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 Endogenous and Exogenous Opioids in the Cont G2.00/0
American Society for Pharmacology and Experimental Therapeutics
Gastrointestinal Motility and Secretion
WOLFGANG KROMER Gastrointestinal Motility and Secretion
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WOLFGANG KROMER

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PHARMACOLOGICAL REVIEWS

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PHARMACOLOGICAL REVIEW

I. Introduction
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 I focus on possible pl THIS REVIEW will focus on possible physiological func-
THIS REVIEW will focus on possible physiological func-
nns of endogenous opioids and, as far as data are 1. **Introduction**
THIS REVIEW will focus on possible physiological funculations of endogenous opioids and, as far as data are point
available, on potential pathophysiological disturbances I. Introduction
THIS REVIEW will focus on possible physiological func-
tions of endogenous opioids and, as far as data are
available, on potential pathophysiological disturbances
thereof in the control of gastrointestinal THIS REVIEW will focus on possible physiological functions of endogenous opioids and, as far as data are por available, on potential pathophysiological disturbances opider thereof in the control of gastrointestinal motilit THIS REVIEW will focus on possible physiological func-
tions of endogenous opioids and, as far as data are
available, on potential pathophysiological disturbances
thereof in the control of gastrointestinal motility and
sec tions of endogenous opioids and, as far as data are pro
available, on potential pathophysiological disturbances op
thereof in the control of gastrointestinal motility and free
secretion. The actions of exogenous opioids w available, on potential pathophysiological disturbances
thereof in the control of gastrointestinal motility and
secretion. The actions of exogenous opioids will also be
devaluated to further characterize gastrointestinal o experiments to in vivo studies. Since the guinear propulated to further characterize gastrointestinal opioid
functions. The discussion will proceed from in vitro
experiments to in vivo studies. Since the guinea pig
intesti secretion. The actions of exogenous opioids will also
evaluated to further characterize gastrointestinal opio
functions. The discussion will proceed from in vi
experiments to in vivo studies. Since the guinea propulation b evaluated to further characterize gastrointestinal opioid
functions. The discussion will proceed from in vitro
experiments to in vivo studies. Since the guinea pig
intestine allows a clear-cut distinction between propul-
 functions. The discussion will proceed from in vitro $\frac{\text{smo}}{\text{inter}}$
experiments to in vivo studies. Since the guinea pig inte
intestine allows a clear-cut distinction between propul-
sive and nonpropulsive motility in vi experiments to in vivo studies. Since the guinea pig
intestine allows a clear-cut distinction between propul-
sive and nonpropulsive motility in vitro as well as easy
quantification, in vitro studies were performed mostly intestine allows a clear-cut distinction between propul-
sive and nonpropulsive motility in vitro as well as easy
quantification, in vitro studies were performed mostly in
this species which, for this reason, will be revi sive and nonpropulsive motility in vitro as well as easy
quantification, in vitro studies were performed mostly in
this species which, for this reason, will be reviewed first.
This is not to mean, however, that only the gu quantification, in vitro studies were performed mostly in
this species which, for this reason, will be reviewed first.
This is not to mean, however, that only the guinea pig
provides the "truth." The procedure will be the This is not to mean, however, that only the guinea pig
provides the "truth." The procedure will be the same
with respect to gastrointestinal secretion. In an attempt
to stimulate future work, preliminary or controversial
r This is not to mean, however, that only the guinea pig
provides the "truth." The procedure will be the same
with respect to gastrointestinal secretion. In an attempt
to stimulate future work, preliminary or controversia
re creatic secretions will not be considered.
The term "opioid" used in this review refers to all Writh respect to gastromestinal secretion. In an attempt
to stimulate future work, preliminary or controversial
reports will also be discussed. Salivary, biliary, and pan-
creatic secretions will not be considered.
The ter

reports will also be discussed. Salivary, biliary, and pancreatic secretions will not be considered.
The term "opioid" used in this review refers to all compounds which bind to and activate opioid receptors.
Where desirabl The term "opioid" used in this review
compounds which bind to and activate opin
Where desirable, specific compounds are
otherwise no distinction will be made betwee
alkaloids and endogenous opioid peptides.
The term "endog compounds which bind to and activate opioid receptors.

Where desirable, specific compounds are named, but

otherwise no distinction will be made between exogenous

alkaloids and endogenous opioid peptides.

The term "endo

otherwise no distinction will be made between exogenous
alkaloids and endogenous opioid peptides.
The term "endogenous opioid" refers to opioid peptides
released into the circulation or within the respective
tissue as oppo alkaloids and endogenous opioid pept
The term "endogenous opioid" refer
released into the circulation or with
tissue as opposed to opioids, either pe
which were administered exogenously
The different accentuation of the The term enaogenous option reters to option peptrices
released into the circulation or within the respective
tissue as opposed to opioids, either peptides or alkaloids,
which were administered exogenously.
The different ac

II. Distribution of Opioid Peptides and Opioid Receptors in Gut and Stomach Receptors in Gut and Stomach Receptors in Gut and Stomach Stomach Recent accentuation of the various charge of the strain in the literation in the literation of Opioid Peptides and Op Receptors in Gut and Stomach
Peptides and Degrading Enzymes

A. Distribution of Opioid Peptides and Receptors in Gut and Stomacleronical Peptides and Degrading Enzymes
A. Opioid Peptides and Degrading Enzymes
A. Neuronal location of opioid peptides in

Pigger 1. Distribution of Optota 1 epitaes and Optota
Receptors in Gut and Stomach
A. Opioid Peptides and Degrading Enzymes
*1. Neuronal location of opioid peptides in the guinea
pig, rat, mouse, cat, and pig.* Since A. Opioid Peptides and Degrading Enzymes
1. Neuronal location of opioid peptides in the guinear
pig, rat, mouse, cat, and pig. Since the first identification
of endogenous opioids by Hughes et al. (183), it is evident
that A. Optoid Peptides and Degrading Enzymes
1. Neuronal location of opioid peptides in the guinea
pig, rat, mouse, cat, and pig. Since the first identification
of endogenous opioids by Hughes et al. (183), it is evident
that 1. *Ivearonal accution of optota peptules in the gain*
pig, rat, mouse, cat, and pig. Since the first identificati
of endogenous opioids by Hughes et al. (183), it is evide
that these endogenous peptides with opiate-like of endogenous opioids by Hughes et al. (183), it is evident
that these endogenous peptides with opiate-like actions
belong to three families derived from different precur-
sors: proopiomelanocortin; proenkephalin; and prod that these endogenous peptides with opiate-like actions
belong to three families derived from different precur-
sors: proopiomelanocortin; proenkephalin; and prody-
norphin (for review see refs. 182, 191, 208, and 160).
En belong to three ramines derived from different precur-
sors: proopiomelanocortin; proenkephalin; and prody-
norphin (for review see refs. 182, 191, 208, and 160).
Endogenous opioids, present in high concentration stamong o morphin (for review see refs. 182, 191, 208, and 160).

Endogenous opioids, present in high concentration s

among other neuropeptides in the intestinal wall, were

detected by immunohistochemical and radioimmunolog-

i among other neuropeptides in the intestinal wall, were
detected by immunohistochemical and radioimmunolog-
ical techniques in neuronal cell bodies and nerve fibers
of the myenteric and submucosal plexus from all parts
of t detected by immunohistochemical and radioimmunolog-
ical techniques in neuronal cell bodies and nerve fibers
of the myenteric and submucosal plexus from all parts
isoprof
the gastrointestinal tract of various species (256 ical techniques in neuronal cell bodies and nerve fibers
of the myenteric and submucosal plexus from all parts
of the gastrointestinal tract of various species (256, 196,
382, 43, 117). Cell processes were found which proj of the myenteric and submucosal plexus from all parts
of the gastrointestinal tract of various species (256, 196,
382, 43, 117). Cell processes were found which project to
the circular muscle. Orally directed processes may of the gastro
382, 43, 117)
the circular
resent dendi
cell bodies.

Sosa et al. (420) demonstrated biosynthesis of enkephalins within the guinea pig myenteric plexus by incor-Sosa et al. (420) demonstrated biosynthesis of enkepiedlines within the guinea pig myenteric plexus by incorration of labeled amino acids in vitro. In addition Sosa et al. (420) demonstrated biosynthesis of enkephalins within the guinea pig myenteric plexus by incorporation of labeled amino acids in vitro. In addition, opioid immunoreactivity was observed in tissue cultures Sosa et al. (420) demonstrated biosynthesis of enkephalins within the guinea pig myenteric plexus by incorporation of labeled amino acids in vitro. In addition, opioid immunoreactivity was observed in tissue cultures from Sosa et al. (420) demonstrated biosynthesis of enkephalins within the guinea pig myenteric plexus by incorporation of labeled amino acids in vitro. In addition, opioid immunoreactivity was observed in tissue cultures from alins within the guinea pig myenteric plexus by in
poration of labeled amino acids in vitro. In addit
opioid immunoreactivity was observed in tissue cult
from myenteric plexus or in the guinea pig cecum a
denervation (196) poration of labeled amino acids in vitro. In addition,
opioid immunoreactivity was observed in tissue cultures
from myenteric plexus or in the guinea pig cecum after
denervation (196). Nerve fibers containing immunore-
act opioid immunoreactivity was observed in tissue cultures
from myenteric plexus or in the guinea pig cecum after
denervation (196). Nerve fibers containing immunore-
active [Met⁵]-enkephalin were also found in the circular from myenteric plexus or in the guinea pig cecum after
denervation (196). Nerve fibers containing immunore-
active [Met⁵]-enkephalin were also found in the circular
smooth muscle layer and in the myenteric plexus of rat
 denervation (196). Nerve fibers containing immunore-
active [Met⁵]-enkephalin were also found in the circular
smooth muscle layer and in the myenteric plexus of rat
intestinal tissue transplants (383) and in fetal mouse
 active [Met⁻]-enkephalin were also found in the circular
smooth muscle layer and in the myenteric plexus of rat
intestinal tissue transplants (383) and in fetal mouse
intestinal tissue cultures, both devoid of extrinsic intestinal tissue transplants (383) and in fetal mouse
intestinal tissue cultures, both devoid of extrinsic neu-
ronal connections (381). These data prove that there are
enkephalin neurons intrinsic to the intestinal wall. intestinal tissue cultures, both devoid of extrinsic neu-
ronal connections (381). These data prove that there are
enkephalin neurons intrinsic to the intestinal wall. This
is further supported by findings showing that th ronal connections (381). These data prove that there are enkephalin neurons intrinsic to the intestinal wall. This is further supported by findings showing that the tissue concentration of $[Met^5]$ -enkephalin immunoreactiv enkephalin neurons
is further supported
concentration of [M
the rat gastrointest
denervation (106).
Aside from the enl further supported by findings showing that the tissue
ncentration of $[Met⁵]$ -enkephalin immunoreactivity in
e rat gastrointestinal tract was not altered by vagal
nervation (106).
Aside from the enkephalins, beta-endor

concentration of $[Met^5]$ -enkephalin immunoreactivity in
the rat gastrointestinal tract was not altered by vagal
denervation (106).
Aside from the enkephalins, beta-endorphin was found
in all parts of the rat gastrointesti the rat gastrointestinal tract was not altered by vaget
denervation (106).
Aside from the enkephalins, beta-endorphin was four
in all parts of the rat gastrointestinal tract (315, 35
and is colocalized with ACTH^{*} in peri denervation (106).

Aside from the enkephalins, beta-endorphin was found

in all parts of the rat gastrointestinal tract (315, 354)

and is colocalized with ACTH^{*} in perikarya of the myen-

teric plexus (478). Both pepti Aside from the enkephalins, beta-endorphin was found
in all parts of the rat gastrointestinal tract (315, 354)
and is colocalized with ACTH* in perikarya of the myen-
teric plexus (478). Both peptides are derived from a
c in all parts of the rat gastrointestinal tract $(315, 354)$
and is colocalized with ACTH* in perikarya of the myen-
teric plexus (478) . Both peptides are derived from a
common precursor (208) . Most unexpectedly, Wolte and is colocalized with ACTH^{*} in perikarya of the myenteric plexus (478). Both peptides are derived from a common precursor (208). Most unexpectedly, Wolter (479) recently demonstrated that [Met⁵]-enkephalin coexists w teric plexus (478). Both peptides are derived from a
common precursor (208). Most unexpectedly, Wolter
(479) recently demonstrated that [Met⁵]-enkephalin co-
exists with alpha-MSH in myenteric neurons of the rat
duodenum (479) recently demonstrated that $[Met⁵]$ -enkephalin coexists with alpha-MSH in myenteric neurons of the rat duodenum, which may point to a common ancestor gene of the two precursors, i.e., preproenkephalin A and pro piomelanocortin. EXISTS WITH alpha-NISTI III in myenteric neurons of the rat duodenum, which may point to a common ancestor gene
of the two precursors, i.e., preproenkephalin A and proo-
piomelanocortin.
Kromer et al. (230) demonstrated bo

of the two precursors, i.e., preproenkephalin A and proopiomelanocortin.
Kromer et al. (230) demonstrated both the occurrence
of immunoreactive dynorphin in, and its release from,
the isolated guinea pig small intestine. I piomelanocortin.
Kromer et al. (230) demonstrated both the occurrence
of immunoreactive dynorphin in, and its release from,
the isolated guinea pig small intestine. Immunoreactive
dynorphin was found in nerve fibers and ne of immunoreactive dynorphin in, and its release from, the isolated guinea pig small intestine. Immunoreactive dynorphin was found in nerve fibers and neurons of the

**1. Distribution of Opioid Peptides and Opioid

1. Receptors in Gut and Stomach**
 1. Opioid Peptides and Degrading Enzymes
 1. Neuronal location of opioid peptides in the guinea
 1. Neuronal location of opioid peptid *^a* Abbreviations used **are:** ACTH, adrenocorticotropin; maxi- **mum** binding capacity; CCK, cholecystokinin; CNS, central nerv-^{*} Abbreviations used are: ACTH, adrenocortic
mum binding capacity; CCK, cholecystokinin;
ous system; CTP, D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Den-Thr-Pen-Thr-Pen-Thr-Pen-Thr-Pen-* Abbreviations used are: ACTH, adrenocorticotropin; B_{mar}, max
mum binding capacity; CCK, cholecystokinin; CNS, central ner
ous system; CTP, D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH
DAGO, [D-Ala², N-methyl-Phe⁴, Gly⁵ mum binding capacity; CCK, cholecystokinin; CNS, central noise ous system; CTP, p-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NDAGO, [D-Ala², N-methyl-Phe⁴, Gly⁵-ol]-enkephalin; dbcAMP, divryl cyclic adenosine 3',5'-monophosph nous system; CTP, p-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH₂;
DAGO, [D-Ala², N-methyl-Phe⁴, Gly⁵-ol]-enkephalin; dbcAMP, dibu-
tyryl cyclic adenosine 3',5'-monophosphate; 2-DG, 2-deoxy-D-glucose;
DMPP, 1,1-dimethyl-4gives yet is adenosine $3', 5'$ -monophosphate; 2-DG,
DMPP, 1,1-dimethyl-4-phenyl-piperazinium; DPI
Pen⁵]-enkephalin; EC cells, enterochromaffin cells
junction potentials; FK 33-824,[D-Ala²,methyl-Phe
lin; GIP, gastric UNPP, 1,1-dimethyl-4-phenyl-piperazinium; DPDPE, [D-Pen², D-Pen²]-enkephalin; EC cells, enterochromaffin cells; EJPs, excitatory junction potentials; FK 33-824, [D-Ala², methyl-Phe⁴-(O)-ol]-enkephalin; GIP, gastri junction potentials; FK 33-824, [D-Ala²,methyl-Phe⁴-(O)-ol]-enkepha-
lin; GIP, gastric inhibitory polypeptide; i.c., intracisternally; ICI
154,129, N,N-bisallyl-Tyr-Gly-Gly- ψ -(CH₂S)-Phe-Leu-OH; i.c.v., in-
tracere lin; GIP, gastric inhibitory polypeptide; i.c., intracisternally; ICI
154,129, N,N-bisallyl-Tyr-Gly-Gly- ψ -(CH₂S)-Phe-Leu-OH; i.c.v., in-
tracerebroventricularly; i.m., intramuscularly; K_a , dissociation con-
stant; L 5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan]tar**trate;** alpha-MSH, alpha-melanocyte-stimulating **hormone;** NANC, stant, Ens., tower esophagear spinner. Leat, reaction (Fig. 5R, 9R, 9R, 95.6).
MMC, migrating motility complex; MR 2034, [(-)-(1R, 5R, 9R, 2
5.9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan]
trate; alpha-MSH, isopropyladenosine; provincy computers, taxe for the postupidar of properties; alpha-MSH, alpha-melanocyte-stimulating hormone; NANC, trate; alpha-MSH, alpha-melanocyte-stimulating hormone; NANC, nonadrenergic-noncho-liner 15-1788, ethyl-2-flama-melanocyte-stinutury--0.--
15-1788, ethyl-8-flama-melanocyte-stinulating
15-1788, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-
115-1788, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-
a][1,4]benzodiazepine ance, upina scenarion, appear and an example in conduction and an example in conclusion of the properties of the main properties of the properties of the 15-1788, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imida
al[1,4]b isopropyladenosine; PL 017, [methyl-Phe³, D-Pro⁴]-morphiceptin; Ro
15-1788, ethyl-8-flüoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazole[1,5-
a][1,4]benzodiazepine-3-carboxylate; RX 783006, Tyr-D-Ala-Gly-
MePheNH(CH₂)₂OH 15-1788, ethyl-8-flüoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazole[1,5-a][1,4]benzodiazepine-3-carboxylate; RX 783006, Tyr-D-Ala-Gly-MePheNH(CH₂)₂OH; SKF 10.047, N-allyl-normetazocine; TRH, thy-rotropin releasing hormone; 3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzene-acedamide-methansulfonate; VIP, vasoactive international contractive international polyper property of the polyper contropin releasing hormone; TTX, tetrodotoxin; U50,488H, translational contropin releasing hormone; TTX, tetr

65a). In the rat, dynorphin- $A(1-8)$ was detected in duo-
denal myenteric plexus perikarya, nerve fibers, and nerve RROME
65a). In the rat, dynorphin-A(1–8) was detected in duo-
denal myenteric plexus perikarya, nerve fibers, and nerve
terminals, which had close contacts to circular smooth KROME
65a). In the rat, dynorphin-A(1–8) was detected in duo-
denal myenteric plexus perikarya, nerve fibers, and nerve
terminals, which had close contacts to circular smooth
muscle cells and arterioles (477). Dynorphin wa muscle cells and arterioles (477). By and arternative methods in the terminals, which had close contacts to circular smooth in the muscle cells and arterioles (477). Dynorphin was also enhisolated from porcine duodenum (43 65a). In the rat, dynorphin-A(1-8) was detected in duo-
denal myenteric plexus perikarya, nerve fibers, and nerve
terminals, which had close contacts to circular smooth
muscle cells and arterioles (477). Dynorphin was als denal myenteric plexus perikarya, nerve fibers, and nerve
terminals, which had close contacts to circular smooth
muscle cells and arterioles (477). Dynorphin was also
isolated from porcine duodenum (435). In the guinea pig muscle cells and arterioles (477). Dynorphin was also isolated from porcine duodenum (435). In the guinea pig small intestine, dynorphin may coexist with enkephalin and VIP in a population of myenteric neurons (65a). As in uscle cells and arterioles (477) . Dynorphin was also
blated from porcine duodenum (435) . In the guinea pig
hall intestine, dynorphin may coexist with enkephalin
d VIP in a population of myenteric neurons $(65a)$.
As i

isolated from porcine duodenum (435) . In the guinea pig
small intestine, dynorphin may coexist with enkephalin
and VIP in a population of myenteric neurons $(65a)$.
As in the guinea pig, rat, and mouse, the cat intestin small intestine, dynorphin may coexist with enkephalin the and VIP in a population of myenteric neurons (65a). In As in the guinea pig, rat, and mouse, the cat intestinal contains $[Met^5]$ -enkephalin immunoreactivity kwith and VIP in a population of myenteric neurons (65a). In
As in the guinea pig, rat, and mouse, the cat intestinal co
wall contains [Met⁵]-enkephalin immunoreactivity kwithin neurons which again are preferentially localize As in the guinea pig, rat, and mouse, the cat intestinal correlation of wall contains [Met⁵]-enkephalin immunoreactivity key within neurons which again are preferentially localized true within the myenteric plexus (88, wall contains [Met⁵]-enkephalin immunoreactivity k
within neurons which again are preferentially localized
within the myenteric plexus (88, 259). In a population of
these neurons, substance P and [Met⁵]-enkephalin may within neurons which again are preferentially localized
within the myenteric plexus $(88, 259)$. In a population of
these neurons, substance P and $[Met⁵]$ -enkephalin may
coexist within the same neuron, both in the fel these neurons, substance P and $[Met⁶]$ -enkephalin may coexist within the same neuron, both in the feline (88) and guinea pig $(449a)$ small intestine. In the cat, cell processes containing $[Met⁶]$ -enkephalin proje these neurons, substance P and [Met⁵]-enkephalin may
coexist within the same neuron, both in the feline (88)
and guinea pig (449a) small intestine. In the cat, cell
processes containing [Met⁵]-enkephalin project to neu coexist within the same neuron, both in the feline (88) and guinea pig (449a) small intestine. In the cat, cell processes containing [Met⁵]-enkephalin project to neurons of both the myenteric and the submucosal plexus, a (376). *2. Neuronal location in man; comparison between spe-*
 2. Neuronal location in man; comparison between spe-
 2. Neuronal location in man; comparison between spe-
 cies. Most important, enkephalins have been detected

an observation also made in the porcine small intestine (376).

2. Neuronal location in man; comparison between species. Most important, enkephalins have been detected in all parts of the human gastrointestinal tract (331, 1376).

2. Neuronal location in man; comparison between spectrus.

103). Consistent with the high concentration of the fore-

103). Consistent with the high concentration of the fore-

103). Consistent with the high conce 2. *Neuronal accument in main*, comparison between species. Most important, enkephalins have been detected in all parts of the human gastrointestinal tract $(331, 364, 103)$. Consistent with the high concentration of the cies. Most important, enkephalins have been detected in
all parts of the human gastrointestinal tract (331, 364,
103). Consistent with the high concentration of the
proenkephalin-derived peptide [Met⁵, Arg⁶, Gly⁷, L all parts of the human gastrointestinal tract (331, 364
103). Consistent with the high concentration of the
proenkephalin-derived peptide [Met⁵, Arg⁶, Gly⁷, Leu⁸]
enkephalin in the muscle layer as opposed to the mu proenkephalin-derived peptide $[Met⁵, Arg⁶, Gly⁷, Leu⁸]-ehkephalin in the muscle layer as opposed to the mucosa and submuco, opioid immunoreactivity has been demonstrated within neurons and nerve fibers (102, 103), among them a few scattered nerve fibers in the basal part of the mucosa and in the muscularis mucosae (102).$ proenkephalin-derived peptide $[Met^S$, Arg^S , Gly^7 , $Leu^8]$ -
enkephalin in the muscle layer as opposed to the mucosa
and submucosa, opioid immunoreactivity has been dem-
onstrated within neurons and nerve fibers $(102, 1$ enkephalin in the muscle layer as opposed to the mucosa
and submucosa, opioid immunoreactivity has been dem-
onstrated within neurons and nerve fibers (102, 103),
among them a few scattered nerve fibers in the basal
part o and submucosa, opioid immunoreactivity has been dem-

onstrated within neurons and nerve fibers $(102, 103)$, $\frac{By}{2}$

among them a few scattered nerve fibers in the basal

part of the mucosa and in the muscularis mucos constrated within neurons and nerve fibers $(102, 103)$, among them a few scattered nerve fibers in the basal d
part of the mucosa and in the muscularis mucosae (102) .
In addition, the human vagus nerve has been found t (261).

contain $[Met^5]$ -enkephalin-immunoreactive nerve fibers (261).

Some direct immunohistochemical comparisons were

made between species concerning enkephalin immuno-

reactivity in the mucosa and submucosa, in addition to
 contain [Met⁵]-enkephalin-immunoreactive nerve fibers

(261).

Some direct immunohistochemical comparisons were

made between species concerning enkephalin immuno-

reactivity in the mucosa and submucosa, in addition to (261).

Some direct immunohistochemical comparisons were

made between species concerning enkephalin immuno-

reactivity in the mucosa and submucosa, in addition to

the other tissue layers. Enkephalin neurons or nerve

f Some direct immunohistochemical comparisons were

made between species concerning enkephalin immuno-

reactivity in the mucosa and submucosa, in addition to

the other tissue layers. Enkephalin neurons or nerve

fibers we made between species concerning enkephalin immuno-
reactivity in the mucosa and submucosa, in addition to
the other tissue layers. Enkephalin neurons or nerve
fibers were found predominantly in the submucosal and
myenteri reactivity in the mucosa and submucosa, in addition to
the other tissue layers. Enkephalin neurons or nerve
fibers were found predominantly in the submucosal and
myenteric plexus or the circular muscle layer of the
guinea the other tissue layers. Enkephalin neurons or
fibers were found predominantly in the submucos
myenteric plexus or the circular muscle layer (
guinea pig, rat, and hamster gastrointestinal tract
382). Keast et al. (204) de fibers were found predominantly in the submucosal and
myenteric plexus or the circular muscle layer of the
guinea pig, rat, and hamster gastrointestinal tract (256,
stage). Keast et al. (204) demonstrated enkephalin-im-
m guinea pig, rat, and hamster gastrointestinal tract (256, 382). Keast et al. (204) demonstrated enkephalin-im-
munoreactive nerve fibers, though at a lower density
compared with a variety of other neuropeptide-staining
ner guinea pig, rat, and hamster gastrointestinal tract $(256, 382)$. Keast et al. (204) demonstrated enkephalin-im-
munoreactive nerve fibers, though at a lower density compared with a variety of other neuropeptide-stainin 382). Keast et al. (204) demonstrated enkephalin-
munoreactive nerve fibers, though at a lower demonpared with a variety of other neuropeptide-stain
nerve fibers, in the mucosa and muscularis mucosa
the guinea pig, rat, do munoreactive
compared with
nerve fibers, ir
the guinea pig,
testinal tract.
In contrast t mpared with a variety of other neuropeptide-stain
rve fibers, in the mucosa and muscularis mucosae
e guinea pig, rat, dog, marmoset, and human gastro
stinal tract.
In contrast to what was found by radioimmunologi
sthods in

metre fibers, in the mucosa and muscularis mucosae of
the guinea pig, rat, dog, marmoset, and human gastroin-
testinal tract.
In contrast to what was found by radioimmunological
methods in extracts from whole gastrointesti (417, 331, 256), Keast et al. (204) reported a relatively

in the discussion of the stracts from whole gastrointestinal wall

(417, 331, 256), Keast et al. (204) reported a relatively

in the duodenal mucosa. However, rela In contrast to what was found by radioimmunological
methods in extracts from whole gastrointestinal wall
(417, 331, 256), Keast et al. (204) reported a relatively
low density of enkephalin-immunoreactive nerve fibers
in th (417, 331, 256), Keast et al. (204) reported a relatively
low density of enkephalin-immunoreactive nerve fibers
in the duodenal mucosa. However, relative to other re-
gions, a high concentration was confirmed in the sto described in extracts from whole gastromessum wand ref. 165). This finding in the rat suggests a functional (417, 331, 256), Keast et al. (204) reported a relatively role of these peptides upon release and receptor activa low density of enkephalin-immunoreactive nerve fibers in the duodenal mucosa. However, relative to other regions, a high concentration was confirmed in the stom-
ach. These authors described in contrast to other species a in the duodenal mucosa. However, relative to other in gions, a high concentration was confirmed in the stone.
Subset of these authors described in contrast to other species different alarge number of enkephalin neurons wit gions, a high concentration was confirmed in the stom-
ach. These authors described in contrast to other species
a large number of enkephalin neurons within the canine
submucosal plexus. Despite other, subtle species diff ach. These authors described in contrast to other species
a large number of enkephalin neurons within the canine
submucosal plexus. Despite other, subtle species differ-
giences, there was a surprisingly close similarity b submucosal plexus. Despite other, subtle species differ-
example muscle and myenteric plexus has been demon-
ences, there was a surprisingly close similarity between
the strated (71). This high affinity binding was reversi

within the external muscle and the myenteric plexus, enkephalin nerve fibers and neurons (450 469a, 204). ER
within the external muscle and the myenteric plexure
enkephalin nerve fibers and neurons (450 469a, 204).
Ferri et al. (104) extracted $[\text{Met}^5, \text{Arg}^6, \text{Gly}^7, \text{Leu}^{-8}]$

R
thin the external muscle and the myenteric plexus,
kephalin nerve fibers and neurons (450 469a, 204).
Ferri et al. (104) extracted [Met⁵, Arg⁶, Gly⁷, Leu⁻⁸]-
kephalin from tissue specimens taken from human within the external muscle and the myenteric plexus,
enkephalin nerve fibers and neurons (450 469a, 204).
Ferri et al. (104) extracted [Met⁵, Arg⁶, Gly⁷, Leu⁻⁸]-
enkephalin from tissue specimens taken from human
s within the external muscle and the myenteric ple-
enkephalin nerve fibers and neurons (450 469a, 204).
Ferri et al. (104) extracted [Met⁵, Arg⁶, Gly⁷, Leu
enkephalin from tissue specimens taken from hun
sphincter re enkephalin nerve fibers and neurons $(450 \t{469a}, 204)$.
Ferri et al. (104) extracted [Met⁵, Arg⁶, Gly⁷, Leu⁻⁸]-
enkephalin from tissue specimens taken from human
sphincter regions. They found, by radioimmunoass enkephalin from tissue specimens taken from human
sphincter regions. They found, by radioimmunoassay,
the highest concentration in the pyloric junction, both
in the submucosa and muscularis externa, and lower
concentration enkephalin from tissue specimens taken from human
sphincter regions. They found, by radioimmunoassay,
the highest concentration in the pyloric junction, both
in the submucosa and muscularis externa, and lower
concentration sphincter regions. They found, by radioimmunoasses
the highest concentration in the pyloric junction, bo
in the submucosa and muscularis externa, and low
concentrations in the cardiac and ileocecal region. E
kephalin immun the highest concentration in the pyloric junction, both
in the submucosa and muscularis externa, and lower
concentrations in the cardiac and ileocecal region. En-
kephalin immunoreactivity was demonstrated by Agges-
trup e In the submitted and muscularis externa, and lower
concentrations in the cardiac and ileocecal region. En-
kephalin immunoreactivity was demonstrated by Agges-
trup et al. (3) in the lower esophageal sphincter of both
pig

part of the mucosa and in the muscularis mucosae (102). matographic systems was also found in G-cells of rat
In addition, the human vagus nerve has been found to
contain [Met⁵]-enkephalin-immunoreactive nerve fibers
(26 kephalin immunoreactivity was demonstrated by Agges-
trup et al. (3) in the lower esophageal sphincter of both
pig and man.
3. Location in endocrine cells in different species. Polak
et al. (331) were able to stain human trup et al. (3) in the lower esophageal sphincter of both
pig and man.
3. Location in endocrine cells in different species. Polak
et al. (331) were able to stain human antral G-cells with
antibodies to $[Met⁵]$ -enkephal pig and man.
3. Location in endocrine cells in different species. Polak
et al. (331) were able to stain human antral G-cells with
antibodies to [Met⁵]-enkephalin, but did not find any
immunoreactivity in other endocrine 3. Location in endocrine cells in different species. Polak
et al. (331) were able to stain human antral G-cells with
antibodies to $[Met⁵]$ -enkephalin, but did not find any
immunoreactivity in other endocrine cells. et al. (331) were able to stain human antral G-cells with
antibodies to [Met⁵]-enkephalin, but did not find any
immunoreactivity in other endocrine cells. In this study,
the antral mucosa showed a higher concentration of antibodies to [Met⁻]-enkephalin, but did not find any
immunoreactivity in other endocrine cells. In this study,
the antral mucosa showed a higher concentration of
immunoreactive enkephalin as compared to the antral
muscl the antral mucosa showed a higher concentration
immunoreactive enkephalin as compared to the an
muscle layers or other regions of the gastrointest
tract. Similar observations were made by Ito et al. (19
The finding is furt immunoreactive enkephalin as compared to the antral
muscle layers or other regions of the gastrointestinal
tract. Similar observations were made by Ito et al. (193a).
The finding is further supported by immunocytochemical
 muscle layers or other regions of the gastrointestinal
tract. Similar observations were made by Ito et al. (193a).
The finding is further supported by immunocytochemical
studies of Larsson and Stengaard-Pedersen (248) who
 tract. Similar observations were made by Ito et al. (193a).
The finding is further supported by immunocytochemical
studies of Larsson and Stengaard-Pedersen (248) who
found, in human antropyloric mucosa and that of some
ot The finding is further supported by immunocytochemical
studies of Larsson and Stengaard-Pedersen (248) who
found, in human antropyloric mucosa and that of some
other species, both gastrin and cholecystokinin cells
stained studies of Larsson and Stengaard-Pedersen (248) who
found, in human antropyloric mucosa and that of some
other species, both gastrin and cholecystokinin cells
stained by antibodies capable of reacting with [Met⁵]-
enkeph found, in human antropyloric mucosa and that of some
other species, both gastrin and cholecystokinin cells
stained by antibodies capable of reacting with [Met⁵]-
enkephalin congeners elongated at the COOH terminus.
By th other species, both gastrin and cholecystokinin cell
stained by antibodies capable of reacting with [Met⁵]
enkephalin congeners elongated at the COOH terminua
By the same group, opioid material which could not b
distingu stained by antibodies capable of reacting with [Met⁵]-
enkephalin congeners elongated at the COOH terminus.
By the same group, opioid material which could not be
distinguished from [Met⁵]-enkephalin by several chro-
ma The antitral mucosa showed a higher concentration of
immunoreactive enkephalin as compared to the antral
mucosa showed a higher concentration of
munoceative enkephalin as compared to the antral
tract. Similar observations By the same group, opioid material which could
distinguished from [Met⁵]-enkephalin by several
matographic systems was also found in G-cells
antropyloric mucosal tissue held in organ cultu
addition, Tanaka et al. (439) r distinguished from [Met⁵]-enkephalin by several chromatographic systems was also found in G-cells of rat antropyloric mucosal tissue held in organ culture. In addition, Tanaka et al. (439) reported on beta-endorphin-like matographic systems was also found in G-cells of rat
antropyloric mucosal tissue held in organ culture. In
addition, Tanaka et al. (439) reported on beta-endorphin-
like immunoreactivity in extracts of human antral mu-
cos antropyloric mucosal tissue held in organ culture. In
addition, Tanaka et al. (439) reported on beta-endorphin
like immunoreactivity in extracts of human antral mu
cosa. Thus, human and rat antral G-cells are probably
capa addition, Tanaka et al. (439) reported on beta-endorphin-
like immunoreactivity in extracts of human antral mu-
cosa. Thus, human and rat antral G-cells are probably
capable of synthesizing enkephalins or endorphins. Sim-
 like immunoreactivity in extracts of human antral mu-
cosa. Thus, human and rat antral G-cells are probably
capable of synthesizing enkephalins or endorphins. Sim-
ilar observations were made by Bu'Lock et al. (43) in the
 cosa. Thus, human and rat antral G-cells are probably
capable of synthesizing enkephalins or endorphins. Sim-
ilar observations were made by Bu'Lock et al. (43) in the
rat, mouse, and guinea pig, and by Jönsson (198) in th capable of synthesizing enkephalins or endorphins. Similar observations were made by Bu'Lock et al. (43) in the rat, mouse, and guinea pig, and by Jönsson (198) in the pig antral mucosa. These observations are of particula ilar observations were made by Bu'Lock et al. (43) in the rat, mouse, and guinea pig, and by Jönsson (198) in the pig antral mucosa. These observations are of particular interest, since the release and/or action of gastrin rat, mouse, and guinea pig, and by Jönsson (198) in
pig antral mucosa. These observations are of partie
interest, since the release and/or action of gastrin, w
stimulates gastric acid secretion, might be modulate
corelease pig antral mucosa. These observations are of particular
interest, since the release and/or action of gastrin, which
stimulates gastric acid secretion, might be modulated by
coreleased endogenous opioids. In addition, enkep interest, since the release and/or action of gastrin, which
stimulates gastric acid secretion, might be modulated by
coreleased endogenous opioids. In addition, enkephalin-
like immunoreactivity was detected in enterochrom stimulates gastric acid secretion, might b
coreleased endogenous opioids. In additic
like immunoreactivity was detected in en
(EC) cells identified by an antiserotonii
porcine gastrointestinal tract (7a, 300).
4. Enkephali coreleased endogenous opioids. In addition, enkephalin-
like immunoreactivity was detected in enterochromaffin
(EC) cells identified by an antiserotonin serum in the
porcine gastrointestinal tract (7a, 300).
4. *Enkephalin*

(EC) cells identified by an antiserotonin serum in the porcine gastrointestinal tract $(7a, 300)$.
4. Enkephalinases. The occurrence of endogenous opioids in the gastrointestinal tract is accompanied by enkephalin degradi porcine gastrointestinal tract (*i*a, 300).
4. Enkephalinases. The occurrence of endogenous
opioids in the gastrointestinal tract is accompanied by
enkephalin degrading enzymes, i.e., enkephalinases, in
the stomach and int opioids in the gastrointestinal tract is accompanied by enkephalin degrading enzymes, i.e., enkephalinases, in the stomach and intestine (257; for nomenclature, see enkephain degrading enzymes, i.e., e
the stomach and intestine (257; for π
ref. 165). This finding in the rat sug
role of these peptides upon release an
tion within the gastrointestinal tract.
P. Onioid Becaptors. **Pref. 165). This finding**
Property Receptides
B. Opioid Receptors
B. Opioid Receptors

role of these peptides upon release and receptor activation within the gastrointestinal tract.

B. Opioid Receptors

Specific binding of a variety of opioid agonists and

antagonists to homogenates of guinea pig intestine B. Opioid Receptors
Specific binding of a variety of opioid agonists antagonists to homogenates of guinea pig intestine left
gitudinal muscle and myenteric plexus has been dem
strated (71). This high affinity binding was r Specific binding of a variety of opioid agonists and antagonists to homogenates of guinea pig intestine longitudinal muscle and myenteric plexus has been demon strated (71). This high affinity binding was reversible satura specific binding of a variety of opioid agonists and
antagonists to homogenates of guinea pig intestine lon-
gitudinal muscle and myenteric plexus has been demon-
strated (71). This high affinity binding was reversible,
sa strated (71). This high affinity binding was reversible,

OPIOIDS AND CONTROL OF GASTROINTES
in inhibiting electrically induced contractions of the dis-
guinea pig intestine in vitro, supporting the conclusion in OPIOIDS AND CONTROL OF GASTROINT
in inhibiting electrically induced contractions of the
guinea pig intestine in vitro, supporting the conclusion
that these binding sites represent neuronal opioid recep-OPIOIDS AND CONTROL OF GASTR
in inhibiting electrically induced contractions of the
guinea pig intestine in vitro, supporting the conclusion
that these binding sites represent neuronal opioid rece
tors. This was further su in inhibiting electrically induced contractions of the guinea pig intestine in vitro, supporting the conclusion that these binding sites represent neuronal opioid receptors. This was further substantiated by findings of Gl in inhibiting electrically induced contractions of the dist
guinea pig intestine in vitro, supporting the conclusion in v
that these binding sites represent neuronal opioid recep-
tors. This was further substantiated by fi guinea pig intestine in vitro, supporting the conclusion in vitrement that these binding sites represent neuronal opioid recep-
tors. This was further substantiated by findings of Glasel already
et al. (136) who demonstrat that these binding sites represent neuronal opioid rectors. This was further substantiated by findings of Glaet al. (136) who demonstrated specific opioid binding a purified synaptosomal fraction from guinea pig ile homoge tors. This was further substantiated by findings of Glasel
et al. (136) who demonstrated specific opioid binding to
a purified synaptosomal fraction from guinea pig ileum
homogenates. In microsomal preparations from longit et al. (136) who demonstrated specific opioid binding to
a purified synaptosomal fraction from guinea pig ileum
homogenates. In microsomal preparations from longitu-
dinal muscle with attached myenteric plexus of the rat
s a purified synaptosomal fraction from guinea pig ileum
homogenates. In microsomal preparations from longitu-
dinal muscle with attached myenteric plexus of the rat
small intestine, Monferini et al. (290) demonstrated
highhomogenates. In microsomal preparations from longitudinal muscle with attached myenteric plexus of the rat small intestine, Monferini et al. (290) demonstrated high-affinity binding of etorphine, which was saturable revers dinal muscle with attached myenteric plexus of the rat small intestine, Monferini et al. (290) demonstrated high-affinity binding of etorphine, which was saturable, reversible, stereospecific, and sensitive to sodium conce small intestine, Monferini et al. (290) demonstrated
high-affinity binding of etorphine, which was saturable,
reversible, stereospecific, and sensitive to sodium con-
centration. Sensitivity to sodium is a well-recognized
 high-affinity bi
reversible, stere
centration. Ser
feature of opio
409 and 418).
In the rat and

feature of opioid agonist binding (for review, see refs. in 409 and 418).
409 and 418). In the rat and guinea pig gastric fundus, the occurrence oppof both mu- and delta-type opioid binding sites has been claimed on the ba 409 and 418).
In the rat and guinea pig gastric fundus, the occurrence
of both mu- and delta-type opioid binding sites has been
claimed on the basis of autoradiographic data within the
circular muscle, muscularis mucosae, In the rat and guinea pig gastric fundus, the occurrence
of both mu- and delta-type opioid binding sites has been
claimed on the basis of autoradiographic data within the
circular muscle, muscularis mucosae, and submucosal of both mu- and delta-type opioid binding sites has been cluster claimed on the basis of autoradiographic data within the receptor muscle, muscularis mucosae, and submucosal acceptor type identification, see For a review o claimed on the basis of autoradiographic data within the circular muscle, muscularis mucosae, and submucosal plexus (302), although poorly selective ligands were used.
For a review of opioid receptor type identification, s circular muscle, muscularis mucosae, and submucosal
plexus (302), although poorly selective ligands were used.
For a review of opioid receptor type identification, see
refs. 141 and 494. In the corpus and antrum region,
bi plexus (302), although poorly selective ligands were used.
For a review of opioid receptor type identification, see
refs. 141 and 494. In the corpus and antrum region,
binding was found in the submucosal and deep muscular
 For a review of opioid receptor type identification, see refs. 141 and 494. In the corpus and antrum regio binding was found in the submucosal and deep musculplexus and in the mucosa. In addition, binding was found beit in fs. 141 and 494. In the corpus and antrum region,
nding was found in the submucosal and deep muscular
exus and in the mucosa. In addition, binding was found,
seit in poor density, in the myenteric plexus (302).
Specific o

binding was found in the submucosal and deep muscular oplexus and in the mucosa. In addition, binding was found, albeit in poor density, in the myenteric plexus (302). Specific opioid binding in the nanomolar range (K_d) plexus and in the mucosa. In addition, binding was found,
albeit in poor density, in the myenteric plexus (302).
Specific opioid binding in the nanomolar range (K_d)
has also been demonstrated in homogenates of isolated
a albeit in poor density, in the myenteric plexus (302).

Specific opioid binding in the nanomolar range (K_d)

has also been demonstrated in homogenates of isolated op

and enriched guinea pig parietal cells (238) or isola Specific opioid binding in the nanomolar range (K_d)
has also been demonstrated in homogenates of isolated
and enriched guinea pig parietal cells (238) or isolated
intestinal epithelial cells from guinea pig small and lar has also been demonstrated in homogenates of isolated
and enriched guinea pig parietal cells (238) or isolated
intestinal epithelial cells from guinea pig small and large
intestinal epithelial cells from guinea pig small intestinal epithelial cells from guinea pig small and large intestinal epithelial cells from guinea pig small and large
intestine (260). The latter binding sites were [Leu⁵]-
enkephalin selective and may differ from delta-type
opioid receptors which have very recently been disti intestine (260). The latter binding sites were $[Leu⁵]$ -
enkephalin selective and may differ from delta-type
opioid receptors which have very recently been distin-
guished as an entity from other types in rat brain by (451). ioid receptors which have very recently been distin-

ished as an entity from other types in rat brain by

ceptor purification and distinct molecular weights
 $\frac{1}{10}$

In conclusion, endogenous opioids of the three kno

guished as an entity from other types in rat brain by
receptor purification and distinct molecular weights
(451).
In conclusion, endogenous opioids of the three known
classes, enkephalins, endorphins, and dynorphins, were receptor purification and distinct molecular weights (451).

In conclusion, endogenous opioids of the three known

classes, enkephalins, endorphins, and dynorphins, were

found throughout the gastrointestinal tract in neur (451). In conclusion, endogenous opioids of the three known
classes, enkephalins, endorphins, and dynorphins, were
found throughout the gastrointestinal tract in neuronal
and endocrine cells with potential receptor sites o In conclusion, endogenous opioids of the three known
classes, enkephalins, endorphins, and dynorphins, were
found throughout the gastrointestinal tract in neuronal
and endocrine cells with potential receptor sites on neuclasses, enkephalins, endorphins, and dynorphins, were
found throughout the gastrointestinal tract in neuronal
and endocrine cells with potential receptor sites on neu-
ronal, smooth muscle, and mucosal cells. As expected found throughou
and endocrine ce
ronal, smooth mu
an intrinsic opic
are also present. Extempt of muscle, and mucosal cells. As expected for a strain opioid system, specific degrading enzymetries of present.
 III. The Role of Opioids in the Control of
 III. The Role of Opioids in the Control of Gastrointe

Gastrointestinal Motility are also present.
 III. The Role of Opioids in the Control of
 A. In Vitro Studies in the Guinea Pig Small Intestine
 A. In Vitro Studies in the Guinea Pig Small Intestine

1. Methodological considerations. It has been questioned repeatedly whether conclusions drawn from guinea-pig data can be applied to other species. Never-Gastrointestinal Motility

A. In Vitro Studies in the Guinea Pig Small Intestine

1. Methodological considerations. It has been ques-

tioned repeatedly whether conclusions drawn from frequen

guinea-pig data can be applie A. In Vitro Studies in the Guinea Pig Small Intestine
1. Methodological considerations. It has been quer-
tioned repeatedly whether conclusions drawn from
guinea-pig data can be applied to other species. Never-
theless, th A. In vuro Studies in the Guinea-pig Small Intestine
1. Methodological considerations. It has been qu
tioned repeatedly whether conclusions drawn fraguinea-pig data can be applied to other species. Nev
theless, the isolat 1. Methodological considerations. It has been ques-
tioned repeatedly whether conclusions drawn from frequinea-pig data can be applied to other species. Never-
theless, the isolated guinea-pig ileum has received partic-
ac tioned repeatedly whether conclusions drawn from
guinea-pig data can be applied to other species. Nevertheless, the isolated guinea-pig ileum has received particular attention for in vitro investigation of gut motility is guinea-pig data can be applied to other species. Never
theless, the isolated guinea-pig ileum has received partic
ular attention for in vitro investigation of gut motility a
it permits, for instance in the experimental set theless, the isolated guinea-pig ileum has received partic-
ular attention for in vitro investigation of gut motility as
it permits, for instance in the experimental setup intro-
pduced by Trendelenburg (446), an accurate ular attention for in vitro investigation of gut motility as
it permits, for instance in the experimental setup intro-
duced by Trendelenburg (446), an accurate measurement
of single propulsive circular muscle contractions it permits, for instance in the experimental setup intro-
duced by Trendelenburg (446), an accurate measurement
of single propulsive circular muscle contractions. In this
review, in vitro peristalsis is defined as phasic c duced by Trendelenburg (446), an accurate measurement sion-induced reflex peristalsis in the isolated guinea-pig
of single propulsive circular muscle contractions. In this ileum. Although naloxone also reversed the inhibit

ESTINAL MOTILITY AND SECRETION 125
distal. Peristalsis is therefore easily distinguished from
in vitro pendular movements or segmentations which ESTINAL MOTILITY AND SECRETION 125
distal. Peristalsis is therefore easily distinguished from
in vitro pendular movements or segmentations which
achieve no or only negligible volume expulsion. It should ESTINAL MOTILITY AND SECRETION 125
distal. Peristalsis is therefore easily distinguished from
in vitro pendular movements or segmentations which
achieve no or only negligible volume expulsion. It should
already be noted at distal. Peristalsis is therefore easily distinguished from
in vitro pendular movements or segmentations which
achieve no or only negligible volume expulsion. It should
already be noted at this stage that it is difficult to distal. Peristalsis is therefore easily distinguished from
in vitro pendular movements or segmentations which
achieve no or only negligible volume expulsion. It should
already be noted at this stage that it is difficult to achieve no or only negligible volume expulsion. It should already be noted at this stage that it is difficult to relate in vitro and in vivo motility parameters to each other. However, it may be speculated that reflex peri already be noted at this stage that it is difficult to relate
in vitro and in vivo motility parameters to each other.
However, it may be speculated that reflex peristalsis as
observed in the isolated intestinal segment is correlate of the MMC (see below) which, in vivo, travels in vitro and in vivo n
However, it may be sp
observed in the isolat
correlate of the MMC
down the whole gut.
Exogenous opioids (by owever, it may be speculated that reflex peristalsis as served in the isolated intestinal segment is the local rrelate of the MMC (see below) which, in vivo, travels wn the whole gut.
Exogenous opioids (both alkaloids a

reversible, stereospecific, and sensitive to sodium con-

leven shown to depress the peristaltic reflex (373, 222,

centration. Sensitivity to sodium is a well-recognized

feature of opioid agonist binding (for review, see feature of opioid agonist binding (for review, see refs. inhibitory effect of exogenous opioids does not necessar-
409 and 418).
In the rat and guinea pig gastric fundus, the occurrence opioids. An essential prerequisite f observed in the isolated intestinal segment is the local
correlate of the MMC (see below) which, in vivo, travels
down the whole gut.
Exogenous opioids (both alkaloids and peptides) have
been shown to depress the peristalt correlate of the MMC (see below) which, in vivo, travels
down the whole gut.
Exogenous opioids (both alkaloids and peptides) have
been shown to depress the peristaltic reflex (373, 222,
177; for review, see refs. 219 and 7 down the whole gut.

