensitive Na^+ current and markedly shif isolated human neocortical pyramidal neurons demonstrated that anoxia and cyanide rapidly decreased a voltage-dependent, TTX-sensitive Na⁺ current and markedly shifted its steady state inactivation curve toward more nega strated that anoxia and cyanide rapidly decreased a
voltage-dependent, TTX-sensitive Na⁺ current and
markedly shifted its steady state inactivation curve to-
ward more negative potentials (Cummins et al., 1993).
The effe voltage-dependent, TTX-sensitive Na⁺ current and markedly shifted its steady state inactivation curve ward more negative potentials (Cummins et al., 199
The effect of anoxia on steady state inactivation variably reduced markedly shifted its steady state inactivation curve to-
ward more negative potentials (Cummins et al., 1993).
The effect of anoxia on steady state inactivation was
greatly reduced when 2 mM ATP was included, suggest-
ing The effect of anoxia on steady state inactivation was
greatly reduced when 2 mM ATP was included, suggest-
ing that anoxic depression of Na^+ currents was linked to
reduced oxidative metabolism.
Reduced membrane exc Reduced members are effect of anoxia on steady state inactivation was eatly reduced when 2 mM ATP was included, suggest-
g that anoxic depression of Na^+ currents was linked to duced oxidative metabolism.
Reduced me

greatly reduced when 2 mM ATP was included, suggesting that anoxic depression of Na^+ currents was linked to reduced oxidative metabolism.
Reduced membrane excitability with preservation of membrane potential and in viously observed in neurons from rat cortex and hip-
pocampus CA1 exposed to 4 to 5 min of O_2 deprivation, reduced oxidative metabolism.
Reduced membrane excitability with preservation of
membrane potential and input resistance has been pre
viously observed in neurons from rat cortex and hip
pocampus CA1 exposed to 4 to 5 min Reduced membrane excitability with preservation of
membrane potential and input resistance has been pre-
viously observed in neurons from rat cortex and hip-
pocampus CA1 exposed to 4 to 5 min of O_2 deprivation,
but no membrane potential and input resistance has been pre-
viously observed in neurons from rat cortex and hip-
pocampus CA1 exposed to 4 to 5 min of O_2 deprivation,
but not in adult rat brainstem neurons, which are more
se viously observed in neurons from rat cortex and hip-
pocampus CA1 exposed to 4 to 5 min of O_2 deprivation,
but not in adult rat brainstem neurons, which are more
sensitive to anoxia (Cummins et al., 1991; Jiang and
Had pocampus CA1 exposed to 4 to 5 min of O_2 deprive
but not in adult rat brainstem neurons, which are is
ensitive to anoxia (Cummins et al., 1991; Jiang
Haddad, 1992), suggesting that these features are
portant for neuron it not in adult rat brainstem neurons, which are more nsitive to anoxia (Cummins et al., 1991; Jiang and addad, 1992), suggesting that these features are im-
rtant for neuronal tolerance to energy depletion.
The apparent sensitive to anoxia (Cummins et al., 1991; Jiang and Haddad, 1992), suggesting that these features are im-

potential. Whole-cell voltage-clamp studies of acutely
solated human neocordical pyramidal neurons demon-
strated that anonia and cyanide rapidly decreased a
voltage-dependent, TTX-sensitive Na⁺ current and
markedly shi Haddad, 1992), suggesting that these features are im-
portant for neuronal tolerance to energy depletion.
The apparent sensitivity of $Na⁺$ channel conductance
to ATP depletion in neocortical neurons contrasts with
pr portant for neuronal tolerance to energy depletion.
The apparent sensitivity of Na^+ channel conductance
to ATP depletion in neocortical neurons contrasts with
previous findings: (a) when the peripheral nerve was
render The apparent sensitivity of $Na⁺$ channel conductance
to ATP depletion in neocortical neurons contrasts with
previous findings: (*a*) when the peripheral nerve was
rendered anoxic, the rate of impulse conduction fell
 previous findings: (a) when the peripheral nerve was rendered anoxic, the rate of impulse conduction fell markedly before there had been more than a small decrease in ATP levels (Stewart et al., 1965); (b) conduction th previous findings: (a) when the peripheral nerve was
rendered anoxic, the rate of impulse conduction fell
markedly before there had been more than a small de-
crease in ATP levels (Stewart et al., 1965); (b) conduc-
tio rendered anoxic, the rate of impulse conduction fell
markedly before there had been more than a small de-
crease in ATP levels (Stewart et al., 1965); (b) conduc-
tion through the superior cervical ganglion was blocked
by markedly before there had been more than a small decrease in ATP levels (Stewart et al., 1965); (*b*) conduction through the superior cervical ganglion was blocked by hypoxia long before high energy phosphates had been exh crease in ATP levels (Stewart et al., 1965); (b) conduction through the superior cervical ganglion was blocked
by hypoxia long before high energy phosphates had been
exhausted (Härkönen et al., 1969); and (c) brain functi by hypoxia long before high energy phosphates had been exhausted (Härkönen et al., 1969); and (c) brain function was severely depressed in severe hypoglycemia with little change in ATP levels (Tarr et al., 1962; King et al by hypoxia long before high energy phosphates had been
exhausted (Härkönen et al., 1969); and (c) brain function
was severely depressed in severe hypoglycemia with
little change in ATP levels (Tarr et al., 1962; King et al exhausted (Härkönen et al., 1969); and (c) brain function
was severely depressed in severe hypoglycemia with
little change in ATP levels (Tarr et al., 1962; King et al.,
1967). All these findings indicate that changes in i was severely depressed in severe hypoglycemia wi
little change in ATP levels (Tarr et al., 1962; King et a
1967). All these findings indicate that changes in is
conductance with reduced energy availability, and t
mechanism little change in ATP levels (Tarr et al., 1
1967). All these findings indicate that
conductance with reduced energy avail
mechanisms leading to these changes, 1
edly with the type of neuron considered
Early down-regulation 67). All these findings indicate that changes in ion
nductance with reduced energy availability, and the
echanisms leading to these changes, may vary mark
ly with the type of neuron considered.
Early down-regulation of Na

conductance with reduced energy availability, and the
mechanisms leading to these changes, may vary mark-
edly with the type of neuron considered.
Early down-regulation of Na⁺ channels during peri-
ods of limited O_2 mechanisms leading to these changes, may vary markedly with the type of neuron considered.
Early down-regulation of Na^+ channels during periods of limited O_2 supply, in order to decrease membrane excitability edly with the type of neuron considered.

Early down-regulation of Na⁺ channels during peri-

ods of limited O_2 supply, in order to decrease membrane

excitability and reduce energy expenditure, is a cellular

mechan Early down-regulation of Na⁺ channels during peri-
ods of limited O_2 supply, in order to decrease membrane
excitability and reduce energy expenditure, is a cellular
mechanism that appears particularly efficient in sp brain. excitability and reduce energy expenditure, is a cellular mechanism that appears particularly efficient in species adapted to long periods of anoxia and in the immature brain.
2. Survival strategy of the turtle brain to an

ATP-dependent K⁺ channels (Mourre et al., 1989; Xie et *tive down-regulation of Na⁺ channels*. Reptiles and es-
al., 1995) (for review, see Obrenovitch et al., 1990a). pecially some fresh-water turtles show an extraor mechanism that appears particularly efficient in species
adapted to long periods of anoxia and in the immature
brain.
2. Survival strategy of the turtle brain to anoxia: adap-
tive down-regulation of Na^+ channels. Reptil adapted to long periods of anoxia and in the immature
brain.
2. Survival strategy of the turtle brain to anoxia: adap-
tive down-regulation of Na^+ channels. Reptiles and es-
pecially some fresh-water turtles show an ext brain.

2. Survival strategy of the turtle brain to anoxia: adaptive down-regulation of Na⁺ channels. Reptiles and especially some fresh-water turtles show an extraordinary capacity to survive prolonged anoxia (Belkin, 2. Survival strategy of the turtle brain to anoxia: adaptive down-regulation of Na^+ channels. Reptiles and especially some fresh-water turtles show an extraordinary capacity to survive prolonged anoxia (Belkin, 1963). T tive down-regulation of Na^+ channels. Reptiles and especially some fresh-water turtles show an extraordinary capacity to survive prolonged anoxia (Belkin, 1963). The near-arctic turtle *Chrysenys picta* can survive anox pecially some fresh-water turtles show an extraordinary capacity to survive prolonged anoxia (Belkin, 1963). The near-arctic turtle *Chrysemys picta* can survive anoxic dives for over 6 months at low-temperature (3°C) (Ult capacity to survive prolonged anoxia (Belkin, 1963). The
near-arctic turtle *Chrysemys picta* can survive anoxic
dives for over 6 months at low-temperature (3°C)
(Ultsch, 1985) and up to 48 h at 25°C (Musacchia, 1959).
Un

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evoked field potentials are reduced, but anoxic depoly
ization does not occur, and ATP levels are preser 38

uRENJAK AND OI

evoked field potentials are reduced, but anoxic depolar-

ization does not occur, and ATP levels are preserved

(Sick et al., 1982; Lutz et al., 1984; Chih et al., 1989a). URENJAK AND

evoked field potentials are reduced, but anoxic depolar-

ization does not occur, and ATP levels are preserved

(Sick et al., 1982; Lutz et al., 1984; Chih et al., 1989a).

The large glycolytic capacity of the evoked field potentials are reduced, but anoxic depolarization does not occur, and ATP levels are preserved (Sick et al., 1982; Lutz et al., 1984; Chih et al., 1989a).
The large glycolytic capacity of the turtle brain (Kel evoked field potentials are reduced, but anoxic depolarization does not occur, and ATP levels are preserved

(Sick et al., 1982; Lutz et al., 1984; Chih et al., 1989a).

The large glycolytic capacity of the turtle brain (ization does not occur, and ATP levels are preserved
(Sick et al., 1982; Lutz et al., 1984; Chih et al., 1989a).
The large glycolytic capacity of the turtle brain (Kelly
and Storey, 1988; Suarez et al., 1989) certainly aid (Sick et al., 1982; Lutz et al., 1984; Chih et al., 1989a).
The large glycolytic capacity of the turtle brain (Kelly
and Storey, 1988; Suarez et al., 1989) certainly aids in
maintaining ATP concentration in anoxic situatio The large glycolytic capacity of the turtle brain (Kelly and Storey, 1988; Suarez et al., 1989) certainly aids in maintaining ATP concentration in anoxic situations, because anoxic depolarization occurs when glycolysis is maintaining ATP concentration in anoxic situations, be-
cause anoxic depolarization occurs when glycolysis is
blocked with iodoacetate (Sick et al., 1982; Doll et al.,
1991). However, another important mechanism contribmaintaining ATP concentration in anoxic situations, be-
cause anoxic depolarization occurs when glycolysis is
blocked with iodoacetate (Sick et al., 1982; Doll et al.,
1991). However, another important mechanism contrib-
u cause anoxic depolarization occurs when glycolysis is
blocked with iodoacetate (Sick et al., 1982; Doll et al.,
1991). However, another important mechanism contrib-
uting to the adaptation of the turtle brain to anoxia is
 1991). However, another important mechanism contributing to the adaptation of the turtle brain to anoxia is
ion channel down-regulation. *Ion channel arrest*
(Hochachka, 1986) reduces energy demand for ion
pumping, promote ion channel down-regulation. Ion channel arrest
(Hochachka, 1986) reduces energy demand for ion
pumping, promotes stabilization of transcellular ion and
electrical gradients, and prevents cytotoxic elevations of
intracell ion channel down-regulation. *Ion channel arrest* (Hochachka, 1986) reduces energy demand for ion pumping, promotes stabilization of transcellular ion and electrical gradients, and prevents cytotoxic elevations of intrace (Hochachka, 1986) reduces energy demand for ion
pumping, promotes stabilization of transcellular ion and
electrical gradients, and prevents cytotoxic elevations of
intracellular Ca^{2+} . For example, anoxia in isolated tu pumping, promotes stabilization of transcellular ion and
electrical gradients, and prevents cytotoxic elevations of
intracellular Ca²⁺. For example, anoxia in isolated tur-
tle cerebellum provoked partial depolarization electrical gradients, and prevents cytotoxic elevations intracellular Ca^{2+} . For example, anoxia in isolated the cerebellum provoked partial depolarization of P kinje cells transmembrane potentials, a shift of N (and pr intracellular Ca²⁺. For example, anoxia in isolated
tle cerebellum provoked partial depolarization of i
kinje cells transmembrane potentials, a shift of i
(and probably Ca²⁺) spike thresholds to a more depo
ized membr tle cerebellum provoked partial depolarization of Purkinje cells transmembrane potentials, a shift of Na⁺ (and probably Ca^{2+}) spike thresholds to a more depolarized membrane potential, and depression of postsynaptic kinje cells transmembrane potentials, a shift of Na⁺
(and probably Ca²⁺) spike thresholds to a more depolar-
ized membrane potential, and depression of postsynap-
tic responses (Pérez-Pinzon et al., 1992a). In additio (and probably Ca^{2+}) spike thresholds to a more depolar-
ized membrane potential, and depression of postsynap-
tic responses (Pérez-Pinzon et al., 1992a). In addition,
efflux of K^+ produced by superfusion of intact t ized membrane potential, and itic responses (Pérez-Pinzon et
efflux of K⁺ produced by supe
brain with ouabain was slower
normoxia (Chih et al., 1989b).
Although a number of mecl Express (Pérez-Pinzon et al., 1992a). In addition,
flux of K⁺ produced by superfusion of intact turtle
ain with ouabain was slower during anoxia than in
rmoxia (Chih et al., 1989b).
Although a number of mechanisms invol

efflux of K^+ produced by superfusion of intact
brain with ouabain was slower during anoxia th
normoxia (Chih et al., 1989b).
Although a number of mechanisms involving
channels, K^+ channels and inhibitory neurotra:
t brain with ouabain was slower during anoxia than in normoxia (Chih et al., 1989b).
Although a number of mechanisms involving Ca^{2+} channels, K^+ channels and inhibitory neurotransmitters also participate in ion channe normoxia (Chih et al., 1989b).

Although a number of mechanisms involving Ca^{2+}

channels, K^+ channels and inhibitory neurotransmit-

ters also participate in ion channel arrest (Bickler and

Gallego, 1993; Nilsson a Although a number of mechanisms involving Ca^{2+}
channels, K^+ channels and inhibitory neurotransmit-
ters also participate in ion channel arrest (Bickler and
Gallego, 1993; Nilsson and Lutz, 1992; Sakurai et al.,
1993 channels, K^+ channels and inhibitory neurotransmit-
ters also participate in ion channel arrest (Bickler and
Gallego, 1993; Nilsson and Lutz, 1992; Sakurai et al.,
1993), down-regulation of voltage-gated Na⁺ channels ters also participate in ion channel arrest (Bickler and Gallego, 1993; Nilsson and Lutz, 1992; Sakurai et al., 1993), down-regulation of voltage-gated Na⁺ channels appears to be a key element. The turtle brain has a mu Gallego, 1993; Nilsson and Lutz, 1992; Sakurai et al., 1993), down-regulation of voltage-gated Na⁺ channels appears to be a key element. The turtle brain has a much lower density of STX-sensitive Na⁺ channels than the 1993), down-regulation of voltage-gated Na⁺ channeappears to be a key element. The turtle brain has a mulower density of STX-sensitive Na⁺ channels than that brain, especially in the rostral areas such as tortex (fig. appears to be a key element. The turtle brain has a much
lower density of STX-sensitive Na^+ channels than the
rat brain, especially in the rostral areas such as the
cortex (fig. 6a) (Xia and Haddad, 1993). In turtle syn lower density of STX-sensitive Na⁺ channels than the rat brain, especially in the rostral areas such as the cortex (fig. 6a) (Xia and Haddad, 1993). In turtle synaptosomes, the maximum binding capacity for brevetoxines rat brain, especially in the rostral areas such as the Clevettex (fig. 6a) (Xia and Haddad, 1993). In turtle synaptosomes, the maximum binding capacity for brevetoxin in is only approximately $\frac{1}{2}$ that in rat synapto cortex (fig. 6a) (Xia and Haddad, 1993). In turtle synaptosomes, the maximum binding capacity for brevetoxin in the synaptosomes (Edwards et al., 1989). However, low Na⁺ channel density homographic cannot account for th tosomes, the maximum binding capacity for brevetoxin ing density is much higher in all rat CNS areas when compared with
is only approximately $\frac{1}{2}$ that in rat synaptosomes (Eduator) that of the turtle. SN, substantia is only approximately $\frac{1}{2}$ that in rat synaptosomes (Edwards et al., 1989). However, low Na⁺ channel density horizannot account for the 80 to 90% reduction in brain lagericannot account for the 80 to 90% reduction wards et al., 1989). However, low Na⁺ channel density in cannot account for the 80 to 90% reduction in brain lametabolism of turtle brain in anoxia (Edwards et al., m 1989; Xia and Haddad, 1993). Additional reduction of cannot account for the 80 to 90% reduction in brain laye metabolism of turtle brain in anoxia (Edwards et al., mox 1989; Xia and Haddad, 1993). Additional reduction of gate bind Na^+ currents is necessary, achieved b metabolism of turtle brain in anoxia (Edwards et al., most 1989; Xia and Haddad, 1993). Additional reduction of gate Na^+ currents is necessary, achieved by a further decline in Na⁺ channel density in anoxia (fig. 6 1989; Xia and Haddad, 1993). Additional reduction $\aleph a^+$ currents is necessary, achieved by a further decline in $\aleph a^+$ channel density in anoxia (fig. 6b) (Pérez-Pinzo et al., 1992b), to which *functional* down-regul $Na⁺$ currents is necessary, achieved by a further decline
in $Na⁺$ channel density in anoxia (fig. 6b) (Pérez-Pinzon
et al., 1992b), to which *functional* down-regulation may
be superimposed (Edwards et al., 1989 in Na⁺ channel density in anoxia (fig. 6b) (Pérez-Pinzon et al., 1992b), to which *functional* down-regulation may be superimposed (Edwards et al., 1989). How the number and conductance of Na⁺ channels are reduced dur et al., 1992b), to which *functional* down-regulation may Hable superimposed (Edwards et al., 1989). How the num-
ber and conductance of Na⁺ channels are reduced dur-
ing anoxia in turtle brains remains undefined. This be superimposed (Edwards et al., 1989). How the num-
ber and conductance of Na⁺ channels are reduced dur-
ing anoxia in turtle brains remains undefined. This pro-
cess may be mediated by second-messenger systems, via
an ber and conductance of Na⁺ channels are reduced during anoxia in turtle brains remains undefined. This process may be mediated by second-messenger systems, vian increase in cA-PK or PKC activity (See section II.C.). Aden ing anoxia in turtle brains remains undefined. This process may be mediated by second-messenger systems, via
an increase in cA-PK or PKC activity (See section II.C.).
Adenosine could also be involved in this mechanism,
bec cess may be mediated by second-messenger systems, via
an increase in cA-PK or PKC activity (See section II.C.).
Adenosine could also be involved in this mechanism,
because it was transiently released into the extracellu-
l an increase in cA-PK or PKC activity (See section II.C.). pret
Adenosine-could also be involved in this mechanism, with
because it was transiently released into the extracellu-
tion
lar space in the anoxic turtle brain (N lar space in the anoxic turtle brain (Nilsson and Lutz, 1992) and adenosine-modulated cAMP levels in CNS neurons (Stone, 1991), and specific adenosine A_1 receptor antagonists caused the isolated turtle cerebellum to de because it was transiently released into the extracellu-
lar space in the anoxic turtle brain (Nilsson and Lutz, 199
1992) and adenosine-modulated cAMP levels in CNS tato
neurons (Stone, 1991), and specific adenosine A_1 1992) and adenosine-modulated cAMP levels in CNS
neurons (Stone, 1991), and specific adenosine A_1 recep-
tor antagonists caused the isolated turtle cerebellum to
depolarize during anoxia (Pérez-Pinzón et al., 1993a).
3 92) and adenosine-modulated cAMP levels in CNS tat
 *x*urons (Stone, 1991), and specific adenosine A_1 recep-
 polarize during anoxia (Pérez-Pinzón et al., 1993a). tiss
 3. Tolerance of the immature brain to anoxia a

neurons (Stone, 1991), and specific adenosine A_1 receptor antagonists caused the isolated turtle cerebellum to depolarize during anoxia (Pérez-Pinzón et al., 1993a).
3. *Tolerance of the immature brain to anoxia and is* tor antagonists caused the isolated turtle cerebellum to
depolarize during anoxia (Pérez-Pinzón et al., 1993a).
3. Tolerance of the immature brain to anoxia and
ischemia. The fact that newborn central mammalian
neurons are depolarize during anoxia (Pérez-Pinzón et al., 1993a). tiss
3. Tolerance of the immature brain to anoxia and (Chischemia. The fact that newborn central mammalian et a
neurons are more tolerant to anoxia/ischemia than their

[³H]-brevetoxin bound (pmol g^{-1})
FIG. 6. Quantitative differences in STX binding density of major
CNS regions between turtle and rat (a) and reduction of [³H]breve-
toxin binding in turtle cerebellum by anoxia (b) toxin binding in turtle cerebellum by anoxia (b). (a) Note STX bindwan binding in our binding the tribution of an experiment of the sum density is much higher in all rat CNS areas when compared
that of the turtle. SN, substantia nigra; NTS, nucleus of the soltract; MR, medullary reticular **layer;** CBm, cerebellum-molecular have consequently that of the turtle. SN, substantia nigra; NTS, nucleus of the solitary tract; MR, medullary reticular nucleus; SD, spinal cord—dorsa horn; SV, spinal cord—ventral horn; tract; MR, medullary reticular nucleus; SD, spinal cord—don-
horn; SV, spinal cord—ventral horn; CVg, cerebellum—granu
layer; CBm, cerebellum—molecular layer. (b) Open circles, r
moxia; closed cirles, anoxia. Brevetoxin bi maco, inc., SV, spinal cord—ventral horn; CVg, cerebellum—granular
layer; CBm, cerebellum—molecular layer. (b) Open circles, nor-
moxia; closed cirles, anoxia. Brevetoxin binds to site 5 of voltage-
gated Na⁺ channels, i horn; SV, spinal cord—ventral horn; CVg, cerebellum—granular
layer; CBm, cerebellum—molecular layer. (b) Open circles, nor-
moxia; closed cirles, anoxia. Brevetoxin binds to site 5 of voltage-
gated Na⁺ channels, indepen **cated Na⁺ channels, independently of membrane potential (i.e., it** binds to active and inactive Na⁺ channels) (Baden, 1989). Values of B_{max} for $[^3H]$ brevetoxin, determined from the Scatchard plot indicated a 42% d B_{max} for [³H]brevetoxin, determined from the Scatchard plot indicated a 42% decline in Na⁺ channel density by anoxia. From Xia and Haddad (1993) (*a*) and Pérez-Pinson and coworkers (1992b) (*b*), with permission cated a 42% decline in Na⁺ channel density by anoxia. From Xia and Haddad (1993) (a) and Pérez-Pinson and coworkers (1992b) (b) , with permission from the authors, Wiley-Liss, Inc. (a subsidiary of John Wiley & Sons, I Haddad (1993) (a) and Pérez-Pinson and coworkers (1992b) (b), with permission from the authors, Wiley-Liss, Inc. (a subsidiary of John Wiley & Sons, Inc.) and the American Physiological Society.
Jiang, 1993). Infant p

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Wiley & Sons, Inc.) and the American Physiological Society.
Jiang, 1993). Infant primates, especially those that are
preterm, can maintain the viability o Wiley & Sons, Inc.) and the American Physiological Society.
Jiang, 1993). Infant primates, especially those that a
preterm, can maintain the viability of cerebral neuro
with blood flow levels that would rapidly produce inf Jiang, 1993). Infant primates, especially those that are preterm, can maintain the viability of cerebral neurons with blood flow levels that would rapidly produce infarction in the adult brain (Altman, et al., 1993; Powers Jiang, 1993). Infant primates, especially those that are
preterm, can maintain the viability of cerebral neurons
with blood flow levels that would rapidly produce infarc
tion in the adult brain (Altman, et al., 1993; Power preterm, can maintain the viability of cerebral neuro
with blood flow levels that would rapidly produce infation in the adult brain (Altman, et al., 1993; Powe
1993). In rat hippocampal slices, anoxia depresses ex
tatory p with blood flow levels that would rapidly produce infarc-
tion in the adult brain (Altman, et al., 1993; Powers,
1993). In rat hippocampal slices, anoxia depresses exci-
tatory postsynaptic potentials, causes an initial hy tion in the adult brain (Altman, et al., 1993; Powers, 1993). In rat hippocampal slices, anoxia depresses excitatory postsynaptic potentials, causes an initial hyper-
polarization and decreases membrane resistance, but
the 1993). In rat hippocampal slices, anoxia depresses excitatory postsynaptic potentials, causes an initial hyper-
polarization and decreases membrane resistance, but
the magnitude of these changes are much smaller in
tissue tatory postsynaptic potentials, causes an initial hyper-
polarization and decreases membrane resistance, but
the magnitude of these changes are much smaller in
tissue slices from immature versus mature animals
(Cherubini e polarization and decreases membrane resistance, b
the magnitude of these changes are much smaller
tissue slices from immature versus mature anima
(Cherubini et al., 1989; Krnjevic et al., 1989; Cummi
et al., 1991). For exa the magnitude of these changes are much smaller in
tissue slices from immature versus mature animals
(Cherubini et al., 1989; Krnjevic et al., 1989; Cummins
et al., 1991). For example, excitatory postsynaptic poten-
tials tissue slices from immature versus mature animals
(Cherubini et al., 1989; Krnjevic et al., 1989; Cummins
et al., 1991). For example, excitatory postsynaptic poten-
tials were depressed by 90% within 2 min of anoxia in

MODULATION OF VOLTAGE-GATED NA⁺ CHANNELS 39

MODULATION OF VOLTAGE
postanoxic recovery was much more rapid in the latter
(Cherubini et al., 1989). As with the turtle brain, several MODULATION OF VOLTAG

postanoxic recovery was much more rapid in the latter

(Cherubini et al., 1989). As with the turtle brain, several

mechanisms contribute to the remarkable anoxic toler-MODULATION OF VOLT
postanoxic recovery was much more rapid in the latte
(Cherubini et al., 1989). As with the turtle brain, severy
mechanisms contribute to the remarkable anoxic toler
ance of the immature brain (Haddad and postanoxic recovery was much more rapid in the latter (Cherubini et al., 1989). As with the turtle brain, several mechanisms contribute to the remarkable anoxic tolerance of the immature brain (Haddad and Jiang, 1993); its (Cherubini et al., 1989). As with the turtle brain, several in
mechanisms contribute to the remarkable anoxic toler-
in
ance of the immature brain (Haddad and Jiang, 1993);
its ability to use alternative substrates (e.g., mechanisms contribute to the remarkable anoxic tolencance of the immature brain (Haddad and Jiang, 1993)
its ability to use alternative substrates (e.g., lactate an
ketone bodies) as a source of energy is certainly one of
 ance of the immature brain (Haddad and Jiang, 1993); points ability to use alternative substrates (e.g., lactate and genergy between bodies) as a source of energy is certainly one of chem (Nehlig and Pereira de Vasconcelo its ability to use alternative substrates (e.g., lactate and generative bodies) as a source of energy is certainly one of clear them (Nehlig and Pereira de Vasconcelos, 1993). How-
ever, the immature brain also has much l ketone bodies) as a source of energy is certainly on
them (Nehlig and Pereira de Vasconcelos, 1993). Hever, the immature brain also has much lower ene
requirements than that of the adult. This was recer
confirmed in the hu them (Nehlig and Pereira de Vasconcelos, 1993). How-
ever, the immature brain also has much lower energy
requirements than that of the adult. This was recently (
confirmed in the human by positron emission tomogra-
phy me ever, the immature brain
requirements than that of
confirmed in the human b
phy measurements of oxy
al., 1993; Powers, 1993).
Low energy expenditure quirements than that of the adult. This was recent
nfirmed in the human by positron emission tomogry
measurements of oxygen consumption (Altman
, 1993; Powers, 1993).
Low energy expenditure of immature brain is prob
y link

confirmed in the human by positron emission tomography measurements of oxygen consumption (Altman et al., 1993; Powers, 1993).
Low energy expenditure of immature brain is probably linked to reduced electrical and synaptic phy measurements of oxygen consumption (Altman et al., 1993; Powers, 1993).
Low energy expenditure of immature brain is probably linked to reduced electrical and synaptic activity, partly because there are fewer neurons, d al., 1993; Powers, 1993).
Low energy expenditure of immature brain is proba-
bly linked to reduced electrical and synaptic activity,
partly because there are fewer neurons, dendritic pro-
cesses, and synapses in the newbor Low energy expenditure of immature brain is probably linked to reduced electrical and synaptic activity, of partly because there are fewer neurons, dendritic processes, and synapses in the newborn. Resting cellular parembr bly linked to reduced electrical and synaptic activity, or partly because there are fewer neurons, dendritic processes, and synapses in the newborn. Resting cellular prombrane potentials, DC potential and EEG activity us partly because there are fewer neurons, dendritic processes, and synapses in the newborn. Resting cellular membrane potentials, DC potential and EEG activity are all lower in the brain of neonatal rats as compared with adu cesses, and synapses in the newborn. Resting cellular
membrane potentials, DC potential and EEG activity
are all lower in the brain of neonatal rats as compared
with adults, and action potentials from cortical neurons
do n membrane potentials, DC potential and EEG activity under all lower in the brain of neonatal rats as compared exith adults, and action potentials from cortical neurons felo not appear until the postnatal day 4 (Deza and Ei are all lower in the brain of neonatal rats as compa
with adults, and action potentials from cortical neur-
do not appear until the postnatal day 4 (Deza and
delberg, 1967). There is also good correlation betw-
developmen do not appear until the postnatal day 4 (Deza and Ei-
delberg, 1967). There is also good correlation between
development of Na^+/K^+ -ATPase activity and maturado not appear until the postnatal day 4 (Deza and Ei-
delberg, 1967). There is also good correlation between les
development of Na^+/K^+ -ATPase activity and matura-
suiton of electrical activity in the developing delberg, 1967). There is also good correlation between l
development of Na⁺/K⁺-ATPase activity and matura-
tion of electrical activity in the developing brain (Abdel-
Latif et al., 1967). In common with the turtle brai tion of electrical activity in the developing brain (Abdel-
Latif et al., 1967). In common with the turtle brain, the
tolerance to anoxia of the immature brain is associated
with a remarkable delay in the development of me tion of electrical activity in the developing brain (Abdel-
Latif et al., 1967). In common with the turtle brain, the
tolerance to anoxia of the immature brain is associated
with a remarkable delay in the development of me Latif et al., 1967). In common with the turtle brain, the al., 198
tolerance to anoxia of the immature brain is associated conside
with a remarkable delay in the development of mem-section
brane failure (i.e., anoxic depo tolerance to anoxia of the immature brain is associated
with a remarkable delay in the development of mem-
brane failure (i.e., anoxic depolarization) (Hansen, 1977;
Haddad and Donnelly, 1990). This is supported by a low
r with a remarkable delay in the development of mem-
brane failure (i.e., anoxic depolarization) (Hansen, 1977;
Haddad and Donnelly, 1990). This is supported by a low
rate of K^+ efflux (Hansen, 1977; Haddad and Donnelly, brane failure (i.e., anoxic depolarization) (Hansen, 1977; laterated of K⁺ efflux (Hansen, 1977; Haddad and Donnelly, (strate of K⁺ efflux (Hansen, 1977; Haddad and Donnelly, (strate of K⁺ efflux (Hansen, 1977; Hadd Haddad and Donnelly, 1990). This is supported by a low
rate of K⁺ efflux (Hansen, 1977; Haddad and Donnelly,
1990; Trippenbach et al., 1990; Pérez-Pinzón et al.,
1993b), markedly delayed influx of Na⁺ and Cl⁻ (Jiang rate of K⁺ efflux (Hansen, 1977; Haddad and Donnelly, (s)
1990; Trippenbach et al., 1990; Pérez-Pinzón et al., si
1993b), markedly delayed influx of Na⁺ and Cl⁻ (Jiang le
et al., 1992), and a delayed increase of int 1990; Trippenbach et al., 1990; Pérez-Pinzón et al., sitestable in the to al., 1993b), markedly delayed in flux of Na⁺ and Cl⁻ (Jiang less et al., 1992), and a delayed increase of intracellular Ca²⁺ of (Friedman and 1993b), markedly delayed influx of Na⁺ and Cl⁻ (Jiang
et al., 1992), and a delayed increase of intracellular Ca²⁻
(Friedman and Haddad, 1993) in the neonatal brain of
neurons subjected to anoxia. There is also a slo et al., 1992), and a delayed increase of intracellular Ca²⁺
(Friedman and Haddad, 1993) in the neonatal brain or
neurons subjected to anoxia. There is also a slower rate
of ATP depletion during complete ischemia in the n (Friedman and Haddad, 1993) in the neonatal brain or
neurons subjected to anoxia. There is also a slower rate
of ATP depletion during complete ischemia in the new-
born brain as compared with adult (Thurston and Mc-
Douga

Down-regulation of $Na⁺$ channels may play an imporof ATP depletion during complete ischemia in the newborn brain as compared with adult (Thurston and I
Dougal, 1969).
Down-regulation of Na⁺ channels may play an imp
tant role in the tolerance of the newborn CNS. Volta
s born brain as compared with adult (Thurston and Mc-
Dougal, 1969).
Down-regulation of Na⁺ channels may play an impor-
tant role in the tolerance of the newborn CNS. Voltage-
sensitive Na⁺ currents are much smaller in Dougal, 1969).

Down-regulation of Na⁺ channels may play an important role in the tolerance of the newborn CNS. Voltage-

sensitive Na⁺ currents are much smaller in newborn

than in adult cortical neurons (Cummins et Down-regulation of Na⁺ channels may play an impor-
tant role in the tolerance of the newborn CNS. Voltage-
sensitive Na⁺ currents are much smaller in newborn
than in adult cortical neurons (Cummins et al., 1994), ma
a tant role in the tolerance of the newborn CNS. Voltage-
sensitive Na^+ currents are much smaller in newborn
than in adult cortical neurons (Cummins et al., 1994).
and Na^+ channel density is markedly lower at birth
than sensitive Na^+ currents are much smaller in newbothan in adult cortical neurons (Cummins et al., 1993) and Na^+ channel density is markedly lower at bithan in the mature brain (Xia and Haddad, 1994). Fundermore, Dargent than in adult cortical neurons (Cummins et al., 1994), matter regions (Lauritzen, 1994). Experimental studies
and Na⁺ channel density is markedly lower at birth of focal ischemia have demonstrated that recurrent SD
than and Na⁺ channel density is markedly lower at birtlem
than in the mature brain (Xia and Haddad, 1994). Fur
thermore, Dargent and Couraud (1990) have demon
strated, in fetal brain neurons developing in vitro,
rapid down-r than in the mature brain (Xia and Haddad, 1994). Fur-
thermore, Dargent and Couraud (1990) have demon-
strated, in fetal brain neurons developing in vitro, a
rapid down-regulation of Na⁺ channels whenever Na⁺-
influx thermore, Dargent and Couraud (1990) have demon-
strated, in fetal brain neurons developing in vitro, a therepid down-regulation of Na⁺ channels whenever Na⁺-
influx was increased. Application of Na⁺ channel acti-
v strated, in fetal brain neurons developing in vitro, a
rapid down-regulation of Na⁺ channels whenever Na⁺-
influx was increased. Application of Na⁺ channel acti-
vators (scorpion α toxin, BTX, and veratridine) pr rapid down-regulation of Na⁺ channels whenever Na⁺-
influx was increased. Application of Na⁺ channel acti-
vators (scorpion α toxin, BTX, and veratridine) produced 19
a partial but rapid ($t_{1/2}$, 15 min) disapp influx was increased. Application of Na⁺ channel acti-
vators (scorpion α toxin, BTX, and veratridine) produced 1995
a partial but rapid ($t_{1/2}$, 15 min) disappearance of sur-
to ne
face Na⁺ channels as measured vators (scorpion α toxin, BTX, and veratridine) produced
a partial but rapid ($t_{1/2}$, 15 min) disappearance of sur-
face Na⁺ channels as measured by a decrease in the
specific binding of $[^{3}H]STX$ or ¹²⁵I-labele a partial but rapid $(t_{1/2}, 15 \text{ min})$ disappearance of sur-
face Na⁺ channels as measured by a decrease in the Har
specific binding of $[^{3}H]STX$ or ^{125}I -labeled scorpion β form
toxin, and a decrease in specific face Na⁺ channels as measured by a decrease in the specific binding of $[^{3}H]STX$ or ^{125}I -labeled scorpion β toxin, and a decrease in specific ^{22}Na uptake. The induced disappearance of Na⁺ channels was aboli specific binding of $[^{3}H]STX$ or ^{125}I -labeled scorpion β for toxin, and a decrease in specific ^{22}Na uptake. The in-
duced disappearance of Na⁺ channels was abolished by size TTX and dependent on external Na⁺ toxin, and a decrease in specific ²²Na uptake. The induced disappearance of Na⁺ channels was abolished by TTX and dependent on external Na⁺ concentration. Amphotericin B, a Na⁺ ionophore, and monensin were able to duced disappearance of Na^+ channels was abolished by
TTX and dependent on external Na^+ concentration. Am-
photericin B, a Na^+ ionophore, and monensin were able
to mimic the effect of the Na^+ channel activators,
wh

postanoxic recovery was much more rapid in the latter teresting aspect of this phenomenon is its apparent spec-
(Cherubini et al., 1989). As with the turtle brain, several ificity to neurons, inasmuch as it has not been o $\begin{array}{ll} \texttt{-GATED NA}^+ \texttt{CHANNELS} & \texttt{33} \ \texttt{teresting aspect of this phenomenon is its apparent spec} \ \texttt{ificity to neurons, inasmuch as it has not been observe} \end{array}$ $\frac{1}{39}$
teresting aspect of this phenomenon is its apparent spec-
ificity to neurons, inasmuch as it has not been observed
in astrocytes or skeletal muscle cells. Here also, as pro- $-$ GATED NA⁺ CHANNELS 39
teresting aspect of this phenomenon is its apparent spec-
ificity to neurons, inasmuch as it has not been observed
in astrocytes or skeletal muscle cells. Here also, as pro-
posed by Dargent teresting aspect of this phenomenon is its apparent
ificity to neurons, inasmuch as it has not been obs
in astrocytes or skeletal muscle cells. Here also, a
posed by Dargent and Couraud (1990), second-me
ger systems may be teresting aspect of this phenomenon is its apparent specificity to neurons, inasmuch as it has not been observed
in astrocytes or skeletal muscle cells. Here also, as pro-
posed by Dargent and Couraud (1990), second-messen incity to neurons, inasmuch as it has not been observe
in astrocytes or skeletal muscle cells. Here also, as pre
posed by Dargent and Couraud (1990), second-messer
ger systems may be involved in the mechanism of Na
channel in astrocytes or skeletal muscle cells. Here also, as p
posed by Dargent and Couraud (1990), second-messe
ger systems may be involved in the mechanism of N
channel down-regulation, especially because $Na⁺$ channel act posed by Dargent and Couraud (1990), second-messen-
ger systems may be involved in the mechanism of $Na⁺$
channel down-regulation, especially because $Na⁺$ chan-
nel activators stimulated phosphatidylinositol diph channel down-regulation, especially because $Na⁺$ channel activators stimulated phosphatidylinositol diphosphate breakdown in a brain synaptosomal preparation (Gusovsky et al., 1986).
D. Potential Benefit from Postisc nel activators stimulated phosphatidylinos
phate breakdown in a brain synaptosomal
(Gusovsky et al., 1986).
D. Potential Benefit from Postischemic Dou
Modulation of Na⁺ Channels phate breakdown in a brain sy

(Gusovsky et al., 1986).
 D. Potential Benefit from Postis
 Modulation of Na⁺ Channels

So far. our analysis has focu

usovsky et al., 1986).
 Potential Benefit from Postischemic Down-
 So far, our analysis has focused on down-modulation
 $Na⁺$ channels as a neuroprotective intervention dur-D. Potential Benefit from Postischemic Down-
Modulation of Na⁺ Channels
So far, our analysis has focused on down-modulation
of Na⁺ channels as a neuroprotective intervention *du*
ing or preceding ischemia. As such, it *ing* or *preceding* in *prometage is considered to the set of Na⁺ Channels*

So far, our analysis has focused on down-modulation

of Na⁺ channels as a neuroprotective intervention *dur-*

ing or *preceding* ischemia. so far, our analysis has focused on down-modulation
of Na⁺ channels as a neuroprotective intervention *during* or *preceding* ischemia. As such, it is relevant to
patients at high risk of cerebral ischemia (e.g., those
 So far, our analysis has focused on down-modula
of Na^+ channels as a neuroprotective intervention α
ing or preceding ischemia. As such, it is relevan
patients at high risk of cerebral ischemia (e.g., th
undergoing ca of $Na⁺$ channels as a neuroprotective intervention $dur-$
ing or preceding ischemia. As such, it is relevant to
patients at high risk of cerebral ischemia (e.g., those
undergoing cardiopulmonary bypass, carotid endarte *ing* or *preceding* ischemia. As such, it is relevant to patients at high risk of cerebral ischemia (e.g., those undergoing cardiopulmonary bypass, carotid endarterectomy or aneurysm surgery), and represents both a ferti patients at high risk of cerebral ischemia (e.g., those undergoing cardiopulmonary bypass, carotid endarter-
ectomy or aneurysm surgery), and represents both a
fertile area for trials and a potentially major clinical
appli undergoing cardiopulmonary bypass, carotid endarter-
ectomy or aneurysm surgery), and represents both a
fertile area for trials and a potentially major clinical
application (Fisher et al., 1994). In contrast, it appears
le ectomy or aneurysm surgery), and represents both a fertile area for trials and a potentially major clinical application (Fisher et al., 1994). In contrast, it appears less relevant to stroke therapy because most patients s fertile area for trials and a potentially major clinical
application (Fisher et al., 1994). In contrast, it appears
less relevant to stroke therapy because most patients
suffering from this condition are admitted to a hosp application (Fisher et al., 1994). In contrast, it appears
less relevant to stroke therapy because most patients
suffering from this condition are admitted to a hospital
several hours after the onset of symptoms (Hantson e less relevant to stroke therapy because most patients
suffering from this condition are admitted to a hospital
several hours after the onset of symptoms (Hantson et
al., 1994; Panayiotou et al., 1994). However, theoretical suffering from this condition are admitted to a hospital
several hours after the onset of symptoms (Hantson et
al., 1994; Panayiotou et al., 1994). However, theoretical
considerations, as well as experimental data (see als several hours after the onset of symptoms (Hantson et al., 1994; Panayiotou et al., 1994). However, theoretical considerations, as well as experimental data (see also sections IV. and V.), strongly suggest that down-modula al., 1994; Panayiotou et al., 1994). However, theoretical considerations, as well as experimental data (see also sections IV. and V.), strongly suggest that down-modulation of Na⁺ channels remains beneficial even when it considerations, as well as experimental data (see also
sections IV. and V.), strongly suggest that down-modu-
lation of Na⁺ channels remains beneficial even when it
is delayed, i.e., after occlusion of a major cerebral a sections IV. and V.), strongly suggest that down-modulation of Na⁺ channels remains beneficial even when it is delayed, i.e., after occlusion of a major cerebral artery (stroke) or following transient global ischemia. In lation of Na⁺ channels remains beneficial even when it
is delayed, i.e., after occlusion of a major cerebral artery
(stroke) or following transient global ischemia. In these
situations, the basis for protection may stil (stroke) or following transient global ischemia. In these situations, the basis for protection may still be linked, at least partly, to reduced energy demand and preservation of ionic gradients. However, the rationale for (stroke) or following transient global ischemia. In the situations, the basis for protection may still be linked least partly, to reduced energy demand and preserva of ionic gradients. However, the rationale for Na^+ situations, the basis for protection may still be linked, a
least partly, to reduced energy demand and preservatio
of ionic gradients. However, the rationale for Na⁺ chan
nel down-modulation differs between delayed inter least partly, to reduced energy demand and preservation
of ionic gradients. However, the rationale for $Na⁺$ chan-
nel down-modulation differs between delayed interven-
tion after stroke, and postischemic treatment af mechanisms. *1 down-modulation differs between delayed interve*
n after stroke, and postischemic treatment after tra
nt ischemia. We focus here on three possib
chanisms.
1. Focal ischemia: Na^+ *channel modulation and recu*

rention after stroke, and postischemic treatment after transient ischemia. We focus here on three possible mechanisms.
 1. Focal ischemia: Na^+ *channel modulation and recurrent spreading depression*. SD is a transie sient ischemia. We focus here on three possible mechanisms.

1. Focal ischemia: Na^+ channel modulation and recurrent spreading depression. SD is a transient suppression

of electrical activity with membrane depolarizati mechanisms.

1. Focal ischemia: Na^+ channel modulation and recurrent spreading depression. SD is a transient suppression

of electrical activity with membrane depolarization,

propagating across the cerebral cortex or o 1. Focal ischemia: Na^+ channel modulation and recurrent spreading depression. SD is a transient suppression of electrical activity with membrane depolarization, propagating across the cerebral cortex or other grey matte rent spreading depression. SD is a transient suppression
of electrical activity with membrane depolarization,
propagating across the cerebral cortex or other grey
matter regions (Lauritzen, 1994). Experimental studies
of of electrical activity with membrane depolarization,
propagating across the cerebral cortex or other grey
matter regions (Lauritzen, 1994). Experimental studies
of focal ischemia have demonstrated that recurrent SD
propaga propagating across the cerebral cortex or other grey
matter regions (Lauritzen, 1994). Experimental studies
of focal ischemia have demonstrated that recurrent SD
propagates from the ischemic core to adjacent regions,
contr matter regions (Lauritzen, 1994). Experimental stude of focal ischemia have demonstrated that recurrent is propagates from the ischemic core to adjacent region contributing to the development of tissue damage, a that selec of focal ischemia have demonstrated that recurrent SD
propagates from the ischemic core to adjacent regions,
contributing to the development of tissue damage, and
that selective protection of the penumbra by NMDA-
receptor propagates from the ischemic core to adjacent regions
contributing to the development of tissue damage, an
that selective protection of the penumbra by NMDA
receptor antagonists may well be linked to inhibition of
SD (for contributing to the development of tissue damage, and
that selective protection of the penumbra by NMDA-
receptor antagonists may well be linked to inhibition of
SD (for review, see Hossmann, 1994a, b; Obrenovitch,
1995a). that selective protection of the penumbra by NMDA-
receptor antagonists may well be linked to inhibition of
SD (for review, see Hossmann, 1994a, b; Obrenovitch,
1995a). Although repeated SD may be a sublethal stress
to neu receptor antagonists may well be linked to inhibition of SD (for review, see Hossmann, 1994a, b; Obrenovitch, 1995a). Although repeated SD may be a sublethal stress to neurons in otherwise normal tissue (Nedergaard and Han SD (for review, see Hossmann, 1994a, b; Obrenovitch, 1995a). Although repeated SD may be a sublethal stress to neurons in otherwise normal tissue (Nedergaard and Hansen, 1988), sensitive markers show that it remains a form 1995a). Although repeated SD may be a sublethal stress
to neurons in otherwise normal tissue (Nedergaard and
Hansen, 1988), sensitive markers show that it remains a
formidable challenge, and in stroke models, the fre-
quen to neurons in otherwise normal tissue (Nedergaard and Hansen, 1988), sensitive markers show that it remains a formidable challenge, and in stroke models, the frequency of SD occurrence correlated well with infarct size, wh Hansen, 1988), sensitive markers show that it remains a formidable challenge, and in stroke models, the frequency of SD occurrence correlated well with infarct size, whether the latter was modulated by dizocilpine (MK-801) formidable challenge, and in stroke models, the frequency of SD occurrence correlated well with infarct size, whether the latter was modulated by dizocilpine (MK-801) (Iijima et al., 1992), hypothermia (Chen et al., 1993b) quency of SD occurrence correlated well with infarct
size, whether the latter was modulated by dizocilpine
(MK-801) (Iijima et al., 1992), hypothermia (Chen et al.,
1993b), AMPA-receptor antagonist (Mies et al., 1994) or
h size, whether the latter was modulated by dizocilpine
(MK-801) (Iijima et al., 1992), hypothermia (Chen et al.,
1993b), AMPA-receptor antagonist (Mies et al., 1994) or
hyperglycaemia (Nedergaard and Astrup, 1986). It is
pr

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cause it produces marked disruption in ionic homeo
sis, increased energy demand, acidosis and neurotra URENJA
Cause it produces marked disruption in ionic home
sis, increased energy demand, acidosis and neurotrantiter efflux in regions where residual blood flow URENJAK AND OBRI

cause it produces marked disruption in ionic homeosta-

sis, increased energy demand, acidosis and neurotrans-

mitter efflux in regions where residual blood flow can

only sustain basal ionic homeostasis cause it produces marked disruption in ionic homeostasis, increased energy demand, acidosis and neurotranimitter efflux in regions where residual blood flow ca only sustain basal ionic homeostasis (Obrenovitch 1995a). 1995a). Eq. increased energy demand, acidosis and neurotran
itter efflux in regions where residual blood flow ca
ly sustain basal ionic homeostasis (Obrenovite
95a).
Within this context, down-modulation of Na⁺ chan
Is may reduc

mitter efflux in regions where residual blood flow
only sustain basal ionic homeostasis (Obrenovi
1995a).
Within this context, down-modulation of Na⁺ ch
nels may reduce energy demand, improve ion homeo
sis, and thus enh only sustain basal ionic homeostasis (Obrenovitch, info
1995a). ory
Within this context, down-modulation of Na⁺ chan-
nels may reduce energy demand, improve ion homeosta-
prot
sis, and thus enhance the resistance of bra 1995a). ory
Within this context, down-modulation of Na⁺ chan-
nels may reduce energy demand, improve ion homeosta-
prot
sis, and thus enhance the resistance of brain tissue to anta
SD. In addition, inhibition of Na⁺ c Within this context, down-modulation of Na⁺ chan-
nels may reduce energy demand, improve ion homeosta-
sis, and thus enhance the resistance of brain tissue to
SD. In addition, inhibition of Na⁺ currents inhibit SD to
 nels may reduce energy demand, improve ion homeostasis, and thus enhance the resistance of brain tissue to SD. In addition, inhibition of Na⁺ currents inhibit SD to some extent (Marrannes et al., 1993) (see also the sec sis, and thus enhance the resistance of brain tissue to an SD. In addition, inhibition of Na⁺ currents inhibit SD to al.
some extent (Marrannes et al., 1993) (see also the sec-
tions on flunarizine and KB-2796 in sectio some extent (Marrannes et al., 1993) (see also the sections on flunarizine and KB-2796 in section V.A.). Tetrodotoxin (> 0.1 μ M) had no effect on SD elicited in the chicken retina (Sheardown, 1993). In contrast, local tions on flunarizine and KB-2796 in section V.A.). Te-
trodotoxin (> 0.1 μ M) had no effect on SD elicited in the
chicken retina (Sheardown, 1993). In contrast, local ap-
plication of this toxin to the rat cerebellum in trodotoxin ($> 0.1 \mu$ M) had no effect on SD elicited in the chicken retina (Sheardown, 1993). In contrast, local application of this toxin to the rat cerebellum inhibited SD elicitation by electrical stimulation, but not chicken retina (Sheardown, 1993). In contrast, local application of this toxin to the rat cerebellum inhibited SD
elicitation by electrical stimulation, but not that elicited
by KCl application or SD propagation (Bures et plication of this toxin to the rat cerebellum inhibited SD
elicitation by electrical stimulation, but not that elicited
by KCl application or SD propagation (Bures et al., 1974; of
Tobiasz and Nicholson, 1982). Two local a elicitation by electrical stimulation, but not that elicited
by KCl application or SD propagation (Bures et al., 1974;
Tobiasz and Nicholson, 1982). Two local anaesthetics
(benzocaine and lidocaine) dose-dependently reduce by KCl application or SD propagation (Bures et al., 1974;
Tobiasz and Nicholson, 1982). Two local anaesthetics
(benzocaine and lidocaine) dose-dependently reduced
the rate of propagation, amplitude, and duration of ret-
i Tobiasz and Nicholson, 1982). Two local anaesthetic (benzocaine and lidocaine) dose-dependently reduce
the rate of propagation, amplitude, and duration of re
inal SD elicited by mechanical stimulation (Chebabo \cdot al., 19 (benzocaine and lidocaine) dose-dependently reduced hilder the rate of propagation, amplitude, and duration of retinal SD elicited by mechanical stimulation (Chebabo et the al., 1993). Phenytoin (an anticonvulsant with $\$ the rate of propagation, amplitude, and duration of
inal SD elicited by mechanical stimulation (Chebabal, 1993). Phenytoin (an anticonvulsant with $Na⁺$ ch
nel blocking properties; see section IV.D.), applied to
retin inal SD elicited by mechanical stimulation (Chebabo et the al., 1993). Phenytoin (an anticonvulsant with Na^+ channel blocking properties; see section IV.D.), applied to the anticina at a concentration range comparable t al., 1993). Phenytoin (an anticonvulsant with Na⁺ channel blocking properties; see section IV.D.), applied to the retina at a concentration range comparable to therapeutic plasma levels of epileptic patients, increased nel blocking properties; see section IV.D.), applied to the
retina at a concentration range comparable to therapetic plasma levels of epileptic patients, increased the
threshold concentration of KCl to initiate SD, decreas retina at a concentration range comparable to therapeutic plasma levels of epileptic patients, increased the threshold concentration of KCl to initiate SD, decreased the velocity of its propagation, and shortened the durat 1991).

the velocity of its propagation, and shortened the duration of the depolarization wave (Chebabo and Do Carmo, 1991).
1991).
Ischemia-induced SD occurs in cats (Strong et al., 1983) and primates (Branston et al., 1977) and tion of the depolarization wave (Chebabo and Do Carmo, me
1991). pe
Ischemia-induced SD occurs in cats (Strong et al., lin
1983) and primates (Branston et al., 1977) and is not
exclusive to the cortex, because it was recor 1991).

Ischemia-induced SD occurs in cats (Strong et al., line

1983) and primates (Branston et al., 1977) and is not

ylexclusive to the cortex, because it was recorded in the wite

striatum of rats subjected to middle Ischemia-induced SD occurs in cats (Strong et al. 1983) and primates (Branston et al., 1977) and is no exclusive to the cortex, because it was recorded in the striatum of rats subjected to middle cerebral arter; (MCA) occl 1983) and primates (Branston et al., 1977) and is not ylamm exclusive to the cortex, because it was recorded in the which striatum of rats subjected to middle cerebral artery The fa (MCA) occlusion (Wahl et al., 1994) and exclusive to the cortex, because it was recorded in the whistriatum of rats subjected to middle cerebral artery The (MCA) occlusion (Wahl et al., 1994) and in hippocampal tire slices (Jing et al., 1993). However, whether o striatum of rats subjected to middle cerebral artery Theorem (MCA) occlusion. (Wahl et al., 1994) and in hippocampal tirslices (Jing et al., 1993). However, whether or not SD miss occurs in man, especially in the neocortex (MCA) occlusion (Wahl et al., 1994) and in hippocampal tislices (Jing et al., 1993). However, whether or not SD m
occurs in man, especially in the neocortex, remains an line
unanswered question. All attempts to elicit SD i slices (Jing et al., 1993). However, whether or not SD
occurs in man, especially in the neocortex, remains an
unanswered question. All attempts to elicit SD in the
human cortex so far have failed, even in the absence of
ge occurs in man, especially in the neocortex, remains an unanswered question. All attempts to elicit SD in the human cortex so far have failed, even in the absence of general anaesthesia (McLachlan and Girvin, 1994). However unanswered question. All attempts to elicit SD in
human cortex so far have failed, even in the absen
general anaesthesia (McLachlan and Girvin, 19
However, this paradox may soon be resolved by re
advances in noninvasive te general anaesthesia (McLachlan and Girvin, 1994).
However, this paradox may soon be resolved by recent
advances in noninvasive techniques such as magnetoen-
cephalography and magnetic resonance imaging.
 $2. Na^+$ channel mo However, this paradox may soon be resolved by recent However, this paradox may soon be resolved by recent
advances in noninvasive techniques such as magnetoen-
cephalography and magnetic resonance imaging.
 $2. Na⁺ channel modulation and postischemic enhance-
ment of synaptic efficiency. Transient cerebral ischemia
induces delayed neuronal loss in the brain, particularly$

advances in noninvasive techniques such as magnetoen-
cephalography and magnetic resonance imaging.
2. $Na⁺ channel modulation and postischematic enhancement of synaptic efficiency. Transient cerebral ischemical
induces delayed neuronal loss in the brain, particularly
in selectively vulnerable neurons of the hippocampus$ cephalography and magnetic resonance imaging.
 $2. Na⁺ channel modulation and postischematic enhancement of synaptic efficiency. Transient cerebral ischemical in duces delayed neuronal loss in the brain, particularly in selectively vulnerable neurons of the hippocampus (Kirino, 1982; Pulsinelli et al., 1982; Petito et al., 1987;$ 2. $Na⁺ channel modulation and postischemic enhance-
ment of synaptic efficiency. Transient cerebral ischemia
induces delayed neuronal loss in the brain, particularly
in selectively vulnerable neurons of the hippocampus
(Kirino, 1982; Pulsinelli et al., 1982; Petito et al., 1987;
Hisu and Buzsáki, 1993). A number of mechanisms based$ ment of synaptic efficiency. Transient cerebral ischemia et
induces delayed neuronal loss in the brain, particularly Je
in selectively vulnerable neurons of the hippocampus
(Kirino, 1982; Pulsinelli et al., 1982; Petito e induces delayed neuronal loss in the brain, particularly Jer
in selectively vulnerable neurons of the hippocampus 1
(Kirino, 1982; Pulsinelli et al., 1982; Petito et al., 1987; neuron
Hsu and Buzsáki, 1993). A number of m in selectively vulnerable neurons of the hippocampus Bot (Kirino, 1982; Pulsinelli et al., 1982; Petito et al., 1987; neuro Hsu and Buzsáki, 1993). A number of mechanisms based aptic upon the accumulation of intracellular (Kirino, 1982; Pulsinelli et al., 1982; Petito et al., 1987; no
Hsu and Buzsáki, 1993). A number of mechanisms based appon the accumulation of intracellular Ca^{2+} have been approposed to explain postischemic neuronal de Hsu and Buzsáki, 1993). A number of mechanisms based appon the accumulation of intracellular Ca^{2+} have been and proposed to explain postischemic neuronal death (Siesjö 19 and Bengtsson, 1989; Lee et al., 1991), and del proposed to explain postischemic neuronal death (Siesjö and Bengtsson, 1989; Lee et al., 1991), and delayed excessive release of excitatory amino acids is a widely quoted triggering event (Szatkowski and Attwell, 1994; see and Bengtsson, 1989; Lee et al., 1991), and delayed excessive release of excitatory amino acids is a widely quoted triggering event (Szatkowski and Attwell, 1994; see, however, Obrenovitch and Richards, 1995). More recentl d Bengtsson, 1989; Lee et al., 1991), and delayed
cessive release of excitatory amino acids is a widely
loted triggering event (Szatkowski and Attwell, 1994;
e, however, Obrenovitch and Richards, 1995).
More recently, it h excessive release of excitatory amino acids is a widely
quoted triggering event (Szatkowski and Attwell, 1994
see, however, Obrenovitch and Richards, 1995).
More recently, it has been suggested that synchronous
and long-la

quoted triggering event (Szatkowski and Attwell, 19
see, however, Obrenovitch and Richards, 1995).
More recently, it has been suggested that synchron
and long-lasting enhancement of the efficiency of e
tatory synapses may see, however, Obrenovitch and Richards, 1995).
More recently, it has been suggested that synchrono
and long-lasting enhancement of the efficiency of ex
tatory synapses may contribute to delayed ischem
induced damage to neu

chicken retina (Sheardown, 1993). In contrast, local ap-
plication of this toxin to the rat cerebellum inhibited SD uptake evoked by electrical stimulation was also en-
elicitation by electrical stimulation, but not that threshold concentration of KCl to initiate SD, decreased to a variety of agents, including Ca^{2+} (Turner et al., the velocity of its propagation, and shortened the dura- 1982), arachidonic acid (Williams et al., 1989), exprese over the setter of the phenomenon may be a
vitch and Richards, 1995). This phenomenon may be a
pathological extension of long-term potentiation (LTP) pathological extension. This phenomenon may be a
pathological extension of long-term potentiation (LTP)
or other forms of synaptic potentiation, which underlies BRENOVITCH
vitch and Richards, 1995). This phenomenon may be a
pathological extension of long-term potentiation (LTP)
or other forms of synaptic potentiation, which underlies
information storage in the brain, i.e., learnin vitch and Richards, 1995). This phenomenon may be
pathological extension of long-term potentiation (LTI
or other forms of synaptic potentiation, which underlit
information storage in the brain, i.e., learning and mem
ory (vitch and Richards, 1995). This phenomenon may be a
pathological extension of long-term potentiation (LTP)
or other forms of synaptic potentiation, which underlies
information storage in the brain, i.e., learning and mem-
 pathological extension of long-term potentiation (LTP)
or other forms of synaptic potentiation, which underlies
information storage in the brain, i.e., learning and mem-
ory (Bliss and Collingridge, 1993). Ischemia-induced or other forms of synaptic potentiation, which underlies
information storage in the brain, i.e., learning and mem-
ory (Bliss and Collingridge, 1993). Ischemia-induced en-
hancement of synaptic efficiency is compatible wit information storage in the brain, i.e., learning and memory (Bliss and Collingridge, 1993). Ischemia-induced enhancement of synaptic efficiency is compatible with the protective action demonstrated by glutamate-receptor an ory (Bliss and Collingridge, 1993). Ischemia-induced en
hancement of synaptic efficiency is compatible with the
protective action demonstrated by glutamate-receptor
antagonists administered after the insult (Sheardown e
al hancement of synaptic efficiency is compatible with the protective action demonstrated by glutamate-receptor antagonists administered after the insult (Sheardown et al., 1990; Swan and Meldrum, 1990; Nellgård and Wieloch, protective action demonstrated by glutamate-recept antagonists administered after the insult (Sheardown al., 1990; Swan and Meldrum, 1990; Nellgård and W
loch, 1992) and is supported by several key findings:
exposure of ra antagonists administered after the insult (Shear
al., 1990; Swan and Meldrum, 1990; Nellgård a
loch, 1992) and is supported by several key find
exposure of rat hippocampal slices to a short
aglycemic episode potentiated NM al., 1990; Swan and Meldrum, 1990; Nellgård and Wieloch, 1992) and is supported by several key findings: (*a*) exposure of rat hippocampal slices to a short anoxically
ceme of rat hippocampal slices to a short anoxically
c exposure of rat hippocampal slices to a short anoxic-
aglycemic episode potentiated NMDA-receptor-medi-
ated excitatory responses (Crépel et al., 1993); (b) Ca²⁺
uptake evoked by electrical stimulation was also en-
hanc aglycemic episode potentiated NMDA-receptor-mediaglycemic episode potentiated NMDA-receptor-mediated excitatory responses (Crépel et al., 1993); $(b) Ca^{2+}$ uptake evoked by electrical stimulation was also enhanced postischemia (Andiné et al., 1988); (c) the degree of mo ated excitatory responses (Crépel et al., 1993); (b) Ca^{2+}
uptake evoked by electrical stimulation was also en-
hanced postischemia (Andiné et al., 1988); (c) the degree
of mossy fibre innervation (major excitatory inpu hanced postischemia (Andiné et al., 1988); (c) the degree
of mossy fibre innervation (major excitatory input) cor-
related with ischemic vulnerability in the hippocampus
hilus neurons and CA3 interneurons (Hsu and Buzsáki hanced postischemia (Andiné et al., 1988); (c) the degree
of mossy fibre innervation (major excitatory input) cor-
related with ischemic vulnerability in the hippocampus
hilus neurons and CA3 interneurons (Hsu and Buzsáki, of mossy fibre innervation (major excitatory input) correlated with ischemic vulnerability in the hippocampus
hilus neurons and CA3 interneurons (Hsu and Buzsáki, 1993); (*d*) glucose utilization is increased for longer in related with ischemic vulnerability in the hippocampus
hilus neurons and CA3 interneurons (Hsu and Buzsáki,
1993); (*d*) glucose utilization is increased for longer in
the hippocampus early postischemia (Levy and Duffy,
19 hilus neurons and CA3 interneurons (Hsu and Buzsáki, 1993); (*d*) glucose utilization is increased for longer in the hippocampus early postischemia (Levy and Duffy, 1977; Diemer and Siemkowicz, 1980; Choki et al., 1983) an 1993); (*d*) glucose utilization is increased for longer in the hippocampus early postischemia (Levy and Duffy, 1977; Diemer and Siemkowicz, 1980; Choki et al., 1983) and postischemic hypermetabolism in the CA1-subfield i the hippocampus early postischemia (Levy and Duffy, 1977; Diemer and Siemkowicz, 1980; Choki et al., 1983) and postischemic hypermetabolism in the CA1-subfield is dependent on its excitatory input (Jørgensen, et al., 1990) 1977; Diemer and Siemkowicz, 1980; Choki et al., 1983)
and postischemic hypermetabolism in the CA1-subfield
is dependent on its excitatory input (Jørgensen, et al.,
1990); and (e) LTP can be induced by transient exposure
 and postischemic hypermetabolism in the CA1-subfield
is dependent on its excitatory input (Jørgensen, et al.,
1990); and (e) LTP can be induced by transient exposure
to a variety of agents, including Ca^{2+} (Turner et al is dependent on its excitatory input (Jørgensen, et 1990); and (e) LTP can be induced by transient expote a variety of agents, including Ca^{2+} (Turner et 1982), arachidonic acid (Williams et al., 1989), metabotropic glu 1990); and (e) LTP can be induced by transient exposure
to a variety of agents, including Ca^{2+} (Turner et al.,
1982), arachidonic acid (Williams et al., 1989), the
metabotropic glutamate receptor agonist aminocyclo-
pe to a variety of agents, including Ca^{2+} (Turner et 1982), arachidonic acid (Williams et al., 1989), metabotropic glutamate receptor agonist aminocy pentane-1S,3R-dicarboxylate (Bortolotto and lingridge, 1993), and the K 1982), arachidonic acid (Williams et al., 1989), the
metabotropic glutamate receptor agonist aminocyclo-
pentane-1S,3R-dicarboxylate (Bortolotto and Col-
lingridge, 1993), and the K⁺ channel blocker, tetraeth-
ylammoniu metabotropic glutamate receptor agonist aminocyclo-
pentane-1S,3R-dicarboxylate (Bortolotto and Col-
lingridge, 1993), and the K⁺ channel blocker, tetraeth-
ylammonium (Anikszteijn and Ben-Ari, 1991), all of
which are in pentane-1S,3R-dicarboxylate (Bortolotto and Collingridge, 1993), and the K⁺ channel blocker, tetraeth-
ylammonium (Anikszteijn and Ben-Ari, 1991), all of
which are involved or mimic ischemic-induced events.
The fact that lingridge, 1993), and the K⁺ channel blocker, tetraeth-
ylammonium (Anikszteijn and Ben-Ari, 1991), all of
which are involved or mimic ischemic-induced events.
The fact that the cytopathology of excitotoxicity is en-
tir ylammonium (Anikszteijn and Ben-Ari, 1991), all of
which are involved or mimic ischemic-induced events.
The fact that the cytopathology of excitotoxicity is en-
tirely postsynaptic, sparing axons and presynaptic ter-
minal which are involved or mimic ischemic-induced events.
The fact that the cytopathology of excitotoxicity is en-
tirely postsynaptic, sparing axons and presynaptic ter-
minals (Simon et al., 1984; Kirino et al., 1990), is als The fact that the cytopathology of excitotoxicity is entirely postsynaptic, sparing axons and presynaptic terminals (Simon et al., 1984; Kirino et al., 1990), is also in line with this hypothesis, because the induction mec tirely postsynaptic, sparing axons and presynaptic terminals (Simon et al., 1984; Kirino et al., 1990), is also in line with this hypothesis, because the induction mechanisms for long-term and short-term potentiation resid minals (Simon et al., 1984; Kirino et al., 1990), is also i
line with this hypothesis, because the induction mecha
nisms for long-term and short-term potentiation residat
least in part, in the postsynaptic membrane (Zi
ber line with this hypothesis, because the induction m
nisms for long-term and short-term potentiation re
at least in part, in the postsynaptic membrane
berter, et al., 1990; Cormier et al., 1993). These a
ments, however, conf nisms for long-term and short-term potentiation reside, at least in part, in the postsynaptic membrane (Zilberter, et al., 1990; Cormier et al., 1993). These arguments, however, conflict with a number of electrophysiologic at least in part, in the postsynaptic membrane (Zil-
berter, et al., 1990; Cormier et al., 1993). These argu-
ments, however, conflict with a number of electrophysi-
ological studies that failed to demonstrate neuronal
hyp berter, et al., 1990; Cormier et al., 1993). These arguments, however, conflict with a number of electrophysiological studies that failed to demonstrate neuronal hyperexcitability in the hippocampus before CA1 cell loss (C ments, however, conflict with a number of electrophysiological studies that failed to demonstrate neuronal
hyperexcitability in the hippocampus before CA1 cell
loss (Chang et al., 1989a, b; Buzsáki et al., 1989; Urban
et a ological studies that
hyperexcitability in t
loss (Chang et al., 198
et al., 1989; Mitani et
Jensen et al., 1991).
Both of these hypotl perexcitability in the hippocampus before CA1 cell
ss (Chang et al., 1989a, b; Buzsáki et al., 1989; Urban
al., 1989; Mitani et al., 1989, 1990a; Imon et al., 1991;
nsen et al., 1991).
Both of these hypotheses, delayed rel

loss (Chang et al., 1989a, b; Buzsáki et al., 1989; Urban
et al., 1989; Mitani et al., 1989, 1990a; Imon et al., 1991;
Jensen et al., 1991).
Both of these hypotheses, delayed release of excitatory
neurotransmitters and lon et al., 1989; Mitani et al., 1989, 1990a; Imon et al., 1991;
Jensen et al., 1991).
Both of these hypotheses, delayed release of excitatory
neurotransmitters and long-lasting enhancement of syn-
aptic efficiency, imply det Jensen et al., 1991).
Both of these hypotheses, delayed release of excitatory
neurotransmitters and long-lasting enhancement of syn-
aptic efficiency, imply detrimental intracellular Ca^{2+}
and Na⁺ overload (Simon et a Both of these hypotheses, delayed release of excitatory
neurotransmitters and long-lasting enhancement of syn-
aptic efficiency, imply detrimental intracellular Ca^{2+}
and Na⁺ overload (Simon et al., 1984; Crowder et a neurotransmitters and long-lasting enhancement of syn-
aptic efficiency, imply detrimental intracellular Ca^{2+}
and Na⁺ overload (Simon et al., 1984; Crowder et al.,
1987; Siesjö and Bengtsson, 1989) and increased ener and Na⁺ overload (Simon et al., 1984; Crowder et al., 1987; Siesjö and Bengtsson, 1989) and increased energy demand, which may be alleviated by down-modulation of Na⁺-channels. Within this context, it is relevant to m and Na⁺ overload (Simon et al., 1984; Crowder et al., 1987; Siesjö and Bengtsson, 1989) and increased energy demand, which may be alleviated by down-modulation of Na⁺-channels. Within this context, it is relevant to m 1987; Siesjö and Bengtsson, 1989) and increased energy
demand, which may be alleviated by down-modulation of
Na⁺-channels. Within this context, it is relevant to men-
tion that induction of LTP in the dentate gyrus is a demand, which may be alleviated by down-modulation of Na⁺-channels. Within this context, it is relevant to mention that induction of LTP in the dentate gyrus is accompanied by a persistent enhancement in the ability of s $Na⁺$ -channels. Within this context, it is relevant to mention that induction of LTP in the dentate gyrus is accompanied by a persistent enhancement in the ability of synaptosomes to release glutamate in response to a tion that induction of LTP in the dentate gyrus is accompanied by a persistent enhancement in the ability of synaptosomes to release glutamate in response to a depolarizing stimulus and that the most significant enhancemen synaptosomes to release glutamate in response to a depolarizing stimulus and that the most significant enhancement of release from potentiated synaptosomes was seen with veratridine (Canevari et al., 1994). Fi-

PHARMACOLOGICAL REVIEWS

PHARMACOLOGICAL REVIEWS

aspet

MODULATION OF VOLTAGE-C
nally, although TTX did not antagonize the initiation or
the maintenance of hippocampal LTP induced by teta-MODULATION OF VOLT.

mally, although TTX did not antagonize the initiation of

the maintenance of hippocampal LTP induced by teta-

nizing stimulation, several local anesthetics blocked the nally, although TTX did not antagonize the initiation or
to some of the complex processes contributing to neuronal
the maintenance of hippocampal LTP induced by teta-
nizing stimulation, several local anesthetics blocked nally, although TTX did not antagonize the initiation or
the maintenance of hippocampal LTP induced by teta-
nizing stimulation, several local anesthetics blocked the
induction of LTP without any effect on the established
 nally, although TTX did not antagonize the initiation
the maintenance of hippocampal LTP induced by tet
nizing stimulation, several local anesthetics blocked t
induction of LTP without any effect on the establish
potentiat the maintenance of hippoonizing stimulation, several
induction of LTP without
potentiated responses, poi
tion (Smith et al., 1993).
3. Persistent up-regulation *3. Persistention, several local anesthetics blocked the* duction of LTP without any effect on the established tentiated responses, possibly via calmodulin inhibi-
3. Persistent up-regulation of voltage-gated Na⁺ cur-

induction of LTP without any effect on the establishe potentiated responses, possibly via calmodulin inhib
tion (Smith et al., 1993).
3. Persistent up-regulation of voltage-gated Na⁺ curns following ischemia: a speculati tion (Smith et al., 1993).

3. Persistent up-regulation of voltage-gated Na⁺ cur-

rents following ischemia: a speculative hypothesis. Sev-

eral studies with a variety of animal models concur:

brain ischemia causes an brain ischemia causes an initial translation of voltage-

3. Persistent up-regulation of voltage-gated Na⁺ cur-

of the

rents following ischemia: a speculative hypothesis. Sev-

eral studies with a variety of animal mo 3. Persistent up-regulation of voltage-gated $Na⁺$ cur-
rents following ischemia: a speculative hypothesis. Sev-
eral studies with a variety of animal models concur: (Ra
brain ischemia causes an initial translocation eral studies with a variety of animal models concur:
brain ischemia causes an initial translocation of PKC
protein from the cytosol to the plasma membrane (i.e., a
prerequisite for PKC activation), followed by rapid inhi-
 eral studies with a variety of animal models concur:

brain ischemia causes an initial translocation of PKC

protein from the cytosol to the plasma membrane (i.e., a

prerequisite for PKC activation), followed by rapid in brain ischemia causes an initial translocation of PKC
protein from the cytosol to the plasma membrane (i.e., a
prerequisite for PKC activation), followed by rapid inhi-
bition of its catalytic activity measured in vitro (L protein from the cytosol to the plasma membrane (i.e., a
prerequisite for PKC activation), followed by rapid inhi-
bition of its catalytic activity measured in vitro (Louis et
al., 1991; Cumrine et al., 1990; Cardell et al prerequisite for PKC activation), followed by rapid inhi-
bition of its catalytic activity measured in vitro (Louis et
al., 1991; Cumrine et al., 1990; Cardell et al., 1990;
Wieloch et al., 1991; Domanska-Janik and Zalewsk bition of its catalytic activity measured in vitro (Louis et al., 1991; Cumrine et al., 1990; Cardell et al., 1990; \overline{d} in Wieloch et al., 1991; Domanska-Janik and Zalewska, because 1992). The molecular mechanisms un al., 1991; Cumrine et al., 1990; Cardell et al., 1990; movied by increased with an allow with the molecular mechanisms underlying these 1992). The molecular mechanisms underlying these 1992 . The molecular mechanisms und Wieloch et al., 1991; Domanska-Janik and Zalewska,
1992). The molecular mechanisms underlying these
changes remain unclear, although the large influx of
Ca²⁺ and increased levels of free arachidonic acid and
diacylglycer 1992). The molecular mechanisms underlying these changes remain unclear, although the large influx of Ca^{2+} and increased levels of free arachidonic acid and diacylglycerols produced by ischemia are probably involved (S changes remain unclear, although the large influx of Ca^{2+} and increased levels of free arachidonic acid and $\frac{1}{2}$ irreduced by ischemia are probably involved (Siesjö and Bengtsson, 1989; Aveldaño and Bazán, 1975; A Ca^{2+} and increased levels of free arachidonic acid and
diacylglycerols produced by ischemia are probably in-
volved (Siesjö and Bengtsson, 1989; Aveldaño and Ba-
zán, 1975; Abe et al., 1987). The significance of the
di diacylglycerols produced by ischemia are probably in-
volved (Siesjö and Bengtsson, 1989; Aveldaño and Ba-
zán, 1975; Abe et al., 1987). The significance of the
observed translocation and down-regulation of PKC
with ischem volved (Siesjö and Bengtsson, 1989; Aveldaño and Ba-
zán, 1975; Abe et al., 1987). The significance of the ated
observed translocation and down-regulation of PKC seement
with ischemia for the development of ischemic neuro observed translocation and down-regulation of PKC
with ischemia for the development of ischemic neuronal
damage is also uncertain, because the effects of PKC
inhibitors on postischemic neuronal damage are conflict-
ing: so observed translocation and down-regulation of PKC
with ischemia for the development of ischemic neuronal
damage is also uncertain, because the effects of PKC
inhibitors on postischemic neuronal damage are conflict-
ing: so with ischemia for the development of ischemic neuronal
damage is also uncertain, because the effects of PKC
inhibitors on postischemic neuronal damage are conflict-
ing: some studies claim that PKC inhibitors aggravate
ne damage is also uncertain, because the effects of PKC
inhibitors on postischemic neuronal damage are conflict-
ing: some studies claim that PKC inhibitors aggravate
neuronal damage (Madden et al., 1991). Others claim
that inhibitors on postischemic neuronal damage are conflict-
ing: some studies claim that PKC inhibitors aggravate
neuronal damage (Madden et al., 1991). Others claim
that staurosporine prevents neuronal cell death (Hara et
a ing: some studies claim that PKC inhibitors aggravate
neuronal damage (Madden et al., 1991). Others claim
that staurosporine prevents neuronal cell death (Hara et
al., 1990) and reduces the postischemic impairment of
worki neuronal damage (Madden et al., 1991). Others claim
that staurosporine prevents neuronal cell death (Hara et
al., 1990) and reduces the postischemic impairment of
working memory in rats exposed to cerebral ischemia
(Ohno e that staurosporine prevents neuronal cell death (Hara et al., 1990) and reduces the postischemic impairment of the working memory in rats exposed to cerebral ischemia in (Ohno et al., 1991). Nevertheless, as phosphorylati al., 1990) and reduces the postischemic impairment of working memory in rats exposed to cerebral ischemia (Ohno et al., 1991). Nevertheless, as phosphorylation was shown to modulate voltage-gated Na^+ channels (see secti working memory in rats exposed to cerebral ischem
(Ohno et al., 1991). Nevertheless, as phosphorylati
was shown to modulate voltage-gated Na^+ channels (s
section II.C.), the possibility that persistent alteratio
of Na^+ (Ohno et al., 1991). Nevertheless, as phosphoryla was shown to modulate voltage-gated Na^+ channels section II.C.), the possibility that persistent alteratiof Na^+ currents may contribute to postischemic nenal deficit r tion. a currents may contribute to postischemic
leficit remains a possibility that deserves inv
IV. Effective Cerebroprotection by Down-
Modulation of Excessive Na⁺ Currents

Ischemia

A. Anoxic Injury to CNS White Matter

Ischemia
 (i.e., moxic Injury to CNS White Matter

Within the mammalian CNS, both gray and white

(i.e., myelinated fiber tracts) matter suffer irreversible

injury after anoxia/ischemia (Waxman et al., 1991), even A. Anoxic Injury to CNS White Matter

Within the mammalian CNS, both gray and white

(i.e., myelinated fiber tracts) matter suffer irreversible

injury after anoxia/ischemia (Waxman et al., 1991), even

though axons are l A. Anoxic Injury to CNS white matter

Within the mammalian CNS, both gray and white

injury after anoxia/ischemia (Waxman et al., 1991), even

though axons are less sensitive than neurons to reduced

blood flow (Marcoux e injury after anoxia/ischemia (Waxman et al., 1991), even
though axons are less sensitive than neurons to reduced
blood flow (Marcoux et al., 1982; Branston et al., 1984).
In comparison to neuronal loss, ischemic white matt (i.e., myelinated fiber tracts) matter suffer irreversible
injury after anoxia/ischemia (Waxman et al., 1991), even
though axons are less sensitive than neurons to reduced
blood flow (Marcoux et al., 1982; Branston et al. injury after anoxia/ischemia (Waxman et al., 1991), even
though axons are less sensitive than neurons to reduced
blood flow (Marcoux et al., 1982; Branston et al., 1984).
In comparison to neuronal loss, ischemic white matt though axons are less sensitive than neurons to reduced
blood flow (Marcoux et al., 1982; Branston et al., 1984).
In comparison to neuronal loss, ischemic white matter cel
injury has received little attention. This should blood flow (Marcoux et al., 1982; Branston et al., 1984). nist
In comparison to neuronal loss, ischemic white matter celli
injury has received little attention. This should be rec-
tified, firstly because action potential In comparison to neuronal loss, ischemic white matter cellingth correcting in the section of the tified, firstly because action potential in white matter is resential for normal neural signaling and is altered in bratroke, injury has received little attention. This should be rec-
tified, firstly because action potential in white matter is
essential for normal neural signaling and is altered in
stroke, traumatic brain damage and spinal cord i tified, firstly because action potential in white matter is resential for normal neural signaling and is altered in b
stroke, traumatic brain damage and spinal cord injury b
(Fisher, 1982; Bamford et al., 1987; Povlishock essential for normal neural signaling and is altered in
stroke, traumatic brain damage and spinal cord injury
(Fisher, 1982; Bamford et al., 1987; Povlishock, 1992
Maxwell et al., 1993); and secondly, because the simple
an stroke, traumatic brain damage and spinal cord injury
(Fisher, 1982; Bamford et al., 1987; Povlishock, 1992;
Maxwell et al., 1993); and secondly, because the simple
and well defined structure of myelinated axons (no neu-
r

some of the complex processes contributing to neuronal -GATED NA⁺ CHANNELS
some of the complex processed
damage (see section III.B.).
1. Na⁺- and Ca²⁺-depende

41
 1. Na⁺ cHANNELS **1.** $\frac{1}{2}$
 1. Na⁺ *- and Ca*²⁺*-dependency*. The ionic mechanisms
 1. Na⁺ *- and Ca*²⁺*-dependency*. The ionic mechanisms

derlying anoxic injury to white matter were recently some of the complex processes contributing to neuronal
damage (see section III.B.).
1. Na^+ - and Ca^{2+} -dependency. The ionic mechanisms
underlying anoxic injury to white matter were recently
characterized by Waxman and some of the complex processes contributing to neurona
damage (see section III.B.).
1. Na^+ - and Ca^{2+} -dependency. The ionic mechanism
underlying anoxic injury to white matter were recentle
characterized by Waxman and c damage (see section III.B.).

1. Na^{+} and Ca^{2+} -dependency. The ionic mechanisms

underlying anoxic injury to white matter were recently

characterized by Waxman and coworkers. They mea-

sured changes in the compound underlying anoxic injury to white matter were recently characterized by Waxman and coworkers. They measured changes in the compound action potentials (CAPs) of the rat optic nerve in vitro, a parameter that provides a rel underlying anoxic injury to white matter were recently
characterized by Waxman and coworkers. They mea-
sured changes in the compound action potentials (CAPs)
of the rat optic nerve in vitro, a parameter that provides
a re characterized by Waxman and coworkers. They mea-
sured changes in the compound action potentials (CAPs)
of the rat optic nerve in vitro, a parameter that provides
a reliable estimate of the number of functional fibres
(Ran sured changes in the compound action potentials (CAPs)
of the rat optic nerve in vitro, a parameter that provides
a reliable estimate of the number of functional fibres
(Ransom et al., 1990). Application of Na⁺-free med before 60 min of anoxia markedly improved the recovery
of CAP, whereas increasing the transmembrane Na⁺
gradient at various times before or during anoxia wor-
sened the injury (Stys et al., 1991, 1992b). As anoxiaa reliable estimate of the number of functional fibres (Ransom et al., 1990). Application of Na⁺-free medium
before 60 min of anoxia markedly improved the recovery
of CAP, whereas increasing the transmembrane Na⁺
gradi (Ransom et al., 1990). Application of $Na⁺$ -free medium before 60 min of anoxia markedly improved the recove of CAP, whereas increasing the transmembrane N gradient at various times before or during anoxia w sened the before 60 min of anoxia markedly improved the recovery
of CAP, whereas increasing the transmembrane Na^+
gradient at various times before or during anoxia wor-
sened the injury (Stys et al., 1991, 1992b). As anoxia-
indu of CAP, whereas increasing the transmembrane Na⁺
gradient at various times before or during anoxia wor-
sened the injury (Stys et al., 1991, 1992b). As anoxia-
induced alteration of CAP had previously been found to
be c gradient at various times before or during anoxia wor-
sened the injury (Stys et al., 1991, 1992b). As anoxia-
induced alteration of CAP had previously been found to
be critically dependent on Ca^{2+} influx (Stys et al., sened the injury (Stys et al., 1991, 1992b). As anoxia-
induced alteration of CAP had previously been found to
be critically dependent on Ca^{2+} influx (Stys et al.,
1990b), these results indicate that both extracellular induced alteration of CAP l
be critically dependent on
1990b), these results indic
Ca²⁺ and a finite Na⁺ perr
irreversible axonal injury.
Several lines of evidence critically dependent on Ca^{2+} influx (Stys et al., 90b), these results indicate that both extracellular a^{2+} and a finite Na⁺ permeability are required before eversible axonal injury.
Several lines of evidence sugg

the Na⁺/Ca²⁺-exchanger (Stys et al., 1991) (see section
IV. **Effective Cerebroprotection by Down-**
Modulation of Excessive Na⁺ Currents in to 40 min *after* the start of anoxia was deleterious, exchanger (Stys et al., 1992b); and (b) pharmacological
Within the mammalian CNS, both gray *and* white inhibition of the Na⁺/Ca²⁺ exchanger with bepridil or
e., myelinated fiber tracts) matter suffer irreversible benz 1990b), these results indicate that both extracell Ca^{2+} and a finite Na^{+} permeability are required be irreversible axonal injury.
Several lines of evidence suggest that Ca^{2+} does penetrate via conventional voltag Ca^{2+} and a finite Na⁺ permeability are required before
irreversible axonal injury.
Several lines of evidence suggest that Ca^{2+} does not
penetrate via conventional voltage-gated or ligand-oper-
ated Ca^{2+} -channel irreversible axonal injury.
Several lines of evidence suggest that Ca^{2+} does repenetrate via conventional voltage-gated or ligand-op ated Ca^{2+} -channels in white matter cells: (*a*) Cs seemed to enter the intracellul Several lines of evidence suggest that Ca^{2+} does ipenetrate via conventional voltage-gated or ligand-op ated Ca^{2+} -channels in white matter cells: (*a*) C₈ seemed to enter the intracellular compartment gradly durin penetrate via conventional voltage-gated or ligand-oper-
ated Ca^{2+} -channels in white matter cells: $(a) Ca^{2+}$
seemed to enter the intracellular compartment gradu-
ally during anoxic conditions, despite its large electro ated Ca²⁺-channels in white matter cells: (a) Ca²⁺
seemed to enter the intracellular compartment gradu-
ally during anoxic conditions, despite its large electro-
chemical gradient (Stys et al., 1992b); (b) Ca²⁺ chan ally during anoxic conditions, despite its large electro-
chemical gradient (Stys et al., 1992b); (b) Ca²⁺ channe-
blockers such as polyvalent cations (Mn²⁺, Co²⁺, c
La³⁺) or dihydropyridines did not protect the op blockers such as polyvalent cations $(Mn^{2+}, Co^{2+}, or La^{3+})$ or dihydropyridines did not protect the optic nerve from anoxia (Stys et al., 1990a); and (c) sustained exposure to high concentrations of glutamate or aspartate did La^{3+}) or dihydropyridines did not protect the optic nerve La^{3+}) or dihydropyridines did not protect the optic nerve
from anoxia (Stys et al., 1990a); and (c) sustained expo-
sure to high concentrations of glutamate or aspartate
did not affect the optic nerve CAP, supporting t from anoxia (Stys et al., 1990a); and (c) sustained exposure to high concentrations of glutamate or aspartate did not affect the optic nerve CAP, supporting the notion that NMDA receptors do not contribute to anoxic injury sure to high concentrations of glutamate or aspartate
did not affect the optic nerve CAP, supporting the notion
that NMDA receptors do not contribute to anoxic injury
in this preparation (Ransom et al., 1990) (see, however did not affect the optic nerve CAP, supporting the notion
that NMDA receptors do not contribute to anoxic injury
in this preparation (Ransom et al., 1990) (see, however:
Kriegler and Chiu, 1993; Jensen and Chiu, 1993). Sty that NMDA receptors do not contribute to anoxic injum
in this preparation (Ransom et al., 1990) (see, howeve
Kriegler and Chiu, 1993; Jensen and Chiu, 1993). Sty
and coworkers (1991) thus proposed that anoxia-induce
Ca²⁺ in this preparation (Ransom et al., 1990) (see, however:
Kriegler and Chiu, 1993; Jensen and Chiu, 1993). Stys
and coworkers (1991) thus proposed that anoxia-induced
 Ca^{2+} -dependent neurotoxicitity may result from mem-
 Kriegler and Chiu, 1993; Jensen and Chiu, 1993). Stys
and coworkers (1991) thus proposed that anoxia-induced
Ca²⁺-dependent neurotoxicitity may result from mem-
brane depolarization subsequent to Na⁺ influx through
Na and coworkers (1991) thus proposed that anoxia-induced Ca^{2+} -dependent neurotoxicitity may result from membrane depolarization subsequent to Na⁺ influx through Na⁺ channels, leading to Ca^{2+} influx through reversa Ca^{2+} -dependent neurotoxicitity may result from mem-
brane depolarization subsequent to Na⁺ influx through
Na⁺ channels, leading to Ca^{2+} influx through reversal of
the Na⁺/Ca²⁺-exchanger (Stys et al., 1991) (brane depolarization subsequent to Na⁺ influx through Na⁺ channels, leading to Ca²⁺ influx through reversal of
the Na⁺/Ca²⁺-exchanger (Stys et al., 1991) (see section
III.B.2.). Two other findings have further s Na⁺ channels, leading to Ca²⁺ influx through reversal of the Na⁺/Ca²⁺-exchanger (Stys et al., 1991) (see section III.B.2.). Two other findings have further strengthenes this hypothesis: (*a*) introduction of Na⁺ the Na⁺/Ca²⁺-exchanger (Stys et al., 1991) (see section III.B.2.). Two other findings have further strengthened this hypothesis: (*a*) introduction of Na⁺-free medium 20 to 40 min *after* the start of anoxia was del III.B.2.). Two other findings have further strengthened
this hypothesis: (*a*) introduction of Na⁺-free medium 20
to 40 min *after* the start of anoxia was deleterious,
presumably because this enhanced the gradient
 $[Na^$ this hypothesis: (*a*) introduction of Na⁺-free medium :
to 40 min *after* the start of anoxia was deleteriou
presumably because this enhanced the gradie
[Na⁺]_i>[Na⁺]₀ and forced more Ca²⁺ into cells via t
exc to 40 min *after* the start of anoxia was deleterious,
presumably because this enhanced the gradient
 $[Na^+]_i > [Na^+]_0$ and forced more Ca^{2+} into cells via the
exchanger (Stys et al., 1992b); and (*b*) pharmacological
inh be critically dependent on Ca^{2+} influx (Stys et al., 1990b), these results indicate that both extractellular
Ca²⁺ and a finite Na⁺ permeability are required before irreversible axonal injury.

Several lines of evid [Na⁺]_i>[Na⁺]₀ and forced more Ca
exchanger (Stys et al., 1992b); and
inhibition of the Na⁺/Ca²⁺ exchan
benzamil significantly protected th
anoxic damage (Stys et al., 1991).
2. Route for Na⁺ entry during is changer (Stys et al., 1992b); and (*b*) pharmacologies hibition of the Na⁺/Ca²⁺ exchanger with bepriding inzamil significantly protected the optic nerve froxic damage (Stys et al., 1991).
2. *Route for Na⁺ entry dur*

inhibition of the Na⁺/Ca²⁺ exchanger with bepridil or benzamil significantly protected the optic nerve from anoxic damage (Stys et al., 1991).

2. Route for Na⁺ entry during ischemia. The mechanism of sustained pene benzamil significantly protected the optic nerve from
anoxic damage (Stys et al., 1991).
2. Route for Na^+ entry during ischemia. The mecha-
nism of sustained penetration of Na^+ into white matter
cells during anoxia is anoxic damage (Stys et al., 1991).