Exogenous opioids (both alkaloids and peptides) h

been shown to depress the peristaltic reflex (373, 1

177; for review, see refs. 219 and 76). However,

inhibitory effect of exogenous opioids does no Exogenous opioids (both alkaloids and peptides) have
been shown to depress the peristaltic reflex (373, 222,
177; for review, see refs. 219 and 76). However, the
inhibitory effect of exogenous opioids does not necessar-
il been shown to depress the peristaltic reflex (373, 222
177; for review, see refs. 219 and 76). However, the
inhibitory effect of exogenous opioids does not necessar-
ily imply a similar physiological role of endogenous
opi 177; for review, see refs. 219 and 76). However, the inhibitory effect of exogenous opioids does not necessarily imply a similar physiological role of endogenous opioids. An essential prerequisite for drawing such conclusi inhibitory effect of exogenous opioids does not necessarily imply a similar physiological role of endogenous opioids. An essential prerequisite for drawing such conclusions is to demonstrate that specific blockade of opio ily imply a similar physiological role of endogenous opioids. An essential prerequisite for drawing such conclusions is to demonstrate that specific blockade of opioid receptors results in the opposite effect as compared t opioids. An essential prerequisite for drawing such conclusions is to demonstrate that specific blockade of opioid
receptors results in the opposite effect as compared to
acute opioid action. Opioid receptor blockade would clusions is to demonstrate that specific blockade of opioid
receptors results in the opposite effect as compared to
acute opioid action. Opioid receptor blockade would un-
mask the physiological role of those receptors tha teceptors results in the opposite effect as compared to
acute opioid action. Opioid receptor blockade would un-
mask the physiological role of those receptors that had
already been endogenously activated at the time of anactue opioid action. Opioid receptor biockade would un-
mask the physiological role of those receptors that had
already been endogenously activated at the time of an-
tagonist administration, whereas administration of ex-
 mask the physiological role of those receptors that had
already been endogenously activated at the time of an-
tagonist administration, whereas administration of ex-
ogenous opioids indiscriminately leads to simultaneous
a already been endogenously activated at the time of antagonist administration, whereas administration of ex-
ogenous opioids indiscriminately leads to simultaneous
activation of all opioid receptors irrespective of their
lo *2. Naloxone as a tool: first proof of a role of intestinal pediation* of ex-
 openous opioids indiscriminately leads to simultaneous
 activation and relative functional significance.
 2. Naloxone as a tool: first pro

activation of all opioid receptors irrespective of their
location and relative functional significance.
2. Naloxone as a tool: first proof of a role of intestinal
opioids. The competitive opioid antagonist (--)naloxone,
a location and relative functional significance.

2. Naloxone as a tool: first proof of a role of intestinal

opioids. The competitive opioid antagonist (-)naloxone,

at concentrations below 1 μ mol/liter, provides a rath 2. Naloxone as a tool: first proof of a role of intestinal
opioids. The competitive opioid antagonist (-)naloxone,
at concentrations below 1 μ mol/liter, provides a rather
specific tool for such experiments, although no opioids. The competitive opioid antagonist $(-)$ naloxone,
at concentrations below 1 μ mol/liter, provides a rather
specific tool for such experiments, although nonspecific
actions may be observed at higher concentrations at concentrations below 1 μ mol/liter, provides a rathe-
specific tool for such experiments, although nonspecif-
actions may be observed at higher concentrations (369
At concentrations of at least up to 1 μ mol/liter, specific tool for such experiments, although nonspecific
actions may be observed at higher concentrations (369).
At concentrations of at least up to $1 \mu \text{mol/liter}$, naloxone
had no influence on the actions of noradrenaline, actions may be observed at higher concentrations (369).
At concentrations of at least up to 1μ mol/liter, naloxone
had no influence on the actions of noradrenaline, dopa-
mine, serotonin, acetylcholine, histamine, or $\$ At concentrations of at least up to 1μ mol/liter, n
had no influence on the actions of noradrenalin
mine, serotonin, acetylcholine, histamine, or PGF
longitudinal muscle myenteric plexus preparatio
guinea-pig ileum (Kro d no influence on the actions of noradrenaline, dopa-
ine, serotonin, acetylcholine, histamine, or PGE_1 in the
ngitudinal muscle myenteric plexus preparation of the
inea-pig ileum (Kromer, unpublished results).
Based on

mine, serotonin, acetylcholine, histamine, or PGE_1 in th
longitudinal muscle myenteric plexus preparation of th
guinea-pig ileum (Kromer, unpublished results).
Based on studies in electrically stimulated guinea-pi
ileum longitudinal muscle myenteric plexus preparation of t
guinea-pig ileum (Kromer, unpublished results).
Based on studies in electrically stimulated guinea-
ileum, inhibition of acetylcholine release by opioid all
loids (325, guinea-pig ileum (Kromer, unpublished results).
Based on studies in electrically stimulated guinea-pig
ileum, inhibition of acetylcholine release by opioid alka-
loids (325, 374) has widely been regarded as the mecha-
nism Based on studies in electrically stimulated guinea-pig
ileum, inhibition of acetylcholine release by opioid alka-
loids (325, 374) has widely been regarded as the mecha-
nism of opioid inhibition of peristalsis in this spe ileum, inhibition of acetylcholine release by opioid alka-
loids (325, 374) has widely been regarded as the mecha-
nism of opioid inhibition of peristalsis in this species. It
was an important finding, therefore, that nalo loids (325, 374) has widely been regarded as the mechanism of opioid inhibition of peristalsis in this species. It was an important finding, therefore, that naloxone was able to enhance the electrically stimulated release nism of opioid inhibition of peristalsis in this species.
was an important finding, therefore, that naloxone w
able to enhance the electrically stimulated release
acetylcholine in the longitudinal muscle myenter
plexus pre was an important finding, therefore, that naloxone was able to enhance the electrically stimulated release of acetylcholine in the longitudinal muscle myenteric plexus preparation of the guinea-pig ileum (467). Stereospeci able to enhance the electrically stimulated release of acetylcholine in the longitudinal muscle myenteric plexus preparation of the guinea-pig ileum (467). Stere-ospecificity of this effect was demonstrated by the use of o acetylcholine in the longitudinal muscle myenteric
plexus preparation of the guinea-pig ileum (467). Stere-
ospecificity of this effect was demonstrated by the use of
optical isomers of antagonists of the benzomorphan se-
 plexus preparation of the guinea-pig ileum (467). Stere
ospecificity of this effect was demonstrated by the use c
optical isomers of antagonists of the benzomorphan se
ries. The finding is consistent with release of endoge ospecificity of this effect was demonstrated by the use of optical isomers of antagonists of the benzomorphan series. The finding is consistent with release of endogenous opioids from the guinea-pig ileum in vitro upon hig optical isomers of antagonists of the benzomorphan series. The finding is consistent with release of endogenous opioids from the guinea-pig ileum in vitro upon high-frequency electrical stimulation (339). Thus, endogenous ries. The finding is consistent with release of endogenous
opioids from the guinea-pig ileum in vitro upon high-
frequency electrical stimulation (339). Thus, endogenous
opioids may have inhibited electrically evoked relea opioids from the guinea-pig ileum in vitro upon high-
frequency electrical stimulation (339). Thus, endogenous
opioids may have inhibited electrically evoked release of
acetylcholine, which was reversed by naloxone (467).
 frequency electrical stimulation (339). Thus, endogenopioids may have inhibited electrically evoked release
acetylcholine, which was reversed by naloxone (46
Moreover, Van Nueten et al. (452) reported an "un
pected reversa opioids may have inhibited electrically evoked release of acetylcholine, which was reversed by naloxone (467).
Moreover, Van Nueten et al. (452) reported an "unex-
pected reversal effect of naloxone" on "fatigued" disten-
 acetylcholine, which was reversed by naloxone (467).
Moreover, Van Nueten et al. (452) reported an "unex-
pected reversal effect of naloxone" on "fatigued" disten-
sion-induced reflex peristalsis in the isolated guinea-pig pected reversal effect of naloxone" on "fatigued" distenpected reversal effect of naloxone" on "fatigued" distension-induced reflex peristalsis in the isolated guinea-pig
ileum. Although naloxone also reversed the inhibition of
peristalsis by adenosine, AMP, ADP, ATP, and halop sion-induced reflex peristalsis in the isolated guinea-pig
ileum. Although naloxone also reversed the inhibition of
peristalsis by adenosine, AMP, ADP, ATP, and haloper-
idol (452), the actions of these compounds were not

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dently of a functional nature (physiological antagonism),
being not inconsistent with a specific blockade of opioid
receptors by naloxone.
Van Nueten et al. (452) concluded from their data (see
above) that naloxone reverse being not inconsistent with a specific blockade of opi
receptors by naloxone.
Van Nueten et al. (452) concluded from their data (
above) that naloxone reversed fatigue of peristalsis
had no influence on "normal peristalsis receptors by naloxone.
Van Nueten et al. (452) concluded from their data (see
above) that naloxone reversed fatigue of peristalsis but
had no influence on "normal peristalsis." This interpre-
tation, however, is at varianc Van Nueten et al. (452) concluded from their data (see
above) that naloxone reversed fatigue of peristalsis but
had no influence on "normal peristalsis." This interpre-
tation, however, is at variance with data showing tha above) that naloxone reversed fatigue of peristalsis but m
had no influence on "normal peristalsis." This interpre-
tation, however, is at variance with data showing that (2
spontaneous, intermittent interruption of perist had no influence on "normal peristalsis." This interpre-
tation, however, is at variance with data showing that (23
spontaneous, intermittent interruption of peristaltic ac-
red
tivity with peristalsis-free intervals (whic tation, however, is at variance with data showing that spontaneous, intermittent interruption of peristaltic activity with peristalsis-free intervals (which was regarded as a fatigue phenomenon; 452) is regularly observed spontaneous, intermittent interruption of peristaltic activity with peristalsis-free intervals (which was regarded the as a fatigue phenomenon; 452) is regularly observed also in vivo (42; for review, see refs. 361 and 470 Evity with peristalsis-free intervals (which was regarded
as a fatigue phenomenon; 452) is regularly observed also
in vivo (42; for review, see refs. 361 and 470). Moreover,
the isolated guinea-pig ileum is capable of prod as a fatigue phenomenon; 452) is regularly observed also not
in vivo (42; for review, see refs. 361 and 470). Moreover, inh
the isolated guinea-pig ileum is capable of producing rea
ongoing peristalsis at extremely high in vivo (42; for review, see refs. 361 and 470). Moreover, in
the isolated guinea-pig ileum is capable of producing re
ongoing peristalsis at extremely high frequency under
conditions of opiate withdrawal without showing the isolated guinea-pig ileum is capable of producing reading peristals at extremely high frequency under conditions of opiate withdrawal without showing any efferigns of fatigue (242). In fact, Kromer et al. (234) have al ongoing peristalsis at extremely high frequency under conditions of opiate withdrawal without showing any signs of fatigue (242). In fact, Kromer et al. (234) have demonstrated that guinea-pig ileal segments, which worked conditions of opiate withdrawal without showing any
signs of fatigue (242). In fact, Kromer et al. (234) have
demonstrated that guinea-pig ileal segments, which
worked against their closed distal end, developed fatigue,
al demonstrated that guinea-pig ileal segments, which
worked against their closed distal end, developed fatigue,
although naloxone increased the number of peristaltic
contractions in these segments by a percentage similar
to demonstrated that guinea-pig ileal segments, which
worked against their closed distal end, developed fatigue,
although naloxone increased the number of peristaltic
contractions in these segments by a percentage similar
to worked against their closed distal end, developed fatigue
although naloxone increased the number of peristalti
contractions in these segments by a percentage simila
to that observed in segments allowed to expel their
conte although naloxone increased the number of peristaltic of the contractions in these segments by a percentage similar that tin to that observed in segments allowed to expel their free information from to protect the gut from contractions in these segments by a percentage similar that observed in segments allowed to expel their ficontents. Thus, endogenous opioids seem to control "nor-
mal peristalsis" rather than to protect the gut from A
beco to that observed in segments allowed to expel their free
contents. Thus, endogenous opioids seem to control "nor-
mal peristalsis" rather than to protect the gut from All
becoming exhausted (i.e., producing "fatigue"). Kad contents. Thus, endogenous opioids seem to control "nor-
mal peristalsis" rather than to protect the gut from A
becoming exhausted (i.e., producing "fatigue"). Kadlec m
and Horácek (201) suppressed the peristaltic reflex i mal peristalsis" rather than to protect the gut from All
becoming exhausted (i.e., producing "fatigue"). Kadlec me
and Horácek (201) suppressed the peristaltic reflex in
the isolated guinea-pig ileum by a 2-min application and Horácek (201) suppressed the peristaltic reflex in the isolated guinea-pig ileum by a 2-min application of high intraluminal pressure corresponding to 12 cm of water, plus increased longitudinal tension. They found tha the isolated guinea-pig ileum by a 2-min application of enhigh intraluminal pressure corresponding to 12 cm of tourneer, plus increased longitudinal tension. They found The that, after cessation of this "stress" stimulus, high intraluminal pressure corresponding to 12 cm
water, plus increased longitudinal tension. They fou
that, after cessation of this "stress" stimulus, peristal
reappeared earlier under the influence of naloxone th
in nalo water, plus increased longitudinal tension. They found T
that, after cessation of this "stress" stimulus, peristalsis the
reappeared earlier under the influence of naloxone than
in naloxone-free "stressed" controls. Howeve that, after cessation of this "stress" stimulus, peristalsis take reappeared earlier under the influence of naloxone than in naloxone-free "stressed" controls. However, no stress-
free controls with and without naloxone we reappeared earlier under the influence of naloxone t
in naloxone-free "stressed" controls. However, no stree
free controls with and without naloxone were tested
spontaneous peristalsis-free intervals and frequency
peristal in naloxone-free "stressed" controls. However, no stress-
free controls with and without naloxone were tested for
spontaneous peristalsis-free intervals and frequency of
peristaltic waves, which may have led to the misinte free controls with and without nalox
spontaneous peristalsis-free interval
peristaltic waves, which may have l
pretation that a "stress" response i
peristalsis was affected by naloxone.
Naloxone enhanced in vitro peri ontaneous peristalsis-free intervals and frequency of
ristaltic waves, which may have led to the misinter-
etation that a "stress" response rather than normal
ristalsis was affected by naloxone.
Naloxone enhanced in vitro

peristaltic waves, which may have led to the misinter-
pretation that a "stress" response rather than normal cific
peristalsis was affected by naloxone. The organ bath of
degree when administered acutely into the organ bat pretation that a "stress" response rather than normal
peristalsis was affected by naloxone.
Naloxone enhanced in vitro peristalsis to a higher
legree when administered acutely into the organ bath
(233) than after preexposu peristalsis was affected by naloxone. Only into the organ bath consider the degree when administered acutely into the organ bath metals of the segments to naloxone declined (231). In the former case, the naloxone effect de Naloxone enhanced in vitro peristalsis to a higher be
degree when administered acutely into the organ bath
(233) than after preexposure of the segments to naloxone de
(231). In the former case, the naloxone effect declined degree when administered acutely into the organ bath m (233) than after preexposure of the segments to naloxone de (231). In the former case, the naloxone effect declined desomewhat over time, although sufficient naloxone (233) than after preexposure of the segments to naloxon (231). In the former case, the naloxone effect decline somewhat over time, although sufficient naloxone was still present to occupy all opioid receptors. These data (231). In the former case, the naloxone somewhat over time, although sufficien still present to occupy all opioid recepts suggest a compensatory mechanism (for ative agents, see refs. 65, 130, and 46).
3. Intestinal actio **3. Intesting** *actions of opioid interfect constants* **of** *semigrest* **a** compensatory mechanism (for potential causative agents, see refs. 65, 130, and 46).

3. Intestinal actions of opioids prior to parturition.

Con

suggest a compensatory mechanism (for potential caus-
ative agents, see refs. 65, 130, and 46).
3. Intestinal actions of opioids prior to parturition.
Consistent with the presence of $[Met⁵]$ -enkephalin im-
munoreactiv ative agents, see refs. 65, 130, and 46).
3. Intestinal actions of opioids prior to parturition.
Consistent with the presence of $[Met⁵]$ -enkephalin im-
munoreactivity in 18-day fetal tissue cultures of mouse
intestine 3. Intestinal actions of opioids prior to parturition.
Consistent with the presence of $[Met⁵]$ -enkephalin im-
munoreactivity in 18-day fetal tissue cultures of mouse
intestine (381) or $[Leu⁵]$ -enkephalin immunore Consistent with the presence of $[Met^3]$ -enkephalin im-
munoreactivity in 18-day fetal tissue cultures of mouse
intestine (381) or $[Leu^5]$ -enkephalin immunoreactivity
in human fetal intestinal tissue (248a), naloxone en-
 munoreactivity in 18-day fetal tissue cultures of mouse
intestine (381) or [Leu⁶]-enkephalin immunoreactivity
in human fetal intestinal tissue (248a), naloxone en-
hanced the peristalsis of fetal and adult intestinal seg intestine (381) or [Leu^s]-enkephalin immunoreactivity
in human fetal intestinal tissue (248a), naloxone en-
hanced the peristalsis of fetal and adult intestinal seg-
ments to the same degree (231). However, naloxone
indu in human fetal intestinal tissue (248a), naloxone
hanced the peristalsis of fetal and adult intestinal s
ments to the same degree (231). However, nalox
induced an opiate withdrawal-like contracture (see
387) in longitudina hanced the peristalsis of fetal and adult intestinal segments to the same degree (231). However, naloxone induced an opiate withdrawal-like contracture (see ref. 387) in longitudinal muscle myenteric plexus preparations ta ments to the same degree (231). However, naloxone induced an opiate withdrawal-like contracture (see ref. 387) in longitudinal muscle myenteric plexus preparations taken from fetuses just prior to parturition, but signific induced an opiate withdrawal-like contracture (see ref. cent
387) in longitudinal muscle myenteric plexus prepara-after
tions taken from fetuses just prior to parturition, but (234
significantly less so in preparations tak

dently of a functional nature (physiological antagonism), opioids produce some degree of intestinal opioid depend-
being not inconsistent with a specific blockade of opioid ence. This was the first time that an indication ER
parturition, either pituitary (229, 73) or gastrointestin
opioids produce some degree of intestinal opioid depen ER
parturition, either pituitary (229, 73) or gastrointesti
opioids produce some degree of intestinal opioid depen
ence. This was the first time that an indication of ER
parturition, either pituitary (229, 73) or gastrointestinal
opioids produce some degree of intestinal opioid depend-
ence. This was the first time that an indication of de-
pendence on the body's own opioids had been de parturition, either pituitary (229, 73) or gastrointestic opioids produce some degree of intestinal opioid depenence. This was the first time that an indication of ependence on the body's own opioids had been demonstrated opioids produce some degree of intestinal opioid dependopioids produce some degree of intestinal opioid depend
ence. This was the first time that an indication of de
pendence on the body's own opioids had been demon
strated (241). The transient withdrawal phenomenon
may have b ence. This was the first time that an indication of dependence on the body's own opioids had been demonstrated (241). The transient withdrawal phenomenon may have been missed under conditions of reflex peristaltis, when th strated (241). The transient withdrawal phenomenon
may have been missed under conditions of reflex peri-
staltis, when the segments were preexposed to naloxone
(231). Interestingly, Ryan et al. (362) recently found a
reduc staltis, when the segments were preexposed to naloxone may have been missed under conditions of reflex peristaltis, when the segments were preexposed to naloxone (231). Interestingly, Ryan et al. (362) recently found a reduction in gastric emptying in pregnant guinea-pigs up t staltis, when the segments were preexposed to naloxone (231). Interestingly, Ryan et al. (362) recently found a reduction in gastric emptying in pregnant guinea-pigs up to 4 days after parturition. Although these authors d (231). Interestingly, Ryan et al. (362) recently found a reduction in gastric emptying in pregnant guinea-pigs up
to 4 days after parturition. Although these authors did
not introduce naloxone in order to search for a poss reduction in gastric emptying in pregnant guinea-pigs up
to 4 days after parturition. Although these authors did
not introduce naloxone in order to search for a possible
inhibitory role of endogenous opioids, this may be a inhibitory role of endogenous opioids, this may be a
reasonable explanation which should be further explored.
4. The contribution of opioids to peristalsis. The acute

inhibitory role of endogenous opioids, this may be a
reasonable explanation which should be further explored.
4. The contribution of opioids to peristalsis. The acute
effect of naloxone on in vitro peristalsis consisted of reasonable explanation which should be further explored.
4. The contribution of opioids to peristalsis. The acute
effect of naloxone on in vitro peristalsis consisted of,
alternately or simultaneously, (a) an increase in 4. The contribution of opioids to peristalsis. The acute
effect of naloxone on in vitro peristalsis consisted of,
alternately or simultaneously, (a) an increase in duration
of individual periods of rhythmic peristaltic a alternately or simultaneously, (a) an increase in duration
of individual periods of rhythmic peristaltic activity in-
duced by distension of the intestinal wall, (b) termination
of the current peristalsis-free interval, of individual periods of rhythmic peristaltic activity in-
duced by distension of the intestinal wall, (b) termination
of the current peristalsis-free interval, if administered at
that time, (c) shortening of the subseq of individual periods of rhythmic peristaltic activity in duced by distension of the intestinal wall, (*b*) termination of the current peristalsis-free interval, if administered a that time, (*c*) shortening of the subsequ duced by distension of the intestinal wall, (b) termination of the current peristalsis-free interval, if administered at that time, (c) shortening of the subsequent peristalsis-free intervals, and (d) increase in the f of the current peristalsis-free interval, if administered that time, (c) shortening of the subsequent peristal free intervals, and (d) increase in the frequency of p staltic waves within periods of peristaltic activity that time, (c) shortening of the subsequent peristalsis-
free intervals, and (d) increase in the frequency of peri-
staltic waves within periods of peristaltic activity (233).
All of these changes resulted eventually in an free intervals, and (d) increase in the frequency of peristaltic waves within periods of peristaltic activity (233) .
All of these changes resulted eventually in an enhancement of overall peristalsis. The volume expelle staltic waves within periods of peristaltic activity (23
All of these changes resulted eventually in an enhancent of overall peristalsis. The volume expelled by sin
peristaltic waves was not significantly altered. The
endo All of these changes resulted eventually in an enhancement of overall peristalsis. The volume expelled by single peristaltic waves was not significantly altered. Thus, endogenous opioids appear to participate, in an inhibi ment of overall peristalsis. The volume experied by slight
peristaltic waves was not significantly altered. Thus,
endogenous opioids appear to participate, in an inhibi-
tory fashion, in the control of periodicity of peris entugenous optotus appear to participate, in an innot-
tory fashion, in the control of periodicity of peristalsis.
The latter might be achieved by superimposition of spon-
taneous rhythmic fluctuations of the smooth muscle The latter might be achieved by superimposition of spontaneous rhythmic fluctuations of the smooth muscle membrane potential ("slow waves" or "slow potentials," depending on the species; 30, 337) and neuronal reflex activi taneous rhythmic fluctuations of the smooth muscle
membrane potential ("slow waves" or "slow potentials,"
depending on the species; 30, 337) and neuronal reflex
activity. The effects of naloxone on both fetal and adult
in membrane potential ("slow waves" or "slow potential
depending on the species; 30, 337) and neuronal ref
activity. The effects of naloxone on both fetal and ad
intestinal tissues were stereospecific and observed at l
concen depending on the species; 30, 337) and neuronal reflex
activity. The effects of naloxone on both fetal and adult
intestinal tissues were stereospecific and observed at low
concentrations (~100 nmol/liter), which makes nons activity. The effects of naloxone on both fetal and adult
intestinal tissues were stereospecific and observed at low
concentrations (~100 nmol/liter), which makes nonspe-
cific actions extremely unlikely. A possible modula mestinal ussues were stereospectic and observed at
concentrations $(-100 \text{ nmol/liter})$, which makes nons
cific actions extremely unlikely. A possible modulat
of mechanoreceptor sensitivity (318) by opioids can
be ruled out as t concentrations (-100 mno) hear), which makes honspecific actions extremely unlikely. A possible modulation of mechanoreceptor sensitivity (318) by opioids cannot be ruled out as they increased the threshold of intralu of mechanoreceptor sensitivity (318) by opioids cannot
be ruled out as they increased the threshold of intralu-
minal pressure in the rat ileum necessary to elicit a
decrease in systemic blood pressure. This effect of co-
 or mechanoreceptor sensitivity (316) by opiods cannot
be ruled out as they increased the threshold of intralu-
minal pressure in the rat ileum necessary to elicit a
decrease in systemic blood pressure. This effect of co-
d be ruled out as they increased the threshold of intralu-
minal pressure in the rat ileum necessary to elicit a
decrease in systemic blood pressure. This effect of co-
deine was reduced by naloxone. It had an, albeit minor, minal pressure in the rat ileum necessary to elicit a decrease in systemic blood pressure. This effect of co-
deine was reduced by naloxone. It had an, albeit minor,
peripheral action component since bilateral vagotomy
inc deine was reduce

peripheral action

increased the refect (64).

5. Intramura ine was reduced by naloxone. It had an, albeit min
 ripheral action component since bilateral vagotor

creased the required codeine dose, but did not aboli
 i effect (64).

5. *Intramural location of the intestinal opi* peripheral action component since bilateral vagotom
increased the required codeine dose, but did not abolis
its effect (64).
5. Intramural location of the intestinal opioid mech
nism. Endogenous opioids most probably contr

Increased the required codeme dose, but did not aboutsh
its effect (64).
5. Intramural location of the intestinal opioid mecha-
nism. Endogenous opioids most probably control intes-
tinal peristalsis at the neuronal level. is enect (o_4).

5. Intramural location of the intestinal opioid mecha-

nism. Endogenous opioids most probably control intes-

tinal peristalsis at the neuronal level. An excitatory

influence of naloxone on distension nism. Endogenous opioids most probably control intestinal peristalsis at the neuronal level. An excitatory influence of naloxone on distension-induced peristalsis is blocked by TTX, hexamethonium, atropine, and desensitiza tinal peristalsis at the neuronal level. An excitatory influence of naloxone on distension-induced peristalsis is blocked by TTX, hexamethonium, atropine, and desensitization of the intestinal segments to serotonin (236) w (236) which is consistent with, but not final proof of, a is blocked by TTX, hexamethonium, atropine, and desensitization of the intestinal segments to serotonin (236) which is consistent with, but not final proof of, a neuronal site of opioid action. A considerably lower concent sensitization of the intestinal segments to serotonin (236) which is consistent with, but not final proof of, a neuronal site of opioid action. A considerably lower concentration of naloxone is needed to enhance peristalsi (236) which is consistent with, but not final proof of, a
neuronal site of opioid action. A considerably lower con-
centration of naloxone is needed to enhance peristalsis
after application to the serosal than to the mucos neuronal site of opioid action. A considerably lower contration of naloxone is needed to enhance perista after application to the serosal than to the mucosal s (234) which may point to a specific role of the myenta versus centration of naloxone is needed to enhance peristalsis
after application to the serosal than to the mucosal side
(234) which may point to a specific role of the myenteric
versus the submucosal plexus. Interestingly, normo

OPIOIDS AND CONTROL OF GASTROINTESTINAL MOTILITY AND SECRETION ¹²⁷

OPIOIDS AND CONTROL OF GASTROINT

oxone concentration dependently enhanced, rhythmic

peristaltic activity not only when induced by distension OPIOIDS AND CONTROL OF GASTROINT

peristaltic activity not only when induced by distension

of the intestinal wall (reflex peristalsis), but also p OPIOIDS AND CONTROL OF GASTROINTEST
oxone concentration dependently enhanced, rhythmic sien
peristaltic activity not only when induced by distension [Microsofthe intestinal wall (reflex peristalsis), but also pre
rhythmic oxone concentration dependently enhanced, rhythmic
peristaltic activity not only when induced by distension
of the intestinal wall (reflex peristalsis), but also
rhythmic propulsive activity elicited by exogenous ace-
tylc peristaltic activity not only when induced by distension
of the intestinal wall (reflex peristalsis), but also
rhythmic propulsive activity elicited by exogenous ace-
tylcholine (236). This acetylcholine effect was TTX sen of the intestinal wall (reflex peristalsis), but also of the intestinal wall (reflex peristalsis), but also
rhythmic propulsive activity elicited by exogenous ace-
tylcholine (236). This acetylcholine effect was TTX sen-
sitive. Therefore, most likely opioid receptors and end rhythmic propulsive activity encited by exogenous ace-
tylcholine (236). This acetylcholine effect was TTX sen-
sitive. Therefore, most likely opioid receptors and endog-
enous opioids also modulate, in addition to its rel sitive. Therefore, most likely opioid receptors and end
enous opioids also modulate, in addition to its releathe action of acetylcholine during induction of perista
activity. Kilbinger and Wessler (205) found that simi
con enous opioids also modulate, in addition to its release the action of acetylcholine during induction of peristal
activity. Kilbinger and Wessler (205) found that simile concentrations of acetylcholine inhibited the stimult the action of acetylcholine during induction of peristals activity. Kilbinger and Wessler (205) found that simil concentrations of acetylcholine inhibited the stimultion-evoked release of [³H] acetylcholine from the myet activity. Knolliger and Wessler (200) found that simm
concentrations of acetylcholine inhibited the stimu
tion-evoked release of [³H]acetylcholine from the my
teric plexus. It is therefore unlikely that, in the expe
ment concentrations of accelydromic inholecul the summation-evoked release of [³H]acetylcholine from the myenteric plexus. It is therefore unlikely that, in the experiments of Kromer and Schmidt (236), exogenous acetylcholine tion-evoked release of [³H]acetylcholine from the myentaric plexus. It is therefore unlikely that, in the experiments of Kromer and Schmidt (236), exogenous acetyl-
choline induced additional release of endogenous (acety teric plexus. It is therefore unlikely that, in the experi-
ments of Kromer and Schmidt (236), exogenous acetyl-
choline induced additional release of endogenous (1-
acetylcholine, which release might have been modulated c inents of Kromer and Scimiat (250), exogenous accety-
choline induced additional release of endogenous
acetylcholine, which release might have been modulated
by opioid receptors. A ganglionic postsynaptic opioid
inhibition acetylcholine, which release might have been modulated chy opioid receptors. A ganglionic postsynaptic opioid thin
thibition of neurotransmission in this tissue is consistent with recent data of Beleslin et al. (17) showin by opiola receptors. A ganglionic postsynaptic op
inhibition of neurotransmission in this tissue is consent with recent data of Beleslin et al. (17) showing to
opioid inhibition of peristalsis in the isolated guinea
ileum tion. t with recent data of Beleslin et al. (17) showing that leavied inhibition of peristalsis in the isolated guinea-pig ap ap um is not overcome by nicotinic ganglionic stimula-
m.
Paton (325) and Schaumann (374) found no opi

opioid inhibition of peristalsis in the isolated guinea-pig aptileum is not overcome by nicotinic ganglionic stimula-
tion.
Paton (325) and Schaumann (374) found no opioid wise
influence on the longitudinal contraction eff ileum is not overcome by nicotinic ganglionic stimulation.

Paton (325) and Schaumann (374) found no opioid

influence on the longitudinal contraction effected by

exogenous acetylcholine in the isolated guinea-pig ileum.
 where the method is an extending the method influence on the longitudinal contraction effected by exogenous acetylcholine in the isolated guinea-pig ileum. picked at are not inconsistent with opioid inhibition of acetylcho Paton (325) and Schaumann (374) found no opioid
influence on the longitudinal contraction effected by
exogenous acetylcholine in the isolated guinea-pig ileum.
These data are not inconsistent with opioid inhibition of
acet influence on the longitudinal contraction effected by enexogenous acetylcholine in the isolated guinea-pig ileum. pli
These data are not inconsistent with opioid inhibition of accetylcholine-induced peristalsis, since both exogenous acetylcholine in
These data are not inconsi
acetylcholine-induced peri
preparations display comp
to their distinct structures
6. Opioid tolerance/deper **Example 16. Example 16. Example 16. Example 16. Example 16. Example 16. Consistent functions** their distinct structures.
 6. *Opioid tolerance/dependence and intestinal peristals.* Consistent with the above

accelyichome-maded peristalsis, since toth messinal
preparations display completely different functions due
to their distinct structures.
6. Opioid tolerance/dependence and intestinal peristal-
sis. Consistent with the abo preparations display completely different functions d
to their distinct structures.
6. Opioid tolerance/dependence and intestinal peristals.
sis. Consistent with the above interpretation, sensitivi
of the peristaltic refle to their distinct structures.
6. Opioid tolerance/dependence and intestinal pesis. Consistent with the above interpretation, sense
of the peristaltic reflex in the intact segment to a
nous acetylcholine was increased in th of consistent with the above interpretation, sensitividents and the period of the peristaltic reflex in the intact segment to exognous acetylcholine was increased in the morphine-tolent state (239). By contrast, the opioid sis. Consistent with the above interpretation, sensitivity poor of the peristaltic reflex in the intact segment to exoge-
nous acetylcholine was increased in the morphine-toler-
nant state (239). By contrast, the opioid-to of the peristant ernex in the match segment to exoge-
nous acetylcholine was increased in the morphine-toler-
ant state (239). By contrast, the opioid-tolerant longi-
tudinal muscle myenteric plexus preparation has been
sh nous acetylcholine was increased in the morphine-toler-
ant state (239). By contrast, the opioid-tolerant longi-
tudinal muscle myenteric plexus preparation has been
shown to be supersensitive to serotonin, with unchanged
 ant state (239). By contrast, the opioid-tolerant longitudinal muscle myenteric plexus preparation has been
shown to be supersensitive to serotonin, with unchanged
sensitivity to acetylcholine (142, 386). Thus, peristalsis tudinal muscle myenteric plexus preparation has been
shown to be supersensitive to serotonin, with unchanged
sensitivity to acetylcholine (142, 386). Thus, peristalsis
is again distinguished from the longitudinal muscle co shown to be supersensitive to serotomin, with different densitivity to acetylcholine (142, 386). Thus, peristalsis the is again distinguished from the longitudinal muscle contraction, which is not a prerequisite of propuls is again distinguished from the longitudinal muscle contraction, which is not a prerequisite of propulsive circular muscle contraction (221). Opioid withdrawal in the guinea-pig ileum in vitro results in a dramatic increas traction, which is not a prerequisite of propulsive circular muscle contraction (221) . Opioid withdrawal in the guinea-pig ileum in vitro results in a dramatic increase of peristaltic waves per min (242) , suggesting t diarrhea. inea-pig ileum in vitro results in a dramatic increaser-
peristaltic waves per min (242), suggesting that enced motility plays a significant role in withdraw
arrhea.
Supersensitivity to acetylcholine in the opioid-tolerant

of peristance waves per $\lim_{z \to z} (z + z)$, suggesting that en-
hanced motility plays a significant role in withdrawal
diarrhea.
Supersensitivity to acetylcholine in the opioid-tolerant
state of the intact intestinal segment hanced motility plays a significant role in withdrawal
diarrhea.
Supersensitivity to acetylcholine in the opioid-tolerant
state of the intact intestinal segment (see above) is just
one aspect of opioid tolerance. For a rev diarrhea.

Supersensitivity to acetylcholine in the opioid-tolerant

state of the intact intestinal segment (see above) is just

one aspect of opioid tolerance. For a review of recent

developments in this field, see Wüste Supersensitivity to acetylcholine in the opioid-toleran state of the intact intestinal segment (see above) is jumore aspect of opioid tolerance. For a review of recendevelopments in this field, see Wüster et al. (488). sho state of the mact mestinal segment (see above) is just agone aspect of opioid tolerance. For a review of recent cendevelopments in this field, see Wüster et al. (488). It should be noted in this context that elevations in developments in this field, see Wüster et al. (488). It should be noted in this context that elevations in intes-
tinal tissue levels of distinct endogenous opioids brought tive
about by both single (388) and chronic (312) should be noted in this context that elevations in intes-
tinal tissue levels of distinct endogenous opioids brought
tive about by both single (388) and chronic (312) opioid nec
treatment indicate feedback and homeostatic tinal tissue levels of distinct endogenous opioids brought tive about by both single (388) and chronic (312) opioid netreatment indicate feedback and homeostatic opioid to mechanisms in the guinea-pig ileum. These app about by both single (388) and chronic (312) opioid
treatment indicate feedback and homeostatic opioid
mechanisms in the guinea-pig ileum. These appear to be
complex, since morphine reduced the electrically evoked
rel treatment indicate feedback and homeostatic opioid to
mechanisms in the guinea-pig ileum. These appear to be ity
complex, since morphine reduced the electrically evoked va
release of [Met⁵]-enkephalin from the guinea-pig mechanisms in the guinea-pig ileum. These appear to b
complex, since morphine reduced the electrically evoke
release of [Met⁵]-enkephalin from the guinea-pig myen
teric plexus in vitro (137), whereas this release from th

siently dependent on morphine (134). Subsequently,
[Met⁵]-enkephalin release from the morphine-withdrawn ESTINAL MOTILITY AND SECRETION 12
siently dependent on morphine (134). Subsequently
[Met⁵]-enkephalin release from the morphine-withdrawn
preparation was enhanced but again inhibited by reex PESTINAL MOTILITY AND SECRETION 12
siently dependent on morphine (134). Subsequently
[Met⁵]-enkephalin release from the morphine-withdrawn
preparation was enhanced but again inhibited by reex-
posure to morphine (134). T siently dependent on morphine (134). Subsequently,
[Met⁵]-enkephalin release from the morphine-withdrawn
preparation was enhanced but again inhibited by reex-
posure to morphine (134). The number of opioid spare
receptor (61). preparation was emianted out again immoted by reex-
posure to morphine (134). The number of opioid spare
receptors was decreased in the morphine-tolerant state
(61).
7. *Involvement of calcium in the opioid action; electro*

teceptors was decreased in the morphine-colerant state
(61).
7. Involvement of calcium in the opioid action; electro-
physiological data. Opioids have been shown to increase
the calcium-dependent potassium conductance and, (31). The interpret of calcium in the opioid action; electro-
physiological data. Opioids have been shown to increase
the calcium-dependent potassium conductance and, thus,
to hyperpolarize myenteric neurons (304, 306, 30 physiological data. Opiolos have been shown to increase
the calcium-dependent potassium conductance and, thus,
to hyperpolarize myenteric neurons (304, 306, 305, 291,
292). In addition, they reduce the entry of calcium dur the calcium-dependent potassium conductance and, thus,
to hyperpolarize myenteric neurons (304, 306, 305, 291,
292). In addition, they reduce the entry of calcium during
the action potential (162, 307, 286, 473), displace 292). In addition, they reduce the entry of calcium during
the action potential (162, 307, 286, 473), displace calcium
bound with high affinity to synaptosomal membranes
(148, 149), and deplete rat cerebral synaptosomes of bound with high affinity to synaptosomal membranes (148, 149), and deplete rat cerebral synaptosomes of calcium in a naloxone-blockable fashion (54). The relationship between these effects is not vet clear, but they bound with ingh arminy to synaptosomal membranes
(148, 149), and deplete rat cerebral synaptosomes of
calcium in a naloxone-blockable fashion (54). The rela-
tionship between these effects is not yet clear, but they
may co (146, 149), and deplete fat cerebral synaptosomer
calcium in a naloxone-blockable fashion (54) . The r
tionship between these effects is not yet clear, but t
may correspond to both inhibition of acetylcholine
lease from calcium in a naloxone-blockable fashion (54). The relationship between these effects is not yet clear, but they may correspond to both inhibition of acetylcholine release from myenteric nerve terminals and its postsynaptic that the may correspond to both inhibition of acetylcholine re-
lease from myenteric nerve terminals and its postsyn-
aptic action. In fact, Kromer et al. (235) demonstrated
that enhancement of peristalsis by naloxone decl may correspond to both inhibition of acetylcholine release from myenteric nerve terminals and its postsyn
aptic action. In fact, Kromer et al. (235) demonstrate
that enhancement of peristalsis by naloxone decline
when the rease from myenteric nerve terminals and its postsyle applic action. In fact, Kromer et al. (235) demonstrate
that enhancement of peristalsis by naloxone decline
when the extracellular calcium concentration was stee
wise i aptic action. In fact, Kromer et al. (235) demonstrated
that enhancement of peristalsis by naloxone declined
when the extracellular calcium concentration was step-
wise increased. A similar depression of excitatory influ-
 plication (235), which enhances the transport of calcium concentration was stepwise increased. A similar depression of excitatory influence by naloxone was found upon 4-aminopyridine application (235), which enhances the catetium in a niauxonie-to-because and the particulation of the relation of a contractionship between these effects is not yet clear, but they may correspond to both inhibition of acetylcholine release from myenteric nerv ence by haloxone was found upon 4-aminopyriume ap-
plication (235), which enhances the transport of calcium
across nerve terminal membranes (195, 262, 189). As was
to be expected, the inhibitory actions of morphine and
of across nerve terminal membranes (195, 262, 189). As was
to be expected, the inhibitory actions of morphine and
of the alpha₂-agonist, clonidine, were likewise reduced
by 4-aminopyridine (235). Since naloxone probably mir be expected, the nimbolity actions of morphine and
of the alpha₂-agonist, clonidine, were likewise reduced
by 4-aminopyridine (235). Since naloxone probably mir-
rors the action of endogenous opioids, these results supby 4-aminopyridine (235). Since naloxone probably mirrors the action of endogenous opioids, these results support the notion that gastrointestinal opioids might inhibit acetylcholine release and thereby peristalsis at leas by 4-aminopyridine (235). Since naloxone probably mir-
rors the action of endogenous opioids, these results sup-
port the notion that gastrointestinal opioids might in-
hibit acetylcholine release and thereby peristalsis a rors the action of endogenous opioids, these results support the notion that gastrointestinal opioids might in-
hibit acetylcholine release and thereby peristalsis at least
partially by decreasing the concentration of intr port the notion that gastroin
hibit acetylcholine release and
partially by decreasing the cor
free calcium at that particula
for stimulus-release coupling.
The data on intestinal peri mont acceylchomic release and thereby peristalsis at least
partially by decreasing the concentration of intracellular
free calcium at that particular site, where it is required
for stimulus-release coupling.
The data on in

free calcium at that particular site, where it is required
for stimulus-release coupling.
The data on intestinal peristalsis are consistent with
those on opioid inhibition of the electrically stimulated
longitudinal muscle In the data on intestinal peristalsis are consistent with
those on opioid inhibition of the electrically stimulated
longitudinal muscle contraction. This opioid effect was
attentuated by an increase in extracellular calciu those on opioid inhibition of the electrically stimulated
longitudinal muscle contraction. This opioid effect was
attentuated by an increase in extracellular calcium con-
centration (313, 314, 184, 185). Interestingly, hi attentuated by an increase in extracellular calcium concentration (313, 314, 184, 185). Interestingly, high-fre-
quency electrical stimulation of the guinea-pig ileum
longitudinal muscle myenteric plexus preparation reattentiated by an increase in extracemular catcium concentration (313, 314, 184, 185). Interestingly, high-frequency electrical stimulation of the guinea-pig ileum longitudinal muscle myenteric plexus preparation resulted quency electrical summation of the guinea-pig heum
longitudinal muscle myenteric plexus preparation re-
sulted in partially naloxone-sensitive inhibition of sub-
sequent low-frequency stimulated contractions. This in-
hibi congitualizat muscle inyenteric plexus preparation resulted in partially naloxone-sensitive inhibition of subsequent low-frequency stimulated contractions. This in hibition is probably caused by endogenous opioids and agai sulted in partially
sequent low-freque
hibition is probab.
again antagonized
centration (314).
8. The opioid m *8. Sequent low-frequency sumulated contractions.* This in-
 Abibition is probably caused by endogenous opioids and
 again antagonized by a rise in extracellular calcium con-
 centration (314).
 8. The opioid mechan

again antagonized by a rise in extracellular calcium contration (314).

8. The opioid mechanism and spontaneous neuro

activity. The proposed opioid neurons which are ope

tive in the gastrointestinal tract may be either s centration (314).
8. The opioid mechanism and spontaneous neuronal
activity. The proposed opioid neurons which are opera-
tive in the gastrointestinal tract may be either sponta-
neously active or driven by pacemaker neuro of the optom mechanism and spondineous neuron activity. The proposed opioid neurons which are oper
tive in the gastrointestinal tract may be either spont
neously active or driven by pacemaker neurons in ord
to suppress, pr tive in the gastromestinal tract may be either sponta-
neously active or driven by pacemaker neurons in order
to suppress, proximal to their location, peristaltic activ-
ity. This notion would be in agreement with the obse neously active or driven by pacemaker neurons in order
to suppress, proximal to their location, peristaltic activ-
ity. This notion would be in agreement with the obser-
vation of Daniel et al. (76a) that opioid neurons lo ity. This notion would be in agreement with the observation of Daniel et al. (76a) that opioid neurons located
in the canine myenteric plexus project orally. Moreover,
spontaneously active neurons of an unknown nature are

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of the intestinal wall by intestinal contents, this pro-

posed, spontaneously active inhibitory mechanism may RROMER
posed, spontaneously active inhibitory mechanism may see
become deactivated, freeing the circular muscle proximal typ kRC
of the intestinal wall by intestinal contents, this pro-
posed, spontaneously active inhibitory mechanism may
become deactivated, freeing the circular muscle proximal
to the distension stimulus from inhibition to produ of the intestinal wall by intestinal contents, this pro-
posed, spontaneously active inhibitory mechanism may s
become deactivated, freeing the circular muscle proximal to
to the distension stimulus from inhibition to prod posed, spontaneously active inhibitory mechanism may
become deactivated, freeing the circular muscle proximal
to the distension stimulus from inhibition to produce
propulsive contractions. Consistent with this hypothesis,
 posed, spontaneously active inhibitory mechanism may see become deactivated, freeing the circular muscle proximal type to the distension stimulus from inhibition to produce an propulsive contractions. Consistent with this become deactivated, freeing the circular muscle proximal
to the distension stimulus from inhibition to produce
propulsive contractions. Consistent with this hypothesis,
both [Met⁵]-enkephalin (63) and dynorphin (230) wer to the distension stimulus from inhibition to produce a
propulsive contractions. Consistent with this hypothesis, (to
both [Met⁵]-enkephalin (63) and dynorphin (230) were in
spontaneously released from resting intestinal propulsive contractions. Consistent with this hypothes
both [Met⁵]-enkephalin (63) and dynorphin (230) we
spontaneously released from resting intestinal segment
into the serosal bathing solution. This release decreas
dur both [Met⁵]-enkephalin (63) and dynorphin (230) were
spontaneously released from resting intestinal segments
into the serosal bathing solution. This release decreased
during reflex peristalsis. Kromer et al. (230) demoninto the serosal bathing solution. This release decreased
during reflex peristalsis. Kromer et al. (230) demon-
strated an inverse relationship between dynorphin re-
lease and peristaltic activity, which again supports the during reflex peristalsis. Kromer et al. (230) demon-
strated an inverse relationship between dynorphin re-
lease and peristaltic activity, which again supports the
indove hypothesis. It should be noted in this context tha strated an inverse relationship between dynorphin release and peristaltic activity, which again supports the above hypothesis. It should be noted in this context that the release of opioid-like material from the guinea-pig lease and peristaltic activity, which again supports the inhouse hypothesis. It should be noted in this context that is the release of opioid-like material from the guinea-pig temperature in the inconsistent with inhibito above hypothesis. It should be noted in this context that illumit the release of opioid-like material from the guinea-pig target impenteric plexus upon electrical stimulation (392) is not long inconsistent with inhibiton o the release of opioid-like material from the guinea-pig tamyenteric plexus upon electrical stimulation (392) is not louronsistent with inhibiton of spontaneous dynorphin favorelease upon activation of peristaltic reflex ac

myenteric plexus upon electrical stimulation (392) is not
inconsistent with inhibiton of spontaneous dynorphin
release upon activation of peristaltic reflex activity. The
electrical stimulus probably depolarizes the vast m inconsistent with inhibiton of spontaneous dy
release upon activation of peristaltic reflex active
lectrical stimulus probably depolarizes the vast
of axons and nerve terminals present in the tise
spective of their relativ electrical stimulus probably depolarizes the vast majority
of axons and nerve terminals present in the tissue, irre-
spective of their relative functional significance.
It is a matter of speculation whether dynorphin is
re of axons and nerve terminals present in the tissue, irre-
spective of their relative functional significance. The relative of speculation whether dynorphin is plus
released to different sides under different conditions be
 spective of their relative functional significance.