2. Route for Na^+ entry during ischemia. The mechanism of sustained penetration of Na^+ into white matter

cells during anoxia is an intriguing question, because

the *classic* voltag nism of sustained penetration of Na⁺ into white matter cells during anoxia is an intriguing question, because the *classic* voltage-gated Na⁺ channels that initiate the rapid upstroke of axonal action potential (i.e., mism of sustained penetration of Na⁺ into white matter cells during anoxia is an intriguing question, because the *classic* voltage-gated Na⁺ channels that initiate the rapid upstroke of axonal action potential (i.e., cells during anoxia is an intriguing question, because
the *classic* voltage-gated Na⁺ channels that initiate the
rapid upstroke of axonal action potential (i.e., mem-
brane depolarization) also contribute to its termina the *classic* voltage-gated Na⁺ channels that initiate t
rapid upstroke of axonal action potential (i.e., me
brane depolarization) also contribute to its terminati
by fast and complete inactivation (Chiu et al., 197
impl rapid upstroke of axonal action potential (i.e., mem-
brane depolarization) also contribute to its termination
by fast and complete inactivation (Chiu et al., 1979),
implying that these channels should also rapidly inacti by fast and complete inactivation (Chiu et al., 197
hy fast and complete inactivation (Chiu et al., 197
implying that these channels should also rapidly inactivate during anoxic depolarization. Stys and coworks
(1991) spec by fast and complete inactivation (Chiu et al., 1979)
implying that these channels should also rapidly inactivate during anoxic depolarization. Stys and coworker
(1991) speculated that a noninactivating Na⁺ conductance,

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was involved. Measurements of the compound mem-

brane potential of rat optic nerves at rest, or depolarized (Stys et al., 19 EXTER URENJAK AND O

brane potential of rat optic nerves at rest, or depolarized

by 15 to 40 mm K⁺, confirmed this hypothesis. A TTX-**42**
was involved. Measurements of the compound mem
brane potential of rat optic nerves at rest, or depolarize
by 15 to 40 mM K⁺, confirmed this hypothesis. A TTX
sensitive Na^+ conductance that was present at rest was involved. Measurements of the compound mem-
brane potential of rat optic nerves at rest, or depolarized
by 15 to 40 mM K^+ , confirmed this hypothesis. A TTX-
sensitive Na⁺ conductance that was present at rest perwas involved. Measurements of the compound mem
brane potential of rat optic nerves at rest, or depolarized
by 15 to 40 mM K⁺, confirmed this hypothesis. A TTX
sensitive Na⁺ conductance that was present at rest per
sis brane potential of rat optic nerves at rest, or depolarized (S
by 15 to 40 mM K⁺, confirmed this hypothesis. A TTX-
sensitive Na⁺ conductance that was present at rest per-
sisted in nerves depolarized sufficiently to by 15 to 40 mm K⁺, confirmed this hypothesis. A TI
sensitive Na⁺ conductance that was present at rest p
sisted in nerves depolarized sufficiently to abolish cl
sical transient Na⁺ currents (Stys et al., 1993). It
im sensitive Na⁺ conductance that was present at rest per-
sisted in nerves depolarized sufficiently to abolish clas-
sical transient Na⁺ currents (Stys et al., 1993). It is
important to mention that noninactivating Na⁺ sisted in nerves depolarized sufficiently to abolish classical transient Na⁺ currents (Stys et al., 1993). It important to mention that noninactivating Na⁺ condutance, which rapidly activates like the *classical* Nich sical transient $Na⁺$ currents (Stys et al., 1993). It important to mention that noninactivating $Na⁺$ condutance, which rapidly activates like the *classical* Ne channels, but inactivates either very slowly or in important to mention that noninactivating $Na⁺$ conductance, which rapidly activates like the *classical* $Na⁺$ channels, but inactivates either very slowly or incompletely, even with prolonged depolarization, was tance, which rapidly activates like the *classical* Na⁺ channels, but inactivates either very slowly or incompletely, even with prolonged depolarization, was previously identified in cerebellar (Llinás and Sugimori, a 19 channels, but inactivates either very slowly or incom-

pletely, even with prolonged depolarization, was previ-

poly identified in cerebellar (Llinás and Sugimori, as

1980; Sugimory and Llinás, 1980), cortical (Connors e pletely, even with prolonged depolarization, was previously identified in cerebellar (Llinás and Sugimori, a 1980; Sugimory and Llinás, 1980), cortical (Connors et cal., 1982; Stafstrom et al., 1985; Lynch et al., 1995) an ously identified in cerebellar (Llinás and Sugimori, a 1980; Sugimory and Llinás, 1980), cortical (Connors et cal., 1982; Stafstrom et al., 1985; Lynch et al., 1995) and (hippocampal neurons (French et al., 1990). Althoug 1980; Sugimory and Llinás, 1980), cortical (Connors et ci
al., 1982; Stafstrom et al., 1985; Lynch et al., 1995) and C
hippocampal neurons (French et al., 1990). Although fe
such noninactivating Na⁺ current (also called al., 1982; Stafstrom et al., 1985; Lynch et al., 1995) and Ca²
hippocampal neurons (French et al., 1990). Although fect
such noninactivating Na⁺ current (also called sustained ene
or persistent Na⁺ current) may only hippocampal neurons (French et al., 1990). Althosuch noninactivating Na⁺ current (also called susta
or persistent Na⁺ current) may only represent 1 to 3
the peak amplitude of Na⁺ current, they may pla
critical role such noninactivating Na^+ current (also called sustained
or persistent Na^+ current) may only represent 1 to 3% of
the peak amplitude of Na^+ current, they may play a
critical role in situations where membrane depolari or persistent Na⁺ current) may only represent 1 to 3% of
the peak amplitude of Na⁺ current, they may play a
critical role in situations where membrane depolariza-
tion is sustained (Taylor, 1993). Also relevant are re critical role in situations where membrane depolariza-
tion is sustained (Taylor, 1993). Also relevant are reports suggesting that oxidative stress and ischemia
modify inactivation gating properties of the Na⁺ chan-
nel in cardiac cells (Burnashev et al., 1989; Bhatnagar et
al., 1990).
B. Protection Against Ischemic Damage by modify inactivation gating properties of the Na⁺ chan-

Tetrodotoxin

1990).
Protection Against Ischemic Damage by
1. In vitro preparations. Selective blockade of volta
ted Na⁺ channels by TTX clearly increases the ano B. Protection Against Ischemic Damage by

Tetrodotoxin

1. In vitro preparations. Selective blockade of voltage-

gated Na⁺ channels by TTX clearly increases the anoxic

tolerance of a number of preparations. In rat hip B. Protection Against Ischemic Damage by
Tetrodotoxin
1. In vitro preparations. Selective blockade of volta
gated Na⁺ channels by TTX clearly increases the an
tolerance of a number of preparations. In rat hippoc
pal slic *I. In vitro preparations.* Selective blockade of voltage-
gated Na⁺ channels by TTX clearly increases the anoxic
tolerance of a number of preparations. In rat hippocam-
pal slices, TTX reduced the fall in ATP concentra 1. In vitro preparations. Selective blockade of voltage-regated Na⁺ channels by TTX clearly increases the anoxic recovers tolerance of a number of preparations. In rat hippocampal slices, TTX reduced the fall in ATP conc gated Na⁺ channels by TTX clearly increases the anoxic tolerance of a number of preparations. In rat hippocampal slices, TTX reduced the fall in ATP concentration during anoxia (5 to 10 min) and improved the recovery of tolerance of a number of preparations. In rat hippocampal slices, TTX reduced the fall in ATP concentration de
during anoxia (5 to 10 min) and improved the recovery of Nevoked population spikes from dentate granule neurons pal slices, TTX reduced the fall in ATP concentration
during anoxia (5 to 10 min) and improved the recovery of
evoked population spikes from dentate granule neurons
and CA1 pyramidal neurons (Boening et al., 1989). Some
of evoked population spikes from dentate granule neurons ischemia and is potentially neuroprotective. Conversely,
and CA1 pyramidal neurons (Boening et al., 1989). Some persistent drug-induced Na⁺ influx is neurotoxic, eve evoked population spikes from dentate granule neurons
and CA1 pyramidal neurons (Boening et al., 1989). Some
of these observations were confirmed by Weber and Tay-
lor (1994), and their histological examinations showed
tha and CA1 pyramidal neurons (Boening et al., 1989). Some
of these observations were confirmed by Weber and Tay-
lor (1994), and their histological examinations showed
that TTX also prevented CA1 pyramidal cell damage
produce of these observations were confirmed by Weber and Tay-
lor (1994), and their histological examinations showed
that TTX also prevented CA1 pyramidal cell damage
produced by anoxia/aglycemia. In the same preparation
exposed lor (1994), and their histological examinations showed set that TTX also prevented CA1 pyramidal cell damage produced by anoxia/aglycemia. In the same preparation C . exposed to 10 min of anoxia, TTX provided better prot that TTX also prevented CA1 pyramidal cell damage produced by anoxia/aglycemia. In the same preparation exposed to 10 min of anoxia, TTX provided better protection than thiopental against long-term loss of the population produced by anoxia/aglycemia. In the same preparation C .
exposed to 10 min of anoxia, TTX provided better pro-
tection than thiopental against long-term loss of the eth
population spike of the CA1 region, even though th exposed to 10 min of anoxia, TTX provided better prection than thiopental against long-term loss of the population spike of the CA1 region, even though thipental was more potent at blocking anoxic Ca^{2+} influ (Kass et a tection than thiopental against long-term loss of the population spike of the CA1 region, even though thio-
pental was more potent at blocking anoxic Ca^{2+} influx (Kass et al., 1992). In rat neocortical slices, TTX mark population spike of the CA1 region, even though thio-
pental was more potent at blocking anoxic Ca^{2+} influx
(Kass et al., 1992). In rat neocortical slices, TTX mark-
edly attenuated the depolarization of layer II to II pental was more potent at blocking anoxic Ca^{2+} influx [(Kass et al., 1992). In rat neocortical slices, TTX mark-
edly attenuated the depolarization of layer II to III py-
ramidal neurons evoked by brief anoxia (Rosen e (Kass et al., 1992). In rat neocortical slices, TTX if edly attenuated the depolarization of layer II to I ramidal neurons evoked by brief anoxia (Rosen (1994) . This specific Na⁺ channel blocker also proteultured hipp edly attenuated the depolarization of layer II to III py-
ramidal neurons evoked by brief anoxia (Rosen et al., an
1994). This specific Na⁺ channel blocker also protected no
cultured hippocampal neurons against hypoglyca ramidal neurons evoked by brief anoxia (Rosen et al., 1994). This specific Na⁺ channel blocker also protected cultured hippocampal neurons against hypoglycaemia-
and cyanide-induced injury, even when applied after the in 1994). This specific Na⁺ channel blocker also protect cultured hippocampal neurons against hypoglycaemiand cyanide-induced injury, even when applied after t insult (Tasker et al., 1992; Vornov et al., 1994). In co trast cultured hippocampal neurons against hypoglycaemia-
and cyanide-induced injury, even when applied after the
insult (Tasker et al., 1992; Vornov et al., 1994). In con-
trast, TTX alone produced a small and variable reduc-
t and cyanide-induced injury, even when applied after the
insult (Tasker et al., 1992; Vornov et al., 1994). In con-
trast, TTX alone produced a small and variable reduc-
tion in neuronal death subsequent to 40 to 50 min oxy insult (Tasker et al., 1992; Vornov et al., 1994). In contrast, TTX alone produced a small and variable reduction in neuronal death subsequent to 40 to 50 min oxygen-glucose deprivation in murine mixed neocortical cell cu trast, TTX alone produced a small and variable reduction in neuronal death subsequent to 40 to 50 min oxygen-glucose deprivation in murine mixed neocortical cell luminosultures (Goldberg and Choi, 1993; Lynch et al., 1995 tion in neuronal death subsequent to 40 to 50 min oxy-
gen-glucose deprivation in murine mixed neocortical cell
cultures (Goldberg and Choi, 1993; Lynch et al., 1995), tio
despite attenuating the increase in $[Na^+]_i$ asso gen-glucose deprivation in murine mixed neocortical cell
cultures (Goldberg and Choi, 1993; Lynch et al., 1995),
despite attenuating the increase in $[Na^+]$ _i associated
with this insult (Lynch et al., 1995). Finally, in cultures (Goldberg and Choi, 1993; Lynch et al., 1995), the despite attenuating the increase in $[Na^+]_i$ associated the with this insult (Lynch et al., 1995). Finally, in the panoxic rat optic nerve, a representative whit despite attenuating the increase in $[Na^+]$ associated
with this insult (Lynch et al., 1995). Finally, in the
anoxic rat optic nerve, a representative white matter
tract (see above, section A.), TTX substantially improved

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that had little effect on the amplitude of the normal CAP
(Stys et al., 1992a) and protected the axonal cytoskele-(BRENOVITCH
that had little effect on the amplitude of the normal C
(Stys et al., 1992a) and protected the axonal cytosk
ton (Waxman et al., 1994). BRENOVITCH
that had little effect on the as
(Stys et al., 1992a) and prot
ton (Waxman et al., 1994).
2. In vivo experimental mo at had little effect on the amplitude of the normal CAP
tys et al., 1992a) and protected the axonal cytoskele-
n (Waxman et al., 1994).
2. *In vivo experimental models*. Increased tolerance to
chemia with TTX was also obse

critical role in situations where membrane depolariza- (Haddad and Donnelly, 1990; Xie et al., 1994b) (fig. 5).

tion is sustained (Taylor, 1993). Also relevant are re-

ports suggesting that oxidative stress and ischemia that had little effect on the amplitude of the normal CAP
(Stys et al., 1992a) and protected the axonal cytoskele-
ton (Waxman et al., 1994).
2. In vivo experimental models. Increased tolerance to
ischemia with TTX was als Stys et al., 1992a) and protected the axonal cytoskele
ton (Waxman et al., 1994).
2. In vivo experimental models. Increased tolerance to
ischemia with TTX was also observed in vivo. TT2
slowed down extracellular acidosis ton (Waxman et al., 1994).
2. In vivo experimental models. Increased tolerance to
ischemia with TTX was also observed in vivo. TTX
slowed down extracellular acidosis produced by com
plete ischemia in the isolated perfused 2. In vivo experimental models. Increased tolerance to ischemia with TTX was also observed in vivo. TTX slowed down extracellular acidosis produced by complete ischemia in the isolated perfused rat brain, indicating a red ischemia with TTX was also observed in vivo. TTX
slowed down extracellular acidosis produced by com-
plete ischemia in the isolated perfused rat brain, indi-
cating a reduction of the anaerobic metabolic rate (fig. 5)
(Xie slowed down extracellular acidosis produced by complete ischemia in the isolated perfused rat brain, indicating a reduction of the anaerobic metabolic rate (fig. 5) (Xie et al., 1994b). It also markedly delayed anoxic depo plete ischemia in the isolated perfused rat brain, indicating a reduction of the anaerobic metabolic rate (fig. 5)
(Xie et al., 1994b). It also markedly delayed anoxic de
polarization (Prenen et al., 1988; Xie et al., 1994 cating a reduction of the anaerobic metabolic rate (fig. 5)
(Xie et al., 1994b). It also markedly delayed anoxic de-
polarization (Prenen et al., 1988; Xie et al., 1994b) and,
as a direct consequence, the critical ionic c (Xie et al., 1994b). It also markedly delayed anoxic de-
polarization (Prenen et al., 1988; Xie et al., 1994b) and,
as a direct consequence, the critical ionic changes asso-
ciated with anoxic depolarization, i.e., Na⁺polarization (Prenen et al., 1988; Xie et al., 1994b) and,
as a direct consequence, the critical ionic changes asso-
ciated with anoxic depolarization, i.e., Na⁺-entry (fig. 5),
Ca²⁺-entry and K⁺-efflux (Xie et al., as a direct consequence, the critical ionic changes asso-
ciated with anoxic depolarization, i.e., Na⁺-entry (fig. 5),
Ca²⁺-entry and K⁺-efflux (Xie et al., 1994b). These ef-
fects of TTX confirm that Na⁺ channel ciated with anoxic depolarization, i.e., Na⁺-entry (fig. 5),
Ca²⁺-entry and K⁺-efflux (Xie et al., 1994b). These ef-
fects of TTX confirm that Na⁺ channel blockade reduces
energy demand, but it is important to note Ca^{2+} -entry and K^+ -efflux (Xie et al., 1994b). These effects of TTX confirm that Na^+ channel blockade reduces energy demand, but it is important to note that TTX does not *prevent* anoxic depolarization, nor does i fects of TTX confirm that Na^+ channel blockade reduces
energy demand, but it is important to note that TTX
does not *prevent* anoxic depolarization, nor does it re-
duce its magnitude when such depolarization does occur energy demand, but it is important to note that TTX
does not *prevent* anoxic depolarization, nor does it re-
duce its magnitude when such depolarization does occur
(Haddad and Donnelly, 1990; Xie et al., 1994b) (fig. 5). does not *prevent* anoxic depolarization, nor does it reduce its magnitude when such depolarization does occur
(Haddad and Donnelly, 1990; Xie et al., 1994b) (fig. 5).
This implies that TTX-sensitive voltage-gated Na⁺
ch duce its magnitude when such depolarization does occu
(Haddad and Donnelly, 1990; Xie et al., 1994b) (fig. 5
This implies that TTX-sensitive voltage-gated Na
channels do not play an essential role in the sudde
increase in (Haddad and Donnelly, 1990; Xie et al., 1994b) (fig. 5).
This implies that TTX-sensitive voltage-gated Na⁺
channels do not play an essential role in the sudden
increase in the ionic permeability of the cellular mem-
bra This implies that TTX-sensitive voltage-gated Na
channels do not play an essential role in the sudde
increase in the ionic permeability of the cellular mem
brane that provokes anoxic depolarization. Finally, di
rect applic channels do not play an essential role in the sudden
increase in the ionic permeability of the cellular mem-
brane that provokes anoxic depolarization. Finally, di-
rect application of TTX to the rat hippocampus dose-
depe increase in the ionic permeability of the cellular mem-
brane that provokes anoxic depolarization. Finally, di-
rect application of TTX to the rat hippocampus dose-
dependently reduced neuronal death following transient
gl brane that provokes anoxic depolarization. Finally, direct application of TTX to the rat hippocampus dose-
dependently reduced neuronal death following transient
global ischemia in rats and gerbils (Yamasaki et al.,
1991; rect application of TTX to the rat hippocampus dose-
dependently reduced neuronal death following transient
global ischemia in rats and gerbils (Yamasaki et al.
1991; Lysko et al., 1993, 1994) and improved functional
recov dependently reduced neuronal death following transposed in Fash and gerbils (Yamasak 1991; Lysko et al., 1993, 1994) and improved functioned recovery (Prenen et al., 1988), again supporting to reprotective potential of Na 1991; Lysko et al., 1993, 1994) and improved functional recovery (Prenen et al., 1988), again supporting the neuroprotective potential of $Na⁺$ channel blockade.
The experimental findings outlined above clearly demons

1991; Lysko et al., 1993, 1994) and improved functional
recovery (Prenen et al., 1988), again supporting the neu-
roprotective potential of Na⁺ channel blockade.
The experimental findings outlined above clearly
demonstr recovery (Prenen et al., 1988), again supporting the neu-
roprotective potential of Na⁺ channel blockade.
The experimental findings outlined above clearly
demonstrate that selective blockade of voltage-gated
Na⁺ chann roprotective potential of Na⁺ channel blockade.
The experimental findings outlined above clearly
demonstrate that selective blockade of voltage-gated
Na⁺ channels reduces the rate of ATP depletion during
ischemia and The experimental findings outlined above clearly demonstrate that selective blockade of voltage-gated Na⁺ channels reduces the rate of ATP depletion during ischemia and is potentially neuroprotective. Conversely, persist ischemia and is potentially neuroprotective. Conversely, persistent drug-induced Na⁺ influx is neurotoxic, even

nen energy supply to the brain is not compromised (see
ction III.B.1.).
Local Anesthetics [i.e., lidocaine, procaine, lidocaine
hochloride (QX314), etc.] *reversibly* block Na⁺ chanection III.B.1.).

C. *Local Anesthetics*

Local anesthetics [i.e., lidocaine, procaine, lidocaine

ethochloride (QX314), etc.] *reversibly* block Na⁺ chan

nels with complex voltage-and frequency-depender C. Local Anesthetics
Local anesthetics [i.e., lidocaine, procaine, lidoc
ethochloride (QX314), etc.] reversibly block Na⁺ cl
nels with complex voltage-and frequency-depend
properties. This is an important feature for the C. Local Anesthetics [i.e., lidocaine, procaine, lidocaine
ethochloride (QX314), etc.] reversibly block Na^+ chan-
nels with complex voltage-and frequency-dependent
properties. This is an important feature for their clin ethochloride (QX314), etc.] reversibly block Na^+ channels with complex voltage-and frequency-dependent properties. This is an important feature for their clinical efficacy, which also indicates that drug binding is ethochloride (QX314), etc.] *reversibly* block Na⁺ channels with complex voltage-and frequency-dependent properties. This is an important feature for their clinical efficacy, which also indicates that drug binding is mod nels with complex voltage-and frequency-dependent
properties. This is an important feature for their clinical
efficacy, which also indicates that drug binding is mod-
ulated by channel state (Catterall, 1987; Butterworth
a properties. This is an important feature for their clinical
efficacy, which also indicates that drug binding is mod-
ulated by channel state (Catterall, 1987; Butterworth
and Strichartz, 1990; Starmer et al., 1990). Indeed efficacy, which also indicates that drug binding is modulated by channel state (Catterall, 1987; Butterworth and Strichartz, 1990; Starmer et al., 1990). Indeed, it is now established that local anesthetics bind to a speci ulated by channel state (Catterall, 1987; Butterworth
and Strichartz, 1990; Starmer et al., 1990). Indeed, it is
now established that local anesthetics bind to a specific
site inside the pore of the channel (see section II and Strichartz, 1990; Starmer et al., 1990). Indeed, it is
now established that local anesthetics bind to a specific
site inside the pore of the channel (see section II.B.3 an
fig. 3), and with a higher affinity when chan now established that local anesthetics bind to a specific
site inside the pore of the channel (see section II.B.3 and
fig. 3), and with a higher affinity when channels are
open or inactivated, thereby promoting inactivati site inside the pore of the channel (see section II.B.3 and
fig. 3), and with a higher affinity when channels are
open or inactivated, thereby promoting inactivation.
These agents also alter the conductance of K^+ chann fig. 3), and with a higher affinity when channels are
open or inactivated, thereby promoting inactivation.
These agents also alter the conductance of K^+ channels,
although to a lesser extent (Swenson, 1981; Stolc, 1988 open or inactivated, thereby promoting inactivation.
These agents also alter the conductance of K^+ channels,
although to a lesser extent (Swenson, 1981; Stolc, 1988).
Despite some conflicting in vivo results (see below These agents also alter the conductance of K^+ channels,
although to a lesser extent (Swenson, 1981; Stolc, 1988).
Despite some conflicting in vivo results (see below, sec-
tion 2.), studies with local anesthetics gener although to a lesser exter
Despite some conflicting
tion 2.), studies with loca
the concept that down-m
potentially neuroprotecti
1. In vitro preparations *1. In vivo results (see below, sec-* in 2.), studies with local anesthetics generally support e concept that down-modulation of Na⁺ channels is tentially neuroprotective.
1. In vitro preparations: action mechanism. Lo tion 2.), studies with local anesthetics generally support
the concept that down-modulation of Na^+ channels is
potentially neuroprotective.
1. In vitro preparations: action mechanism. Local an-
esthetics have been s

the concept that down-modulation of $Na⁺$ channels is
potentially neuroprotective.
1. In vitro preparations: action mechanism. Local an-
esthetics have been shown to be neuroprotective against
ischemia in several in

PHARMACOLOGICAL REVIEW

MODULATION OF VOLTAGE-GAT
slices, the recovery rate of synaptic function following 15 alre
min of hypoxia was significantly improved by previous char MODULATION OF VOLTAGE

slices, the recovery rate of synaptic function following 15

min of hypoxia was significantly improved by previous

incubation for 60 min with 0.1 mM of lidocaine, 2-chlor-

procaine or cocaine. It i sinces, the recovery rate of synaptic function following 15 amin of hypoxia was significantly improved by previous clincubation for 60 min with 0.1 mM of lidocaine, 2-chlor-laprocaine or cocaine. It is important to record min of hypoxia was significantly improved by previous
incubation for 60 min with 0.1 mM of lidocaine, 2-chlor-
procaine or cocaine. It is important to record that 0.1 mM
of these agents preserved normal synaptic function
(incubation for 60 min with 0.1 mM of lidocaine, 2-chlor-
procaine or cocaine. It is important to record that 0.1 mM
of these agents preserved normal synaptic function
(Schurr et al., 1986; Lucas et al., 1989). The protecti procaine or cocaine. It is important to record that 0.1 mm
of these agents preserved normal synaptic function (se
(Schurr et al., 1986; Lucas et al., 1989). The protective co
effect of lidocaine in this preparation was rec firmed by Weber and Taylor (1994), who also showed firmed by Weber and Taylor (1994), who also showed of
that this drug prevented CA1 pyramidal cell damage F
produced by 12 min of anoxia/aglycaemia. is
in primary cultures of rat brain neurons, the neuro-
toxic effect of 1

produced by 12 min of anoxia/aglycaemia.
In primary cultures of rat brain neurons, the neuro-
toxic effect of 16 h exposure to 30 μ M veratridine was that this drug prevented CA1 pyramidal cell damage
produced by 12 min of anoxia/aglycaemia.
In primary cultures of rat brain neurons, the neuro-
toxic effect of 16 h exposure to 30 μ M veratridine was
Ca²⁺-dependent a produced by 12 min of anoxia/aglycaemia.

In primary cultures of rat brain neurons, the neuro-

toxic effect of 16 h exposure to 30 μ M veratridine was

Ca²⁺-dependent and only partially inhibited by local

anesthetic In primary cultures of rat brain neurons, the neuro-
toxic effect of 16 h exposure to 30 μ M veratridine was
Ca²⁺-dependent and only partially inhibited by local
anesthetics. Nevertheless, there was good correlation
b toxic effect of 16 h exposure to 30 μ M veratridine wa
Ca²⁺-dependent and only partially inhibited by loca
anesthetics. Nevertheless, there was good correlatio
between the potency of these drugs and several Ca²
anta Ca^{2+} -dependent and only partially inhibited by locanes
thetics. Nevertheless, there was good correlation between the potency of these drugs and several Ca^{2} antagonists, and their binding affinity for the BTX binding anesthetics. Nevertheless, there was good correlation ebetween the potency of these drugs and several Ca^{2+} vantagonists, and their binding affinity for the BTX binding site of Na⁺ channels in rat cortex synaptosomal antagonists, and their binding affinity for the BTX bind-
ing site of Na⁺ channels in rat cortex synaptosomal
preparations (fig. 6) (Pauwels et al., 1990). In cultured
mixed neocortical cells exposed to transient oxygen ing site of Na⁺ channels in rat cortex synaptosomal no
preparations (fig. 6) (Pauwels et al., 1990). In cultured Fi
mixed neocortical cells exposed to transient oxygen-glu-
cose deprivation, lidocaine (100 μ M), quini preparations (fig. 6) (Pauwels et al., 1990). In cultured F-
mixed neocortical cells exposed to transient oxygen-glu-
cose deprivation, lidocaine (100 μ M), quinidine (100 μ M), th
lorcainide (10 or 100 μ M) and, un mixed neocortical cells exposed to transient oxygen-glu-
cose deprivation, lidocaine (100 μ M), quinidine (100 μ M),
lorcainide (10 or 100 μ M) and, unexpectedly, 1 mM of the
impermeant QX314 (see section II.B.3.) f cose deprivation, lidocaine (100 μ M), quarrelation (10 or 100 μ M) and, unexpection permeant QX314 (see section II.B.3 neuronal death when superimposed up ceptor blockade (Lynch et al., 1995). The ability of local an cainide (10 or 100 μ M) and, unexpectedly, 1 mM of the expermeant QX314 (see section II.B.3.) further reduced
uronal death when superimposed upon glutamate re-
ptor blockade (Lynch et al., 1995). it
The ability of local

impermeant QX314 (see section II.B.3.) further reduced
neuronal death when superimposed upon glutamate re-
ceptor blockade (Lynch et al., 1995).
The ability of local anesthetics to protect CNS white
matter (i.e., myelinate neuronal death when superimposed upon glutamate receptor blockade (Lynch et al., 1995). ii
ceptor blockade (Lynch et al., 1995). The ability of local anesthetics to protect CNS white matter (i.e., myelinated fibre tract) w ceptor blockade (Lynch et al., 1995). ity
The ability of local anesthetics to protect CNS white
matter (i.e., myelinated fibre tract) was also studied, ina
using rat optic nerves subjected to 60 min of anoxia (Stys tru
et The ability of local anesthetics to protect CNS white
matter (i.e., myelinated fibre tract) was also studied,
using rat optic nerves subjected to 60 min of anoxia (Stys
et al. 1992b; Stys, 1995). Lidocaine and procaine (0. matter (i.e., myelinated fibre tract) was also studied,
using rat optic nerves subjected to 60 min of anoxia (Stys
et al. 1992b; Stys, 1995). Lidocaine and procaine (0.1 and
1 mM) applied for 1 h before anoxia significantl using rat optic nerves subjected to 60 min of anoxia (Stys et al. 1992b; Stys, 1995). Lidocaine and procaine (0.1 and 1 mM) applied for 1 h before anoxia significantly improved postanoxic recovery of the CAP, but preanoxic et al. 1992b; Stys, 1995). Lidocaine and procaine (0.1 and 1 mM) applied for 1 h before anoxia significantly im-
proved postanoxic recovery of the CAP, but preanoxic
CAP was also depressed. The quaternary derivatives
QX314 1 mM) applied for 1 h before anoxia significantly im-
proved postanoxic recovery of the CAP, but preanoxic The
CAP was also depressed. The quaternary derivatives leak
 $QX314$ (fig. 3) (0.1 to 1.0 mM) and $QX222$ (0.3 to 3 CAP was also depressed. The quaternary derivatives $\frac{QX314}{f(g. 3)}$ (0.1 to 1.0 mM) and $\frac{QX222}{f(0.3 \text{ to } 3 \text{ mM})}$, as well as the tertiary amine bupivacaine (10 and 30 μ M), were more effective; they further improv CAP was also depressed. The quaternary derivatives leady QX314 (fig. 3) (0.1 to 1.0 mM) and QX222 (0.3 to 3 mM), et as well as the tertiary amine bupivacaine (10 and 30 water). When the term is covery from anoxia at conce $QX314$ (fig. 3) (0.1 to 1.0 mM) and $QX222$ (0.3 to 3 mM), et as well as the tertiary amine bupivacaine (10 and 30 waters), were more effective; they further improved the recovery from anoxia at concentrations that did n as well as the tertiary amine bupivacaine (10 and 30 μ M), were more effective; they further improved the recovery from anoxia at concentrations that did not block conduction. Lidocaine (0.1 mM) had previously been cond μ M), were more effective; they further improved the re-
covery from anoxia at concentrations that did not block In
conduction. Lidocaine (0.1 mM) had previously been circ
shown to delay the onset of CAP depression and conduction. Lidocaine (0.1 mM) had previously been
shown to delay the onset of CAP depression and reduce
 K^+ and Na^+ changes caused by glucose-free medium in
rabbit vagus nerve (Fink, 1982).
The fact that, at least mduction. Lidocaine (0.1 mM) had previously been
own to delay the onset of CAP depression and reduce
 $^+$ and Na⁺ changes caused by glucose-free medium in
bbit vagus nerve (Fink, 1982).
The fact that, at least in som

shown to delay the onset of CAP depression and reduce K^+ and Na^+ changes caused by glucose-free medium in rabbit vagus nerve (Fink, 1982).
The fact that, at least in some cases, local anesthetics were protective at co mal conduction is promising and particularly relevant to rabbit vagus nerve (Fink, 1982).
The fact that, at least in some cases, local anesthetics
were protective at concentrations that did not block nor-
mal conduction is promising and particularly relevant to
pharmacological The fact that, at least in some cases, local anesthetics correspondence protective at concentrations that did not block normal conduction is promising and particularly relevant to spharmacological neuroprotection. It clea were protective at concentrations that did not block normal conduction is promising and particularly relevant to pharmacological neuroprotection. It clearly suggests that it may be possible to block Na⁺ channels selectiv mal conduction is promising and particularly relevant to
pharmacological neuroprotection. It clearly suggests this
that it may be possible to block Na^+ channels selectively kg⁻¹
in anoxic regions of the CNS (i.e., wit pharmacological neuroprotection. It clearly suggests that it may be possible to block Na^+ channels selectively k in anoxic regions of the CNS (i.e., with compromised hermbrane potential) while sparing normal tissue that it may be possible to block Na⁺ channels selectively
in anoxic regions of the CNS (i.e., with compromised
membrane potential) while sparing normal tissue and
function. This can be explained in two different ways: in anoxic regions of the CNS (i.e., with compromised
membrane potential) while sparing normal tissue and
function. This can be explained in two different ways: (*a*)
the blockade of Na⁺ channels by local anesthetic is e membrane potential) while sparing normal tissue and formation. This can be explained in two different ways: (*a*) und the blockade of Na⁺ channels by local anesthetic is enhanced with membrane depolarization because the the blockade of Na⁺ channels by local anesthetic is enhanced with membrane depolarization because their actions are use- and frequency-dependent; and/or (*b*) some of these agents may be more selective to noninactivatin hanced with membrane depolarization because their actions are use- and frequency-dependent; and/or (b) some of these agents may be more selective to noninactivating (persistent) Na^+ channels. The first hypothesis may a tions are use- and frequency-dependent; and/or (b) some lives of these agents may be more selective to noninactivating we (persistent) Na⁺ channels. The first hypothesis may apply more to lidocaine and procaine, as the of these agents may be more selective to noninactivating which
(persistent) Na⁺ channels. The first hypothesis may ap-
ply more to lidocaine and procaine, as they were recain
ported to preferentially block fast Na⁺ ch ply more to lidocaine and procaine, as they were re-

ported to preferentially block fast Na^+ channels while

preserving the noninactivating Na^+ conductance (Llinás

and rapid distribution to all tissues (Gelb et al., ported to preferentially block fast $Na⁺$ channels while

(Schurr et al., 1986; Lucas et al., 1989). The protective conductance is not completely inactivated by prolonged
effect of lidocaine in this preparation was recently con-
firmed by Weber and Taylor (1994), who also showed -GATED NA⁺ CHANNELS 43
already stated (see section A.2.), fast-inactivating Na⁺
channels should not remain open in membranes depo--GATED NA⁺ CHANNELS 43
already stated (see section A.2.), fast-inactivating Na⁺
channels should not remain open in membranes depo-
larized by anoxia. This is supported by the finding that -GATED NA⁺ CHANNELS 43

already stated (see section A.2.), fast-inactivating Na⁺

channels should not remain open in membranes depo-

larized by anoxia. This is supported by the finding that

TTX delayed but did not m already stated (see section A.2.), fast-inactivating Na⁺
channels should not remain open in membranes depo-
larized by anoxia. This is supported by the finding that
TTX delayed but did not modify anoxic depolarization
(channels should not remain open in membranes depo-
larized by anoxia. This is supported by the finding that
TTX delayed but did not modify anoxic depolarization (see above, section B.). There is also evidence that $Na⁺$ larized by anoxia. This is supported by the finding that TTX delayed but did not modify anoxic depolarization (see above, section B.). There is also evidence that Na⁺ conductance is not completely inactivated by prolong TTX delayed but did not modify anoxic depolarization
(see above, section B.). There is also evidence that $Na⁺$
conductance is not completely inactivated by prolonged
depolarization, presumably because of a subpopulat (see above, section B.). There is also evidence that $Na⁺$ conductance is not completely inactivated by prolonged depolarization, presumably because of a subpopulation of persistent $Na⁺$ channels (Stafstrom et al conductance is not completely inactivated by prolonged
depolarization, presumably because of a subpopulation
of persistent Na⁺ channels (Stafstrom et al., 1985;
French et al., 1990). As the persistent Na⁺ conductance
 depolarization, presumably because of a subpopulation
of persistent Na⁺ channels (Stafstrom et al., 1985;
French et al., 1990). As the persistent Na⁺ conductance
is activated at more negative membrane potentials than
 of persistent Na⁺ channels (Stafstrom et al., 1985;
French et al., 1990). As the persistent Na⁺ conductance
is activated at more negative membrane potentials than
transient Na⁺ currents (French et al., 1990), the fo French et al., 1990). As the persistent Na⁺ conductance
is activated at more negative membrane potentials than
transient Na⁺ currents (French et al., 1990), the former
may play a dominant role in mediating Na⁺ influ is activated at more negative membrane potentials than transient Na^+ currents (French et al., 1990), the former may play a dominant role in mediating Na^+ influx during the initial stages of anoxia and energy failure (transient Na⁺ currents (French et al., 1990), the former
may play a dominant role in mediating Na⁺ influx dur-
ing the initial stages of anoxia and energy failure (Stys
et al., 1992b). Indeed, in contrast to lidocaine may play a dominant role in mediating Na^+ influx during the initial stages of anoxia and energy failure (Stys et al., 1992b). Indeed, in contrast to lidocaine, QX314, which was more effective in protecting the optic ner ing the initial stages of anoxia and energy failure (Stys et al., 1992b). Indeed, in contrast to lidocaine, QX314, which was more effective in protecting the optic nerve against anoxia, was found to be relatively specific et al., 1992b). Indeed, in contrast to lidocaine, QX314, which was more effective in protecting the optic nerve against anoxia, was found to be relatively specific for noninactivating Na^+ channels (Stafstrom et al., 198 which was more effective in protecting the optic nervagainst anoxia, was found to be relatively specific for
noninactivating Na^+ channels (Stafstrom et al., 1985
Finally, and independent of these considerations, conduct against anoxia, was found to be relatively specific
noninactivating Na^+ channels (Stafstrom et al., 19
Finally, and independent of these considerations,
comitant, partial block of K^+ conductance by local a
thetics ma noninactivating Na^+ channels (Stafstrom et al., 1988)
Finally, and independent of these considerations, co
comitant, partial block of K^+ conductance by local ane
thetics may also contribute to preservation of electro mally, and independent of these considerations, con-

mitant, partial block of K^+ conductance by local anes-

etics may also contribute to preservation of electrogen-

is (Swenson, 1981; Stolc, 1988; Stys et al., 1992b

comitant, partial block of K^+ conductance by local ane
thetics may also contribute to preservation of electrogen
esis (Swenson, 1981; Stolc, 1988; Stys et al., 1992b).
2. In vivo experimental models. High doses (i.e., which was more effective in protecting the optic nerve
against anoxia, was found to be relatively specific for
noninarity
ating Na⁺ channels (Stafstrom et al., 1985).
Finally, and independent of these considerations, co mg kg^{-1}) of lidocaine rapidly abolished electrical activity in dogs and, unlike barbiturates, reduced the brain metabolic rate 15 to 20% beyond that achieved by eliminating synaptic transmission (Astrup et al. 1981a 2. In vivo experimental models. High doses (i.e., 160 mg kg^{-1}) of lidocaine rapidly abolished electrical activity in dogs and, unlike barbiturates, reduced the brain metabolic rate 15 to 20% beyond that achieved by mg kg⁻¹) of lidocaine rapidly abolished electrical activity in dogs and, unlike barbiturates, reduced the brain metabolic rate 15 to 20% beyond that achieved by eliminating synaptic transmission (Astrup et al. 1981a; As ity in dogs and, unlike barbiturates, reduced the brain
metabolic rate 15 to 20% beyond that achieved by elim-
inating synaptic transmission (Astrup et al. 1981a; As-
trup and Sørensen, 1981). Lidocaine also delayed and
s metabolic rate 15 to 20% beyond that achieved by eliminating synaptic transmission (Astrup et al. 1981a; Astrup and Sørensen, 1981). Lidocaine also delayed and slowed K⁺ efflux produced by circulatory arrest in the dog b inating synaptic transmission (Astrup et al. 1981a; Astrup and Sørensen, 1981). Lidocaine also delayed and slowed K^+ efflux produced by circulatory arrest in the dog brain (Astrup et al., 1981c; Lantos et al., 1990b). trup and Sørensen, 1981). Lidocaine also delayed and slowed K⁺ efflux produced by circulatory arrest in the dog brain (Astrup et al., 1981c; Lantos et al., 1990b). These pioneering findings, attributed to reduction of io slowed K⁺ efflux produced by circulatory arrest in the dog brain (Astrup et al., 1981c; Lantos et al., 1990b). These pioneering findings, attributed to reduction of ion leakage (*membrane stabilizing or sealing* effect; dog brain (Astrup et al., 1981c; Lantos et al., 1990b).
These pioneering findings, attributed to reduction of ion
leakage (*membrane stabilizing or sealing* effect; Astrup
et al., 1981a, c), triggered much interest, and li ischemia. akage (*membrane stabilizing or sealing* effect; Astrup al., 1981a, c), triggered much interest, and lidocaine as subsequently tested in various models of cerebral chemia.
In contrast to the beneficial effects observed fo

et al., 1981a, c), triggered much interest, and lidocaine
was subsequently tested in various models of cerebral
ischemia.
In contrast to the beneficial effects observed following
circulatory arrest in dogs, high prophylac was subsequently tested in various models of cerebral
ischemia.
In contrast to the beneficial effects observed following
circulatory arrest in dogs, high prophylactic doses of
lidocaine (50 mg bolus followed by 50 mg kg⁻ ischemia.

In contrast to the beneficial effects observed following

circulatory arrest in dogs, high prophylactic doses of

lidocaine (50 mg bolus followed by 50 mg kg⁻¹ h⁻¹)

failed to reduce the size of infarct pro In contrast to the beneficial effects observed following
circulatory arrest in dogs, high prophylactic doses of
lidocaine (50 mg bolus followed by 50 mg kg⁻¹ h⁻¹)
failed to reduce the size of infarct produced by MCA
o lidocaine (50 mg bolus followed by 50 mg kg⁻¹ h⁻¹) failed to reduce the size of infarct produced by MCA occlusion in cats (Shokunbi et al., 1986). A much lower dose, administered as a single bolus (10 mg kg⁻¹), did lidocaine (50 mg bolus followed by 50 mg $kg^{-1} h^{-1}$)
failed to reduce the size of infarct produced by MCA
occlusion in cats (Shokunbi et al., 1986). A much lower
dose, administered as a single bolus (10 mg kg^{-1}), did
no failed to reduce the size of infarct produced by MCA occlusion in cats (Shokunbi et al., 1986). A much lower dose, administered as a single bolus (10 mg kg⁻¹), did $\frac{1}{\infty}$ not alter the infarct volume, but temporari somatosensory evoked potentials (Gelb et al., 1988). In this model, only intermediary, prolonged dosage (5 mg kg^{-1} in 3 to 5 min, immediately followed by 3 mg kg^{-1} dose, administered as a single bolus (10 mg kg⁻¹), did
not alter the infarct volume, but temporarily preserved
somatosensory evoked potentials (Gelb et al., 1988). In
this model, only intermediary, prolonged dosage (5 m somatosensory evoked potentials (Gelb et al., 1988). In
this model, only intermediary, prolonged dosage (5 mg
kg⁻¹ in 3 to 5 min, immediately followed by 3 mg kg⁻¹
h⁻¹ for 25 min before MCA occlusion; and 2 mg kg⁻¹ this model, only intermediary, prolonged dosage $(5 \text{ mg} \text{ kg}^{-1} \text{ in } 3 \text{ to } 5 \text{ min}, \text{immediately followed by } 3 \text{ mg kg}^{-1} \text{ h}^{-1}$ for 25 min before MCA occlusion; and 2 mg kg⁻¹ h⁻¹ for the rest of the experiment) reduced the infarct vo kg⁻¹ in 3 to 5 min, immediately followed by 3 mg kg⁻¹ h⁻¹ for 25 min before MCA occlusion; and 2 mg kg⁻¹ h⁻¹ for the rest of the experiment) reduced the infarct volume produced by 3 h of MCA occlusion and preser h^{-1} for 25 min before MCA occlusion; and 2 mg kg⁻¹ h^{-1}
for the rest of the experiment) reduced the infarct vol-
ume produced by 3 h of MCA occlusion and preserved
local cerebral blood flow in the infarct border (S for the rest of the experiment) reduced the infarct volume produced by 3 h of MCA occlusion and preserved local cerebral blood flow in the infarct border (Shokunbi et al., 1990). The lack of protection with high doses of l ume produced by 3 h of MCA occlusion and preserved
local cerebral blood flow in the infarct border (Shokunbi
et al., 1990). The lack of protection with high doses of
lidocaine in focal ischemia may be due to hypotension,
 local cerebral blood flow in the infarct border (Shokunb et al., 1990). The lack of protection with high doses of lidocaine in focal ischemia may be due to hypotension which may further impair cerebral perfusion (Shokunb et al., 1990). The lack of protection with high doses of lidocaine in focal ischemia may be due to hypotension, which may further impair cerebral perfusion (Shokunbi et al., 1986). With the single bolus of 10 mg kg⁻¹ lid lidocaine in focal ischemia may be due to hypotension,
which may further impair cerebral perfusion (Shokunbi
et al., 1986). With the single bolus of 10 mg kg^{-1} lido-
caine, plasma concentrations of lidocaine may hav which may further impair cerebral perfusion (Shokunbi
et al., 1986). With the single bolus of 10 mg kg^{-1} lido-
caine, plasma concentrations of lidocaine may have de-
cayed rapidly because of extensive hepatic metabolism al., 1986). With the single bolus of 10 mg kg^{-1} lido-
ine, plasma concentrations of lidocaine may have de-
yed rapidly because of extensive hepatic metabolism
ind rapid distribution to all tissues (Gelb et al., 1988 caine, plasma concentrations of lidocaine may have de-
cayed rapidly because of extensive hepatic metabolism
and rapid distribution to all tissues (Gelb et al., 1988).
The protective effect of prolonged lidocaine treatment

⁴⁴
to prevention of Na⁺ influx with a concomitant reduc-
tion in energy demand, supplemented by *membrane st* URENJAK AND OBRENOVITCH
to prevention of Na⁺ influx with a concomitant reduc- D. Anticonvi
tion in energy demand, supplemented by *membrane sta*-
bilization. However, prevention of high intracranial to a lesser of *Bilization* of Na⁺ influx with a concomitant reduction in energy demand, supplemented by *membrane* stabilization. However, prevention of high intracranial pressure and improved perfusion of the infarct border to prevention of Na^+ influx with a concomitant reduction in energy demand, supplemented by *membrane stabilization*. However, prevention of high intracranial pressure and improved perfusion of the infarct border could a to prevention of Na⁺ influx with a concomitant reduction in energy demand, supplemented by *membrane stabilization*. However, prevention of high intracranial pressure and improved perfusion of the infarct border could al tion in energy demand, supplemented by *membrane stoilization*. However, prevention of high intracraniing pressure and improved perfusion of the infarct bordcould also have played a part (Shokunbi et al., 1990) The latter bilization. However, prevention of high intracranial to a pressure and improved perfusion of the infarct border avais could also have played a part (Shokunbi et al., 1990). devided to the latter must be emphasized: lidoca pressure and improved perfusion of the infarct border
could also have played a part (Shokunbi et al., 1990).
The latter must be emphasized: lidocaine pretreatment
(5 to 15 mg kg⁻¹) was not beneficial in rats subjected t (5 to 15 mg kg⁻¹) was not beneficial in rats subjected to
transient global cerebral ischemia, because there was no
potential for collateral circulation (Warner et al., 1988;
Sutherland et al., 1989).
In a rabbit model o

transient global cerebral ischemia, because there was no
potential for collateral circulation (Warner et al., 1988;
Sutherland et al., 1989).
In a rabbit model of 20-min incomplete global isch-
emia, sustained treatment w transient global cerebral ischemia, because there was no
potential for collateral circulation (Warner et al., 1988; tl
Sutherland et al., 1989).
In a rabbit model of 20-min incomplete global isch-
emia, sustained treatment Sutherland et al., 1989).
In a rabbit model of 20-min incomplete global isemia, sustained treatment with lidocaine (12 mg kg h⁻¹ starting 15 min before ischemia and continuing 60 min after the ischemia onset) significan In a rabbit model of 20-min incomplete global isomia, sustained treatment with lidocaine $(12 \text{ mg} \text{ kg})$
 h^{-1} starting 15 min before ischemia and continuing $f(60 \text{ min})$ after the ischemia onset) significantly acceled
 emia, sustained treatment with lidocaine (12 mg kg^{-1})
h⁻¹ starting 15 min before ischemia and continuing for
60 min after the ischemia onset) significantly acceler-
ated the recovery of EEG and evoked-potential ampli h^{-1} starting 15 min before ischemia and continuing for B
60 min after the ischemia onset) significantly acceler-
ated the recovery of EEG and evoked-potential ampli-
tudes (Rasool et al., 1990). However, this effect ma 60 min after the ischemia onset) significantly acc
ated the recovery of EEG and evoked-potential ar
tudes (Rasool et al., 1990). However, this effect may
represent strict cerebral protection, because 20 m
incomplete global ated the recovery of EEG and evoked-potential amplitudes (Rasool et al., 1990). However, this effect may no
represent strict cerebral protection, because 20 min o
incomplete global ischemia may not lead to histopatho
logic tudes (Rasool et al., 1990). However, this effect may not liprepresent strict cerebral protection, because 20 min of adincomplete global ischemia may not lead to histopathological changes in this model (Rasool et al., 199 represent strict cerebral protection, because 20 min of incomplete global ischemia may not lead to histopatho-
logical changes in this model (Rasool et al., 1990). Similarly, in dogs subjected to repeated short episodes of incomplete global ischemia may not lead to histopatho-
logical changes in this model (Rasool et al., 1990). Sim-
ilarly, in dogs subjected to repeated short episodes of
circulatory arrest, 100 mg kg^{-1} lidocaine favourab logical changes in this model (Rasool et al., 1990).
ilarly, in dogs subjected to repeated short episod
circulatory arrest, 100 mg kg^{-1} lidocaine favourabl
fluenced both the cessation of EEG activity and its
titution du rly, in dogs subjected to repeated short episodes of
culatory arrest, 100 mg kg⁻¹ lidocaine favourably in-
lenced both the cessation of EEG activity and its res-
ution during reperfusion (Lantos et al., 1990a).
Intraven

fluenced both the cessation of EEG activity and its restitution during reperfusion (Lantos et al., 1990a).
Intravenous administration of lidocaine (5 mg kg⁻¹)
before acute cerebral ischemia induced by air embolism
in ca titution during reperfusion (Lantos et al., 1990a).

Intravenous administration of lidocaine (5 mg kg^{-1})

before acute cerebral ischemia induced by air embolism

in cats reduced the decrement in cortical somatosensory
 Intravenous administration of lidocaine (5 mg kg⁻before acute cerebral ischemia induced by air embolision cats reduced the decrement in cortical somatosensor evoked responses and improved their recovery (Evans d., 1984). before acute cerebral ischemia induced by air embolism
in cats reduced the decrement in cortical somatosensory
evoked responses and improved their recovery (Evans et
al., 1984). A similar effect was observed with this trea in cats reduced the decrement in cortical somatosensory
evoked responses and improved their recovery (Evans et
al., 1984). A similar effect was observed with this treat-
ment after experimental spinal cord injury in cats (evoked responses and improved their recovery (Evans et al., 1984). A similar effect was observed with this treatment after experimental spinal cord injury in cats (Kobrine et al., 1984). Repeated administration of lidocain al., 1984). A similar effect was observed with this treat-
ment after experimental spinal cord injury in cats (Kobrine et al., 1984). Repeated administration of lidocaine,
superimposed upon hyperbaric treatment, ameliorat ment after experimental spinal cord injury in cats (Kobrine et al., 1984). Repeated administration of lidocaine, superimposed upon hyperbaric treatment, ameliorated the delayed deterioration of evoked potential associated brine et al., 1984). Repeated administration of lidocaine
superimposed upon hyperbaric treatment, ameliorate
the delayed deterioration of evoked potential associate
with internal carotid air embolism in dogs (Dutka et al.
 superimposed upon hyperbaric treatment, ameliorated
the delayed deterioration of evoked potential associated Na
with internal carotid air embolism in dogs (Dutka et al., pan
1992). However, as the vascular endothelium is the delayed deterioration of evoked potential associat
with internal carotid air embolism in dogs (Dutka et a
1992). However, as the vascular endothelium is da
aged in all of these models, lidocaine protection could
linked with internal carotid air emboli
1992). However, as the vascul
aged in all of these models, lido
linked to its effect on granulocy
tion (MacGregor et al., 1980).
The variety of animal models 92). However, as the vascular endothelium is damed in all of these models, lidocaine protection could be zure and the variety of animal models and dose regimens used these studies preclude a reliable synthesis of the data

aged in all of these models, lidocaine protection could be linked to its effect on granulocyte adherence and migration (MacGregor et al., 1980).
The variety of animal models and dose regimens used in these studies preclude linked to its effect on granulocyte adherence and migration (MacGregor et al., 1980).
The variety of animal models and dose regimens used
in these studies preclude a reliable synthesis of the data.
Nevertheless, several i The variety of animal models and dose regimens used
in these studies preclude a reliable synthesis of the data.
Nevertheless, several important features emerge: (a) as
with other drugs, lidocaine treatment may be effecti Nevertheless, several important features emerge: (a) as
with other drugs, lidocaine treatment may be effective
only with focal or incomplete global ischemia; (b) sys-
temic administration of lidocaine must be sustained; with other drugs, lidenly with focal or internic administration
temic administration
and (c) high doses m
diovascular toxicity.
3. Clinical observa only with focal or incomplete global ischemia; (b) systemic administration of lidocaine must be sustained;
and (c) high doses may not be effective because of car-
diovascular toxicity.
3. Clinical observations. Artru and c

ity. temic administration of lidocaine must be sustained;
and (c) high doses may not be effective because of car-
diovascular toxicity.
3. Clinical observations. Artru and coworkers (1991)
have advocated i.v. perfusion of lidoc and (c) high doses may not be effective because of cadiovascular toxicity.
3. Clinical observations. Artru and coworkers (199)
have advocated i.v. perfusion of lidocaine at high dose, i
replace or supplement barbiturate (t diovascular toxicity.

3. Clinical observations. Artru and coworkers (1991)

have advocated i.v. perfusion of lidocaine at high dose, to

replace or supplement barbiturate (thiopental) treat-

ment of refractory intracrani 3. Clinical observations. Artru and coworkers (1991)
have advocated i.v. perfusion of lidocaine at high dose, to
replace or supplement barbiturate (thiopental) treat-
ment of refractory intracranial hypertension and acute
 have advocated i.v. perfusion of lidocaine at high dose, to
replace or supplement barbiturate (thiopental) treat-
ment of refractory intracranial hypertension and acute
cerebral ischemia. One major advantage of lidocaine
o replace or supplement barbiturate (thiopental) treatment of refractory intracranial hypertension and acute cerebral ischemia. One major advantage of lidocaine over barbiturate is its rapid elimination upon cessation of tre cerebral ischemia. One major advantage of lidocaine
over barbiturate is its rapid elimination upon cessation
of treatment. Naturally, the authors have stressed the
necessity for simultaneous anticonvulsant therapy be-
caus over barbiturate is its rapid elimination upon cessation cause of lidocaine epileptogenicity and for close cardio-

D. Anticonvulsants Acting on Na⁺ Channels
This section focuses on phenytoin (and carbamazepine

could also have played a part (Shokunbi et al., 1990).

The latter must be emphasized: lidocaine pretreatment

(5 to 15 mg kg⁻¹) was not beneficial in rats subjected to

transient global cerebral ischemia, because there fluenced both the cessation of EEG activity and its res-
itution during reperfusion (Lantos et al., 1990a).
 $30 \mu M$) concentrations in some preparations (Twombly et
Intravenous administration of lidocaine (5 mg kg^{-1}) al D. Anticonvulsants Acting on $Na⁺$ Channels
This section focuses on phenytoin (and carbamazepine
to a lesser extent) because large amounts of data are
available for this drug (fig. 7). However, the rationale D. Anticonvulsants Acting on $Na⁺$ Channels
This section focuses on phenytoin (and carbamazepine
to a lesser extent) because large amounts of data are
available for this drug (fig. 7). However, the rationale
developed D. Anticonvulsants Acting on Na Channels
This section focuses on phenytoin (and carbamazepine
to a lesser extent) because large amounts of data are
available for this drug (fig. 7). However, the rationale
developed here a This section focuses on phenytoin (and carbamaze)
to a lesser extent) because large amounts of data
available for this drug (fig. 7). However, the ration
developed here applies to other anticonvulsants
primarily target Na to a lesser extent) because large amounts of data are available for this drug (fig. 7). However, the rationale developed here applies to other anticonvulsants that primarily target Na⁺ channels at therapeutic concentrat available for this drug (fig. 7). However, the rationale developed here applies to other anticonvulsants that primarily target Na^+ channels at therapeutic concentrations (Catterall, 1987). These include valproate (Van d developed here applies to other anticonvulsants that
primarily target Na⁺ channels at therapeutic concentra-
tions (Catterall, 1987). These include valproate (Van den
Berg et al., 1993), flunarizine (fig. 8) (see section primarily target Na⁺ channels at therapeutic concentrations (Catterall, 1987). These include valproate (Van den Berg et al., 1993), flunarizine (fig. 8) (see section V.A.1.) that has also anticonvulsant activity (Wauquie Berg et al., 1993), flunarizine (fig. 8) (see section V.A
that has also anticonvulsant activity (Wauquier et
1986; Rogawski and Porter, 1990), lamotrigine (fig
see section V.B.), and compounds under developme
such as remac Berg et al., 1993), flunarizine (fig. 8) (see section V.A.1.)
that has also anticonvulsant activity (Wauquier et al.,
1986; Rogawski and Porter, 1990), lamotrigine (fig. 9;
see section V.B.), and compounds under developmen that has also anticonvulsant activity (Wauquier et al., 1986; Rogawski and Porter, 1990), lamotrigine (fig. 9; see section V.B.), and compounds under development, such as remacemide (FPL 12924; Palmer et al., 1993; Bannan 1986; Rogawski and Porter, 1990), lamotrigine (fig. 9
see section V.B.), and compounds under developmen
such as remacemide (FPL 12924; Palmer et al., 199
Bannan et al., 1994). Our analysis is also intentionall
focused on such as remacemide (FPL 12924; Palmer et al., 1993; Bannan et al., 1994). Our analysis is also intentionally focused on anticonvulsant interactions with Na^+ channels, but, as clinically effective anticonvulsants are Bannan et al., 1994). Our analysis is also intentional focused on anticonvulsant interactions with Na^+ channels, but, as clinically effective anticonvulsants are ilipophilic compounds, they are expected to have mult focused on anticonvulsant interactions with Na^+ channels, but, as clinically effective anticonvulsants are all lipophilic compounds, they are expected to have multiple actions on excitable membranes, particularly at nels, but, as clinically effective anticonvulsants are
lipophilic compounds, they are expected to have mult
actions on excitable membranes, particularly at sur
therapeutic concentrations. For example, phenytoin
reported to lipophilic compounds, they are expected to have multiple
actions on excitable membranes, particularly at supra-
therapeutic concentrations. For example, phenytoin was
reported to displace [³H]benzodiazepine from synapto therapeutic concentrations. For example, phenytoin was
reported to displace $[{}^{3}H]$ benzodiazepine from synaptosomal receptors (Bowling and DeLorenzo, 1982), and to therapeutic concentrations. For example, phenytoin was

reported to displace [³H]benzodiazepine from synaptoso-

mal receptors (Bowling and DeLorenzo, 1982), and to

block voltage-sensitive Ca²⁺ channels (Messing et a reported to displace [³H]benzodiazepine from synaptosomal receptors (Bowling and DeLorenzo, 1982), and to block voltage-sensitive Ca^{2+} channels (Messing et al., 1985; Yaari et al., 1986), even at the relatively low (mal receptors (Bowling and DeLorenzo, 1982), and to
block voltage-sensitive Ca^{2+} channels (Messing et al.,
1985; Yaari et al., 1986), even at the relatively low (3 to
30 μ M) concentrations in some preparations (Twom 1985; Yaari et al., 1986), even at the relatively low (3 to 1985; Yaari et al., 1986), even at the relatively low $(3 \text{ to } 30 \mu)$ concentrations in some preparations (Twombly et al., 1988). Wamil and McLean (1993) reported that phenytoin inhibited NMDA receptor-mediated depolari 30μ M) concentrations in some preparations (Twombly et al., 1988). Wamil and McLean (1993) reported that phenytoin inhibited NMDA receptor-mediated depolarizing responses of mouse spinal neurons in culture, but this obs al., 1988). Wamil and McLean (1993) reported that phe-
nytoin inhibited NMDA receptor-mediated depolarizing
responses of mouse spinal neurons in culture, but this
observation was not confirmed (Sheridan et al., 1994;
Laffl nytoin inhibited NMDA receptor-mediated depolarizing
responses of mouse spinal neurons in culture, but this
observation was not confirmed (Sheridan et al., 1994;
Laffling et al., 1995). These secondary actions may con-
tri responses of mouse spinal neurons in
observation was not confirmed (Sheri
Laffling et al., 1995). These secondary
tribute significantly to the therapeut
type of drug in epilepsy and ischemia.
1. Phenytoin and carbamazepine *1. Phenytoin was not confirmed (Sheridan et al., 1994;*
1. Phing et al., 1995). These *secondary* actions may con-
bute significantly to the therapeutic effects of this
pe of drug in epilepsy and ischemia.
1. Phenytoin

fribute significantly to the therapeutic effects of this type of drug in epilepsy and ischemia.

1. Phenytoin and carbamazepine: interactions with Na^+ channels. Phenytoin and carbamazepine (fig. 7) are particularly effe type of drug in epilepsy and ischemia.

1. Phenytoin and carbamazepine: interactions with
 Na^+ channels. Phenytoin and carbamazepine (fig. 7) are

particularly effective anticonvulsants in the manage-

ment of partial s 1. Phenytoin and carbamazepine: interactions with $Na⁺ channels$. Phenytoin and carbamazepine (fig. 7) are particularly effective anticonvulsants in the management of partial seizures and generalized tonic-clonic seizures. Th $Na⁺ channels.$ Phenytoin and carbamazepine (fig. 7) are particularly effective anticonvulsants in the management of partial seizures and generalized tonic-clonic seizures. Their effectiveness is probably related to their abi particularly effective anticonvulsants in the management of partial seizures and generalized tonic-clonic seizures. Their effectiveness is probably related to their ability to inhibit high-frequency action potential firing

FIG. 7. Structure of the anticonvulsants phenytoin and carbam-**EXECUTE 25 CH₃**
PD85,639
FIG. 7. Structure of the anticonvulsants phenytoin and carbam-
azepine, acting primarily via Na⁺ channel block at therapeutic con-
centrations, and of PD85,639, a novel phenylacetamide struct PD85,639
FIG. 7. Structure of the anticonvulsants phenytoin and carbam-
azepine, acting primarily via Na⁺ channel block at therapeutic con-
centrations, and of PD85,639, a novel phenylacetamide structurally
related to te

HARMACOLOGICAL REVIEW

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me, **lifarizine and KB-2796.**

FIG. 9. Structures of the anticonvulsant lamotrigine and it rivatives BW100CC87 and BW619C89 (often named *glutama* **lease inhibitors).** FIG. 9. Structures of the anticonvulsant lamotrigine and its derivatives BW100CC87 and BW619C89 (often named *glutamate-re-*
lease inhibitors).
(Yaari et al., 1986; Rogawski and Porter, 1990). At ther-

rivatives BW100CC87 and BW619C89 (often named *glutamate-re-*
lease inhibitors).
(Yaari et al., 1986; Rogawski and Porter, 1990). At ther-
apeutic concentrations, phenytoin and carbamazepine
interact preferentially with ne iease inhibitors).
(Yaari et al., 1986; Rogawski and Porter, 1990). At ther-
apeutic concentrations, phenytoin and carbamazepine
interact preferentially with neuronal Na⁺ channels
(Catterall, 1987; Rogawski and Porter, 1 (Yaari et al., 1986; Rogawski and Porter, 1990). At ther-
apeutic concentrations, phenytoin and carbamazepine
interact preferentially with neuronal Na⁺ channels
(Catterall, 1987; Rogawski and Porter, 1990). They dis-
pla (Yaari et al., 1986; Rogawski and Porter, 1990). At therapeutic concentrations, phenytoin and carbamazepine
interact preferentially with neuronal $Na⁺$ channels
(Catterall, 1987; Rogawski and Porter, 1990). They dis-
 apeutic concentrations, phenytoin and carbamazepine
interact preferentially with neuronal Na⁺ channels
(Catterall, 1987; Rogawski and Porter, 1990). They dis-
place BTX, partly by increasing the rate of dissociation
of t interact preferentially with neuronal Na⁺ channels (Catterall, 1987; Rogawski and Porter, 1990). They dis-
place BTX, partly by increasing the rate of dissociation
of the toxin-receptor complex (Willow and Catterall,
19 (Catterall, 1987; Rogawski and Porter, 1990). They dis-
place BTX, partly by increasing the rate of dissociation shif
of the toxin-receptor complex (Willow and Catterall, syn
1982; Francis and McIntyre-Burnham, 1992) and place BTX, partly by increasing the rate of dissociation
of the toxin-receptor complex (Willow and Catteral
1982; Francis and McIntyre-Burnham, 1992) and inhibi
veratridine- and BTX-induced Na⁺ and Ca²⁺ uptake is
mous of the toxin-receptor complex (Willow and Catterall, 1982; Francis and McIntyre-Burnham, 1992) and inhibit veratridine- and BTX-induced Na⁺ and Ca²⁺ uptake in mouse neuroblastoma and rat brain synaptosomes (Catterall, 1982; Francis and McIntyre-Burnham, 1992) and inhibit
veratridine- and BTX-induced Na⁺ and Ca²⁺ uptake in
mouse neuroblastoma and rat brain synaptosomes (Cat-
terall, 1981; Ferrendelli and Daniels-McQueen, 1982;
Willo veratridine- and BTX-induced Na⁺ and Ca²⁺ uptake in
mouse neuroblastoma and rat brain synaptosomes (Cat-
terall, 1981; Ferrendelli and Daniels-McQueen, 1982;
Willow et al., 1984). Taken together, these studies dem-
on mouse neuroblastoma and rat brain synaptosomes (Caterall, 1981; Ferrendelli and Daniels-McQueen, 1982
Willow et al., 1984). Taken together, these studies demonstrate that phenytoin and carbamazepine, like locates
anestheti terall, 1981; Ferrendelli and Daniels-McQueen, 1982;
Willow et al., 1984). Taken together, these studies demonstrate that phenytoin and carbamazepine, like local
anesthetics, are allosteric inhibitors of neurotoxin bind-
i onstrate that phenytoin and carbamazepine, like local anesthetics, are allosteric inhibitors of neurotoxin binding and action at receptor 2 on Na⁺ channels (fig. 3). Specific [³H]phenytoin binding to rat brain membran onstrate that phenytoin and carbamazepine, like local
anesthetics, are allosteric inhibitors of neurotoxin bind-
ing and action at receptor 2 on Na⁺ channels (fig. 3).
Specific [³H]phenytoin binding to rat brain membr anesthetics, are allosteric inhibitors of neurotoxin binding and action at receptor 2 on Na^+ channels (fig. 3 Specific [³H]phenytoin binding to rat brain membrane was also inhibited by drugs known to interact with Na ing and action at receptor 2 on Na⁺ channels (fig. Specific [³H]phenytoin binding to rat brain membra was also inhibited by drugs known to interact with l channels, including site-specific neurotoxins, local and theti Burnham, 1992). as also inhibited by drugs known to interact with Na⁺ ade
annels, including site-specific neurotoxins, local anes-
etics and antiarrhythmics (Francis and McIntyre-effic
rrhham, 1992).
Voltage-clamp studies have shown tha

thetics and antiarrhythmics (Francis and McIntyre-Burnham, 1992).
Voltage-clamp studies have shown that phenytoin and carbamazepine block, in a voltage- and frequency-depen-

 $-$ GATED NA⁺ CHANNELS 45
dent manner, Na⁺ channels in central neurons, with a
stronger block at more depolarized voltage and higher -GATED NA⁺ CHANNELS 45
dent manner, Na⁺ channels in central neurons, with a
stronger block at more depolarized voltage and higher
frequencies (Connors, 1981; McLean and MacDonald, GATED NA⁺ CHANNELS
dent manner, Na⁺ channels in central neurons, with a
stronger block at more depolarized voltage and highe
frequencies (Connors, 1981; McLean and MacDonald
1983; Matsuki et al., 1984; Willow et al., 1 dent manner, Na⁺ channels in central neurons, with a
stronger block at more depolarized voltage and higher
frequencies (Connors, 1981; McLean and MacDonald,
1983; Matsuki et al., 1984; Willow et al., 1985). Several
featu stronger block at more depolarized voltage and higher
frequencies (Connors, 1981; McLean and MacDonald,
1983; Matsuki et al., 1984; Willow et al., 1985). Several
features of phenytoin's action on Na⁺ currents have
sugge frequencies (Connors, 1981; McLean and MacDonald, 1983; Matsuki et al., 1984; Willow et al., 1985). Several features of phenytoin's action on Na⁺ currents have suggested preferential binding of the drug to the inacti-va frequencies (Connors, 1981; McLean and MacDonald, 1983; Matsuki et al., 1984; Willow et al., 1985). Several features of phenytoin's action on Na⁺ currents have suggested preferential binding of the drug to the inactivat 1983; Matsuki et al., 1984; Willow et al., 1985). Several features of phenytoin's action on $Na⁺$ currents have suggested preferential binding of the drug to the inactivated state of the channel. For example, phenytoi features of phenytoin's action on $Na⁺$ currents has suggested preferential binding of the drug to the inaccuted state of the channel. For example, phenyto shifted the steady state inactivation curve for $Na⁺$ cur suggested preferential binding of the drug to the inactivated state of the channel. For example, phenytoin shifted the steady state inactivation curve for Na⁺ current to more hyperpolarized potentials and also markedly vated state of the channel. For example, phenytoin
shifted the steady state inactivation curve for Na⁺ cur-
rent to more hyperpolarized potentials and also mark-
edly slowed recovery from inactivation (Matsuki et al.,
19 shifted the steady state inactivation curve for Na⁺ current to more hyperpolarized potentials and also markedly slowed recovery from inactivation (Matsuki et al., 1984; Willow et al., 1985; Shwartz and Grigat, 1989; Rags rent to more hyperpolarized potentials and also markedly slowed recovery from inactivation (Matsuki et al., 1984; Willow et al., 1985; Shwartz and Grigat, 1989; Ragsdale et al., 1991; Lang et al., 1993). A feature that may edly slowed recovery from inactivation (Matsuki et al., 1984; Willow et al., 1985; Shwartz and Grigat, 1989; Ragsdale et al., 1991; Lang et al., 1993). A feature that may be peculiar to phenytoin is that effective blockade 1984; Willow et al., 1985; Shwartz and Grigat, 1989;
Ragsdale et al., 1991; Lang et al., 1993). A feature that
may be peculiar to phenytoin is that effective blockade
requires relatively long depolarizations (at least 1 s) Ragsdale et al., 1991; Lang et al., 1993). A feature that
may be peculiar to phenytoin is that effective blockade
requires relatively long depolarizations (at least 1 s)
(Matsuki et al., 1984; Willow et al., 1985; Kuo and may be peculiar to phenytoin is that effective blockade
requires relatively long depolarizations (at least 1 s)
(Matsuki et al., 1984; Willow et al., 1985; Kuo and Bean,
1994). Kuo and Bean (1994) showed in voltage-clamped requires relatively long depolarizations (at least 1 s)
(Matsuki et al., 1984; Willow et al., 1985; Kuo and Bean,
1994). Kuo and Bean (1994) showed in voltage-clamped
rat hippocampal neurons that slow development of
blocka 1994). Kuo and Bean (1994) showed in voltage-clamped
rat hippocampal neurons that slow development of
blockade does not reflect selective binding of phenytoin
to slow inactivated states of the channels, because block-
ade rat hippocampal neurons that slow development of blockade does not reflect selective binding of phenytoin to slow inactivated states of the channels, because blockade developed faster, and required less depolarized voltage rat hippocampal neurons that slow development of blockade does not reflect selective binding of phenytoin to slow inactivated states of the channels, because blockade developed faster, and required less depolarized voltage blockade does not reflect selective binding of phenytoin
to slow inactivated states of the channels, because block-
ade developed faster, and required less depolarized volt-
ages, than did slow inactivation. Instead, it ap to slow inactivated states of the channels, because block-
ade developed faster, and required less depolarized volt-
ages, than did slow inactivation. Instead, it appears that
phenytoin binds tightly but slowly to fast in ade developed faster, and required less depolarized voltages, than did slow inactivation. Instead, it appears that phenytoin binds tightly but slowly to fast inactivated states of the Na⁺ channels. Regardless of how phe ages, than did slow inactivation. Instead, it appears the phenytoin binds tightly but slowly to fast inactivated states of the Na⁺ channels. Regardless of how phenytoi blocks inactivated Na⁺ channels, the end result i phenytoin binds tightly but slowly to fast inactivated
states of the Na⁺ channels. Regardless of how phenytoin
blocks inactivated Na⁺ channels, the end result is a
delayed transition from inactivated to closed and avai states of the Na⁺ channels. Regardless of how phenytoin
blocks inactivated Na⁺ channels, the end result is a
delayed transition from inactivated to closed and avail-
able channels and therefore to an increased fraction blocks inactivated Na⁺ channels, the end redelayed transition from inactivated to closed a
able channels and therefore to an increased fichannels in the inactivated state (Matsuki et
Catterall, 1987; Rogawski and Porter, *2. Neuroprotection in accession in accessed and avail-*
2. Neuroprotection in the inactivated state (Matsuki et al., 1984;
2. Neuroprotection in vitro. In the rat optic nerve, a
presentative white matter tract (see se

representative which are increased fraction of channels in the inactivated state (Matsuki et al., 1984; Catterall, 1987; Rogawski and Porter, 1990).

2. *Neuroprotection in vitro*. In the rat optic nerve, a representative channels in the inactivated state (Matsuki et al., 1984;
Catterall, 1987; Rogawski and Porter, 1990).
2. Neuroprotection in vitro. In the rat optic nerve, a
representative white matter tract (see section IV.A.),
both pheny Catterall, 1987; Rogawski and Porter, 1990).

2. Neuroprotection in vitro. In the rat optic nerve, a

representative white matter tract (see section IV.A.),

both phenytoin and carbamazepine protected against

anoxic injur 2. *Neuroprotection in vitro*. In the rat optic nerve, a representative white matter tract (see section IV.A.), both phenytoin and carbamazepine protected against anoxic injury at concentrations below those inhibiting CAP representative white matter tract (see section IV.A
both phenytoin and carbamazepine protected again
anoxic injury at concentrations below those inhibiti
CAP and below (1/6) the therapeutic range used to cont
epilepsy (Fe both phenytoin and carbamazepine protected against
anoxic injury at concentrations below those inhibiting
CAP and below $(\frac{1}{6})$ the therapeutic range used to control
epilepsy (Fern et al., 1993). Pretreatment with pheny anoxic injury at concentrations below those inhibiting CAP and below $\frac{1}{6}$ the therapeutic range used to control epilepsy (Fern et al., 1993). Pretreatment with phenytoin $(20 \mu M)$ also protected rat hippocampal slice CAP and below $(\frac{1}{6})$ the therapeutic range used to contrepilepsy (Fern et al., 1993). Pretreatment with phention (20 μ M) also protected rat hippocampal slice against 10 min of hypoxia, as assessed by improve recover epilepsy (Fern et al., 1993). Pretreatment with phenytoin (20 μ M) also protected rat hippocampal slices against 10 min of hypoxia, as assessed by improved recovery of synaptically evoked population spikes (Ken-
ny and toin (20 μ M) also protected rat hippocampal slices
against 10 min of hypoxia, as assessed by improved
recovery of synaptically evoked population spikes (Ken-
ny and Sheridan, 1992). In the same preparation ex-
posed to against 10 min of hypoxia, as assessed by improved
recovery of synaptically evoked population spikes (Ken-
ny and Sheridan, 1992). In the same preparation ex-
posed to hypoxia/glucose-free medium, phenytoin (5 to
 $\frac{3}{8}$ recovery of synaptically evoked population spikes (Ken-
ny and Sheridan, 1992). In the same preparation ex-
posed to hypoxia/glucose-free medium, phenytoin (5 to
100 μ M) concentration-dependently delayed negative DC
shi ny and Sheridan, 1992). In the same preparation ex-
posed to hypoxia/glucose-free medium, phenytoin (5 to
 100μ M) concentration-dependently delayed negative DC
shifts (i.e., anoxic depolarization), improved recovery of
 posed to hypoxia/glucose-free medium, phenytoin (5 to 100μ M) concentration-dependently delayed negative DC shifts (i.e., anoxic depolarization), improved recovery of synaptic potentials and protected against histologic 100μ M) concentration-dependently delayed negative DC
shifts (i.e., anoxic depolarization), improved recovery of
synaptic potentials and protected against histologica
damage (Weber and Taylor, 1994). It is important to
 shifts (i.e., anoxic depolarization), improved recover
synaptic potentials and protected against histolog
damage (Weber and Taylor, 1994). It is importan
emphasize that, as with TTX (in some models) and l
caine (see above, synaptic potentials and protected against histological
damage (Weber and Taylor, 1994). It is important to
emphasize that, as with TTX (in some models) and lido-
caine (see above, sections B. and C.), effective neuropro-
t damage (Weber and Taylor, 1994). It is important to emphasize that, as with TTX (in some models) and lidecaine (see above, sections B. and C.), effective neuroprotection by phenytoin was achievable without blocking synapt emphasize that, as with TTX (in some models) and lido-
caine (see above, sections B. and C.), effective neuropro-
tection by phenytoin was achievable without blocking
synaptic potentials or presynaptic fiber volleys. In co caine (see above, sections B. and C.), effective neuroprotection by phenytoin was achievable without blocking synaptic potentials or presynaptic fiber volleys. In contrast, 10 and 100 μ M of phenytoin alone failed to pr tection by phenytoin was achievable without blocking
synaptic potentials or presynaptic fiber volleys. In con-
trast, 10 and 100 μ M of phenytoin alone failed to protect
murine cultured cortical neurons from injury indu synaptic potentials or presynaptic fiber volleys. In co
trast, 10 and 100 μ M of phenytoin alone failed to prote
murine cultured cortical neurons from injury induced loxygen-glucose deprivation; phenytoin only became $\$ trast, 10 and 100 μ M of ph
murine cultured cortical noxygen-glucose deprivatio
fective when combined w.
ade (Lynch et al., 1995).
Phenytoin was reporte

oxygen-glucose deprivation; phenytoin only became effective when combined with glutamate receptor block-
ade (Lynch et al., 1995).
Phenytoin was reported to have limited antagonist
efficacy against kainate neurotoxicity in fective when combined with glutamate receptor block-
ade (Lynch et al., 1995).
Phenytoin was reported to have limited antagonist
efficacy against kainate neurotoxicity in vivo (Zaczek et
al., 1978), and studies of its acti ade (Lynch et al., 1995).

Phenytoin was reported to have limited antagonist

efficacy against kainate neurotoxicity in vivo (Zaczek et

al., 1978), and studies of its action on excitotoxicity in

vitro have produced confl Phenytoin was reported to have limited antagonist
efficacy against kainate neurotoxicity in vivo (Zaczek et
al., 1978), and studies of its action on excitotoxicity in
vitro have produced conflicting results. Cell death, pr

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1 mM of kainic acid or NMDA for 24 h, was reduced in an duc
incomplete but concentration-dependent manner by pre- Hof URENJAK ANI
1 mM of kainic acid or NMDA for 24 h, was reduced in an
incomplete but concentration-dependent manner by pre-
treatment with phenytoin (10 to 100 μ M) and carbamaztreatment with phenytoin (10 to 100 μ m) and carbamaz-
thromplete but concentration-dependent manner by
treatment with phenytoin (10 to 100 μ m) and carbar
epine (10 to 1000 μ m) (Lakics and Erdö, 1994). In 1 mM of kainic acid or NMDA for 24 h, was reduced in an incomplete but concentration-dependent manner by pre-
treatment with phenytoin (10 to 100 μ M) and carbamaz-
epine (10 to 1000 μ M) (Lakics and Erdö, 1994). In c incomplete but concentration-dependent manner by pre-
treatment with phenytoin (10 to 100 μ M) and carbamaz-
epine (10 to 1000 μ M) (Lakics and Erdö, 1994). In con-
trast, 100 μ M phenytoin was ineffective against a treatment with phenytoin (10 to 100
epine (10 to 1000 μ M) (Lakics and
trast, 100 μ M phenytoin was ineffer
glutamate neurotoxicity (500 μ M ft
cell culture (Koh and Choi, 1987).
3. Beneficial effects in experimente

3. Beneficial effective against acute alternate neurotoxicity (500 μ M for 5 min) in cortical cell culture (Koh and Choi, 1987).
 3. Beneficial effects in experimental models of cerebral ischemia. Phenytoin pret glutamate neurotoxicity (500 μ M for 5 min) in cortical tell culture (Koh and Choi, 1987).

3. Beneficial effects in experimental models of cerebral lischemia. Phenytoin pretreatment (200 mg kg⁻¹) significantly protec cell culture (Koh and Choi, 1987). surface 3. Beneficial effects in experimental models of cerebral It is ischemia. Phenytoin pretreatment (200 mg kg⁻¹) signifgrees is intended by protected hippocampal CA1 neurons in ge 3. Beneficial effects in experimental models of cerebischemia. Phenytoin pretreatment (200 mg kg^{-1}) signicantly protected hippocampal CA1 neurons in gerb subjected to 5 min of forebrain ischemia produced bilateral carot ischemia. Phenytoin pretreatment (200 mg kg^{-1}) significantly protected hippocampal CA1 neurons in gerbils subjected to 5 min of forebrain ischemia produced by bilateral carotid artery occlusion under various experimenta icantly protected hippocampal CA1 neurons in gerbils
subjected to 5 min of forebrain ischemia produced by
bilateral carotid artery occlusion under various experi-
mental conditions (Clifton et al., 1989; Taft et al., 1989) subjected to 5 min of forebrain ischemia produced by bilateral carotid artery occlusion under various experimental conditions (Clifton et al., 1989; Taft et al., 1989) but Deshpande and Wieloch (1986) failed to demonstrate bilateral carotid artery occlusion under various experimental conditions (Clifton et al., 1989; Taft et al., 1989), but Deshpande and Wieloch (1986) failed to demonstrate protection by phenytoin in a rat model of global is mental conditions (Clifton et al., 1989; Taft et al., 1989),
but Deshpande and Wieloch (1986) failed to demonstrate
protection by phenytoin in a rat model of global isch-
emia. A much lower dose (15 mg kg⁻¹) still atten but Deshpande and Wieloch (1986) failed to demonstrate oprotection by phenytoin in a rat model of global ischemia. A much lower dose (15 mg kg⁻¹) still attenuated sboth necrosis and neurological deficits in the rabbit o protection by phenytoin in a rat model of global ischemia. A much lower dose (15 mg kg^{-1}) still attenuated both necrosis and neurological deficits in the rabbit brain subjected to transient global ischemia (Aldrete et a both necrosis and neurological deficits in the rabbit chrain subjected to transient global ischemia (Aldrete et E
al., 1979; Cullen et al., 1979). At 50 to 300 mg kg^{-1} , neurological statement of brain free lasty acids d brain subjected to transient global ischemia (Aldrete et al., 1979; Cullen et al., 1979). At 50 to 300 mg kg^{-1} , phenytoin attenuated the accumulation of brain free fatty acids during 10 min of complete ischemia produced al., 1979; Cullen et al., 1979). At 50 to 300 mg kg^{-1} , more phenytoin attenuated the accumulation of brain free laterty acids during 10 min of complete ischemia produced and by decapitation in rats (Shiu et al., 1983). phenytoin attenuated the accumulation of brain free
fatty acids during 10 min of complete ischemia produced
by decapitation in rats (Shiu et al., 1983). Finally, phe-
nytoin was also neuroprotective in a model of in utero by decapitation in rats (

nytoin was also neuropr

hypoxic brain injury as a

K⁺-ATPase activity an

(Lampley et al., 1995).

Phenytoin (28 mg kg⁻ toin was also neuroprotective in a model of in ut
poxic brain injury as assessed by maintenance of N
F-ATPase activity and reduced lipid peroxidat
ampley et al., 1995).
Phenytoin (28 mg kg⁻¹, i.v.; i.e., an effective an

hypoxic brain injury as assessed by maintenance of N
K⁺-ATPase activity and reduced lipid peroxidat
(Lampley et al., 1995).
Phenytoin (28 mg kg⁻¹, i.v.; i.e., an effective antic
vulsant dose) administered 30 min and 2 K^+ -ATPase activity and reduced lipid peroxidation 150

(Lampley et al., 1995). $[K^+$

Phenytoin (28 mg kg⁻¹, i.v.; i.e., an effective anticon- 10 a

vulsant dose) administered 30 min and 24 h *postisch*- nyto

emia m (Lampley et al., 1995).

Phenytoin (28 mg kg^{-1} , i.v.; i.e., an effective anticon-

vulsant dose) administered 30 min and 24 h *postisch*-

emia markedly reduced ischemic damage subsequent to

permanent occlusion of the Phenytoin $(28 \text{ mg kg}^{-1}, \text{i.v.}; \text{i.e., an effective anticonvulsant dose})$ administered 30 min and 24 h *postisch*-
prima markedly reduced ischemic damage subsequent to mage
permanent occlusion of the MCA in mice (Kenny et al., edl
1992). This action vulsant dose) administered 30 min and 24 h *postischemia markedly reduced ischemic damage subsequent to* permanent occlusion of the MCA in mice (Kenny et al., 1992). This action was confirmed in rats. Phenytoin and carbama emia markedly reduced ischemic damage subsequent to
permanent occlusion of the MCA in mice (Kenny et al.,
1992). This action was confirmed in rats. Phenytoin and
carbamazepine (but not valproic acid) preserved the ac-
tivi permanent occlusion of the MCA in mice (Kenny et al.
1992). This action was confirmed in rats. Phenytoin and
carbamazepine (but not valproic acid) preserved the ac
tivity of Na⁺/K⁺-ATPase measured in several brain re
g 1992). This action was confirmed in rats. Phenytoin and Michen
carbamazepine (but not valproic acid) preserved the ac-
tivity of Na⁺/K⁺-ATPase measured in several brain re-
gions of rats killed after 30 min of MCA occ carbamazepine (but not valproic acid) preserved the activity of Na⁺/K⁺-ATPase measured in several brain regions of rats killed after 30 min of MCA occlusion (Mu-
rakami and Furui, 1994). When administered 30 min sand tivity of Na⁺/K⁺-ATPase measured in several brain regions of rats killed after 30 min of MCA occlusion (Murakami and Furui, 1994). When administered 30 min and 24.5 h after insult, phenytoin $(2 \times 100 \text{ mg kg}^{-1})$; p.) a gions of rats killed after 30 min of MCA occlusion (Murrakami and Furui, 1994). When administered 30 min and 24.5 h after insult, phenytoin $(2 \times 100 \text{ mg kg}^{-1})$ i. p.) and carbamazepine $(2 \times 50 \text{ mg kg}^{-1})$ reduced the infar rakami and Furui, 1994). When administered 30 min
and 24.5 h after insult, phenytoin $(2 \times 100 \text{ mg kg}^{-1})$ i. p.)
and carbamazepine $(2 \times 50 \text{ mg kg}^{-1})$ reduced the infarct
size produced by MCA occlusion in rats by 40 and 24% and 24.5 h after insult, phenytoin $(2 \times 100 \text{ mg kg}^{-1} \text{ i. p.})$ (D
and carbamazepine $(2 \times 50 \text{ mg kg}^{-1})$ reduced the infarct als
size produced by MCA occlusion in rats by 40 and 24%, an
respectively (Rataud et al., 1994). W and carbamazepine $(2 \times 50 \text{ mg kg}^{-1})$ reduced the infarct also
size produced by MCA occlusion in rats by 40 and 24%, and
respectively (Rataud et al., 1994). With dual ipsilateral deca
occlusion of MCA and common carotid ar size produced by MCA occlusion in rats by 40 and 24%, and
respectively (Rataud et al., 1994). With dual ipsilateral deca
occlusion of MCA and common carotid artery in the
same species, phenytoin (28 mg kg⁻¹, i.v., 30 mi respectively (Rataud et al., 1994). With dual ipsilateral de
occlusion of MCA and common carotid artery in the
same species, phenytoin (28 mg kg⁻¹, i.v., 30 min and 24
h after arterial occlusion) reduced the infarct vol occlusion of MCA and common carotid artery in the same species, phenytoin $(28 \text{ mg kg}^{-1}, \text{i.v.}, 30 \text{ min and } 24 \text{ h after arterial occlusion})$ reduced the infarct volume by 45% , i.e., was more effective in this model than the noncompetitive NM same species, phenytoin $(28 \text{ mg kg}^{-1}, \text{i.v.}, 30 \text{ min and } 24 \text{ V.})$

h after arterial occlusion) reduced the infarct volume by

45%, i.e., was more effective in this model than the

noncompetitive NMDA-receptor antagonists diz h after arterial occlusion) reduced the infarct volume 45%, i.e., was more effective in this model than noncompetitive NMDA-receptor antagonists dizocylp maleate (MK-801, 0.1 mg kg⁻¹) and phencyclidine (3 kg⁻¹) (Boxer 45%, i.e., was more effective in this model than the noncompetitive NMDA-receptor antagonists dizocylpin maleate (MK-801, 0.1 mg kg⁻¹) and phencyclidine (3 m kg⁻¹) (Boxer et al., 1990). A single dose of this anticon v noncompetitive NMDA-receptor antagonists dizocyl
maleate (MK-801, 0.1 mg kg⁻¹) and phencyclidine (
kg⁻¹) (Boxer et al., 1990). A single dose of this ant
vulsant (28 mg kg⁻¹) administered 30 min after o
sion was neur maleate (MK-801, 0.1 mg kg⁻¹) and phencyclidine (3 mg kg⁻¹) (Boxer et al., 1990). A single dose of this anticon-
vulsant (28 mg kg⁻¹) administered 30 min after occlu-
sion was neuroprotective, but delaying its admin kg⁻¹) (Boxer et al., 1990). A single dose of this anticon-
vulsant (28 mg kg⁻¹) administered 30 min after occlu-
sion was neuroprotective, but delaying its administra-
og tion by more than 2 h rendered it ineffective vulsant (28 mg kg^{-1}) administered 30 min after occlusion was neuroprotective, but delaying its administration by more than 2 h rendered it ineffective (Boxer et C al., 1990). Finally, 30 mg kg⁻¹ of phenytoin was as se sion was neuroprotective, but delaying its administration by more than 2 h rendered it ineffective (Boxer et al., 1990). Finally, 30 mg kg^{-1} of phenytoin was as efficient as steroid therapy in preventing both edema and tion by more than 2 h rendered it ineffective (Boxer al., 1990). Finally, 30 mg kg^{-1} of phenytoin was efficient as steroid therapy in preventing both eder and infarction in the primate cortex after embolization of the i 4. 1990). Finally, 30 mg kg^{-1} of phenytoin was as ficient as steroid therapy in preventing both edemained infarction in the primate cortex after embolization the internal carotid artery (Bremer et al., 1980).
4. Increas

efficient as steroid therapy in preventing both edemand infarction in the primate cortex after embolization of the internal carotid artery (Bremer et al., 1980).
4. Increased tolerance to anoxia/ischemia and delayed anoxic and infarction in the primate cortex after embolization given by the internal carotid artery (Bremer et al., 1980).
4. Increased tolerance to anoxia/ischemia and delayed of anoxic depolarization. Several studies indicate t of the internal carotid artery (Bremer et al., 1980).
4. Increased tolerance to anoxia/ischemia and delayed
anoxic depolarization. Several studies indicate that phe-
nytoin minimizes residual energy demand and thereby
incr

incomplete but concentration-dependent manner by pre-
trastment with phenytoin (10 to 100 μ m) and carbamaz-
epine (10 to 1000 μ m) (Lakics and Erdö, 1994). In con-
trast, 100 μ m phenytoin was ineffective against a by decapitation in rats (Shiu et al., 1983). Finally, phe-
 K^+ efflux (Artru and Michenfelder, 1980). This latter

nytoin was also neuroprotective in a model of in utero

hypoxic brain injury as assessed by maintenance BRENOVITCH
ducing Na⁺ influx) (see section III.A.). As early as 1944,
Hoff and Yahn reported that phenytoin pretreatment of BRENOVITCH
ducing Na⁺ influx) (see section III.A.). As early as 1944,
Hoff and Yahn reported that phenytoin pretreatment of
mice and rats increased their resistance to hypoxia pro-URENJAK AND OBRENOVITCH
educed in an clucing Na⁺ influx) (see section III.A.). As early as 1944, ducing Na⁺ influx) (see section III.A.). As early as 1944,
Hoff and Yahn reported that phenytoin pretreatment of
mice and rats increased their resistance to hypoxia pro-
duced by hypobaric exposure. This was confirmed by Hoff and Yahn reported that phenytoin pretreatment of mice and rats increased their resistance to hypoxia produced by hypobaric exposure. This was confirmed by measuring survival time of mice breathing 5% oxygen; the optim mice and rats increased their resistance to hypoxia produced by hypobaric exposure. This was confirmed by measuring survival time of mice breathing 5% oxygen; the optimal dose of 200 mg kg⁻¹ phenytoin increased survival measuring survival time of mice breathing 5% oxygen;
the optimal dose of 200 mg kg^{-1} phenytoin increased
survival time by 123% (Artru and Michenfelder, 1980).
It is interesting to note that this effect was significantly survival time by 123% (Artru and Michenfelder, 1980).
It is interesting to note that this effect was significantly
greater than that of diazepam (benzodiazepine, with survival time by 123% (Artru and Michenfelder, 1980).
It is interesting to note that this effect was significantly
greater than that of diazepam (benzodiazepine, with
little action on Na⁺ channels at therapeutic concentr tions), even though the latter was more effective in suppressing hypoxemic convulsions in this model, which suggested that phenytoin protection was not dependent on its anticonvulsant effect *per se* (Artu and Michengreater than that of diazepam (benzodiazepine, with little action on Na⁺ channels at therapeutic concentrations), even though the latter was more effective in suppressing hypoxemic convulsions in this model, which sugges pressing hypoxemic convulsions in this model, which
suggested that phenytoin protection was not dependent
on its anticonvulsant effect *per se* (Artu and Michen-
felder, 1980). Increased survival time following anoxia
and pressing hypoxemic convulsions in this model, which
suggested that phenytoin protection was not dependent
on its anticonvulsant effect *per se* (Artu and Michen-
felder, 1980). Increased survival time following anoxia
and suggested that phenytoin protection was not dependent
on its anticonvulsant effect *per se* (Artu and Michen-
felder, 1980). Increased survival time following anoxia
and global ischemia by phenytoin was also reported in
ca on its anticonvulsant effect *per se* (Artu and Michelder, 1980). Increased survival time following and and global ischemia by phenytoin was also reported cats and guinea pigs (Naiman and Williams, 1981). Is dog studies, felder, 1980). Increased survival time following ano
and global ischemia by phenytoin was also reported
cats and guinea pigs (Naiman and Williams, 19
Baldy-Moulinier, 1971–1972). In dog studies, pretre
ment with phenytoin and global ischemia by phenytoin was also reported in cats and guinea pigs (Naiman and Williams, 1964; Baldy-Moulinier, 1971–1972). In dog studies, pretreatment with phenytoin decreased the rate of K^+ accumulation in c cats and guinea pigs (Naiman and Williams, 1964;
Baldy-Moulinier, 1971–1972). In dog studies, pretreat-
ment with phenytoin decreased the rate of K^+ accumu-
lation in cisternal cerebrospinal fluid following 20 min of
a Baldy-Moulinier, 1971–1972). In dog studies, pretreatment with phenytoin decreased the rate of K^+ accumulation in cisternal cerebrospinal fluid following 20 min of anoxia, suggesting that this drug prevented or delayed ment with phenytoin decreased the rate of K^+ accumulation in cisternal cerebrospinal fluid following 20 min of anoxia, suggesting that this drug prevented or delayed K^+ efflux (Artru and Michenfelder, 1980). This la lation in cisternal cerebrospinal fluid following 20 min of
anoxia, suggesting that this drug prevented or delayed
 K^+ efflux (Artru and Michenfelder, 1980). This latter
effect was confirmed in rabbits subjected to circ anoxia, suggesting that this drug prevented or delayed K^+ efflux (Artru and Michenfelder, 1980). This latter effect was confirmed in rabbits subjected to circulatory arrest provoked by complete anoxia. Phenytoin (50 an K^+ efflux (Artru and Michenfelder, 1980). This latter effect was confirmed in rabbits subjected to circulatory arrest provoked by complete anoxia. Phenytoin (50 and 150 mg kg⁻¹) dose-dependently reduced the increase effect was confirmed in rabbits subjected to circulatory
arrest provoked by complete anoxia. Phenytoin (50 and
150 mg kg^{-1}) dose-dependently reduced the increase in
 $[K^+]$ (and the slight drop in $[Na^+]$) in the cisterna arrest provoked by complete anoxia. Phenytoin (50 and 150 mg kg⁻¹) dose-dependently reduced the increase in $[K^+]$ (and the slight drop in $[Na^+]$) in the cisterna magna 10 and 20 min after cardiac arrest. Interestingly, [K⁺] (and the slight drop in [Na⁺]) in the cisterna magna 10 and 20 min after cardiac arrest. Interestingly, phenytoin was more potent than either phenobarbital (33 mg kg⁻¹) or mild hypothermia (35°C) and did not ma felder, 1980). Increased survival time following anoxia

and global ischemia by phenytoin was also reported in

ends and guinea pigs (Naiman and Williams, 1964;

Baldy-Moulinier, 1971–1972). In dog studies, pretreat-

men nytoin was more potent than either phenobarbital (33 g kg⁻¹) or mild hypothermia (35°C) and did not mark-
ly alter the time to loss of EEG activity (Artru and
ichenfelder, 1981), thus suggesting a selective effect
residual energy demand (see section III.A.).
Carbamazepine

on residual energy demand (see section III.A.).
Carbamazepine (13 to 50 mg kg^{-1}) was also found to
markedly prolong the survival time of mice subjected to edly alter the time to loss of EEG activity (Artru and

Michenfelder, 1981), thus suggesting a selective effect

on residual energy demand (see section III.A.).