It is a matter of speculation whether dynorphin is

released to different sides under different conditions

from neurons and/or endocrine cells which may have

different It is a matter of speculation whether dynorphin is pleased to different sides under different conditions be
from neurons and/or endocrine cells which may have katedifferent functional significances. Thus, Donnerer et al. 1 released to different sides under different conditions
from neurons and/or endocrine cells which may have
different functional significances. Thus, Donnerer et al.
(89) found an increase in dynorphin release from isolated
 different functional significances. Thus, Donnerer et al.
(89) found an increase in dynorphin release from isolated
guinea-pig ileum during reflex peristalsis into the vas-
cular effluent of vascularly perfused segments.

The assumption that gastrointestinal opioids are involved in the control of gut motility and are subject to feedback control is once more underlined by recent find-(89) found an increase in dynorphin release from isolated vation is appropriate when extrapolating from one type
guinea-pig ileum during reflex peristalsis into the vas-
cular effluent of vascularly perfused segments.
The guinea-pig ileum during reflex peristalsis into the vascular effluent of vascularly perfused segments.
The assumption that gastrointestinal opioids are involved in the control of gut motility and are subject to feedback co cular effluent of vascularly perfused segments. The assumption that gastrointestinal opioids are in-
volved in the control of gut motility and are subject to 11
feedback control is once more underlined by recent find-
a The assumption that gastrointestinal opioids are ivolved in the control of gut motility and are subject feedback control is once more underlined by recent fings of Glass et al. (137) . They reported an increase spontaneo volved in the control of gut motility and are subject to
feedback control is once more underlined by recent find-
alings of Glass et al. (137). They reported an increase in of:
spontaneous [Met⁵]-enkephalin release from feedback control is once more underlined by recent find-
ings of Glass et al. (137). They reported an increase in
spontaneous [Met⁵]-enkephalin release from the guinea-
opig myenteric plexus in vitro upon stereospecific ings of Glass et al. (137). They reported an increase in contained spontaneous [Met⁵]-enkephalin release from the guinea-
pig myenteric plexus in vitro upon stereospecific opioid preceptor blockade by naloxone. Stimulate spontaneous [Met⁵]-enkephalin release from the guinea-
pig myenteric plexus in vitro upon stereospecific opioid
receptor blockade by naloxone. Stimulated release was
seeduced by morphine. Spontaneous release of dynorphin pig myenteric plexus in vitro upon stereospecific opioid
receptor blockade by naloxone. Stimulated release was
reduced by morphine. Spontaneous release of dynorphin
from the isolated intact guinea-pig ileum, however, was
n receptor blockade by naloxone. Stimulated release was
reduced by morphine. Spontaneous release of dynorphin
from the isolated intact guinea-pig ileum, however, was
not enhanced by naloxone (230), suggesting a more sig-
nif reduced by morphine
from the isolated int
not enhanced by nal
nificant role of reflex
as discussed above.
9. Distribution of t 9. It enhanced by naloxone (230), suggesting a more sigment role of reflex mechanisms under these conditions discussed above.

9. *Distribution of the opioid mechanism over the intes*

19. *Distribution of the opioid mecha*

not enhanced by naloxone (230), suggesting a more sig-

inficant role of reflex mechanisms under these conditions

as discussed above.

9. Distribution of the opioid mechanism over the intes-

how

throughout the gut. Surp mificant role of reflex mechanisms under these conditions
as discussed above.
9. Distribution of the opioid mechanism over the intes-
time. The intestinal opioid mechanism operates in vitro
southroughout the gut. Surprisin event is a discussed above. The opioid mechanism over the intes-
influence. The intestinal opioid mechanism operates in vitro
influence of naloxone, its functional role increases from depend
the duodenum to the ileum (234) 9. Distribution of the opioid mechanism over the intes-
tine. The intestinal opioid mechanism operates in vitrosom
throughout the gut. Surprisingly, as judged from the prol
influence of naloxone, its functional role incre tine. The intestinal opioid mechanism operates in vitro
throughout the gut. Surprisingly, as judged from the
influence of naloxone, its functional role increases from
the duodenum to the ileum (234). This contrasts with an influence of naloxone, its functional role increases from dependent on their length preceding drug application
the duodenum to the ileum (234). This contrasts with an (243) . An assessment of the functional significance influence of naloxone, its functional role increases from
the duodenum to the ileum (234) . This contrasts with an
earlier report showing that opioids are at their highest
concentration in the duodenum (417) . However, the duodenum to the ileum (234). This contrasts with an (earlier report showing that opioids are at their highest econcentration in the duodenum (417). However, a high doncentration may well correspond to a low functional earlier report showing that opioids are at their highe
concentration in the duodenum (417). However, a higeoncentration may well correspond to a low function
significance of that pool. The gradient in the excitato:
influen concentration in the duodenum (417). However, a high
concentration may well correspond to a low functional
significance of that pool. The gradient in the excitatory
influence of naloxone, which probably mirrors an inhib-
i concentration may well correspond to a low functional designificance of that pool. The gradient in the excitatory sm
influence of naloxone, which probably mirrors an inhibcatory role of endogenous opioids, from oral to abo influence of naloxone, which probably mirrors an inhibitory role of endogenous opioids, from oral to aboral
might partially explain the well-known "gradient of the
intestine" (8, 446). This gradient describes the phenom-
e itory role of endogenous opioids, from oral to aboral both conditions, however, dynorphin increased the fremight partially explain the well-known "gradient of the quency of spontaneous action potentials of smooth musintest itory role of endogenous opioids, from oral to abomight partially explain the well-known "gradient of t intestine" (8, 446). This gradient describes the phenomenon, from oral to aboral, of decreasing frequency peristaltic might partially
intestine" (8, 4
penon, from or
peristaltic wav
sion stimulus.
10. Involven Investine (8, 440). I his gradient describes the phenom-

enon, from oral to aboral, of decreasing frequency of

peristaltic waves and decreasing sensitivity to the disten-

sion stimulus.

10. Involvement of different opi

spontaneously released from resting intestinal segments of intestinal peristalsis in the intact segment. The differinto the serosal bathing solution. This release decreased ence between the electrically stimulated longitud release upon activation of peristaltic reflex activity. The rhythmic peristaltic contractions elicited by acetylcho-
electrical stimulus probably depolarizes the vast majority line (240). N-Allyl-normetazocine shifted the ER
and kappa-types, have been distinguished (for review,
see refs. 487, 324, 494, and 323) and mu- and kappa-ER
and kappa-types, have been distinguished (for revie
see refs. 487, 324, 494, and 323) and mu- and kapp
types identified in the guinea-pig ileum circular (197 The guine of the guinear sets and kappa-types, have been distinguished (for review, see refs. 487, 324, 494, and 323) and mu- and kappa-types identified in the guinea-pig ileum circular (197a) and longitudinal muscle myent and kappa-types, have been distinguished (for review, see refs. 487, 324, 494, and 323) and mu- and kappa-types identified in the guinea-pig ileum circular (197a) and longitudinal muscle myenteric plexus preparation (60, 3 and kappa-types, have been distinguished (for review, see refs. 487, 324, 494, and 323) and mu- and kappa-types identified in the guinea-pig ileum circular (197a) and longitudinal muscle myenteric plexus preparation (60, 3 see refs. 487, 324, 494, and 323) and mu- and kappa-
types identified in the guinea-pig ileum circular (197a)
and longitudinal muscle myenteric plexus preparation
(60, 391, 492, 436, 463), little is known about the relativ types identified in the guinea-pig ileum circular (197 and longitudinal muscle myenteric plexus preparation (60, 391, 492, 436, 463), little is known about the relation
importance of the different receptor types in the con and longitudinal muscle myenteric plexus preparation (60, 391, 492, 436, 463), little is known about the relative importance of the different receptor types in the control of intestinal peristalsis in the intact segment. T $(60, 391, 492, 436, 463)$, little is known about the relative importance of the different receptor types in the control of intestinal peristalsis in the intact segment. The difference between the electrically stimulated importance of the different receptor types in the control
of intestinal peristalsis in the intact segment. The differ-
ence between the electrically stimulated longitudinal
muscle myenteric plexus preparation, which is wid of intestinal peristalsis in the intact segment. The difference between the electrically stimulated longitudinal muscle myenteric plexus preparation, which is widely used for investigations on opioid receptor types, and th used for investigations on opioid receptor types, and the muscle myenteric plexus preparation, which is widely
used for investigations on opioid receptor types, and the
intact segment which displays reflex peristalsis is best
illustrated by the differential effects of N-allyl-nor used for investigations on opioid receptor types, and the intact segment which displays reflex peristalsis is best illustrated by the differential effects of N-allyl-norme-
tazocine (SKF 10.047). This opioid alkaloid inhib intact segment which displays reflex peristalsis is best
illustrated by the differential effects of N-allyl-norme-
tazocine (SKF 10.047). This opioid alkaloid inhibited the
longitudinal muscle contraction in a naloxone rev illustrated by the differential effects of N-allyl-nor-
tazocine (SKF 10.047). This opioid alkaloid inhibited
longitudinal muscle contraction in a naloxone revers
fashion, but enhanced both reflex peristalsis
rhythmic peri tazocine (SKF 10.047). This opioid alkaloid inhibited
longitudinal muscle contraction in a naloxone revers
fashion, but enhanced both reflex peristalsis
rhythmic peristaltic contractions elicited by acetyle
line (240). N-A longitudinal muscle contraction in a naloxone reversible
fashion, but enhanced both reflex peristalsis and
rhythmic peristaltic contractions elicited by acetylcho-
line (240). N-Allyl-normetazocine shifted the concentra-
t fashion, but enhanced both reflex peristalsis and
rhythmic peristaltic contractions elicited by acetylcho-
line (240). N-Allyl-normetazocine shifted the concentra-
tion-response curve of the mu-agonist normorphine, with
re rhythmic peristaltic contractions elicited by acetylcholine (240). N-Allyl-normetazocine shifted the concentration-response curve of the mu-agonist normorphine, with respect to inhibition of peristalsis, to the right. It d line (240). N-Allyl-normetazocine shifted the concentra-
tion-response curve of the mu-agonist normorphine, with
respect to inhibition of peristalsis, to the right. It dis-
played high affinity to opioid mu-receptors (485) tion-response curve of the mu-agonist normorphine, with
respect to inhibition of peristalsis, to the right. It dis-
played high affinity to opioid mu-receptors (485) and has
been proposed from in vivo studies to block mu respect to inhibition of peristalsis, to the right. It displayed high affinity to opioid mu-receptors (485) and have been proposed from in vivo studies to block mu- an kappa-receptors but to activate sigma-receptors (27.19 played high affinity to opioid mu-receptors (485) and has
been proposed from in vivo studies to block mu- and
kappa-receptors but to activate sigma-receptors (274,
194, 407). This example clearly shows that some reser-
vat been proposed from in vivo statues to block mu- and kappa-receptors but to activate sigma-receptors (274, 194, 407). This example clearly shows that some reservation is appropriate when extrapolating from one type of guine 194, 407). This example clearly shows that some reservation is appropriate when extrapolating from one type of guinea-pig ileum preparation to another, with both respect to receptor populations and presynaptic versus posts of guinea-pig ileum preparation to another, with both respect to receptor populations and presynaptic versus

al. (297) demonstrated a dual excitatory-inhibitory effect
of naloxone on both spontaneous and electrically induced
contractions even within the same test model (guineapostsynaptic actions.

11. Dual intestinal opioid effects in vitro. Nakayama

al. (297) demonstrated a dual excitatory-inhibitory eff

of naloxone on both spontaneous and electrically induc

contractions even within the sa 11. Dual intestinal opioid effects in vitro. Nakayama et al. (297) demonstrated a dual excitatory-inhibitory effect of naloxone on both spontaneous and electrically induced contractions even within the same test model (gui al. (297) demonstrated a dual excitatory-inhibitory effectof naloxone on both spontaneous and electrically induce
contractions even within the same test model (guinearing pig ileum in vitro). Although Kromer (unpublished o of naloxone on both spontaneous and electrically induced
contractions even within the same test model (guinea-
pig ileum in vitro). Although Kromer (unpublished ob-
servations) detected an increase in the duration of sponcontractions even within the same test model (guinea-
pig ileum in vitro). Although Kromer (unpublished ob-
servations) detected an increase in the duration of spon-
taneous peristalsis-free intervals in the intact guineapig ileum in vitro). Although Kromer (unpublished observations) detected an increase in the duration of spontaneous peristalsis-free intervals in the intact guinea-pig ileum upon naloxone application, such an inhibitory in bervations) detected an increase in the duration of spontaneous peristalsis-free intervals in the intact guinea-pig
ileum upon naloxone application, such an inhibitory
influence of naloxone on propulsive peristalsis, as op taneous peristalsis-free intervals in the intact guinea-pig
ileum upon naloxone application, such an inhibitory
influence of naloxone on propulsive peristalsis, as op-
posed to the usual excitatory effect, is an extremely ileum upon naloxone application, such an inhibitory
influence of naloxone on propulsive peristalsis, as op-
posed to the usual excitatory effect, is an extremely rare
event in the guinea-pig small intestine. In principle,
 influence of naloxone on propulsive peristalsis, as opposed to the usual excitatory effect, is an extremely rare event in the guinea-pig small intestine. In principle, however, this property of opioids reminds of that of s posed to the usual excitatory effect, is an extremely rare
event in the guinea-pig small intestine. In principle,
however, this property of opioids reminds of that of
somatostatin which, in the isolated guinea-pig ileum,
p event in the guinea-pig small intestine. In principle,
however, this property of opioids reminds of that of
somatostatin which, in the isolated guinea-pig ileum,
prolongs or shortens regular peristalsis-free intervals
depe mowever, this property of opiolal reminds of that of
somatostatin which, in the isolated guinea-pig ileum,
prolongs or shortens regular peristalsis-free intervals
dependent on their length preceding drug application
(243). dependent on their length preceding drug application (243) . An assessment of the functional significance of electrophysiological data by Ohkawa (309) is even more electrophysiological data by Ohkawa (309) is even more difficult, since dynorphin, in the guinea-pig duodenum, decreased the amplitude of inhibitory potentials of smooth muscle cells in the absence of atropine, but caused difficult, since dynorphin, in the guinea-pig duodenum, decreased the amplitude of inhibitory potentials of smooth muscle cells in the absence of atropine, but caused an increase in the presence of atropine. Under both con caused an increase in the presence of atropine. Under smooth muscle cells in the absence of atropine, but
caused an increase in the presence of atropine. Under
both conditions, however, dynorphin increased the fre-
quency of spontaneous action potentials of smooth mus-
cle ce caused an increase in the presence of atropine. Underboth conditions, however, dynorphin increased the frequency of spontaneous action potentials of smooth muscle cells. A dual opioid effect was also demonstrated in the is both conditions, however, dynorphin increased the frequency of spontaneous action potentials of smooth muscle cells. A dual opioid effect was also demonstrated in the isolated guinea-pig colon circular muscle, where morphi quency of spontaneous action potentials of smooth mus-
cle cells. A dual opioid effect was also demonstrated in
the isolated guinea-pig colon circular muscle, where mor-
phine reduced high spontaneous muscle tone, and in-
 cle cells. A dual opioid effect was also demonstrated in
the isolated guinea-pig colon circular muscle, where mor-
phine reduced high spontaneous muscle tone, and in-
creased muscle tone in a naloxone-reversible fashion
wh the isolated guinea-pig colon circular muscle, where morphine reduced high spontaneous muscle tone, and increased muscle tone in a naloxone-reversible fashion when the circular muscle had been relaxed beforehand by hyoscin

OPIOIDS AND CONTROL OF GASTR

opioid mechanisms appear to modulate intestinal motity

in vitro, although the inhibitory component clear OPIOIDS AND CONTROL OF GASTROINTES

opioid mechanisms appear to modulate intestinal motil-

ity in vitro, although the inhibitory component clearly

predominates in the guinea-pig.

in provid mechanisms appear to modulate intestinal motility in vitro, although the inhibitory component clearly predominates in the guinea-pig.
B. Comparison with in Vitro Data on Small Intestinal *B. Comparison with in Vitro Data on Small Intestinal mostly in vitro, although the inhibitory component clear-

<i>B. Comparison with in Vitro Data on Small Intestina*
 Motility from Rabbit, Rat, Cat, and Dog
 I. Rabbit.

1. Rabbit. The guinea-pig.
 1. Rabbit. There are only few reports on opioid effects

1. Rabbit. There are only few reports on opioid effects

1. Rabbit. There are only few reports on opioid effects

1. Yitro on intesti Einteed in view of the Same of B. Comparison with in Vitro Data on Small Intestinal

Motility from Rabbit, Rat, Cat, and Dog

1. Rabbit. There are only few reports on opioid effects

in vitro on intestinal peristalsis in s B. Comparison with in Vitro Data on Small Intestinal
Motility from Rabbit, Rat, Cat, and Dog
1. Rabbit. There are only few reports on opioid effects
in vitro on intestinal peristalsis in species other than the
guinea-pig. Motility from Rabbit, Rat, Cat, and Dog
1. Rabbit. There are only few reports on opioid effects
in vitro on intestinal peristalsis in species other than the
guinea-pig. In the rabbit isolated ileum, opioids inhibited,
and in vitro on intestinal peristalsis in species other than the guinea-pig. In the rabbit isolated ileum, opioids inhibited, and naloxone stereospecifically enhanced propulsive peristaltic contractions (232). In a large numbe guinea-pig. In the rabbit isolated ileum, opioids inhibited,
and naloxone stereospecifically enhanced propulsive per-
istaltic contractions (232). In a large number of experi-
ments, segmental contractions, which result in and naloxone stereospecifically enhanced propulsive per-
istaltic contractions (232). In a large number of experi-
ments, segmental contractions, which result in an un-
different experimental conditions (see section III D istaltic contractions (232). In a large number of experiments, segmental contractions, which result in an unsteady base line, disappeared upon induction of rhythmic propulsive contractions, and vice versa (Kromer, unpub-
l istaltic contractions (232). In a large number of experiments, segmental contractions, which result in an unsteady base line, disappeared upon induction of rhythmic propulsive contractions, and vice versa (Kromer, unpublis ments, segmental contractions, which result in an unsteady base line, disappeared upon induction of rhythmic propulsive contractions, and vice versa (Kromer, unpublished observations). These opioid effects have been essent steady base line, disappeared upon induction of rhythmic
propulsive contractions, and vice versa (Kromer, unpub-
lished observations). These opioid effects have been es-
sentially confirmed by Beleslin and Terzić (16). How propulsive contractions, and vice versa (Kromer, unpul
lished observations). These opioid effects have been e
sentially confirmed by Beleslin and Terzić (16). Howeve
the functional relationship of opioid-effected inhibitio lished observations). These opioid effects have been es-
sentially confirmed by Beleslin and Terzić (16). However,
the functional relationship of opioid-effected inhibition
of electrically induced contractions in the rabbi the functional relationship of opioid-effected inhibition
of electrically induced contractions in the rabbit longi-
tudinal muscle myenteric plexus preparation (310) to
inhibition of peristalsis is unknown.
2. Rat. Propuls e functional relationship of opioid-effected inhibition
electrically induced contractions in the rabbit longi-
dinal muscle myenteric plexus preparation (310) to
hibition of peristalsis is unknown.
2. *Rat.* Propulsive per

of electrically induced contractions in the rabbit longitudinal muscle myenteric plexus preparation (310) to inhibition of peristalsis is unknown.
2. Rat. Propulsive peristaltic contractions in the rat small intestine, as tudinal muscle myenteric plexus preparation (310) to cumhibition of peristalsis is unknown.

2. Rat. Propulsive peristaltic contractions in the rat moral intestine, as in the guinea-pig and rabbit intestine, viewere inh inhibition of peristalsis is unknown.

2. Rat. Propulsive peristaltic contractions in the small intestine, as in the guinea-pig and rabbit intestine

were inhibited by opioids in a stereospecific fashi

(232). Naloxone al 2. Rat. Propulsive peristaltic contractions in the rasmall intestine, as in the guinea-pig and rabbit intestine were inhibited by opioids in a stereospecific fashio. (232). Naloxone alone, in some of the segments, stimulat small intestine, as in the guinea-pig and rabbit intestine,
were inhibited by opioids in a stereospecific fashion
(232). Naloxone alone, in some of the segments, stimu-
lated peristalsis, which again suggests an inhibitory were inhibited by opioids in a stereospecific fashion p
(232). Naloxone alone, in some of the segments, stimulated peristalsis, which again suggests an inhibitory mod-
ulation of peristalsis by intestinal opioids. Dahl et (232). Naloxone alone, in some of the segments, stimu-
lated peristalsis, which again suggests an inhibitory mod-
ulation of peristalsis by intestinal opioids. Dahl et al.
(75) reported very recently that partial chemical lated peristalsis, which again suggests an inhibitory mod-
ulation of peristalsis by intestinal opioids. Dahl et al.
(75) reported very recently that partial chemical ablation
of myenteric neurons increased $[Leu⁵]$ -e ulation of peristalsis by intestinal opioids. Dahl et al. (75) reported very recently that partial chemical ablation of myenteric neurons increased [Leu⁶]-enkephalin concentrations in the rat jejunum. Thus, there may be (75) reported very recently
of myenteric neurons inc
centrations in the rat je
more than compensatory
in the surviving neurons.
3. Cat. In the cat isolar myenteric neurons increased [Leu⁶]-enkephalin con-
ntrations in the rat jejunum. Thus, there may be a
ore than compensatory increase in opioid biosynthesis
the surviving neurons.
3. *Cat*. In the cat isolated small inte

more than compensatory increase in opioid biosynthesis
in the surviving neurons.
3. Cat. In the cat isolated small intestine, Kromer et
al. (232) found both enhancement and inhibition of per-
istalsis by opioids as well more than compensatory increase in opioid biosynthesis white the surviving neurons.

3. Cat. In the cat isolated small intestine, Kromer et production of per-

al. (232) found both enhancement and inhibition of per-

ista in the surviving neurons.
 $3. \text{ Cat.}$ In the cat isolated small intestine, Kromer et production of per-

al. (232) found both enhancement and inhibition of per-

istalsis by opioids as well as by naloxone, the agonist an 3. Cat. In the cat isolated small intestine, Kromer et al. (232) found both enhancement and inhibition of peristalsis by opioids as well as by naloxone, the agonist and antagonist operating in an opposite manner in each si al. (232) found both enhancement and inhibition of periods as well as by naloxone, the agonist and determing in an opposite manner in each or single preparation. This dual effect of opioids may correspond to an increased, istalsis by opioids as well as by naloxone, the agonist and
antagonist operating in an opposite manner in each
single preparation. This dual effect of opioids may cor-
respond to an increased, decreased, or unchanged spike antagonist operating in an opposite manner in each
single preparation. This dual effect of opioids may cor-
respond to an increased, decreased, or unchanged spike
activity of extracellularly recorded cat myenteric neurons
 single preparation. This dual effect of opioids may correspond to an increased, decreased, or unchanged spike
activity of extracellularly recorded cat myenteric neurons
upon morphine application (97). Intracellular recordi respond to an increased, decreased, or unchanged spike
activity of extracellularly recorded cat myenteric neurons
upon morphine application (97). Intracellular recordings,
however, revealed naloxone-blockable hyperpolariza activity of extracellularly recorded cat myenteric neurons U . U
upon morphine application (97). Intracellular recordings, Dif
however, revealed naloxone-blockable hyperpolarization It
and suppression of current-evoke upon morphine application (97). Intracellular recordings, Dij
however, revealed naloxone-blockable hyperpolarization I
and suppression of current-evoked spike discharge of S/ stu
type 1 neurons by morphine (484), leading however, revealed naloxone-blockable hyperpolarization I
and suppression of current-evoked spike discharge of S/ stu
type 1 neurons by morphine (484), leading the author to inh
conclude that this reduced neuronal excitabil and suppression of current-evoked spike discharge of S/
type 1 neurons by morphine (484), leading the author to
conclude that this reduced neuronal excitability may be
the basis for induction of myogenic segmentations and
 type 1 neurons by morphine (484), leading the auth
conclude that this reduced neuronal excitability m
the basis for induction of myogenic segmentations
inhibition of neurogenic peristalsis with no specie
ferences observed conclude that this reduced neuronal excitability may be the basis for induction of myogenic segmentations and inhibition of neurogenic peristalsis with no species differences observed at least with respect to electrophysio the basis for induction of myogenic segmentations and opic
inhibition of neurogenic peristalsis with no species difcon-
ferences observed at least with respect to electrophysio-
interpolarization by interpolarization by io inhibition of neurogenic peristalsis with no species dif-
ferences observed at least with respect to electrophysio-
logical findings, even in comparison with the guinea-pig. The
It should be noted that uniform hyperpolariz ferences observed at least with respect to electrophysio-intestinal segment proximal to distension stimulus (234).
logical findings, even in comparison with the guinea-pig. The different parameters may represent distinct p differences. provides of either excitatory or inhibitory neurons may
well explain contrasting opioid effects and, thus, species
indifferences.
4. Dog. The dog isolated intestine might well be an
exception, since only induction by opio

well explain contrasting opioid effects and, thus, species
differences.
4. Dog. The dog isolated intestine might well be an
exception, since only induction by opioids and inhibition
by naloxone of in vitro peristalsis were differences. potential political intestine might well be an by-
exception, since only induction by opioids and inhibition
by naloxone of in vitro peristalsis were observed (232). and
These effects were again stereospecific 4. Dog. The dog isolated intestine might well be a
exception, since only induction by opioids and inhibition
by naloxone of in vitro peristalsis were observed (232)
These effects were again stereospecific. In a number c
ex These effects were again stereospecific. In a number of consistent with an inverse relationship between segerorients, on the other hand, opioids converted high-
frequency but low-amplitude propulsive contractions of sectio

the isolated dog small intestine into low-frequency but high-amplitude ones, possibly brought about by a shift ESTINAL MOTILITY AND SECRETION 129
the isolated dog small intestine into low-frequency but
high-amplitude ones, possibly brought about by a shift
in the time relationship of single contractions with sub-ESTINAL MOTILITY AND SECRETION 129
the isolated dog small intestine into low-frequency but
high-amplitude ones, possibly brought about by a shift
in the time relationship of single contractions with sub-
sequent superimpos the isolated dog small intestine into low-frequency but high-amplitude ones, possibly brought about by a shift in the time relationship of single contractions with subsequent superimposition (Kromer, unpublished results). the isolated dog small intestine into low-frequency but
high-amplitude ones, possibly brought about by a shift
in the time relationship of single contractions with sub-
sequent superimposition (Kromer, unpublished results) high-amplitude ones, possibly brought about by a shift
in the time relationship of single contractions with sub-
sequent superimposition (Kromer, unpublished results).
Thus, even in the dog, it is uncertain whether we are
 in the time relationship of single contractions with subsequent superimposition (Kromer, unpublished results).
Thus, even in the dog, it is uncertain whether we are dealing with opioid excitation or inhibition of in vitro
 sequent superimposition (Kromer, unpublished result
Thus, even in the dog, it is uncertain whether we a
dealing with opioid excitation or inhibition of in vir
peristalsis. Potentially, the dog may be a special constree mor Thus, even in the dog, it is uncertain whether we are dealing with opioid excitation or inhibition of in vitro peristalsis. Potentially, the dog may be a special case where morphine may cause diarrhea rather than constinua dealing with opioid excitation or inhibition of in vitro
peristalsis. Potentially, the dog may be a special case
where morphine may cause diarrhea rather than consti-
pation, as already noted by Schaumann (372). This issue peristalsis. Potentially, the dog may be a special case
where morphine may cause diarrhea rather than consti-
pation, as already noted by Schaumann (372). This issue,
however, is controversial. Conflicting views may arise
 where morphine may cause diarrhea rather than constipation, as already noted by Schaumann (372). This issue, however, is controversial. Conflicting views may arise from dual opioid actions observed in sequence or under dif tion, as already noted by Schaumann (372). This issue,
wever, is controversial. Conflicting views may arise
om dual opioid actions observed in sequence or under
fferent experimental conditions (see section III D 2 c).
Burk

however, is controversial. Conflicting views may arise
from dual opioid actions observed in sequence or under
different experimental conditions (see section III D 2 c).
Burks and coworkers, using in vitro or in situ dog
pr from dual opioid actions observed in sequence or under
different experimental conditions (see section III D 2 c).
Burks and coworkers, using in vitro or in situ dog
preparations, found that opioids invariably induced tonic different experimental conditions (see section III D 2 c).
Burks and coworkers, using in vitro or in situ dog
preparations, found that opioids invariably induced tonic
increases in intraluminal pressure and secondary phasi Burks and coworkers, using in vitro or in situ preparations, found that opioids invariably induced to increases in intraluminal pressure and secondary phacontractions associated with release of serotonin into vasculature preparations, found that opioids invariably induced tonic
increases in intraluminal pressure and secondary phasic
contractions associated with release of serotonin into the
vasculature (48, 44). Since TTX barely affected c increases in intraluminal pressure and secondary phasic
contractions associated with release of serotonin into the
vasculature (48, 44). Since TTX barely affected contrac-
tions elicited by $[Met⁵]$ -enkephalin, the aut contractions associated with release of serotonin into the vasculature (48, 44). Since TTX barely affected contractions elicited by [Met⁵]-enkephalin, the authors discussed direct stimulation of smooth muscle cells by th vasculature (48, 44). Since TTX barely affected contractions elicited by [Met⁵]-enkephalin, the authors discussed direct stimulation of smooth muscle cells by this particular opioid (47). According to their data, mu- bu tions elicited by [Met⁵]-enkephalin, the authors
cussed direct stimulation of smooth muscle cells by
particular opioid (47). According to their data, mu-
not kappa-opioid agonists induced contractions in th
vivo canine s cussed direct stimulation of smooth muscle cells by this
particular opioid (47). According to their data, mu- but
not kappa-opioid agonists induced contractions in the ex
vivo canine small intestine (167). Moreover, betaparticular opioid (47). According to their data, mu- but
not kappa-opioid agonists induced contractions in the ex
vivo canine small intestine (167). Moreover, beta-endor-
phin-related peptides produced phasic contractions increases in intraluminal pressure and secondary phasic
contractions associated with release of serotonin into the
vasculature (48, 44). Since TTX barely affected contrac-
tions elicited by [Met²]-enkephalin, the author vivo canine small intestine (167). Moreover, beta-endor-
phin-related peptides produced phasic contractions in
the isolated canine intestinal segment (80). None of these
reports, however, does allow any conclusion as to th phin-related peptides produced phasic contractions in
the isolated canine intestinal segment (80). None of these
reports, however, does allow any conclusion as to the
opioid effect on propulsive peristaltic contractions. I the isolated canine intestinal segment (80). None of these
reports, however, does allow any conclusion as to the
opioid effect on propulsive peristaltic contractions. It
appears from in vitro studies that the small intesti reports, however, does allow any conclusion as to the opioid effect on propulsive peristaltic contractions. I
appears from in vitro studies that the small intestine call species examined so far contains different opioid
me opioid effect on propulsive peristaltic contractions. It
appears from in vitro studies that the small intestine of
all species examined so far contains different opioid
mechanisms of contrasting functional significances,
w appears from in vitro studies that the small intestine of
all species examined so far contains different opioid
mechanisms of contrasting functional significances,
which are probably involved in the control of both local
s all species examined so far contains different opioid mechanisms of contrasting functional significances, which are probably involved in the control of both local segmenting contractions, being per se nonpropulsive, and pr mechanisms of contrasting functional significances,
which are probably involved in the control of both local
segmenting contractions, being per se nonpropulsive, and
propulsive peristaltic contractions to a varying degree. which are probably involved in the control of both local
segmenting contractions, being per se nonpropulsive, and
propulsive peristaltic contractions to a varying degree.
The prevalence of one of these mechanisms may then segmenting contractions, being per se nonpropulsive, and
propulsive peristaltic contractions to a varying degree.
The prevalence of one of these mechanisms may then
determine whether inhibitory, excitatory, dual, or no
opi differences. determine whether inhibitory, excitatory, dual, or no opioid effects are observed. This may define species differences.
C. Opioid Effects on the Isolated Large Intestine from
Different Species opioid effects are observed. This may define species

4. Dog. The dog isolated intestine might well be an by opioids, respectively. In the latter case, the amplitude exception, since only induction by opioids and inhibition was unaffected (233, 234), and naloxone alone worked Ifferences.
 It has been concluded very recently from in vitro

It has been concluded very recently from in vitro

udies in the guinea-pig and rat colon that opioids C. Opioid Effects on the Isolated Large Intestine from
Different Species
It has been concluded very recently from in vitro
studies in the guinea-pig and rat colon that opioids
inhibit relaxation distal to and augment contr C. Opioid Effects on the Isolated Large Intestine from
Different Species
It has been concluded very recently from in vitro
studies in the guinea-pig and rat colon that opioids
inhibit relaxation distal to and augment contr Different Species
It has been concluded very recently from in vitro
studies in the guinea-pig and rat colon that opioids
inhibit relaxation distal to and augment contraction
proximal to radial stretch (145a). This contrast It has been concluded very recently from in vitro
studies in the guinea-pig and rat colon that opioids
inhibit relaxation distal to and augment contraction
proximal to radial stretch (145a). This contrasts with
opioid inhi studies in the guinea-pig and rat colon that opioids
inhibit relaxation distal to and augment contraction
proximal to radial stretch (145a). This contrasts with
opioid inhibition of rhythmic, propulsive circular muscle
con inhibit relaxation distal to and augment contraction
proximal to radial stretch (145a). This contrasts with
opioid inhibition of rhythmic, propulsive circular muscle
contractions elicited in vitro in the guinea-pig intact
 proximal to radial stretch (145a). This contrasts with opioid inhibition of rhythmic, propulsive circular musc
contractions elicited in vitro in the guinea-pig intaintestinal segment proximal to distension stimulus (234
Th opioid inhibition of rhythmic, propulsive circular muscle
contractions elicited in vitro in the guinea-pig intact
intestinal segment proximal to distension stimulus (234).
The different parameters may represent distinct ph contractions elicited in vitro in the guinea-pig intact intestinal segment proximal to distension stimulus (234). The different parameters may represent distinct physiological events, for example, segmenting (145a) versus
peristaltic (234) contractions. The amplitude of ascending contractions (145a) and the frequency of expulsive
peri iological events, for example, segmenting (145a) versus
peristaltic (234) contractions. The amplitude of ascend-
ing contractions (145a) and the frequency of expulsive
peristaltic contractions (234) were increased or decre peristaltic (234) contractions. The amplitude of ascending contractions (145a) and the frequency of expulsive
peristaltic contractions (234) were increased or decreased
by opioids, respectively. In the latter case, the amp ing contractions (145a) and the frequency of expulsive
peristaltic contractions (234) were increased or decreased
by opioids, respectively. In the latter case, the amplitude
was unaffected (233, 234), and naloxone alone wo peristaltic contractions (234) were increased or decreased
by opioids, respectively. In the latter case, the amplitude
was unaffected (233, 234), and naloxone alone worked in
an opposite fashion (233, 234). Actually, these by opioids, respectively. In the latter case, the amplitude was unaffected (233, 234), and naloxone alone worked in an opposite fashion (233, 234). Actually, these data are consistent with an inverse relationship between s

In vitro, spontaneous nonpropulsive contractions were in intro, spontaneous nonpropulsive contractions were interestion in the rat (301, sis kROM
In vitro, spontaneous nonpropulsive contractions were
also enhanced upon opioid application in the rat (301,
133, 186, 377), mouse (114), and cat large intestine (475), KROM

In vitro, spontaneous nonpropulsive contractions were

also enhanced upon opioid application in the rat (301,

133, 186, 377), mouse (114), and cat large intestine (475),

although contractions elicited by electrical In vitro, spontaneous nonpropulsive contractions were
also enhanced upon opioid application in the rat $(301, 133, 186, 377)$, mouse (114) , and cat large intestine (475) ,
although contractions elicited by electrical o In vitro, spontaneous nonpropulsive contractions were
also enhanced upon opioid application in the rat (301
133, 186, 377), mouse (114), and cat large intestine (475)
although contractions elicited by electrical or chemica also enhanced upon opioid application in the rat (301, 133, 186, 377), mouse (114), and cat large intestine (475), although contractions elicited by electrical or chemical stimulation were inhibited as expected. Confusingl 133, 186, 377), mouse (114), and cat large intestine (475), traithough contractions elicited by electrical or chemical (76) attimulation were inhibited as expected. Confusingly, for opioid-effected contractions in the rat although contractions elicited by electrical or chemical (7
stimulation were inhibited as expected. Confusingly, for
opioid-effected contractions in the rat colon were either ac
augmented (133) or abolished (186) by TTX. T stimulation were inhibited as expected. Confusingly,
opioid-effected contractions in the rat colon were either
augmented (133) or abolished (186) by TTX. The reason
for this discrepancy is unknown, but it might be related
 popioid-effected contractions in the rat colon were eithe
augmented (133) or abolished (186) by TTX. The reaso
for this discrepancy is unknown, but it might be relate
to lower morphine concentrations used in the latte
stud augmented (133) or abolished (186) by TTX. The reason at for this discrepancy is unknown, but it might be related in to lower morphine concentrations used in the latter me study. In the rabbit, opioids enhanced EJPs in the for this discrepancy is unknown, but it might be related in
to lower morphine concentrations used in the latter m
study. In the rabbit, opioids enhanced EJPs in the prox-
timal, and decreased them in the distal, isolated c to lower morphine concentrations used in the latter
study. In the rabbit, opioids enhanced EJPs in the prox-
imal, and decreased them in the distal, isolated colon
(28). Depression of EJPs was observed in the cat isolated
 erally decreased them in the distal, isolated colon correlational, and decreased them in the distal, isolated colon correlation (28). Depression of EJPs was observed in the cat isolated opic colon only (28). Inhibitory jun imal, and decreased them in the distal, isolated colon (28). Depression of EJPs was observed in the cat isolated colon only (28). Inhibitory junction potentials were generally decreased, except in the cat after morphine, w (28). Depression of EJPs was observed in the cat isolated colon only (28). Inhibitory junction potentials were generally decreased, except in the cat after morphine, when they were increased, and spike activity was enhance colon only (28). Inhibitory junction potentials were gen-
erally decreased, except in the cat after morphine, when
they were increased, and spike activity was enhanced.
These data, once again, support a dual action of opio erally decreased, except in the cat after morphine, when
they were increased, and spike activity was enhanced.
These data, once again, support a dual action of opioids,
but it is hardly possible to establish any firm conce they were increased, and spike activity was enhanced. d
These data, once again, support a dual action of opioids,
but it is hardly possible to establish any firm concept on
this basis. Sacral parasympathetic outflow to the These data, once again, support a dual action
but it is hardly possible to establish any firm
this basis. Sacral parasympathetic outflow
tudinal muscle of cat distal colon may linhibited by opioid delta-receptors (204a).
I is hardly possible to establish any firm concept on
is basis. Sacral parasympathetic outflow to the longi-
dinal muscle of cat distal colon may be primarily in
inbited by opioid delta-receptors (204a).
In accordance with i

this basis. Sacral parasympathetic outflow to the longitudinal muscle of cat distal colon may be primarily inhibited by opioid delta-receptors (204a).

In accordance with inhibition of electrically induced electricalis, m tudinal muscle of cat distal colon may be primarily
inhibited by opioid delta-receptors (204a).
In accordance with inhibition of electrically induced
contractions, morphine attenuated the electrically
evoked release of [³ inhibited by opioid delta-receptors (204a). The accordance with inhibition of electrically induced
contractions, morphine attenuated the electrically operated release of $[^3H]$ acetylcholine from the human sig-
imoid taen In accordance with inhibition of electrically induced
contractions, morphine attenuated the electrically op
evoked release of [³H]acetylcholine from the human sig-
in moid taenia coli strip (50), and various opioids inh contractions, morphine attenuated the electrically open obvious evoked release of [³H] acetylcholine from the human sigmoid taenia coli strip (50), and various opioids inhibited method in the electrically stimulated con evoked release of [³H]acetylcholine from the human sigmoid taenia coli strip (50), and various opioids inhibited
the electrically stimulated contraction of the rat isolated
rectum (405). Again, there is no obvious basis stalsis. *Prectum (405). Again, there is no obvious basis for relating*
 D. In Vivo Data on Gastrointestinal Motility in Various
 D. In Vivo Data on Gastrointestinal Motility in Various
 Species: Stomach; Small Intestine; Larg

Species: **Stalsis:**
 *Species: Stomach; Small Intestinal Motility in Var Species: Stomach; Small Intestine; Large Intestine;

<i>Gastrointestinal Sphincters*
 1. Stomach. Opioids have been shown to delay g *In Vivo Data on Gastrointestinal Motility in Various*
ecies: Stomach, Small Intestine; Large Intestine; in
strointestinal Sphincters
1. Stomach. Opioids have been shown to delay gastric
ptying and/or to inhibit gastric co

D. In Vivo Data on Gastrointestinal Motility in Various
Species: Stomach; Small Intestine; Large Intestine;

distrointestinal Sphincters

1. Stomach. Opioids have been shown to delay gastric

emptying and/or to inhibit ga species: Stomach, Small Intestine; Large Intestine;

Gastrointestinal Sphincters

1. Stomach. Opioids have been shown to delay gastric

emptying and/or to inhibit gastric contractions in the Vaug

sheep (359, 264), goat (2 Gastrointestinal Sphincters
1. Stomach. Opioids have been shown to delay ga
emptying and/or to inhibiti gastric contractions in
sheep (359, 264), goat (263), cat (311), dog (108),
man (288). Prolonged inhibition after i.c. 1. Stomach. Opioids have been shown to delay gastric emptying and/or to inhibit gastric contractions in the sheep (359, 264), goat (263), cat (311), dog (108), and man (288). Prolonged inhibition after i.c.v. administrati emptying and/or to inhibit gastric contractions in the sheep (359, 264), goat (263), cat (311), dog (108), and man (288). Prolonged inhibition after i.c.v. administration to the dog was preceded by transient stimulation (1 sheep (359, 264), goat (263), cat (311), dog (108), and
man (288). Prolonged inhibition after i.c.v. administra-
tion to the dog was preceded by transient stimulation
(108). Abbott and Pendergrass (1) concluded that mor-
p man (288). Prolonged inhibition after i.c.v. administration to the dog was preceded by transient stimulation colline (108). Abbott and Pendergrass (1) concluded that morphine delayed gastric emptying at least partially by tion to the dog was preceded by transient stimulation (108). Abbott and Pendergrass (1) concluded that morphine delayed gastric emptying at least partially by increasing the tone, not propulsive contractions, of the duode emptying. ine delayed gastric emptying at least partially by in-
prevasing the tone, not propulsive contractions, of the earl
odenum. This would increase the resistance to gastric veloc
ptying.
In the conscious dog, morphine clearly

creasing the tone, not propulsive contractions, of the duodenum. This would increase the resistance to gastric emptying.
In the conscious dog, morphine clearly produced a naloxone-blockable dual effect, which consisted of duodenum. This would increase the resistance to gastric time
emptying.
In the conscious dog, morphine clearly produced a high
naloxone-blockable dual effect, which consisted of a de-
crease in gastric tone with superimpose emptying.

In the conscious dog, morphine clearly produced a high

maloxone-blockable dual effect, which consisted of a de-

to

contractions (251). Interestingly, naloxone alone slightly

increased both the frequency and In the conscious dog, morphine clearly produced a
naloxone-blockable dual effect, which consisted of a de-
crease in gastric tone with superimposed transient phasic
contractions (251). Interestingly, naloxone alone slightl naloxone-blockable dual effect, which consisted of a de-
crease in gastric tone with superimposed transient phasic discussed by Krüger in a review as early as 1937 (244).
contractions (251). Interestingly, naloxone alone contractions (251). Interestingly, naloxone alone slightly
increased both the frequency and amplitude of ruminal
contractions in sheep (359, 264). This was only observed
is not known. Any statement on "contractile" or "re contractions (251). Interestingly, naloxone alone slightly
increased both the frequency and amplitude of ruminal
contractions in sheep (359, 264). This was only observed
inder well-defined feeding conditions (264), sugges increased both the frequency and amplitude of ruminicontractions in sheep (359, 264). This was only observed under well-defined feeding conditions (264), suggestine that a small modulatory influence of endogenous opioid mi contractions in sheep $(359, 264)$. This was only observed intendent well-defined feeding conditions (264) , suggesting 8 that a small modulatory influence of endogenous opioids the might be missed if no care was taken under well-defined feeding conditions (264) , suggesting ant^{*}
that a small modulatory influence of endogenous opioids ther
might be missed if no care was taken to minimize intra-
info
and interindividual variations. Na that a small modulatory influence of endogenous opioids
might be missed if no care was taken to minimize intra-
and interindividual variations. Naloxone also stimulated
ruminal contractions in the goat (263) and tended to
 might be missed if no care was taken to minimize intra-
and interindividual variations. Naloxone also stimulated
ruminal contractions in the goat (263) and tended to
enhance gastric emptying in man (288). Mittal et al.
(28 and interindividual variations. Naloxone also stimulated turninal contractions in the goat (263) and tended to Q
enhance gastric emptying in man (288). Mittal et al.
(288) speculated that this might be relevant at differen ruminal contractions in the goat (263) and tended to Quigley et al. (340) .

enhance gastric emptying in man (288) . Mittal et al. Excellent studies done in the first half of this century
 (288) speculated that this

ER
inhibitory modulators of gastric emptying which is con-
sistent with the inhibition of electrically stimulated con-ER
inhibitory modulators of gastric emptying which is con-
sistent with the inhibition of electrically stimulated con-
tractions of the canine corpus and antrum by opioids ER
inhibitory modulators of gastric emptying which is con-
sistent with the inhibition of electrically stimulated con-
tractions of the canine corpus and antrum by opioids
(76a). By contrast, Liberge et al. (255a) very rec inhibitory modulators of gastric emptying which is consistent with the inhibition of electrically stimulated contractions of the canine corpus and antrum by opioids (76a). By contrast, Liberge et al. (255a) very recently f inhibitory modulators of gastric emptying which is consistent with the inhibition of electrically stimulated contractions of the canine corpus and antrum by opioids (76a). By contrast, Liberge et al. (255a) very recently f tractions of the canine corpus and antrum by opioids (76a). By contrast, Liberge et al. (255a) very recently found that two enkephalinase inhibitors (thiorphan and acetorphan) as well as $[D-Ala^2, Met^5]$ -enkephalin-amide, at tractions of the canine corpus and antrum by opioids (76a). By contrast, Liberge et al. (255a) very recently found that two enkephalinase inhibitors (thiorphan and acetorphan) as well as $[D-Ala^2, Met^5]$ -enkephalin-amide, at (76a). By contrast, Liberge et al. (255a) very recently found that two enkephalinase inhibitors (thiorphan and acetorphan) as well as $[D-Ala^2, Met^5]$ -enkephalin-amide, at low doses, increased gastric emptying of a fatty meal found that two enkephalinase inhibitors (thiorphan and acetorphan) as well as [D-Ala², Met⁵]-enkephalin-amide, at low doses, increased gastric emptying of a fatty meal in mice. The effect was antagonized by the quatern acetorphan) as well as [D-Ala², Met⁵]-enkephalin-amide,
at low doses, increased gastric emptying of a fatty meal
in mice. The effect was antagonized by the quaternary
methylnaloxone which indicates a peripheral site of at low doses, increased gastric emptying of a fatty meal
in mice. The effect was antagonized by the quaternary
methylnaloxone which indicates a peripheral site of ac-
tion. It was counteracted by a central inhibitory actio in mice. The effect was antagonized by the quaternary
methylnaloxone which indicates a peripheral site of ac-
tion. It was counteracted by a central inhibitory action
component at higher doses of the opioid peptide. No
opi methylnaloxone which indicates a peripheral site of action. It was counteracted by a central inhibitory action
component at higher doses of the opioid peptide. No
opioid-specific effects were detected following a non-fat
m tion. It was counteracted by a central inhibitory action
component at higher doses of the opioid peptide. No
opioid-specific effects were detected following a non-fat
meal. Thus, dual opioid effects (see also section III D opioid-specific effects were detected following a non-fat
meal. Thus, dual opioid effects (see also section III D 2)
were superimposed at different dose levels and were
dependent on the meal composition.
2. Small intestine *2. Small intestine.* a. PERIPHERAL VERSUS CENTRAL PHONO MECHANISMS. There is now sound evidence for both a peripherally and centrally mediated inhibition of

were superimposed at different dose levels and were
dependent on the meal composition.
2. Small intestine. a. PERIPHERAL VERSUS CENTRAL
OPIOID MECHANISMS. There is now sound evidence for
both a peripherally and centrally m dependent on the meal composition.