Carbamazepine (13 to 50 mg kg⁻¹) was also found to

marke Michenfelder, 1981), thus suggesting a selective effect
on residual energy demand (see section III.A.).
Carbamazepine (13 to 50 mg kg^{-1}) was also found to
markedly prolong the survival time of mice subjected to
severe h on residual energy demand (see section III.A.).
Carbamazepine (13 to 50 mg kg⁻¹) was also found to
markedly prolong the survival time of mice subjected to
severe hypoxia or bilateral carotid artery occlusion
(Dong et al Carbamazepine (13 to 50 mg kg^{-1}) was also found to
markedly prolong the survival time of mice subjected to
severe hypoxia or bilateral carotid artery occlusion
(Dong et al., 1994). At 25 to 70 mg kg^{-1} , carbamazepine
a markedly prolong the survival time of mice subjected to severe hypoxia or bilateral carotid artery occlusion (Dong et al., 1994). At 25 to 70 mg kg^{-1} , carbamazepine also reduced both ATP and phosphocreatine depletion, a severe hypoxia or bilateral car
(Dong et al., 1994). At 25 to 70 mg
also reduced both ATP and phos_l
and lactic acid accumulation, in n
decapitation (Dong et al., 1994). also reduced both ATP and phosphocreatine depletion,
and lactic acid accumulation, in mouse brain 30 s after
decapitation (Dong et al., 1994).
V. Neuroprotective Drugs, Presumably Acting on
Na⁺ Channels

mulation, in mou
et al., 1994).
**re Drugs, Presu
Na⁺ Channels**
dulators with act **A. Neuroprotective Drugs, Presumably Acting Ma⁺ Channels
A. Ca²⁺ channel modulators with actions on Na⁺ channels**

channels

 $Na⁺$ **Channels**
Ca²⁺ channel modulators with actions on Na⁺
annels
Voltage-gated Na⁺, Ca²⁺ and K⁺ channels are men
rs of a related gene family (e.g., 55% sequence homo A. Ca^{2+} channel modulators with actions on Na^+
channels
Voltage-gated Na⁺, Ca^{2+} and K⁺ channels are mem-
bers of a related gene family (e.g., 55% sequence homol-
ogy remains between the principal subunits of N A. Ca channel modulators with actions on Na
channels
Voltage-gated Na⁺, Ca²⁺ and K⁺ channels are mem-
bers of a related gene family (e.g., 55% sequence homol-
ogy remains between the principal subunits of Na⁺ and
 Channels

Voltage-gated Na⁺, Ca²⁺ and K⁺ channels are mem-

bers of a related gene family (e.g., 55% sequence homol-

ogy remains between the principal subunits of Na⁺ and

Ca²⁺ channels; Tanabe et al., 1987), a Voltage-gated Na⁺, Ca²⁺ and K⁺ channels are me
bers of a related gene family (e.g., 55% sequence hon
ogy remains between the principal subunits of Na⁺ ϵ
Ca²⁺ channels; Tanabe et al., 1987), and they sh
strong bers of a related gene family (e.g., 55% sequence homology remains between the principal subunits of Na⁺ and Ca²⁺ channels; Tanabe et al., 1987), and they share strong functional analogies such as voltage-dependent ac ogy remains between the principal subunits of Na⁺ and Ca^{2+} channels; Tanabe et al., 1987), and they share strong functional analogies such as voltage-dependent activation and inactivation (Catterall, 1988a). With reg strong functional analogies such as voltage-dependent
activation and inactivation (Catterall, 1988a). With re-
gard to ion conductance, Na^+ channel selectivity is al-
tered by neurotoxins (see section II.B.4.), and muta strong functional analogies such as voltage-dependent
activation and inactivation (Catterall, 1988a). With re-
gard to ion conductance, Na^+ channel selectivity is al-
tered by neurotoxins (see section II.B.4.), and muta activation and inactivation (Catterall, 1988a). With regard to ion conductance, Na^+ channel selectivity is a tered by neurotoxins (see section II.B.4.), and mutation of only two amino acid residues in the Na^+ channel gard to ion conductance, Na⁺ channel selectivity is altered by neurotoxins (see section II.B.4.), and mutation of only two amino acid residues in the Na⁺ channel is sufficient to confer Ca²⁺ channel-like permeabilit tered by neurotoxins (see section II.B.4.), and mutation
of only two amino acid residues in the Na⁺ channel is
sufficient to confer Ca^{2+} channel-like permeability prop-
erties (see section II.B.2). Therefore, it is n

PHARMACOLOGICAL REVIEWS

MODULATION OF VOLTAGENERS also interact strongly with Na⁺ channels (McNeal et
al., 1985; Velly et al., 1987, Pauwels et al., 1991; Rags-MODULATION OF VOL1
ers also interact strongly with Na⁺ channels (McNeal of
al., 1985; Velly et al., 1987, Pauwels et al., 1991; Rag
dale et al., 1991) (fig. 6), and that the anti-ischem ers also interact strongly with Na⁺ channels (McNeal et al., 1985; Velly et al., 1987, Pauwels et al., 1991; Rags-
dale et al., 1991) (fig. 6), and that the anti-ischemic
properties of such Ca^{2+} antagonists may be li ers also interact strongly with Na⁺ channels (McNeal et and al., 1985; Velly et al., 1987, Pauwels et al., 1991; Rags-
dale et al., 1991) (fig. 6), and that the anti-ischemic the
properties of such Ca²⁺ antagonists may al., 1985; Velly
dale et al., 19
properties of s
least in part, to
et al., 1987).
*1. Flunariz*i le et al., 1991) (fig. 6), and that the anti-ischemic
operties of such Ca^{2+} antagonists may be linked, at
ast in part, to down-modulation of Na^+ channels (Velly
al., 1987).
1. Flunarizine. The diphenylalkylamine fl

properties of such Ca^{2+} antagonists may be linked, at least in part, to down-modulation of Na⁺ channels (Velly et al., 1987).

1. Flunarizine. The diphenylalkylamine flunarizine (fig. 8) has beneficial effects agains least in part, to down-modulation of Na⁺ channels (Velly
et al., 1987).
1. Flunarizine. The diphenylalkylamine flunarizine
(fig. 8) has beneficial effects against global (Desphande
and Wieloch, 1985; Kumar et al., 1987 I. Flunarizine. The diphenylalkylamine flunarizine severals, the set of ig. 8) has beneficial effects against global (Desphande in and Wieloch, 1985; Kumar et al., 1987; Alps et al., 1988; (Party Tegtmeier et al., 1989) an 1. Flunarizine. The diphenylalkylamine flunarizine (fig. 8) has beneficial effects against global (Desphande and Wieloch, 1985; Kumar et al., 1987; Alps et al., 1988; Tegtmeier et al., 1989) and focal cerebral ischemia (V (fig. 8) has beneficial effects against global (Desphande in and Wieloch, 1985; Kumar et al., 1987; Alps et al., 1988; (Tegtmeier et al., 1989) and focal cerebral ischemia (Van 1 Reempts et al., 1987; De Ryck et al., 1989 and Wieloch, 1985; Kumar et al., 1987; Alps et al., 1988; (Par
 Tegtmeier et al., 1989) and focal cerebral ischemia (Van 199
 Reempts et al., 1987; De Ryck et al., 1989, 1991). Flu-
 et a
 narizine (40 mg kg⁻¹, p.o., 3 Tegtmeier et al., 1989) and focal cerebral ischemia (Van 19. Reempts et al., 1987; De Ryck et al., 1989, 1991). Flu-
narizine (40 mg kg⁻¹, p.o., 3 h before insult) decreased of by half the size of infarcts produced phot Reempts et al., 1987; De Ryck et al., 1989, 1991).
narizine (40 mg kg^{-1} , p.o., 3 h before insult) decree
by half the size of infarcts produced photochemicall
the cortex of rats (Van Reempts et al., 1987) and redu
neurol narizine (40 mg kg⁻¹, p.o., 3 h before insult) decreased
by half the size of infarcts produced photochemically in
the cortex of rats (Van Reempts et al., 1987) and reduced
neurological deficit in this model, even when a by half the size of infarcts produced photochemically in of N
the cortex of rats (Van Reempts et al., 1987) and reduced al.,
neurological deficit in this model, even when adminis-
neltered 5 to 30 min after the insult [0. the cortex of rats (Van Reempts et al., 1987) and redu
neurological deficit in this model, even when admit
tered 5 to 30 min after the insult [0.16 to 5 mg kg⁻¹,
median effective dose (ED₅₀) approximately 0.85
kg⁻¹] neurological deficit in this model, even when administered 5 to 30 min after the insult [0.16 to 5 mg kg⁻¹, i.v.; median effective dose (ED₅₀) approximately 0.85 mg kg⁻¹] (De Ryck et al., 1989, 1991). In contrast, f tered 5 to 30 min after the insult [0.16 to 5 mg kg⁻¹, i.v.; from
median effective dose (ED₅₀) approximately 0.85 mg 199
kg⁻¹] (De Ryck et al., 1989, 1991). In contrast, flunariz-celli
ine showed no clear neuroprote kg⁻¹] (De Ryck et al., 1989, 1991). In contrast, flunariz-
ine showed no clear neuroprotective potential when ad-
ministered repeatedly after coagulation of the MCA in
mice (2.5 to 20 mg kg⁻¹ i.p., starting 5 min afte ine showed no clear neuroprotective potential when ad-
ministered repeatedly after coagulation of the MCA in
mice $(2.5 \text{ to } 20 \text{ mg kg}^{-1} \text{ i.p., starting } 5 \text{ min after coag-
ulation) (Gotti et al., 1990). In global ischemia, flunariz-
ine decreased the incidence of delayed neuronal death in
the hippocampus of rats (Desphande and Wieloch, 1985),$ ministered repeatedly after coagulation of the MCA in wels et al., 1989, 1990, 1991; Roufos et al., 1994).
mice $(2.5 \text{ to } 20 \text{ mg kg}^{-1} \text{ i.p., starting } 5 \text{ min after coag}$ Patch-clamp studies with isolated rat cerebellar neu-
ulation) (Got mice $(2.5 \text{ to } 20 \text{ mg kg}^{-1} \text{ i.p., starting } 5 \text{ min after coag-
ulation) (Gotti et al., 1990). In global ischemia, flunariz-
ine decreased the incidence of delayed neuronal death in
the hippocampus of rats (Desphande and Wieloch, 1985),
dogs (Kumar et al., 1987) and gerbils (Alps et al., 1988)
(see however Hossmann et al., 1983; Newberg et al.,$ mice $(2.5 \text{ to } 20 \text{ mg kg}^{-1} \text{ i.p., starting } 5 \text{ min after coagulation})$ (Gotti et al., 1990). In global ischemia, flunarizine decreased the incidence of delayed neuronal death in the hippocampus of rats (Desphande and Wieloch, 1985), dogs (Kumar ulation) (Gotti et al., 1990). In global ischemia, flunariz-
ine decreased the incidence of delayed neuronal death in
the hippocampus of rats (Desphande and Wieloch, 1985),
dogs (Kumar et al., 1987) and gerbils (Alps et al ine decreased the incidence of delayed neuronal death in
the hippocampus of rats (Desphande and Wieloch, 1985),
dogs (Kumar et al., 1987) and gerbils (Alps et al., 1988)
(see however Hossmann et al., 1983; Newberg et al.,
 the hippocampus of rats (Desphande and Wieloch, 1988
dogs (Kumar et al., 1987) and gerbils (Alps et al., 198
(see however Hossmann et al., 1983; Newberg et a
1984; Araki et al., 1990; Xie et al., 1992). In gerk
models of c dogs (Kumar et al., 1987) and gerbils (Alps et al., 1988)
(see however Hossmann et al., 1983; Newberg et al., 1984; Araki et al., 1990; Xie et al., 1992). In gerbil
models of cerebral ischemia, pretreatment with fluna-
riz (see however Hossmann et al., 1983; Newberg et al., 1984; Araki et al., 1990; Xie et al., 1992). In gerbil models of cerebral ischemia, pretreatment with flunarizine also improved neurological symptoms (Cohan et al., 1992; 1984; Araki et al., 1990; Xie et al., 1992). In gerbil metables of cerebral ischemia, pretreatment with fluna-
rizine also improved neurological symptoms (Cohan et mod., 1992; Ito et al., 1994). The neuroprotective potenti models of cerebral ischemia, pretreatment with fluna-
rizine also improved neurological symptoms (Cohan et
al., 1992; Ito et al., 1994). The neuroprotective potential
of flunarizine was confirmed in vitro. Pretreatment wit rizine also improved neurological symptoms (Cohan et al., 1992; Ito et al., 1994). The neuroprotective potential of flunarizine was confirmed in vitro. Pretreatment with this drug prevented glutamate-induced toxicity in r al., 1992; Ito et al., 1994). The neuroprotective poten
of flunarizine was confirmed in vitro. Pretreatment w
this drug prevented glutamate-induced toxicity in
hippocampal primary cell cultures (Hara et al., 1995
inhibite of flunarizine was confirmed in vitro. Pretreatment with
this drug prevented glutamate-induced toxicity in rat
hippocampal primary cell cultures (Hara et al., 1993b),
inhibited ouabain-induced Na^+ influx into synapto-
s this drug prevented glutamate-induced toxicity in ra
hippocampal primary cell cultures (Hara et al., 1993b)
inhibited ouabain-induced Na⁺ influx into synapto
somes (Cousin et al., 1995) and protected neuroblastoma
cells hippocampal primary cell cultures (Hara et al., 1993b
inhibited ouabain-induced Na⁺ influx into synapt
somes (Cousin et al., 1995) and protected neuroblastom
cells against cytotoxic hypoxia (Peruche and Krieglstein
1991) inhibited ouabain-induced Na⁺ influx into synaptosomes (Cousin et al., 1995) and protected neuroblastoma
cells against cytotoxic hypoxia (Peruche and Krieglstein, 1991), providing the insults remained moderate (Pau-
wel cells against cytotoxic hypoxia (Peruche and Krieglstein, pla
1991), providing the insults remained moderate (Pau-
wels et al., 1989). Flunarizine, however, failed to prevent cel
neurotoxicity induced by depolarization wit 1991), providing the in
wels et al., 1989). Fluna
neurotoxicity induced h
for 30 min in rat hippo
kahashi et al., 1995).
Despite being classif els et al., 1989). Flunarizine, however, failed to prever
urotoxicity induced by depolarization with 90 mM K
r 30 min in rat hippocampal organotypic cultures (Ti
hashi et al., 1995).
Despite being classified as a nonselec

neurotoxicity induced by depolarization with 90 mM K^+
for 30 min in rat hippocampal organotypic cultures (Ta-
kahashi et al., 1995).
Despite being classified as a nonselective Ca^{2+} chan-
nel modulator (Pauwels et al kahashi et al., 1995).

Despite being classified as a nonselective Ca^{2+} channel modulator (Pauwels et al., 1991; Spedding and Pa-

oletti, 1992; Akaike et al., 1993; Panchenko et al., 1993),

flunarizine clearly intera kahashi et al., 1995).

Despite being classified as a nonselective Ca^{2+} channel modulator (Pauwels et al., 1991; Spedding and Pachetti, 1992; Akaike et al., 1993; Panchenko et al., 1993), flunarizine clearly interacts Despite being classified as a nonselective Ca^{2+} channel modulator (Pauwels et al., 1991; Spedding and Paoletti, 1992; Akaike et al., 1993; Panchenko et al., 1993), flunarizine clearly interacts with voltage-gated Na⁺ nel modulator (Pauwels et al., 1991; Spedding and Pa-
oletti, 1992; Akaike et al., 1993; Panchenko et al., 1993),
flunarizine clearly interacts with voltage-gated Na⁺
channels. Among 180 compounds, including classical l oletti, 1992; Akaike et al., 1993; Panchenko et al., 199
flunarizine clearly interacts with voltage-gated N
channels. Among 180 compounds, including classical
cal anesthetics, anticonvulsants and Ca^{2+} chan
blockers, thi channels. Among 180 compounds, including classical locations on key enzymes of energy metabolism (Bielencal anesthetics, anticonvulsants and Ca^{2+} channel berg et al., 1986) or Na⁺/K⁺-ATPase activity (Urenjak et blo channels. Among 180 compounds, including classical local anesthetics, anticonvulsants and Ca^{2+} channel
blockers, this drug was among the most potent inhibi-
tors of BTX-B (see section II.B.4.) binding to guinea pig
cer cal anesthetics, anticonvulsants and Ca^{2+} channel blockers, this drug was among the most potent inhibitions of BTX-B (see section II.B.4.) binding to guinea pig terrebral cortex vesicles [flunarizine IC_{50} (concentrat tors of BTX-B (see section II.B.4.) binding to guinea pig to
cerebral cortex vesicles [flunarizine IC_{50} (concentration pu
that produces 50% of its maximum possible inhibition) = ten
0.6 μ M versus lidocaine $IC_{50} = 24$ cerebral cortex vesicles [flunarizine IC_{50} (concentration that produces 50% of its maximum possible inhibition) = 0.6 μ M versus lidocaine $IC_{50} = 240 \ \mu$ M] (McNeal et al., 1985), and this property was confirmed with 0.6 μ M versus lidocaine IC₅₀ = 240 μ M] (McNeal et al., 1985), and this property was confirmed with rat brain synaptosomes (fig. 6) (Velly et al., 1987; Pauwels et al., 1986, 1990; Roufos et al., 1994). In contrast 0.6 μ M versus lidocaine IC₅₀ = 240 μ M] (McNeal et al., 1985), and this property was confirmed with rat brain synaptosomes (fig. 6) (Velly et al., 1987; Pauwels et al., 1986, 1990; Roufos et al., 1994). In contrast 1985), and this property was confirmed with rat brain compared synaptosomes (fig. 6) (Velly et al., 1987; Pauwels et al., 1986, 1990; Roufos et al., 1994). In contrast, flunarizine was a poor inhibitor of $[^{3}H]$ -tetraca

-GATED NA⁺ CHANNELS
and demonstrated relatively weak local anesthetic po-
tency (Hay and Wadworth, 1982; Pauwels et al., 1986), -GATED NA⁺ CHANNELS 47
and demonstrated relatively weak local anesthetic po-
tency (Hay and Wadworth, 1982; Pauwels et al., 1986),
thus illustrating that high affinity to the BTX binding -GATED NA⁺ CHANNELS 47
and demonstrated relatively weak local anesthetic po-
tency (Hay and Wadworth, 1982; Pauwels et al., 1986),
thus illustrating that high affinity to the BTX binding
site is *not* a property exclusi and demonstrated relatively weak local anesthetic p
tency (Hay and Wadworth, 1982; Pauwels et al., 1986
thus illustrating that high affinity to the BTX bindis
site is *not* a property exclusive to local anesthetics (M
Neal and demonstrated if
tency (Hay and Wa
thus illustrating th
site is *not* a propert
Neal et al., 1985).
Flunarizine inhib thus illustrating that high affinity to the BTX binding
site is *not* a property exclusive to local anesthetics (Mc-
Neal et al., 1985).
Flunarizine inhibited also the effects of veratridine in
several in vitro preparatio

Flunarizine inhibited also the effects of veratridine in several in vitro preparations, for example: (a) Na⁺ influx in synaptosomes and cultured cerebellar granule cells site is *not* a property exclusive to local anesthetics (Mc-
Neal et al., 1985).
Flunarizine inhibited also the effects of veratridine in
several in vitro preparations, for example: (a) Na⁺ influx
in synaptosomes and cu Neal et al., 1985).

Flunarizine inhibited also the effects of veratridine in

several in vitro preparations, for example: (a) Na⁺ influx

in synaptosomes and cultured cerebellar granule cells

(Pauwels et al., 1986; V Flunarizine inhibited also the effects of veratridine in
several in vitro preparations, for example: (*a*) Na⁺ influx
in synaptosomes and cultured cerebellar granule cells
(Pauwels et al., 1986; Velly et al., 1987; Cousi several in vitro preparations, for example: (a) Na⁺ influx
in synaptosomes and cultured cerebellar granule cells
(Pauwels et al., 1986; Velly et al., 1987; Cousin et al.,
1995); *(b)* increased synaptosomal respiration in synaptosomes and cultured cerebellar granule cells

(Pauwels et al., 1986; Velly et al., 1987; Cousin et al.,

1995); (*b*) increased synaptosomal respiration (Urenjak

et al., 1991; Wermelskirchen et al., 1992); (*c*) 1995); (b) increased synaptosomal respiration (Urenjak et al., 1991; Wermelskirchen et al., 1992); (c) stimulation of $[^{14}C]$ guanidine uptake (i.e., a representative measure of Na⁺ fluxes; Reith, 1990) in synaptosomes et al., 1991; Wermelskirchen et al., 1992); (c) stimulation
of $[^{14}C]$ guanidine uptake (i.e., a representative measure
of Na⁺ fluxes; Reith, 1990) in synaptosomes (Pauwels et
al., 1986) and CHO cells expressing type I et al., 1991; Wermelskirchen et al., 1992); *(c)* stimulation
of [¹⁴C]guanidine uptake (i.e., a representative measure
of Na⁺ fluxes; Reith, 1990) in synaptosomes (Pauwels et
al., 1986) and CHO cells expressing type II of $[^{44}C]$ guanidine uptake (i.e., a representative measure
of Na⁺ fluxes; Reith, 1990) in synaptosomes (Pauwels et
al., 1986) and CHO cells expressing type IIA Na⁺ chan-
nels (Roufos et al., 1994); (*d*) neurotransm al., 1986) and CHO cells expressing type IIA $Na⁺$ channels (Roufos et al., 1994); (*d*) neurotransmitter release from synaptosomes and cultured neurons (Cousin et al., 1995); (*e*) spreading depression and ion fluxes al., 1986) and CHO cells expressing type IIA Na⁺ channels (Roufos et al., 1994); (*d*) neurotransmitter release from synaptosomes and cultured neurons (Cousin et al., 1995); (*e*) spreading depression and ion fluxes acr nels (Roufos et al., 1994); (*d*) neurotransmitter releas
from synaptosomes and cultured neurons (Cousin et al
1995); (*e*) spreading depression and ion fluxes across th
cellular membrane in hippocampal slices (Ashton et a from synaptosomes and cultured neurons (Cousin e
1995); (e) spreading depression and ion fluxes across
cellular membrane in hippocampal slices (Ashton et
1990); and (f) neuronal cell degeneration (fig. 6) (
wels et al., 1 95); (e) spreading depression and ion fluxes across the
llular membrane in hippocampal slices (Ashton et al.
90); and (f) neuronal cell degeneration (fig. 6) (Pau-
els et al., 1989, 1990, 1991; Roufos et al., 1994).
Patch

cellular membrane in hippocampal slices (Ashton et al., 1990); and (f) neuronal cell degeneration (fig. 6) (Pau-
wels et al., 1989, 1990, 1991; Roufos et al., 1994).
Patch-clamp studies with isolated rat cerebellar neu-1990); and (f) neuronal cell degeneration (fig. 6) (P wels et al., 1989, 1990, 1991; Roufos et al., 1994).
Patch-clamp studies with isolated rat cerebellar nons clearly confirmed that flunarizine blocks Na^+ crents and r wels et al., 1989, 1990, 1991; Roufos et al., 1994).

Patch-clamp studies with isolated rat cerebellar neu-

rons clearly confirmed that flunarizine blocks Na⁺ cur-

rents and revealed that this drug interacts predomi-
 Patch-clamp studies with isolated rat cerebellar neu-
rons clearly confirmed that flunarizine blocks Na^+ cur-
rents and revealed that this drug interacts predomi-
nantly with inactivated Na^+ channels (Kiskin et al.,
1 rons clearly confirmed that flunarizine blocks Na^+ currents and revealed that this drug interacts predominantly with inactivated Na^+ channels (Kiskin et al., 1993). Supporting findings include: (*a*) increased Na^+ c rents and revealed that this drug interacts predominantly with inactivated Na^+ channels (Kiskin et al., 1993). Supporting findings include: (a) increased Na^+ channel block with the frequency of stimulation and membra nantly with inactivated Na⁺ channels (Kiskin et al., 1993). Supporting findings include: (*a*) increased Na⁺ channel block with the frequency of stimulation and membrane depolarization; (*b*) shift of the steady state 1993). Supporting findings include: (a) increased Na⁺ channel block with the frequency of stimulation and membrane depolarization; (b) shift of the steady state voltage-dependence of Na⁺ channel inactivation toward channel block with the frequency of stimulation and
membrane depolarization; (b) shift of the steady state
voltage-dependence of Na^+ channel inactivation toward
more negative potentials; and (c) marked slowdown of
 Na^+ membrane depolarization; (b) shift of the steady stat voltage-dependence of Na⁺ channel inactivation toware more negative potentials; and (c) marked slowdown c Na⁺ channel recovery from inactivation. As with local ane voltage-dependence of Na⁺ channel inactivation towar
more negative potentials; and (c) marked slowdown Na^+ channel recovery from inactivation. As with locanes
the probably increases the probability of channel ina more negative potentials; and (c) marked slowdown of Na⁺ channel recovery from inactivation. As with local anesthetics (Catterall, 1987), this high affinity for inactivated states probably increases the probability of Na⁺ channel recovery from inactivation. As with local anesthetics (Catterall, 1987), this high affinity for inactivated states probably increases the probability of channel inactivation at negative membrane potentials a anesthetics (Catterall, 1987), this high affinity for inactivated states probably increases the probability of chan-
nel inactivation at negative membrane potentials and
thereby stabilizes the Na⁺ channels in this state tivated states probably increases the probability of chan-
nel inactivation at negative membrane potentials and
thereby stabilizes the Na⁺ channels in this state relative
to resting or active states. This property may a nel inactivation at negative membrane potentials and
thereby stabilizes the Na⁺ channels in this state relative
to resting or active states. This property may also ex-
plain why flunarizine did not interfere with Na⁺ c thereby stabilizes the Na⁺ channels in this state relative
to resting or active states. This property may also ex-
plain why flunarizine did not interfere with Na⁺ cur-
rents under normal conditions in both isolated c to resting or active states. This property
plain why flunarizine did not interfere
rents under normal conditions in both is
cells and synaptosomes (Tytgat et al., 19
al., 1991; Wermelskirchen et al., 1992).
Finally, invest plain why flunarizine did not interfere with $Na⁺$ currents under normal conditions in both isolated cardiac cells and synaptosomes (Tytgat et al., 1990; Urenjak et al., 1991; Wermelskirchen et al., 1992). Finally, in rents under normal conditions in both isolated cardiac
cells and synaptosomes (Tytgat et al., 1990; Urenjak et
al., 1991; Wermelskirchen et al., 1992).
Finally, investigations into the mechanism of neuro-
protection by flu

cells and synaptosomes (Tytgat et al., 1990; Urenjak et al., 1991; Wermelskirchen et al., 1992).
Finally, investigations into the mechanism of neuro-
protection by flunarizine have shown that it markedly
delays anoxic depo al., 1991; Wermelskirchen et al., 1992).
Finally, investigations into the mechanism of neuro-
protection by flunarizine have shown that it markedly
delays anoxic depolarization (Marrannes et al., 1989;
Scheller et al., 198 Finally, investigations into the mechanism of neuro-
protection by flunarizine have shown that it markedly
delays anoxic depolarization (Marrannes et al., 1989;
Scheller et al., 1989; Xie et al., 1995), a characteristic
f protection by flunarizine have shown that it markedly delays anoxic depolarization (Marrannes et al., 1989; Scheller et al., 1989; Xie et al., 1995), a characteristic feature of Na⁺ channel down-modulation in ischemia (s Scheller et al., 1989; Xie et al., 1995), a characteristic feature of Na⁺ channel down-modulation in ischemia Scheller et al., 1989; Xie et al., 1995), a characteristic feature of Na⁺ channel down-modulation in ischemia (see sections III and IV.B.), independently of any direct actions on key enzymes of energy metabolism (Bielen feature of Na⁺ channel down-modulation in ischemia (see sections III and IV.B.), independently of any direct actions on key enzymes of energy metabolism (Bielenberg et al., 1986) or Na⁺/K⁺-ATPase activity (Urenjak e pus against delayed neuronal loss following carotid aractions on key enzymes of energy metabolism (Bielen-
berg et al., 1986) or Na⁺/K⁺-ATPase activity (Urenjak et
al., 1991; Wermelskirchen et al., 1992). It is interesting
to note that flunarizine protected the gerbil hi berg et al., 1986) or Na⁺/K⁺-ATPase activity (Urenjak al., 1991; Wermelskirchen et al., 1992). It is interestito note that flunarizine protected the gerbil hippoca pus against delayed neuronal loss following carotid a al., 1991; Wermelskirchen et al., 1992). It is interesting
to note that flunarizine protected the gerbil hippocam-
pus against delayed neuronal loss following carotid ar-
tery occlusion, whereas the dihydropyridine Ca²⁺ to note that flunarizine protected the gerbil hippocampus against delayed neuronal loss following carotid artery occlusion, whereas the dihydropyridine Ca²⁺ antagonist nimodipine, which interacts only slightly with Na⁺ pus against delayed neuronal loss following carotid artery occlusion, whereas the dihydropyridine Ca²⁺ antagonist nimodipine, which interacts only slightly with Na⁺ channels (fig. 6) (Pauwels et al., 1990), was ineffec tery occlusion, whereas the dihydropyridine Ca^{2+} antagonist nimodipine, which interacts only slightly with $Na⁺$
channels (fig. 6) (Pauwels et al., 1990), was ineffective in
this model (Alps et al., 1988). Similarl onist nimodipine, which interacts only slightly with Na⁺
channels (fig. 6) (Pauwels et al., 1990), was ineffective in
this model (Alps et al., 1988). Similarly, nimodipine did
not delay anoxic depolarization, nor did it channels (fig. 6) (Pauwels et al., 1990), was ineffective in
this model (Alps et al., 1988). Similarly, nimodipine did
not delay anoxic depolarization, nor did it alter any of
the ionic changes associated with this event (

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48 URENJAK ANI
dition to interacting with Ca^{2+} and Na^{+} channels, flu-
narizine has other pharmacological properties that may 48 URENJAK AND OBR
dition to interacting with Ca^{2+} and Na^{+} channels, flu-
narizine has other pharmacological properties that may nee
also contribute to neuroprotection, such as inhibition of TT URENJAK AND OB
dition to interacting with Ca^{2+} and Na^{+} channels, flu-
narizine has other pharmacological properties that may
also contribute to neuroprotection, such as inhibition of T
adenosine exchange systems and dition to interacting with Ca²⁺ and Na⁺ channels, flu-
narizine has other pharmacological properties that may
also contribute to neuroprotection, such as inhibition of
adenosine exchange systems and/or catabolism (Di-p narizine has other pharmacological properties that may
also contribute to neuroprotection, such as inhibition of
adenosine exchange systems and/or catabolism (Di-perri
et al., 1989; Ferrandon et al., 1994; Rudolphi et al., also contribute to neuroprotection, such as inhibition of
adenosine exchange systems and/or catabolism (Di-perri
et al., 1989; Ferrandon et al., 1994; Rudolphi et al., 1992)
and, possibly, free-radical scavenging (Aruoma e lenosine exchange systems and/or catabolism (Di-per al., 1989; Ferrandon et al., 1994; Rudolphi et al., 199
d, possibly, free-radical scavenging (Aruoma et al., 1991; Goncalves et al., 1991; Nemoto and Chavko, 199
2. *Lifa*

et al., 1989; Ferrandon et al., 1994; Rudolphi et al., 1992)
and, possibly, free-radical scavenging (Aruoma et al.,
1991; Goncalves et al., 1991; Nemoto and Chavko, 1993).
2. *Lifarizine*. Lifarizine (RS-87476) is another and, possibly, free-radical scavenging (Aruoma et al. 1991; Goncalves et al., 1991; Nemoto and Chavko, 1993)
2. Lifarizine. Lifarizine (RS-87476) is another diphe
nylpiperazine (fig. 8) that has a broad neuroprotective
pro 1991; Goncalves et al., 1991; Nemoto and Chavko, 1993). n

2. Lifarizine. Lifarizine (RS-87476) is another diphe-

nylpiperazine (fig. 8) that has a broad neuroprotective

profile in both global and focal models of cerebra 2. Lifarizine. Lifarizine (RS-87476) is another diphaylpiperazine (fig. 8) that has a broad neuroprotection profile in both global and focal models of cerebral is emia (Alps, 1992): a phase 2 (efficacy) trial in stropatie profile in both global and focal models of cerebral
emia (Alps, 1992): a phase 2 (efficacy) trial in s
patients is nearing completion (Lipton and Roser
1994). Lifarizine has been shown to protect dose-d
dently the gerbil s profile in both global and focal models of cerebral ischemia (Alps, 1992): a phase 2 (efficacy) trial in stroke patients is nearing completion (Lipton and Rosenberg, 1994). Lifarizine has been shown to protect dose-depende emia (Alps, 1992): a phase 2 (efficacy) trial in stroke hopatients is nearing completion (Lipton and Rosenberg, perpendently the gerbil striatum against ischemia-induced do-
pamine depletion (Brown et al., 1993) and sever patients is nearing completion (Lipton and Rosenberg 1994). Lifarizine has been shown to protect dose-dependently the gerbil striatum against ischemia-induced do pamine depletion (Brown et al., 1993) and several brain regi 1994). Lifarizine has been shown to protect dose-depen-
dently the gerbil striatum against ischemia-induced do-
pamine depletion (Brown et al., 1993) and several brain μ M
regions against damage produced by 10 min of fo dently the gerbil striatum against ischemia-induced do-
pamine depletion (Brown et al., 1993) and several brain μ
regions against damage produced by 10 min of four-
vessel occlusion in rats (Alps et al., 1990, 1995). I regions against damage produced by 10 min of four-
vessel occlusion in rats (Alps et al., 1990, 1995). In
severe global ischemia, provoked by two-vessel occlusion
superimposed on halothane-induced reduction of arte-
rial b regions against damage produced by 10 min of four-
vessel occlusion in rats (Alps et al., 1990, 1995). In
severe global ischemia, provoked by two-vessel occlusion
superimposed on halothane-induced reduction of arte-
rial vessel occlusion in rats (Alps et al., 1990, 1995). In 20 severe global ischemia, provoked by two-vessel occlusion slow superimposed on halothane-induced reduction of arte-
rial blood pressure (50 mmHg), repeated administ severe global ischemia, provoked by two-vessel occlusion alsuperimposed on halothane-induced reduction of arte-
rial blood pressure (50 mmHg), repeated administration wof lifarizine (0.1 mg kg⁻¹, 5 min postocclusion; 0. superimposed on halothane-induced reduction of arte rial blood pressure (50 mmHg), repeated administration of lifarizine (0.1 mg kg^{-1} , 5 min postocclusion; 0.5 m kg^{-1} , 15 min postocclusion and twice daily for 72 h) was rial blood pressure (50 mmHg), repeated administration was
of lifarizine (0.1 mg kg⁻¹, 5 min postocclusion; 0.5 mg resti
kg⁻¹, 15 min postocclusion and twice daily for 72 h) was had
able to achieve significant protect kg⁻¹, 15 min postocclusion and twice daily for 72 h) was
able to achieve significant protection of hippocampal
CA1, cortex, thalamus, and cerebellar brainstem
(McBean et al., 1995a). With permanent MCA occlusion
in cats able to achieve significant protection of hippocampal (i.CA1, cortex, thalamus, and cerebellar brainstem slot (McBean et al., 1995a). With permanent MCA occlusion N_i in cats, 2 μ g kg⁻¹ of lifarizine administered i. (McBean et al., 1995a). With permanent MCA occlusion Na
in cats, 2 μ g kg⁻¹ of lifarizine administered i.v. after the
ischemia onset, followed by infusion at 0.7 μ g kg⁻¹ h⁻¹ Na
over 12 h, reduced by 70% the siz in cats, 2 μ g kg⁻¹ of lifarizine administered i.v. after tlischemia onset, followed by infusion at 0.7 μ g kg⁻¹ h⁻¹ N
over 12 h, reduced by 70% the size of the infarct. The fi
highest dose tested in this study over 12 h, reduced by 70% the size of the infarct. The f
highest dose tested in this study (50 μ g kg⁻¹ i.v., with
17.5 μ g kg⁻¹ h⁻¹ maintenance dose) was able to reduce
the infarct size by as much as 88% (Kucha 17.5 μ g kg⁻¹ h⁻¹ maintenance dose) was able to reduce
the infarct size by as much as 88% (Kucharczyk et al.
1990, 1991). Monitoring of the developing lesions using
magnetic resonance imaging and spectroscopy also s 17.5 μ g kg⁻¹ h⁻¹ maintenance dose) was able to reduce h
the infarct size by as much as 88% (Kucharczyk et al., m
1990, 1991). Monitoring of the developing lesions using st
magnetic resonance imaging and spectroscop the infarct size by as much as 88% (Kucharczyk et al., ma
1990, 1991). Monitoring of the developing lesions using sturnagnetic resonance imaging and spectroscopy also sug-
inegested that energy levels were preserved and ti 1990, 1991). Monitoring of the developing lesions using magnetic resonance imaging and spectroscopy also suggested that energy levels were preserved and tissue acidosis and edema reduced in animals treated with lifarizine magnetic resonance imaging and spectroscopy also sug-
gested that energy levels were preserved and tissue ca
acidosis and edema reduced in animals treated with
lifarizine (Kucharczyk et al., 1990, 1991). Repeated ad-
minis gested that energy levels were preserved and tissue
acidosis and edema reduced in animals treated with
lifarizine (Kucharczyk et al., 1990, 1991). Repeated ad-
ministration of lifarizine also reduced the size of the
infarc acidosis and edema reduced in animals treated with the diffarizine (Kucharczyk et al., 1990, 1991). Repeated adreministration of lifarizine also reduced the size of the diffared infarct produced by MCA occlusion in mice (B lifarizine (Kucharczyk et al., 1990, 1991). Repeated a
ministration of lifarizine also reduced the size of th
infarct produced by MCA occlusion in mice (Brown et a
1994a, 1995), but high doses of lifarizine (200 times th
d infarct produced by MCA occlusion in mice (Brown et al., 1994a, 1995), but high doses of lifarizine (200 times the dose effective in the mouse) failed to protect the corresponding rat model (Rataud et al., 1994). Finally, infarct produced by MCA occlusion in mice (Brown et ε 1994a, 1995), but high doses of lifarizine (200 times t dose effective in the mouse) failed to protect the corresponding rat model (Rataud et al., 1994). Finally, 1994a, 1995), but high doses of lifarizine (200 times the by dose effective in the mouse) failed to protect the corre-
sponding rat model (Rataud et al., 1994). Finally, lifariz-
ine was also beneficial when administered dose effective in the movel
sponding rat model (Rataine was also beneficial v
tion of photothromboti
(McBean et al., 1995b).
Like flunarizine, lifari onding rat model (Rataud et al., 1994). Finally, lifariz-

e was also beneficial when administered after induc-

in of photothrombotic infarcts in the rat cortex of

is

like flunarizine, lifarizine was initially introduc

ine was also beneficial when administered after induction of photothrombotic infarcts in the rat cortex (McBean et al., 1995b).

Like flunarizine, lifarizine was initially introduced as Ca^{2+} -modulator (Alps et al., 199 (McBean et al., 1995b).
Like flunarizine, lifarizine was initially introduced as Ca^{2+} -modulator (Alps et al., 1990). This drug however did not act as a conventional dihydropyridine Ca^{2+} antagonist in the taenia smoo (McBean et al., 1995b).

Like flunarizine, lifarizine was initially introduced as
 Ca^{2+} -modulator (Alps et al., 1990). This drug however

did not act as a conventional dihydropyridine Ca^{2+} an-

tagonist in the taeni Like flunarizine, lifarizine was initially introduced ϵ Ca²⁺-modulator (Alps et al., 1990). This drug howeved did not act as a conventional dihydropyridine Ca²⁺ and tagonist in the taenia smooth muscle preparation, Ca^{2+} -modulator (Alps et al., 1990). This drug however and
did not act as a conventional dihydropyridine Ca^{2+} an-
tagonist in the taenia smooth muscle preparation, be-
suggest is potently inhibited the responses to did not act as a conventional dihydropyridine Ca^{2+} antagonist in the taenia smooth muscle preparation, because it potently inhibited the responses to Ca^{2+} channel activators such as Bay K 8644 but had little effect tagonist in the taenia smooth muscle preparation, be-
cause it potently inhibited the responses to Ca^{2+} chan-
nel activators such as Bay K 8644 but had little effect on 3.
responses to Ca^{2+} (Fraser and Spedding, 199 cause it potently inhibited the responses to Ca^{2+} channel activators such as Bay K 8644 but had little effect on responses to Ca^{2+} (Fraser and Spedding, 1991). In contrast to these indistinct and relatively weak eff nel activators such as Bay K 8644 but had little effect on
responses to Ca^{2+} (Fraser and Spedding, 1991). In con-
trast to these indistinct and relatively weak effects on
 Ca^{2+} channels, ligand binding and functional responses to Ca^{2+} (Fraser and Spedding, 1991). In contrast to these indistinct and relatively weak effects on Ca^{2+} channels, ligand binding and functional assays a have clearly suggested that lifarizine interacts po trast to these indistinct and relatively weak effects on trin Ca^{2+} channels, ligand binding and functional assays ano have clearly suggested that lifarizine interacts potently al., with voltage-gated Na⁺ channels: (have clearly suggested that lifarizine interacts potently al., 1993; Handa et al., 1990) with proven protective with voltage-gated Na⁺ channels: (*a*) lifarizine displaced effects against cerebral ischemia, both in vitr

dition to interacting with Ca²⁺ and Na⁺ channels, flu-
narizine has other pharmacological properties that may
neurotoxicity with an IC_{50} of 0.4 μ M (versus 30 nM for
also contribute to neuroprotection, such as in **protected cultured cortical neurons against veratridine**
neurotoxicity with an IC_{50} of 0.4 μ m (versus 30 nm for DERENOVITCH
protected cultured cortical neurons against veratridine
neurotoxicity with an IC_{50} of 0.4 μ M (versus 30 nM for
TTX, and 30 μ M for the dihydropyridine Ca²⁺ channel DERENOVITCH
protected cultured cortical neurons against veratridine
neurotoxicity with an IC_{50} of 0.4 μ M (versus 30 nM for
TTX, and 30 μ M for the dihydropyridine Ca²⁺ channel
antagonist nitrendipine) (May et al protected cultured cortical neurons against veratridin
neurotoxicity with an IC_{50} of 0.4 μ M (versus 30 nM fo
TTX, and 30 μ M for the dihydropyridine Ca^{2+} channe
antagonist nitrendipine) (May et al., 1995); and protected cultured cortical neurons against veratrid
neurotoxicity with an IC_{50} of 0.4 μ M (versus 30 nM
TTX, and 30 μ M for the dihydropyridine Ca²⁺ chan
antagonist nitrendipine) (May et al., 1995); and (c) s
il neurotoxicity with an IC₅₀ of 0.4 μ M (versus 30 nM for TTX, and 30 μ M for the dihydropyridine Ca²⁺ channel antagonist nitrendipine) (May et al., 1995); and (c) similar to TTX and flunarizine, lifarizine inhibite ilar to TTX and flunarizine, lifarizine inhibited veratridine-induced contractions of embryonic chick cardiac

kg⁻¹, 15 min postocclusion and twice daily for 72 h) was had no effect on Na⁺ currents modified by chloramine-T
able to achieve significant protection of hippocampal (i.e., oxidizing agent producing currents that deca over 12 h, reduced by 70% the size of the infarct. The from an interaction with the inactivated state of the highest dose tested in this study (50 μ g kg⁻¹ i.v., with channel (McGivern et al., 1995b). Voltage-dependen myocytes $(IC_{50} = 1.6 \mu M)$ (Patmore et al., 1991).
Patch-clamp studies in mouse neuroblastoma cells
have confirmed and clarified the potent actions of lifarizdine-induced contractions of embryonic chick cardiac
myocytes $(IC_{50} = 1.6 \mu M)$ (Patmore et al., 1991).
Patch-clamp studies in mouse neuroblastoma cells
have confirmed and clarified the potent actions of lifariz-
ine on myocytes $(IC_{50} = 1.6 \mu M)$ (Patmore et al., 1991).
Patch-clamp studies in mouse neuroblastoma cells
have confirmed and clarified the potent actions of lifariz-
ine on Na⁺ currents (McGivern et al., 1995b): (*a*) at
hold Patch-clamp studies in mouse neuroblastoma cells
have confirmed and clarified the potent actions of lifariz-
ine on Na⁺ currents (McGivern et al., 1995b): (*a*) at
holding potentials, the potency of lifarizine to reduce have confirmed and clarified the potent actions of lifariz-
ine on Na⁺ currents (McGivern et al., 1995b): (*a*) at
holding potentials, the potency of lifarizine to reduce the
peak Na⁺ current evoked by a 10 ms depolar ine on Na⁺ currents (McGivern et al., 1995b): (*a*) at holding potentials, the potency of lifarizine to reduce the peak Na⁺ current evoked by a 10 ms depolarizing step was markedly increased when the holding potential holding potentials, the potency of lifarizine to reduce the
peak Na⁺ current evoked by a 10 ms depolarizing step
was markedly increased when the holding potential be-
came increasingly less negative (IC_{50} of 7.3, 1.3 peak Na⁺ current evoked by a 10 ms depolarizing step
was markedly increased when the holding potential be-
came increasingly less negative $(IC_{50}$ of 7.3, 1.3 and 0.3
 μ M for a corresponding holding potential of -10 was markedly increased when the holding potential be-
came increasingly less negative $(IC_{50}$ of 7.3, 1.3 and 0.3
 μ M for a corresponding holding potential of -100 , -80
and -60 mV); (*b*) recovery from inactivati came increasingly less negative $(IC_{50}$ of 7.3, 1.3 and 0.3 μ M for a corresponding holding potential of -100 , -80 and -60 mV); *(b)* recovery from inactivation following a 20 s depolarization from -100 to 0 mV μ M for a corresponding holding potential of -100 , -80
and -60 mV); (*b*) recovery from inactivation following a
20 s depolarization from -100 to 0 mV was markedly
slowed by 3 μ M lifarizine; (*c*) the apparen and -60 mV); (*b*) recovery from inactivation following a 20 s depolarization from -100 to 0 mV was markedly slowed by 3 μ M lifarizine; (*c*) the apparent affinity of lifarizine for the inactivated state of the cha 20 s depolarization from -100 to 0 mV was markedly slowed by 3 μ M lifarizine; (c) the apparent affinity of lifarizine for the inactivated state of the channel (K_I) was 0.19 μ M, i.e., much higher than that estima slowed by 3 μ M lifarizine; (c) the apparent affinity of lifarizine for the inactivated state of the channel (K_I) was 0.19 μ M, i.e., much higher than that estimated for resting channels ($K_R = 7.3 \mu$ M); and (d) 1 $\$ lifarizine for the inactivated state of the channel (K_1)
was 0.19 μ M, i.e., much higher than that estimated for
resting channels $(K_R = 7.3 \mu$ M); and $(d) 1 \mu$ M lifarizine
had no effect on Na⁺ currents modified by chl was 0.19 μ M, i.e., much higher than that estimated for
resting channels ($K_R = 7.3 \mu$ M); and (d) 1 μ M lifarizine
had no effect on Na⁺ currents modified by chloramine-T
(i.e., oxidizing agent producing currents that had no effect on $Na⁺$ currents modified by chloramine-T had no effect on Na⁺ currents modified by chloramine-T (i.e., oxidizing agent producing currents that decay very slowly), suggesting no significant interaction with open Na⁺ channels. Taken together, these data demons (i.e., oxidizing agent producing currents that decay very
slowly), suggesting no significant interaction with open
Na⁺ channels. Taken together, these data demonstrate
that lifarizine is a potent voltage-dependent inhib slowly), suggesting no significant interaction with open Na^+ channels. Taken together, these data demonstrate that lifarizine is a potent voltage-dependent inhibitor of Na^+ currents and that the voltage depend $Na⁺$ channels. Taken together, these data demonstrat
that lifarizine is a potent voltage-dependent inhibitor $Na⁺$ currents and that the voltage dependence arise
from an interaction with the inactivated state of that lifarizine is a potent voltage-dependent inhibitor of Na^+ currents and that the voltage dependence arises from an interaction with the inactivated state of the channel (McGivern et al., 1995b). Voltage-dependent in Na⁺ currents and that the voltage dependence arises
from an interaction with the inactivated state of the
channel (McGivern et al., 1995b). Voltage-dependent in-
hibition of Na⁺ currents was also demonstrated in hu-
m from an interaction with the inactivated state of the channel (McGivern et al., 1995b). Voltage-dependent hibition of Na⁺ currents was also demonstrated in hean neuroblastoma cells (Brown et al., 1994b), and the study c channel (McGivern et al., 1995b). Voltage-dependent in-
hibition of Na⁺ currents was also demonstrated in hu-
man neuroblastoma cells (Brown et al., 1994b), and this
study clarified further the action mechanism of lifar hibition of Na⁺ currents was also demonstrated in human neuroblastoma cells (Brown et al., 1994b), and this study clarified further the action mechanism of lifarizine. The fact that TTX did not prevent the inhibition ca man neuroblastoma cells (Brown et al., 1994b), and this study clarified further the action mechanism of lifarizine. The fact that TTX did not prevent the inhibition caused by a subsequent application of lifarizine, and th study clarified further the action mechanism of lifariz-
ine. The fact that TTX did not prevent the inhibition
caused by a subsequent application of lifarizine, and
that the block of Na⁺ currents by lifarizine did not
r ine. The fact that TTX did not prevent the inhibitio caused by a subsequent application of lifarizine, an that the block of Na⁺ currents by lifarizine did not require Na⁺ channel activation, confirmed that the drug do caused by a subsequent application of lifarizine, and
that the block of Na^+ currents by lifarizine did not
require Na^+ channel activation, confirmed that this
drug does not interact with the open state of the chan-
ne that the block of Na⁺ currents by lifarizine did not require Na⁺ channel activation, confirmed that this drug does not interact with the open state of the channel. In contrast, the depression of Na⁺ currents caused require Na^+ channel activation, confirmed that this drug does not interact with the open state of the channel. In contrast, the depression of Na^+ currents caused by the local anesthetic lignocaine was readily reversib drug does not interact with the open state of the char
nel. In contrast, the depression of Na^+ currents cause
by the local anesthetic lignocaine was readily reversibl
after pretreatment of cells with lifarizine, suggest nel. In contrast, the depression of $Na⁺$ currents caused
by the local anesthetic lignocaine was readily reversible
after pretreatment of cells with lifarizine, suggesting an
allosteric interaction of lifarizine with by the local anesthetic lignocaine was readily reversible
after pretreatment of cells with lifarizine, suggesting an
allosteric interaction of lifarizine with the local anes-
thetic binding site (fig. 3), or selective bind after pretreatment of cells with lifarizine, suggesting
allosteric interaction of lifarizine with the local an
thetic binding site (fig. 3), or selective binding to a st
of the channel that is modulated by local anesthetic allosteric interaction of lifarizine with the local anesthetic binding site (fig. 3), or selective binding to a state of the channel that is modulated by local anesthetics. It is interesting to note that, in comparison to thetic binding site (fig. 3), or selective binding to a state
of the channel that is modulated by local anesthetics. It
is interesting to note that, in comparison to the anticon-
vulsants phenytoin and lamotrigine (see se of the channel that is modulated by local anesthetics. It
is interesting to note that, in comparison to the anticon-
vulsants phenytoin and lamotrigine (see sections IV.D.1.
and V.B.2.), the lifarizine block of Na⁺ chan is interesting to note that, in comparison to the anticon-
vulsants phenytoin and lamotrigine (see sections IV.D.1.
and V.B.2.), the lifarizine block of Na⁺ channels showed
limited use dependence and frequency dependenc neuroprotection. 12. **3. I. Lomerizing in Sole is that the set of Na** \uparrow channels shownited use dependence and frequency dependence is ggests that this property may not be essential uroprotection.
3. *Lomerizine hydrochloride*. Lome limited use dependence and frequency depend
suggests that this property may not be esse
neuroprotection.
3. *Lomerizine hydrochloride*. Lomerizine h
ride (KB-2796) {1-[bis(4-fluorophenyl)methyl]
trimethoxybenzyl)piperazine

suggests that this property may not be essential for
neuroprotection.
3. Lomerizine hydrochloride. Lomerizine hydrochlo-
ride (KB-2796) {1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-
trimethoxybenzyl)piperazine dihydrochloride} neuroprotection.