2. Small intestine. a. PERIPHERAL VERSUS CENTRAL

OPIOID MECHANISMS. There is now sound evidence for

both a peripherally and centrally mediated inhibition of

intestinal transit by opio 2. Small intestine. a. PERIPHERAL VERSUS CENTRAL
OPIOID MECHANISMS. There is now sound evidence for
both a peripherally and centrally mediated inhibition of
intestinal transit by opioids (45a, 389, 181, 271, 333).
This mak OPIOID MECHANISMS. There is now sound evidence for
both a peripherally and centrally mediated inhibition of
intestinal transit by opioids (45a, 389, 181, 271, 333).
This makes an interpretation of opioid effects in vivo
ev both a peripherally and centrally mediated inhibition of intestinal transit by opioids (45a, 389, 181, 271, 333).
This makes an interpretation of opioid effects in vivo
even more complex. Although i.c.v. administration of
 intestinal transit by opioids (45a, 389, 181, 271, 333).
This makes an interpretation of opioid effects in vivo
even more complex. Although i.c.v. administration of
opioids proved to be extremely effective in inhibiting
in This makes an interpretation of opioid effects in vivo
even more complex. Although i.c.v. administration of
opioids proved to be extremely effective in inhibiting
intestinal transit (389), peripheral administration of
morp even more complex. Although i.c.v. administration of
opioids proved to be extremely effective in inhibiting
intestinal transit (389), peripheral administration of
morphine inhibited intestinal transit in the rat predom-
in popioids proved to be extremely effective in inhibiting
intestinal transit (389), peripheral administration of
morphine inhibited intestinal transit in the rat predom-
inantly via a peripheral mechanism. This was judged
fr intestinal transit (389) , peripheral administration of morphine inhibited intestinal transit in the rat predom
inantly via a peripheral mechanism. This was judge
from the antagonism by a quaternary antagonist an
from hi morphine inhibited intestinal transit in the rat predominantly via a peripheral mechanism. This was judged
from the antagonism by a quaternary antagonist and
from higher morphine concentrations found in the intes-
tinal wa inantly via a peripheral mechanism. This was judged
from the antagonism by a quaternary antagonist and
from higher morphine concentrations found in the intes-
tinal wall as compared with the brain (272). In addition,
intra were superimposed at uniterent use we solution of option in the meal composition.

2. Small intestine. a. PERIPHERAL VERSUS CENTRAL

2. Small intestine. a. PERIPHERAL VERSUS CENTRAL

booth a peripherally and centrally med tinal wall as compared with the brain (272). In addition,

intrathecal administration of opioids to spinalized and
intact rats and mice revealed a spinal site of opioid
inhibition of intestinal propulsion (332, 457, 218).
b. DUAL OPIOID EFFECTS: EARLY INVESTIGATIONS.
Vaughan-Willi intact rats and mice revealed a spinal site of opic
inhibition of intestinal propulsion (332, 457, 218).
b. DUAL OPIOID EFFECTS: EARLY INVESTIGATION
Vaughan-Williams (455) stressed that opiates increa
the tone of the intes inhibition of intestinal propulsion (332, 457, 218).
b. DUAL OPIOID EFFECTS: EARLY INVESTIGATIONS.
Vaughan-Williams (455) stressed that opiates increase
the tone of the intestinal wall, while depressing propul-
sive perist b. DUAL OPIOID EFFECTS: EARLY INVESTIGATIONS.
Vaughan-Williams (455) stressed that opiates increase
the tone of the intestinal wall, while depressing propul-
sive peristalsis. Both effects should contribute to the
constipa Vaughan-Williams (455) stressed that opiates increase
the tone of the intestinal wall, while depressing propul-
sive peristalsis. Both effects should contribute to the
constipating effect. It is noteworthy that segmentatio the tone of the intestinal wall, while depressing propulsive peristalsis. Both effects should contribute to the constipating effect. It is noteworthy that segmentations and spasms of the circular muscle coat probably do no sive peristalsis. Both effects should contribute to the constipating effect. It is noteworthy that segmentations and spasms of the circular muscle coat probably do not prevent transit by increasing resistance as assumed by constipating effect. It is noteworthy that segmentational spasms of the circular muscle coat probably do prevent transit by increasing resistance as assumed early investigators because peristaltic contractions velop forces and spasms of the circular muscle coat probably do not prevent transit by increasing resistance as assumed by early investigators because peristaltic contractions develop forces 15 to 20 times the magnitude of segmentation prevent transit by increasing resistance as assumed by
early investigators because peristaltic contractions de-
velop forces 15 to 20 times the magnitude of segmenta-
tions (372). Rather, induction of segmentations and inearly investigators because peristaltic contractions develop forces 15 to 20 times the magnitude of segmentations (372). Rather, induction of segmentations and inhibition of peristaltic contractions are inversely related velop forces 15 to 20 times the magnitude of segmentations (372). Rather, induction of segmentations and in-
hibition of peristaltic contractions are inversely related
to each other via intrinsic reflex mechanisms, a probl tions (372). Rather, induction of segmentations and in-
hibition of peristaltic contractions are inversely related
to each other via intrinsic reflex mechanisms, a problem
discussed by Krüger in a review as early as 1937 hibition of peristaltic contractions are inversely related
to each other via intrinsic reflex mechanisms, a problem
discussed by Krüger in a review as early as 1937 (244).
This may relate to different motility patterns fou to each other via intrinsic reflex mechanisms, a proble
discussed by Krüger in a review as early as 1937 (24
This may relate to different motility patterns found
the fasted or fed state (470), but the precise relationsh
is discussed by Krüger in a review as early as 1937 (244).
This may relate to different motility patterns found in
the fasted or fed state (470), but the precise relationship
is not known. Any statement on "contractile" or "r This may relate to different motility patterns found in
the fasted or fed state (470), but the precise relationship
is not known. Any statement on "contractile" or "relax-
ant" effects of opioids in the gastrointestinal tr the fasted or fed state (470), but the precise relationship
is not known. Any statement on "contractile" or "relax-
ant" effects of opioids in the gastrointestinal tract is,
therefore, only meaningful within the context of is not known. Any statement on "contractile" or "relax-
ant" effects of opioids in the gastrointestinal tract is,
therefore, only meaningful within the context of further
information on the propulsive versus nonpropulsive ant" effects of opioid
therefore, only meani
information on the pi
ture of that particula
Quigley et al. (340).
Excellent studies de erefore, only meaningful within the context of further
formation on the propulsive versus nonpropulsive na-
re of that particular motility measure, as stressed by
higley et al. (340).
Excellent studies done in the first ha

information on the propulsive versus nonpropulsive nature of that particular motility measure, as stressed by Quigley et al. (340) .
Excellent studies done in the first half of this century mostly come to the conclusion ture of that particular motility measure, as stressed by
Quigley et al. (340).
Excellent studies done in the first half of this century
mostly come to the conclusion that in both man (1, 355)
and dog (456) as well as in ot Quigley et al. (340).
Excellent studies done in the first half of this century
mostly come to the conclusion that in both man (1, 355)
and dog (456) as well as in other species opioids exert a
long lasting depression of pr

PHARMACOLOGICAL REVIEWS

OPIOIDS AND CONTROL OF GASTROINTE
intestine and thus inhibit transit. This may be preceded esp a shorter, stimulatory period lasting up to 90 min. opioids and contract of GASTROIN
intestine and thus inhibit transit. This may be preceded
by a shorter, stimulatory period lasting up to 90 min.
Krueger (244) and Vaughan Williams and Streeten (456) OPIOIDS AND CONTROL OF GASTROINT
intestine and thus inhibit transit. This may be preceded
by a shorter, stimulatory period lasting up to 90 min.
Krueger (244) and Vaughan Williams and Streeten (456)
make critical comments intestine and thus inhibit transit. This may be preceded every a shorter, stimulatory period lasting up to 90 min. op Krueger (244) and Vaughan Williams and Streeten (456) op make critical comments on the methodical pitfal intestine and thus inhibit transit. This may be preceded
by a shorter, stimulatory period lasting up to 90 min.
Krueger (244) and Vaughan Williams and Streeten (456)
make critical comments on the methodical pitfalls which
 Krueger (244) and Vaughan Williams and Streeten (456) op
make critical comments on the methodical pitfalls which of
lead to controversial interpretations of inhibitory versus the
stimulatory opioid actions. These publicati

stimulatory opioid actions. These publications may be in consulted for further references to earlier publications. to c. DUAL OPIOID EFFECTS: CURRENT INVESTIGATIONS; side COMPARISON BETWEEN MOTILITY PARAMETERS. More confer consulted for further references to earlier publications. to
c. DUAL OPIOID EFFECTS: CURRENT INVESTIGATIONS; si
COMPARISON BETWEEN MOTILITY PARAMETERS. More
recent studies confirmed that the overall outcome of both
entral c. DUAL OPIOID EFFECTS: CURRENT INVESTIGATIONS; sibly
COMPARISON BETWEEN MOTILITY PARAMETERS. More com
recent studies confirmed that the overall outcome of both effecentral and peripheral opioid actions on gut motility was COMPARISON BETWEEN MOTILITY PARAMETERS. More
recent studies confirmed that the overall outcome of both
central and peripheral opioid actions on gut motility was
inhibition of gastric emptying and intestinal transit in
the recent studies confirmed that the overall outcome of both efficientral and peripheral opioid actions on gut motility was didinhibition of gastric emptying and intestinal transit in (28) the rat (427, 442, 441, 49, 107, 123 central and peripheral opioid actions on gut motility was diinhibition of gastric emptying and intestinal transit in (2) the rat (427, 442, 441, 49, 107, 123, 124, 365, 426, 218, wat 273, 272, 139, 119), mouse (482, 332, 2 in mouth-to-ileum transit by morphine in healthy vol-
273, 272, 139, 119), mouse (482, 332, 23, 481), and man
273, 272, 139, 119), mouse (482, 332, 23, 481), and man
20, although Borody et al. (32) did not find any slowin

(2), although Borody et al. (32) did not find any slowing seein mouth-to-ileum transit by morphine in healthy volumeters.

A number of current investigations on gastrointestinal ramotility deal with the migrating motility in mouth-to-ileum transit by morphine in healthy volunteers.

A number of current investigations on gastrointestinal

motility deal with the migrating motility complex

(MMC) as determined electrically (migrating myoelectr as

A number of current investigations on gastrointestinal

motility deal with the migrating motility complex h

(MMC) as determined electrically (migrating myoelectric

complex) or mechanically (migrating motor complex; f A number of current investigations on gastrointestinal radio
motility deal with the migrating motility complex hibit
(MMC) as determined electrically (migrating myoelectric M
complex) or mechanically (migrating motor compl motility deal with the migrating motility complement (MMC) as determined electrically (migrating myoelec complex) or mechanically (migrating motor complex; review, see ref. 470). "Phase III activity" of the Mi has been reg (MMC) as determined electrically (migrating myoelectric
complex) or mechanically (migrating motor complex; for
review, see ref. 470). "Phase III activity" of the MMC tiv
has been regarded as "intestinal housekeeper" respo complex) or mechanically (migrating motor complex; for of order review, see ref. 470). "Phase III activity" of the MMC tivit
has been regarded as "intestinal housekeeper" responsi- In t
ble for rapid propulsion of intestin review, see ref. 470). "Phase III activity" of the MMC tives been regarded as "intestinal housekeeper" responsi-
hele for rapid propulsion of intestinal contents during the confested state. Other investigators determined c has been regarded as "intestinal housekeeper" responsible for rapid propulsion of intestinal contents during the fasted state. Other investigators determined changes in intraluminal pressure without any information about t ble for rapid propulsion of intestinal contents during the cofasted state. Other investigators determined changes in tion intraluminal pressure without any information about the protential functional significance for intes fasted state. Other investigators determined changes in tionitral
uminal pressure without any information about the protential functional significance for intestinal transit.
Opioids were found to reduce myoelectric activi intraluminal pressure without any information about the potential functional significance for intestinal transit.
Opioids were found to reduce myoelectric activity in the rat small intestine (335, 471), although conflictin potential functional significance for intestinal transit.
Opioids were found to reduce myoelectric activity in the
rat small intestine (335, 471), although conflicting data
have been obtained with different agonists or dif Opioids were found to reduce myoelectric activity in the
rat small intestine $(335, 471)$, although conflicting data
have been obtained with different agonists or different
routes of administration (360) . Weisbrodt et a rat small intestine (335, 471), although conflicting data
have been obtained with different agonists or different
routes of administration (360). Weisbrodt et al. (471)
demonstrated a positive correlation between inhibitio have been obtained with different agonists or different
routes of administration (360). Weisbrodt et al. (471)
demonstrated a positive correlation between inhibition
of myoelectric activity and inhibition of intestinal
tra routes of administration (360). Weisbrodt et al. (471) or idemonstrated a positive correlation between inhibition ACT
of myoelectric activity and inhibition of intestinal failutransit, questioning the theory of segmental c of myoelectric activity and inhibition of intestinal failure of naloxone alone to alter intestinal motility transit, questioning the theory of segmental contractions measures in man (52) . Since naloxone blocks, at a suf of myoelectric activity and inhibition of intestinal
transit, questioning the theory of segmental contractions
and spasms as a cause of opioid-effected constipation. In
fact, it has been proposed that irregular segmenting
 transit, questioning the theory of segmental contractions meand spasms as a cause of opioid-effected constipation. In cienties fact, it has been proposed that irregular segmenting specontractions are related to transit of and spasms as a cause of opioid-effected constipation. In ciented fact, it has been proposed that irregular segmenting spectractions are related to transit of intestinal contents alteduring the fed state (470) . This may fact, it has been proposed that irregular segmenting speculations are related to transit of intestinal contents alter during the fed state (470). This may be achieved by a indecreasing frequency of segmentations from proxi contractions are related to transit of intestinal contents during the fed state (470). This may be achieved by a decreasing frequency of segmentations from proximal to distal, but again this is still speculative. In any ca during the fed state (4'
decreasing frequency of
distal, but again this is a
pattern of intestinal mo
on intestinal propulsion
Sarna and Lang (366 creasing frequency of segmentations from proximal to all, stal, but again this is still speculative. In any case, the Candidation of intestinal motility has a considerable impact ago intestinal propulsion.
Sarna and Lang (

though MMC phase III activity, which is considered on intestinal propulsion.

Sarna and Lang (366b) pointed out that in their do

studies smooth muscle contractions were present ever

though MMC phase III activity, which is considere

propulsive (432) during the fasted sta Sarna and Lang $(366b)$ pointed out that in their dog
studies smooth muscle contractions were present even
though MMC phase III activity, which is considered
propulsive (432) during the fasted state, had been abol-
ished studies smooth muscle contractions were present even upo
though MMC phase III activity, which is considered ami
propulsive (432) during the fasted state, had been abol-
of c
ished by morphine. In addition to morphine (366b though MMC phase III activity, which is considered an propulsive (432) during the fasted state, had been abolished by morphine. In addition to morphine (366b), la [Met⁵]-enkephalin (216) inhibited myoelectric activity in propulsive (432) during the fasted state, had been abolished by morphine. In addition to morphine (366b), [Met⁵]-enkephalin (216) inhibited myoelectric activity in the canine small intestine. The effect of morphine was p [Met⁶]-enkephalin (216) inhibited myoelectric activity in turn, any further effect by the exogenous opioid. The the canine small intestine. The effect of morphine was other way round, an inactive opioid system in the fo [Met⁵]-enkephalin (216) inhibited myoelectric activity if the canine small intestine. The effect of morphine was preceded by a transient stimulatory action correspondint to a premature MMC cycle (366a, b). This indicates the canine small intestine. The effect of morphine was
preceded by a transient stimulatory action corresponding
to a premature MMC cycle (366a, b). This indicates a
dual opioid action and may possibly explain why Kon-
ture preceded by a transient stimulatory action corresponding study
to a premature MMC cycle (366a, b). This indicates a No e
dual opioid action and may possibly explain why Kon-
turek et al. (216) found stimulation of interdig to a premature MMC cycle (366a, b). This indicates a N
dual opioid action and may possibly explain why Kon-
turek et al. (216) found stimulation of interdigestive of
MMCs by morphine. Induction of a premature MMC st
cycle dual opioid action and may possibly explain why Kon-have turek et al. (216) found stimulation of interdigestive of l
MMCs by morphine. Induction of a premature MMC state cycle by morphine may correspond to the period of of

Krueger (244) and Vaughan Williams and Streeten (456) opioid receptor subtypes and the predrug functional state
make critical comments on the methodical pitfalls which of the gut $(115b)$. This notion is further suppo estinal motility and secretion and the series of the period (340). Dual excitatory/inhibitor
even longer time period (340). Dual excitatory/inhibitor
opioid effects in the dog intestine may depend on bot ESTINAL MOTILITY AND SECRETION 131
even longer time period (340). Dual excitatory/inhibitory
opioid effects in the dog intestine may depend on both
opioid receptor subtypes and the predrug functional state ESTINAL MOTILITY AND SECRETION 131
even longer time period (340). Dual excitatory/inhibitory
opioid effects in the dog intestine may depend on both
opioid receptor subtypes and the predrug functional state
of the gut (115b even longer time period (340). Dual excitatory/inhibitory
opioid effects in the dog intestine may depend on both
opioid receptor subtypes and the predrug functional state
of the gut (115b). This notion is further supported even longer time period (340). Dual excitatory/inhibitory
opioid effects in the dog intestine may depend on both
opioid receptor subtypes and the predrug functional state
of the gut (115b). This notion is further supported opioid receptor subtypes and the predrug functional state of the gut (115b). This notion is further supported by the observation that stimulation of myoelectrical activity the observation that stimulation of myoelectrical activity
in the canine small intestine by morphine was converted
to inhibition under repeated administration (472), pos-
sibly indicating tolerance developed to the stimula in the canine small intestine by morphine was converted
to inhibition under repeated administration (472), pos-
sibly indicating tolerance developed to the stimulatory
component. By contrast, tolerance to the stimulatory
e to inhibition under repeated administration (472), possibly indicating tolerance developed to the stimulatory component. By contrast, tolerance to the stimulatory effect of morphine on canine ileal intraluminal pressure di sibly indicating tolerance developed to the stimulatory component. By contrast, tolerance to the stimulatory effect of morphine on canine ileal intraluminal pressure did not develop over several weeks in an earlier study (effect of morphine on canine ileal intraluminal pressure
did not develop over several weeks in an earlier study
(284). It may be speculated that the action of morphine
was counterbalanced by a decreased release of endoge-
 effect of morphine on canine ileal intraluminal pressure
did not develop over several weeks in an earlier study
(284). It may be speculated that the action of morphine
was counterbalanced by a decreased release of endoge-
 did not develop over several weeks in an earlier study (284). It may be speculated that the action of morphine was counterbalanced by a decreased release of endogenous opioids, thus avoiding the development of any subsensi was counterbalanced by a decreased release of endogenous opioids, thus avoiding the development of any subsensitivity in the system. No sound explanation of these apparent discrepancies is available to date. In the conwas counterbalanced by a decreased release of endogenous opioids, thus avoiding the development of any subsensitivity in the system. No sound explanation of these apparent discrepancies is available to date. In the consci radiopolicies, thus avoiding the development of any subsensitivity in the system. No sound explanation of these apparent discrepancies is available to date. In the conscious cat, both myoelectric activity and transit of a sensitivity in the system. No sound explane
apparent discrepancies is available to data
scious cat, both myoelectric activity and
radiopaque marker in the small intestine
hibited by an enkephalin analogue (474).
Most impor parent discrepancies is available to date. In the con-
ious cat, both myoelectric activity and transit of a
diopaque marker in the small intestine were also in-
bited by an enkephalin analogue (474).
Most important, a dual

scious cat, both myoelectric activity and transit of a
radiopaque marker in the small intestine were also in-
hibited by an enkephalin analogue (474).
Most important, a dual stimulatory-inhibitory effect
of opioids on smal radiopaque marker in the small intestine were also in-
hibited by an enkephalin analogue (474) .
Most important, a dual stimulatory-inhibitory effect
of opioids on small bowel electrical and mechanical ac-
tivity has bee hibited by an enkephalin analogue (474).

Most important, a dual stimulatory-inhibitory effect

of opioids on small bowel electrical and mechanical ac-

tivity has been shown in the monkey (95) and man (52).

In the monkey Most important, a dual stimulatory-inhibitory eff
of opioids on small bowel electrical and mechanical
tivity has been shown in the monkey (95) and man ({
In the monkey, pethidine and morphine increased, ι
codeine decr of opioids on small bowel electrical and mechanical activity has been shown in the monkey (95) and man (52).
In the monkey, pethidine and morphine increased, and codeine decreased, the frequency of small bowel contractions tivity has been shown in the monkey (95) and man (52)
In the monkey, pethidine and morphine increased, an
codeine decreased, the frequency of small bowel contractions, although no information was provided on their
propulsi In the monkey, pethidine and morphine increased, and codeine decreased, the frequency of small bowel contractions, although no information was provided on their propulsive versus nonpropulsive nature. In man, beta-endorphi codeine decreased, the frequency of
tions, although no information we
propulsive versus nonpropulsive na
endorphin provoked a burst of rh
followed by "relative quiescence."
d. THE EFFECT OF NALOXONE I

pattern of intestinal motility has a considerable impact agonist effect in man, did not find any influence of the
on intestinal propulsion.
Sarna and Lang (366b) pointed out that in their dog also in man, a decrease in ant propulsive versus nonpropulsive nature. In man, beta-
endorphin provoked a burst of rhythmic contractions
followed by "relative quiescence."
d. THE EFFECT OF NALOXONE IN THE ABSENCE OF
EXOGENOUS OPIOIDS: RELATION TO THE AC followed by "relative quiescence."

d. THE EFFECT OF NALOXONE IN THE ABSENCE OF

EXOGENOUS OPIOIDS: RELATION TO THE ACTIVITY STATE

OF ENDOGENOUS OPIOIDS AND TO EXOGENOUS OPIOID

ACTIONS. The dual action of opioids may exp d. THE EFFECT OF NALOXONE IN THE ABSENCE OF EXOGENOUS OPIOIDS: RELATION TO THE ACTIVITY STATE
OF ENDOGENOUS OPIOIDS AND TO EXOGENOUS OPIOID
ACTIONS. The dual action of opioids may explain the
failure of naloxone alone to a EXOGENOUS OPIOIDS: RELATION TO THE ACTIVITY STAT
OF ENDOGENOUS OPIOIDS AND TO EXOGENOUS OPIOI
ACTIONS. The dual action of opioids may explain th
failure of naloxone alone to alter intestinal motilit
measures in man (52). S OF ENDOGENOUS OPIOIDS AND TO EXOGENOUS OPIOID
ACTIONS. The dual action of opioids may explain the
failure of naloxone alone to alter intestinal motility
measures in man (52). Since naloxone blocks, at a suffi-
cient dose, sensitivity in the system. No sound explanation of these
apparent discrepancies is available to date. In the con-
scious cat, both myoelectric activity and transit of a
radiopaque marker in the small intestine were also i failure of naloxone alone to alter intestinal motimeasures in man (52). Since naloxone blocks, at a sucient dose, more or less all opioid receptor types is spective of their location and functional significance, alternatin measures in man (52). Since naloxone blocks, at a sufficient dose, more or less all opioid receptor types irrespective of their location and functional significance, the alternating operation of opioid mechanisms of contra cient dose, more or less all opioid receptor types irre-
spective of their location and functional significance, the
alternating operation of opioid mechanisms of contrast-
ing functional significance would evidently preve spective of their location and functional significance, the alternating operation of opioid mechanisms of contrasting functional significance would evidently prevent, over-
all, any influence of naloxone. It is quite puzzl alternating operation of opioid mechanisms of contrast-
ing functional significance would evidently prevent, over-
all, any influence of naloxone. It is quite puzzling that
Camilleri et al. (52), though observing a stimula ing functional significance would evidently prevent, overall, any influence of naloxone. It is quite puzzling that Camilleri et al. (52), though observing a stimulatory agonist effect in man, did not find any influence of all, any influence of naloxone. It is quite puzzling that
Camilleri et al. (52), though observing a stimulatory
agonist effect in man, did not find any influence of the
antagonist naloxone. By contrast, Rees et al. (347) f Camilleri et al. (52), though observing a stimulato.
agonist effect in man, did not find any influence of the antagonist naloxone. By contrast, Rees et al. (347) foundles
also in man, a decrease in antroduodenal contractil agonist effect in man, did not find any influence of the
antagonist naloxone. By contrast, Rees et al. (347) found,
also in man, a decrease in antroduodenal contractility
upon i.v. naloxone, but no effect of the agonist lo antagonist naloxone. By contrast, Rees et al. (347) found, also in man, a decrease in antroduodenal contractility upon i.v. naloxone, but no effect of the agonist loperamide. One sensible explanation may be that stimulatio also in man, a decrease in antroduodenal contractility
upon i.v. naloxone, but no effect of the agonist loper-
amide. One sensible explanation may be that stimulation
of opioid receptors by endogenous opioids was, in the
l upon i.v. naloxone, but no effect of the agonist loper-
amide. One sensible explanation may be that stimulation
of opioid receptors by endogenous opioids was, in the
latter study, unmasked by naloxone but prevented, in
tur amide. One sensible explanation may be that stimulation
of opioid receptors by endogenous opioids was, in the
latter study, unmasked by naloxone but prevented, in
turn, any further effect by the exogenous opioid. The
other of opioid receptors by endogenous opioids was, in the latter study, unmasked by naloxone but prevented, in turn, any further effect by the exogenous opioid. The other way round, an inactive opioid system in the former stud latter study, unmasked by naloxone but prevented, in
turn, any further effect by the exogenous opioid. The
other way round, an inactive opioid system in the former
study may have been activated by the exogenous opioid.
No turn, any further effect by the exogenous opioid. The other way round, an inactive opioid system in the former
study may have been activated by the exogenous opioid.
No endogenous activity was likely present that could
hav other way round, an inactive opioid system in the former
study may have been activated by the exogenous opioid.
No endogenous activity was likely present that could
have been detected by naloxone administration. The data
o study may have been activated by the exogenous opioid.
No endogenous activity was likely present that could
have been detected by naloxone administration. The data
of Rees et al. (347), as they stand, do not allow any
stat have been detected by naloxone administration. The data
of Rees et al. (347), as they stand, do not allow any
statement on the propulsive versus nonpropulsive nature
of the contractions suppressed by naloxone.

Similar arguments may be valid in the fasted rat, where

RR

132 KR

naloxone alone had no effect upon transit time of my-

oelectrical activity of the small intestine (119, 247, 335). KROM

132

maloxone alone had no effect upon transit time of my-

oelectrical activity of the small intestine (119, 247, 335).

Thus, the stimulatory effect of some, but not all, opioids KROM

naloxone alone had no effect upon transit time of my-

oelectrical activity of the small intestine (119, 247, 335).

Thus, the stimulatory effect of some, but not all, opioids

observed under certain conditions in th maloxone alone had no effect upon transit time of my-
oelectrical activity of the small intestine (119, 247, 335).
Thus, the stimulatory effect of some, but not all, opioids
observed under certain conditions in the rat (36 naloxone alone had no effect upon transit time of my-
oelectrical activity of the small intestine (119, 247, 335). fro
Thus, the stimulatory effect of some, but not all, opioids (78
observed under certain conditions in the belectrical activity of the small intestine (119, 247, 338)
Thus, the stimulatory effect of some, but not all, opioio
observed under certain conditions in the rat (360), c
(317), and dog (472, 77, 330, 443, 458) may just b Thus, the stimulatory effect of some, but not all, opioiobserved under certain conditions in the rat (360), c (317), and dog (472, 77, 330, 443, 458) may just be of approped to inhitiary ones. Both may be differently manif observed under certain conditions in the rat (360), cat (317), and dog (472, 77, 330, 443, 458) may just be one aspect of intestinal opioid functions as opposed to inhibitory ones. Both may be differently manifested in dif

aspect of intestinal opioid functions as opposed to inhibitory ones. Both may be differently manifested in different species and under different conditions.

e. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR

TYPES. Both the exc itory ones. Both may be differently manifested in different species and under different conditions.

e. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR

TYPES. Both the excitatory and inhibitory opioid effects

in the dog were an ent species and under different conditions. factor is not the excitatory of DIFFERENT OPIOID RECEPTOR carry res. Both the excitatory and inhibitory opioid effects more in the dog were antagonized by naloxone and attributed e. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR carry FRS. Both the excitatory and inhibitory opioid effects moin the dog were antagonized by naloxone and attributed set to mu-type opioid receptors (366b). Similarly, as judged TYPES. Both the excitatory and inhibitory opioid effects
in the dog were antagonized by naloxone and attributed
to mu-type opioid receptors (366b). Similarly, as judged
from the relative potencies of agonists and from the
 in the dog were antagonized by naloxone and attributed set to mu-type opioid receptors (366b). Similarly, as judged to from the relative potencies of agonists and from the signtagonistic potency of naloxone against differe to mu-type opioid receptors (366b). Similarly, as judged to
from the relative potencies of agonists and from the sicentagonistic potency of naloxone against different ago-
mists, mu- and delta-, but not kappa-type receptor from the relative potencies of agonists and from the sicantagonistic potency of naloxone against different ago-
mists, mu- and delta-, but not kappa-type receptors have different implicated in the opioid-effected contracti antagonistic potency of naloxone against different ago-
mists, mu- and delta-, but not kappa-type receptors have
dibeen implicated in the opioid-effected contraction of the
incanine small intestine (458). Opioid receptors, nists, mu- and delta-, but not kappa-type receptors have d
been implicated in the opioid-effected contraction of the in
canine small intestine (458). Opioid receptors, which in
mediate the supraspinal (i.c.v.) and peripher been implicated in the opioid-effected contraction of the inhibition, not stimulation, of contraction by morphine
canine small intestine (458). Opioid receptors, which in the isolated rat, rabbit, guinea-pig, dog, and huma (408a) used, in their recent mouse studies, rather selecmediate the supraspinal (i.c.v.) and peripheral opioid sm
inhibition of intestinal transit in mice and rats, probably
belong to the mu-type (125, 334, 408a, 464). Shook et al. sie:
(408a) used, in their recent mouse studie inhibition of intestinal transit in mice and rats, probably
belong to the mu-type (125, 334, 408a, 464). Shook et al. sien
(408a) used, in their recent mouse studies, rather selec- ind
tive compounds like PL 017 (mu-agonis belong to the mu-type (125, 334, 408a, 464). Shook et al. sie
(408a) used, in their recent mouse studies, rather selec-
tive compounds like PL 017 (mu-agonist), DPDPE no
(delta-agonist), dynorphin(1-9) (kappa-agonist), and (408a) used, in their recent mouse studies, rather selec-
tive compounds like PL 017 (mu-agonist), DPDPE no
(delta-agonist), dynorphin(1-9) (kappa-agonist), and CTP (33
(mu-antagonist). These peptides poorly penetrate the tive compounds like PL 017 (mu-agonist), DPDPE
(delta-agonist), dynorphin(1-9) (kappa-agonist), and CTP
(mu-antagonist). These peptides poorly penetrate the
blood-brain barrier. Delta-type opioid receptors may be
additiona (delta-agonist), dynorphin(1-9) (kappa-agonist), and CTP (334).
(mu-antagonist). These peptides poorly penetrate the den
blood-brain barrier. Delta-type opioid receptors may be served
ditionally involved in spinal inhibiti (mu-antagonist). These peptides poorly penetrate the doblood-brain barrier. Delta-type opioid receptors may be seen additionally involved in spinal inhibition of intestinal latransit in the mouse (334). By contrast, Sivam blood-brain barrier. Delta-type opioid receptors may
additionally involved in spinal inhibition of intest
transit in the mouse (334). By contrast, Sivam and
(410) concluded from the rank order of potencies
morphine, ketocy additionally involved in spinal inhibition of intestinal
transit in the mouse (334). By contrast, Sivam and Ho
(410) concluded from the rank order of potencies of
morphine, ketocyclazocine, and $[D-Ala^2, D-Leu^6]$ -en-
kephalin transit in the mouse (334). By contrast, Sivam and Ho (410) concluded from the rank order of potencies of morphine, ketocyclazocine, and $[D-Ala^2$, $D-Leu^5]$ -enkephalin after i.c.v. administration to the mouse that delta-typ (410) concluded from the rank order of potencies of morphine, ketocyclazocine, and $[D-Ala^2$, $D-Leu^5]$ -en-
kephalin after i.c.v. administration to the mouse that m
delta-type receptors were preferentially involved in su-
pr morphine, ketocyclazocine, and [D-Ala², D-Leu⁵]-en-
kephalin after i.c.v. administration to the mouse that
delta-type receptors were preferentially involved in su-
praspinal inhibition of intestinal transit. However, t kephalin after i.c.v. administration to the mouse the delta-type receptors were preferentially involved in increasional inhibition of intestinal transit. However, the agonists poorly discriminate between opioid receptypes. delta-type receptors were preferentially involved in su-
praspinal inhibition of intestinal transit. However, these
animagonists poorly discriminate between opioid receptor
min
types. Apart from poor receptor selectivity, praspinal inhibition of intestinal transit. However, these and agonists poorly discriminate between opioid receptor mitypes. Apart from poor receptor selectivity, any conclusion based solely on agonist potencies is dangero agonists poorly discriminate between opioid receptor mitypes. Apart from poor receptor selectivity, any conclusion based solely on agonist potencies is dangerous in cerview of possible differences in intrinsic activities o types. Apart from poor receptor selectivity, any conclusion based solely on agonist potencies is dangerous in certive of possible differences in intrinsic activities of the detested opioids as well as in spare receptor poo sion based solely on agonist potencies is dangerous in cerview of possible differences in intrinsic activities of the detested opioids as well as in spare receptor pools of the opitest systems (285). Similar objections app view of possible differences in intrinsic activities of the detested opioids as well as in spare receptor pools of the opitest systems (285). Similar objections apply also to the rationalision of Culpepper-Morgan et al. (7 tested opioids as well as in spare receptor pools of the optest systems (285). Similar objections apply also to the rate conclusion of Culpepper-Morgan et al. (73a) that both of kappa- and mu-type opioid receptors may slow test systems (285). Similar objections apply also to the rate conclusion of Culpepper-Morgan et al. (73a) that both of kappa- and mu-type opioid receptors may slow down every gastrointestinal transit in the guinea-pig, whi conclusion of Culpepper-Morgan et al. (73a) that both of kappa- and mu-type opioid receptors may slow down evergastrointestinal transit in the guinea-pig, while the 3. kappa-selective agonist U-50,488H was ineffective in t kappa- and mu-type opioid receptors may slow down ever to varying degrees (see section III D 2 c).

gastrointestinal transit in the guinea-pig, while the 3. Large Intestine. In the large intestine, a dual excita-

kappa-s gastrointestinal transit
kappa-selective agonist
rat in vivo in another
based primarily on agon
mentioned shortcoming
f. SPECIES DIFFERENC ppa-selective agonist U-50,488H was ineffective in the to
t in vivo in another study. Again, the conclusion is weld primarily on agonist potencies with all of the above (1
entioned shortcomings.
f. SPECIES DIFFERENCES. It rat in vivo in another study. Again, the conclusion is
based primarily on agonist potencies with all of the above
mentioned shortcomings.
f. SPECIES DIFFERENCES. It appears from the foregoing
discussion that, with regard t

based primarily on agonist potencies with all of the above
mentioned shortcomings.
f. SPECIES DIFFERENCES. It appears from the foregoing
discussion that, with regard to the relative importance
of different sites of action, mentioned shortcomings.

f. SPECIES DIFFERENCES. It appears from the foregoir

discussion that, with regard to the relative importanc

of different sites of action, different receptor population

involved, and different mo f. SPECIES DIFFERENCES. It appears from the foregoing discussion that, with regard to the relative importance of different sites of action, different receptor populations involved, and different motility measures affected, discussion that, with regard to the relative importance and thus the predrug motility pattern, the time interval
of different sites of action, different receptor populations between drug administration and measurement, and of different sites of action, different receptor populations be
involved, and different motility measures affected, quan-
titative rather than qualitative species differences exist. tr
However, basic species differences ha involved, and different motility measures affected, quantitative rather than qualitative species differences exist. the However, basic species differences have been claimed be repeatedly. Only recently, Coupar (69) raised titative rather than qualitative species differences exist.
However, basic species differences have been claimed
repeatedly. Only recently, Coupar (69) raised the issue
by pointing out that morphine inhibited the release o However, basic species differences have been claimed
repeatedly. Only recently, Coupar (69) raised the issue
by pointing out that morphine inhibited the release of
acetylcholine from the isolated guinea-pig ileum (325),
bu repeatedly. Only recently, Coupar (69) raised the issue by pointing out that morphine inhibited the release of Sacetylcholine from the isolated guinea-pig ileum (325), mot might have even stimulated this release in the rat

ER
measured, albeit biologically, the release of acetylcholine
from the isolated guinea-pig ileum, while Daniel et al. FR
measured, albeit biologically, the release of acetylcholine
from the isolated guinea-pig ileum, while Daniel et al.
(78) determined changes of the intraluminal pressure in ER
measured, albeit biologically, the release of acetylcholine
from the isolated guinea-pig ileum, while Daniel et al.
(78) determined changes of the intraluminal pressure in
the human and canine small intestine in vivo. M The measured, albeit biologically, the release of acetylcholine from the isolated guinea-pig ileum, while Daniel et al. (78) determined changes of the intraluminal pressure in the human and canine small intestine in vivo. measured, albeit biologically, the release of acetylcho
from the isolated guinea-pig ileum, while Daniel et
(78) determined changes of the intraluminal pressur
the human and canine small intestine in vivo. Mediat
of the sp from the isolated guinea-pig ileum, while Daniel et al. (78) determined changes of the intraluminal pressure in the human and canine small intestine in vivo. Mediation of the spassmogenic opioid effect by release of acetyl (78) determined changes of the intraluminal pressure in
the human and canine small intestine in vivo. Mediation
of the spasmogenic opioid effect by release of acetylcho-
line may be inferred from antagonism by atropine, b the human and canine small intestine in vivo. Mediation of the spassmogenic opioid effect by release of acetylcho line may be inferred from antagonism by atropine, bu evidently other hypothetical explanations exist such a of the spassmogenic opioid effect by release of acetylcholine may be inferred from antagonism by atropine, but evidently other hypothetical explanations exist such as facilitation (i.e., modulation) of the opioid effect by evidently other hypothetical explanations exist such as
facilitation (i.e., modulation) of the opioid effect by mus-
carinic receptors. It has further been argued (69) that
morphine contracted the rat ileum possibly by rel evidently other hypothetical explanations exist such a facilitation (i.e., modulation) of the opioid effect by mus
carinic receptors. It has further been argued (69) tha
morphine contracted the rat ileum possibly by releas facilitation (i.e., modulation) of the opioid effect by m
carinic receptors. It has further been argued (69) tl
morphine contracted the rat ileum possibly by releasi
serotonin (45), although it had no such effect on se
ton carinic receptors. It has further been argued (69) that
morphine contracted the rat ileum possibly by releasing
serotonin (45), although it had no such effect on sero-
tonin release in the guinea-pig ileum (385). No conclu morphine contracted the rat ileum possibly by releasing
serotonin (45), although it had no such effect on sero-
tonin release in the guinea-pig ileum (385). No conclu-
sion as to species differences can be drawn by compari tonin release in the guinea-pig ileum (385). No conclusion as to species differences can be drawn by comparing these data which were obtained under heterogenous conditions. Moreover, Daniel et al. (78) invariably found inh sion as to species differences can be drawn by comparing
these data which were obtained under heterogenous con-
ditions. Moreover, Daniel et al. (78) invariably found
inhibition, not stimulation, of contraction by morphine these data which were ob
ditions. Moreover, Danii
inhibition, not stimulation
in the isolated rat, rabbi
small intestine in vitro.
Morphine apparently d tions. Moreover, Daniel et al. (78) invariably foun
hibition, not stimulation, of contraction by morphin
the isolated rat, rabbit, guinea-pig, dog, and huma
nall intestine in vitro.
Morphine apparently decreased the amplit

tonin release in the guinea-pig ileum (385). No conclu-
sion as to species differences can be drawn by comparing
these data which were obtained under heterogenous con-
ditions. Moreover, Daniel et al. (78) invariably foun inhibition, not stimulation, of contraction by morphine
in the isolated rat, rabbit, guinea-pig, dog, and human
small intestine in vitro.
Morphine apparently decreased the amplitude of tran-
sient tonic and phasic increase in the isolated rat, rabbit, guinea-pig, dog, and human
small intestine in vitro.
Morphine apparently decreased the amplitude of tran-
sient tonic and phasic increases in intraluminal pressure
induced by serotonin in the g small intestine in vitro.

Morphine apparently decreased the amplitude of transient tonic and phasic increases in intraluminal pressure

induced by serotonin in the guinea-pig intestine but had

mo effect in the canine, fe Morphine apparently decreased the amplitude of tran-
sient tonic and phasic increases in intraluminal pressure
induced by serotonin in the guinea-pig intestine but had
no effect in the canine, feline, or simian intestine i sient tonic and phasic increases in intraluminal pressure
induced by serotonin in the guinea-pig intestine but had
no effect in the canine, feline, or simian intestine in vivo
(338). It should be noted, however, that these induced by serotonin in the guinea-pig intestine but had
no effect in the canine, feline, or simian intestine in vivo
(338). It should be noted, however, that these authors
demonstrated tachyphylaxis to the stimulatory eff no effect in the canine, feline, or simian intestine in vivo

(338). It should be noted, however, that these authors

demonstrated tachyphylaxis to the stimulatory effect of

serotonin, in the guinea-pig ileum, but noneth (338). It should be noted, however, that these authors demonstrated tachyphylaxis to the stimulatory effect of serotonin, in the guinea-pig ileum, but nonetheless related the serotonin effect after morphine application to demonstrated tachyphylaxis to the stimulatory effect of serotonin, in the guinea-pig ileum, but nonetheless related the serotonin effect after morphine application to its effect before morphine application in the same anim serotonin, in the guinea-pig ileum, but nonetheless related the serotonin effect after morphine application to
its effect before morphine application in the same ani-
mal. It might turn out that these authors found a spec its effect before morphine application in the same ani-
mal. It might turn out that these authors found a species
difference in serotonin tachyphylaxis, rather than in
morphine action, since no controls for tachyphylaxis t its effect before morphine application in the same ani-
mal. It might turn out that these authors found a species
difference in serotonin tachyphylaxis, rather than in
morphine-action, since no controls for tachyphylaxis t mal. It might turn out that these authors found a specifierence in serotonin tachyphylaxis, rather than morphine action, since no controls for tachyphylaxis serotonin were run or accounted for in morphine-fanimals. Moreove difference in serotonin tachyphylaxis, rather than in
morphine action, since no controls for tachyphylaxis to
serotonin were run or accounted for in morphine-free
animals. Moreover, the relevance of changes in intralu-
min morphine action, since no controls for tachyphylaxis to
serotonin were run or accounted for in morphine-free
animals. Moreover, the relevance of changes in intralu-
minal pressure or longitudinal muscle contraction, as
use serotonin were run or accounted for in morphine-free
animals. Moreover, the relevance of changes in intralu-
minal pressure or longitudinal muscle contraction, as
used in various studies, for propulsive peristalsis is un-
 animals. Moreover, the relevance of changes in intraluminal pressure or longitudinal muscle contraction, as used in various studies, for propulsive peristalsis is uncertain (221). As a whole, available data do not allow a minal pressure or longitudinal muscle contraction, as
used in various studies, for propulsive peristalsis is un-
certain (221). As a whole, available data do not allow any
definite statement on "basic" species differences used in various studies, for propulsive peristalists is uncertain (221). As a whole, available data do not allow any definite statement on "basic" species differences in opioid actions on gut motility. Species differences definite statement on "basic" species differem
opioid actions on gut motility. Species different
rather be of a quantitative nature due to superimp
of contrasting opioid effects observed in all specie
ever to varying degre opioid actions on gut motility. Species differences m
rather be of a quantitative nature due to superimpositi
of contrasting opioid effects observed in all species, ho
ever to varying degrees (see section III D 2 c).
3. *L* rather be of a quantitative nature due to superimposition
of contrasting opioid effects observed in all species, how-
ever to varying degrees (see section III D 2 c).
3. *Large Intestine*. In the large intestine, a dual e

% of contrasting opioid effects observed in all species, how-
ever to varying degrees (see section III D 2 c).
3. Large Intestine. In the large intestine, a dual excita-
tory-inhibitory (or vice verca) effect of various o ever to varying degrees (see section III D 2 c).
3. *Large Intestine*. In the large intestine, a dual excita-
tory-inhibitory (or vice verca) effect of various opioids
was found in the rat (322a), rabbit (320), cat (474), 3. Large Intestine. In the large intestine, a dual excitatory-inhibitory (or vice verca) effect of various opioid was found in the rat $(322a)$, rabbit (320) , cat (474) , do $(13, 41)$, and man (371) . The particular tory-inhibitory (or vice verca) effect of various opioids
was found in the rat (322a), rabbit (320), cat (474), dog
(13, 41), and man (371). The particular effect depended
on the colonic portion examined, the opioid invest was found in the rat (322a), rabbit (320), cat (474), dog (13, 41), and man (371). The particular effect depended on the colonic portion examined, the opioid investigated, the motility parameter looked at, the feeding cond on the colonic portion examined, the opioid investigated, the motility parameter looked at, the feeding conditions the mothly parameter looked at, the leeding conditions
and thus the predrug motility pattern, the time interval
between drug administration and measurement, and the
route of administration (i.e., peripherally versus cen-
t between drug administration and measurement, and the route of administration (i.e., peripherally versus centrally). However, as far as tested, naloxone antagonized both stimulatory and inhibitory responses, proving that bo route of administration (i.e., peripherally versus centrally). However, as far as tested, naloxone antagonized
both stimulatory and inhibitory responses, proving that
both were mediated by opioid receptors (421, 371, 474). trally). However, as far as tested, naloxone antagonized
both stimulatory and inhibitory responses, proving that
both were mediated by opioid receptors (421, 371, 474).
Supraspinal opioid inhibition of colonic transit in t both were mediated by opioid receptors (421, 371, 474).
Supraspinal opioid inhibition of colonic transit in the
mouse was attributed to mu- and (possibly) delta-type
receptors (342a). There has been one exception to nal-
o Supraspinal opioid inhibition of colonic transit in the

OPIOIDS AND CONTROL OF GASTROI
Here morphine and the more specific mu-receptor
agonist [D-Ala², N-methyl-Phe⁴, Gly⁵-ol]-enkephalin opioids and contract of GASTROI
Here morphine and the more specific mu-receptor
agonist [D-Ala², N-methyl-Phe⁴, Gly⁵-ol]-enkephalin
(DAGO) induced one jejunal MMC and enhanced colonic OPIOIDS AND CONTROL OF GASTROINTE

Here morphine and the more specific mu-receptor ((

agonist [D-Ala², N-methyl-Phe⁴, Gly⁵-ol]-enkephalin o

(DAGO) induced one jejunal MMC and enhanced colonic U

motility after both Here morphine and the more specific mu-receptor agonist [D-Ala², N-methyl-Phe⁴, Gly⁵-ol]-enkephalin (DAGO) induced one jejunal MMC and enhanced colonic motility after both i.v. and i.c.v. administration (110). Wherea Here morphine and the more specific mu-receptor $(9 \text{ agonist} [D-Ala^2, N-methyl-Phe^4, Gly^5-ol]-enkephalin of (DAGO) induced one jejunal MMC and enhanced colonic Unotility after both i.v. and i.c.v. administration (110). UpWhereas the effects upon i.v. administration were blocked by i.v. naloxone, the effects upon i.c.v. adminis- L$ (DAGO) induced one jejunal MMC and enhanced colonic motility after both i.v. and i.c.v. administration (110).
Whereas the effects upon i.v. administration were blocked by i.v. naloxone, the effects upon i.c.v. adminis-(DAGO) induced one jejunal MMC and enhanced colonic Unfortunately, naloxone was not tested for any physiomotility after both i.v. and i.c.v. administration (110). logical role of esophageal opioids. There are, however, Wh motility after both i.v. and i.c.v. administration (110). log
Whereas the effects upon i.v. administration were rep
blocked by i.v. naloxone, the effects upon i.c.v. adminis-
tration were not. Interestingly, the increased Whereas the effects upon i.v. administration were
blocked by i.v. naloxone, the effects upon i.c.v. adminis-
tration were not. Interestingly, the increased colonic
motility after i.c.v. administration was prevented by the
 blocked by i.v. naloxone, the effects upon i.c.v. administration were not. Interestingly, the increased colonic motility after i.c.v. administration was prevented by the benzodiazepine antagonist RO 15-1788, leading the au motility after i.c.v. administration was prevented by the Again, systemic administration of the drug implied that
benzodiazepine antagonist RO 15-1788, leading the au-
opioid receptors with potentially different functional motility after i.c.v. administration was prevented by the
benzodiazepine antagonist RO 15-1788, leading the au-
thors to suggest that benzodiazepine, rather than opioid,
receptors were involved in this central action on co behizodazephe antagonist ito 15-1100, leading the ad-
thors to suggest that benzodiazepine, rather than opioid, nif
receptors were involved in this central action on colonic fun
motility. Alternatively, i.v. naloxone at th receptors were involved in this central action on color
motility. Alternatively, i.v. naloxone at the dose en
ployed might not have reached the opioid receptors whi
were possibly activated upon i.c.v. administration of t
o motility. Alternatively, i.v. naloxone at the dose em-
ployed might not have reached the opioid receptors which
were possibly activated upon i.c.v. administration of the
opioid, and the antagonism by the benzodiazepine ant were possibly activated upon i.c.v. administration of the kappa receptors, possibly located on the sphincter mus-
opioid, and the antagonism by the benzodiazepine antag-
only the mediate inhibition while smooth muscle delt were possibly activated upon i.c.v. administration of the opioid, and the antagonism by the benzodiazepine antagonist may be functional. This interesting issue deserve further attention. On the other hand, Daniel et al. (7 opioid, and the antagonism by the benzodiazepine antagonist may be functional. This interesting issue deserves
further attention. On the other hand, Daniel et al. (76a)
never observed excitatory responses to close intraart onist may be functional. This interesting issue deserves net
further attention. On the other hand, Daniel et al. (76a) the
never observed excitatory responses to close intraarterial pre
opioid injections in the canine colo further attention. On the other hand, Daniel et al. (never observed excitatory responses to close intraart opioid injections in the canine colon but found transinhibition of electrically induced contractions, as the expect mever observed
opioid injection
inhibition of el
expected from
mitter release.
Schang et al. ioid injections in the canine colon but found transient
hibition of electrically induced contractions, as to be
pected from prejunctional inhibition of neurotrans-
itter release.
Schang et al. (371) concluded from their h inhibition of electrically induced contractions, as to be viewpected from prejunctional inhibition of neurotrans-
in $\frac{1}{2}$ in $\frac{1}{2}$ schang et al. (371) concluded from their human studies
that morphine promoted sta

expected from prejunctional inhibition of neurotransmitter release.

Schang et al. (371) concluded from their human studies

that morphine promoted stationary spiking activity

(mixing segmentations) and suppressed propaga mitter release.
Schang et al. (371) concluded from their human studies
that morphine promoted stationary spiking activity
(mixing segmentations) and suppressed propagating
spike bursts (which may relate to propulsive circu Schang et al. (371) concluded from their human studies
that morphine promoted stationary spiking activity
(mixing segmentations) and suppressed propagating
spike bursts (which may relate to propulsive circulan
muscle contr that morphine promoted stationary spiking activity
(mixing segmentations) and suppressed propagating
spike bursts (which may relate to propulsive circular
muscle contractions) in the colon of healthy volunteers.
As already (mixing segmentations) and suppressed propagating
spike bursts (which may relate to propulsive circular
muscle contractions) in the colon of healthy volunteers.
As already discussed with respect to the small intestine
and spike bursts (which may relate to propulsive circula
muscle contractions) in the colon of healthy volunteer
As already discussed with respect to the small intestir
and stomach, the failure of naloxone alone to alter co
lon muscle contractions) in the colon of healthy voluntee
As already discussed with respect to the small intesti
and stomach, the failure of naloxone alone to alter a
lonic motility patterns (371) may be related to a cou
terba As already discussed with respect to the small intestine eno
and stomach, the failure of naloxone alone to alter co-
lonic motility patterns (371) may be related to a coun-
tior-
terbalance between a blockade of inhibitory and stomach, the failure of naloxone alone to alter co-
lonic motility patterns (371) may be related to a coun-
terbalance between a blockade of inhibitory and excita-
tory opioid mechanisms. These might be active in an
a lonic motility patterns (371) may be related to a counterbalance between a blockade of inhibitory and excitatory opioid mechanisms. These might be active in an malternating fashion in order to modulate the periodicity fies terbalance between a blockade of inhibitory and excita-
tory opioid mechanisms. These might be active in an
alternating fashion in order to modulate the periodicity
of peristalsis (233). A predominance of excitatory opioid tory opioid mechanisms. These might be active in an alternating fashion in order to modulate the periodicity of peristalsis (233). A predominance of excitatory opioid influences on colonic motility (319, 40, 433, 109, 161, alternating fashion in order to modulate the periodicity
of peristalsis (233). A predominance of excitatory opioid
influences on colonic motility (319, 40, 433, 109, 161, 33)
may develop under certain conditions, which are of peristalsis (233). A predominance of excitatory opioid opioinfluences on colonic motility (319, 40, 433, 109, 161, 33) the may develop under certain conditions, which are not yet K
fully understood. Sun et al. (433) rep influences on colonic motility (319, 40, 433, 109, 161, 33
may develop under certain conditions, which are not ye
fully understood. Sun et al. (433) reported that the gas
trocolonic response, i.e., a vagally mediated incre may develop under certain conditions, which are not yet
fully understood. Sun et al. (433) reported that the gas-
trocolonic response, i.e., a vagally mediated increase in
distal colonic spiking activity after eating, was trocolonic response, i.e., a vagally mediated increase in cat and dog. This is consonant with data by Rattan and
distal colonic spiking activity after eating, was com-
pletely abolished by naloxone in healthy volunteers. T have been detected in the human vagus nerve (261). pletely abolished by naloxone in healthy volunteers. This
suggests a stimulatory role of endogenous opioids, which
have been detected in the human vagus nerve (261).
4. Gastrointestinal sphincters. The effects of opioids o

suggests a stimulatory role of endogenous opioids, which is
have been detected in the human vagus nerve (261). The 4. Gastrointestinal sphincters. The effects of opioids on T
pressure and relaxation of the lower esophageal have been detected in the human vagus nerve (261).
4. *Gastrointestinal sphincters*. The effects of opioids on
pressure and relaxation of the lower esophageal sphincter
(LES) are even less understood than those on other pa 4. Gastrointestinal sphincters. The effects of opioids on
pressure and relaxation of the lower esophageal sphincter
(LES) are even less understood than those on other parts
of the gastrointestinal tract. In the dog, i.v. p pressure and relaxation of the lower esophageal sphincter
(LES) are even less understood than those on other parts
of the gastrointestinal tract. In the dog, i.v. pethidine
induced phasic increases in gastroesophageal (rsp (LES) are even less understood than those on other parts
of the gastrointestinal tract. In the dog, i.v. pethidine
induced phasic increases in gastroesophageal (rsp. LES)
sphincter pressure (428). Potential blockade by nal of the gastrointestinal tract. In the dog, i.v. pethidine cordination correlation in the dog, i.v. pethidine cordination of the sphincter pressure (428). Potential blockade by naloxone repowers not tested. Howard et al. (1 induced phasic increases in gastroesophageal (rsp. LES)
sphincter pressure (428). Potential blockade by naloxone
was not tested. Howard et al. (178) reported that en-
kephalin reduced LES relaxation upon swallowing in
heal sphincter pressure (428). Potential blockade by naloxone
was not tested. Howard et al. (178) reported that en-
kephalin reduced LES relaxation upon swallowing in
healthy volunteers without any effect on LES pressure
or per was not tested. Howard et al. (178) reported that en-
kephalin reduced LES relaxation upon swallowing in
healthy volunteers without any effect on LES pressure
or peristalsis otherwise. They did not find any influence
of na kephalin reduced LES relaxation upon swallowing in two
healthy volunteers without any effect on LES pressure adm
or peristalsis otherwise. They did not find any influence bees
of naloxone alone on LES motility. Endogenous healthy volunteers without any effect on LES pressure adm
or peristalsis otherwise. They did not find any influence been
of naloxone alone on LES motility. Endogenous opioids sphi
might, therefore, not exert any major impa of naloxone alone on LES motility. Endogenous opioids sphincter, were probably inhibitory in these experiments.
might, therefore, not exert any major impact on LES The data are at variance with those of Rattan and Culver
f

ESTINAL MOTILITY AND SECRETION 133
(91). The authors (91) speculated about a potential role
of excessively released endogenous opioids in achalasia. ESTINAL MOTILITY AND SECRETION 133
(91). The authors (91) speculated about a potential role
of excessively released endogenous opioids in achalasia.
Unfortunately, naloxone was not tested for any physio-ESTINAL MOTILITY AND SECRETION
(91). The authors (91) speculated about a potential r
of excessively released endogenous opioids in achalas
Unfortunately, naloxone was not tested for any phys
logical role of esophageal opio (91). The authors (91) speculated about a potential role of excessively released endogenous opioids in achalasia. Unfortunately, naloxone was not tested for any physiological role of esophageal opioids. There are, however, (91). The authors (91) speculated about a potential role of excessively released endogenous opioids in achalasia. Unfortunately, naloxone was not tested for any physiological role of esophageal opioids. There are, however, logical role of esophageal opioids. There are, however, Unfortunately, naloxone was not tested for any physiological role of esophageal opioids. There are, however, reports on just the opposite opioid effect, i.e., enhanced LES relaxation with an increased likelihood of gastroe logical role of esophageal opioids. There are, however,
reports on just the opposite opioid effect, i.e., enhanced
LES relaxation with an increased likelihood of gastro-
esophageal reflux in man and monkey (152, 166, 288). reports on just the opposite opioid effect, i.e., enhanced LES relaxation with an increased likelihood of gastro-
esophageal reflux in man and monkey (152, 166, 288).
Again, systemic administration of the drug implied that LES relaxation with an increased likelihood of gastro-
esophageal reflux in man and monkey (152, 166, 288).
Again, systemic administration of the drug implied that
opioid receptors with potentially different functional sig opioid receptors with potentially different functional sig-Again, systemic administration of the drug implied that
opioid receptors with potentially different functional sig-
nificance were activated, depending on the particular
functional state of the tissue at the time of drug a opioid receptors with potentially different functional significance were activated, depending on the particular functional state of the tissue at the time of drug administration. In fact, Rattan and Goyal (344) suggested f mificance were activated, depending on the particula
functional state of the tissue at the time of drug admin
istration. In fact, Rattan and Goyal (344) suggested from
in vivo experiments in the opossum that opioid mu- and functional state of the tissue at the time of drug administration. In fact, Rattan and Goyal (344) suggested from
in vivo experiments in the opossum that opioid mu- and
kappa receptors, possibly located on the sphincter mu istration. In fact, Rattan and Goyal (344) suggested from
in vivo experiments in the opossum that opioid mu- and
kappa receptors, possibly located on the sphincter mus-
cle, mediate inhibition while smooth muscle delta- an in vivo experiments in the opossum that opioid mu- and
kappa receptors, possibly located on the sphincter mus-
cle, mediate inhibition while smooth muscle delta- and
neuronal sigma opioid receptors mediate contraction of
 kappa receptors, possibly located on the sphincter mus-
cle, mediate inhibition while smooth muscle delta- and
neuronal sigma opioid receptors mediate contraction of
the LES. Mittal et al. (288) reported an increase in LE cle, mediate inhibition while smooth muscle delta- and
neuronal sigma opioid receptors mediate contraction of
the LES. Mittal et al. (288) reported an increase in LES
pressure in man by naloxone alone, which may point to
 neuronal sigma opioid receptors mediate contraction
the LES. Mittal et al. (288) reported an increase in
pressure in man by naloxone alone, which may poin
a physiological relaxant role of endogenous opioid
view of the conf the LES. Mittal et al. (288) reported an increase in LES
pressure in man by naloxone alone, which may point to
a physiological relaxant role of endogenous opioids. In
view of the conflicting reports, however, the pathophys pressure in man by naloxone alone, which may point to a physiological relaxant role of endogenous opioids. In view of the conflicting reports, however, the pathophysiological significance of possibly diminished enkephaline physiological relaxant role of endogenous opioids. In
ew of the conflicting reports, however, the pathophys-
logical significance of possibly diminished enkephalin
pers in achalasia (4) cannot be assessed at this time.
Opi

view of the conflicting reports, however, the pathophysiological significance of possibly diminished enkephalin
fibers in achalasia (4) cannot be assessed at this time.
Opioid peptides have been demonstrated in myenteric
n iological significance of possibly diminished enkephalin
fibers in achalasia (4) cannot be assessed at this time.
Opioid peptides have been demonstrated in myenteric
neurons of the feline pylorus (94) and in the feline and fibers in achalasia (4) cannot be assessed at this time
Opioid peptides have been demonstrated in myent
neurons of the feline pylorus (94) and in the feline i
human vagus nerve (261). These findings add to th
on pyloric Opioid peptides have been demonstrated in myenterineurons of the feline pylorus (94) and in the feline an human vagus nerve (261). These findings add to thos on pyloric phasic contractions upon electrical stimulation of th neurons of the feline pylorus (94) and in the feline and
human vagus nerve (261). These findings add to those
on pyloric phasic contractions upon electrical stimula-
tion of the vagus nerve or upon administration of exog-
 human vagus nerve (261). These findings add to those
on pyloric phasic contractions upon electrical stimula-
tion of the vagus nerve or upon administration of exog-
enous opioids in the cat (93, 348). Both effects as well tion were antagonized by naloxone (93, 348), indicating tion of the vagus nerve or upon administration of exog-
enous opioids in the cat (93, 348). Both effects as well as
the pyloric contractions induced by duodenal acidifica-
tion were antagonized by naloxone (93, 348), indic enous opioids in the cat (93, 348). Both effects as well as
the pyloric contractions induced by duodenal acidifica-
tion were antagonized by naloxone (93, 348), indicating
an involvement of endogenous opioids in this refl the pyloric contractions induced by duodenal acidification were antagonized by naloxone (93, 348), indicating
an involvement of endogenous opioids in this reflex
mechanism. In the dog, pyloric contraction elicited by
fiel tion were antagonized by naloxone (93, 348), indicating
an involvement of endogenous opioids in this reflex
mechanism. In the dog, pyloric contraction elicited by
field stimulation of duodenal nerves was inhibited by
opio an involvement of endogenous
mechanism. In the dog, pyloric of
field stimulation of duodenal ne
opioids (76a). A purely inhibitory
the canine pylorus was concluded.
Koppanyi and Murphy (217) re field stimulation of duodenal nerves was inhibited by
opioids (76a). A purely inhibitory function of opioids in
the canine pylorus was concluded.
Koppanyi and Murphy (217) reported that morphine

4. Gastrointestinal sphincters. The effects of opioids on field stimulation of duodenal nerves was inhibited by
opioids (76a). A purely inhibitory function of opioids in
the canine pylorus was concluded.
Koppanyi and Murphy (217) reported that morphine
produced pronounced anal sp opioids (76a). A purely inhibitory function of opioids in
the canine pylorus was concluded.
Koppanyi and Murphy (217) reported that morphine
produced pronounced anal sphincter contractions in the
cat and dog. This is conso the canine pylorus was concluded.

Koppanyi and Murphy (217) reported that morph

produced pronounced anal sphincter contractions in

cat and dog. This is consonant with data by Rattan

Culver (343) in the opossum showing Koppanyi and Murphy (217) reported that morphine
produced pronounced anal sphincter contractions in the
cat and dog. This is consonant with data by Rattan and
Culver (343) in the opossum showing that the peripher-
ally ac cat and dog. This is consonant with data by Rattan and cat and dog. This is consonant with data by Rattan and
Culver (343) in the opossum showing that the peripher
ally acting opioid loperamide (486a) caused a rise in
internal anal sphincter pressure and a decrease in inter-
n Culver (343) in the opossum showing that the peripherally acting opioid loperamide (486a) caused a rise in internal anal sphincter pressure and a decrease in internal anal sphincter relaxation upon rectal distension.
These ally acting opioid loperamide (486a) caused a rise in
internal anal sphincter pressure and a decrease in inter-
nal anal sphincter relaxation upon rectal distension.
These effects were antagonized by naloxone. By contrast, internal anal sphincter pressure and a decrease in internal anal sphincter relaxation upon rectal distension.
These effects were antagonized by naloxone. By contrast,
Bouvier et al. (34) demonstrated an inhibitory effect o next may be from the feline internal muscles. By contrast,
Bouvier et al. (34) demonstrated an inhibitory effect of
morphine and enkephalins on the electromyogram re-
corded from the feline internal smooth muscle sphincter Bouvier et al. (34) demonstrated an inhibitory effect of morphine and enkephalins on the electromyogram recorded from the feline internal smooth muscle sphincter of the anus both in vivo and in vitro. These authors reporte morphine and enkephalins on the electromyogram re-
corded from the feline internal smooth muscle sphincter
of the anus both in vivo and in vitro. These authors
reported that intramural nerve stimulation, which ex-
cites th corded from the feline internal smooth muscle sphincter
of the anus both in vivo and in vitro. These authors
reported that intramural nerve stimulation, which ex-
cites the sphincter via sympathetic nerve fibers, was, in
t of the anus both in vivo and in vitro. These authors
reported that intramural nerve stimulation, which ex-
cites the sphincter via sympathetic nerve fibers, was, in
two of their experiments, only effective after naloxone
a reported that intramural nerve stimulation, which excites the sphincter via sympathetic nerve fibers, was, in two of their experiments, only effective after naloxone administration. Thus, endogenous opioids, which have bee cites the sphincter via sympathetic nerve fibers, was, i
two of their experiments, only effective after naloxon
administration. Thus, endogenous opioids, which hav
been demonstrated immunohistochemically in the ana
sphinct two of their experiments, only effective after naloxone administration. Thus, endogenous opioids, which have been demonstrated immunohistochemically in the anal sphincter, were probably inhibitory in these experiments. The been demonstrated immunohistochemically in the anal loperamide inhibited internal anal sphincter relaxation

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caused by sacral nerve stimulation, but not that caused ne
by local intramural stimulation or administration of nickR

caused by sacral nerve stimulation, but not that caused

by local intramural stimulation or administration of nic-

otine. The opioid effect was antagonized by naloxone. KRC

caused by sacral nerve stimulation, but not that caused

by local intramural stimulation or administration of nic-

otine. The opioid effect was antagonized by naloxone.

The authors concluded that opioid receptors in The authors caused by sacral nerve stimulation, but not that caused
hy local intramural stimulation or administration of niction.
The authors concluded that opioid receptors inhibited V
neurotransmitter release from pregan caused by sacral nerve stimulation, but not that caused not
by local intramural stimulation or administration of nic-
otine. The opioid effect was antagonized by naloxone. re
The authors concluded that opioid receptors inh by local intramural stimulation or administration of nicotine. The opioid effect was antagonized by naloxone.
The authors concluded that opioid receptors inhibited
neurotransmitter release from preganglionic sacral nerve
f

The authors concluded that opioid receptors inhibited V
neurotransmitter release from preganglionic sacral nerve
fibers. The issue awaits further clarification. ((
A dual excitatory-inhibitory effect of morphine was
in als neurotransmitter release from preganglionic sacral nerve
fibers. The issue awaits further clarification.
A dual excitatory-inhibitory effect of morphine was
islso detected in the canine choledochoduodenal junction
in vivo fibers. The issue awaits further clarification. (6

A dual excitatory-inhibitory effect of morphine was

inless than the canine choledochoduodenal junction

in vivo (197). The excitatory action was observed at

lower doses A dual excitatory-inhibitory effect of morphine was
also detected in the canine choledochoduodenal junction
in vivo (197). The excitatory action was observed at
lower doses than the inhibitory effect. Naloxone alone
had no also detected in the canine choledochoduodenal jund
in vivo (197). The excitatory action was observe
lower doses than the inhibitory effect. Naloxone a
had no effect, but elicited strong withdrawal contract
when administer in vivo (197). The excitatory action was observed at lower doses than the inhibitory effect. Naloxone alone had no effect, but elicited strong withdrawal contractions when administered after repeated morphine administratio lower doses than the inhibitory effect. Naloxone alone
had no effect, but elicited strong withdrawal contractions
when administered after repeated morphine administra-
ions. CCK-induced gallbladder emptying was, in man,
i when administered after repeated morphine administrations. CCK-induced gallbladder emptying was, in man, inhibited by morphine and by the enkephalin analogue FK 33-824, an effect prevented by naloxone (486). Nalwhen administered after repeated morphine administra-
tions. CCK-induced gallbladder emptying was, in man, radial stretch by inhibition of VIP release (145a; see also
inhibited by morphine and by the enkephalin analogue s tions. CCK-induced gallbladder emptying was, in man,
inhibited by morphine and by the enkephalin analogue
FK 33-824, an effect prevented by naloxone (486). Nal-
oxone alone had no effect. Whether endogenous opioids
were in inhibited by morphine and by the enkephalin analogue sect FK 33-824, an effect prevented by naloxone (486) . Naloxone alone had no effect. Whether endogenous opioids censume were involved in the control of the tone of th $\begin{array}{l} \text{FK 33-824} \ \text{oxone alone} \ \text{above} \ \text{or odd} \ \text{is} \ \text{and} \ 486. \ \text{\textit{F. Onoid}} \ \text{\textit{F. Onoid}} \end{array}$ were involved in the control of the tone of the sphincter
of Oddi is still unknown. For further references, see 197
and 486.
E. Opioid Interactions with Gastrointestinal

Neurotransmitters and Neuromodulators

1. 486
1. Opioid Interactions with Gastrointestinal
1. Acetylcholine. Presynaptic inhibition of acetylc
1. Acetylcholine. Presynaptic inhibition of acetylc
release (325, 374, 461) and postsynaptic inhibition E. Opioid Interactions with Gastrointestinal

Neurotransmitters and Neuromodulators

1. Acetylcholine. Presynaptic inhibition of acetylcho-

line release (325, 374, 461) and postsynaptic inhibition

of the action of acety E. Optoid Interactions with Gastrointestinal

Neurotransmitters and Neuromodulators

1. Acetylcholine. Presynaptic inhibition of acetylcho-

line release (325, 374, 461) and postsynaptic inhibition

of the action of acety Neurotransmitters and Neuromodulators

1. Acetylcholine. Presynaptic inhibition of acetylcho-

line release (325, 374, 461) and postsynaptic inhibition

of the action of acetylcholine (236) have been discussed

as possibl 1. Acetylcholine. Presynaptic inhibition of acetylcholine release (325, 374, 461) and postsynaptic inhibition of the action of acetylcholine (236) have been discussed as possible modes of opioid action in depressing the pe line release (325, 374, 461) and postsynaptic inhibition
of the action of acetylcholine (236) have been discussed
as possible modes of opioid action in depressing the
peristaltic reflex (see section III A). On the other ha of the action of acetylcholine (236) have been discussed
as possible modes of opioid action in depressing the
peristaltic reflex (see section III A). On the other hand,
truncal vagotomy neither affected the initiation of p as possible modes of opioid action in depressing the peristaltic reflex (see section III A). On the other hand, truncal vagotomy neither affected the initiation of premature phase III activity by morphine in the dog $(367$ peristaltic reflex (see section III A). On the other han
truncal vagotomy neither affected the initiation of pr
mature phase III activity by morphine in the dog (36
nor did it alter tissue concentrations of immunoreacti
[M truncal vagotomy neither affected the initiation of pre-

mature phase III activity by morphine in the dog (367)

nor did it alter tissue concentrations of immunoreactive

[Met⁵]-enkephalin in any part of the rat gastro mature phase III activity by morphine in the dog (367
nor did it alter tissue concentrations of immunoreactiv
[Met⁵]-enkephalin in any part of the rat gastrointestine
tract (106). Vagal input appears, therefore, not nece nor did it alter tissue concentrations of immunoreactive [Met⁵]-enkephalin in any part of the rat gastrointestinal tract (106). Vagal input appears, therefore, not necessary for peripheral excitatory opioid action or int [Met⁵]-enkephalin in any part of the rat gastrointestinal
tract (106). Vagal input appears, therefore, not necessary
for peripheral excitatory opioid action or intrinsic regu-
lation of gastrointestinal opioids. Little i tract (106). Vagal input appears, therefore, not necessary
for peripheral excitatory opioid action or intrinsic regu-
distinct the reduced secured whose re-
lation of gastrointestinal opioids. Little is known about
the rol for peripheral excitatory opioid action or intrinsic regulation of gastrointestinal opioids. Little is known about the role of the sympathetic nervous system as a target for peripheral opioid actions. Although Bornstein an lation of gastrointestinal opioids. Little is known about
the role of the sympathetic nervous system as a target
for peripheral opioid actions. Although Bornstein and
Fields (31) needed high morphine concentrations to re-
 the role of the sympathetic nervous system as a targ
for peripheral opioid actions. Although Bornstein a
Fields (31) needed high morphine concentrations to 1
duce sympathetic transmission in the inferior mesenter
ganglion for peripheral opioid actions. Although Bornstein and
Fields (31) needed high morphine concentrations to reduce sympathetic transmission in the inferior mesenteric
ganglion of the guinea-pig in vitro, this effect was antag Fields (31) needed high morphine concentrations to reduce sympathetic transmission in the inferior mesenteric ganglion of the guinea-pig in vitro, this effect was antagonized by naloxone. It may have some physiological sig duce sympathetic transmission in the inferior mesent
ganglion of the guinea-pig in vitro, this effect was ant
onized by naloxone. It may have some physiologi
significance for acetylcholine release at these synaps
consideri ganglion of the guinea-pig in vitro, this effect was antionized by naloxone. It may have some physiologies
ignificance for acetylcholine release at these synaps
considering that Schultzberg et al. (384) found enkep
alin-im onized by naloxone. It may have some physiolog
significance for acetylcholine release at these synap
considering that Schultzberg et al. (384) found enke
alin-immunoreactive nerve fibers and neurons in guir
pig and rat sym significance for acetylcholine release at these synapses, A s
considering that Schultzberg et al. (384) found enkeph-
alin-immunoreactive nerve fibers and neurons in guinea-
pig and rat sympathetic ganglia. Aside from a considering that Schultzberg et al. (384) found enkephalin-immunoreactive nerve fibers and neurons in guinea-
pig and rat sympathetic ganglia. Aside from acetylcho-
line, a number of additional neurotransmitters may be
ind alin-immunoreactive nerve fibers and neurons in guinea-
pig and rat sympathetic ganglia. Aside from acetylcho-
line, a number of additional neurotransmitters may be
indirectly involved in this complex system, both in relapig and rat sympathetic ganglia. Aside fro
line, a number of additional neurotransmi
indirectly involved in this complex system,
tion to acetylcholine release and indepen
Possible interactions are discussed below.
2. Vasoa is a number of additional neurotransmitters may be
directly involved in this complex system, both in rela-
on to acetylcholine release and independent thereof.
ssible interactions are discussed below.
2. Vasoactive intesti

indirectly involved in this complex system, both in rela-
tion to acetylcholine release and independent thereof.
 $\frac{44}{10}$
Possible interactions are discussed below. m
2. Vasoactive intestinal polypeptide (VIP). The act Possible interactions are discussed below.
2. Vasoactive intestinal polypeptide (VIP). The actions
of neurotransmitter substances on gut motility and their
occurrence in the intestinal wall have been reviewed
elsewhere (21 2. Vasoactive intestinal polypeptide (VIP). The actions is
of neurotransmitter substances on gut motility and their
occurrence in the intestinal wall have been reviewed the
lesswhere (219, 76, 223, 130, 46, 87, 470). Both of neurotransmitter substances on gut motility and their opencurrence in the intestinal wall have been reviewed the elsewhere (219, 76, 223, 130, 46, 87, 470). Both ATP and, compress of more recently, VIP have been ascribe occurrence in the intestinal wall have been reviewed the elsewhere (219, 76, 223, 130, 46, 87, 470). Both ATP and, compore recently, VIP have been ascribed the properties of operation of "nonadrenergic" inhibitory neurotra elsewhere (219, 76, 223, 130, 46, 87, 470). Both ATP and, com
more recently, VIP have been ascribed the properties of opic
a "nonadrenergic" inhibitory neurotransmitter in the relegut, although this issue is still far from more recently, VIP have been ascribed the properties
a "nonadrenergic" inhibitory neurotransmitter in
gut, although this issue is still far from being sett
(470). A similar inhibitory system may be operative
the human gut

ine. The opioid effect was antagonized by naloxone. relation of these data to any possible interaction with
he authors concluded that opioid receptors inhibited VIP is unknown. Endogenous opioids and VIP coexist
eurotransm ER
nergic-noncholinergic (NANC) neuromuscular transm
sion in the human colon in vitro (180), although ER
nergic-noncholinergic (NANC) neuromuscular transmis-
sion in the human colon in vitro (180), although the
relation of these data to any possible interaction with FR
nergic-noncholinergic (NANC) neuromuscular transmission in the human colon in vitro (180), although the
relation of these data to any possible interaction with
VIP is unknown. Endogenous opioids and VIP coexist The mergic-noncholinergic (NANC) neuromuscular transmission in the human colon in vitro (180), although the relation of these data to any possible interaction with VIP is unknown. Endogenous opioids and VIP coexist within nergic-noncholinergic (NANC) neuromuscular transmission in the human colon in vitro (180), although the relation of these data to any possible interaction with VIP is unknown. Endogenous opioids and VIP coexist within a su sion in the human colon in vitro (180), although the relation of these data to any possible interaction with VIP is unknown. Endogenous opioids and VIP coexist within a subpopulation of guinea-pig myenteric neurons (65a). relation of these data to any possible interaction wit
VIP is unknown. Endogenous opioids and VIP coexis
within a subpopulation of guinea-pig myenteric neurons
(65a). On the other hand, neither naloxone nor opioids
influen VIP is unknown. Endogenous opioids and VIP coex
within a subpopulation of guinea-pig myenteric neuro
(65a). On the other hand, neither naloxone nor opio
influenced the NANC relaxation brought about by el
trical stimulation within a subpopulation of guinea-pig myenteric neurons (65a). On the other hand, neither naloxone nor opioids influenced the NANC relaxation brought about by electrical stimulation in the reserpinized, atropine-treated, an (65a). On the other hand, neither naloxone nor opioids
influenced the NANC relaxation brought about by elec-
trical stimulation in the reserpinized, atropine-treated,
and serotonin-contracted longitudinal or circular muscl influenced the NANC relaxation brought about by electrical stimulation in the reserpinized, atropine-treated, and serotonin-contracted longitudinal or circular muscle strip from the feline stomach (250). In the guinea-pig trical stimulation in the reserpinized, atropine-treated,
and serotonin-contracted longitudinal or circular muscle
strip from the feline stomach (250). In the guinea-pig
and rat colon in vitro, opioids were suggested to in and serotonin-contracted longitudinal or circular muscle
strip from the feline stomach (250). In the guinea-pig
and rat colon in vitro, opioids were suggested to inhibit
relaxation distal and augment contraction proximal t and rat colon in vitro, opioids were suggested to inhibit
relaxation distal and augment contraction proximal to
radial stretch by inhibition of VIP release (145a; see also
section III C).
 β . Cholecystokinin (CCK) and s dellepted to inhibit axation distal and augment contraction proximal to dial stretch by inhibition of VIP release (145a; see also ction III C).
3. *Cholecystokinin (CCK) and substance P*. Most re-
ntly, Gilbert et al relaxation distal and augment contraction proximal to radial stretch by inhibition of VIP release (145a; see also section III C).
3. *Cholecystokinin (CCK) and substance P*. Most recently, Gilbert et al. (132) reported tha

radial stretch by inhibition of VIP release (145a; see also
section III C).
3. Cholecystokinin (CCK) and substance P. Most recently, Gilbert et al. (132) reported that morphine hy-
perpolarized, probably through an increa section III C).
3. Cholecystokinin (CCK) and substance P. Most re
cently, Gilbert et al. (132) reported that morphine hy
perpolarized, probably through an increase in potassiun
conductance, circular but not longitudinal sm 3. Cholecystokinin (CCK) and substance P. Most recently, Gilbert et al. (132) reported that morphine hyperpolarized, probably through an increase in potassium conductance, circular but not longitudinal smooth muscle cells cently, Gilbert et al. (132) reported that morphine hyperpolarized, probably through an increase in potassium conductance, circular but not longitudinal smooth muscle cells in canine jejunum. The effect was blocked by nalo perpolarized, probably through an increase in potassium
conductance, circular but not longitudinal smooth mus-
cle cells in canine jejunum. The effect was blocked by
naloxone and TTX, but not by cholinergic or adrenergic
a conductance, circular but not longitudinal smooth mus-
cle cells in canine jejunum. The effect was blocked by
naloxone and TTX, but not by cholinergic or adrenergic
antagonists. This is consistent with the proposition of
a cle cells in canine jejunum. The effect was blocked by
naloxone and TTX, but not by cholinergic or adrenergic
antagonists. This is consistent with the proposition of
an NANC inhibitor released by morphine via an action
wit antagonists. This is consistent with the proposition of
an NANC inhibitor released by morphine via an action
within the myenteric plexus and contrasts with opioid
inhibition of NANC neurotransmission in the human
colon in section in the contraction in a substance P. Most recently, Gilbert et al. (132) reported that morphine hyperpolarized, probably through an increase in potassium conductance, circular but not longitudinal smooth musical c an NANC inhibitor released by morphine via an action
within the myenteric plexus and contrasts with opioid
inhibition of NANC neurotransmission in the human
colon in vitro (180). As an alternative explanation, the
authors within the myenteric plexus and contrasts with opioid
inhibition of NANC neurotransmission in the human
colon in vitro (180). As an alternative explanation, the
authors (132) also discussed inhibition of release of an
exci inhibition of NANC neurotransmission in the human colon in vitro (180). As an alternative explanation, then discussed inhibition of release of an excitatory neurotransmitter like acetylcholine by the opioid. This possibili colon in vitro (180). As an alternative explanation, the authors (132) also discussed inhibition of release of an excitatory neurotransmitter like acetylcholine by the opioid. This possibility was then discarded, since atr authors (132) also discussed inhibition of release of an excitatory neurotransmitter like acetylcholine by the opioid. This possibility was then discarded, since atro-
pine neither mimicked nor prevented opioid-effected hy excitatory neurotransmitter like acetylcholine by the
opioid. This possibility was then discarded, since atro-
pine neither mimicked nor prevented opioid-effected hy-
perpolarization. However, CCK-8 may release both sub-
 opioid. This possibility was then discarded, since atro-
pine neither mimicked nor prevented opioid-effected hy-
perpolarization. However, CCK-8 may release both sub-
stance P and endogenous opioids (127), and substance P
 pine neither mimicked nor prevented opioid-effected hyperpolarization. However, CCK-8 may release both substance P and endogenous opioids (127), and substance P may be an endogenous excitatory compound whose release is, in stance P and endogenous opioids (127), and substance P stance P and endogenous opioids (127), and substance P may be an endogenous excitatory compound whose release is, in turn, inhibited by endogenous opioids (15).
This was concluded from experiments showing that nalozone pr may be an endogenous excitatory compound whose release is, in turn, inhibited by endogenous opioids (15).
This was concluded from experiments showing that naloxone produced a contraction of the guinea-pig ileum
longitudina lease is, in turn, inhibited by endogenous opioids (15).
This was concluded from experiments showing that nal-
oxone produced a contraction of the guinea-pig ileum
longitudinal muscle myenteric plexus preparation when
appl This was concluded from experiments showing that nal-
oxone produced a contraction of the guinea-pig ileum
longitudinal muscle myenteric plexus preparation when
applied shortly after an excitatory neuropeptide like
CCK-8 (oxone produced a contraction of the guinea-pig ileum
longitudinal muscle myenteric plexus preparation when
applied shortly after an excitatory neuropeptide like
CCK-8 (127, 128). The response to CCK-8 alone was
dose depend longitudinal muscle myenteric plexus preparation when
applied shortly after an excitatory neuropeptide like
CCK-8 (127, 128). The response to CCK-8 alone was
dose dependently impaired by an enkephalin analogue.
A smaller c applied shortly after an excitatory neuropeptide lCCK-8 (127, 128). The response to CCK-8 alone v
dose dependently impaired by an enkephalin analog
A smaller contraction by naloxone following CCK-8 v
still detectable when CCK-8 (127, 128). The response to CCK-8 alone was
dose dependently impaired by an enkephalin analogue.
A smaller contraction by naloxone following CCK-8 was
still detectable when the muscarinic action of endoge-
nous acety dose dependently impaired by an enkephalin analogue.
A smaller contraction by naloxone following CCK-8 was
still detectable when the muscarinic action of endoge-
nous acetylcholine was blocked by atropine and was
abolished A smaller contraction by naloxone following CCK-8 was
still detectable when the muscarinic action of endoge-
nous acetylcholine was blocked by atropine and was
abolished by desensitization of the preparation to sub-
stanc still detectable when the muscarinic action of endogenous acetylcholine was blocked by atropine and was abolished by desensitization of the preparation to substance P (127). Since substance P and [Met⁵]-enkephalin coexis nous acetylcholine was blocked by atropine and was
abolished by desensitization of the preparation to sub-
stance P (127). Since substance P and [Met⁵]-enkephalin
coexist within a subpopulation of myenteric neurons (88,
 abolished by desensitization of the preparation to substance P (127). Since substance P and [Met⁵]-enkephalin coexist within a subpopulation of myenteric neurons (88, 449a), the opioid may serve as a cotransmitter substa stance P (127). Since substance P and $[Met⁵]$ -enkephalin coexist within a subpopulation of myenteric neurons (88, 449a), the opioid may serve as a cotransmitter substance mediating negative feedback of substance P rel 449a), the opioid may serve as a cotransmitter substance 449a), the opioid may serve as a cotransmitter substance mediating negative feedback of substance P release. This is still hypothetical. These findings may correspond to opioid inhibition of the contractile effect of CCKmediating negative feedback of substance P release. This
is still hypothetical. These findings may correspond to
opioid inhibition of the contractile effect of CCK-8 in
the intact guinea-pig ileum in vitro (493). To furthe is still hypothetical. These findings may correspond to opioid inhibition of the contractile effect of CCK-8 in the intact guinea-pig ileum in vitro (493). To further complicate the situation, Yau et al. (491) demonstrated opioid inhibition of the contractile effect of CCK-8 in
the intact guinea-pig ileum in vitro (493). To further
complicate the situation, Yau et al. (491) demonstrated
opioid inhibition of substance P-induced acetylcholine
 ileum. mplicate the situation, Yau et al. (491) demonstrated
ioid inhibition of substance P-induced acetylcholine
lease from the myenteric plexus of the guinea-pig
um.
The significance of the results on CCK-8 obtained in
e longit opioid inhibition of substance P-induced acetylcholine
release from the myenteric plexus of the guinea-pig
ileum.
The significance of the results on CCK-8 obtained in
the longitudinal muscle myenteric plexus preparation in

OPIOIDS AND CONTROL OF GASTROINTEST
terms of propulsive peristalsis is not quite clear since, in show
the intact segment of the guinea-pig ileum, naloxone the OPIOIDS AND CONTROL OF GASTROINT
terms of propulsive peristalsis is not quite clear since, in
the intact segment of the guinea-pig ileum, naloxone
significantly decreased the number of peristatic waves opioned and contract of GASTROINTI
terms of propulsive peristalsis is not quite clear since, in
the intact segment of the guinea-pig ileum, naloxone
significantly decreased the number of peristatic waves
elicited by CCK-8 terms of propulsive peristalsis is not quite clear since, in
the intact segment of the guinea-pig ileum, naloxone
significantly decreased the number of peristatic waves
elicited by CCK-8 instead of increasing them (Kromer, terms of propulsive
the intact segment
significantly decrea
elicited by CCK-8 is
unpublished data).
4. Prostaglandins, *4. Prostaglandins, bradykinin, neurotensing them (Kromer, unpublished data).*
4. *Prostaglandins, bradykinin, neurotensin, bombesin, and motilin.* Normorphine and morphine antagonized, as

and and and and and and and motiling and motilin. Normorphine and morphine and morphine antagonized, as the noradrenaline and an adenosine analogue (PIA) did, the operators are also as the normorphine a elicited by CCK-8 instead of increasing them (Kromer,
unpublished data). iso
4. Prostaglandins, bradykinin, neurotensin, bombesin, mo
and motilin. Normorphine and morphine antagonized, as
the noradrenaline and an adenosine unpublished data).
4. Prostaglandins, bradykinin, neurotensin, bombesin, mor
and motilin. Normorphine and morphine antagonized, as this
noradrenaline and an adenosine analogue (PIA) did, the opic
contractile response to P 4. Prostaglandins, bradykinin, neurotensin, bombesin, and motilin. Normorphine and morphine antagonized, as noradrenaline and an adenosine analogue (PIA) did, the contractile response to PGI_2 of the guinea-pig ileum in and motilin. Normorphine and morphine antagonized,
noradrenaline and an adenosine analogue (PIA) did, t
contractile response to PGI_2 of the guinea-pig ileum
vitro (122). In the canine stomach in vivo, [Met
enkephalin de noradrenaline and an adenosine analogue (PIA) did, the opicontractile response to PGI_2 of the guinea-pig ileum in opicitro (122). In the canine stomach in vivo, [Met⁵]- sugenkephalin decreased the frequency of paceset contractile response to PGI_2 of the guinea-pig ileum in outro (122). In the canine stomach in vivo, [Met⁵]-
enkephalin decreased the frequency of pacesetter potentials recorded serosally. However, as both naloxone and vitro (122). In the canine stomach in vivo, [Met⁵]
enkephalin decreased the frequency of pacesetter poten
tials recorded serosally. However, as both naloxone an
indometacin prevented and PGE₂ partially mimicke
this inh enkephalin decreased the frequency of pacesetter potentials recorded serosally. However, as both naloxone an indometacin prevented and PGE₂ partially mimicked this inhibitory opioid effect, its mediation by local protagl tials recorded serosally. However, as both indometacin prevented and PGE_2 partial
this inhibitory opioid effect, its mediation is
taglandins was suggested (206) . Thus, opioi
act with prostaglandins at different sites. dometacin prevented and PGE_2 partially mimicked the inhibitory opioid effect, its mediation by local pros-
glandins was suggested (206). Thus, opioids may inter-
t with prostaglandins at different sites.
Inhibition of e

this inhibitory opioid effect, its mediation by local protaglandins was suggested (206). Thus, opioids may intent act with prostaglandins at different sites.
Inhibition of electrically induced acetylcholine releared conseq taglandins was suggested (206). Thus, opioids may inter-
act with prostaglandins at different sites. syntentially induced acetylcholine release the
and consequent twitch of the longitudinal muscle myen-
teric plexus prepar act with prostaglandins at different sites.

Inhibition of electrically induced acetylcholine release

and consequent twitch of the longitudinal muscle myen-

teric plexus preparation of the guinea-pig ileum by

opioids wa Inhibition of electrically induced acetylcholine release
and consequent twitch of the longitudinal muscle myen-
teric plexus preparation of the guinea-pig ileum by
opioids was functionally antagonized by bradykinin
(143). and consequent twitch of the longitudinal muscle myen-
teric plexus preparation of the guinea-pig ileum by call
opioids was functionally antagonized by bradykinin tion
(143). In the same preparation from rabbit, a synergi teric plexus preparation of the guinea-pig ileum by
opioids was functionally antagonized by bradykinin
(143). In the same preparation from rabbit, a synergistic
interaction between the TTX-resistant relaxation by
neurotens opioids was functionally antagonized by
(143). In the same preparation from rabbit,
interaction between the TTX-resistant re-
neurotensin and an inhibition of spontanee
activity by dynorphin was observed (187).
The situati 43). In the same preparation from rabbit, a synergiateraction between the TTX-resistant relaxation urotensin and an inhibition of spontaneous pendutivity by dynorphin was observed (187). The situation is even more complex

meurotensin and an inhibition of spontaneous pendular
activity by dynorphin was observed (187).
The situation is even more complex in vivo, exempli-
fied by bombesin, which delays intestinal transit in the
rat (140). Alth activity by dynorphin was observed (187).

The situation is even more complex in vivo, exempli-

fied by bombesin, which delays intestinal transit in the

rat (140). Although the opiate antagonist naltrexone did

not affe The situation is even more complex in vivo, exemp
fied by bombesin, which delays intestinal transit in the
rat (140). Although the opiate antagonist naltrexone d
not affect bombesin action, two-way cross-tolerance
morphine fied by bombesin, which delays intestinent (140). Although the opiate antagonism ot affect bombesin action, two-way comprehensive morphine developed. Consequently, a po anism for tolerance has been discussed. A candidate f

not affect bombesin action, two-way cross-tolerance to
morphine developed. Consequently, a postreceptor mechanism for tolerance has been discussed.
A candidate for an excitatory neuromodulator involved
in the control of g morphine developed. Consequently, a postreceptor mechanism for tolerance has been discussed.
A candidate for an excitatory neuromodulator involved
in the control of gastrointestinal motility is motilin (for
review, see re anism for tolerance has been discussed.
A candidate for an excitatory neuromodulator involve
in the control of gastrointestinal motility is motilin (for
eview, see ref. 115a). This neuropeptide stimulates the
release of ne A candidate for an excitatory neuromodulator involved
in the control of gastrointestinal motility is motilin (for
review, see ref. 115a). This neuropeptide stimulates the
release of neurotransmitters, for example acetylcho review, see ref. 115a). This neuropeptide stimulates the
release of neurotransmitters, for example acetylcholine,
within the myenteric plexus and may, at least in the dog,
be responsible for initiation of phase III activit review, see ref. 115a). This neuropeptide stimulates the celease of neurotransmitters, for example acetylcholine, time within the myenteric plexus and may, at least in the dog, be responsible for initiation of phase III a release of neurotransmitters, for example acetylcholine, in within the myenteric plexus and may, at least in the dog, be responsible for initiation of phase III activity fronts of the migrating motility complex. Since the within the myenteric plexus and may, at least in the dog,
be responsible for initiation of phase III activity fronts
of the migrating motility complex. Since the release of
motilin was impaired by opioids in man (402), th be responsible for initiation of phase III activity fronts of the migrating motility complex. Since the release of motilin was impaired by opioids in man (402), these authors suggested this might be the mode of action is motilin was impaired by opioids in man (402), these
authors suggested this might be the mode of action motilin was impaired by opioids in man (402) , these interactions suggested this might be the mode of action is st
behind the constipating effect of opioids. The situation traction
is, however, not as simple since opioid authors suggested this might be the mode of action is
behind the constipating effect of opioids. The situation ir
is, however, not as simple since opioids may themselves
transiently initiate phase III activity (see sectio behind the constipating effect of opioids. The situation
is, however, not as simple since opioids may themselves
transiently initiate phase III activity (see section III D 2
c). In fact, it has been suggested that, in the is, however, not as simple since opioids may themselves variated transiently initiate phase III activity (see section III D 2 were c). In fact, it has been suggested that, in the dog, motilin continuity triangled in the r transiently initiate phase III activity (see section III D 2 α). In fact, it has been suggested that, in the dog, motilin might stimulate the release of endogenous opioids and divice versa (76a). Although the publicati c). In fact, it has been suggested that, in the dog, motilin might stimulate the release of endogenous opioids and vice versa (76a). Although the publications quoted in support of this (366, 366a) do not substantiate this ight stimulate the release of endogenous opioids and
ce versa (76a). Although the publications quoted in
pport of this (366, 366a) do not substantiate this
tion, recent data (115c) indirectly support its first part.
5. *Ca*

vice versa (76a). Although the publications quoted in neupport of this (366, 366a) do not substantiate this stell notion, recent data (115c) indirectly support its first part. tiv 5. Catecholamines and serotonin. The well support of this (366, 366a) do not substantiate this standing notion, recent data (115c) indirectly support its first part.
5. Catecholamines and serotonin. The well-known in-
hibition of acetylcholine release by activati notion, recent data (115c) indirectly support its first part.
5. Catecholamines and serotonin. The well-known in-
hibition of acetylcholine release by activation of both
opioid and alpha₂-receptors on nerve terminals in 5. Catecholamines and serotonin. The well-known is
hibition of acetylcholine release by activation of bo
poioid and alpha₂-receptors on nerve terminals in t
guinea-pig myenteric plexus (374, 326, 220, 423, 4²
may expl hibition of acetylcholine release by activation of both mopioid and alpha₂-receptors on nerve terminals in the oguinea-pig myenteric plexus (374, 326, 220, 423, 476) dimay explain why the alpha₂-receptor-antagonist yo opioid and alpha₂-receptors on nerve terminals in t
guinea-pig myenteric plexus $(374, 326, 220, 423, 47)$
may explain why the alpha₂-receptor-antagonist yohin
bine functionally antagonized the antitransit effect
morp guinea-pig myenteric plexus $(374, 326, 220, 423, 476)$ diany explain why the alpha₂-receptor-antagonist yohim-
bine functionally antagonized the antitransit effect of on
morphine in the mouse in vivo (480) , i.e., und may explain why the alpha₂-receptor-antagonist yohim-controls, claimed a direct inhibitory influence of opioids
bine functionally antagonized the antitransit effect of on chemically induced smooth muscle contractions in

ESTINAL MOTILITY AND SECRETION 135
showing that both reserpine and neostigmine impaired
the antipropulsive effect of morphine in the rat small THE AND SECRETION 135
showing that both reserpine and neostigmine impaired
the antipropulsive effect of morphine in the rat small
intestine in vivo. ESTINAL MOTILITY
showing that both
the antipropulsive
intestine in vivo.
An enhanced re An enhanced release of serotonin from the canine
antipropulsive effect of morphine in the rat small
testine in vivo.
An enhanced release of serotonin from the canine
plated intestinal segment into the vasculature upon

showing that both reserpine and neostigmine impaired
the antipropulsive effect of morphine in the rat small
intestine in vivo.
An enhanced release of serotonin from the canine
isolated intestinal segment into the vasculatu the antipropulsive effect of morphine in the rat small
intestine in vivo.
An enhanced release of serotonin from the canine
isolated intestinal segment into the vasculature upon
morphine administration has been mentioned ea intestine in vivo.