3. Lomerizine hydrochloride. Lomerizine hydrochloride (KB-2796) {1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-

trimethoxybenzyl)piperazine dihydrochloride} (fig. 8) is

another diphenylpiperazine Ca^{2+} anta 3. Lomerizine hydrochloride. Lomerizine hydrochloride (KB-2796) {1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-
trimethoxybenzyl)piperazine dihydrochloride} (fig. 8) is
another diphenylpiperazine Ca^{2+} antagonist (Akaike et
al ride (KB-2796) (1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-
trimethoxybenzyl)piperazine dihydrochloride) (fig. 8) is
another diphenylpiperazine Ca^{2+} antagonist (Akaike et
al., 1993; Handa et al., 1990) with proven protecti trimethoxybenzyl)piperazine dihydrochloride} (fig. 8) is
another diphenylpiperazine Ca^{2+} antagonist (Akaike et
al., 1993; Handa et al., 1990) with proven protective
effects against cerebral ischemia, both in vitro and another diphenylpiperazine Ca^{2+} antagonist (Akaike et al., 1993; Handa et al., 1990) with proven protective effects against cerebral ischemia, both in vitro and in vivo (Handa et al., 1990; Hara et al., 1993a, b; Yamas

PHARMACOLOGICAL REVIEWS

MODULATION OF VOLTAGE-GATED NA CHANNELS ⁴⁹

guinea pig slices with KB-2796 (0.1 and 1 μ M) significantly accelerated the recovery of population spikes of MODULATION OF VOLTAGE-G
guinea pig slices with KB-2796 (0.1 and 1 μ M) signifi-
cantly accelerated the recovery of population spikes of
dentate granule cell layers following mild hypoxia (Hara MODULATION OF VOLTAGE-C
guinea pig slices with KB-2796 (0.1 and 1 μ M) signifi-
cantly accelerated the recovery of population spikes of
dentate granule cell layers following mild hypoxia (Hara
et al., 1988). The same tr guinea pig slices with KB-2796 $(0.1 \text{ and } 1 \mu)$ signtly accelerated the recovery of population spike dentate granule cell layers following mild hypoxia (I et al., 1988). The same treatment prevented glutam induced neuroto guinea pig slices with KB-2796 (0.1 and 1μ M) significantly accelerated the recovery of population spikes of dentate granule cell layers following mild hypoxia (Hara et al., 1988). The same treatment prevented glutamate cantly accelerated the recovery of population spikes of dentate granule cell layers following mild hypoxia (Harantiet al., 1988). The same treatment prevented glutamate induced neurotoxicity in rat hippocampal primary celc dentate granule cell layers following mild hypoxia (Hara et al., 1988). The same treatment prevented glutamate-
induced neurotoxicity in rat hippocampal primary cell
cultures, even though KB-2796 has no affinity for ionoet al., 1988). The same treatment prevented glutamate-
induced neurotoxicity in rat hippocampal primary cell
cultures, even though KB-2796 has no affinity for iono-
tropic glutamate receptors (Hara et al., 1993b). In vivo nduced neurotoxicity in rat hippocampal primary cell
cultures, even though KB-2796 has no affinity for iono-
tropic glutamate receptors (Hara et al., 1993b). In vivo,
KB-2796 (10 mg kg⁻¹ i.p.) reduced infarct size and s cultures, even though KB-2796 has no affinity for ionotropic glutamate receptors (Hara et al., 1993b). In vivo, KB-2796 (10 mg kg^{-1} i.p.) reduced infarct size and significantly improved neurological recovery in the rat tropic glutamate receptors (Hara et al., 1993b). In vivo, $KB-2796$ (10 mg kg^{-1} i.p.) reduced infarct size and significantly improved neurological recovery in the rat MCA occlusion model (Harada et al., 1989; Hara et al. nificantly improved neurological recovery in the rat MCA occlusion model (Harada et al., 1989; Hara et al., 1993a); it also prevented delayed neuronal death produced by 5-min bilateral carotid occlusion in the gerbil hippo MCA occlusion model (Harada et al., 1989; Hara et al., 93a); it also prevented delayed neuronal death pro-
ceed by 5-min bilateral carotid occlusion in the gerbil
ppocampal CA1 subfield, even when the drug was
ministered postischemia (Yoshidomi et al., 1989).
With some experi

With some experimental models, the anti-ischemic duced by 5-min bilateral carotid occlusion in the gerbil
hippocampal CA1 subfield, even when the drug was
administered postischemia (Yoshidomi et al., 1989).
With some experimental models, the anti-ischemic
properties of hippocampal CA1 subfield, even when the drug was
administered postischemia (Yoshidomi et al., 1989).
With some experimental models, the anti-ischemic
properties of KB-2796 may be partly linked to Ca²⁺
antagonistic and c administered postischemia (Yoshidomi et al., 1989).
With some experimental models, the anti-ischemic
properties of KB-2796 may be partly linked to Ca^{2+}
antagonistic and cerebrovascular effects (Handa, 1990).
Neverthele properties of KB-2796 may be partly linked to Ca^{2+}
antagonistic and cerebrovascular effects (Handa, 1990).
Nevertheless, strong evidence points to Na⁺ channel
down-modulation as the primary neuroprotective mech-
anism antagonistic and cerebrovascular effects (Handa, 19:
Nevertheless, strong evidence points to Na⁺ chandown-modulation as the primary neuroprotective me
anism: (a) KB-2796 minimized the deficits in brain
ergy metabolism d Nevertheless, strong evidence points to $Na⁺$ channel down-modulation as the primary neuroprotective mechanism: (a) KB-2796 minimized the deficits in brain energy metabolism during ischemia produced by decapitation down-modulation as the primary neuroprotective mechanism: (a) KB-2796 minimized the deficits in brain energy metabolism during ischemia produced by decapitation or four-vessel occlusion (Yamashita et al., 1993), suggest anism: (a) KB-2796 minimized the deficits in brain energy metabolism during ischemia produced by decapitation or four-vessel occlusion (Yamashita et al., 1993), suggesting a reduction of residual energy demand by the drug ergy metabolism during ischemia produced by decapita-
tion or four-vessel occlusion (Yamashita et al., 1993),
suggesting a reduction of residual energy demand by the
drug (see sections III.A. and B.); (b) similarly, KB-27 tion or four-vessel occlusion (Yamashita et al., 1993), suggesting a reduction of residual energy demand by the drug (see sections III.A. and B.); (b) similarly, KB-2796 concentration-dependently prolonged both latency an suggesting a reduction of residual energy demand by the drug (see sections III.A. and B.); (b) similarly, KB-2796 concentration-dependently prolonged both latency and interval of spreading depression produced by a brief p drug (see sections III.A. and B.); (b) similarly, KB-2796 concentration-dependently prolonged both latency and interval of spreading depression produced by a brief period of hypoxia: it was 10 and 1000 times more potent t concentration-dependently prolonged both latency and interval of spreading depression produced by a brie period of hypoxia: it was 10 and 1000 times more poten than flunarizine in prolonging the latency and interva of SD, interval of spreading depression produced by a brique priod of hypoxia: it was 10 and 1000 times more potenthan flunarizine in prolonging the latency and intervation of SD, respectively (Takagi et al., 1994); (c) this com period of hypoxia: it was 10 and 1000 times more potent
than flunarizine in prolonging the latency and interval
of SD, respectively (Takagi et al., 1994); (c) this com-
pound was proposed to potently displace the Na⁺ cha than flunarizine in prolonging the latency and interval
of SD, respectively (Takagi et al., 1994); (c) this com-
pound was proposed to potently displace the Na⁺ chan-
nel ligand BTX-B from rat brain synaptosomes (Brown
 of SD, respectively (Takagi et al., 1994); (c) this com-
pound was proposed to potently displace the Na⁺ chan-
nel ligand BTX-B from rat brain synaptosomes (Brown
C. M. et al., unpublished data; cited by McGivern et al. pound was proposed to potently displace the Na⁺ chan-
nel ligand BTX-B from rat brain synaptosomes (Brown carc
C. M. et al., unpublished data; cited by McGivern et al., tent
1995a); and (*d*) voltage-clamp studies in N1 nel ligand BTX-B from rat brain synaptosomes (Brown cc C. M. et al., unpublished data; cited by McGivern et al., te 1995a); and (d) voltage-clamp studies in N1E-115 cells glashowed that KB-2796 potently inhibits Na⁺ cu C. M. et al., unpublished data; cited by McGivern et al., te 1995a); and (d) voltage-clamp studies in N1E-115 cells glas showed that KB-2796 potently inhibits Na⁺ currents by et interacting predominantly with the inacti 1995a); and (*d*) voltage-clamp studies in N1E-115 cells glob
showed that KB-2796 potently inhibits Na⁺ currents by et a
interacting predominantly with the inactivated state of the
Na⁺ channels, but also with their op showed that KB-2796 potently inhibits Na⁺ currents by et al., interacting predominantly with the inactivated state of the onl
Na⁺ channels, but also with their open and resting age- ar
states (McGivern et al., 1995a). interacting predominantly with the inactivated state of Na⁺ channels, but also with their open and resting states (McGivern et al., 1995a). Finally, KB-2796 (1 mg kg⁻¹ i.p.), administered before elicitation of cortica $Na⁺$ channels, but also with their open and resting states (McGivern et al., 1995a). Finally, KB-2796 (1 mg kg^{-1} i.p.), administered before elicitation of cortical SD by topical application of KCl, inhibited th states (McGivern et al., 1995a). Finally, KB-2796 (1 mg

kg⁻¹ i.p.), administered before elicitation of cortical SD

by topical application of KCl, inhibited the subsequent

inyoperfusion and reduced the expression of c kg⁻¹ i.p.), administered before elicitation of cortical SD measured 5 min after anoxic depolarization (Xie et al., by topical application of KCl, inhibited the subsequent 1995). As this reduction was not obtained with T immunoreactivity (Shimazawa et al., 1994), suggesting
a depressing effect of KB-2796 on SD elicitation (see
section III.D.1.).
4. R56865 and related benzothiazoles. The benzothiapoperfusion and reduced the expression of c-Fos-

munoreactivity (Shimazawa et al., 1994), sugges

depressing effect of KB-2796 on SD elicitation

ction III.D.1.).

4. *R56865 and related benzothiazoles*. The benzot

lamin immunoreactivity (Shimazawa et al., 1994
a depressing effect of KB-2796 on SD eli
section III.D.1.).
4. R56865 and related benzothiazoles. Th
zolamine R56865 [N-(1-(4-(4-fluorophenox
peridinyl)-N-methyl-2-benzothiazolamine

a depressing effect of KB-2796 on SD elicitation (see insection III.D.1.).

be

4. R56865 and related benzothiazoles. The benzothia-

It is related benzothiazoles. The benzothia-

peridinyl)-N-methyl-2-benzothiazolamine] section III.D.1.).
4. R56865 and related benzothiazoles. The benzothiazolamine R56865 [N-(1-(4-(4-fluorophenoxy)butyl)-4-pi-
peridinyl)-N-methyl-2-benzothiazolamine] (fig. 10) is
another Ca^{2+} channel modulator (Panchen 4. R56865 and related benzothiazoles. The benzothiazolamine R56865 [N-(1-(4-(4-fluorophenoxy)butyl)-4-piperidinyl)-N-methyl-2-benzothiazolamine] (fig. 10) is another Ca²⁺ channel modulator (Panchenko et al 1993) that in zolamine R56865 [N-(1-(4-(4-fluorophenoxy)butyl)-4-pi-
peridinyl)-N-methyl-2-benzothiazolamine] (fig. 10) is m
another Ca²⁺ channel modulator (Panchenko et al., μ
1993) that interacts strongly with Na⁺ channels (Ve peridinyl)-N-methyl-2-benzothiazolamine] (fig. 10) is nanother Ca^{2+} channel modulator (Panchenko et al., 1993) that interacts strongly with Na⁺ channels (Veridonck et al., 1991; Kiskin et al., 1993). Primarily studie another Ca^{2+} channel modulator (Panchenko et al., 1993) that interacts strongly with Na⁺ channels (Verdonck et al., 1991; Kiskin et al., 1993). Primarily studied as an antianginal drug (Vollmer et al., 1987; Verdonck 1993) that interacts strongly with Na^+ channels (Ver-
donck et al., 1991; Kiskin et al., 1993). Primarily studied P
as an antianginal drug (Vollmer et al., 1987; Verdonck et
al., 1991; Chen et al., 1993a), R56865 also s aonck et al., 1991; Kiskin et al., 1993). Primarly studied
as an antianginal drug (Vollmer et al., 1987; Verdonck et
al., 1991; Chen et al., 1993a), R56865 also showed ben-
eficial effects in cerebral ischemia, and a numbe al., 1991; Chen et al., 1993a), R56865 also showed ben-
eficial effects in cerebral ischemia, and a number of
studies clearly suggested that its anti-ischemic proper-
ties in heart and brain may be linked to actions on Na eficial effects in cerebral ischemia, and a number
studies clearly suggested that its anti-ischemic properties in heart and brain may be linked to actions on N
channels. As with flunarizine, R56865 dose-dependen
 $(10^{-6} \text$ studies clearly suggested that its anti-ischemic proper-
ties in heart and brain may be linked to actions on Na⁺
channels. As with flunarizine, R56865 dose-dependently
 $(10^{-6} \text{-} 10^{-5} \text{ M})$ inhibited the marked increa

emic properties.

FIG. 10. Structures of benzothiazole derivatives with *anti-ischemic* properties.

Na⁺ influx (Urenjak et al., 1991; Wermelskirchen et al., 1992), and a similar action was reported with adult emic properties.
Na⁺ influx (Urenjak et al., 1991; Wermelskirchen et al.,
1992), and a similar action was reported with adult
cardiac myocytes (Haigney et al., 1994). R56865 consis-Na⁺ influx (Urenjak et al., 1991; Wermelskirchen et al., 1992), and a similar action was reported with adult cardiac myocytes (Haigney et al., 1994). R56865 consis-Na⁺ influx (Urenjak et al., 1991; Wermelskirchen et al., 1992), and a similar action was reported with adult cardiac myocytes (Haigney et al., 1994). R56865 consistently delayed anoxic depolarization in several models of Na⁺ influx (Urenjak et al., 1991; Wermelskirchen et al., 1992), and a similar action was reported with adult cardiac myocytes (Haigney et al., 1994). R56865 consistently delayed anoxic depolarization in several models of tently delayed anoxic depolarization in several models of global cerebral ischemia (Scheller et al., 1989; Tegtmeier et al., 1992; Xie et al., 1995). Furthermore, R56865 was the only drug among various selective inhibitors age- and ligand-operated ion channels to reduce slightly, tently delayed anoxic depolarization in several models of global cerebral ischemia (Scheller et al., 1989; Tegtmeier et al., 1992; Xie et al., 1995). Furthermore, R56865 was the only drug among various selective inhibitor global cerebral ischemia (Scheller et al., 1989; Tegtmeier
et al., 1992; Xie et al., 1995). Furthermore, R56865 was
the only drug among various selective inhibitors of volt-
age- and ligand-operated ion channels to reduce et al., 1992; Xie et al., 1995). Furthermore, R56865 was
the only drug among various selective inhibitors of volt-
age- and ligand-operated ion channels to reduce slightly,
but significantly, the amplitude of the drop in the only drug among various selective inhibitors of voltage- and ligand-operated ion channels to reduce slightly, but significantly, the amplitude of the drop in $[Na⁺]$ _o measured 5 min after anoxic depolarization (X age- and ligand-operated ion channels to reduce slightly,
but significantly, the amplitude of the drop in $[Na^+]$ _o
measured 5 min after anoxic depolarization (Xie et al.,
1995). As this reduction was not obtained with TT but significantly, the amplitude of the drop in $[Na^+]$,
measured 5 min after anoxic depolarization (Xie et al.
1995). As this reduction was not obtained with TTX (fig
5) (Xie et al., 1994b), these data suggested that R568 measured 5 min after anoxic depolarization (Xie et al., 1995). As this reduction was not obtained with TTX (fig. 5) (Xie et al., 1994b), these data suggested that R56865 may be capable of reducing Na^+ currents throu 1995). As this reduction was not obtained with TTX (fig. 5) (Xie et al., 1994b), these data suggested that R5686 may be capable of reducing Na⁺ currents through nor inactivating, TTX-resistant Na⁺ channels, which make 5) (Xie et al., 1994b), these data suggested that R56 may be capable of reducing Na^+ currents through inactivating, TTX-resistant Na^+ channels, which become predominant with depolarized CNS membra It is releva may be capable of reducing Na⁺ currents through n
inactivating, TTX-resistant Na⁺ channels, which m
become predominant with depolarized CNS membran
It is relevant to mention here that sustained depolari
tion (3 min) of inactivating, TTX-resistant Na⁺ channels, which may
become predominant with depolarized CNS membranes.
It is relevant to mention here that sustained depolariza-
tion (3 min) of *Xenopus* oocytes resulted in the developbecome predominant with depolarized CNS membranes It is relevant to mention here that sustained depolarize
tion (3 min) of *Xenopus* oocytes resulted in the development of a slow inward current, TTX-resistant (5 to 3 μ It is relevant to mention here that sustained depolariza-
tion (3 min) of *Xenopus* oocytes resulted in the develop-
ment of a slow inward current, TTX-resistant (5 to 30
 μ M), caused by the induction of slowly activate tion (3 min) of *Xenopus* oocytes resulted in the development of a slow inward current, TTX-resistant (5 to 3 μ M), caused by the induction of slowly activated TTX insensitive Na⁺ channels (native), possibly mediated ment of a slow inward current, TTX-resistant (5 to 30 μ M), caused by the induction of slowly activated TTX-
insensitive Na⁺ channels (native), possibly mediated by
PKC phosphorylation (Charpentier et al., 1993). Volt μ M), caused by the induction of slowly activated TTX insensitive Na⁺ channels (native), possibly mediated by PKC phosphorylation (Charpentier et al., 1993). Volt age-clamp studies are consistent with an action of R56 insensitive Na⁺ channels (native), possibly mediated PKC phosphorylation (Charpentier et al., 1993). V age-clamp studies are consistent with an action R56865 on slow Na⁺ currents. In isolated cardiac P kinje cells, vo PKC phosphorylation (Charpentier et al., 1993). Volt age-clamp studies are consistent with an action of R56865 on slow Na^+ currents. In isolated cardiac Purkinje cells, voltage-clamped in the presence of veratridine, R5 age-clamp studies are consistent with an action $R56865$ on slow $Na⁺$ currents. In isolated cardiac Pukinje cells, voltage-clamped in the presence of veratre dine, R56865 was more effective in inhibiting the nor inac R56865 on slow Na⁺ currents. In isolated cardiac Pur-
kinje cells, voltage-clamped in the presence of veratri-
dine, R56865 was more effective in inhibiting the non-
inactivating Na⁺ current than in inhibiting the tim kinje cells, voltage-clamped in the presence of veratri-
dine, R56865 was more effective in inhibiting the non-
inactivating Na⁺ current than in inhibiting the time-
dependent Na⁺ currents elicited by short depolarizi dependent $Na⁺$ currents elicited by short depolarizing

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bellum, R56865 showed similar actions on Na⁺ currents wels et al., 19

to flunarizine (Kiskin et al., 1993; see above section 1.) gated Na⁺ ch 50 URENJAK AND OB
bellum, R56865 showed similar actions on Na⁺ currents w
to flunarizine (Kiskin et al., 1993; see above section 1.) g
but with a greater ability to block open channels (Na⁺ bellum, R56865 showed similar actions on Na⁺ currents
to flunarizine (Kiskin et al., 1993; see above section 1.)
but with a greater ability to block open channels (Na⁺
current inactivation suppressed by treatment with bellum, R56865 showed similar actions on Na⁺ currents
to flunarizine (Kiskin et al., 1993; see above section 1.)
but with a greater ability to block open channels (Na⁺
current inactivation suppressed by treatment with bellum, R56865 showed similar actions on
to flunarizine (Kiskin et al., 1993; see about with a greater ability to block open c
current inactivation suppressed by treatm
nase) and a greater frequency dependence
Lubeluzole (flunarizine (Kiskin et al., 1993; see above set with a greater ability to block open chann
rrent inactivation suppressed by treatment v
se) and a greater frequency dependence.
Lubeluzole (the S-isomer of a 3,4-difluoro-be

but with a greater ability to block open channels (Na⁺ current inactivation suppressed by treatment with pro-
nase) and a greater frequency dependence.
Lubeluzole (the S-isomer of a 3,4-difluoro-benzothia-
zole) is a clo current inactivation suppressed by treatment with pro-
nase) and a greater frequency dependence.
Lubeluzole (the S-isomer of a 3,4-difluoro-benzothia-
zole) is a close structural analogue of R56865 (fig. 10).
When administ nase) and a greater frequency dependence.
Lubeluzole (the S-isomer of a 3,4-difluoro-benzot
zole) is a close structural analogue of R56865 (fig.
When administered as a single i.v. bolus, 5 min a
induction of photochemical Lubeluzole (the S-isomer of a 3,4-difluoro-benzothia-
zole) is a close structural analogue of R56865 (fig. 10). When administered as a single i.v. bolus, 5 min after neurological function of photochemical infarcts in the zole) is a close structural analogue of R56865 (fig. 10).
When administered as a single i.v. bolus, 5 min after
induction of photochemical infarcts in the rat sensorim-
otor cortex, lubeluzole protected neurological funct When administered as a single i.v. bolus, 5 min after ninduction of photochemical infarcts in the rat sensorim-
otor cortex, lubeluzole protected neurological function in
with an ED_{50} of 0.16 mg kg⁻¹ (De Ryck et al., induction of photochemical infarcts in the rat sensorim-
otor cortex, lubeluzole protected neurological function
with an ED_{50} of 0.16 mg kg⁻¹ (De Ryck et al., 1994).
Protection remained near-maximal when treatment wa otor cortex, lubeluzole protected neurological function in the with an ED₅₀ of 0.16 mg kg⁻¹ (De Ryck et al., 1994). senl
Protection remained near-maximal when treatment was protection remained near-maximal when treatm with an ED₅₀ of 0.16 mg kg⁻¹ (De Ryck et al., 1994). senheimer, 1994; Meldrum et al., 1994), but they also
Protection remained near-maximal when treatment was protect the CNS against ischemic and traumatic injury.
del Protection remained near-maximal when treatment was
delayed for up to 1 h after infarct induction, and then
progressively diminished as measured as 3 and 6 h $synn$
postinfarct. With a different regimen (i.v. bolus of 0.31 delayed for up to 1 h after infarct induction, and then
progressively diminished as measured as 3 and 6 h
postinfarct. With a different regimen (i.v. bolus of 0.31 $^{-1}$
mg kg⁻¹ starting 5 min after infarct, followed by progressively diminished as measured as 3 and 6 h
postinfarct. With a different regimen (i.v. bolus of 0.31
mg kg⁻¹ starting 5 min after infarct, followed by a 1-h
infusion of 0.31 or 0.63 mg kg⁻¹) the infarct volume postinfarct. With a different regimen (i.v. bolus of 0.31 $\text{mg}\text{ kg}^{-1}$ starting 5 min after infarct, followed by a 1-h strong infusion of 0.31 or 0.63 mg kg⁻¹) the infarct volume was inveduced by approximately 22 to 2 mg kg⁻¹ starting 5 min after infarct, followed by a 1-h infusion of 0.31 or 0.63 mg kg⁻¹) the infarct volume was reduced by approximately 22 to 24% (De Ryck et al., 1994). An interesting feature of lubeluzole is its s reduced by approximately 22 to 24% (De Ryck et al.,
1994). An interesting feature of lubeluzole is its strong pen
stereospecific effect, because the R-isomer was virtually mat
inactive in this model. A phase II trial has 1994). An interesting feature of lubeluzole is its stron stereospecific effect, because the R-isomer was virtuall inactive in this model. A phase II trial has investigate the effect of 5-day treatment with lubeluzole $(10$ stereospecific effect, because the R-isomer was virtually
inactive in this model. A phase II trial has investigated μ
the effect of 5-day treatment with lubeluzole (10 or 20 or
mg per day, versus placebo) on neurologic inactive in this model. A phase II trial has investigated the effect of 5-day treatment with lubeluzole (10 or 20 or mg per day, versus placebo) on neurological and functional recovery, and mortality in 232 ischemic strok the effect of 5-day treatment with lubeluzole (10 or 20 mg per day, versus placebo) on neurological and functional recovery, and mortality in 232 ischemic stroke patients. The low dose of lubeluzole showed a trend for more mg per day, versus placebo) on neurological and functional recovery, and mortality in 232 ischemic stroke patients. The low dose of lubeluzole showed a trend for more favourable outcome than placebo for all the efficacy pa tional recovery, and mortality in 232 ischemic strokendients. The low dose of lubeluzole showed a trend for more favourable outcome than placebo for all the efficacy parameters considered (Diener et al., 1995; Mui and Lees patients. The low dose of lubeluzole showed a trend for more favourable outcome than placebo for all the eff cacy parameters considered (Diener et al., 1995; Mu and Lees, 1995). The molecular target(s) of this compound rem more favourable outcome than placebo for all the efficacy parameters considered (Diener et al., 1995; Muir and Lees, 1995). The molecular target(s) of this compound remain speculative (Lesage et al., 1994). However, the s cacy parameters considered (Diener et al., 1995; Muir
and Lees, 1995). The molecular target(s) of this com-
pound remain speculative (Lesage et al., 1994). How-
ever, the structural analogy with R56865 and the fact
that l and Lees, 1995). The molecular target(s) of this com
pound remain speculative (Lesage et al., 1994). How
ever, the structural analogy with R56865 and the fact
that lubeluzole displaced BTX (0.1 to 1 μ M) (Lesage et
al., pound remain speculatiever, the structural ana
that lubeluzole displaced
al., 1994) warrant furthe
age-gated Na⁺ channels.
Sabeluzole is another er, the structural analogy with R56865 and the fact
at lubeluzole displaced BTX (0.1 to 1 μ M) (Lesage et
., 1994) warrant further studies on its action on volt-
e-gated Na⁺ channels.
Sabeluzole is another close struc

that lubeluzole displaced BTX (0.1 to 1 μ M) (Lesage et al., 1994) warrant further studies on its action on voltage-gated Na⁺ channels.
Sabeluzole is another close structural analogue of R56865 (fig. 10) with cerebrop al., 1994) warrant further studies on its action on voltage-gated Na⁺ channels.
Sabeluzole is another close structural analogue of R56865 (fig. 10) with cerebroprotective effects in several models of hypoxia and ischemia age-gated Na⁺ channels.
Sabeluzole is another close structural analogue of R56865 (fig. 10) with cerebroprotective effects in severa models of hypoxia and ischemia (Wauquier et al., 1986 Van Reempts et al., 1986; Nikolo Sabeluzole is another close structural analogue of R56865 (fig. 10) with cerebroprotective effects in several models of hypoxia and ischemia (Wauquier et al., 1986; models of hypoxia and ischemia (Wauquier et al., 1986; m R56865 (fig. 10) with cerebroprotective effects in several
models of hypoxia and ischemia (Wauquier et al., 1986;
Van Reempts et al., 1986; Nikolov et al., 1991; Wer-
brouck et al., 1991). For example, pretreatment of mic models of hypoxia and ischemia (Wauquier et al., 1986; models of hypoxia and ischemic to the hypoxic survival to hypoxia and increased the gasping time after decapitation (Nikolov et al., 1991; the gasping time after deca Van Reempts et al., 1986; Nikolov et al., 1991; Wer-
brouck et al., 1991). For example, pretreatment of mice
with sabeluzole (20 to 40 mg kg^{-1} i.p.) significantly
prolonged their survival to hypoxia and increased the
ga brouck et al., 1991). For example, pretreatment of mice
with sabeluzole (20 to 40 mg kg⁻¹ i.p.) significantly
prolonged their survival to hypoxia and increased the
gasping time after decapitation (Nikolov et al., 1991;
 with sabelizzole (20 to 40 mg kg⁻¹.p.) significantly fact that TTX (1 μ M) completely blocks veratrine-in-
prolonged their survival to hypoxia and increased the gasping time after decapitation (Nikolov et al., 1991; t prolonged their survival to hypoxia and increased t
gasping time after decapitation (Nikolov et al., 19
Werbrouck et al., 1991). Positive effects in the gaspi
test suggest that this compound increases the tolerar
of brain Werbrouck et al., 1991). Positive effects in the gasping inducted intervalses the tolerance action of brain tissue to oxygen deprivation via local mechanisms within the CNS, without an involvement of the This cardiovascul test suggest that this compound increases the tolerance
of brain tissue to oxygen deprivation via local mecha-
nisms within the CNS, without an involvement of the
cardiovascular system. Sabeluzole (19 mg kg⁻¹, i.p., 1 h of brain tissue to oxygen deprivation via local mechanisms within the CNS, without an involvement of the This cardiovascular system. Sabeluzole (19 mg kg⁻¹, i.p., 1 h 2. before ischemia) also reduced significantly the n cardiovascular system. Sabeluzole (19 mg kg⁻¹, i.p., 1 h 2. Down-modulation of Na⁺ channels. Binding exper-
before ischemia) also reduced significantly the neuronal iments carried out with rat brain synaptosomes showe cardiovascular system. Sabeluzole (19 mg kg⁻¹, i.p., 1
before ischemia) also reduced significantly the neurona
damage in the ipsilateral cortex of rats, as assessed 24
after unilateral carotid artery occlusion and hypox before ischemia) also reduced significantly the neuronal in
damage in the ipsilateral cortex of rats, as assessed 24 h
after unilateral carotid artery occlusion and hypoxia
(Van Reempts et al., 1986). This compound was or damage in the ipsilateral cortex of rats, as assessed 24 h
after unilateral carotid artery occlusion and hypoxia
(Van Reempts et al., 1986). This compound was origi-
nally proposed as a Ca^{2+} entry blocker on the basis after unilateral carotid artery occlusion and hypoxia

(Van Reempts et al., 1986). This compound was originally proposed as a Ca^{2+} entry blocker on the basis of

functional and electrophysiological data (Wilhelm et al. (Van Reempts et al., 1986). This compound was originally proposed as a Ca^{2+} entry blocker on the basis of functional and electrophysiological data (Wilhelm et al., 1986; Boddeke et al., 1986). However, its structural s 1986; Boddeke et al., 1986). However, its structural sim-

wels et al., 1992) strongly suggest an action on volta
gated Na⁺ channels. EXENOVITCH
wels et al., 1992) strated Na⁺ channels. BRENOVIICH

Wels et al., 1992) strongly suggest an action on voltage-

gated Na⁺ channels.
 B. Lamotrigine and Structural Analogues BW1003C87
 and BW619C89 and Bwels et al., 1992) *a* gated Na⁺ channe
B. Lamotrigine and BW619C89
Lamotrigine and

ted Na⁺ channels.
Lamotrigine and Structural Analogues BW1003C87
d BW619C89
Lamotrigine and its derivatives BW1003C87 [5-(2,3,5-
chlorophenyl)-2,4-diaminopyrimidine ethane sulpho-1. *Lamotrigine and Structural Analogues BW1003Cand BW619C89*
Lamotrigine and its derivatives BW1003C87 [5-(2,3
trichlorophenyl)-2,4-diaminopyrimidine ethane sulphotel and BW619C89 [4-amino-2-(4-methyl-1-pipera nately and BW619C89

Lamotrigine and its derivatives BW1003C

trichlorophenyl)-2,4-diaminopyrimidine eth

natel and BW619C89 [4-amino-2-(4-methy

nyl)-5-(2,3,5-trichlorophenyl pyrimidine)] and BW019C89
Lamotrigine and its derivatives BW1003C87 [5-(2,3,5-
trichlorophenyl)-2,4-diaminopyrimidine ethane sulpho-
nate] and BW619C89 [4-amino-2-(4-methyl-1-piperazi-
nyl)-5-(2,3,5-trichlorophenyl pyrimidine)] (fig. 9 Lamotrigine and its derivatives BW1003C87 [5-(2,3,4
trichlorophenyl)-2,4-diaminopyrimidine ethane sulph
nate] and BW619C89 [4-amino-2-(4-methyl-1-piperaz
nyl)-5-(2,3,5-trichlorophenyl pyrimidine)] (fig. 9) we
initially sel trichlorophenyl)-2,4-diaminopyrimidine ethane sulphonate] and BW619C89 [4-amino-2-(4-methyl-1-piperazi-
nyl)-5-(2,3,5-trichlorophenyl pyrimidine)] (fig. 9) were
initially selected for their anticonvulsant efficacy (Mes-
se nate] and BW619C89 [4-amino-2-(4-methyl-1-piperazi-
nyl)-5-(2,3,5-trichlorophenyl pyrimidine)] (fig. 9) were
initially selected for their anticonvulsant efficacy (Mes-
senheimer, 1994; Meldrum et al., 1994), but they also
 initially selected for their anticonvulsant efficacy (Mesinitially selected for their anticonvulsant efficacy (Messenheimer, 1994; Meldrum et al., 1994), but they also protect the CNS against ischemic and traumatic injury.
Although these compounds are often referred to as *(pres* senheimer, 1994; Meldrum et al., 1994), but they also
protect the CNS against ischemic and traumatic injury.
Although these compounds are often referred to as *(pre-*
synaptic) glutamate release inhibitors (Leach et al.,
1 protect the CNS against ischemic and traumatic injury
Although these compounds are often referred to as (*pre*
synaptic) glutamate release inhibitors (Leach et al.
1986; 1993; Meldrum et al., 1992; Graham et al., 1993)
st synaptic) glutamate release inhibitors (Leach et al., 1986; 1993; Meldrum et al., 1992; Graham et al., 1993), strong evidence suggests that their actions actually originate from use-dependent inhibition of Na⁺ channels. 1986; 1993; Meldrum et al., 1992; Graham et al., 1993), strong evidence suggests that their actions actually originate from use-dependent inhibition of Na⁺ channels.
1. Action on glutamate release. Lamotrigine dose-dep

reduced by approximately 22 to 24% (De Ryck et al., μ . Action on glutamate release. Lamotrigine dose-de-
1994). An interesting feature of lubeluzole is its strong pendently inhibited the release of endogenous gluta-
st 1986; 1993; Meldrum et al., 1992; Graham et al., 1993
strong evidence suggests that their actions actually ori
inate from use-dependent inhibition of Na⁺ channels
1. Action on glutamate release. Lamotrigine dose-d
pende strong evidence suggests that their actions actually originate from use-dependent inhibition of Na⁺ channels.
1. Action on glutamate release. Lamotrigine dose-dependently inhibited the release of endogenous glutamate ev inate from use-dependent inhibition of Na⁺ channels.

1. Action on glutamate release. Lamotrigine dose-dependently inhibited the release of endogenous glutamate evoked by veratrine in rat cortical slices (IC₅₀ = 2 μ T. Action on glutamate release. Lamotrigine dose-de-
pendently inhibited the release of endogenous gluta-
mate evoked by veratrine in rat cortical slices $(IC_{50} = 21 \mu)$, but this action was not exclusive to glutamate (la mate evoked by veratrine in rat cortical slices $(IC_{50} = 21 \mu M)$, but this action was not exclusive to glutamate (lamotrigine was only 2 times less potent in its inhibition of γ -aminobutyric acid (GABA) release; IC_{50} μ M), but this action was not exclusive to glutamate (lam-
otrigine was only 2 times less potent in its inhibition of
 γ -aminobutyric acid (GABA) release; IC₅₀ = 44 μ M) and,
at concentrations of up to 300 μ M, otrigine was only 2 times less potent in its inhibiti γ -aminobutyric acid (GABA) release; IC₅₀ = 44 μ M) at concentrations of up to 300 μ M, lamotrigine has effect on K⁺-induced glutamate release (Leach e 1986, γ -aminobutyric acid (GABA) release; IC₅₀ = 44 μ M) ar
at concentrations of up to 300 μ M, lamotrigine had
effect on K⁺-induced glutamate release (Leach et a
1986, 1991). These effects of lamotrigine on neurotra at concentrations of up to 300 μ M, lamotrigine had no
effect on K⁺-induced glutamate release (Leach et al.,
1986, 1991). These effects of lamotrigine on neurotrans-
mitter release were recently confirmed in vivo by m effect on K⁺-induced glutamate release (Leach et al., 1986, 1991). These effects of lamotrigine on neurotransmitter release were recently confirmed in vivo by microdialysis (Ahmad et al., 1995). BW1003C87 and BW619C89 a 1986, 1991). These effects of lamotrigine on neurotrans
mitter release were recently confirmed in vivo by micre
dialysis (Ahmad et al., 1995). BW1003C87 an
BW619C89 also inhibited veratrine- (but not K^+
evoked glutamat mitter release were recently confirmed in vivo by microdialysis (Ahmad et al., 1995). BW1003C87 and BW619C89 also inhibited veratrine- (but not K⁺-) evoked glutamate release from rat cortical slices (Meldrum et al., 1992 dialysis (Ahmad et al., 1995). BW1003C87 and
BW619C89 also inhibited veratrine- (but not K⁺-)
evoked glutamate release from rat cortical slices (Mel-
drum et al., 1992; Leach et al., 1993). In comparison to
lamotrigine, BW619C89 also inhibited veratrine- (but not K⁺-)
evoked glutamate release from rat cortical slices (Mel-
drum et al., 1992; Leach et al., 1993). In comparison to
lamotrigine, however, BW619C89 was more potent in
reducin drum et al., 1992; Leach et al., 1993). In collamotrigine, however, BW619C89 was mor reducing the release of glutamate and aspart 5 μ M) than that of acetylcholine (IC $_{50} =$ $^{6}_{6}$ GABA (IC₅₀ = 51 μ M) (Leach et a motrigine, however, BW619C89 was more potent in
ducing the release of glutamate and aspartate $(IC_{50} = \mu M)$ than that of acetylcholine $(IC_{50} = 21 \mu M)$ and
ABA $(IC_{50} = 51 \mu M)$ (Leach et al., 1993).
Although lamotrigine a

reducing the release of glutamate and aspartate $(IC_{50} = 5 \mu M)$ than that of acetylcholine $(IC_{50} = 21 \mu M)$ and GABA $(IC_{50} = 51 \mu M)$ (Leach et al., 1993).
Although lamotrigine and BW619C89 were slightly more potent in re 5 μ M) than that of acetylcholine (IC $_{50} = 21 \mu$ M) and GABA (IC₅₀ = 51 μ M) (Leach et al., 1993).
Although lamotrigine and BW619C89 were slightly more potent in reducing veratrine-induced glutamate release, this p GABA (IC₅₀ = 51 μ M) (Leach et al., 1993).
Although lamotrigine and BW619C89 were slightly
more potent in reducing veratrine-induced glutamate
release, this property by itself is not sufficient to classify
these compo Although lamotrigine and BW619C89 were sli
more potent in reducing veratrine-induced gluta
release, this property by itself is not sufficient to cla
these compounds as *glutamate release inhibitors*
fact that TTX (1 μ M more potent in reducing veratrine-induced glutamate
release, this property by itself is not sufficient to classify
these compounds as *glutamate release inhibitors*. The
fact that TTX $(1 \mu M)$ completely blocks veratrinerelease, this property by itself is not sufficient to classify
these compounds as *glutamate release inhibitors*. The
fact that TTX $(1 \mu M)$ completely blocks veratrine-in-
duced neurotransmitter release (Leach et al., 19 these compounds as *glutamate release inhibitors*. The fact that TTX $(1 \mu M)$ completely blocks veratrine-in-
duced neurotransmitter release (Leach et al., 1986), and
that lamotrigine analogues were ineffective against K fact that TTX $(1 \mu M)$ completely blocks veratrine-in-
duced neurotransmitter release (Leach et al., 1986), and
that lamotrigine analogues were ineffective against K^+ -
induced glutamate release, strongly suggested that duced neurotransmitter release (Leach et al., 1986), an
that lamotrigine analogues were ineffective against K⁻
induced glutamate release, strongly suggested that the
actions on neurotransmitter release were *secondary* that lamotrigine analogues were ineffective agains
induced glutamate release, strongly suggested that
actions on neurotransmitter release were *seconda*
down-modulation of voltage-gated Na^+ conduct
This action mechanism duced glutamate release, strongly suggested that the tions on neurotransmitter release were *secondary* wwn-modulation of voltage-gated Na^+ conductan is action mechanism is now largely substantiated.
2. Down-modulation

nally proposed as a Ca²⁺ entry blocker on the basis of (1991). BW1003C87 was also mentioned to share this functional and electrophysiological data (Wilhelm et al., property (M. Leach, personal communication to Graham 19 2. Down-modulation of Na⁺ channels. Binding experdown-modulation of voltage-gated Na⁺ conductance.
This action mechanism is now largely substantiated.
2. Down-modulation of Na⁺ channels. Binding exper-
iments carried out with rat brain synaptosomes showed
a concentr This action mechanism is now largely substantiated.
2. Down-modulation of Na^+ channels. Binding experiments carried out with rat brain synaptosomes showed
a concentration-dependent inhibition of BTX-B binding
by lamotri 2. Down-modulation of Na^+ channels. Binding experiments carried out with rat brain synaptosomes showed
a concentration-dependent inhibition of BTX-B binding
by lamotrigine ($K_D = 114 \mu M$) (Cheung et al., 1992),
confirmin iments carried out with rat brain synaptosomes showed
a concentration-dependent inhibition of BTX-B binding
by lamotrigine $(K_D = 114 \mu M)$ (Cheung et al., 1992),
confirming a preliminary report by Leach and coworkers
(1991) a concentration-dependent inhibition or $B1A-B$ binding
by lamotrigine $(K_D = 114 \mu M)$ (Cheung et al., 1992),
confirming a preliminary report by Leach and coworkers
(1991). BW1003C87 was also mentioned to share this
property confirming a preliminary report by Leach and coworkers comfriming a preminiary report by Leach and coworkers (1991). BW1003C87 was also mentioned to share this property (M. Leach, personal communication to Graham et al., 1994a). Voltage-clamp experiments in cultured rat corti property (M. Leach, personal communication to Graham
et al., 1994a). Voltage-clamp experiments in cultured rat
cortical neurons showed that 100 μ M lamotrigine, but
not 10 μ M, inhibited indiscriminately both excitato

aspet

MODULATION OF VOLTAGE
Leach, 1993). This suggested that, even at high doses,
lamotrigine did not preferentially depress excitatory, MODULATION OF VOLTA
Leach, 1993). This suggested that, even at high doses,
lamotrigine did not preferentially depress excitatory,
probably glutamate-mediated, synaptic events. In the MODULATION OF VOLTAGE-GA
Leach, 1993). This suggested that, even at high doses, ge
lamotrigine did not preferentially depress excitatory, hij
probably glutamate-mediated, synaptic events. In the in
same preparation, presum Leach, 1993). This suggested that, even at high doses, glamotrigine did not preferentially depress excitatory, left probably glutamate-mediated, synaptic events. In the issume preparation, presumptive Na^+ spikes evoked Leach, 1993). This suggested that, even at high doses
lamotrigine did not preferentially depress excitatory
probably glutamate-mediated, synaptic events. In the
same preparation, presumptive Na^+ spikes evoked at
low fre lamotrigine did not preterentially depress excitatory,
probably glutamate-mediated, synaptic events. In the
same preparation, presumptive Na^+ spikes evoked at
low frequencies were not blocked significantly by lam-
o probably glutamate-mediated, synaptic events. In the same preparation, presumptive Na^+ spikes evoked at low frequencies were not blocked significantly by lamotrigine. In contrast, 10 μ M of lamotrigine already depress low frequencies were not blocked significantly by lam-
otrigine. In contrast, 10 μ M of lamotrigine already de-
pressed burst firing produced by either glutamate or K⁺
(Lees and Leach, 1993). Sustained, repetitive fir otrigine. In contrast, 10 μ M of lamotrigine already deotrigine. In contrast, 10 μ M of lamotrigine already de-
pressed burst firing produced by either glutamate or K⁺ Me
(Lees and Leach, 1993). Sustained, repetitive firing pro-
duced by depolarizing pulses in mouse spina pressed burst firing produced by either glutamate of (Lees and Leach, 1993). Sustained, repetitive firing duced by depolarizing pulses in mouse spinal cord tured neurons were also blocked by lamotrigine is concentration- (Lees and Leach, 1993). Sustained, repetitive firing produced by depolarizing pulses in mouse spinal cord cultured neurons were also blocked by lamotrigine in a concentration- ($IC_{50} = 20 \mu M$), voltage-, and use-dependent duced by depolarizing pulses in mouse spinal cord cultured neurons were also blocked by lamotrigine in a concentration- $(IC_{50} = 20 \mu M)$, voltage-, and use-dependent manner (i.e., lamotrigine had no effect on the first ac tured neurons were also blocked by lamotrigine in a concentration- $(IC_{50} = 20 \ \mu M)$, voltage-, and use-dependent manner (i.e., lamotrigine had no effect on the first faction potential elicited by a depolarizing step but concentration- $(IC_{50} = 20 \mu M)$, voltage-, and use-dependent manner (i.e., lamotrigine had no effect on the first action potential elicited by a depolarizing step but reduced firing of subsequent action potentials) (Cheun dent manner (i.e., lamotrigine had no effect on the first action potential elicited by a depolarizing step but reduced firing of subsequent action potentials) (Cheung et al., 1992). In mouse neuroblastoma cells, Lang and action potential elicited by a depolarizing step but re-
duced firing of subsequent action potentials) (Cheung et al., 1992). In mouse neuroblastoma cells, Lang and co-
workers (1991, 1993) found that at 100 μ M, lamotr duced firing of subsequent action potentials) (Cheung et al., 1992). In mouse neuroblastoma cells, Lang and co-
workers (1991, 1993) found that at 100 μ M, lamotrigine
as well as phenytoin and carbamazepine produced a
u al., 1992). In mouse neuroblastoma cells, Lang and co-
workers (1991, 1993) found that at 100 μ M, lamotrigine
as well as phenytoin and carbamazepine produced a et al., 1992; Lekieffre and Meldrum, 1993; Gilland
as well use-dependent inhibition of $Na⁺$ channels, even at lowas well as phenytoin and carbamazepine produced a et al.,
use-dependent inhibition of Na⁺ channels, even at low-
frequency stimulation, shifting the voltage dependency to be m
of steady state inactivation toward more ne use-dependent inhibition of Na⁺ channels, even at low-
frequency stimulation, shifting the voltage dependency
of steady state inactivation toward more negative poten-
tials by 7 to 15 mV, and slowing the rate of recover frequency stimulation, shifting the voltage dependency to of steady state inactivation toward more negative potentials by 7 to 15 mV, and slowing the rate of recovery from Binactivation. Weak actions on Ca^{2+} and K^+ of steady state inactivation toward more negative potentials by 7 to 15 mV, and slowing the rate of recovery from BW inactivation. Weak actions on Ca^{2+} and K^+ conductance proported by high concentrations of lamotrig tials by 7 to 15 mV, and slowing the rationation. Weak actions on Ca^{2+} and by high concentrations of lamotrigine v
but remained inadequately characted Wang, 1991; Lees and Leach, 1993). In spite of the conflicting find activation. Weak actions on Ca^{2+} and K^+ conductar
high concentrations of lamotrigine were also report
t remained inadequately characterized (Lang a
ang, 1991; Lees and Leach, 1993).
In spite of the conflicting findi by high concentrations of lamotrigine were also reported
but remained inadequately characterized (Lang and 1
Wang, 1991; Lees and Leach, 1993). In spite of the conflicting finding of Lang and cowork-
ers (i.e., inhibition

but remained inadequately characterized (Lang a Wang, 1991; Lees and Leach, 1993).
In spite of the conflicting finding of Lang and cowor
ers (i.e., inhibition of Na⁺ conductance at *low* frequentimulation), possibly res Wang, 1991; Lees and Leach, 1993).
In spite of the conflicting finding of Lang and cowork
ers (i.e., inhibition of Na⁺ conductance at *low* frequency
stimulation), possibly resulting from different experi-
mental proced In spite of the conflicting finding of Lang and cowork-
ers (i.e., inhibition of Na⁺ conductance at *low* frequency
stimulation), possibly resulting from different experi-
mental procedures and cell types, all these stu ers (i.e., inhibition of Na⁺ conductance at *low* frequency
stimulation), possibly resulting from different experi-
mental procedures and cell types, all these studies indi-
cated that the primary action of lamotrigine stimulation), possibly resulting from different experiented procedures and cell types, all these studies in cated that the primary action of lamotrigine is undependent inhibition of Na⁺ conductance, presumal by stabiliza mental procedures and cell types, all these studies indi-
cated that the primary action of lamotrigine is use-
dependent inhibition of Na^+ conductance, presumably flu
by stabilization of the channel inactivation state. cated that the primary action of lamotrigine is use-
dependent inhibition of Na⁺ conductance, presumably flu
by stabilization of the channel inactivation state. Whole-
ticell voltage clamp recordings of recombinant rat dependent inhibition of Na^+ conductance, presumably
by stabilization of the channel inactivation state. Whole-
cell voltage clamp recordings of recombinant rat brain
type IIA Na^+ channels expressed in CHO cells have
r by stabilization of the channel inactivation state. Whole-
cell voltage clamp recordings of recombinant rat brain
type IIA Na⁺ channels expressed in CHO cells have
recently suggested that BW619C89 has similar actions
and cell voltage clamp recordings of recombinant rat brain
type IIA Na⁺ channels expressed in CHO cells have
recently suggested that BW619C89 has similar actions
and may be more potent than lamotrigine (Xie et al.,
1994a; Xi type IIA Na⁺ channels expressed in CHO cells herecently suggested that BW619C89 has similar act and may be more potent than lamotrigine (Xie et 1994a; Xie and Garthwaite, 1995). Note that the placement of BTX-B by lamotr and may be more potent than lamotrigine (Xie et al., 1994a; Xie and Garthwaite, 1995). Note that the displacement of BTX-B by lamotrigine required concentra-1994a; Xie and Garthwaite, 1995). Note that the dis-
placement of BTX-B by lamotrigine required concentra-
tions approximately 5 times higher than those for func-
tional inhibition of neurotransmitter release (see above,
s 1994a; Xie and Garthwaite, 1995). Note that the dis-
placement of BTX-B by lamotrigine required concentra-
tions approximately 5 times higher than those for func-
coinal inhibition of neurotransmitter release (see above, placement of BTX-B by lamotrigine required concentra-
tions approximately 5 times higher than those for func-
tional inhibition of neurotransmitter release (see above
section 1.) and burst firing. This apparent discrepancy tional inhibition of neurotransmitter release (see above,
section 1.) and burst firing. This apparent discrepancy is
consistent with use-dependent action because the neu-
rotoxin site 2 is highly sensitive to the conforma tional inhibition of neurotransmitter release (see above
section 1.) and burst firing. This apparent discrepancy is
consistent with use-dependent action because the neurotoxin site 2 is highly sensitive to the conformatio consistent with use-dependent action because the neu-
rotoxin site 2 is highly sensitive to the conformational
state of the Na^+ channel protein.
3. Neuroprotective actions. In comparison to its effec-
tiveness against s

rotoxin site 2 is highly sensitive to the conformational
state of the $Na⁺$ channel protein.
3. Neuroprotective actions. In comparison to its effec-
tiveness against seizures, lamotrigine has only modest
neuroprotecti state of the Na⁺ channel protein. proton 3. Neuroprotective actions. In comparison to its effec-
iveness against seizures, lamotrigine has only modest 4.
neuroprotective potency against ischemia. In the gerbil *neuronod* 3. Neuroprotective actions. In comparison to its effec-
tiveness against seizures, lamotrigine has only modest
neuroprotective potency against ischemia. In the gerbil
model of global ischemia, high doses of lamotrigine (3 tiveness against seizures, lamotrigine has only modest
neuroprotective potency against ischemia. In the gerbil *ne*
model of global ischemia, high doses of lamotrigine (30 to iss
50 mg kg⁻¹ p.o.; i.e., 6 times the antic neuroprotective potency against ischemia. In the gemodel of global ischemia, high doses of lamotrigine $(350 \text{ mg kg}^{-1} \text{ p.o.}; i.e., 6 \text{ times the anticonvulsant El given 2 h before and immediately after 5 min of car
occlusion, provided some protection against hippoc
pal CA1 damage (Beek, personal communication$ model of global ischemia, high doses of lamotrigine (30 to isch 50 mg kg⁻¹ p.o.; i.e., 6 times the anticonvulsant ED_{50}) fluid given 2 h before and immediately after 5 min of carotid erecocclusion, provided some prote given 2 h before and immediately after 5 min of carotid occlusion, provided some protection against hippocampal CA1 damage (Beek, personal communication to Leach et al., 1991). This observation was substantiated by Wiard pal CA1 damage (Beek, personal communication to Leach et al., 1991). This observation was substantiated by Wiard and coworkers (1995): 100 mg kg⁻¹, p.o., ad-ministered immediately after 5 to 15 min bilateral caocclusion, provided some protection against hippocam-
pal CA1 damage (Beek, personal communication to
Leach et al., 1991). This observation was substantiated
by Wiard and coworkers (1995): 100 mg kg⁻¹, p.o., ad-
ministe pal CA1 damage (Beek, personal communication to pleach et al., 1991). This observation was substantiated by Wiard and coworkers (1995): 100 mg kg⁻¹, p.o., ad-
ministered immediately after 5 to 15 min bilateral ca-
rotid Leach et al., 1991). This observation was substantiated row Wiard and coworkers (1995): 100 mg kg⁻¹, p.o., ad-
ministered immediately after 5 to 15 min bilateral carrotid occlusion, or in two equal doses of 30 to 50 mg

gerbils against behavioural deficits and greatly reduced $\,$ -GATED NA⁺ CHANNELS 51
gerbils against behavioural deficits and greatly reduced
hippocampal damage. With permanent MCA occlusion
in rats, when lamotrigine was administered i.v. over 10 -GATED NA⁺ CHANNELS 51
gerbils against behavioural deficits and greatly reduced
hippocampal damage. With permanent MCA occlusion
in rats, when lamotrigine was administered i.v. over 10
min immediately after ischemia ons gerbils against behavioural deficits and greatly reduced
hippocampal damage. With permanent MCA occlusion
in rats, when lamotrigine was administered i.v. over 10
min immediately after ischemia onset, the optimum
dose (20 m gerolls against benavioural dencits and greatly reduced
hippocampal damage. With permanent MCA occlusion
in rats, when lamotrigine was administered i.v. over 10
min immediately after ischemia onset, the optimum
dose (20 mg mppocampal damage. With permanent MCA occlusion
in rats, when lamotrigine was administered i.v. over 10
min immediately after ischemia onset, the optimum
dose (20 mg kg⁻¹) reduced the volume of total infarct by
31% and min immediately after ischemia onset, the optimum
dose (20 mg kg⁻¹) reduced the volume of total infarct by
31% and cortical infarct volume by 52% (Smith and
Meldrum, 1995). At 50 mg kg⁻¹, lamotrigine was no
longer cer min immediately after ischemia onset, the optimum
dose (20 mg kg⁻¹) reduced the volume of total infarct by
31% and cortical infarct volume by 52% (Smith and
Meldrum, 1995). At 50 mg kg⁻¹, lamotrigine was no
longer cer dose (20 mg kg⁻¹) reduced the volume of total infarct by 31% and cortical infarct volume by 52% (Smith and Meldrum, 1995). At 50 mg kg⁻¹, lamotrigine was no longer cerebroprotective, presumably because arterial blood 31% and cortical infarct volume by 52% (Smith a Meldrum, 1995). At 50 mg kg⁻¹, lamotrigine was longer cerebroprotective, presumably because arte blood pressure was significantly reduced. The optidose of 20 mg kg⁻¹ rem Meldrum, 1995). At 50 mg kg^{-1} , lamotrigine was nonger cerebroprotective, presumably because arteria
blood pressure was significantly reduced. The optima
dose of 20 mg kg^{-1} remained protective when adminis
tered with 1 longer cerebroprotective, presumably because arterial
blood pressure was significantly reduced. The optimal
dose of 20 mg kg^{-1} remained protective when adminis-
tered with 1-h delay after MCA occlusion but was inef-
fec dose of 20 mg kg^{-1} remained protective when administered with 1-h delay after MCA occlusion but was ineffective when this delay was extended to 2 h (Smith and Meldrum, 1995; see also Rataud et al., 1994).
The protective tered with 1-h delay after MCA occlusion but was inef-

tered with 1-h delay after MCA occlusion but was ineffective when this delay was extended to 2 h (Smith and Meldrum, 1995; see also Rataud et al., 1994).
The protective effects of BW1003C87 and BW619C89 have been studied e fective when this delay was extended to 2 h (Smith and Meldrum, 1995; see also Rataud et al., 1994).
The protective effects of BW1003C87 and BW619C89
have been studied extensively in models of global (Mel-
drum et al., 199 Meldrum, 1995; see also Rataud et al., 1994).
The protective effects of BW1003C87 and BW619C89
have been studied extensively in models of global (Mel-
drum et al., 1992; Lekieffre and Meldrum, 1993; Gilland
et al., 1994) a The protective effects of BW1003C87 and BW619C89
have been studied extensively in models of global (Mel-
drum et al., 1992; Lekieffre and Meldrum, 1993; Gilland
et al., 1994) and focal ischemia (Leach et al., 1993;
Graham have been studied extensively in models of global (Mel-
drum et al., 1992; Lekieffre and Meldrum, 1993; Gilland
et al., 1994) and focal ischemia (Leach et al., 1993;
Graham et al., 1993, 1994b), and both analogues appear
 drum et al., 1992; Lekieffre and Meldrum, 1993; Gilland
et al., 1994) and focal ischemia (Leach et al., 1993;
Graham et al., 1993, 1994b), and both analogues appear
to be more potent neuroprotectors than lamotrigine. For
 et al., 1994) and focal ischemia (Leach et al., 1993;
Graham et al., 1993, 1994b), and both analogues appear
to be more potent neuroprotectors than lamotrigine. For
example, at 20 mg kg^{-1} (i.v., 5 min after MCA occlusio Graham et al., 1993, 1994b), and both analogues appear
to be more potent neuroprotectors than lamotrigine. For
example, at 20 mg kg⁻¹ (i.v., 5 min after MCA occlusion),
BW619C89 reduced total infarct volume by 57% and
p to be more potent neuroprotectors than lamotrigine. For example, at 20 mg kg^{-1} (i.v., 5 min after MCA occlusion), BW619C89 reduced total infarct volume by 57% and protected even the basal ganglia, a region reputedly ref have been studied extensively in models of global (Mel-
drum et al., 1992; Lekieffre and Meldrum, 1993; Gilland
et al., 1994) and focal ischemia (Leach et al., 1993)
Graham et al., 1993, 1994b), and both analogues appear
 BW619C89 reduced total infarct volume by 57% and
protected even the basal ganglia, a region reputedly
refractory to protection in this model (Leach et al.,
1993). In the optic nerve preparation, BW619C89 (1 to
100 μ M) d protected even the basal ganglia, a region reputedly refractory to protection in this model (Leach et al., 1993). In the optic nerve preparation, BW619C89 (1 to 100μ M) dose-dependently prevented the axonopathy induced refractory to protection in this model (Leach et al., 1993). In the optic nerve preparation, BW619C89 (1 to 100μ M) dose-dependently prevented the axonopathy induced by oxygen and glucose deprivation, without impairing 1993). In the optic nerve preparation, BW619C89 (1 to 100μ M) dose-dependently prevented the axonopathy induced by oxygen and glucose deprivation, without impairing axonal conduction (Garthwaite et al., 1995). In additi 100 μ M) dose-dependently prevented the axonopathy in-
duced by oxygen and glucose deprivation, without im-
pairing axonal conduction (Garthwaite et al., 1995). In
addition to their *anti-ischemic* effects, BW1003C87 (1 duced by oxygen and glucose deprivation, without im-
pairing axonal conduction (Garthwaite et al., 1995). In
addition to their *anti-ischemic* effects, BW1003C87 (10
mg kg⁻¹, i.v.) and BW619C89 (30 mg kg⁻¹, i.v.) propairing axonal conduction (Garthwaite et al., 1995). In addition to their *anti-ischemic* effects, BW1003C87 (10 mg kg⁻¹, i.v.) and BW619C89 (30 mg kg⁻¹, i.v.) protected against brain injury induced in rats by lateral addition to their *anti-ischemic* effects, BW1003C87 (10 mg kg^{-1} , i.v.) and BW619C89 (30 mg kg^{-1} , i.v.) protected against brain injury induced in rats by lateral fluid percussion, reducing regional edema, astrocytic a tected against brain injury induced in rats by lateral fluid percussion, reducing regional edema, astrocytic activation, neuronal loss and neurological deficit (Sun and Faden, 1995; Okiyama et al., 1995). Lamotrigine and B tected against brain injury induced in rats by later
fluid percussion, reducing regional edema, astrocytic a
tivation, neuronal loss and neurological deficit (Sun a
Faden, 1995; Okiyama et al., 1995). Lamotrigine a
BW1003C fluid percussion, reducing regional edema, astrocytic activation, neuronal loss and neurological deficit (Sun and Faden, 1995; Okiyama et al., 1995). Lamotrigine and BW1003C87 were also found to protect against excitotoxic tivation, neuronal loss and neurological deficit (Sun and Faden, 1995; Okiyama et al., 1995). Lamotrigine and BW1003C87 were also found to protect against excitotoxic lesions induced in the rat striatum by kainate (McGeer raden, 1995; Okryama et al., 1995). Lamotrigine and
BW1003C87 were also found to protect against excito
toxic lesions induced in the rat striatum by kainata
(McGeer and Zhu, 1990; Moncada et al., 1994). Here, it
is relevan toxic lesions induced in the rat striatum by kainate (McGeer and Zhu, 1990; Moncada et al., 1994). Here, it is relevant to mention that the mechanisms of excitotoxin-induced neuronal damage also includes a $Na⁺-Cl⁻$ (McGeer and Zhu, 1990; Moncada et al., 1994). Here, is relevant to mention that the mechanisms of excitition-induced neuronal damage also includes a Na⁺-Cl component (Rothman, 1985; Dessi et al., 1994), whose deleteriou is relevant to mention that the mechanisms of excitotoxin-induced neuronal damage also includes a Na^+ -Cl⁻
component (Rothman, 1985; Dessi et al., 1994), whose
deleterious action may be reduced and/or better toler-
ate toxin-induced neuronal damage also includes a Na⁺-Cl⁻
component (Rothman, 1985; Dessi et al., 1994), whose
deleterious action may be reduced and/or better toler-
ated when further Na⁺ influx through voltage-gated
Na component (Rothman, 1985; Dessi et al., 1994), whose
deleterious action may be reduced and/or better toler-
ated when further Na⁺ influx through voltage-gated
Na⁺ channels is inhibited. Finally, as one could expect,
B deleterious action may be reduced and/or better tolerated when further Na^+ influx through voltage-gated Na^+ channels is inhibited. Finally, as one could expect, BW1003C87 reduced veratridine toxicity but failed to pro 1992). Na⁺ channels is inhibited. Finally, as one could expect,
BW1003C87 reduced veratridine toxicity but failed to
protect against depolarization with KCl (Lustig et al.,
1992).
4. Reduction of ischemia-induced glutamate effl

BW1003C87 reduced veratridine toxicity but failed to protect against depolarization with KCl (Lustig et al., 1992).
4. Reduction of ischemia-induced glutamate efflux and neuroprotection: a critical appraisal. The reducti protect against depolarization with KCl (Lustig et al.,
1992).
4. Reduction of ischemia-induced glutamate efflux and
neuroprotection: a critical appraisal. The reduction of
ischemia-induced glutamate efflux in the extracel 1992).
4. Reduction of ischemia-induced glutamate efflux a
neuroprotection: a critical appraisal. The reduction
ischemia-induced glutamate efflux in the extracellu
fluid by lamotrigine and its analogues is often cons
ered 4. Reduction of ischemia-induced glutamate efflux and
neuroprotection: a critical appraisal. The reduction of
ischemia-induced glutamate efflux in the extracellular
fluid by lamotrigine and its analogues is often consid
e neuroprotection: a critical appraisal. The reduction of
ischemia-induced glutamate efflux in the extracellular
fluid by lamotrigine and its analogues is often consid-
ered as causative of neuroprotection (Lekieffre and Mel ischemia-induced glutamate efflux in the extracellular
fluid by lamotrigine and its analogues is often considered as causative of neuroprotection (Lekieffre and Mel-
drum, 1993; Graham et al., 1993, 1994a, b), but this
pre fluid by lamotrigine and its analogues is often considered as causative of neuroprotection (Lekieffre and Meldrum, 1993; Graham et al., 1993, 1994a, b), but this prevalent interpretation conflicts with key findings (Obreno 1995): Nevalent interpretation conflicts with key findings (Ob-
hovitch and Urenjak, 1994; Obrenovitch and Richards,
95):
• The action of these drugs on high extracellular lev-
els of glutamate during ischemia is not specific; renovitch and Urenjak, 1994; Obrenovitch and Richards, 1995):
• The action of these drugs on high extracellular levels of glutamate during ischemia is not specific;

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URENJAK AND OBR
high extracellular aspartate, GABA, glycine and
taurine are reduced to a similar extent (Lekieffre pea URENJAK AND O
high extracellular aspartate, GABA, glycine and
taurine are reduced to a similar extent (Lekieffre
and Meldrum, 1993; Graham et al., 1993, 1994a). URENJAK AND
high extracellular aspartate, GABA, glycine and
taurine are reduced to a similar extent (Lekieffre
and Meldrum, 1993; Graham et al., 1993, 1994a).
Presumably, the unspecific reduction in neurohigh extracellular aspartate, GABA, glycine a
taurine are reduced to a similar extent (Lekief
and Meldrum, 1993; Graham et al., 1993, 1994
Presumably, the unspecific reduction in neuro-
transmitter efflux is due to these c high extracellular aspartate, GABA, glycine at taurine are reduced to a similar extent (Lekieff and Meldrum, 1993; Graham et al., 1993, 1994. Presumably, the unspecific reduction in neutransmitter efflux is due to these co taurine are reduced to a similar extent (Lekies
and Meldrum, 1993; Graham et al., 1993, 1994
Presumably, the unspecific reduction in neu
transmitter efflux is due to these compounds red
ing the severity of ischemia throug and Meldrum, 1993; Graham et al., 1993, 1994a)
Presumably, the unspecific reduction in neuro
transmitter efflux is due to these compounds reduc
ing the severity of ischemia through their interac
tion with Na^+ channels (Presumably, the unspecific reduction in neuro-
transmitter efflux is due to these compounds reduc-
ing the severity of ischemia through their interac-
tion with Na⁺ channels (see above, section III.).
• BW1003C87 reduce

- transmitter efflux is due to these compounds reducing the severity of ischemia through their interaction with Na^+ channels (see above, section III.).
BW1003C87 reduced hippocampal CA1 lesions (even when administered up ing the severity of ischemia through their inters
tion with Na^+ channels (see above, section III.).
BW1003C87 reduced hippocampal CA1 lesion
even when administered up to 2 h after forebra
ischemia, i.e., long after comp tion with Na⁺ channels (see above, section III.). poch
BW1003C87 reduced hippocampal CA1 lesions (M_i
even when administered up to 2 h after forebrain al.,
ischemia, i.e., long after complete return of extra-
cellular 1990b). ischemia, i.e., long after complete return of extra-

cellular glutamate to normal levels (Lekieffre and

Meldrum, 1993; Ueda et al., 1992a, b; Mitani et al.,

8W1003C87 reduced extracellular glutamate levels

in both cor
- cellular glutamate to normal levels (Lekieffre and rilu

Meldrum, 1993; Ueda et al., 1992a, b; Mitani et al., al.,

1990b).

BW1003C87 reduced extracellular glutamate levels epir

in both cortex and caudate during MCA occl Meldrum, 1993; Ueda et al., 1992a, b; Mitani et al., al., 1
1990b).
BW1003C87 reduced extracellular glutamate levels epine
in both cortex and caudate during MCA occlusion in neuro
rats, but only the cortex was protected (G 1990b).
BW1003C87 reduced extracellular glutamate levels
in both cortex and caudate during MCA occlusion in
rats, but only the cortex was protected (Graham
et al., 1993). Similarly, the reduction in microdia-
lysate glutam (Graham et a!., 1994b).

In addition, it is becoming increasingly clear that in-
creased extracellular glutamate levels may not be the not relate to cerebroprotection in the striatum tate
(Graham et al., 1994b).
In addition, it is becoming increasingly clear that in-
creased extracellular glutamate levels may not be the tion
key to excitotoxicity in ische (Graham et al., 1994b).

In addition, it is becoming increasingly clear that in-

creased extracellular glutamate levels may not be the

key to excitotoxicity in ischemia (Hossmann, 1994a, b;

Obrenovitch and Richards, 19 In addition, it is becoming increasingly clear that increased extracellular glutamate levels may not be the they to excitotoxicity in ischemia (Hossmann, 1994a, b; the Obrenovitch and Richards, 1995). Apart from increased In addition, it is becoming increasingly clear that in-
creased extracellular glutamate levels may not be the
key to excitotoxicity in ischemia (Hossmann, 1994a, b;
Obrenovitch and Richards, 1995). Apart from increased $\$ creased extracellular glutamate levels may not be the
hey to excitotoxicity in ischemia (Hossmann, 1994a, b;
Obrenovitch and Richards, 1995). Apart from increased
extracellular glutamate, the exceptional complexity of
glu key to excitotoxicity in ischemia (Hossmann, 1994a, b;
Obrenovitch and Richards, 1995). Apart from increased act
extracellular glutamate, the exceptional complexity of tra
glutamate-operated ion channels can give rise to Obrenovitch and Richards, 1995). Apart from increased extracellular glutamate, the exceptional complexity of glutamate-operated ion channels can give rise to many potentially damaging mechanisms (Obrenovitch and Richards, extracellular glutamate, the exceptional complexity of
glutamate-operated ion channels can give rise to many
potentially damaging mechanisms (Obrenovitch and 19
Richards, 1995). It is also established that most of glu-
ta glutamate-operated ion channels can give rise to many
potentially damaging mechanisms (Obrenovitch and
Richards, 1995). It is also established that most of glu-
tamate released in ischemia is of metabolic origin, which
que potentially damaging mechanisms (Obrenovitch and
Richards, 1995). It is also established that most of glu-
tamate released in ischemia is of metabolic origin, which
questions the validity of therapeutic strategies aimed at tamate released in ischemia is of metabolic origin, which tamate released in ischemia is of metabolic origin
questions the validity of therapeutic strategies a
preventing or reducing excessive release of *neur*
mitter glutamate in ischemia (Wahl et al., 1994; C
vitch and Richar restions the validity of therapeutic strategies aime
eventing or reducing excessive release of *neurotr*
itter glutamate in ischemia (Wahl et al., 1994; Obr
tch and Richards, 1995; Obrenovitch, 1995b).
This analysis strong

preventing or reducing excessive release of *neurotransmitter* glutamate in ischemia (Wahl et al., 1994; Obrenovitch and Richards, 1995; Obrenovitch, 1995b). This analysis strongly suggests that the cerebroprotective actio vitch and Richards, 1995; Obrenovitch, 1995b).
This analysis strongly suggests that the cerebrop
tective actions of lamotrigine and structural analogy
are a *direct* consequence of use-dependent down-moo
lation of voltage This analysis strongly suggests that the cerebropro-
tective actions of lamotrigine and structural analogues
are a *direct* consequence of use-dependent down-modu-
lation of voltage-gated Na⁺ channels, and this mecha-
n tective actions of lamotrigine and structural analogues
are a *direct* consequence of use-dependent down-modu-
lation of voltage-gated Na^+ channels, and this mecha-
nism of action should be recognized as such. Reduction are a *direct* consequence of use-dependent down-modulation of voltage-gated Na⁺ channels, and this mechanism of action should be recognized as such. Reduction the fischemia-induced neurotransmitter efflux by putative t lation of voltage-gated $Na⁺$ channels, and this mechanism of action should be recognized as such. Reduction of ischemia-induced neurotransmitter efflux by putative neuroprotective agents does not imply that the forme of ischemia-induced neurotransmitter efflux by putative
neuroprotective agents does not imply that the former is
causative. Testing whether glutamate neuroprotection
correlates with reduced glutamate efflux during isch-
em of ischemia-induced neurotransmitter efflux by putative
neuroprotective agents does not imply that the former is
causative. Testing whether glutamate neuroprotection
correlates with reduced glutamate efflux during isch-
em neuroprotective agents does not imply that the f
causative. Testing whether glutamate neuropr
correlates with reduced glutamate efflux duri
emia is clearly beset by the difficulty of separati
from effect (Obrenovitch and R emia is clearly beset by the difficulty of separating cause
from effect (Obrenovitch and Richards, 1995).
C. Riluzole

The benzothiazole derivative riluzole (2-amino-6-tri-Fluoromethoxybenzothiazole, PK 26124, RP 54274) was
first described as an anticonvulsant because it protected
animals against convulsions induced by maximal elec-The benzothiazole derivative riluzole (2-amino-6-tri-
fluoromethoxybenzothiazole, PK 26124, RP 54274) was GA
first described as an anticonvulsiant because it protected
animals against convulsions induced by maximal elec-
G fluoromethoxybenzothiazole, PK 26124, RP 54274) was
first described as an anticonvulsant because it protected
animals against convulsions induced by maximal elec-
troshock, inhibitors of GABA synthesis, glutamate and
kaina first described as an anticonvulsant because it protected
animals against convulsions induced by maximal elec-
troshock, inhibitors of GABA synthesis, glutamate and
kainate (Mizoule et al., 1985). Subsequently, it was re-
 animals against convulsions induced by maximal electroshock, inhibitors of GABA synthesis, glutamate and kainate (Mizoule et al., 1985). Subsequently, it was reported to also exhibit hypnotic (Stutzmann et al., 1988), anxi troshock, inhibitors of GABA synthesis
kainate (Mizoule et al., 1985). Subsequ
ported to also exhibit hypnotic (Stutzma
anxiolytic (Stutzmann et al., 1989), aneal., 1992), and anti-ischemic properties

BW1003C87 reduced hippocampal CA1 lesions (Malgouris et al., 1989) and improved the EEG (Pratt et even when administered up to 2 h after forebrain al., 1992) in gerbils subjected to transient bilateral caischemia, i.e., lo in both cortex and caudate during MCA occlusion in neurological and memory deficits in this model (Wahl et rats, but only the cortex was protected (Graham al., 1993) and, as other drugs, did not reduce the striatal et al., rats, but only the cortex was protected (Graham al., 1993) and, as other drugs, did not reduce the striatal et al., 1993). Similarly, the reduction in microdia-
lesion (Pratt et al., 1992). Despite the inhibitory action
ly *1. Neuroprotective actions of riluzole in ischemia.* Re-DBRENOVITCH
1. Neuroprotective actions of riluzole in ischemia. Re-
peated administration of riluzole, starting before or
shortly after ischemia onset and pursued for up to sev-BRENOVITCH
1. Neuroprotective actions of riluzole in ischemia. Re-
peated administration of riluzole, starting before or
shortly after ischemia onset and pursued for up to sev-
eral days, was effective in a number of exper peated administration of riluzole, starting before or shortly after ischemia onset and pursued for up to several days, was effective in a number of experimental models. For example, repeated doses of riluzole (4 to 8) 1. Neuroprotective actions of riluzole in ischemia. Repeated administration of riluzole, starting before or shortly after ischemia onset and pursued for up to several days, was effective in a number of experimental models peated administration of riluzole, starting before or shortly after ischemia onset and pursued for up to several days, was effective in a number of experimental models. For example, repeated doses of riluzole (4 to 8 mg shortly after ischemia onset and pursued for up to several days, was effective in a number of experimental models. For example, repeated doses of riluzole (4 to 8 mg kg^{-1} , i.p.) significantly reduced degeneration of hip eral days, was effective in a number of experimental
models. For example, repeated doses of riluzole (4 to 8
mg kg^{-1} , i.p.) significantly reduced degeneration of hip-
pocampal CA1 pyramidal cells, prevented memory loss
 models. For example, repeated doses of riluzole $(4 \text{ to } 8 \text{ mg kg}^{-1}, i.p.)$ significantly reduced degeneration of hip-
pocampal CA1 pyramidal cells, prevented memory loss
(Malgouris et al., 1989) and improved the EEG (Pratt e mg kg^{-1} , i.p.) significantly reduced degeneration of hip-
pocampal CA1 pyramidal cells, prevented memory loss
(Malgouris et al., 1989) and improved the EEG (Pratt et
al., 1992) in gerbils subjected to transient bilatera pocampar CAT pyramidar cens, prevented memory loss
(Malgouris et al., 1989) and improved the EEG (Pratt et
al., 1992) in gerbils subjected to transient bilateral ca-
rotid artery occlusion. In the rat MCA occlusion model,
 rotid artery occlusion. In the rat MCA occlusion model, rotid artery occlusion. In the rat MCA occlusion model,
riluzole reduced the volume of infarcted cortex (Pratt et
al., 1992; Wahl et al., 1993; Rataud et al., 1994) with an
efficacy similar to that of lamotrigine and carba riluzole reduced the volume of infarcted cortex (Pratt et al., 1992; Wahl et al., 1993; Rataud et al., 1994) with an efficacy similar to that of lamotrigine and carbamazepine (Rataud et al., 1994). However, it failed to im al., 1992; Wahl et al., 1993; Rataud et al., 1994) with an
efficacy similar to that of lamotrigine and carbamaz-
epine (Rataud et al., 1994). However, it failed to improve
neurological and memory deficits in this model (Wa efficacy similar to that of lamotrigine and carbamaz-
epine (Rataud et al., 1994). However, it failed to improve
neurological and memory deficits in this model (Wahl et
al., 1993) and, as other drugs, did not reduce the st epine (Rataud et al., 1994). However, it failed to improve
neurological and memory deficits in this model (Wahl e
al., 1993) and, as other drugs, did not reduce the striata
lesion (Pratt et al., 1992). Despite the inhibito neurological and memory deficits in this model (Wahl et al., 1993) and, as other drugs, did not reduce the striata
lesion (Pratt et al., 1992). Despite the inhibitory action
of riluzole on various responses evoked in vitro al., 1993) and, as other drugs, did not reduce the striata
lesion (Pratt et al., 1992). Despite the inhibitory action
of riluzole on various responses evoked in vitro by excitatory amino acids (see below), riluzole was fou lesion (Pratt et al., 1992). Despite the inhibitory action
of riluzole on various responses evoked in vitro by exci-
tatory amino acids (see below), riluzole was found inef-
fective against lesions produced by direct intra riluzole on various responses evoked in vitro by excitory amino acids (see below), riluzole was found inefective against lesions produced by direct intracerebral jection of quinolinic or kainic acid (Doble et al., 1993).
2

tatory amino acids (see below), riluzole was found ineffective against lesions produced by direct intracerebral
injection of quinolinic or kainic acid (Doble et al., 1993).
2. Actions on amino acid neurotransmitters. The a fective against lesions produced by direct intracerebral
injection of quinolinic or kainic acid (Doble et al., 1993).
2. Actions on amino acid neurotransmitters. The ac-
tions of riluzole against seizures and ischemia-indu injection of quinolinic or kainic acid (Doble et al., 1993).

2. Actions on amino acid neurotransmitters. The actions of riluzole against seizures and ischemia-induced

brain damage are often attributed to an *antiglutamat* 2. Actions on amino acid neurotransmitters. The actions of riluzole against seizures and ischemia-induced brain damage are often attributed to an *antiglutamate* action because of unusual effects on glutamatergic transmiss tions of riluzole against seizures and ischemia-induced
brain damage are often attributed to an *antiglutamate*
action because of unusual effects on glutamatergic
transmission (Malgouris et al., 1989; Pratt et al., 1992;
W brain damage are often attributed to an *antiglutamate*

action because of unusual effects on glutamatergic

transmission (Malgouris et al., 1989; Pratt et al., 1992;

Wahl et al., 1993; Stutzmann et al., 1993; Rataud et transmission (Malgouris et al., 1989; Pratt et al., 1992; Wahl et al., 1993; Stutzmann et al., 1993; Rataud et al., 1994). Riluzole inhibited various responses evoked by excitatory amino acids (Benavides et al., 1985; Drej transmission (Malgouris et al., 1989; Pratt et al., 1992;
Wahl et al., 1993; Stutzmann et al., 1993; Rataud et al.,
1994). Riluzole inhibited various responses evoked by
excitatory amino acids (Benavides et al., 1985; Drej Wahl et al., 1993; Stutzmann et al., 1993; Rataud et al., 1994). Riluzole inhibited various responses evoked by excitatory amino acids (Benavides et al., 1985; Drejer et al., 1986; Hubert and Doble, 1989; Debono et al., 19 1994). Riluzole inhibited various responses evoked
excitatory amino acids (Benavides et al., 1985; Drejer
al., 1986; Hubert and Doble, 1989; Debono et al., 19
Malgouris et al., 1994; Hubert et al., 1994), but with
binding excitatory amino acids (Benavides et al., 1985; Drejer et al., 1986; Hubert and Doble, 1989; Debono et al., 1993; Malgouris et al., 1994; Hubert et al., 1994), but without binding to AMPA, kainate or NMDA receptors (Benavi al., 1986; Hubert and Doble, 1989; Debono et al., 1993;
Malgouris et al., 1994; Hubert et al., 1994), but without
binding to AMPA, kainate or NMDA receptors (Benav-
ides et al., 1985; Hays et al., 1991b; Doble et al., 1993 Malgouris et al., 1994; Hubert et al., 1994), but without
binding to AMPA, kainate or NMDA receptors (Benav-
ides et al., 1985; Hays et al., 1991b; Doble et al., 1993),
nor to any of the known NMDA-receptor modulatory
site binding to AMPA, kainate of NMDA receptors (Benavides et al., 1985; Hays et al., 1991b; Doble et al., 1993), nor to any of the known NMDA-receptor modulatory sites (Hays et al., 1991b). It is interesting to note that riluz nor to any of the known NMDA-receptor modulatory
sites (Hays et al., 1991b). It is interesting to note that
riluzole could no longer block responses to excitatory
amino acids when cultured neurons were pretreated
with pert sites (Hays et al., 1991b). It is interesting to note that riluzole could no longer block responses to excitatory amino acids when cultured neurons were pretreated with pertussis toxin (pertussis toxin reduces the level of riluzole could no longer block responses to excitatory
amino acids when cultured neurons were pretreated
with pertussis toxin (pertussis toxin reduces the level of
the activated form of pertussis toxin-sensitive G pro-
tei amino acids when cultured neurons were pretreated
with pertussis toxin (pertussis toxin reduces the level of
the activated form of pertussis toxin-sensitive G pro-
teins; Gilman, 1987), which suggested an action of ri-
luz with pertussis toxin (pertussis toxin reduces the leve
the activated form of pertussis toxin-sensitive G p
teins; Gilman, 1987), which suggested an action of
luzole on G proteins-dependent processes (Hubert et
1994). In ad the activated form of pertussis toxin-sensitive G proteins; Gilman, 1987), which suggested an action of ri-
luzole on G proteins-dependent processes (Hubert et al., 1994). In addition, riluzole was shown to reduce sponta-
 teins; Gilman, 1987), which suggested an action of ri-
luzole on G proteins-dependent processes (Hubert et al.,
1994). In addition, riluzole was shown to reduce sponta-
neous glutamate release and to increase the size of i luzole on G proteins-dependent processes (Hubert et al., 1994). In addition, riluzole was shown to reduce spontaneous glutamate release and to increase the size of its K⁺-releasable pool (Chéramy et al., 1992), although 1994). In addition, riluzole was shown to reduce spontaneous glutamate release and to increase the size of its K^+ -releasable pool (Chéramy et al., 1992), although this study did not rule out the possibility that riluzo neous glutamate release and to increase the size of its K⁺-releasable pool (Chéramy et al., 1992), although this study did not rule out the possibility that riluzole may have similar effects on other neurotransmitters. F K^+ -releasable pool (Chéramy et al., 1992), although this study did not rule out the possibility that riluzole may have similar effects on other neurotransmitters. Finally, Mantz and coworkers (1994) have suggested th study did not rule out the possibility that riluzole may
have similar effects on other neurotransmitters. Finally,
Mantz and coworkers (1994) have suggested that ri-
luzole may promote GABA accumulation in the synaptic
cl have similar effects on other neurotransmitters. Finally,
Mantz and coworkers (1994) have suggested that ri-
luzole may promote GABA accumulation in the synaptic
cleft because the compound dose-dependently inhibited
GABA Mantz and coworkers (1994) have suggested that ri-
luzole may promote GABA accumulation in the synaptic
cleft because the compound dose-dependently inhibited
GABA uptake by striatal synaptosomes (IC_{50} of 43 μ M;
vers luzole may promote GABA accumulation in the synaptic
cleft because the compound dose-dependently inhibited
GABA uptake by striatal synaptosomes $(IC_{50}$ of 43 μ M;
versus 3.6 μ M for nipecotic acid, a classical blocke

GABA uptake by striatal synaptosomes (IC₅₀ of 43 μ M;
versus 3.6 μ M for nipecotic acid, a classical blocker of
GABA uptake).
3. Modulation of Na⁺ currents. Besides this unclear
action of riluzole on glutamatergic versus 3.6 μ M for nipecotic acid, a classical blocker of GABA uptake).
3. Modulation of Na^+ currents. Besides this unclear action of riluzole on glutamatergic transmission, a strong body of evidence has indicated tha GABA uptake).

3. Modulation of Na^+ currents. Besides this unclear

action of riluzole on glutamatergic transmission, a

strong body of evidence has indicated that this drug acts

on Na^+ channels at *therapeutic* conc 3. Modulation of Na^+ currents. Besides this unclear
action of riluzole on glutamatergic transmission, a
strong body of evidence has indicated that this drug acts
on Na^+ channels at therapeutic concentrations. Riluzole

to inhibit veratridine-induced acetylcholine release from rat striatal slices (Hays et al., 1991b). In a Na⁺ flux assay using rat cortical slices, riluzole was the most expressing rat brain type IIA Na⁺ channel with an IC₅₀ of potent in a series of 32 substituted 2-benzothiazo- 2.7 μ M (TTX, 0.014 μ M; flunarizine, 0.42 μ M MODULATION OF VOLTAGE
to inhibit veratridine-induced acetylcholine release from
rat striatal slices (Hays et al., 1991b). In a Na⁺ flux
assay using rat cortical slices, riluzole was the most
potent in a series of 32 sub to inhibit veratridine-induced acetylcholine release
rat striatal slices (Hays et al., 1991b). In a Na⁺
assay using rat cortical slices, riluzole was the
potent in a series of 32 substituted 2-benzoth
lamines inhibiting to inhibit veratriaine-induced acetylcholine release from (nM
rat striatal slices (Hays et al., 1991b). In a Na⁺ flux bloc
assay using rat cortical slices, riluzole was the most exp
potent in a series of 32 substituted rat striatal slices (Hays et al., 1991b). In a Na Ilux
assay using rat cortical slices, riluzole was the most
potent in a series of 32 substituted 2-benzothiazo-
lamines inhibiting $[^{14}C]$ guanidine uptake with an IC₅₀ assay using rat cortical slices, riluzole was the most
potent in a series of 32 substituted 2-benzothiazo-
lamines inhibiting $[$ ¹⁴Clguanidine uptake with an IC₅₀
of 4.1 μ M (versus 23 μ M for phenytoin) (Hays et potent in a series of 32 substituted 2-benzothiazo-
lamines inhibiting $[^{14}C]$ guanidine uptake with an IC₅₀
of 4.1 μ M (versus 23 μ M for phenytoin) (Hays et al.,
1994). It also inhibited veratridine-induced (but lamines inhibiting $[^{44}C]$ guanidine uptake with an IC₅₀
of 4.1 μ M (versus 23 μ M for phenytoin) (Hays et al.,
1994). It also inhibited veratridine-induced (but not K⁺-
induced) increase of intracellular Ca²⁺ of 4.1 μ M (versus 23 μ M for phenytoin) (Hays et al.
1994). It also inhibited veratridine-induced (but not K⁺
induced) increase of intracellular Ca²⁺ in cultured ra
cerebellar granule neurons with an IC₅₀ of 0. 1994). It also inhibited veratridine-induced (but not K^+
induced) increase of intracellular Ca^{2+} in cultured ra
cerebellar granule neurons with an IC_{50} of 0.31 μ M (Hu
bert et al., 1994), and veratridine neurot induced) increase of intracellular Ca^{2+} in cultured rat al., cerebellar granule neurons with an IC_{50} of 0.31 μ M (Hubre et al., 1994), and veratridine neurotoxicity as measured by LDH release from immature rat hip bert et al., 1994), and veratridine neurotoxicity as measured by LDH release from immature rat hippocampal slices (Malgouris et al., 1994), although a single high (100μ) concentration of riluzole was used in the latter bert et al., 1994), and veratridine neurotoxicity as measured by LDH release from immature rat hippocampal slices (Malgouris et al., 1994), although a single high (100 μ M) concentration of riluzole was used in the latt sured by LDH release from immature rat hippocampal
slices (Malgouris et al., 1994), although a single high
(100 μ M) concentration of riluzole was used in the latter
study. Voltage-clamp studies clearly confirmed the in slices (Malgouris et al., 1994), although a single high u

(100 μ M) concentration of riluzole was used in the latter P

study. Voltage-clamp studies clearly confirmed the in-

teraction of riluzole with voltage-gated N (100 μ M) concentration of riluzole was used in the latter study. Voltage-clamp studies clearly confirmed the interaction of riluzole with voltage-gated Na⁺ channels: (*a*) in isolated myelinated nerve fibres of the f study. Voltage-clamp studies clearly confirmed the interaction of riluzole with voltage-gated Na⁺ channels:
(*a*) in isolated myelinated nerve fibres of the frog, riluzole was a highly specific blocker of inactivated Na teraction of riluzole with voltage-gated Na^+ channels:

(*a*) in isolated myelinated nerve fibres of the frog, ri-

luzole was a highly specific blocker of inactivated Na^+

channels, 300 times more effective on these (*a*) in isolated myelinated nerve fibres of the frog, ri-
luzole was a highly specific blocker of inactivated Na⁺ spec
channels, 300 times more effective on these channels bind
than on K⁺ or resting Na⁺ channels (B luzole was a highly specific blocker of inactivated Na⁺
channels, 300 times more effective on these channels
than on K^+ or resting Na⁺ channels (Benoit and Es-
cande, 1991); (*b*) in cultured neurons, riluzole (1 t channels, 300 times more effective on these channels
than on K^+ or resting Na^+ channels (Benoit and Es-
cande, 1991); (b) in cultured neurons, riluzole (1 to 30
 μ M) produced a 5 to 30 mV negative shift of the Na⁺ cande, 1991); (b) in cultured neurons, riluzole (1 to 30 rotoxin receptor site 2 (see section II.B.3.; fig. 3).
 μ M) produced a 5 to 30 mV negative shift of the Na⁺ As it could be expected from the structural analogi cande, 1991); (b) in cultured neurons, riluzole (1 to μ M) produced a 5 to 30 mV negative shift of the leurrent steady state inactivation curve, with moeffects on Na⁺ channel activation and recovery finactivation—inhi μ M) produced a 5 to 30 mV negative shift of the Na⁺ A
current steady state inactivation curve, with modest bets
effects on Na⁺ channel activation and recovery from et a
inactivation—inhibition of Na⁺ currents was current steady state inactivation curve, with modest be effects on Na⁺ channel activation and recovery from etimactivation—inhibition of Na⁺ currents was frequency- volupeendent only at activation frequencies exceedin effects on Na⁺ channel activation and recovery from inactivation—inhibition of Na⁺ currents was frequency dependent only at activation frequencies exceeding $\overline{\text{SL}}$ (Randle et al., 1994); and (c) with these effects inactivation—inhibition of Na⁺ currents was frequen
dependent only at activation frequencies exceeding
Hz (Randle et al., 1994); and (c) with these effects w
confirmed with rat brain IIA Na⁺ channel α -subu
expresse pendent only at activation frequencies exce
 z (Randle et al., 1994); and (c) with these effer

infirmed with rat brain IIA Na^+ channel c

pressed in *Xenopus* oocytes (Hebert et al., 19

RP 66055 (3-{2-[4-(4-fluor

Hz (Randle et al., 1994); and (c) with these effects were nonfirmed with rat brain IIA Na⁺ channel α -subunit undexpressed in *Xenopus* occytes (Hebert et al., 1994). RP 66055 (3-{2-[4-(4-fluorophenyl}-1-piperazinyl}confirmed with rat brain IIA Na⁺ channel α -subunit expressed in *Xenopus* occytes (Hebert et al., 1994).