An enhanced release of serotonin from the canine

isolated intestinal segment into the vasculature upon

morphine administration has been mentioned earlier in

this review (48, 44). Serotonin is a possi An enhanced release of serotonin from the canine
isolated intestinal segment into the vasculature upon
morphine administration has been mentioned earlier in
this review (48, 44). Serotonin is a possible mediator of
opioidisolated intestinal segment into the vasculature upon
morphine administration has been mentioned earlier in
this review (48, 44). Serotonin is a possible mediator of
opioid-induced intestinal motility and mimicks this
opio morphine administration has been mentioned earlier in
this review (48, 44). Serotonin is a possible mediator of
opioid-induced intestinal motility and mimicks this
opioid effect. The other way round, Majeed et al. (268)
su opioid-induced intestinal motility and mimicks this opioid effect. The other way round, Majeed et al. (268) suggested, on the basis of decreased tissue concentrations of immunoreactive dynorphin, that activation of sertoni opioid-induced intestinal motility and mimicks this
opioid effect. The other way round, Majeed et al. (268)
suggested, on the basis of decreased tissue concentrations
of immunoreactive dynorphin, that activation of sertoni opioid effect. The other way round, Majeed et al. (26)
suggested, on the basis of decreased tissue concentration
of immunoreactive dynorphin, that activation of sertoni
receptors may stimulate the release of dynorphin fro
 suggested, on the basis of decrease of immunoreactive dynorphin, receptors may stimulate the r
the rat myenteric plexus. How
tinal peristalsis is not known.
Indirect pharmacological ev immunoreactive dynorphin, that activation of sertonin
ceptors may stimulate the release of dynorphin from
e rat myenteric plexus. How these data relate to intes-
al peristalsis is not known.
Indirect pharmacological eviden receptors may stimulate the release of dynorphin from
the rat myenteric plexus. How these data relate to intes-
tinal peristalsis is not known.
Indirect pharmacological evidence suggests that bio-
synthesis and release of

the rat myenteric plexus. How these data relate to intestinal peristalsis is not known.
Indirect pharmacological evidence suggests that bio-
synthesis and release of myenteric opioids may be under
the inhibitory control of tinal peristalsis is not known.

Indirect pharmacological evidence suggests that b

synthesis and release of myenteric opioids may be une

the inhibitory control of receptors activated by dopami

(453, 454); these data hav Indirect pharmacological evidence suggests that l synthesis and release of myenteric opioids may be un the inhibitory control of receptors activated by dopam (453, 454); these data have been obtained with eleccally stimula synthesis and release of myenteric opioids may be under
the inhibitory control of receptors activated by dopamine
(453, 454); these data have been obtained with electri-
cally stimulated preparations, and there is no infor Ily stimulated preparations, and there is no informa-
on as to the significance for peristalsis.
Neuronal versus Smooth Muscle Opioid Effects
Naloxone did not elicit any contractile activity in the
inea-pig ileum in vitro

F. Neuronal versus Smooth Muscle Opioid Effects

Flementation between the 1111 resistant relatation by

neurotensin and an inhibition of spontaneous pendular

activity by dynorphin was observed (187).

This proves that spontaneous smooth muscle activity,

flementation is not affect bombesin action, two-way cross-tolerance to
morphine developed. Consequently, a postreceptor mech-
anism for tolerance has been discussed.
A candidate for an excitatory neuromodulator involved
muscle contraction tion as to the significance for peristalsis.
F. Neuronal versus Smooth Muscle Opioid Effects
Naloxone did not elicit any contractile activity in the
guinea-pig ileum in vitro in the presence of TTX (236).
This proves that F. Neuronal versus Smooth Muscle Opioid Effects
Naloxone did not elicit any contractile activity in the
guinea-pig ileum in vitro in the presence of TTX (236).
This proves that spontaneous smooth muscle activity,
which mig F. Neuronal versus Smooth Muscle Optold Effects
Naloxone did not elicit any contractile activity in the
guinea-pig ileum in vitro in the presence of TTX (236).
This proves that spontaneous smooth muscle activity,
which mig Naloxone did not elicit any contractile activity in the guinea-pig ileum in vitro in the presence of TTX (236).
This proves that spontaneous smooth muscle activity, which might theoretically become phase locked in the pres guinea-pig ileum in vitro in the presence of TTX (236).
This proves that spontaneous smooth muscle activity,
which might theoretically become phase locked in the
presence of naloxone and in the absence of any neuronal
inhi This proves that spontaneous smooth muscle activity,
which might theoretically become phase locked in the
presence of naloxone and in the absence of any neuronal
inhibition, is not the basis of enhancement of peristalsis
b which might theoretically become phase locked in the presence of naloxone and in the absence of any neuronal inhibition, is not the basis of enhancement of peristalsis by naloxone. It should be noted that the situation mig presence of naloxone and in the absence of any neuronal
inhibition, is not the basis of enhancement of peristalsis
by naloxone. It should be noted that the situation might
be different in other species where blockade of in inhibition, is not the basis of enhancement of peristalsis
by naloxone. It should be noted that the situation might
be different in other species where blockade of inhibitory
neuronal activity by TTX may lead to phasic sm by naloxone. It should be noted that the situation might
be different in other species where blockade of inhibitory
neuronal activity by TTX may lead to phasic smooth
muscle contractions due to myogenic fluctuations (slow
 be different in other species where blockade of inhibitd
neuronal activity by TTX may lead to phasic smoot
muscle contractions due to myogenic fluctuations (slow
aves) of the membrane potential of the smooth muscles
(337). neuronal activity by TTX may lead to phasic smooth
muscle contractions due to myogenic fluctuations (slow
waves) of the membrane potential of the smooth muscle
cells (337). In the guinea-pig, spontaneous slow poten-
tials muscle contractions due to myogenic fluctuations (slow
waves) of the membrane potential of the smooth muscle
cells (337). In the guinea-pig, spontaneous slow poten-
tials of smooth muscle cells have first to be converted t waves) of the membrane potential of the smooth muscle
cells (337). In the guinea-pig, spontaneous slow poten-
tials of smooth muscle cells have first to be converted to
slow waves by acetylcholine (30) in order to produce
 cells (337). In the guinea-pig, spontaneous slow potentials of smooth muscle cells have first to be converted to slow waves by acetylcholine (30) in order to produce contractions. The physiological significance of opioid r tials of smooth muscle cells have first to be converted to slow waves by acetylcholine (30) in order to produce contractions. The physiological significance of opioid receptors on smooth muscle cells from the guinea-pig in slow waves by acetylcholine (30) in order to produce
contractions. The physiological significance of opioid
receptors on smooth muscle cells from the guinea-pig
intestine circular muscle (27) with respect to peristalsis
is contractions. The physiological significance of opioid
receptors on smooth muscle cells from the guinea-pig
intestine circular muscle (27) with respect to peristalsis
is still unclear. These isolated smooth muscle cells c receptors on smooth muscle cells from the guinea-pig
intestine circular muscle (27) with respect to peristalsis
is still unclear. These isolated smooth muscle cells con-
tracted upon application of 0.1 to 100 nmol/liter o is still unclear. These isolated smooth muscle cells contracted upon application of 0.1 to 100 nmol/liter of a
variety of opioids. The concentration-response curves
were shallow covering 3 to 4 orders of magnitude. By
contrast, Furukawa et al. (118) using isolated rat duo-
denu variety of opioids. The concentration-response curves
were shallow covering 3 to 4 orders of magnitude. By
contrast, Furukawa et al. (118) using isolated rat duo-
denum of days 8 to 45 postnatally found a TTX-sensitive
neu were shallow covering 3 to 4 orders of magnitud
contrast, Furukawa et al. (118) using isolated rat
denum of days 8 to 45 postnatally found a TTX-sen
neurogenic relaxation by opioids up to day 40, whic
stepwise replaced fro contrast, Furukawa et al. (118) using isolated rat duo-
denum of days 8 to 45 postnatally found a TTX-sensitive
neurogenic relaxation by opioids up to day 40, which was
stepwise replaced from days 20 to 40 by a TTX-insensi denum of days 8 to 45 postnatally found a TTX-sensitive
neurogenic relaxation by opioids up to day 40, which was
stepwise replaced from days 20 to 40 by a TTX-insensi-
tive myogenic relaxant opioid effect. It is unknown
wh meurogenic relaxation by opioids up to day 40, which was
stepwise replaced from days 20 to 40 by a TTX-insensi-
tive myogenic relaxant opioid effect. It is unknown
whether a similar postnatal switch from neurogenic to
myog stepwise replaced from days 20 to 40 by a TTX-insensi-
tive myogenic relaxant opioid effect. It is unknown
whether a similar postnatal switch from neurogenic to
myogenic nature of an opioid relaxant mechanism also
occurs i tive myogenic relaxant opioid effect. It is unknown
whether a similar postnatal switch from neurogenic to
myogenic nature of an opioid relaxant mechanism also
occurs in the guinea-pig (135). Mitznegg et al. (289), who
did whether a similar postnatal switch from neurogenic to
myogenic nature of an opioid relaxant mechanism also
occurs in the guinea-pig (135). Mitznegg et al. (289), who
did not present their data in detail and did not show an myogenic nature of an opioid relaxant mechanism also
occurs in the guinea-pig (135). Mitznegg et al. (289), who
did not present their data in detail and did not show any
controls, claimed a direct inhibitory influence of o occurs in the guinea-pig (135). Mitznegg et al. (289), who
did not present their data in detail and did not show any
controls, claimed a direct inhibitory influence of opioids
on chemically induced smooth muscle contractio did not present their data in detail and did not show any

Both hyperpolarization (probably related to relaxa-

136 KROME

tion) of smooth muscle cells under the influence of est

morphine (132) and increases in intraluminal pressure in 136 **KROM**

ion) of smooth muscle cells under the influence of

morphine (132) and increases in intraluminal pressure

is by heroin (308) in canine small intestine were antago-136
tion) of smooth muscle cells under the influence
morphine (132) and increases in intraluminal presse
by heroin (308) in canine small intestine were antago-
nized by TTX. These data are indicative of action nized tion) of smooth muscle cells under the influence of morphine (132) and increases in intraluminal pressure by heroin (308) in canine small intestine were antagonized by TTX. These data are indicative of actions within tion) of smooth muscle cells under the influence of morphine (132) and increases in intraluminal pressure
by heroin (308) in canine small intestine were antago-
nized by TTX. These data are indicative of actions
within the morphine (132) and increases in intraluminal pressure
by heroin (308) in canine small intestine were antago-
nized by TTX. These data are indicative of actions
within the nervous plexus, although at functionally dif-
fere by heroin (308) in canine small intestine were antago-
nized by TTX. These data are indicative of actions
within the nervous plexus, although at functionally dif-
ferent sites. On the other hand, the contractile response
o mized by TTX. These data are indicative of actions
within the nervous plexus, although at functionally of
erent sites. On the other hand, the contractile respone
of the dog (47) and the cat (317) small intestine
[Met within the nervous plexus, although at functionally different sites. On the other hand, the contractile response of the dog (47) and the cat (317) small intestine to [Met⁵]-enkephalin was hardly affected by TTX, sug ferent sites. On the other hand, the contractile response smoot the dog (47) and the cat (317) small intestine to norm [Met⁵]-enkephalin was hardly affected by TTX, suggesting a direct stimulation of smooth muscle c of the dog (47) and the cat (317) small intestine to [Met⁵]-enkephalin was hardly affected by TTX, suggesting a direct stimulation of smooth muscle cell receptors (27). These different sites of action possibly relate to [Met⁵]-enkephalin was hardly affected by TTX, sugging a direct stimulation of smooth muscle cell reception (27). These different sites of action possibly relat different receptor types and may explain, to some extapparen ing a direct stimulation of smooth muscle cell receptors (27). These different sites of action possibly relate to different receptor types and may explain, to some extent, apparent inconsistencies also with respect opioid-7). These different sites of action possibly relate to referent receptor types and may explain, to some extent, no
parent inconsistencies also with respect opioid-neu-
transmitter interactions.
Tonini et al. (445) separ

different receptor types and may explain, to some extent,
apparent inconsistencies also with respect opioid-neu-
rotransmitter interactions.
Tonini et al. (445) separated the circular muscle of the
guinea-pig colon from t apparent inconsistencies also with respect opioid-neu-

rotransmitter interactions.

Tonini et al. (445) separated the circular muscle of the

guinea-pig colon from the longitudinal muscle and found

that TTX blocked mo rotransmitter interactions.

Tonini et al. (445) separated the circular muscle of

guinea-pig colon from the longitudinal muscle and fot

that TTX blocked morphine-induced relaxation in

longitudinal muscle, but not morphi Tonini et al. (445) separated the circular muscle of the guinea-pig colon from the longitudinal muscle and found that TTX blocked morphine-induced relaxation in the longitudinal muscle, but not morphine-induced contraction guinea-pig colon from the longitudinal muscle and found
that TTX blocked morphine-induced relaxation in the
longitudinal muscle, but not morphine-induced contraction
in the circular muscle. This important distinction
was that TTX blocked morphine-induced relaxation in the longitudinal muscle, but not morphine-induced contraction in the circular muscle. This important distinction was less clearly drawn by other investigators. Hellströn (161 longitudinal muscle, but not morphine-induced contraction in the circular muscle. This important distinction was less clearly drawn by other investigators. Hellström (161) measured, in the cat in vivo, colonic intraluminal tion in the circular muscle. This important distinction
was less clearly drawn by other investigators. Hellström
(161) measured, in the cat in vivo, colonic intraluminal
volume and pressure changes via a balloon, a techniq was less clearly drawn by other investigators. Hellst
(161) measured, in the cat in vivo, colonic intralumi
volume and pressure changes via a balloon, a techni
predominantly detecting circular muscle activ
whereas Gillan a (161) measured, in the cat in vivo, colonic intraluminal volume and pressure changes via a balloon, a technique predominantly detecting circular muscle activity, whereas Gillan and Pollock (133) determined longitudi-
nal volume and pressure changes via a balloon, a technique predominantly detecting circular muscle activity whereas Gillan and Pollock (133) determined longitudinal contractions of the intact rat colonic segment in vitro and w whereas Gillan and Pollock (133) determined longitudinal contractions of the intact rat colonic segment in vitro
and were probably dealing with a mixture of longitudinal
and circular muscle activity. Both groups found TTX
 nal contractions of the intact rat colonic segment in vitro

and were probably dealing with a mixture of longitudinal

and circular muscle activity. Both groups found TTX

ineffective in preventing opioid-induced contract and were probably dealing with a mixture of longitudinal
and circular muscle activity. Both groups found TTX
ineffective in preventing opioid-induced contractile ac-
tivity. In fact, TTX mimicked and potentiated the opioid and circular muscle activity. Both groups found
ineffective in preventing opioid-induced contractil
tivity. In fact, TTX mimicked and potentiated the o
effect (133). This was considered evidence for a c
stimulation of smoo effective in preventing opioid-induced contractile ac-

ity. In fact, TTX mimicked and potentiated the opioid

fect (133). This was considered evidence for a direct

mulation of smooth muscle cell opioid receptors.

It is tivity. In fact, TTX mimicked and potentiated the opioid
effect (133). This was considered evidence for a direct
stimulation of smooth muscle cell opioid receptors.
It is not clear why Tonini et al. (445) found a relaxati

effect (133). This was considered evidence for a direct
stimulation of smooth muscle cell opioid receptors.
It is not clear why Tonini et al. (445) found a relaxation
of longitudinal muscle tone in the guinea-pig colon in stimulation of smooth muscle cell opioid receptors.
It is not clear why Tonini et al. (445) found a relaxation
of longitudinal muscle tone in the guinea-pig colon in
vitro using concentrations of morphine $(1 \mu mol/liter)$
sim It is not clear why Tonini et al. (445) found a relaxation
of longitudinal muscle tone in the guinea-pig colon in
vitro using concentrations of morphine $(1 \mu mol/liter)$
similar to those that produced longitudinal muscle conof longitudinal muscle tone in the guinea-pig colon in
vitro using concentrations of morphine $(1 \mu mol/liter)$
similar to those that produced longitudinal muscle con-
traction in the rat $(186, 207)$ and mouse colon (114) .
As vitro using concentrations of morphine $(1 \mu \text{mol/liter})$ signilar to those that produced longitudinal muscle contraction in the rat $(186, 207)$ and mouse colon (114) . tionation from true species differences, potential diff similar to those that produced longitudinal muscle contraction in the rat (186, 207) and mouse colon (11) Aside from true species differences, potential different in the removal of the circular muscle might be the rease fo traction in the rat (186, 207) and mouse colon (114).
Aside from true species differences, potential differences
in the removal of the circular muscle might be the reason
for discrepant results (see preceding paragraph). O Aside from true species differences, potential differences
in the removal of the circular muscle might be the reason
for discrepant results (see preceding paragraph). Opioid-
induced longitudinal contractions of isolated c the removal of the circular muscle might be the reason

r discrepant results (see preceding paragraph). Opioid-

the rat

duced longitudinal contractions of isolated colonic tis-

e were blocked by TTX to indicate neuronal for discrepant results (see preceding paragraph). Opioid-
induced longitudinal contractions of isolated colonic tis-
sue were blocked by TTX to indicate neuronal mediation.
Another source of discrepant results may arise fr

induced longitudinal contractions of isolated colonic to sue were blocked by TTX to indicate neuronal mediation.
Another source of discrepant results may arise from differential sensitivities and control mechanisms in dife sue were blocked by TTX to indicate neuronal mediation
Another source of discrepant results may arise from
differential sensitivities and control mechanisms in different parts of the colon. Scheurer et al. (378) demon
stra Another source of discrepant results may arise free differential sensitivities and control mechanisms in deferent parts of the colon. Scheurer et al. (378) demostrated that TTX counteracted tonic intraluminal presure chang differential sensitivities and control mechanisms in different parts of the colon. Scheurer et al. (378) demonstrated that TTX counteracted tonic intraluminal pressure changes, induced by opioids in the whole (undissected) ferent parts of the colon. Scheurer et al. (378) demonstrated that TTX counteracted tonic intraluminal pressure changes, induced by opioids in the whole (undis-sected) rat colon and its dissected proximal segment. However, strated that TTX counteracted tonic intraluminal pres-
sure changes, induced by opioids in the whole (undis-
sected) rat colon and its dissected proximal segment.
However, TTX enhanced those contractions in the dis-
sected sure changes, induced by opioids in the whole (undis-
sected) rat colon and its dissected proximal segment.
However, TTX enhanced those contractions in the dis-
sected middle and distal segments. Available data are
mostly sected) rat colon and its dissected proximal segment.
However, TTX enhanced those contractions in the dissected middle and distal segments. Available data are
mostly consistent with the assumption that colonic
smooth muscl However, TTX enhanced those contractions in the dissected middle and distal segments. Available data are mostly consistent with the assumption that colonic smooth muscle may be released from tonic neuronal inhibition (483) sected middle and distal segments. Available data are
mostly consistent with the assumption that colonic
smooth muscle may be released from tonic neuronal
inhibition (483) by opioids and TTX to produce rhythmic
contraction mostly consistent with the assumption that colonic sorption and appearance of the first flatus after the end
smooth muscle may be released from tonic neuronal
inhibition (483) by opioids and TTX to produce rhythmic and "pu smooth muscle may be released from tonic neuronal

G. Pathophysiological Aspects

1. Achalasia and hypertrophic pyloric stenosis. A potential involvement of endogenous opioids in the pathogenesis of achalasia has been discussed in section III D 4. In infants of achalasia has been discussed in section III D 4. In infants suffering from hypertrophic pyloric stenosis, a nonselective loss of $[Met^5]$ -enkephalin immunoreactive ER
esis of achalasia has been discussed in section III D 4. In
infants suffering from hypertrophic pyloric stenosis, a
nonselective loss of $[Met^5]$ -enkephalin immunoreactive
nerve fibers, along with a decrease in other ne nerve fields and as been discussed in section III D 4. In infants suffering from hypertrophic pyloric stenosis, a nonselective loss of $[Met^5]$ -enkephalin immunoreactive nerve fibers, along with a decrease in other neuropep esis of achalasia has been discussed in section III D 4. In infants suffering from hypertrophic pyloric stenosis, a nonselective loss of [Met⁵]-enkephalin immunoreactive nerve fibers, along with a decrease in other neuro infants suffering from hypertrophic pyloric stenosis,
nonselective loss of [Met⁵]-enkephalin immunoreacti
nerve fibers, along with a decrease in other neuropeptic
containing nerve fibers, was observed in hypertroph
smoot nonselective loss of [Met^o]-enkephalin immunoreactive
nerve fibers, along with a decrease in other neuropeptides
containing nerve fibers, was observed in hypertrophic
smooth muscle (270, 469). No such decrease in immu-
n nerve fibers, along with a decrease in other neuropep
containing nerve fibers, was observed in hypertro
smooth muscle (270, 469). No such decrease in in
noreactivity was found within the myenteric plexus.
kephalin contract containing nerve fibers, was observed in hypertrol smooth muscle (270, 469). No such decrease in im nore
activity was found within the myenteric plexus.
kephalin contracts the pylorus (94, 348). A pathoph
ological role of smooth muscle (270, 469). No such decrease in immu-
noreactivity was found within the myenteric plexus. En-
kephalin contracts the pylorus (94, 348). A pathophysi-
ological role of a potentially elevated tonic enkephali-
n noreactivity was found within the myenteric plexus. En-
kephalin contracts the pylorus (94, 348). A pathophysi-
ological role of a potentially elevated tonic enkephali-
nergic input to the hypertrophic pylorus can obviousl phalin contracts the pylorus (94, 348). A pathophogical role of a potentially elevated tonic enkeplergic input to the hypertrophic pylorus can obviot be inferred from these results as a cause of stend 2. *Hirschsprung's di*

predominantly detecting circular muscle activity,
whereas Gillan and Pollock (133) determined longitudi-
nal contractions of the intact rat colonic segment in vitro
and contractions of the intact rat colonic segment in vit ological role of a potentially elevated tonic enkephali-
nergic input to the hypertrophic pylorus can obviously
not be inferred from these results as a cause of stenosis.
2. Hirschsprung's disease. Bishop et al. (26) inves nergic input to the hypertrophic pylorus can obviously
not be inferred from these results as a cause of stenosis.
2. Hirschsprung's disease. Bishop et al. (26) investigat-
ing children suffering from Hirschsprung's disease not be inferred from these results as a cause of stenosis.
2. Hirschsprung's disease. Bishop et al. (26) investigating children suffering from Hirschsprung's disease found
a decrease in the tissue concentration of vasoacti 2. Hirschsprung's disease. Bishop et al. (26) investigating children suffering from Hirschsprung's disease found a decrease in the tissue concentration of vasoactive intestinal polypeptide as well as of somatostatin and e ing children suffering from Hirschsprung's disease found a decrease in the tissue concentration of vasoactive in testinal polypeptide as well as of somatostatin and enteroglucagon cells within the aganglionic segment. No c a decrease in the tissue concentration of vasoactive intestinal polypeptide as well as of somatostatin and enteroglucagon cells within the aganglionic segment. No
clear-cut decrease in [Met⁵]-enkephalin-containing
merve teroglucagon cells within the aganglionic segment. No
clear-cut decrease in $[Met⁵]$ -enkephalin-containing
nerve fibers was found when compared with a rather low
concentration in controls. By contrast, Larsson et al.
($clear-cut$ decrease in $[Met⁵]$ -enkephalin-containing clear-cut decrease in [Met⁵]-enkephalin-containing
nerve fibers was found when compared with a rather low
concentration in controls. By contrast, Larsson et al.
(248b) and Tsuto et al. (447) found complete disappear-
anc nerve fibers was found when compared with a rather low concentration in controls. By contrast, Larsson et al. (248b) and Tsuto et al. (447) found complete disappearance of enkephalin-immunoreactive neurons and nerve fibers concentration in controls. By contrast, Larsson et al. (248b) and Tsuto et al. (447) found complete disappearance of enkephalin-immunoreactive neurons and nerve fibers in the aganglionic segment. Moreover, Lolova et al. (2 (248b) and Tsuto et al. (447) found complete disappear-
ance of enkephalin-immunoreactive neurons and nerve
fibers in the aganglionic segment. Moreover, Lolova et
al. (258) reported that substance P -, serotonin-, an a tecture is the taste contentination of vascative interesting on the deterministic deterministic deterministic contention in controls. By contrast, Larsson et al. (248b) and Tsuto et al. (447) found complete disappear-
co fibers in the aganglionic segment. Moreover, Lolova et al. (258) reported that substance P-, serotonin-, and $[Met⁵]$ -enkephalin-immunoreactive nerve fibers were diminished in the aganglionic segment, speculating on th al. (258) reported that substance P-, serotonin-, and

[Met⁵]-enkephalin-immunoreactive nerve fibers were di-

minished in the aganglionic segment, speculating on the

role of changes in the density of inhibitory neuron [Met⁸]-enkephalin-immunoreactive nerve fibers were di-
minished in the aganglionic segment, speculating on the
role of changes in the density of inhibitory neurons in
the pathogenesis of Hirschsprung's disease, especiall role of changes in the density of inhibitory neurons in the pathogenesis of Hirschsprung's disease, especially in the development of spasm in the aganglionic segment. However, in one clinical case investigated by Bouvier e the pathogenesis of Hirschsprung's disease, especially in
the development of spasm in the aganglionic segment.
However, in one clinical case investigated by Bouvier et
al. (33), morphine did not elicit any myoelectric acti the pathogenesis of Hirschsprung's disease, especially in
the development of spasm in the aganglionic segment.
However, in one clinical case investigated by Bouvier et
al. (33), morphine did not elicit any myoelectric acti the development of spasm in the aganglionic segment.
However, in one clinical case investigated by Bouvier et
al. (33), morphine did not elicit any myoelectric activity
in the aganglionic rectum, which obviously showed no
 3. Intestinal case investigated by bouvier et al. (33), morphine did not elicit any myoelectric activity in the aganglionic rectum, which obviously showed no signs of spasm and did not respond to naloxone either.
 3. In

in the aganglionic rectum, which obviously showed no
signs of spasm and did not respond to naloxone either.
3. Intestinal hypomotility, chronic idiopathic constipa-
tion, and pseudoobstruction. Intestinal hypomotility folsigns of spasm and did not respond to naloxone either.

3. Intestinal hypomotility, chronic idiopathic constipation, and pseudoobstruction. Intestinal hypomotility following surgical stress has been discussed in terms of 3. Intestinal hypomotility, chronic idiopathic constipation, and pseudoobstruction. Intestinal hypomotility following surgical stress has been discussed in terms of stress-induced release of endorphins, which was, from the tion, and pseudoobstruction. Intestinal hypomotility fol-
lowing surgical stress has been discussed in terms of
stress-induced release of endorphins, which was, from
the rat pituitary, first demonstrated by Guillemin et al hypomotical stress has been discussed in terms of stress-induced release of endorphins, which was, from the rat pituitary, first demonstrated by Guillemin et al. (150). However, naloxone failed to antagonize intestinal hyp stress-induced release of endorphins, which was, from
the rat pituitary, first demonstrated by Guillemin et al.
(150). However, naloxone failed to antagonize intestinal
hypomotility in rats submitted to surgical stress (17 the rat pituitary, first demonstrated by Guillemin et ϵ (150). However, naloxone failed to antagonize intestin
hypomotility in rats submitted to surgical stress (179
In fact, opioid agonists increased the frequency of (150). However, naloxone failed to antagonize intestinal
hypomotility in rats submitted to surgical stress (179).
In fact, opioid agonists increased the frequency of mi-
grating motor complexes in the duodenum, not the sto hypomotility in rats submitted to surgical stress (179).
In fact, opioid agonists increased the frequency of migrating motor complexes in the duodenum, not the stom-
ach, of patients following surgery (192). These patients In fact, opioid agonists increased the frequency of migrating motor complexes in the duodenum, not the stom-
ach, of patients following surgery (192). These patients
displayed gastric, no duodenal, hypomotility. Moreover,
 grating motor complexes in the duodenum, not the stom-
ach, of patients following surgery (192). These patients
displayed gastric, no duodenal, hypomotility. Moreover,
the functional significance of the opioid effect in te ach, of patients following surgery (192). These patients displayed gastric, no duodenal, hypomotility. Moreover, the functional significance of the opioid effect in terms of propulsion is, as discussed earlier, still uncle displayed gastric, no duodenal, hypomotility. Moreover,
the functional significance of the opioid effect in terms
of propulsion is, as discussed earlier, still unclear. Shah
et al. (404) concluded from a delay in paracetam the functional significance of the opioid effect in terms
of propulsion is, as discussed earlier, still unclear. Shah
et al. (404) concluded from a delay in paracetamol ab-
sorption and appearance of the first flatus after of propulsion is, as discussed earlier, still unclear. Shahet al. (404) concluded from a delay in paracetamol absorption and appearance of the first flatus after the end of surgery that morphine impaired both gastric empty et al. (404) concluded from a delay in paracetamol as
sorption and appearance of the first flatus after the e
of surgery that morphine impaired both gastric emptyi
and "purposeful" intestinal motility in their patien
There sorption and appearance of the first flatus after the end
of surgery that morphine impaired both gastric emptying
and "purposeful" intestinal motility in their patients.
There is, however, no indication as to a possible in of surgery that morphine impair
and "purposeful" intestinal mor
There is, however, no indication
ment of endogenous opioids in th
hypomotility following surgery.
Central stimuli such as hypo d "purposeful" intestinal motility in their patients.
here is, however, no indication as to a possible involve-
ent of endogenous opioids in the mechanism underlying
pomotility following surgery.
Central stimuli such as hy

There is, however, no indication as to a possible involument of endogenous opioids in the mechanism underly hypomotility following surgery.
Central stimuli such as hypothermia or labyrinth stimulation elevated the plasma b ment of endogenous opioids in the mechanism underlying
hypomotility following surgery.
Central stimuli such as hypothermia or labyrinthine
stimulation elevated the plasma beta-endorphin concen-
tration and suppressed antra hypomotility following surgery.
Central stimuli such as hypothermia or labyrinthine
stimulation elevated the plasma beta-endorphin concen-
tration and suppressed antral motility in healthy sub-
jects. The latter effect was

Under particular conditions, therefore, endogenous
opioids might be released to inhibit gastrointestinal moopioids and contract of GASTROI
Under particular conditions, therefore, endogenous
opioids might be released to inhibit gastrointestinal mo-
tility. On the other hand, an enkephalin analogue has OPIOIDS AND CONTROL OF GASTROINTE
Under particular conditions, therefore, endogenous po
pioids might be released to inhibit gastrointestinal mo-
tility. On the other hand, an enkephalin analogue has
been suggested as a dru Under particular conditions, therefore, endogenous
opioids might be released to inhibit gastrointestinal mo-
tility. On the other hand, an enkephalin analogue has
been suggested as a drug to treat paralyzing ileus (24).
Al Under particular conditions, therefore, endogenously
opioids might be released to inhibit gastrointestinal m
tility. On the other hand, an enkephalin analogue h
been suggested as a drug to treat paralyzing ileus (24
Althou opioids might be released to inhibit gastrointestinal mo-
tility. On the other hand, an enkephalin analogue has not
been suggested as a drug to treat paralyzing ileus (24). pri
Although the opioid may stimulate canine jej been suggested as a drug to treat paralyzing ileus (24).
Although the opioid may stimulate canine jejunal diges-
tive motility, and a propulsive nature of this effect may
be inferred from human data (196a), the effect seem Although the opioid may stimulate canine jejunal diges-
tive motility, and a propulsive nature of this effect may
be inferred from human data (196a), the effect seems to
of be transient. Considering the foregoing discussio tive motility, and a propulsive nature of this effect may
be inferred from human data (196a), the effect seems to
be transient. Considering the foregoing discussion of dual
opioid effects on small and large bowel motility be inferred from human data (196a), the effect seems to
be transient. Considering the foregoing discussion of dual
opioid effects on small and large bowel motility and the
potential risks incurred in terms of induction of be transient. Considering the foregoing discussion of dual opioid effects on small and large bowel motility and the potential risks incurred in terms of induction of spasms and paralysis of peristalsis, plus the lack of cl potential risks incurred in terms of induction of spasms
and paralysis of peristalsis, plus the lack of clinical
support, there is no basis for such treatment at present.
Two case reports by Kreek et al. (226) on the nalox

potential risks incurred in terms of induction of spasms
and paralysis of peristalsis, plus the lack of clinical
support, there is no basis for such treatment at present.
Two case reports by Kreek et al. (226) on the nalox and paralysis of peristalsis, plus the lack of clinical enduport, there is no basis for such treatment at present. In Two case reports by Kreek et al. (226) on the naloxone-effected improvement of chronic idiopathic consti support, there is no basis for such treatment at present.
Two case reports by Kreek et al. (226) on the naloxone
effected improvement of chronic idiopathic constipation
suggest that at least in selected cases an excess act Two case reports by Kreek et al. (226) on the naloxone-
effected improvement of chronic idiopathic constipation v
suggest that at least in selected cases an excess activity the
of endogenous opioids may be causal in thi effected improvement of chronic idiopathic constipation
suggest that at least in selected cases an excess activity
of endogenous opioids may be causal in this pathological
condition. In support of this, naloxone normalized suggest that at least in selected cases an excess activity the
of endogenous opioids may be causal in this pathological opic
condition. In support of this, naloxone normalized gastric sig
emptying in patients with duodenal of endogenous opioids may be causal in this pathologic:
condition. In support of this, naloxone normalized gastric emptying in patients with duodenal dyskinesia (298).
had no such effect in another subgroup of patients wit condition. In support of this, naloxone normalized gastric supprying in patients with duodenal dyskinesia (298). It the had no such effect in another subgroup of patients with functional dyspepsia who displayed gastric hyp emptying in patients with duodenal dyskinesia (298).
had no such effect in another subgroup of patients with
functional dyspepsia who displayed gastric hypomotilit
Schang and DeVroede (370) observed improvement ("intestina had no such effect in another subgroup of patients with
functional dyspepsia who displayed gastric hypomotility.
Schang and DeVroede (370) observed improvement of
"intestinal pseudo-obstruction" upon naloxone treat-
ment i functional dyspepsia who displayed gastric hypomotility.

Schang and DeVroede (370) observed improvement of in

"intestinal pseudo-obstruction" upon naloxone treat-

ment in one patient who had unsuccessfully undergone Schang and DeVroede (

"intestinal pseudo-obstr

ment in one patient who

subtotal colectomy. The

course not be overvalued

4. Ulcerative colitis, div mestinal pseudo-obstraction upon haloxone treat-

ment in one patient who had unsuccessfully undergone

subtotal colectomy. The above case reports should of

course not be overvalued.

4. Ulcerative colitis, diverticulosis

subtotal colectomy. The above case reports should of elections course not be overvalued.

4. Ulcerative colitis, diverticulosis, and Crohn's disease. differents with ulcerative colitis display decreased colonic all motili course not be overvalued. The sum of the overvalued.

4. Ulcerative colitis, diverticulosis, and Crohn's disease. di

Patients with ulcerative colitis display decreased colonic all

motility and suffer from diarrhea, which 4. Ulcerative colitis, diverticulosis, and Crohn's disease.
Patients with ulcerative colitis display decreased colonic motility and suffer from diarrhea, which can be treated with opioids. Tincture of opium stimulated colo Patients with ulcerative colitis display decreased colonic motility and suffer from diarrhea, which can be treated with opioids. Tincture of opium stimulated colonic type I-IV contractions (for definition, see ref. 470) in motility and suffer from diarrhea, which can be treated
with opioids. Tincture of opium stimulated colonic type
I-IV contractions (for definition, see ref. 470) in patients
with ulcerative colitis, but not in healthy contr with opioids. Tincture of opium stimulated colonic type I-IV contractions (for definition, see ref. 470) in patients with ulcerative colitis, but not in healthy controls (126). The increased resistance to intestinal transi I-IV contractions (for definition, see ref. 470) in patients with ulcerative colitis, but not in healthy controls (126). The increased resistance to intestinal transit brought about by these segmentations may contribute t with ulcerative colitis, but not in healthy controls (126).
The increased resistance to intestinal transit brought
about by these segmentations may contribute to proximal
dilation of the inflamed colonic wall, carrying the The increased resistance to intestinal transit brought
about by these segmentations may contribute to proximal
dilation of the inflamed colonic wall, carrying the risk of
toxic megacolon and perforation. It is not known w about by these segmentations may contribute to proximal
dilation of the inflamed colonic wall, carrying the risk of
toxic megacolon and perforation. It is not known whether
an imbalance of endogenous opioids is implicated dilation of the inflamed colonic wall, carrying the risk toxic megacolon and perforation. It is not known wheth
an imbalance of endogenous opioids is implicated in the
pathophysiology of this disease. The same holds true f toxic megacolon and perforation. It is not known whether
an imbalance of endogenous opioids is implicated in the
pathophysiology of this disease. The same holds true for
diverticulosis, where i.v. morphine caused higher in (319). thophysiology of this disease. The same holds true for
verticulosis, where i.v. morphine caused higher intra-
minal pressures than in unaffected intestinal segments
19).
Immunocytochemical data of Sjölund et al. (411) sug-

diverticulosis, where i.v. morphine caused higher introduction
luminal pressures than in unaffected intestinal segmen
(319).
Immunocytochemical data of Sjölund et al. (411) su
gest an increase in enkephalin neurons within duminal pressures than in unaffected intestinal segments

(319).

Immunocytochemical data of Sjölund et al. (411) sug-

gest an increase in enkephalin neurons within the myen-

teric plexus of the nonafflicted part of the (319).
Immunocytochemical data of Sjölund et al. (411) suggest an increase in enkephalin neurons within the myen-
teric plexus of the nonafflicted part of the ileum in
patients with Crohn's disease, as compared with contro Immunocytochemical data of Sjölund et al. (411) sug-
gest an increase in enkephalin neurons within the myen-
teric plexus of the nonafflicted part of the ileum in
patients with Crohn's disease, as compared with controls gest an increase in enkephalin neurons within the myenteric plexus of the nonafflicted part of the ileum in patients with Crohn's disease, as compared with controls.
Coarse enkephalin-containing nerve fibers were found in patients with Crohn's disease, as compared with control
Coarse enkephalin-containing nerve fibers were found i
both the nonafflicted and afflicted ileum, but not i
controls not suffering from Crohn's disease. The patho
phy parse enkephalin-containing nerve fibers were found in
the the nonafflicted and afflicted ileum, but not in
mtrols not suffering from Crohn's disease. The patho-
siological implication of these findings is unknown.
5. Stre

both the nonafflicted and afflicted ileum, but not in controls not suffering from Crohn's disease. The patho-
physiological implication of these findings is unknown.
5. Stress-induced opioid dependence of the gut. It is a controls not suffering from Crohn's disease. The path
physiological implication of these findings is unknown
5. Stress-induced opioid dependence of the gut. It is
interesting observation that ilea taken from acutely (2
or physiological implication of these findings is unknown.
5. Stress-induced opioid dependence of the gut. It is an
interesting observation that ilea taken from acutely (29)
or chronically (299) stressed guinea-pigs or rats, 5. Stress-induced opioid dependence of the gut. It is an interesting observation that ilea taken from acutely (29) or chronically (299) stressed guinea-pigs or rats, respectively, displayed an opioid withdrawal-like contra interesting observation that ilea taken from acutely (29) con
or chronically (299) stressed guinea-pigs or rats, respec-
tively, displayed an opioid withdrawal-like contracture laye
upon naloxone application to the organ b or chronically (299) stressed guinea-pigs or rats, respectively, displayed an opioid withdrawal-like contracture laupon naloxone application to the organ bath. Moreover, Sileal segments removed from guinea pigs submitted upon naloxone application to the organ bath. Moreover, ileal segments removed from guinea pigs submitted to neurogenic stress (light and sound) over 23 h displayed more spontaneous peristaltic waves over time as com-

tility. On the other hand, an enkephalin analogue has nomena resemble those seen in fetal guinea-pig ilea just
been suggested as a drug to treat paralyzing ileus (24). prior to parturition (241) and may be interpreted in t pared with nonstressed controls (Kromer and Steige-ESTINAL MOTILITY AND SECRETION 137
pared with nonstressed controls (Kromer and Steige-
mann, unpublished results). These withdrawal-like phe-
nomena resemble those seen in fetal guinea-pig ilea just ESTINAL MOTILITY AND SECRETION 137
pared with nonstressed controls (Kromer and Steige-
mann, unpublished results). These withdrawal-like phe-
nomena resemble those seen in fetal guinea-pig ilea just
prior to parturition (2 pared with nonstressed controls (Kromer and Steige-
mann, unpublished results). These withdrawal-like phe-
nomena resemble those seen in fetal guinea-pig ilea just
prior to parturition (241) and may be interpreted in terms pared with nonstressed controls (Kromer and Steige-
mann, unpublished results). These withdrawal-like phe-
nomena resemble those seen in fetal guinea-pig ilea just
prior to parturition (241) and may be interpreted in terms mann, unpublished results). These withdrawal-like phe-
nomena resemble those seen in fetal guinea-pig ilea just
prior to parturition (241) and may be interpreted in terms
of acute or chronic development of dependence on op nomena resemble those seen in fetal guinea-pig ilea just
prior to parturition (241) and may be interpreted in terms
of acute or chronic development of dependence on opioids
possibly released from the pituitary. In fact, pl prior to parturition (241) and may be interpreted in terms
of acute or chronic development of dependence on opioids
possibly released from the pituitary. In fact, plasma levels
of beta-endorphin in pregnant women undergoin to a stressful condition.

6. Gastrointestinal tumors and inflammation. Betaof beta-endorphin in pregnant women undergoing label and parturition were elevated (73), which may also relation to a stressful condition.
6. Gastrointestinal tumors and inflammation. Bet endorphin- and [Met⁵]- as well and parturition were elevated (73), which may also relate
to a stressful condition.
6. Gastrointestinal tumors and inflammation. Beta-
endorphin- and [Met⁵]- as well as [Leu⁶]-enkephalin-like
immunoreactivities have b to a stressful condition.
6. Gastrointestinal tumors and inflammation. Beta-
endorphin- and $[Met⁵]$ - as well as $[Leu⁵]$ -enkephalin-like
immunoreactivities have been demonstrated in gastric
carcinomas (489, 440). 6. Gastrointestinal tumors and inflammation. Beta-
endorphin- and $[Met⁵]$ - as well as $[Leu⁵]$ -enkephalin-like
immunoreactivities have been demonstrated in gastric
carcinomas (489, 440). On occasion, these tumors endorphin- and $[Met⁵]$ - as well as $[Leu⁵]$ -enkephalin-like
immunoreactivities have been demonstrated in gastric
carcinomas (489, 440). On occasion, these tumors contain
very high opioid concentrations. Also, para immunoreactivities have been demonstrated in gastric carcinomas (489, 440). On occasion, these tumors contain very high opioid concentrations. Also, paraganglioma of the duodenum (147) and rectal carcinoids (7) contain opi carcinomas (489, 440). On occasion, these tumors contain
very high opioid concentrations. Also, paraganglioma of
the duodenum (147) and rectal carcinoids (7) contain
opioid activity. There were, however, no evident clinica the duodenum (147) and rectal carcinoids (7) contain opioid activity. There were, however, no evident clinical signs of gastrointestinal disturbances related to an altered functional state of endogenous opioids. Davis opioid activity. There were, however, no evident clinical opioid activity. There were, however, no evident clinical
signs of gastrointestinal disturbances related to an al-
tered functional state of endogenous opioids. Davis et al.
(81) found increased tissue concentrations of [M signs of gastrointestinal disturbances related to an
tered functional state of endogenous opioids. Davis et
(81) found increased tissue concentrations of [Met
enkephalin in adenocarcinomas of the colon and in t
inflamed ap tered functional state of endogenous opioids. Davis et (81) found increased tissue concentrations of [Metenkephalin in adenocarcinomas of the colon and in t
inflamed appendix. The authors speculated that constation, which (81) found increased tissue concentrations of [Met enkephalin in adenocarcinomas of the colon and in t
inflamed appendix. The authors speculated that cons
pation, which is not uncommon in nonperforated appe
dicitis, may co inflamed appendix. The authors speculated that consti-
pation, which is not uncommon in nonperforated appen-
dicitis, may correspond to an enhanced release of endog-
enous opioids upon distension of the inflamed tissue
sim inflamed appendix. The authors speculated that consti-
pation, which is not uncommon in nonperforated appen-
dicitis, may correspond to an enhanced release of endog-
enous opioids upon distension of the inflamed tissue
sim pation, which is not uncommon in nonperforated appendicitis, may correspond to an enhanced release of endogenous opioids upon distension of the inflamed tissue similar to the release of opioid-like activity from the disten dicitis, may correspendent and similar to the relationships in vitro.

distended guinea-

al. (452) in vitro.

7. Possible biolog ous opioids upon distension of the inflamed tissue inlar to the release of opioid-like activity from the stended guinea-pig ileum observed by van Nueten (452) in vitro.
(452) in vitro.
7. *Possible biological significance* similar to the release of opioid-like activity from the
distended guinea-pig ileum observed by van Nueten et
al. (452) in vitro.
7. Possible biological significance of exorphins. A phys-
iological aspect possibly related

distended guinea-pig ileum observed by van Nuet
al. (452) in vitro.
7. Possible biological significance of exorphins. A
iological aspect possibly related to particular stag
life may be influenced by exorphins like beta-cas al. (452) in vitro.
7. Possible biological significance of exorphins. A phiological aspect possibly related to particular stages
life may be influenced by exorphins like beta-casom
phins. These opioid peptides were identif 7. Possible biological significance of exorphins. A physiological aspect possibly related to particular stages i
life may be influenced by exorphins like beta-casomor
phins. These opioid peptides were identified by Tesche
 iological aspect possibly related to particular stages in
life may be influenced by exorphins like beta-casomor-
phins. These opioid peptides were identified by Tesche-
macher and coworkers (35) in hydrolysates of beta-
ca life may be influenced by exorphins like beta-casomorphins. These opioid peptides were identified by Tesche macher and coworkers (35) in hydrolysates of beta casein, a milk constituent. Beta-casomorphin-5 inhibite intestin phins. These opioid peptides were identified by Teschemacher and coworkers (35) in hydrolysates of beta-casein, a milk constituent. Beta-casomorphin-5 inhibited intestinal peristalsis in vitro (233). Moreover, beta-casomor macher and coworkers (35) in hydrolysates of beta-casein, a milk constituent. Beta-casomorphin-5 inhibited intestinal peristalsis in vitro (233). Moreover, beta-casomorphins impaired intestinal secretion (159). Thus, betacasein, a milk constituent. Beta-casomorphin-5 inhibited
intestinal peristalsis in vitro (233). Moreover, beta-
casomorphins impaired intestinal secretion (159). Thus,
beta-casomorphins may act as "food hormones" (293).
T intestinal peristalsis in vitro (233). Moreover, beta-casomorphins impaired intestinal secretion (159). Thus, beta-casomorphins may act as "food hormones" (293). They are acid stable and may have been designed by nature to casomorphins impaired intestinal secretion (159). Thus
beta-casomorphins may act as "food hormones" (293)
They are acid stable and may have been designed b
nature to protect the irritable infantile gut from frequen
diarrhe beta-casomorphins may act as "food hormones" (293).
They are acid stable and may have been designed by
nature to protect the irritable infantile gut from frequent
diarrhea. While Petrilli et al. (328) were unable to dem-
 They are acid stable and may have been designed b nature to protect the irritable infantile gut from frequentiar
rhea. While Petrilli et al. (328) were unable to den
onstrate any in vitro cleavage of buffalo beta-casein be nature to protect the irritable infantile gut from frequent
diarrhea. While Petrilli et al. (328) were unable to dem-
onstrate any in vitro cleavage of buffalo beta-casein to
beta-casomorphins by various peptidases and by diarrhea. While Petrilli et al. (328) were unable to onstrate any in vitro cleavage of buffalo beta-case beta-casomorphins by various peptidases and by tinal brush border enzymes, Hamel et al. (154) s. the generation of be onstrate any in vitro cleavage of buffalo beta-casein to
beta-casomorphins by various peptidases and by intes-
tinal brush border enzymes, Hamel et al. (154) showed
the generation of beta-casomorphin-like immunoreactiv-
it beta-casomorphins by various peptidases and by int
tinal brush border enzymes, Hamel et al. (154) show
the generation of beta-casomorphin-like immunoreact
ity from cow's milk by caseolytic bacteria. The ident
of the materi tinal brush border enzymes, Hamel et al. (154) showed
the generation of beta-casomorphin-like immunoreactiv-
ity from cow's milk by caseolytic bacteria. The identity
of the material was characterized by gel chromatography. field. of the material
These exciting
field.
H. Conclusions
The involven The involvement of endogenous opioid peptides in the
idd.
The involvement of endogenous opioid peptides in the
ntrol of gastrointestinal motility was anticipated from

Field.

Field.

Field.

Field.