RP 66055 (3-{2-[4-(4-fluorophenyl)-1-piperazinyl]-

ethyl}-2-imino-6-trifluoromethoxy-benzothiazoline), a ri-
 expressed in *Xenopus* oocytes (Hebert et al., 1994).

RP 66055 (3-{2-[4-(4-fluorophenyl)-1-piperazin

ethyl}-2-imino-6-trifluoromethoxy-benzothiazoline), a

luzole derivative, is also a potent neuroprotective ag

in roden RP 66055 (3-{2-[4-(4-fluorophenyl)-1-piperazinyl]-
ethyl}-2-imino-6-trifluoromethoxy-benzothiazoline), a ri-
luzole derivative, is also a potent neuroprotective agent
in rodent models of hypoxia and ischemia with anticonethyl}-2-imino-6-trifluoromethoxy-benzothiazoline), a ri-
luzole derivative, is also a potent neuroprotective agent
in rodent models of hypoxia and ischemia with anticon-
vulsant properties (Stutzmann et al., 1993; Rataud luzole derivative, is also a potent neuroprotective agent universion in rodent models of hypoxia and ischemia with anticon-
vulsant properties (Stutzmann et al., 1993; Rataud et university al., 1994). So far, this compoun in rodent models of hypoxia and ischemia with anticon-
vulsant properties (Stutzmann et al., 1993; Rataud et
al., 1994). So far, this compound is described as a Na⁺
channel blocker, because binding assays only revealed
 vulsant properties (Stutzmann et al., 1994). So far, this compound is channel blocker, because binding an affinity for voltage-gated Na⁺ (et al., 1993; Rataud et al., 1994). channel blocker, because binding assays only revealed
an affinity for voltage-gated Na⁺ channels (Stutzmann
et al., 1993; Rataud et al., 1994).
D. Miscellaneous Neuroprotective Agents Acting on
Na⁺ Channels

Na Channels
 Na Channels
 Na ⁺ *Channels*
 1. PD85,639. PD85,639 (*N*-[3-(2,6-dimethy
 Na ⁺ *Channels*
 1. PD85,639. PD85,639 (*N*-[3-(2,6-dimethy

dinyl)propyl]-*a*-phenylbenzeneacetamide) belon $D.$ Miscellaneous Neuroprotective Agents Acting on the the Na^+ Channels dep
 dA^+ Channels dep
 $1.$ PD85,639. PD85,639 (N-[3-(2,6-dimethyl-1-piperi- nor
dinyl)propyl]-a-phenylbenzeneacetamide) belongs to a fect
novel $1.$ Miscellaneous Neuroprotective Agents Acting on
 Na^+ Channels
 $1.$ PD85,639. PD85,639 (N-[3-(2,6-dimethyl-1-piperi-

noridinyl)propyl]- α -phenylbenzeneacetamide) belongs to a fect

novel series of phenylacetamide both Channels

1. PD85,639. PD85,639 (N-[3-(2,6-dimethyl-1-piperi-

dinyl)propyl]- α -phenylbenzeneacetamide) belongs to a

novel series of phenylacetamides structurally related to

both local anesthetics and phenytoin (1. $PD85,639$. $PD85,639$ $(N-[3-(2,6-dimethyl-1-pipe-diny])propyl]-\alpha-phenylbenzeneacetamide) belongs to novel series of phenylacetamides structurally related both local anesthetics and phenytoin (fig. 10) (Thomsen al., 1993; Routos et al., 1994). Preliminary in vitro biological assays have suggested that this compound may ha$ dinyl)propyl]-*a*-phenylbenzeneacetamide) belongs to a fe-
novel series of phenylacetamides structurally related to
both local anesthetics and phenytoin (fig. 10) (Thomsen et
al., 1993; Roufos et al., 1994). Preliminary in novel series of phenylacetamides structurally related
both local anesthetics and phenytoin (fig. 10) (Thomsen
al., 1993; Roufos et al., 1994). Preliminary in vitro biol
ical assays have suggested that this compound may ha
 both local anesthetics and phenytoin (fig. 10) (Thomsen et PD
al., 1993; Roufos et al., 1994). Preliminary in vitro biolog-
ical assays have suggested that this compound may have 14-
some neuroprotective potential, as it al., 1993; Roufos et al., 1994). Preliminary in vitro biological assays have suggested that this compound may have
some neuroprotective potential, as it inhibited hypoxia-
induced LDH release from cultured rat brain neuro ical assays have suggested that this compound may have
some neuroprotective potential, as it inhibited hypoxia-
induced LDH release from cultured rat brain neurons with
an IC_{50} of 89 μ M (versus 7.3 μ M for flunari induced LDH release from cultured rat brain neurons with
an IC₅₀ of 89 μ M (versus 7.3 μ M for flunarizine) (Roufos et (
al., 1994). PD85,639 interacts strongly with voltage-gated
Na⁺ channels, especially with the an IC₅₀ of 89 μ M (versus 7.3 μ M for flunarizine) (Roufo
al., 1994). PD85,639 interacts strongly with voltage-ga
Na⁺ channels, especially with the neurotoxin binding
2: (a) it displaced BTX-B binding to rat neoco al., 1994). PD85,639 interacts strongly with voltage-gated Yancheva, 1976). It is already marketed as a nootropic Na⁺ channels, especially with the neurotoxin binding site peripheral vasodilator for treatment of senile Na⁺ channels, especially with the neurotoxin binding sit 2: (*a*) it displaced BTX-B binding to rat neocortical membranes with a K_i of 0.26 μ M (versus 0.053 μ M for flunarizine, and 0.077 μ M for lidoflazine in 2: (*a*) it displaced BTX-B binding to rat neocortical mem-
branes with a K_i of 0.26 μ M (versus 0.053 μ M for flunariz-
ine, and 0.077 μ M for lidoflazine in the same test) (Roufos the
et al., 1994); (*b*) PD85,6 branes with a K_i of 0.26 μ M (versus 0.053 μ M for flunarizine, and 0.077 μ M for lidoflazine in the same test) (Roufos the et al., 1994); (*b*) PD85,639 inhibited veratridine-stimulated poot influx of $[14C]$ guan

MODULATION OF VOLTAGE-GATED NA⁺ CHANNELS 53
tylcholine release from (nM) and low (μ M) affinity (Hays et al., 1991a); (c) it blocked veratridine-stimulated Na⁺ influx into CHO cells -GATED NA⁺ CHANNELS 53

(nM) and low (μ M) affinity (Hays et al., 1991a); (c) it

blocked veratridine-stimulated Na⁺ influx into CHO cells

expressing rat brain type IIA Na⁺ channel with an IC₅₀ of -GATED NA⁺ CHANNELS 53

(nM) and low (μM) affinity (Hays et al., 1991a); (c) it

blocked veratridine-stimulated Na⁺ influx into CHO cells

expressing rat brain type IIA Na⁺ channel with an IC₅₀ of

2.7 μ M (TT (nM) and low (μ) affinity (Hays et al., 1991a); (c) it blocked veratridine-stimulated Na⁺ influx into CHO cells expressing rat brain type IIA Na⁺ channel with an IC₅₀ of 2.7 μ M (TTX, 0.014 μ M; flunarizine, 0 (nM) and low (μ M) amnity (Hays et al., 1991a); (c) it blocked veratridine-stimulated Na⁺ influx into CHO cells expressing rat brain type IIA Na⁺ channel with an IC₅₀ of 2.7 μ M (TTX, 0.014 μ M; flunarizine, 0 blocked veratridine-stimulated Na¹ initiux into CHO cells
expressing rat brain type IIA Na⁺ channel with an IC₅₀ of
2.7 μ M (TTX, 0.014 μ M; flunarizine, 0.42 μ M; lidoflazine,
2.4 μ M) (Roufos et al., 1994) expressing rat brain type IIA Na⁺ channel with an IC₅₀ of 2.7 μ M (TTX, 0.014 μ M; flunarizine, 0.42 μ M; lidoflazine, 2.4 μ M) (Roufos et al., 1994); and (d) PD85,639 inhibited veratridine induced LDH release $2.7 \mu M$ (TT)
 $2.4 \mu M$) (Ro
veratridine
cultures wit
al., 1994).
Thompse 4 μ M) (Roufos et al., 1994); and (*d*) PD85,639 inhibited
ratridine induced LDH release in rat brain neuronal cell
ltures with an IC₅₀ of 5 μ M (flunarizine 2 μ M) (Roufos et
, 1994).
Thompsen and coworkers (1993

veratridine induced LDH release in rat brain neuronal c
cultures with an IC_{50} of 5 μ M (flunarizine 2 μ M) (Roufos
al., 1994).
Thompsen and coworkers (1993) have demonstrat
that PD85,639 binds directly and specific cultures with an IC_{50} of 5 μ M (flunarizine 2 μ M) (Roufos
al., 1994).
Thompsen and coworkers (1993) have demonstrat
that PD85,639 binds directly and specifically to reco
stituted Na⁺ channels and type IIA Na⁺ al., 1994).

Thompsen and coworkers (1993) have demonstrated

that PD85,639 binds directly and specifically to reconstituted Na⁺ channels and type IIA Na⁺ channels α -sub-

units expressed in transfected CHO cells. Thompsen and coworkers (1993) have demonstrated
that PD85,639 binds directly and specifically to recon-
stituted Na⁺ channels and type IIA Na⁺ channels α -sub-
units expressed in transfected CHO cells. Binding of
PD that PD85,639 binds directly and specifically to reconstituted Na⁺ channels and type IIA Na⁺ channels α -sub-
units expressed in transfected CHO cells. Binding of
PD85,639 to these preparations was inhibited by seve stituted Na⁻ channels and type IIA Na⁻ channels α -sub
units expressed in transfected CHO cells. Binding o
PD85,639 to these preparations was inhibited by severa
tertiary amine local anesthetics at concentrations in units expressed in transfected CHO cells. Binding of PD85,639 to these preparations was inhibited by several tertiary amine local anesthetics at concentrations in the same range as those that inhibits $Na⁺$ channels. $PD85,639$ to these preparations was inhibited by several
tertiary amine local anesthetics at concentrations in the
same range as those that inhibits $Na⁺$ channels. Fur-
thermore, veratridine and BTX inhibited complet tertiary amine local anesthetics at concentrations in the same range as those that inhibits Na^+ channels. Furthermore, veratridine and BTX inhibited completely specific PD85,639 binding. Thus, PD85,639 appears to bind s same range as those that inhibits Na^+ channels. Fur
thermore, veratridine and BTX inhibited completely
specific PD85,639 binding. Thus, PD85,639 appears to
bind specifically, and with high affinity, to the loca
anesthet thermore, veratridine and BTX inhibited comple
specific PD85,639 binding. Thus, PD85,639 appear
bind specifically, and with high affinity, to the l
anesthetic receptor that is allosterically linked to r
rotoxin receptor si ecific PD85,639 binding. Thus, PD85,639 appears to
nd specifically, and with high affinity, to the local
nesthetic receptor that is allosterically linked to neu-
toxin receptor site 2 (see section II.B.3.; fig. 3).
As it c

bind specifically, and with high affinity, to the local anesthetic receptor that is allosterically linked to neurotoxin receptor site 2 (see section II.B.3.; fig. 3). As it could be expected from the structural analogies b anesthetic receptor that is allosterically linked to neu-
rotoxin receptor site 2 (see section II.B.3.; fig. 3).
As it could be expected from the structural analogies
between PD85,639, lidocaine and tetracaine (Ragsdale
et rotoxin receptor site 2 (see section II.B.3.; fig. 3).
As it could be expected from the structural analogies
between PD85,639, lidocaine and tetracaine (Ragsdale
et al., 1993), as well as from the data outlined above,
vol As it could be expected from the structural analogies
between PD85,639, lidocaine and tetracaine (Ragsdale
et al., 1993), as well as from the data outlined above,
voltage-clamp recordings from CHO cells expressing
brain t et al., 1993), as well as from the data outlined above, voltage-clamp recordings from CHO cells expressing brain type IIA Na^+ channel and dissociated rat brain neurons have confirmed that PD85,639 strongly atten-uated et al., 1993), as well as from the data outlined above, voltage-clamp recordings from CHO cells expressing brain type IIA Na⁺ channel and dissociated rat brain neurons have confirmed that PD85,639 strongly attenuated Na brain type IIA $Na⁺$ channel and dissociated rat brain brain type IIA Na⁺ channel and dissociated rat brain neurons have confirmed that PD85,639 strongly attenuated Na⁺ currents when applied either in the external bath or in the internal pipette solution, with properties neurons have confirmed that PD85,639 strongly attenuated Na⁺ currents when applied either in the external bath or in the internal pipette solution, with properties close to those of local anesthetics (Ragsdale et al., 1 uated Na⁺ currents when applied either in the extern
bath or in the internal pipette solution, with propert
close to those of local anesthetics (Ragsdale et al., 199
The most striking effect of PD85,639 was its pronounc close to those of local anesthetics (Ragsdale et al., 1993).
The most striking effect of PD85,639 was its pronounced
use-dependent block of Na⁺ currents, which was detect-
able at much lower frequencies than those requir The most striking effect of PD85,639 was its pronounced
use-dependent block of $Na⁺$ currents, which was detect-
able at much lower frequencies than those required for
use-dependent block with tertiary amine local ane The most striking effect of PD85,639 was its pronounced
use-dependent block of Na⁺ currents, which was detect-
able at much lower frequencies than those required for
use-dependent block with tertiary amine local anesthet use-dependent block of Na^+ currents, which was detectable at much lower frequencies than those required for use-dependent block with tertiary amine local anesthetics, and far below those that are physiologically relevan able at much lower frequencies than those required for
use-dependent block with tertiary amine local anesthet-
ics, and far below those that are physiologically relevant
in cardiac cells or brain neurons. In addition, toni use-dependent block with tertiary amine local anesthet-
ics, and far below those that are physiologically relevant
in cardiac cells or brain neurons. In addition, tonic block
with PD85,639 was not strongly dependent on hol ics, and far below those that are physiologically relevant
in cardiac cells or brain neurons. In addition, tonic block
with PD85,639 was not strongly dependent on holding
potential. In theory, these properties are not favo in cardiac cells or brain neurons. In addition, tonic block
with PD85,639 was not strongly dependent on holding
potential. In theory, these properties are not favourable
to antiarrhythmic and anticonvulsant therapy for whi with PD85,639 was not strongly dependent on holding
potential. In theory, these properties are not favourable
to antiarrhythmic and anticonvulsant therapy for which
the strategy is to induce a more potent block at the more potential. In theory, these properties are not favourable
to antiarrhythmic and anticonvulsant therapy for which
the strategy is to induce a more potent block at the more
depolarized membrane potentials, and to filter out to antiarrhythmic and anticonvulsant therapy for which the strategy is to induce a more potent block at the modepolarized membrane potentials, and to filter out a normal high frequency depolarizations with nominal efect on depolarized membrane potentials, and to filter out abnormal high frequency depolarizations with nominal effect on normal activity. Nevertheless, it would be interesting to explore further the neuroprotective action of PD8 PD85,639 in stroke models. *2. Vinpocetion area activity.* Nevertheless, it would the component activity. Nevertheless, it would the the comport of the neuroprotective a $2.85,639$ in stroke models.
2. *Vinpocetine*. Vinpocetine $[(3\alpha, 16\alpha)$ -eburn

fect on normal activity. Nevertheless, it would be interesting to explore further the neuroprotective action of PD85,639 in stroke models.
2. Vinpocetine. Vinpocetine $[(3\alpha, 16\alpha)$ -eburnamenine-
14-carboxylic acid ethyl e esting to explore further the neuroprotective action (PD85,639 in stroke models.
2. Vinpocetine. Vinpocetine $[(3\alpha, 16\alpha)$ -eburnamenine
14-carboxylic acid ethyl ester], a synthetic ethyl ester a
povincamine, is beneficial PD85,639 in stroke models.

2. Vinpocetine. Vinpocetine $[(3\alpha, 16\alpha)$ -eburnamenine-

14-carboxylic acid ethyl ester], a synthetic ethyl ester of

apovincamine, is beneficial in a series of cerebrovascular

diseases that a 2. Vinpocetine. Vinpocetine $[(3\alpha, 16\alpha)$ -eburnamenine-
14-carboxylic acid ethyl ester], a synthetic ethyl ester of
apovincamine, is beneficial in a series of cerebrovascular
diseases that are accompanied by hypoxia and i 14-carboxylic acid ethyl ester], a synthetic ethyl ester of apovincamine, is beneficial in a series of cerebrovascular diseases that are accompanied by hypoxia and ischemia (Werner et al., 1986; Otomo et al., 1985; Hadjiev apovincamine, is beneficial in a series of cerebrovascular
diseases that are accompanied by hypoxia and ischemia
(Werner et al., 1986; Otomo et al., 1985; Hadjiev and
Yancheva, 1976). It is already marketed as a nootropic
 diseases that are accompanied by hypoxia and ischemia
(Werner et al., 1986; Otomo et al., 1985; Hadjiev and
Yancheva, 1976). It is already marketed as a nootropic
peripheral vasodilator for treatment of senile dementia
in (Werner et al., 1986; Otomo et al., 1985; Hadjiev and Yancheva, 1976). It is already marketed as a nootropic
peripheral vasodilator for treatment of senile dementia
in a number of countries, including Japan and Portugal.
I Yancheva, 1976). It is already marketed as a nootropic peripheral vasodilator for treatment of senile dementia
in a number of countries, including Japan and Portugal.
It is awaiting Food and Drug Administration approval in
the United States. In experimental animal models, vinin a number of countries, including Japan and Portugal.
It is awaiting Food and Drug Administration approval in
the United States. In experimental animal models, vin-
pocetine increased the tolerance to anoxia (King, 1987; It is awaiting Food and Drug Administration approval in
the United States. In experimental animal models, vin-
pocetine increased the tolerance to anoxia (King, 1987;
Biró et al., 1976), reduced delayed neuronal death sub-

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URENJAK AND OBRI
Rischke and Krieglstein, 1990; Araki et al., 1990) and ma
reduced the infarct size in stroke models (Rischke and nM URENJAK AND OBRI
Rischke and Krieglstein, 1990; Araki et al., 1990) and ma
reduced the infarct size in stroke models (Rischke and nM
Krieglstein, 1990; Karkoutly et al., 1990). For example, stre URENJAK ANI
Rischke and Krieglstein, 1990; Araki et al., 1990) and
reduced the infarct size in stroke models (Rischke and
Krieglstein, 1990; Karkoutly et al., 1990). For example,
vinpocetine increased dose-dependently the Rischke and Krieglstein, 1990; Araki et al., 1990) and m
reduced the infarct size in stroke models (Rischke and nu
Krieglstein, 1990; Karkoutly et al., 1990). For example, st
vinpocetine increased dose-dependently the numb reduced the infarct size in stroke models (Rischke and Krieglstein, 1990; Karkoutly et al., 1990). For example, vinpocetine increased dose-dependently the number of mice surviving 80 s of exposure to pure nitrogen gas (i.e reduced the infarct size in stroke models (Rischke and nM and 63 nM, respectively (Lakics et al., 1995). This Krieglstein, 1990; Karkoutly et al., 1990). For example, strong protective effect of vinpocetine against veratr Krieglstein, 1990; Karkoutly et al., 1990). For example, vinpocetine increased dose-dependently the number of mice surviving 80 s of exposure to pure nitrogen gas (i.e., a lethal insult in control animals) with 100% survi vinpocetine increased dose-dependently the number of dine-in
mice surviving 80 s of exposure to pure nitrogen gas (i.e., nitude
a lethal insult in control animals) with 100% survival at despite
50 mg kg⁻¹ (i.p.) (King, mice surviving 80 s of exposure to pure nitrogen gas (i.e., ni
a lethal insult in control animals) with 100% survival at de
50 mg kg⁻¹ (i.p.) (King, 1987). In global ischemia, advertinistration of vinpocetine (10 mg kg a lethal insult in control animals) with 100% survival at 50 mg kg^{-1} (i.p.) (King, 1987). In global ischemia, administration of vinpocetine (10 mg kg^{-1} , i.p.) 15 min before or immediately after the insult reduced dela 50 mg kg⁻¹ (i.p.) (King, 1987). In global ischemia, advo
ministration of vinpocetine (10 mg kg⁻¹, i.p.) 15 min ná
before or immediately after the insult reduced delayed eti
neuronal death in the rat CA1 subfield (Saue ministration of vinpocetine $(10 \text{ mg kg}^{-1}, i.p.)$ 15 min
before or immediately after the insult reduced delayee
neuronal death in the rat CA1 subfield (Sauer et al.
1988; Rischke and Krieglstein, 1990). Doubling this dose
bec before or immediately after the insult reduced delay
neuronal death in the rat CA1 subfield (Sauer et a
1988; Rischke and Krieglstein, 1990). Doubling this do
became ineffective however, presumably because ar
rial blood pr neuronal death in the rat CA1 subfield (Sauer et al., rat 1
1988; Rischke and Krieglstein, 1990). Doubling this dose
became ineffective however, presumably because arte-
rial blood pressure was lowered (Rischke and Kriegl 1988; Rischke and Krieglstein, 1990). Doubling this dos
became ineffective however, presumably because arte
rial blood pressure was lowered (Rischke and Krieg
stein, 1990). With MCA occlusion in mice and rats, 1
mg kg⁻¹ became ineffective however, presumably because arte-
rial blood pressure was lowered (Rischke and Kriegl-
stein, 1990). With MCA occlusion in mice and rats, 10 evidence suggests that selective down-modulation of
mg kg⁻¹ rial blood pressure was lowered (Rischke and Krieg
stein, 1990). With MCA occlusion in mice and rats, 1
mg kg^{-1} (i.p.) reduced significantly the volume of cort
cal infarct (Rischke and Krieglstein, 1990; Karkoutly
al., action, 1990). With MCA occlusion in mice and rats, 10 evid mg kg⁻¹ (i.p.) reduced significantly the volume of cortical infarct (Rischke and Krieglstein, 1990; Karkoutly et strad., 1990). Finally, vinpocetine showed ant mg kg⁻¹ (i.p.) reduced significantly the volume of cortical infarct (Rischke and Krieglstein, 1990); Karkoutly et al., 1990). Finally, vinpocetine showed anticonvulsant activity in mice, preventing maximal electroshock cal infarct (Rischke and Krieglstein, 1990; Karkoutly et al., 1990). Finally, vinpocetine showed anticonvulsant activity in mice, preventing maximal electroshock (IC₅₀ = 18.3 mg kg⁻¹, i.p.); metrazol induced convulsio , 1990). Finally, vinpocetine showed anticonvulsant
tivity in mice, preventing maximal electroshock $(IC_{50}$
18.3 mg kg⁻¹, i.p.); metrazol induced convulsions
 $C_{50} = 62.1$ mg kg⁻¹, i.p.) (Pálosi and Szporny, 1976).
I

activity in mice, preventing maximal electroshock (IC₅₀ ing with
= 18.3 mg kg⁻¹, i.p.); metrazol induced convulsions only lifar
(IC₅₀ = 62.1 mg kg⁻¹, i.p.) (Pálosi and Szporny, 1976). this way
In vitro, vinpocetin ($IC_{50} = 62.1$ mg kg^{-1} , i.p.) (Pálosi and Szporny, 1976).
In vitro, vinpocetine potentiated the neuroprotective
effect of adenosine against chemical hypoxia (1 mM
NaCN) in primary neuronal cultures from chick embryo
cer In vitro, vinpocetine potentiated the neuroprotective
effect of adenosine against chemical hypoxia (1 mM
NaCN) in primary neuronal cultures from chick embryo
cerebral hemispheres, suggesting that the neuroprotec-
tive effe effect of adenosine against chemical hypoxia (1 mM nisi
NaCN) in primary neuronal cultures from chick embryo BW
cerebral hemispheres, suggesting that the neuroprotection
tive effect of vinpocetine may be mediated by adeno NaCN) in primary neuronal cultures from chick embryo BW
cerebral hemispheres, suggesting that the neuroprotec-
tive effect of vinpocetine may be mediated by adenosine mor
(Krieglstein and Rischke, 1991). In contrast, up t cerebral hemispheres, suggesting that the neuroprotec-
tive effect of vinpocetine may be mediated by adenosine mor
(Krieglstein and Rischke, 1991). In contrast, up to 100 mitri
 μ mol l^{-1} of this drug did not prevent μ mol l^{-1} of this drug did not prevent protein and ATP loss in neuroblastoma cells during cytotoxic hypoxia (1 mM NaCN for 30 min) superimposed on glucose deprivation (Peruche and Krieglstein, 1991)

The cerebroprotective mechanism of vinpocintine re-
mains unresolved. It may result partly from cerebrovas-
cular effects in some models (e.g., improvement of postloss in neuroblastoma cells during cytotoxic hypoxia (1 mM NaCN for 30 min) superimposed on glucose deprivation (Peruche and Krieglstein, 1991)
The cerebroprotective mechanism of vinpocintine remains unresolved. It may res The cerebroprotective mechanism of vinpocintine remains unresolved. It may result partly from cerebrovas-
cular effects in some models (e.g., improvement of post-
ischemic local cerebral blood flow) (Béncsáth et al., 1
197 mains unresolved. It may result partly from cerebrovas-
cular effects in some models (e.g., improvement of post-
ischemic local cerebral blood flow) (Béncsáth et al.,
1976), but a direct action on brain parenchyma seems
al cular effects in some models (e.g., improvement of post-
ischemic local cerebral blood flow) (Béncsáth et al., m
1976), but a direct action on brain parenchyma seems be
also plausible (Rischke and Krieglstein, 1990). Atte ischemic local cerebral blood flow) (Béncsáth et a 1976), but a direct action on brain parenchyma seen also plausible (Rischke and Krieglstein, 1990). Attempto identify the molecular target(s) of vinpocetine has shown a w 1976), but a direct action on brain parenchyma seems
also plausible (Rischke and Krieglstein, 1990). Attempts
to identify the molecular target(s) of vinpocetine have
shown a wide range of effects, including: (a) Ca^{2+} a also plausible (Rischke and Krieglstein, 1990). Attempts
to identify the molecular target(s) of vinpocetine have
shown a wide range of effects, including: (a) Ca^{2+} antag-
onistic activity at 100 μ M but not 10 μ M to identify the molecular target(s) of vinpocetine has
hown a wide range of effects, including: $(a) Ca^{2+}$ anti-
onistic activity at 100 μ M but not 10 μ M (Kaneko et a
1990); (b) interactions with glutamate receptors shown a wide range of effects, including: $(a) Ca^{2+}$ antagonistic activity at 100 μ M but not 10 μ M (Kaneko et al., to 1990); (*b*) interactions with glutamate receptors (e.g., at sapproximately 100 μ M, vinpocetine onistic activity at 100 μ M but not 10 μ M (Kaneko et al., 1990); (*b*) interactions with glutamate receptors (e.g., at approximately 100 μ M, vinpocetine displaced [³H]MK-801 from guinea pig forebrain membranes) 1990); (b) interactions with glutamate receptors (e.g., at approximately 100 μ M, vinpocetine displaced [³H]MK-801 from guinea pig forebrain membranes) (Kaneko et al., 1991; Kiss et al., 1991); and (c) protection agai approximately 100
801 from guinea pi
al., 1991; Kiss et a
excitotoxins (Miyar
Kiss et al., 1991).
However, all the al., 1991; Kiss et al., 1991); and (c) protection against excitotoxins (Miyamoto et al., 1989; Erdö et al., 1990; Kiss et al., 1991).
However, all these actions only occurred at high con-centrations and remained weak or in

extent that none of them has been accepted as the primark and an independent matrix of the neuron-

matrix of the neuron-origin of the neuron-origin of the neuroprotective effects of the drug. A

mary origin of the neuroprotective effects of the drug. A

mary origin of the n However, all these actions only occurred at high concentrations and remained weak or incomplete to such an clear extent that none of them has been accepted as the primary origin of the neuroprotective effects of the drug. centrations and remained weak or incomplete to such an channel extent that none of them has been accepted as the primary origin of the neuroprotective effects of the drug. A Finereent study by Lakics and coworkers (1995) mary origin of the neuroprotective effects of the drug. A recent study by Lakics and coworkers (1995) strongly suggested that voltage-gated Na^+ channels may be the predominant target of vinpocetine at therapeutic con-ce mary origin of the neuroprotective effects of the drug. μ recent study by Lakics and coworkers (1995) strongl
suggested that voltage-gated Na⁺ channels may be the
predominant target of vinpocetine at therapeutic conc recent study by Lakics and coworkers (1995) strongly fun
suggested that voltage-gated Na⁺ channels may be the a p
predominant target of vinpocetine at therapeutic con-
centrations. Vinpocetine inhibited veratridine-me suggested that voltage-gated $Na⁺$ channels may be the predominant target of vinpocetine at therapeutic concentrations. Vinpocetine inhibited veratridine-mediated cell death in primary cultures of rat cerebral cortex predominant target of vinpocetine at therapeutic concentrations. Vinpocetine inhibited veratridine-mediated ticell death in primary cultures of rat cerebral cortex in a ticoncentration-dependent and complete manner; in co centrations. Vinpocetine inhibited veratridine-mediated
cell death in primary cultures of rat cerebral cortex in a
concentration-dependent and complete manner; in con-
trast to the high doses required for the actions outl

BRENOVITCH
maximal and half-maximal toxicity) toxicity were 490
nM and 63 nM, respectively (Lakics et al., 1995). This BRENOVITCH
maximal and half-maximal toxicity) toxicity were 490
nM and 63 nM, respectively (Lakics et al., 1995). This
strong protective effect of vinpocetine against veratri-BRENOVITCH
maximal and half-maximal toxicity) toxicity were 4
nM and 63 nM, respectively (Lakics et al., 1995). T
strong protective effect of vinpocetine against verat
dine-induced cell death exceeded by two orders of m maximal and half-maximal toxicity) toxicity were 49 nM and 63 nM, respectively (Lakics et al., 1995). The strong protective effect of vinpocetine against veratre dine-induced cell death exceeded by two orders of mag-
initu maximal and half-maximal toxicity) toxicity were 490
nM and 63 nM, respectively (Lakics et al., 1995). This
strong protective effect of vinpocetine against veratri-
dine-induced cell death exceeded by two orders of mag-
ni nM and 63 nM, respectively (Lakics et al., 1995). This
strong protective effect of vinpocetine against veratri-
dine-induced cell death exceeded by two orders of mag-
nitude the potency of phenytoin (Lakics et al., 1995), strong protective effect of vinpocetine against veratridine-induced cell death exceeded by two orders of magnitude the potency of phenytoin (Lakics et al., 1995), despite the equipotency of these two drugs in blocking volt dine-induced cell death exceeded by two orders of magnitude the potency of phenytoin (Lakics et al., 1995), despite the equipotency of these two drugs in blocking voltage-gated Na⁺ channels in rat cortical neurons (Moln mitude the potency of phenytoin (Lakics et al., 1995),
despite the equipotency of these two drugs in blocking
voltage-gated Na⁺ channels in rat cortical neurons (Mol-
nár and Erdö, 1995). In an earlier study, 10 μ M v despite the equipotency of these two drugs in blocking
voltage-gated Na⁺ channels in rat cortical neurons (Mol-
nár and Erdö, 1995). In an earlier study, 10 μ M vinpoc-
etine inhibited veratridine-induced purine relea Na Chainles in rat cortical 1
1995). In an earlier study, 1
d veratridine-induced purine
mic synaptosomes (Fredholm
VI. Concluding Remarks

ine inhibited veratridine-induced purine release from

t hypothalamic synaptosomes (Fredholm et al., 1983).
 VI. Concluding Remarks

As it is apparent from this analysis, a wide array of

idence suggests that selective d **VI. Concluding Remarks**
As it is apparent from this analysis, a wide array of
evidence suggests that selective down-modulation of **VI. Concluding Remarks**
As it is apparent from this analysis, a wide array of
evidence suggests that selective down-modulation of
voltage-gated Na^+ channels is a rational and effective
strategy against ischemic brain d VI. CONCILIATES
As it is apparent from this analysis, a wide array of
evidence suggests that selective down-modulation of
voltage-gated Na⁺ channels is a rational and effective
strategy against ischemic brain damage. It evidence suggests that selective down-modulation
voltage-gated Na^+ channels is a rational and effecti
strategy against ischemic brain damage. It is therefore
surprising that among all the neuroprotectors interaction
ing voltage-gated Na^+ channels is a rational and effective strategy against ischemic brain damage. It is therefore surprising that among all the neuroprotectors interacting with Na^+ channels at therapeutic concent surprising that among all the neuroprotectors interacting with $Na⁺$ channels at therapeutic concentration only lifarizine is promoted unambiguously as acting this way (see section V.A.2.). Despite their strong inteac only lifarizine is promoted unambiguously as acting in
this way (see section V.A.2.). Despite their strong inter
actions with Na⁺ channels, the favored action mecha
nism advanced for the prominent compounds
BW1003C87, BW only lifarizine is promoted unambiguously as acting
this way (see section V.A.2.). Despite their strong int
actions with Na⁺ channels, the favored action mech
nism advanced for the prominent compoun
BW1003C87, BW619C89 this way (see section V.A.2.). Despite their strong inter-
actions with Na⁺ channels, the favored action mecha-
nism advanced for the prominent compounds
BW1003C87, BW619C89 and riluzole remains inhibi-
tion of glutamate actions with Na⁺ channels, the favored action mechanism advanced for the prominent compounds BW1003C87, BW619C89 and riluzole remains inhibition of glutamate release (see section V.B. and C.) and, more recently, seconda nism advanced for the prominent compound
BW1003C87, BW619C89 and riluzole remains inhib
tion of glutamate release (see section V.B. and C.) and
more recently, secondary inhibition of the synthesis
initric oxide (Lizasoain BW1003C87, BW619C89 and riluzole remains inhibition of glutamate release (see section V.B. and C.) and, more recently, secondary inhibition of the synthesis of nitric oxide (Lizasoain et al., 1995). Why does Na⁺ channel tion of glutamate release (see section V.B. and C.) and,
more recently, secondary inhibition of the synthesis of
nitric oxide (Lizasoain et al., 1995). Why does $Na⁺ channel$
mechanism against ischemic damage? One possibilit more recently, secondary inhibition of the synthesis onitric oxide (Lizasoain et al., 1995). Why does Na^+ chan-
nel modulation fail to be recognized as a valid action
mechanism against ischemic damage? One possibilit
ma nitric oxide (Lizasoain et al., 1995). Why does Na⁺ channel modulation fail to be recognized as a valid action
mechanism against ischemic damage? One possibility
may be the concern of potential side effects of Na⁺ chan voltage-gated Na⁺ channels is a rational and effective strategy against is
chemic brain damage. It is therefore surprising that among all the neuro
protectors interacting with Na⁺ channels at the
rapeutic concentratio mechanism against ischemic damage? One possibilit
may be the concern of potential side effects of Na⁺ chan
nel blockers, examplified by the cardiotoxicity of lide
caine. However, it is now clear that neuroprotection ca
b may be the concern of potential side effects of Na⁺ channel blockers, examplified by the cardiotoxicity of lido-
caine. However, it is now clear that neuroprotection can
be achieved by *selective* down-modulation of Na⁺ caine. However, it is now clear that neuroprotection can
be achieved by *selective* down-modulation of Na^+ chan-
nels, without conspicuous undesirable effects on the nor-
mal function of brain and heart. Another possibi be achieved by *selective* down-modulation of $Na⁺$ channels, without conspicuous undesirable effects on the normal function of brain and heart. Another possibility may be the investigators' tendency to favour action nels, without conspicuous undesirable effects on the normal function of brain and heart. Another possibility may
be the investigators' tendency to favour action mecha-
nisms related to novel and exciting hypotheses. Over t mal function of brain and heart. Another possibility n
be the investigators' tendency to favour action mec
nisms related to novel and exciting hypotheses. Over
last 20 years, several classes of drugs have successiv
been t nisms related to novel and exciting hypotheses. Over the last 20 years, several classes of drugs have successively been the focus of attention, including cerebral vasodilators, voltage-sensitive Ca^{2+} -blockers, and free last 20 years, several classes of drugs have successive
been the focus of attention, including cerebral vasodi
tors, voltage-sensitive Ca^{2+} -blockers, and free-radia
scavengers. At present, a large number of compoun
und been the focus of attention, including cerebral vasodilators, voltage-sensitive Ca²⁺-blockers, and free-radical scavengers. At present, a large number of compounds under development are either glutamate receptor antagoni tors, voltage-sensitive Ca^{2+} -blockers, and free-radical scavengers. At present, a large number of compounds under development are either glutamate receptor antagonists or so-called glutamate release inhibitors (Muir an scavengers. At present, a large number of compounds
under development are either glutamate receptor antag-
onists or so-called glutamate release inhibitors (Muir
and Lees, 1995), and there is little doubt that the next
tre and *anti-apoptosis* drugs. ists or so-called glutamate release inhibitors (Muir
d Lees, 1995), and there is little doubt that the next
end will be selective nitric oxide-synthase inhibitors
d *anti-apoptosis* drugs.
Selective down-modulation of vol

excitotoxins (Miyamoto et al., 1989; Erdö et al., 1990; trend will be selective nitric oxide-synthase inhibitors
Kiss et al., 1991).
Mowever, all these actions only occurred at high con-
centrations and remained weak or i and Lees, 1995), and there is little doubt that the next
trend will be selective nitric oxide-synthase inhibitors
and *anti-apoptosis* drugs.
Selective down-modulation of voltage-gated Na⁺
channels should be recognized, channels should be recognized, not only as a valid apand *anti-apoptosis* drugs.

Selective down-modulation of voltage-gated Na⁺

channels should be recognized, not only as a valid ap-

proach to cerebroprotection, but also as a timely one.

Firstly, because our understan Selective down-modulation of voltage-gated $Na⁺$
channels should be recognized, not only as a valid ap-
proach to cerebroprotection, but also as a timely one.
Firstly, because our understanding of the structure and
fu channels should be recognized, not only as a valid a
proach to cerebroprotection, but also as a timely of
Firstly, because our understanding of the structure a
function of voltage-gated Na⁺ channels has improved
a point proach to cerebroprotection, but also as a timely on Firstly, because our understanding of the structure an function of voltage-gated Na^+ channels has improved to a point where it should allow development of site-d rect Firstly, because our understanding of the structure and
function of voltage-gated Na⁺ channels has improved t
a point where it should allow development of site-di
rected Na⁺ channel blockers. Secondly, because selec
t function of voltage-gated Na⁺ channels has improved to
a point where it should allow development of site-di-
rected Na⁺ channel blockers. Secondly, because selec-
tive modulation of voltage-gated Na⁺ channels, in ad a point where it should allow development of site-di-
rected Na^+ channel blockers. Secondly, because selec-
tive modulation of voltage-gated Na^+ channels, in addi-
tion to ischemia, may be relevant to a wide range of
 rected $Na⁺$ channel blockers. Secondly, because selective modulation of voltage-gated $Na⁺$ channels, in addition to ischemia, may be relevant to a wide range of neurological disorders. For example, riluzole was tive modulation of voltage-gated Na⁺ channels, in addition to ischemia, may be relevant to a wide range of neurological disorders. For example, riluzole was recently reported to slow the progression of amyotrophic latera

PHARMACOLOGICAL REVIEWS

REVIEW

ARMACOLOGIO

MODULATION OF VOLTAGE
which there is no adequate treatment (Bensimon et al.,
1994) (See however Rowland, 1994; and the related cor-MODULATION OF VOLTA

which there is no adequate treatment (Bensimon et al.,

1994) (See however Rowland, 1994; and the related cor-

respondence in N. Engl. J. Med. 331: 272–274, 1994) MODULATION OF VOLTAGE-
which there is no adequate treatment (Bensimon et al.,
1994) (See however Rowland, 1994; and the related cor-
respondence in N. Engl. J. Med. 331: 272–274, 1994)
(Note also that in the study of Eisen which there is no adequate treatment (Bensimon et al., 1994) (See however Rowland, 1994; and the related correspondence in N. Engl. J. Med. 331: 272–274, 1994) (Note also that in the study of Eisen and coworkers, 1993, 100 which there is no adequate treatment (Bensimon et al., $\frac{10}{10}$
1994) (See however Rowland, 1994; and the related cor-
respondence in N. Engl. J. Med. 331: 272–274, 1994)
1993, 100 mg oral daily lamotrigine did not alt 1994) (See however Kowland, 1994; and the related cor-
respondence in N. Engl. J. Med. 331: 272–274, 1994)
(Note also that in the study of Eisen and coworkers,
1993, 100 mg oral daily lamotrigine did not alter the
course o respondence in N. Engl. J. Med. 331: 272–274, 199
(Note also that in the study of Eisen and coworker
1993, 100 mg oral daily lamotrigine did not alter th
course of amyotrophic lateral sclerosis). Here, agai
riluzole was pr (Note also that in the study of Eisen and coworkers, 1993, 100 mg oral daily lamotrigine did not alter the course of amyotrophic lateral sclerosis). Here, again, riluzole was presented as an *antiglutamate agent* (Bensimon 1993, 100 mg oral daily lamotrigine did not alter course of amyotrophic lateral sclerosis). Here, age riluzole was presented as an *antiglutamate agent* (B simon et al., 1994; Couratier et al., 1994), but the rec discover course of amyotrophic lateral sclerosis). Here, again,
riluzole was presented as an *antiglutamate agent* (Ben-
simon et al., 1994; Couratier et al., 1994), but the recent
discovery of axonal ion channel dysfunction in am riluzole was presented as an *antiglutamate agent* (Bensimon et al., 1994; Couratier et al., 1994), but the recent discovery of axonal ion channel dysfunction in amyotrophic lateral sclerosis patients (Bostock et al., 1995 simon et al., 1994; Couratier et al., 1994), but the recent
discovery of axonal ion channel dysfunction in amyotro-
phic lateral sclerosis patients (Bostock et al., 1995)
strongly suggests that the beneficial effects of ri discovery of axonal ion channel dysfunction in amyotro-
phic lateral sclerosis patients (Bostock et al., 1995)
strongly suggests that the beneficial effects of riluzole
against this disorder may rather result from its dire phic lateral sclerosis patients (Bostock et al., 1995)
strongly suggests that the beneficial effects of riluzole
against this disorder may rather result from its direct
action on voltage-gated Na⁺ channels. Another rele strongly suggests that the beneficial effects of riluzole against this disorder may rather result from its direct and action on voltage-gated Na⁺ channels. Another relevant $\frac{1}{6}$ finding is that of Takigawa and cowo against this disorder may rather result from its direct
action on voltage-gated Na⁺ channels. Another relevant
finding is that of Takigawa and coworkers (1995), who
showed that antibodies against GM₁ gangliosides, whic action on voltage-gated Na⁺ channels. Another relevant
finding is that of Takigawa and coworkers (1995), who
showed that antibodies against GM_1 gangliosides, which
are found in patients with lower motor neuron disease finding is that of Takigawa and coworkers (1995), who showed that antibodies against GM_1 gangliosides, which are found in patients with lower motor neuron disease, motor neuropathy and Guillain-Barré syndrome, can alter showed that antibodies against GM_1 gangliosides, which
are found in patients with lower motor neuron disease
motor neuropathy and Guillain-Barré syndrome, can al-
ter voltage-gated Na^+ currents, suggesting that Na^+
 are found in patients with lower motor neuron disease,
motor neuropathy and Guillain-Barré syndrome, can al-
ter voltage-gated Na⁺ currents, suggesting that Na⁺
channels may be targets of immune attack in some neu-
ro motor neuropathy and Guillain-Barré syndrome, can alter voltage-gated Na⁺ currents, suggesting that Na⁺ channels may be targets of immune attack in some neurological disorders (Waxman, 1995). In the study of Takigawa a ter voltage-gated Na^+ currents, suggesting that Na^+
channels may be targets of immune attack in some neu-
rological disorders (Waxman, 1995). In the study of
Takigawa and coworkers, Na^+ currents were sup-
pressed by channels may be targets of immune attack in some neu-
rological disorders (Waxman, 1995). In the study of
Takigawa and coworkers, Na^+ currents were sup-
pressed by antibodies against GM_1 gangliosides, but
immune effec Takigawa and coworkers, NA^+ currents were sup-

pressed by antibodies against GM_1 gangliosides, but

immune effects on Na^+ channels could also render neu-

rons hyperexcitable by interfering with deactivation or

in immune effects on Na⁺ channels could also render neu-In activation (Waxman, 1995).
Acknowledgements. The authors' work on cerebral ischemia and
Acknowledgements. The authors' work on cerebral ischemia and
Archroprotection was supported by The Wellcome Trust, The Medical

inactivation (Waxman, 1995).
Acknowledgements. The authors' work on cerebral ischemia and
neuroprotection was supported by The Wellcome Trust, The Medical
Council, The Brain Research Trust, The Mihara Trust (Tokyo). Acknowledgements. The authors' work on cerebral ischemia and neuroprotection was supported by The Wellcome Trust, The Medical Council, The Brain Research Trust, The Mihara Trust (Tokyo), Pfizer Central Research (UK), and J neuroprotection was supported by The Wellcome Trust, The Medical Council, The Brain Research Trust, The Mihara Trust (Tokyo), Pfizer Central Research (UK), and Johnson & Johnson (UK). We are grateful to Dr. D. A. Richards **Council, The Brain Research Trust, The Mihara Trust (Tokyo),**
Pfizer Central Research (UK), and Johnson & Johnson (UK). We are
grateful to Dr. D. A. Richards (Department of Pharmacology, School A
of Pharmacy, London) for

- Wish to thank the referees for their constructive comments.

Wish to thank the referees for their constructive comments.

ABDEL-LATIF, A. A., BRODY, J., AND RAMAHI, H.: Studies on sodium-potassium

adenosine triphosphate o
- REFERENCES
ABDEL-LATIF, A. A., BRODY, J., AND RAMAHI, H.: Studies on sodium-potassium
adenosine triphosphate of the nerve endings and appearance of electrical
activity in developing rat brain. J. Neurochem. 14: 1133–1141,
- ABDEL-LATIF, A. A., BRODY, J., AND RAMAHI, H.: Studies on sodium-potassium
adenosine triphosphate of the nerve endings and appearance of electrical
activity in developing rat brain. J. Neurochem. 14: 1133-1141, 1967.
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