Conclusions

The involvement of endogenous opioid peptides in the

control of gastrointestinal motility was anticipated from

their occurrence within the intramural plexus and muscle H. Conclusions
The involvement of endogenous opioid peptides in the
control of gastrointestinal motility was anticipated from
their occurrence within the intramural plexus and muscle
layers and from motility effects of exo H. Conclusions
The involvement of endogenous opioid peptides in the
control of gastrointestinal motility was anticipated from
their occurrence within the intramural plexis and muscle
layers and from motility effects of exo The involvement of endogenous opioid peptides in the control of gastrointestinal motility was anticipated from their occurrence within the intramural plexus and muscle layers and from motility effects of exogenous opioids. control of gastrointestinal motility was anticipated from
their occurrence within the intramural plexus and muscle
layers and from motility effects of exogenous opioids.
Since administration of exogenous agonists causes ac their occurrence within the intramural plexus and muscle
layers and from motility effects of exogenous opioids.
Since administration of exogenous agonists causes acti-
vation of receptors at different locations, of differe of different types simultaneously, the outcome of this

Experimental approach may well distort the true picture
experimental approach may well distort the true picture
of endogenous opioid functions. In fact, distinct opioid KROMENT 138

experimental approach may well distort the true picture ob

of endogenous opioid functions. In fact, distinct opioid ral

mechanisms, which might be operative at different func-KI
experimental approach may well distort the true pictur
of endogenous opioid functions. In fact, distinct opioi
mechanisms, which might be operative at different func
tional stages of gastrointestinal motility, probably experimental approach may well distort the true picture of endogenous opioid functions. In fact, distinct opioid ramechanisms, which might be operative at different functional stages of gastrointestinal motility, probably experimental approach may well distort the true picture
of endogenous opioid functions. In fact, distinct opioid
mechanisms, which might be operative at different func-
tional stages of gastrointestinal motility, probably of endogenous opioid functions. In fact, distinct opin
mechanisms, which might be operative at different furtional stages of gastrointestinal motility, probably ha
to be activated at the proper time relative to each otlet
 mechanisms, which might be operative at different fun
tional stages of gastrointestinal motility, probably has
to be activated at the proper time relative to each oth
for physiological function to develop. The most promi
i tional stages of gastrointestinal motility, probably have to be activated at the proper time relative to each otlefor physiological function to develop. The most prom
ing strategy to uncover physiological function is, the to be activated at the proper time relative to each other
for physiological function to develop. The most promis-
ing strategy to uncover physiological function is, there-
fore, to block opioid receptors by opioid-specific for physiological function to develop. The most promising strategy to uncover physiological function is, therefore, to block opioid receptors by opioid-specific antagonists like naloxone. Since naloxone is not opioid recep ing strategy to uncover physiological function is, there-
fore, to block opioid receptors by opioid-specific antago-
mists like naloxone. Since naloxone is not opioid receptor att
type selective, opioid functions mediated fore, to block opioid receptors by opioid-specific antagonists like naloxone. Since naloxone is not opioid receptor type-selective, opioid functions mediated by distinct receptor types-will not be distinguished. This may b nists like naloxone. Since naloxone is not opioid receptor
type selective, opioid functions mediated by distinct re-
ceptor types will not be distinguished. This may be
achieved by use of the newer opioid receptor type-sel type selective, opioid functions mediated by distinct receptor types will not be distinguished. This may be standieved by use of the newer opioid receptor type-selective antagonists, but functions of opioid receptors not a ceptor types will not be distinguished. This may be schieved by use of the newer opioid receptor type-selective antagonists, but functions of opioid receptors not a blocked will then be missed. Although, immediately upon n achieved by use of the newer opioid receptor type-selective antagonists, but functions of opioid receptors not
blocked will then be missed. Although, immediately upon
administration, only blockade of endogenously activated tive antagonists, but functions of opioid receptors not and blocked will then be missed. Although, immediately upon madministration, only blockade of endogenously activated opioid receptors should be manifest as functional blocked will then be missed. Although, immediately upon
administration, only blockade of endogenously activated
opioid receptors should be manifest as functional deficits,
even this strategy might, to some extent, obscure administration, only blockade of endogenously activated
opioid receptors should be manifest as functional deficits,
even this strategy might, to some extent, obscure true
physiological functions. The reason is that during opioid receptors should be ma
even this strategy might, to
physiological functions. The
longed receptor blockade, fu
might progressively develop.
Irrespective of these poten en this strategy might, to some extent, obscure true sysiological functions. The reason is that during propressively develop.
Irrespective of these potential shortcomings, a clear-
Irrespective of these potential shortcomi

physiological functions. The reason is that during pro-
longed receptor blockade, functional counterregulation Stimight progressively develop.
Irrespective of these potential shortcomings, a clear-
cut functional role of g longed receptor blockade, functional counterregulation
might progressively develop.
Irrespective of these potential shortcomings, a clear-
cut functional role of gastrointestinal opioids in the
control of reflex peristalsi might progressively develop. the Irrespective of these potential shortcomings, a clear-
cut functional role of gastrointestinal opioids in the at
control of reflex peristalsis has emerged in several spe-
cies. In the guine Irrespective of these potential shortcomings, a clear-
cut functional role of gastrointestinal opioids in the atte
control of reflex peristalsis has emerged in several spe-
cies. In the guinea-pig, it appears that the peri cut functional role of gastrointestinal opioids in the a
control of reflex peristalsis has emerged in several spe-
cies. In the guinea-pig, it appears that the periodicity of t
peristaltsis, not a fatigue phenomenon, is mo control of reflex peristalsis has emerged in several species. In the guinea-pig, it appears that the periodicity of tige
peristaltsis, not a fatigue phenomenon, is modulated in the
vitro by an opioid mechanism. This leads peristaltsis, not a fatigue phenomenon, is modulated in
vitro by an opioid mechanism. This leads to periodic
interruption of bursts of peristaltic activity and to a
decrease in the frequency of peristaltic waves. The opioi vitro by an opioid mechanism. This leads to periodic pointerruption of bursts of peristaltic activity and to a sedecrease in the frequency of peristaltic waves. The opioid comechanism is found throughout the gut in accorda interruption of bursts of peristaltic activity and to a decrease in the frequency of peristaltic waves. The opioid mechanism is found throughout the gut in accordance with the "gradient of the intestine," i.e., with increa decrease in the frequency of peristaltic waves. The opioid mechanism is found throughout the gut in accordance with the "gradient of the intestine," i.e., with increasing functional significance from proximal to distal sma mechanism is found throughout the gut in accordance
with the "gradient of the intestine," i.e., with increasing
functional significance from proximal to distal small
intestine. It is antagonized by calcium ions, causes hywith the "gradient of the intestine," i.e., with increasin
functional significance from proximal to distal sma
intestine. It is antagonized by calcium ions, causes hy
perpolarization of myenteric neurons, and modulates no
 functional significance from proximal to distal small
intestine. It is antagonized by calcium ions, causes hy-
perpolarization of myenteric neurons, and modulates not
only the release, but also the action of acetylcholine. intestine. It is antagonized by calcium ions, causes hy-
perpolarization of myenteric neurons, and modulates not
monly the release, but also the action of acetylcholine. op
Spontaneously active neurons within the myenteric perpolarization of myenteric neurons, and modulates nonly the release, but also the action of acetylcholine Spontaneously active neurons within the myenteriplexus may constitute or drive, at least partially, the intestinal only the release, but also the action of acetylcholine. op
Spontaneously active neurons within the myenteric con-
plexus may constitute or drive, at least partially, the spintestinal opioid mechanism and probably become de Spontaneously active neurons within the myenteric
plexus may constitute or drive, at least partially, the
intestinal opioid mechanism and probably become deac-
tivated upon stimulation of mechanoreceptors which
trigger the plexus may constitute or drive, at least partially, the intestinal opioid mechanism and probably become deactivated upon stimulation of mechanoreceptors which trigger the peristaltic reflex. Distinct opioid receptor types intestinal opioid mechanism and probably become deactivated upon stimulation of mechanoreceptors which trigger the peristaltic reflex. Distinct opioid receptor lypes may be involved at different sites within the neuronal p tivated upon stimulation of mechanoreceptors which
trigger the peristaltic reflex. Distinct opioid receptor
types may be involved at different sites within the neu-
ronal plexus, as judged from contrasting in vitro actions trigger the peristaltic reflex. Distinct opioid receptor types may be involved at different sites within the neuronal plexus, as judged from contrasting in vitro actions of N-allyl-normetazocine on the longitudinal muscle types may be involved at different sites within the neu-
ronal plexus, as judged from contrasting in vitro actions
of N-allyl-normetazocine on the longitudinal muscle ver-
sus the propulsive circular muscle contraction. Ac ronal plexus, as judged from contrasting in vitro actions to be of N-allyl-normetazocine on the longitudinal muscle ver-
sus the propulsive circular muscle contraction. Actually, somether contrasting effects of N-allyl-nor of N-allyl-normetazocine on the longitudinal muscle ver-
sus the propulsive circular muscle contraction. Actually,
the contrasting effects of N-allyl-normetazocine (i.e.,
inhibition *versus* excitation) can only be explain sus the propulsive circular muscle contraction. Actuall the contrasting effects of N-allyl-normetazocine (i.e. inhibition versus excitation) can only be explained behistinct receptor types, provided one takes into account the contrasting
inhibition versus
distinct receptor
that other opioid
tinal preparation
The opioid mee hibition versus excitation) can only be explained by
stinct receptor types, provided one takes into account
at other opioids exert consistent effects in both intes-
al preparations.
The opioid mechanism is subject to parti distinct receptor types, provided one takes into a
that other opioids exert consistent effects in both
tinal preparations.
The opioid mechanism is subject to partial fun
counterregulation and development of tolerance/d
enc

that other opioids exert consistent effects in both intes-
tinal preparations.
The opioid mechanism is subject to partial functional
counterregulation and development of tolerance/depend-
ence. Dependence on the body's own tinal preparations.
The opioid mechanism is subject to partial function
counterregulation and development of tolerance/deper
ence. Dependence on the body's own opioids probal
develops in the fetal intestine just prior to p The opioid mechanism is subject to partial functional
unterregulation and development of tolerance/depend-
ce. Dependence on the body's own opioids probably
velops in the fetal intestine just prior to parturition.
In all s

counterregulation and development of tolerance/dependence. Dependence on the body's own opioids probable develops in the fetal intestine just prior to parturition.
In all species tested, opioids seem to exert a due excitat ence. Dependence on the body's own opioids probably I
develops in the fetal intestine just prior to parturition.
In all species tested, opioids seem to exert a dual p
excitatory-inhibitory effect in the small and large int

ER
obviously of a higher significance in the dog. The rat and
rabbit small intestine behaves, in vitro, very much like raheta
bit small intestine behaves, in the dog. The rat and
rabbit small intestine behaves, in vitro, very much like
that of the guinea pig, whereas the cat small intestine THER
obviously of a higher significance in the dog. The rat and
rabbit small intestine behaves, in vitro, very much like
that of the guinea pig, whereas the cat small intestine
displays both the inhibitory and excitatory r obviously of a higher significance in the dog. The rat and rabbit small intestine behaves, in vitro, very much like that of the guinea pig, whereas the cat small intestine displays both the inhibitory and excitatory respon obviously of a higher significance in the dog. The rat and
rabbit small intestine behaves, in vitro, very much like
that of the guinea pig, whereas the cat small intestine
displays both the inhibitory and excitatory respon that of the guinea pig, whereas the cat small intestine
displays both the inhibitory and excitatory response in a
rather unpredictable manner. The actual functional state
of the reflex mechanism at the time of drug applica may determine the overall outcome. rather unpredictable manner. The actual functional state
of the reflex mechanism at the time of drug application
may determine the overall outcome.
The stimulatory opioid effect on gut motility has been
attributed to a rel

rather unpredictable manner. The actual functional state
of the reflex mechanism at the time of drug application
may determine the overall outcome.
The stimulatory opioid effect on gut motility has been
attributed to a rel of the reflex mechanism at the time of drug application
may determine the overall outcome.
The stimulatory opioid effect on gut motility has been
attributed to a release of serotonin within the intestinal
wall, although ot may determine the overall outcome.
The stimulatory opioid effect on gut motility has been
attributed to a release of serotonin within the intestinal
wall, although other endogenous compounds like sub-
stance P or motilin m The stimulatory opioid effect on gut motility has been
attributed to a release of serotonin within the intestinal
wall, although other endogenous compounds like sub-
stance P or motilin might also be involved. Aside from
n attributed to a release of serotonin within the intestinal
wall, although other endogenous compounds like sub-
stance P or motilin might also be involved. Aside from
neuronal location, components of both the stimulatory
an wall, although other endogenous compounds like su
stance P or motilin might also be involved. Aside fro
neuronal location, components of both the stimulate
and inhibitory effects may be localized on the smoo
muscle membran ance P or motilin might also be involved. Aside from
uronal location, components of both the stimulatory
d inhibitory effects may be localized on the smooth
uscle membrane, but this needs further investigation.
In vivo st

peristaltsis, not a fatigue phenomenon, is modulated in the intestine should receive more attention, since both vitro by an opioid mechanism. This leads to periodic peristaltic contractions travelling down the intestinal i neuronal location, components of both the stimulatory
and inhibitory effects may be localized on the smooth
muscle membrane, but this needs further investigation.
In vivo studies provide no consistent picture, but in
most and inhibitory effects may be localized on the smooth
muscle membrane, but this needs further investigation.
In vivo studies provide no consistent picture, but in
most species, including man, inhibition of propulsive and
 muscle membrane, but this needs further investigation.
In vivo studies provide no consistent picture, but in
most species, including man, inhibition of propulsive and
stimulation of segmenting contractions by opioids, in
b In vivo studies provide no consistent picture, but in

most species, including man, inhibition of propulsive and

stimulation of segmenting contractions by opioids, in

both the small and large intestine, evidently prevai stimulation of segmenting contractions by opioids, in both the small and large intestine, evidently prevail.
Stimulation of segmenting contractions is not seen in the guinea pig. Certain discrepancies resulting from dif-
f stimulation of segmenting contractions by opioids, in both the small and large intestine, evidently prevail.
Stimulation of segmenting contractions is not seen in the guinea pig. Certain discrepancies resulting from differ both the small and large intestine, evidently prevail.
Stimulation of segmenting contractions is not seen in
the guinea pig. Certain discrepancies resulting from dif-
ferent methodological approaches should receive greater Stimulation of segmenting contractions is not seen
the guinea pig. Certain discrepancies resulting from different methodological approaches should receive great
attention in the future to define the propulsive verse
the se the guinea pig. Certain discrepancies resulting from different methodological approaches should receive greater attention in the future to define the propulsive versus the segmenting nature of any motility parameter invest ferent methodological approaches should receive greater
attention in the future to define the propulsive versus
the segmenting nature of any motility parameter inves-
tigated. Also their temporal pattern and distribution o attention in the future to define the propulsive versus
the segmenting nature of any motility parameter inves-
tigated. Also their temporal pattern and distribution over
the intestine should receive more attention, since b the segmenting nature of any motility parameter inves-
tigated. Also their temporal pattern and distribution over
the intestine should receive more attention, since both
peristaltic contractions travelling down the intest tigated. Also their temporal pattern and distribution over
the intestine should receive more attention, since both
peristaltic contractions travelling down the intestinal
segment and the decreasing frequency from proximal the intestine should receive more attention, since both
peristaltic contractions travelling down the intestinal
segment and the decreasing frequency from proximal to
distal of segmentations may contribute to transit of
int peristaltic contractions travelling
segment and the decreasing frequen
distal of segmentations may cont
intestinal contents, however under
versus fed) physiological conditions
A field of particular interest during gment and the decreasing frequency from proximal to
stal of segmentations may contribute to transit of
testinal contents, however under different (i.e., fasted
rsus fed) physiological conditions.
A field of particular inte

distal of segmentations may contribute to transit of intestinal contents, however under different (i.e., fasted versus fed) physiological conditions.
A field of particular interest during the past few years has been the co intestinal contents, however under different (i.e., fasted
versus fed) physiological conditions.
A field of particular interest during the past few years
has been the comparison between peripheral and central
motility effe versus fed) physiological conditions.
A field of particular interest during the past few years
has been the comparison between peripheral and central
motility effects of opioids. The major outcome of central
opioid recepto A field of particular interest during the past few years
has been the comparison between peripheral and central
motility effects of opioids. The major outcome of central
opioid receptor activation is, as far as gut motilit has been the comparison between peripheral and central motility effects of opioids. The major outcome of central opioid receptor activation is, as far as gut motility is concerned, a delay in gastrointestinal transit. In m motility effects of opioids. The major outcome of central opioid receptor activation is, as far as gut motility is concerned, a delay in gastrointestinal transit. In murin species, both central and peripheral opioid inhibi opioid receptor activation is, as far as gut motility is concerned, a delay in gastrointestinal transit. In murine species, both central and peripheral opioid inhibition of intestinal transit is mediated by mu-receptors. I concerned, a delay in gastrointestinal transit. In murine species, both central and peripheral opioid inhibition of intestinal transit is mediated by mu-receptors. In addition, delta-type receptors contribute at the spinal intestinal transit is mediated by mu-receptors. In addition, delta-type receptors contribute at the spinal and, possibly, the supraspinal level. Both opioid inhibition and stimulation of intestinal motility in the dog appe intestinal transit is mediated by mu-receptors. In addition, delta-type receptors contribute at the spinal and, possibly, the supraspinal level. Both opioid inhibition and stimulation of intestinal motility in the dog appe tion, delta-type receptors contribute at the spinal and, possibly, the supraspinal level. Both opioid inhibition and stimulation of intestinal motility in the dog appear to be mediated by mu-receptors, but this attributio possibly, the supraspi
and stimulation of int
to be mediated by mu-
well as the central vers
some extent uncertain.
In contrast to in vitre In contrast to intertinal motility in the dog appear
be mediated by mu-receptors, but this attribution as
ill as the central versus peripheral location remains to
me extent uncertain.
In contrast to in vitro studies, nalox

develops in the fetal intestine just prior to parturition. oxone alone have been reported occasionally under
In all species tested, opioids seem to exert a dual poorly defined conditions. The situation is even less clear
e to be mediated by mu-receptors, but this attribution as
well as the central versus peripheral location remains to
some extent uncertain.
In contrast to in vitro studies, naloxone administration
in vivo failed to unequivoca well as the central versus peripheral location remains to
some extent uncertain.
In contrast to in vitro studies, naloxone administration
in vivo failed to unequivocally unmask any physiological
role of endogenous opioids some extent uncertain.

In contrast to in vitro studies, naloxone administration

in vivo failed to unequivocally unmask any physiological

role of endogenous opioids in gastrointestinal motility.

This does not mean, howe In contrast to in vitro studies, naloxone administration vivo failed to unequivocally unmask any physiologic
role of endogenous opioids in gastrointestinal motili
This does not mean, however, that such opioid function
is a in vivo failed to unequivocally unmask any physiologic
role of endogenous opioids in gastrointestinal motilit
This does not mean, however, that such opioid functio
is absent. Rather, it is difficult to detect a small modu
 role of endogenous opioids in gastrointestinal motil
This does not mean, however, that such opioid funct
is absent. Rather, it is difficult to detect a small mo
latory influence composed of both inhibitory and ex
atory mec This does not mean, however, that such opioid function
is absent. Rather, it is difficult to detect a small modu-
latory influence composed of both inhibitory and excit-
atory mechanisms in the presence of counterregulatio is absent. Rather, it is difficult to detect a small modulatory influence composed of both inhibitory and excitatory mechanisms in the presence of counterregulation.
In the small and large intestine, motility effects of na latory influence composed of both inhibitory and excitatory mechanisms in the presence of counterregulation.
In the small and large intestine, motility effects of naloxone alone have been reported occasionally under poorly In the small and large intestine, motility effects of nal-In the small and large intestine, motility effects of naloxone alone have been reported occasionally under poorly defined conditions. The situation is even less clear with regard to the function of the lower esophageal sph oxone alone have been reported occasionally under
poorly defined conditions. The situation is even less clear
with regard to the function of the lower esophageal
sphincter, the pylorus, and the anal sphincter. The con-
clu

OPIOIDS AND CONTROL OF GASTROINT
least in some species including man, their constipating
effect by a decrease in propulsive activity in the whole opioids and contract of GASTROINTE
least in some species including man, their constipating meffect by a decrease in propulsive activity in the whole
gastrointestinal tract as well as by an increase in the ri oppoint of CONTROL OF GASTROINTES
least in some species including man, their constipating mi
effect by a decrease in propulsive activity in the whole
gastrointestinal tract as well as by an increase in the ric
tone of the least in some species including man, their constipating mineffect by a decrease in propulsive activity in the whole efferent gastrointestinal tract as well as by an increase in the rich tone of the pylorus and duodenum, an least in some species including man, their constipating
effect by a decrease in propulsive activity in the whole
gastrointestinal tract as well as by an increase in the
tone of the pylorus and duodenum, and possibly by
enh tone of the pylorus and duodenum, and possibly by tone of the pylorus and duodenum, and possibly by orthancing segmentations in the duodenum and colon, (still appears to be valid. The guinea pig may be an rexception as stimulatory opioid action components probably do not enhancing segmentations in the duodenum and colon, (238
still appears to be valid. The guinea pig may be an
exception as stimulatory opioid action components prob-
effect ably do not contribute to the constipating effect. still appears to be valid. The guinea pig may be an recever exception as stimulatory opioid action components prob-
ably do not contribute to the constipating effect. This out may define one extreme of the spectrum obtaine exception as stimulatory opioid action components prob-
ably do not contribute to the constipating effect. This ou
may define one extreme of the spectrum obtained by on
comparisons between species. The other extreme may be ably do not contribute to
may define one extreme
comparisons between speci
best defined by the dog v
effect has a major impact.
Interactions of opioid m Example the spectrum obtained by
mparisons between species. The other extreme may be
at defined by the dog where the stimulatory opioid
fect has a major impact.
Interactions of opioid mechanisms with a variety of
surotrans

comparisons between species. The other extreme may be
best defined by the dog where the stimulatory opioid
effect has a major impact.
Interactions of opioid mechanisms with a variety of
neurotransmitters or neuropeptides h best defined by the dog where the stimulatory opioid
effect has a major impact.
Interactions of opioid mechanisms with a variety of
neurotransmitters or neuropeptides have been described.
Their significance in the control effect has a major impact.

Interactions of opioid mechanisms with a variety of

neurotransmitters or neuropeptides have been described.

Their significance in the control of intestinal peristalsis

is only partially under Interactions of opioid mechanisms with a variety of sect
neurotransmitters or neuropeptides have been described.
Their significance in the control of intestinal peristalsis unn
is only partially understood. For example, op neurotransmitters or neuropeptides have been described. ti
Their significance in the control of intestinal peristalsis us
is only partially understood. For example, opioids inhibit fit
the release of acetylcholine and, pos Their significance in the control of intestinal peristalsis unn
is only partially understood. For example, opioids inhibit furt
the release of acetylcholine and, possibly, substance P in
is suppressed the intestinal wall. is only partially understood. For example, opioids inhibit
the release of acetylcholine and, possibly, substance P in
the intestinal wall. Under conditions not known, release
of motilin may be either stimulated or inhibite the release of acetylcholine and, possibly, substance P in
the intestinal wall. Under conditions not known, release
of motilin may be either stimulated or inhibited by
opioids but motilin, and CCK alike, may itself stimula the intestinal wall. Under conditions not known, release
of motilin may be either stimulated or inhibited by
opioids but motilin, and CCK alike, may itself stimulate
the release of opioids. Similarly, serotonin may be re-
 of motilin may be either stimulated or inhibited opioids but motilin, and CCK alike, may itself stimulate release of opioids. Similarly, serotonin may between gastrointes-
These conclusions on interrelations between gastro opioids but motilin, and CCK alike, may itself stimulate
the release of opioids. Similarly, serotonin may be re-
leased by opioids but may itself stimulate opioid release.
These conclusions on interrelations between gastro the release of opioids. Similarly, serotonin may be re-
leased by opioids but may itself stimulate opioid release.
These conclusions on interrelations between gastrointes-
cinal neurotransmitter systems are to some extent leased by opioids but may itself stimu
These conclusions on interrelations be
tinal neurotransmitter systems are t
pothetical and need confirmation, ext
conceptual integration in the future.
Attempts to define malfunctions dese conclusions on interrelations between gastrointes-

and neurotransmitter systems are to some extent hy-

thetical and need confirmation, extension, and finally

streptual integration in the future.

Attempts to defin

tinal neurotransmitter systems are to some extent hypothetical and need confirmation, extension, and finally conceptual integration in the future.
Attempts to define malfunctions of endogenous opioin-
mechanisms have so fa conceptual integration in the future. as a according term of endogenous opioid mechanisms have so far been unsuccessful. The complexity of gastrointestinal functions and the modulatory why. There of endogenous opioids may Attempts to define malfunctions of endogenous opioid
mechanisms have so far been unsuccessful. The com-
plexity of gastrointestinal functions and the modulatory
were of endogenous opioids may be the reason why. There
are a mechanisms have so far been unsuccessful. The complexity of gastrointestinal functions and the modulatory role of endogenous opioids may be the reason why. There are a few very preliminary indications of a potential role o plexity of gastrointestinal functions and the modulatory
role of endogenous opioids may be the reason why. There
are a few very preliminary indications of a potential role
of endogenous opioids in chronic idiopathic const role of endogenous opioids may be the reasure a few very preliminary indications of ϵ of endogenous opioids in chronic idiopath or related conditions, but these data should by future well-controlled clinical studies.

IV. The Role of Opioids in the Control of Gastric *A. In Vitro Studies in the Control of Gast*
A. In Vitro Studies in Guinea Pig and Rat Tissues
A. In Vitro Studies in Guinea Pig and Rat Tissues
1 Isolated cell preparations Early reports on in

V. The Role of Opioids in the Control of Gastric where
Acid Secretion call
In Vitro Studies in Guinea Pig and Rat Tissues not
1. Isolated cell preparations. Early reports on in vivo alos
tions of opioids on gastric Action action and Rat Tissues

A. In Vitro Studies in Guinea Pig and Rat Tissues

1. Isolated cell preparations. Early reports on in vivo

actions of opioids on gastric acid secretion document a

complex situation of both A. In Vitro Studies in Guinea Pig and Rat Tissues
1. Isolated cell preparations. Early reports on in vivo
actions of opioids on gastric acid secretion document a
complex situation of both stimulatory and inhibitory
compon actions of opioids on gastric acid secretion document a
compents situation of both stimulatory and inhibitory
components (349, 176). These early and current in vivo
fect. Since opioids augmented also dbcAMP-stimulated
inv actions of opioids on gastric acid secretion document a complex situation of both stimulatory and inhibitory components (349, 176). These early and current in vivo investigations will be discussed later on. In vitro studie complex situation of both stimulatory and inhibitory os
components (349, 176). These early and current in vivo
feculies investigations will be discussed later on. In vitro studies
on the opioid influence on acid secretion on the opioid influence on acid secretion at the parietal suggeste
cell level were performed recently in order to reduce the ments, complexity of in vivo studies. Kromer et al. (238) dem-
crude ce
onstrated for the first t cell level were performed recently in order to reduce t complexity of in vivo studies. Kromer et al. (238) denonstrated for the first time opioid receptors in a guin pig gastric mucosal cell preparation enriched up to 70 w complexity of in vivo studies. Kromer et al. (238) demonstrated for the first time opioid receptors in a guinea
pig gastric mucosal cell preparation enriched up to 70% l
with parietal cells by counterflow centrifugat onstrated for the first time opioid receptors in a guinea
pig gastric mucosal cell preparation enriched up to 70%
with parietal cells by counterflow centrifugation. Secre-
tion of HCl into the tubulovesicular system of sus pig gastric mucosal cell preparation enriched up to 70% with parietal cells by counterflow centrifugation. Secretion of HCl into the tubulovesicular system of suspended parietal cells was determined indirectly by accumulat with parietal cells by counterflow centrifugation. Section of HCl into the tubulovesicular system of suspend
parietal cells was determined indirectly by accumulat
of $[^{14}C]$ aminopyrine, a weak base which freely penetra
t tion of HCl into the tubulovesicular system of suspended
parietal cells was determined indirectly by accumulation et
of $[^{14}C]$ aminopyrine, a weak base which freely penetrates ac
the cell membrane at neutral pH, but bec parietal cells was determined indirectly by accumulation
of [¹⁴C]aminopyrine, a weak base which freely penetrates
the cell membrane at neutral pH, but becomes proton-
ated and thus entrapped in an acidic environment. The of $[14C]$ aminopyrine, a weak base which freely penetrates
the cell membrane at neutral pH, but becomes proton-
ated and thus entrapped in an acidic environment. The
enkephalin analogue $[D-Ala^2, D-Leu^6]$ -enkephalin did not
a

gastrointestinal tract as well as by an increase in the riched parietal cells showed saturable and displaceable
tone of the pylorus and duodenum, and possibly by opioid binding with both a high- and low-affinity site
enhan mine-stimulated acid secretion by roughly 20%. This effect was blocked by naloxone. A homogenate of enriched parietal cells showed saturable and displaceable ESTINAL MOTILITY AND SECRETION 139
mine-stimulated acid secretion by roughly 20%. This
effect was blocked by naloxone. A homogenate of en-
riched parietal cells showed saturable and displaceable
opioid binding with both a mine-stimulated acid secretion by roughly 20%. This
effect was blocked by naloxone. A homogenate of en-
riched parietal cells showed saturable and displaceable
opioid binding with both a high- and low-affinity site
(238). mine-stimulated acid secretion by roughly 20%. This
effect was blocked by naloxone. A homogenate of en-
riched parietal cells showed saturable and displaceable
opioid binding with both a high- and low-affinity site
(238). effect was blocked by naloxone. A homogenate of en-
riched parietal cells showed saturable and displaceable
opioid binding with both a high- and low-affinity site
(238). Available data do not allow definition of the opioid riched parietal cells showed saturable and displaceable
opioid binding with both a high- and low-affinity site
(238). Available data do not allow definition of the opioid
receptor types involved. However, inhibition of the opioid binding with both a high- and low-affinity si

(238). Available data do not allow definition of the opic

receptor types involved. However, inhibition of the opic

effect on acid secretion in this parietal cell syst (238). Available data do not allow definition of the opioi
receptor types involved. However, inhibition of the opioi
effect on acid secretion in this parietal cell system turne
out to be stereospecific (237). Most interes receptor types involved. However, inhibition of the opioid
effect on acid secretion in this parietal cell system turned
out to be stereospecific (237). Most interestingly, nalox-
one stereospecifically impaired histamine-s fect on acid secretion in this parietal cell system turned
it to be stereospecific (237). Most interestingly, nalox-
ee stereospecifically impaired histamine-stimulated
id secretion also in the absence of exogenous opioids

pothetical and need confirmation, extension, and inally stroyed upon cell isolation by both endogenous pepsin
conceptual integration in the future.
Attempts to define malfunctions of endogenous opioid
mechanisms have so fa out to be stereospecific (237). Most interestingly, nalox-
one stereospecifically impaired histamine-stimulated
acid secretion also in the absence of exogenous opioids.
Thus, it appears that endogenous opioids, which have
 one stereospecifically impaired histamine-stimulate acid secretion also in the absence of exogenous opioids. Thus, it appears that endogenous opioids, which has so far been demonstrated within the antral mucosa (section II acid secretion also in the absence of exogenous opioids.
Thus, it appears that endogenous opioids, which have
so far been demonstrated within the antral mucosa (see
section II), modulate histamine-stimulated acid secre-
ti Thus, it appears that endogenous opioids, which have
so far been demonstrated within the antral mucosa (see
section II), modulate histamine-stimulated acid secre-
tion. Endogenous activation of opioid receptors would be
un so far been demonstrated within the antral mucosa (see
section II), modulate histamine-stimulated acid secre-
tion. Endogenous activation of opioid receptors would be
unmasked by naloxone, but would impair or even prevent
 section II), modulate histamine-stimulated acid secretion. Endogenous activation of opioid receptors would be unmasked by naloxone, but would impair or even prevent further activation by exogenous opioids. This assumption tion. Endogenous activation of opioid receptors would be
unmasked by naloxone, but would impair or even prevent
further activation by exogenous opioids. This assumption
is supported by observations that the effect of nalo unmasked by naloxone, but would impair or even prevent
further activation by exogenous opioids. This assumption
is supported by observations that the effect of naloxone
alone is negatively correlated to the effect of opioi further activation by exogenous opioids. This assumption
is supported by observations that the effect of naloxone
alone is negatively correlated to the effect of opioids in
the same cell preparation (237). The activity of alone is negatively correlated to the effect of opioids in the same cell preparation (237). The activity of this modulatory system may be subject to seasonal variation (237), but this question needs more extensive explorat alone is negatively correlated to the effect of opioids in the same cell preparation (237). The activity of this modulatory system may be subject to seasonal variation (237), but this question needs more extensive explorat the same cell preparation (237). The activity of this modulatory system may be subject to seasonal variation (237), but this question needs more extensive exploration. The activity of opioids may depend on the particular c modulatory system may be subject to seasonal variation (237), but this question needs more extensive exploration. The activity of opioids may depend on the particular cell preparation as well, because a varying portion of (237), but this question needs more extensive exploration. The activity of opioids may depend on the particular cell preparation as well, because a varying portion of membrane receptors might get damaged or even destroyed tion. The activity of opioids may depend on the particular
cell preparation as well, because a varying portion of
membrane receptors might get damaged or even de-
stroyed upon cell isolation by both endogenous pepsin
and e cell preparation as well, because a varying portion of
membrane receptors might get damaged or even de-
stroyed upon cell isolation by both endogenous pepsin
and exogenous Pronase and collagenase, which makes
this type of membrane receptors might get damaged or even de-
stroyed upon cell isolation by both endogenous pepsin
and exogenous Pronase and collagenase, which makes
this type of study extremely difficult. This may also
explain why, a stroyed upon cell isolation by both endogenous pepsi
and exogenous Pronase and collagenase, which make
this type of study extremely difficult. This may als
explain why, although nanomolar opioid concentration-
were effecti and exogenous Pronauthis type of study ex-
explain why, although
were effective, no clear
tionship was detected.
Modulatory enhand explain why, although nanomolar opioid concentrations
were effective, no clear-cut concentration-response rela-
tionship was detected.
Modulatory enhancement of histamine-stimulated
acid secretion by opioids was later conf unmasked by naloxone, but would impair or even prevent
further activation by exogenous spioids. This assumption
is is apported by observations that the effect of naloxone
alone is negatively correlated to the effect of op

of endogenous opioids in chronic idiopathic constipation
or related conditions, but these data should be challenged
by future well-controlled clinical studies.
IV. The Role of Opioids in the Control of Gastric
 $\begin{array}{r} \$ A. In Vitro Studies in Guinea Pig and Rat Tissues noted, however, that the inhibitory effect of $(-)$ -naloxone 1. Isolated cell preparations. Early reports on in vivo alone, in guinea pig parietal cells (237), was observed explain why, although nanomolar opioid concentrations
were effective, no clear-cut concentration-response rela-
tionship was detected.
Modulatory enhancement of histamine-stimulated
acid secretion by opioids was later conf were effective, no clear-cut concentration-response rela-
tionship was detected.
Modulatory enhancement of histamine-stimulated
acid secretion by opioids was later confirmed in rat
isolated parietal cells (375). These aut tionship was detected.

Modulatory enhancement of histamine-stimulated

acid secretion by opioids was later confirmed in rat

isolated parietal cells (375). These authors described a

nonspecific inhibition of acid secret Modulatory enhancement of histamine-stimulated
acid secretion by opioids was later confirmed in rat
isolated parietal cells (375). These authors described a
nonspecific inhibition of acid secretion by both $(-)$ - and
 $(+)$ acid secretion by opioids was later confirmed in isolated parietal cells (375). These authors described nonspecific inhibition of acid secretion by both $(-)$ - a $(+)$ -naloxone at concentrations above 10 μ mol/lit whereas isolated parietal cells (375). These authors described a
nonspecific inhibition of acid secretion by both (-)- and
(+)-naloxone at concentrations above 10 μ mol/liter,
whereas (-)-naloxone at lower concentrations specif nonspecific inhibition of acid secretion by both $(-)$ - and $(+)$ -naloxone at concentrations above 10 μ mol/liter, whereas $(-)$ -naloxone at lower concentrations specifically antagonized the effects of opioids. It should b (+)-naloxone at concentrations above 10 μ mol/liter,
whereas (-)-naloxone at lower concentrations specifi-
cally antagonized the effects of opioids. It should be
noted, however, that the inhibitory effect of (-)-naloxon whereas $(-)$ -naloxone at lower concentrations specifically antagonized the effects of opioids. It should hoted, however, that the inhibitory effect of $(-)$ -naloxon alone, in guinea pig parietal cells (237), was observed a cally antagonized the effects of opioids. It should b noted, however, that the inhibitory effect of $(-)$ -naloxon alone, in guinea pig parietal cells (237), was observed a concentrations of 1 μ mol/liter and below and wa noted, however, that the inhibitory effect of $(-)$ -naloxone
alone, in guinea pig parietal cells (237), was observed at
concentrations of 1 μ mol/liter and below and was stere
ospecific, which is indicative of a receptor alone, in guinea pig parietal cells (237), was observed at concentrations of 1 μ mol/liter and below and was stere-
ospecific, which is indicative of a receptor-mediated ef-
fect. Since opioids augmented also dbcAMP-sti concentrations of 1 μ mol/liter and below and was ster ospecific, which is indicative of a receptor-mediated of fect. Since opioids augmented also dbcAMP-stimulat acid secretion in rat parietal cells, Schepp et al. (37 fect. Since opioids augmented also dbcAMP-stimulated acid secretion in rat parietal cells, Schepp et al. (375) suggested a postreceptor interaction. In their experiments, opioids showed the same percentage effect in a crud acid secretion in rat parietal cells, Schepp et al. (375)
suggested a postreceptor interaction. In their experi-
ments, opioids showed the same percentage effect in a
crude cell preparation as in enriched parietal cells, w suggested a postreceptor interaction. In their experiments, opioids showed the same percentage effect in a crude cell preparation as in enriched parietal cells, which once again points to a direct action at the parietal ce ments, opioids showed the same percentage effect in crude cell preparation as in enriched parietal cells, whonce again points to a direct action at the parietal (level as opposed to mediation by, e.g., potential rele of en crude cell preparation as in enriched parietal cells, which
once again points to a direct action at the parietal cell
level as opposed to mediation by, e.g., potential release
of endogenous histamine. This is in line with once again points to a direct action at the parietal cell
level as opposed to mediation by, e.g., potential release
of endogenous histamine. This is in line with observa-
tions made by both Kromer et al. (238, 237) and Sch level as opposed to mediation by, e.g., potential release
of endogenous histamine. This is in line with observa-
tions made by both Kromer et al. (238, 237) and Schepp
et al. (375), confirming that opioids do not affect ba *z ions* made by both Kromer et al. $(238, 237)$ and Schepp

et al. (375), confirming that opioids do not affect basal
acid secretion.
2. Isolated gastric mucosa and stomach preparations.
Ho et al. (173) found no influence of morphine on his-
tamine- or bethanechol-stimulated acid s et al. (375), confirming that opioids do not affect basal
acid secretion.
2. Isolated gastric mucosa and stomach preparations.
Ho et al. (173) found no influence of morphine on his-
tamine- or bethanechol-stimulated acid s acid secretion.

2. Isolated gastric mucosa and stomach preparations.

Ho et al. (173) found no influence of morphine on his-

tamine- or bethanechol-stimulated acid secretion in the

isolated rat gastric mucosa. However,

PHARMACOLOGICAL REVIEWS

140 KROM
trations of both the secretagogues and morphine greater
than 100μ mol/liter. At those high concentrations, 140
trations of both the secretagogues and morphine great
than 100 μ mol/liter. At those high concentration
opioids are to be expected to exert nonspecific inhibito 140
trations of both the secretagogues and morphine greater
than 100 μ mol/liter. At those high concentrations, a
opioids are to be expected to exert nonspecific inhibitory
effects which might be superimposed on specifi trations of both the secretagogues and morphine great
than 100μ mol/liter. At those high concentration
opioids are to be expected to exert nonspecific inhibite
effects which might be superimposed on specific stimulation trations of both the secretagogues and morphine greater than 100μ mol/liter. At those high concentrations, as opioids are to be expected to exert nonspecific inhibitory galentics which might be superimposed on specific than 100 μ mol/liter. At those high concentrations, at opioids are to be expected to exert nonspecific inhibitory gate offects which might be superimposed on specific stimu-
actory actions. Moreover, supramaximal stimul opioids are to be expected to exert nonspecific inhibit
effects which might be superimposed on specific stil
latory actions. Moreover, supramaximal stimulation
acid output by histamine or bethanechol might h
prevented dete effects which might be superimposed on specific stimu-
latory actions. Moreover, supramaximal stimulation of indi
acid output by histamine or bethanechol might have con
prevented detection of any further significant enhan latory actions. Moreover, supramaximal stimulation acid output by histamine or bethanechol might have prevented detection of any further significant enhancement by opioids. These negative results, therefore, cont conflict id output by histamine or bethanechol might have concevented detection of any further significant enhance-
ent by opioids. These negative results, therefore, do term
t conflict with the positive results discussed above.
S prevented detection of any further significant enhancement by opioids. These negative results, therefore, do not conflict with the positive results discussed above.
Similar objections may apply to the negative data by Can

ment by opioids. These negative results, therefore, do
not conflict with the positive results discussed above.
Similar objections may apply to the negative data by
Canfield and Spencer (53) who preincubated isolated rat
s not conflict with the positive results discussed above.
Similar objections may apply to the negative data by
Canfield and Spencer (53) who preincubated isolated rat
stomachs in the presence of 1 μ mol/liter of morphine Similar objections may apply to the negative data l
Canfield and Spencer (53) who preincubated isolated r
stomachs in the presence of $1 \mu \text{mol/liter}$ of morphine
naloxone for 1 h and stimulated acid secretion thereaft
b Canfield and Spencer (53) who preincubated isolated rat
stomachs in the presence of 1 μ mol/liter of morphine or
naloxone for 1 h and stimulated acid secretion thereafter
by various secretagogues. Under these conditio omachs in the presence of 1 μ mol/liter of morphine or loxone for 1 h and stimulated acid secretion thereafter various secretagogues. Under these conditions, develment of acute tolerance to morphine may be expected. Nis

release of $[Leu^5]$ -enkephalin into the vasculature of the vasculature of flux and McIntosh (303) found a spontaneous
release of $[Leu^5]$ -enkephalin into the vasculature of the isolated rat stomach. This release was augme by various secretagogues. Under these conditions, development of acute tolerance to morphine may be expected.

(96,

Nishimura and McIntosh (303) found a spontaneous effection

release of [Leu⁶]-enkephalin into the vasc opment of acute tolerance to morphine may be expected.
Nishimura and McIntosh (303) found a spontaneous
release of [Leu⁵]-enkephalin into the vasculature of the
isolated rat stomach. This release was augmented by 50
mmol Nishimura and McIntosh (303) found a spontaneous
release of $[Leu^5]$ -enkephalin into the vasculature of the
isolated rat stomach. This release was augmented by 50
mmol/liter of potassium and by the nicotinic agonist
DMPP release of [Leu⁵]-enkephalin into the vasculature of the isolated rat stomach. This release was augmented by 50 istriction in mol/liter of potassium and by the nicotinic agonist known whether this opioid pool has any fu isolated rat stomach. This release was augmented by 50 mmol/liter of potassium and by the nicotinic agonist

DMPP in a calcium-dependent manner. Although it is

not known whether this opioid pool has any function in

the mmol/liter of potassium and by
DMPP in a calcium-dependent n
not known whether this opioid po
the control of acid secretion, the
consistent with such a hypothesis
3. Opioid effects on somatostatin **EXECUTE:** In a calcum-dependent manner. Although it is

at known whether this opioid pool has any function in

a control of acid secretion, the observation would be

in positent with such a hypothesis.

3. Opioid effects

not known whether this opioid pool has any function in
the control of acid secretion, the observation would be
consistent with such a hypothesis.
3. Opioid effects on somatostatin, bombesin, and gastrin
release. Somatostat the control of acid secretion, the observation would be consistent with such a hypothesis.
3. Opioid effects on somatostatin, bombesin, and gastrin
release. Somatostatin inhibits and bombesin stimulates
gastric acid secret consistent with such a hypothesis.

3. Opioid effects on somatostatin, bombesin, and gastrin

release. Somatostatin inhibits and bombesin stimulates

gastric acid secretion (for review, see refs. 82 and 350).

It should b 3. Opioid effects on somatostatin, bombesin, and gastrin release. Somatostatin inhibits and bombesin stimulates gastric acid secretion (for review, see refs. 82 and 350). It should be noted that enkephalins inhibited basal release. Somatostatin inhibits and bombesin stimulates gastric acid secretion (for review, see refs. 82 and 350).
It should be noted that enkephalins inhibited basal (62) wand GIP-stimulated (278) release of somatostatingastric acid secretion (for review, see refs. 82 and 350).
It should be noted that enkephalins inhibited basal (62)
and GIP-stimulated (278) release of somatostatin-like
immunoreactivity from the isolated, vascularly perf It should be noted that enkephalins inhibited basal (62)
and GIP-stimulated (278) release of somatostatin-like
immunoreactivity from the isolated, vascularly perfused
rat stomach, although the antagonist naloxone had the
s and GIP-stimulated (278) release of somatostatin-like
immunoreactivity from the isolated, vascularly perfused
rat stomach, although the antagonist naloxone had the
same effect under basal conditions (301a). However,
opioi immunoreactivity from the isolated, vascularly perfused
rat stomach, although the antagonist naloxone had the
same effect under basal conditions (301a). However,
opioid inhibition of basal somatostatin release (62) was
not rat stomach, although the antagonist naloxone had the same effect under basal conditions (301a). However, opioid inhibition of basal somatostatin release (62) was not reproduced though it appeared from that publication (39 same effect under basal conditions $(301a)$. Howev
opioid inhibition of basal somatostatin release (62) v
not reproduced though it appeared from that publicat
 (397) that such an effect was not definitely preclud
An in opioid inhibition of basal somatostatin release (62) was
not reproduced though it appeared from that publication
 (397) that such an effect was not definitely precluded.
An inhibition by exogenous acetylcholine of soma not reproduced though it appeared from that publication (397) that such an effect was not definitely precluded.
An inhibition by exogenous acetylcholine of somato-statin release in the isolated rat stomach may be caused
by (397) that such an effect was not definitely precluded.
An inhibition by exogenous acetylcholine of somato-
statin release in the isolated rat stomach may be caused
by endogenously released opioids, since naloxone pre-
ve (557) that such an effect was not definitely precident.

An inhibition by exogenous acetylcholine of somato-

statin release in the isolated rat stomach may be caused

by endogenously released opioids, since naloxone pre-
 vented this effect (398). However, dependent on the by endogenously released opioids, since naloxone pre-
vented this effect (398). However, dependent on the a
glucose concentration in the perfusate, naloxone lost its
influence on acetylcholine-effected inhibition of somavented this effect (398). However, dependent on the glucose concentration in the perfusate, naloxone lost its influence on acetylcholine-effected inhibition of somatostatin release, which points to a complex situation (398 glucose concentration in the perfusate, naloxone lost its op
influence on acetylcholine-effected inhibition of soma-
tostatin release, which points to a complex situation
(398). Moreover, in the presence of naloxone, [Leu influence on acetylcholine-effected inhibition of soma-
tostatin release, which points to a complex situation
(398). Moreover, in the presence of naloxone, $[Leu⁵]-$
enkephalin stimulated somatostatin release from the tostatin release, which points to a complex situal (398). Moreover, in the presence of naloxone, [L] enkephalin stimulated somatostatin release from vascularly perfused rat stomach, suggestive of a opioid action of this co 98). Moreover, in the presence of naloxone, $[Leu⁵]$
kephalin stimulated somatostatin release from the
scularly perfused rat stomach, suggestive of a non
ioid action of this compound at low concentrations.
In the pres

enkephalin stimulated somatostatin release from the vascularly perfused rat stomach, suggestive of a non-
opioid action of this compound at low concentrations.
In the presence of insulin or glucose, release of bom-
besin-l vascularly perfused rat stomach, suggestive of a non-
opioid action of this compound at low concentrations.
In the presence of insulin or glucose, release of bom-
besin-like immunoreactivity was enhanced by $[Leu^5]$ -
enkep opioid action of this compound at low concentrations.
In the presence of insulin or glucose, release of bombesin-like immunoreactivity was enhanced by [Leu⁵]-
enkephalin, although no effect on gastrin release was (obser In the presence of insulin or glucose, release of bo
besin-like immunoreactivity was enhanced by [Leu
enkephalin, although no effect on gastrin release v
observed in this rat model in vitro (399, 400). Bombe
might be expec besin-like immunoreactivity was enhanced by [Leu⁵]-
enkephalin, although no effect on gastrin release was
observed in this rat model in vitro (399, 400). Bombesin
might be expected to release gastrin. In fact, in a preli enkephalin, although no effect on gastrin release w
observed in this rat model in vitro (399, 400). Bombee
might be expected to release gastrin. In fact, in a preli
inary in vitro study done in the vascularly perfused i
st observed in this rat model in vitro (399, 400). Bombesi
might be expected to release gastrin. In fact, in a prelim
inary in vitro study done in the vascularly perfused ratomach, morphine had a dose-dependent dual inhib
tor might be expected to release gastrin. In fact, in a prelimitation in the view in a prelimitation in the vascularly perfused rat isolated stomach, morphine had a dose-dependent dual inhibiand i.c tory-stimulatory effect on inary in vitro study done in the vascularly perfused rat stomach, morphine had a dose-dependent dual inhibitory-stimulatory effect on gastrin release, with no influence on somatostatin release (363). As concluded from the stomach, morphine had a dose-dependent dual inhibi-

THER
trin release in the anesthetized rat in the presence of
atropine (6). However, naloxone partially inhibited va-ER
trin release in the anesthetized rat in the presence of
atropine (6). However, naloxone partially inhibited va-
gally induced gastrin release from the isolated rat stom-ER
trin release in the anesthetized rat in the presence
atropine (6). However, naloxone partially inhibited v:
gally induced gastrin release from the isolated rat ston
ach in the presence of hexamethonium (301a). Th trin release in the anesthetized rat in the presence of atropine (6). However, naloxone partially inhibited vagally induced gastrin release from the isolated rat stomach in the presence of hexamethonium (301a). This indica trin release in the anesthetized rat in the presence of atropine (6). However, naloxone partially inhibited vagally induced gastrin release from the isolated rat stomach in the presence of hexamethonium (301a). This indica atropine (6). However, naloxone partially inhibited vagally induced gastrin release from the isolated rat stom-
ach in the presence of hexamethonium (301a). This
indicates facilitation by endogenous opioids under these
con gally induced gastrin release from the isolated rat stom-
ach in the presence of hexamethonium (301a). This
indicates facilitation by endogenous opioids under these
conditions. Again, opioid systems opposing each other
may ach in the presence of hexame
indicates facilitation by endogeno
conditions. Again, opioid system
may be superimposed, the overal
termined by their actual balance.
B. In Vivo Studies in Rat. Cat. De *B. In Vivo Studies in Rat, Cat, Dog, Monkey, and Man*
B. In Vivo Studies in Rat, Cat, Dog, Monkey, and Man
I. Rat. a. DECREASE IN ACID SECRETION AND INHIBI-

1. *Rat.* a. Decrease in Rat. *Cat.* Dog. Monkey, and Man
1. *Rat.* a. DECREASE IN ACID SECRETION AND INHIBI-
TION OF ACETYLCHOLINE RELEASE. In the rat, only
depression (or no effect) of gastric acid output has been B. In Vivo Studies in Rat, Cat, Dog, Monkey, and Man
1. Rat. a. DECREASE IN ACID SECRETION AND INHIBI-
TION OF ACETYLCHOLINE RELEASE. In the rat, only
depression (or no effect) of gastric acid output has been
reported upon B. In Vwo Studies in Rat, Cat, Dog, Monkey, and Man
1. Rat. a. DECREASE IN ACID SECRETION AND INHIBI-
TION OF ACETYLCHOLINE RELEASE. In the rat, only
depression (or no effect) of gastric acid output has been
reported upon 1. Rat. a. DECREASE IN ACID SECRETION AND INHIBITION OF ACETYLCHOLINE RELEASE. In the rat, only depression (or no effect) of gastric acid output has been reported upon i.c.v., i.c., and peripheral administration (96, 356, TION OF ACETYLCHOLINE RELEASE. In the rat, only depression (or no effect) of gastric acid output has been reported upon i.c.v., i.c., and peripheral administration (96, 356, 434, 357, 190, 295, 105, 175, 83). This inhibit depression (or no effect) of gastric acid output has be
reported upon i.c.v., i.c., and peripheral administrati
(96, 356, 434, 357, 190, 295, 105, 175, 83). This inhibite
effect was observed both under basal conditions and (96, 356, 434, 357, 190, 295, 105, 175, 83). This inhibitory
effect was observed both under basal conditions and after
enertral vagal stimulation by 2-DG or i.e.v. TRH administration, and after pyloric ligation. Pyloric l (96, 356, 434, 357, 190, 295, 105, 175, 83). This inhibitory
effect was observed both under basal conditions and after
central vagal stimulation by 2-DG or i.c.v. TRH admin-
istration, and after pyloric ligation. Pyloric l effect was observed both under basal conditions and after
central vagal stimulation by 2-DG or i.c.v. TRH admin-
istration, and after pyloric ligation. Pyloric ligation is
known to vagally stimulate acid secretion (151a, 4 central vagal stimulation by 2-DG or i.c.v. TRH admin
istration, and after pyloric ligation. Pyloric ligation i
known to vagally stimulate acid secretion (151a, 451a)
These inhibitory opioid effects on acid secretion wer
b istration, and after pyloric ligation. Pyloric ligation i
known to vagally stimulate acid secretion (151a, 451a)
These inhibitory opioid effects on acid secretion wer
blocked by naloxone, indicating receptor-mediated ac
ti known to vagally stimulate acid secretion (151a, 451a).
These inhibitory opioid effects on acid secretion were
blocked by naloxone, indicating receptor-mediated ac-
tions. Acid secretion was reduced by morphine and atro-
 These inhibitory opioid effects on acid secretion were
blocked by naloxone, indicating receptor-mediated ac-
tions. Acid secretion was reduced by morphine and atro-
pine to the same degree, and a further decrease by
morphi blocked by naloxone, indicating receptor-mediated actions. Acid secretion was reduced by morphine and atro-
pine to the same degree, and a further decrease by
morphine after pretreatment of the rat with atropine was
no lon tions. Acid secretion was reduced by morphine and atro-
pine to the same degree, and a further decrease by
morphine after pretreatment of the rat with atropine was
no longer observed (175). Opioids may, therefore, depress
 pine to the same degree, and a further decrease by
morphine after pretreatment of the rat with atropine was
no longer observed (175). Opioids may, therefore, depress
acid secretion in vivo at least partially by inhibiting morphine after pretreatment of the rat with atropine was
no longer observed (175). Opioids may, therefore, depress
acid secretion in vivo at least partially by inhibiting vagal
release of acetylcholine within the gastric w no longer observed (175). Opioids may, therefore, depress
acid secretion in vivo at least partially by inhibiting vagal
release of acetylcholine within the gastric wall. However,
while Rozé et al. (357) found opioid inhibi acid secretion in vivo at least partially by inhibiting va
release of acetylcholine within the gastric wall. Howev
while Rozé et al. (357) found opioid inhibition of a
secretion after electrical vagal stimulation, Ho et al release of acetylcholine within the gastric wall. However, while Rozé et al. (357) found opioid inhibition of acid secretion after electrical vagal stimulation, Ho et al. (172) did not. Both groups were using similar stimu while Rozé et al. (357) found opioid inhibition of acid
secretion after electrical vagal stimulation, Ho et al. (172)
did not. Both groups were using similar stimulus param-
eters. Rozé et al. (357) related acid secretion secretion after electrical vagal stimulation, Ho et al. (172)
did not. Both groups were using similar stimulus param-
eters. Rozé et al. (357) related acid secretion under
methadone treatment to the predrug value, whereas eters. Rozé et al. (357) related acid secretion under
methadone treatment to the predrug value, whereas Ho
et al. (172) ran parallel controls to the morphine groups
throughout the experiment. A spontaneous decline in
elect methadone treatment to the predrug value, whereas Ho
et al. (172) ran parallel controls to the morphine groups
throughout the experiment. A spontaneous decline in
electrically induced acid secretion over time in the ex-
pe et al. (172) ran parallel controls to the morphine groups throughout the experiment. A spontaneous decline in electrically induced acid secretion over time in the experiments by Rozé et al. (357) may have indicated drug ac throughout the experiment. A spontaneous decline in electrically induced acid secretion over time in the experiments by Rozé et al. (357) may have indicated drug action, but this is entirely speculative. Ho et al. (172) di electrically induced acid secretion over time in the experiments by Rozé et al. (357) may have indicated drug
action, but this is entirely speculative. Ho et al. (172)
discussed their failure to reduce electrically stimula periments by Rozé et al. (357) may have indicated drug
action, but this is entirely speculative. Ho et al. (172)
discussed their failure to reduce electrically stimulated
acid secretion by morphine in terms of a central as action, but this is entirely speculative. Ho et al. (172) discussed their failure to reduce electrically stimulated acid secretion by morphine in terms of a central as opposed to a peripheral opioid mechanism, but evidentl scussed their failure to reduce electrically stimulated
id secretion by morphine in terms of a central as
posed to a peripheral opioid mechanism, but evidently
chnical as well as other explanations may also apply.
Toleranc

acid secretion by morphine in terms of a centr
opposed to a peripheral opioid mechanism, but evid
technical as well as other explanations may also ap
Tolerance appears to develop to the inhibitory of
effect on gastric acid opposed to a peripheral opioid mechanism, but evidently
technical as well as other explanations may also apply.
Tolerance appears to develop to the inhibitory opioid
effect on gastric acid secretion, although naloxone-pretechnical as well as other explant
Tolerance appears to develop
effect on gastric acid secretion,
cipitated morphine withdrawa
change gastric secretion (171).
b. OPIOID EFFECTS ON ACET effect on gastric acid secretion, although naloxone-pre-
cipitated morphine withdrawal did not significantly
change gastric secretion (171).
b. OPIOID EFFECTS ON ACETYLCHOLINE AND HISTA-
MINE ACTIONS. Since acid secretion

cipitated morphine withdrawal did not significantly
change gastric secretion (171).
b. OPIOID EFFECTS ON ACETYLCHOLINE AND HISTA-
MINE ACTIONS. Since acid secretion in the rat due to i.v.
infusion of acetylcholine was impa change gastric secretion (171).

b. OPIOID EFFECTS ON ACETYLCHOLINE AND HISTA-

MINE ACTIONS. Since acid secretion in the rat due to i.v.

infusion of acetylcholine was impaired by methadone

(357), opioid receptors may al b. OPIOID EFFECTS ON ACETYLCHOLINE AND HISTA-
MINE ACTIONS. Since acid secretion in the rat due to i.v.
infusion of acetylcholine was impaired by methadone
(357), opioid receptors may also modulate the action of
acetylchol MINE ACTIONS. Since acid secretion in the rat due to i.v.
infusion of acetylcholine was impaired by methadone
(357), opioid receptors may also modulate the action of
acetylcholine on acid secretion. The situation resembles infusion of acetylcholine was impaired by methadone (357), opioid receptors may also modulate the action of acetylcholine on acid secretion. The situation resembles that observed with respect to control of motility in the (357), opioid receptors may also modulate the action of acetylcholine on acid secretion. The situation resembles that observed with respect to control of motility in the isolated guinea pig ileum (236). However, while both acetylcholine on acid secretion. The situation resembles
that observed with respect to control of motility in the
isolated guinea pig ileum (236). However, while both s.c.
and i.c.v. dermorphin reduced basal acid secretion that observed with respect to control of motility in the isolated guinea pig ileum (236). However, while both s.c. and i.c.v. dermorphin reduced basal acid secretion and i.c.v. dermorphin also reduced insulin-stimulated ac isolated guinea pig ileum (236). However, while both s.c.
and i.c.v. dermorphin reduced basal acid secretion and
i.c.v. dermorphin also reduced insulin-stimulated acid
secretion, i.c.v. dermorphin was ineffective against h and i.c.v. dermorphin reduced basal acid secretion and
i.c.v. dermorphin also reduced insulin-stimulated acid
secretion, i.c.v. dermorphin was ineffective against his-
tamine-stimulated acid secretion in the rat (190). Sin

PHARMACOLOGICAL REVIEWS

OPIOIDS AND CONTROL OF GASTROINT
hance histamine-stimulated acid production (238, 237,
375), this peripheral effect may counteract any potential OPIOIDS AND CONTROL OF GASTROIS
hance histamine-stimulated acid production (238, 237,
375), this peripheral effect may counteract any potential
inhibitory effect upstream from the parietal cell. OPIOIDS AND CONTROL OF GASTROINTEST
hance histamine-stimulated acid production (238, 237, 2
375), this peripheral effect may counteract any potential in t
inhibitory effect upstream from the parietal cell. or s
c. PERIPHER

375), this peripheral effect may counteract any potential inhibitory effect upstream from the parietal cell.

c. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS; INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR TYPES. By

comparing effe inhibitory effect upstream from the parietal cell. concluded that versus CENTRAL OPIOID EFFECTS; IN-
vOLVEMENT OF DIFFERENT OPIOID RECEPTOR TYPES. By
comparing effects after i.c.v. and i.v. administration, it
was concluded c. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS; IN-
vOLVEMENT OF DIFFERENT OPIOID RECEPTOR TYPES. By
nalcomparing effects after i.c.v. and i.v. administration, it
acis was concluded that opioids inhibit gastric acid secretion VOLVEMENT OF DIFFERENT OPIOID RECEPTOR TYPES. By
comparing effects after i.c.v. and i.v. administration, it
was concluded that opioids inhibit gastric acid secretion
by a central, not peripheral, mechanism (295, 356). Very comparing effects after i.c.v. and i.v. administration, it
was concluded that opioids inhibit gastric acid secretion
by a central, not peripheral, mechanism (295, 356). Very
recently, Fox and Burks (115) found by compariso was concluded that opioids inhibit gastric acid secretion
by a central, not peripheral, mechanism (295, 356). Very
recently, Fox and Burks (115) found by comparison
between the effects of i.v. and i.c.v. administered recep by a central, not peripheral, mechanism (295, 356). Very
recently, Fox and Burks (115) found by comparison
between the effects of i.v. and i.c.v. administered receptor
type-selective opioids and by introducing the quaterna type-selective opioids and by introducing the quaterna
naltrexone-methylbromide that central and possibly μ
ripheral mu-receptors (selectively activated by PL C
and DAGO) inhibit gastric acid secretion. An opio
delta-ag naltrexone-methylbromide that central and possibly p
ripheral mu-receptors (selectively activated by PL 0
and DAGO) inhibit gastric acid secretion. An opid
delta-agonist (DPDPE) had no effect, while the kapp
agonist U-50,4 and DAGO) inhibit gastric acid secretion. An opioid delta-agonist (DPDPE) had no effect, while the kappa-agonist U-50,488H increased acid secretion at a peripheral site. Thus, both central and peripheral opioid mech-anisms and DAGO) inhibit gastric acid secretion. An opioid show delta-agonist (DPDPE) had no effect, while the kappa-
agonist U-50,488H increased acid secretion at a periph-
nis eral site. Thus, both central and peripheral opioid delta-agonist (DPDPE) had no effect, while the kappa-
agonist U-50,488H increased acid secretion at a periph-
eral site. Thus, both central and peripheral opioid mech-
anisms may be involved in inhibition of gastric acid
s agonist U-50,488H increased acid secretion at a periph-
eral site. Thus, both central and peripheral opioid mech-
anisms may be involved in inhibition of gastric acid avecretion (357, 105, 115) in addition to stimulatory, eral site. Thus, both central and peripheral opioid mecanisms may be involved in inhibition of gastric assecretion (357, 105, 115) in addition to stimulatory, pripheral sites of action (115, 238, 237, 375). Detection one o anisms may be involved in inhibition of gastric acid
secretion (357, 105, 115) in addition to stimulatory, pe-
ripheral sites of action (115, 238, 237, 375). Detection of
one or the other mechanism may depend on the experi secretion (357, 105, 115) in addition to stimulatory, pe-
interest that acetorphan, an enkephalinase inhibitor,
ripheral sites of action (115, 238, 237, 375). Detection of reduced gastric acid secretion stimulated by pent ripheral sites of action (115, 238, 237, 375). Detection of
one or the other mechanism may depend on the experi-
mental conditions. In fact, morphine inhibited acid se-
cretion induced centrally by 2-DG but not that induce one or the other mechanism may depend on the experimental conditions. In fact, morphine inhibited acid secretion induced centrally by 2-DG but not that induced eby peripheral vagal stimulation (466a). The latter result bap mental conditions. In fact, morphine inhibited acid secretion induced centrally by 2-DG but not that induced
by peripheral vagal stimulation (466a). The latter result
appears to be at variance with the data of Fox and Burk by peripheral vagal stimulation (466a). The latter result became detectable by slowing down opioid degradation.
appears to be at variance with the data of Fox and Burks 3. Dog. a. INCREASE IN BASAL ACID SECRETION BY
(115) by peripheral vagal stimulation (466a). The latter result
appears to be at variance with the data of Fox and Burks
(115). Moreover, i.c.v. dynorphin inhibited TRH-stimu-
lated acid secretion but not basal acid secretion, w appears to be at variance with the data of Fox and I
(115). Moreover, i.c.v. dynorphin inhibited TRH-st
lated acid secretion but not basal acid secretion,
beta-endorphin did just the opposite, and [D-
Met⁵]-enkephalin im Met⁵]-enkephalin impaired both basal and TRH-stimu-
lated acid secretion (294). These confusing and partially transiently inhibited and then stimulated acid secretion.
conflicting data need further clarification. The sti lated acid secretion but not basal acid is
beta-endorphin did just the opposite
Met⁵]-enkephalin impaired both basal an
lated acid secretion (294). These confusin
conflicting data need further clarification
d. THE EFFECT

Met⁵]-enkephalin impaired both basal and TRH-stimu-
lated acid secretion (294). These confusing and partially
conflicting data need further clarification.
d. THE EFFECTS OF OPIOID ANTAGONISTS IN THE AB-
SENCE OF EXOGENOU lated acid secretion (294). These confusing and partially
conflicting data need further clarification.
d. THE EFFECTS OF OPIOID ANTAGONISTS IN THE AB-
SENCE OF EXOGENOUS OPIOIDS. Whereas basal acid se-
cretion was not affe conflicting data need further clarification. The
d. THE EFFECTS OF OPIOID ANTAGONISTS IN THE AB-
sENCE OF EXOGENOUS OPIOIDS. Whereas basal acid se-
cretion was not affected by s.c. naloxone (294) or s.c. was
naltrexone (29 SENCE OF EXOGENOUS OPIOIDS. Whereas basal acid secretion was not affected by s.c. naloxone (294) or s.c. naltrexone (295), Stapelfeldt et al. (422) stated in a cretion was not affected by s.c. naloxone (294) or s.c. was vagally mediated. However, a peripheral stimulatory
naltrexone (295) , Stapelfeldt et al. (422) stated in a modulation of vagal function cannot be precluded cretion was not affected by s.c. naloxone (294) or s.
naltrexone (295), Stapelfeldt et al. (422) stated in
preliminary publication that, in the anesthetized ra
naloxone augmented gastric acid secretion induced b
electrical naltrexone (295), Stapelfeldt et al. (422) stated in a more
preliminary publication that, in the anesthetized rat, the
naloxone augmented gastric acid secretion induced by to
electrical stimulation of the vagus nerves. Con naloxone augmented gastric acid secretion induced by to be enhancement, not inhibition, of acid secretion.
electrical stimulation of the vagus nerves. Consequently, b. INCREASE IN STIMULATED COMPARED TO BASAL
an inhibitory naloxone augmented gastric acid secretion induced by
electrical stimulation of the vagus nerves. Consequently,
an inhibitory role of endogenous opioids during vagally
induced acid secretion was suggested. Glavin et al. (13 electrical stimulation of the vagus nerves. Consequently,
an inhibitory role of endogenous opioids during vagally
induced acid secretion was suggested. Glavin et al. (138) in
demonstrated a clear-cut increase in gastric ac an inhibitory role of endogenous opioids during vagally Accordinated a clear-cut increase in gastric acid output component and 2 h post injection was dose according the effect observed between 1 and 2 h post injection was induced acid secretion was suggested. Glavin et al. (138) in
demonstrated a clear-cut increase in gastric acid output
by i.v. naloxone in the conscious gastric fistula rat. The
deffect observed between 1 and 2 h post in demonstrated a clear-cut increase in gastric acid output
by i.v. naloxone in the conscious gastric fistula rat. The
effect observed between 1 and 2 h post injection was dose
dependent up to 25 mg/kg, when a 200% increase a effect observed between 1 and 2 h post injection was dose acid secretion in a chambered stomach preparation by dependent up to 25 mg/kg, when a 200% increase above close intraarterial infusion of $[Met⁵]$ -enkephalin. T dependent up to 25 mg/kg, when a 200% increase above dependent up to 25 mg/kg, when a 200% increase above clobasal values was achieved. Fifty mg/kg of naloxone, opinowever, resulted in an increase of barely 50%, giving a blocal-shaped dose-response curve. Thus, although this basal values was achieved. Fifty mg/kg of naloxom
however, resulted in an increase of barely 50%, giving
bell-shaped dose-response curve. Thus, although thigh dose of naloxone may exert nonspecific effects, bot
inhibitory however, resulted in an increase of barely 50%, giving a bell-shaped dose-response curve. Thus, although this high dose of naloxone may exert nonspecific effects, both inhibitory and stimulatory endogenous opioid mechanism high dose of naloxone may exert nonspecific effects, both inhibitory and stimulatory endogenous opioid mechanisms may modulate gastric acid secretion at different sites. Since these effects may be superimposed dependent on high dose of naloxone may exert nonspecific effects, both [I
inhibitory and stimulatory endogenous opioid mecha-
misms may modulate gastric acid secretion at different as
sites. Since these effects may be superimposed depe inhibitory and stimulatory endogenous opioid mechanisms may modulate gastric acid secretion at different sites. Since these effects may be superimposed dependent on the particular predrug functional state of this complesys nisms may modulate gastric acid secretion at different
sites. Since these effects may be superimposed dependent
on the particular predrug functional state of this complex
system, absolute values of opioid effects should be sites. Since these effects may be superimposed depender
on the particular predrug functional state of this comple
system, absolute values of opioid effects should be inter
preted with caution. Even a failure of opioids to on the particular predrug functional
system, absolute values of opioid eff
preted with caution. Even a failure
acid secretion may result from supe
tionally opposite action components

between the effects of i.v. and i.c.v. administered receptor being possibly increased by opioids, and on acetylcholine
type-selective opioids and by introducing the quaternary release, being inhibited by opioids. These hyp type-selective opioids and by introducing the quaternary release, being inhibited by opioids. These hypothetical
naltrexone-methylbromide that central and possibly pe-
opioid mechanisms would influence acid secretion in an 2. *Cat.* Continuous i.v. infusion of [Met⁵]-enkephalin in the conscious cat failed to affect basal acid secretion or secretion stimulated submaximally by histamine or in the conscious cat failed to affect basal acid secretion **ESTINAL MOTILITY AND SECRETION** 141
2. *Cat.* Continuous i.v. infusion of $[Met⁵]$ -enkephalin
in the conscious cat failed to affect basal acid secretion
or secretion stimulated submaximally by histamine or
pentagastri 2. Cat. Continuous i.v. infusion of [Met⁵]-enkephalin
in the conscious cat failed to affect basal acid secretion
or secretion stimulated submaximally by histamine or
pentagastrin (129). Similarly, continuous i.v. infusio 2. Cat. Continuous i.v. infusion of [Met⁸]-enkephalin
in the conscious cat failed to affect basal acid secretion
or secretion stimulated submaximally by histamine or
pentagastrin (129). Similarly, continuous i.v. infusio in the conscious cat failed to affect basal acid secretion
or secretion stimulated submaximally by histamine or
pentagastrin (129). Similarly, continuous i.v. infusion of
naloxone alone had no influence on insulin-stimulat or secretion stimulated submaximally by histamine or
pentagastrin (129). Similarly, continuous i.v. infusion of
naloxone alone had no influence on insulin-stimulated
acid secretion in the cat. There was also no opioid effe pentagastrin (129). Similarly, continuous i.v. infusion of naloxone alone had no influence on insulin-stimulated acid secretion in the cat. There was also no opioid effect on pepsin secretion (129). One of the authors, Hir naloxone alone had no influence on insulin-stimulated
acid secretion in the cat. There was also no opioid effect
on pepsin secretion (129). One of the authors, Hirst
(169), speculated on multiple opioid effects on histamin acid secretion in the cat. There was also no opioid effect
on pepsin secretion (129). One of the authors, Hirst
(169), speculated on multiple opioid effects on histamine
and gastrin release as well as mucosal blood flow, a on pepsin secretion (129). One of the authors, Hirs (169), speculated on multiple opioid effects on histamine and gastrin release as well as mucosal blood flow, al being possibly increased by opioids, and on acetylcholine (169), speculated on multiple opioid effects on histamine
and gastrin release as well as mucosal blood flow, all
being possibly increased by opioids, and on acetylcholine
release, being inhibited by opioids. These hypothet being possibly increased by opioids, and on acetylcholine being possibly increased by opioids, and on acetylchol
release, being inhibited by opioids. These hypotheti
opioid mechanisms would influence acid secretion in
opposite manner, thereby counteracting each other.
should be n release, being inhibited by opioids. These hypothetiopioid mechanisms would influence acid secretion in opposite manner, thereby counteracting each other.
should be noted, however, that, while exogenous admistration of opi opioid mechanisms would influence acid secretion in an
opposite manner, thereby counteracting each other. It
should be noted, however, that, while exogenous admin-
istration of opioids is likely to activate different mecha opposite manner, thereby counteracting each other. It should be noted, however, that, while exogenous administration of opioids is likely to activate different mechanisms simultaneously, endogenous activation probably take should be noted, however, that, while exogenous administration of opioids is likely to activate different mechanisms simultaneously, endogenous activation probably takes place at specific sites at the proper time, possibly istration of opioids is likely to activate different mechanisms simultaneously, endogenous activation probably
takes place at specific sites at the proper time, possibly
avoiding superimposition. It is therefore of particu nisms simultaneously, endogenous activation probatakes place at specific sites at the proper time, possession avoiding superimposition. It is therefore of particinterest that acetorphan, an enkephalinase inhibitiveduced ga takes place at specific sites at the proper time, possibly
avoiding superimposition. It is therefore of particular
interest that acetorphan, an enkephalinase inhibitor,
reduced gastric acid secretion stimulated by pentagas avoiding superimposition. It is therefore of particu
interest that acetorphan, an enkephalinase inhibit
reduced gastric acid secretion stimulated by pentag
trin, histamine, or 2-DG by 40 to 60% (11). The eff
was prevented became detectable by slowing down opioid degradation.
3. Dog. a. INCREASE IN BASAL ACID SECRETION BY

istration of opioids is likely to activate different mechanisms simultaneously, endogenous activation probably and space at specific site at the proper time, possibly avoiding superimposition. It is therefore of particula **OPIOIDS VIA VAGAL STIMULATION. Riegel (349) and Smir**enous opioids probably inhibited acid secretion, which
became detectable by slowing down opioid degradation.
3. Dog. a. INCREASE IN BASAL ACID SECRETION BY
OPIOIDS VIA VAGAL STIMULATION. Riegel (349) and Smir-
now and Schi became detectable by slowing down opioid degradation.
3. Dog. a. INCREASE IN BASAL ACID SECRETION BY
OPIOIDS VIA VAGAL STIMULATION. Riegel (349) and Smir-
now and Schirokij (416) found in dog and man an en-
hancement of ba 3. Dog. a. INCREASE IN BASAL ACID SECRETION BY
OPIOIDS VIA VAGAL STIMULATION. Riegel (349) and Smir-
now and Schirokij (416) found in dog and man an en-
hancement of basal acid secretion from the innervated
stomach by low OPIOIDS VIA VAGAL STIMULATION. Riegel (349) and Smirnow and Schirokij (416) found in dog and man an enhancement of basal acid secretion from the innervated stomach by low s.c. doses of morphine. Higher doses transiently in now and Schirokij (416) found in dog and man an en
hancement of basal acid secretion from the innervate
stomach by low s.c. doses of morphine. Higher dose
transiently inhibited and then stimulated acid secretion
The stimul stomach by low s.c. doses of morphine. Higher doses
transiently inhibited and then stimulated acid secretion.
The stimulatory effect in the dog was abolished by atro-
pine and vagotomy, leading Smirnow and Shirokij (416) stomach by low s.c. doses of morphine. Higher doses
transiently inhibited and then stimulated acid secretion.
The stimulatory effect in the dog was abolished by atro-
pine and vagotomy, leading Smirnow and Shirokij (416)
t transiently inhibited and then stimulated acid secretion.
The stimulatory effect in the dog was abolished by atro-
pine and vagotomy, leading Smirnow and Shirokij (416)
to conclude that a central stimulatory effect of morp The stimulatory effect in the dog was abolished by atro-
pine and vagotomy, leading Smirnow and Shirokij (416)
to conclude that a central stimulatory effect of morphine
was vagally mediated. However, a peripheral stimulat pine and vagotomy, leading Smirnow and Shirokij (416)
to conclude that a central stimulatory effect of morphine
was vagally mediated. However, a peripheral stimulatory
modulation of vagal function cannot be precluded by
th was vagally mediated. However, a peripheral stimulatory

modulation of vagal function cannot be precluded by
these experiments. The main effect of opioids appeared
to be enhancement, not inhibition, of acid secretion.
b. INCREASE IN STIMULATED COMPARED TO BASAL
ACID SECRETION BY these experiments. The main effect of opioids appeare
to be enhancement, not inhibition, of acid secretion.
b. INCREASE IN STIMULATED COMPARED TO BASA
ACID SECRETION BY OPIOIDS. Data from dogs are conflict
ing probably due to be enhancement, not inhibition, of acid secretion.

b. INCREASE IN STIMULATED COMPARED TO BASAL

ACID SECRETION BY OPIOIDS. Data from dogs are conflict-

ing probably due to largely noncomparable experimental

condition b. INCREASE IN STIMULATED COMPARED TO BASAL
ACID SECRETION BY OPIOIDS. Data from dogs are conflict-
ing probably due to largely noncomparable experimental
conditions. In the anesthetized dog, Konturek et al. (214)
demonstr ACID SECRETION BY OPIOIDS. Data from dogs are conflicting probably due to largely noncomparable experimental
conditions. In the anesthetized dog, Konturek et al. (214)
demonstrated an enhancement of histamine-induced
acid ing probably due to largely noncomparable experimental
conditions. In the anesthetized dog, Konturek et al. (214)
demonstrated an enhancement of histamine-induced
acid secretion in a chambered stomach preparation by
close conditions. In the anesthetized dog, Konturek et al. (214)
demonstrated an enhancement of histamine-induced
acid secretion in a chambered stomach preparation by
close intraarterial infusion of [Met⁵]-enkephalin. The
opio demonstrated an enhancement of histamine-induced
acid secretion in a chambered stomach preparation by
close intraarterial infusion of $[Met⁵]$ -enkephalin. The
opioid effect was accompanied by an elevated mucosal
blood f acid secretion in a chambered stomach preparation by
close intraarterial infusion of $[Met⁵]$ -enkephalin. The
opioid effect was accompanied by an elevated mucosal
blood flow and was antagonized by naloxone. A similar
ef close intraarterial infusion of [Met⁵]-enkephalin. Thopioid effect was accompanied by an elevated mucos
blood flow and was antagonized by naloxone. A similateffect was also found with morphine (214, 462). Bot
[Met⁵]-en opioid effect was accompanied by an elevated mucosal
blood flow and was antagonized by naloxone. A similar
effect was also found with morphine (214, 462). Both
[Met⁵]-enkephalin and morphine also augmented hista-
mine-in blood flow and was antagonized by naloxone. A similar effect was also found with morphine (214, 462). Both [Met⁵]-enkephalin and morphine also augmented hista-
mine-induced pepsin release. However, no effect on basal aci effect was also found with morphine (214, 462). Both [Met⁵]-enkephalin and morphine also augmented histamine-induced pepsin release. However, no effect on basal acid secretion in this anesthetized dog preparation was obs [Met⁵]-enkephalin and morphine also augmented hist
mine-induced pepsin release. However, no effect on ba
acid secretion in this anesthetized dog preparation w
observed, although mucosal blood flow was still elevate
A pe mine-induced pepsin release. However, no effect on basal
acid secretion in this anesthetized dog preparation was
observed, although mucosal blood flow was still elevated.
A peripheral effect on mucosal blood flow with a su acid secretion in this anesthetized dog preparation was observed, although mucosal blood flow was still elevated.
A peripheral effect on mucosal blood flow with a subsequent increase in histamine delivery to the mucosa was observed, althou
A peripheral eff
quent increase is
suggested, but a
not ruled out.
In the conscio quent increase in histamine delivery to the mucosa was
suggested, but a direct opioid effect on mucosal cells was
not ruled out.
In the conscious dog, $[Met^b]$ -enkephalin and morphine

KROMER
enhanced gastric acid secretion from the Heidenhain d. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS.
pouch, which is denervated, and from the innervated Opioids enhance gastric acid secretion in the dog not KROM
enhanced gastric acid secretion from the Heidenhain
pouch, which is denervated, and from the innervated
main stomach, both under basal conditions and after KROM
enhanced gastric acid secretion from the Heidenhain
pouch, which is denervated, and from the innervated
main stomach, both under basal conditions and after
stimulation by pentagastrin or histamine (215). Again, enhanced gastric acid secretion from the Heidenhain
pouch, which is denervated, and from the innervated
main stomach, both under basal conditions and after
stimulation by pentagastrin or histamine (215). Again,
mucosal blo enhanced gastric acid secretion from the Heidenhain d.
pouch, which is denervated, and from the innervated Opimain stomach, both under basal conditions and after experimulation by pentagastrin or histamine (215). Again, ac pouch, which is denervated, and from the innervated main stomach, both under basal conditions and afte stimulation by pentagastrin or histamine (215). Again mucosal blood flow was increased, but no change in serum gastrin stimulation by pentagastrin or histamine (215). Again, mucosal blood flow was increased, but no change in serum gastrin concentration was observed. Opioids, however, inhibited the release of somatostatin from the iso-lated stimulation by pentagastrin or histamine (215). Agamucosal blood flow was increased, but no change
serum gastrin concentration was observed. Opioids, hever, inhibited the release of somatostatin from the is
lated dog pancr mucosal blood flow was increased, but no change in gast
serum gastrin concentration was observed. Opioids, how-
basever, inhibited the release of somatostatin from the iso-
was
lated dog pancreas (193). This may provide an serum gastrin concentration was observed. Opioids, how-
ever, inhibited the release of somatostatin from the iso-
wated dog pancreas (193). This may provide an explana-
tion of enhanced acid secretion, since somatostatin i ever, inhibited the release of somatostatin from the iso-
lated dog pancreas (193). This may provide an explana-
tion of enhanced acid secretion, since somatostatin is an
inhibitor of gastric acid secretion (82, 350). Sinc lated dog pancreas (193). This may provide an explanation of enhanced acid secretion, since somatostatin is an inhibitor of gastric acid secretion (82, 350). Since the stimulatory opioid effect on basal acid secretion was inhibitor of gastric acid secretion $(82, 350)$. Since the
stimulatory opioid effect on basal acid secretion was
blocked by naloxone and by atropine or metiamide alike,
a cooperative interaction between opioid, muscarinic and H_2 -receptor systems was suggested (215). imulatory opioid effect on basal acid secretion was
ocked by naloxone and by atropine or metiamide alike,
cooperative interaction between opioid, muscarinic,
d H_2 -receptor systems was suggested (215).
A plausible reaso

blocked by naloxone and by atropine or metiamide alike,
a cooperative interaction between opioid, muscarinic,
and H_2 -receptor systems was suggested (215).
A plausible reason for the discrepancies (see above)
between th and H_2 -receptor systems was suggested (215).
A plausible reason for the discrepancies (see abo
between the data on basal secretion in the anestheti
(214) versus the conscious dog (215) may be that, in
conscious dog, th A plausible reason for the discrepancies (see above)
between the data on basal secretion in the anesthetized
(214) versus the conscious dog (215) may be that, in the
conscious dog, the activity state of endogenous stimulabetween the data on basal secretion in the anesthetized ing (214) versus the conscious dog (215) may be that, in the conscious dog, the activity state of endogenous stimula-
tory mechanisms may differ from that in anesthet (214) versus the conscious dog (215) may be that, in the conscious dog, the activity state of endogenous stimula-
tory mechanisms may differ from that in anesthetized cenanimals. On the other hand, the enhancement of acid conscious dog, the activity state of endogenous stimula-
tory mechanisms may differ from that in anesthetized
animals. On the other hand, the enhancement of acid
secretion by opioids in the denervated Heidenhain pouch
of t tory mechanisms may differ from that in anesthetized
animals. On the other hand, the enhancement of acid
secretion by opioids in the denervated Heidenhain pouch
of the dog (215) indicated that vagal drive was not
essential animals. On the other hand, the enhancement of acid
secretion by opioids in the denervated Heidenhain pouch
of the dog (215) indicated that vagal drive was not
sesential under these particular conditions. Consistent
with t secretion by opioids in the denervated Heidenhain pouch
of the dog (215) indicated that vagal drive was not
essential under these particular conditions. Consistent
with this notion, Shefner et al. (408) found no influence
 of the dog (215) indicated that vagal drive was ressential under these particular conditions. Consiste with this notion, Shefner et al. (408) found no influer of opioids on intracellularly recorded electrical propert of ra with this notion, Shefner et al. (408) found no influence secretion in the denervated Heidenhain pouch. It is not
of opioids on intracellularly recorded electrical properties clear why Magee (265) and Soldani et al. (419) with this notion, Shefner et al. (408) found no influence
of opioids on intracellularly recorded electrical properties
of rabbit nodose ganglion cells or on extracellular record-
ings from the infranodose vagus nerve in vi of opioids on intracellularly recorded electrical properties
of rabbit nodose ganglion cells or on extracellular record-
ings from the infrance or agus nerve in vitro. An opioid
influence on vagal function may nevertheless of rabbit nodose ganglion cells or on extracellular record-
ings from the infranodose vagus nerve in vitro. An opioid men
influence on vagal function may nevertheless contribute fist
to basal acid secretion or participate

to basal acid secretion or participate in opioid inhibition
of gastric acid secretion (see section IV B 3 d).
c. INHIBITION OF STIMULATED ACID SECRETION BY
OPIOIDS. In contrast to the above mentioned results,
Konturek e to basal acid secretion or participate in opioid inhibition times to f gastric acid secretion (see section IV B 3 d). et al. (212) expression of shame of the above mentioned results, 30 minum Konturek et al. (212) also rep of gastric acid secretion (see section IV B 3 d).

c. INHIBITION OF STIMULATED ACID SECRETION BY

OPIOIDS. In contrast to the above mentioned results,

Konturek et al. (212) also reported an inhibition of sham

feeding-ind c. INHIBITION OF STIMULATED ACID SECRETION
OPIOIDS. In contrast to the above mentioned result onture it al. (212) also reported an inhibition of sheeding-induced gastric acid secretion in the gastric
tula dog by similar d OPIOIDS. In contrast to the above mentioned results,
Konturek et al. (212) also reported an inhibition of sham
feeding-induced gastric acid secretion in the gastric fis-
tula dog by similar doses of $[Met⁵]$ -enkephalin Konturek et al. (212) also reported an inhibition of sham
feeding-induced gastric acid secretion in the gastric fis-
tula dog by similar doses of $[Met⁵]$ -enkephalin adminis-
tered by continuous i.v. infusion. Similarl feeding-induced gastric acid secretion in the gastric fis-
tula dog by similar doses of $[Met^5]$ -enkephalin adminis-
tered by continuous i.v. infusion. Similarly, i.v. $[Met^5]$ -
enkephalin suppressed pentagastrin-stimulated tula dog by similar doses of $[Met^5]$ -enkephalin administered by continuous i.v. infusion. Similarly, i.v. $[Met^5]$ -
enkephalin suppressed pentagastrin-stimulated acid se-
acretion from the innervated canine main stomach (4 tered by continuous i.v. infusion. Similarly, i.v. [Met^tenkephalin suppressed pentagastrin-stimulated acid scretion from the innervated canine main stomach (41 and acid secretion stimulated by a meal (287). In the latter enkephalin suppressed pentagastrin-stimulated acid secretion from the innervated canine main stomach (414) and acid secretion stimulated by a meal (287). In the latter case, postprandial gastrin release was also inhibited. cretion from the innervated canine main stomach (414) M
and acid secretion stimulated by a meal (287). In the
latter case, postprandial gastrin release was also inhibitited. The reason for this discrepancy between stimulat and acid secretion stimulated by a meal (287). In the proletion states postprandial gastrin release was also inhibited. The reason for this discrepancy between stimulatory was also inhibitory effects is not clear, but it m latter case, postprandial gastrin release was also inhibited. The reason for this discrepancy between stimulatory and inhibitory effects is not clear, but it may be related to the activity states of contrasting endogenous ited. The reason for this discrepancy between stimulatory
and inhibitory effects is not clear, but it may be related has
to the activity states of contrasting endogenous opioid
systems. Naloxone not only blocked the opioid and inhibitory effects is not clear, but it may be relate
to the activity states of contrasting endogenous opioi
systems. Naloxone not only blocked the opioid effect bu
inhibited, when administered alone, acid secretion a
 systems. Naloxone not only blocked the opioid effect but
inhibited, when administered alone, acid secretion as
compared to controls (212). Thus, opioid receptors stim-
ulating acid secretion were possibly activated endogesystems. Naloxone not only blocked the opioid effect but
inhibited, when administered alone, acid secretion as
compared to controls (212). Thus, opioid receptors stim-
ulating acid secretion were possibly activated endogeinhibited, when administered alone, acid secretion as
compared to controls (212). Thus, opioid receptors stim-
ulating acid secretion were possibly activated endoge-
nously, leaving inhibitory opioid receptors to the acticompared to controls (212). Thus, opioid receptors st
ulating acid secretion were possibly activated end
nously, leaving inhibitory opioid receptors to the ε
vation by the exogenous opioid. Confusingly, howe
naloxone d ulating acid secretion were possibly activated endogenously, leaving inhibitory opioid receptors to the activation by the exogenous opioid. Confusingly, however, naloxone did not antagonize inhibition of bombesin-
induced nously, leaving inhibitory opioid receptors to the acti-
vation by the exogenous opioid. Confusingly, however, or
naloxone did not antagonize inhibition of bombesin-
induced gastric acid secretion by i.v. infusion of [Met vation by the exogenous opioid. Confusingly, however, opional oxone did not antagonize inhibition of bombesin-
induced gastric acid secretion by i.v. infusion of [Met⁵]- opional
enkephalin (275), whereas inhibition of pe naloxone did not antagonize inhibition of bom

induced gastric acid secretion by i.v. infusion of [N

enkephalin (275), whereas inhibition of pentagastr

2-DG-stimulated acid secretion in the gastric fistul

by i.c.v. beta induced gastric acid secretion by i.v. infusion of $[Met⁵]$ - opic
enkephalin (275), whereas inhibition of pentagastrin- or deg
2-DG-stimulated acid secretion in the gastric fistula dog may
by i.c.v. beta-endorphin (255 naloxone.

a cooperative interaction between opioid, muscarinic, pouch, and by dermorphin in the innervated main stom-
and H_2 -receptor systems was suggested (215).
A plausible reason for the discrepancies (see above) both naloxon d. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS. Opioids enhance gastric acid secretion in the dog not ER
d. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS.
Opioids enhance gastric acid secretion in the dog not
exposed to exogenous stimulants at a peripheral site of
action. Thus, in both the Heidenhain pouch dog and the d. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS.
Opioids enhance gastric acid secretion in the dog not
exposed to exogenous stimulants at a peripheral site of
action. Thus, in both the Heidenhain pouch dog and the
gastric fist d. PERIPHERAL VERSUS CENTRAL OPIOID EFFECTS.
Opioids enhance gastric acid secretion in the dog not
exposed to exogenous stimulants at a peripheral site of
action. Thus, in both the Heidenhain pouch dog and the
gastric fist Opioids enhance gastric acid secretion in the dog not exposed to exogenous stimulants at a peripheral site of action. Thus, in both the Heidenhain pouch dog and the gastric fistula dog, dermorphine and morphine increased b exposed to exogenous stimulants at a peripheral site
action. Thus, in both the Heidenhain pouch dog and if
gastric fistula dog, dermorphine and morphine increas
basal acid secretion after i.v. administration. This eff
was action. Thus, in both the Heidenhain pouch dog and the gastric fistula dog, dermorphine and morphine increased
basal acid secretion after i.v. administration. This effect
was blocked by naloxone as well as naltrexone methy gastric fistula dog, dermorphine and morphine increased
basal acid secretion after i.v. administration. This effect
was blocked by naloxone as well as naltrexone methyl-
bromide and N-methyl-levallorphan (419). The latter
 basal acid secretion after i.v. administration. This effect
was blocked by naloxone as well as naltrexone methyl-
bromide and N-methyl-levallorphan (419). The latter
antagonists are quaternary compounds, which more or
less was blocked by naloxone as well as naltrexone methyl-
bromide and N-methyl-levallorphan (419). The latter
antagonists are quaternary compounds, which more or
less block only peripheral opioid effects. In addition,
pentagas bromide and N-methyl-levallorphan (419). The latter
antagonists are quaternary compounds, which more or
less block only peripheral opioid effects. In addition,
pentagastrin-stimulated acid secretion was enhanced by
morphin antagonists are quaternary compounds, which more dess block only peripheral opioid effects. In addition pentagastrin-stimulated acid secretion was enhanced morphine and dermorphin in the denervated Heidenhain pouch, and by less block only peripheral opioid effects. In addition,
pentagastrin-stimulated acid secretion was enhanced by
morphine and dermorphin in the denervated Heidenhain
pouch, and by dermorphin in the innervated main stom-
ach pentagastrin-stimulated acid secretion was enhanced imorphine and dermorphin in the denervated Heidenhapouch, and by dermorphin in the innervated main stone ach with gastric fistula (419). This effect was blocked both nalo morphine and dermorphin in the denerva
pouch, and by dermorphin in the innervi
ach with gastric fistula (419). This effect
both naloxone and N-methyl-levallorphi
ing to a peripheral site of action (419).
However, opioids m uch, and by dermorphin in the innervated main stom-
h with gastric fistula (419). This effect was blocked by
th naloxone and N-methyl-levallorphan, again point-
g to a peripheral site of action (419).
However, opioids may

ach with gastric fistula (419). This effect was blocked by
both naloxone and N-methyl-levallorphan, again point-
ing to a peripheral site of action (419).
However, opioids may also affect acid secretion at a
central site o both naloxone and N-methyl-levallorphan, again point-
ing to a peripheral site of action (419).
However, opioids may also affect acid secretion at a
central site of action. Gastric acid secretion stimulated
centrally by 2ing to a peripheral site of action (419).
However, opioids may also affect acid secretion at a
central site of action. Gastric acid secretion stimulated
centrally by 2-DG (168) was inhibited by morphine in
the innervated s However, opioids may also affect acid secretion at central site of action. Gastric acid secretion stimulate centrally by 2-DG (168) was inhibited by morphine the innervated stomach (419). This effect of morphine was not an central site of action. Gastric acid secretion stimulated
centrally by 2-DG (168) was inhibited by morphine in
the innervated stomach (419). This effect of morphine
was not antagonized by the peripherally acting quater-
na centrally by 2-DG (168) was inhibited by morphine in
the innervated stomach (419). This effect of morphine
was not antagonized by the peripherally acting quater-
nary antagonist N-methyl-levallorphan. Consistent with
its c the innervated stomach (419). This effect of morphine
was not antagonized by the peripherally acting quater-
nary antagonist N-methyl-levallorphan. Consistent with
its central site of action, 2-DG did not stimulate acid
se was not antagonized by the peripherally acting quater-
nary antagonist N-methyl-levallorphan. Consistent with
its central site of action, 2-DG did not stimulate acid
secretion in the denervated Heidenhain pouch. It is not
 nary antagonist N-methyl-levallorphan. Consistent v
its central site of action, 2-DG did not stimulate a
secretion in the denervated Heidenhain pouch. It is
clear why Magee (265) and Soldani et al. (419) found
inhibition, secretion in the denervated Heidenhain pouch. It is not secretion in the denervated Heidenhain pouch. It is not
clear why Magee (265) and Soldani et al. (419) found
inhibition, whereas Anderson et al. (9) found enhance-
ment of 2-DG-stimulated acid secretion in the chronic
fis clear why Magee (265) and Soldani et al. (419) found
inhibition, whereas Anderson et al. (9) found enhance-
ment of 2-DG-stimulated acid secretion in the chronic
fistula dog by morphine. Magee (265) used roughly 10
times t inhibition, whereas Anderson et al. (9) found enhancement of 2-DG-stimulated acid secretion in the chronic fistula dog by morphine. Magee (265) used roughly 10 times the morphine dose as an i.v. bolus that Anderson et al. ment of 2-DG-stimulated acid secretion in the chronic
fistula dog by morphine. Magee (265) used roughly 10
times the morphine dose as an i.v. bolus that Anderson
et al. (9) administered as an i.v. infusion over 2 h. Soldan fistula dog by morphine. Magee (265) used roughly 10
times the morphine dose as an i.v. bolus that Anderson
et al. (9) administered as an i.v. infusion over 2 h. Soldani
et al. (419) infused a similar total dose of times the morphine dose as an i.v. bolus that Anderson
et al. (9) administered as an i.v. infusion over 2 h. Soldani
et al. (419) infused a similar total dose of morphine over
30 min as Anderson et al. (9) infused over 2 h et al. (9) administered as an i.v.
et al. (419) infused a similar to
30 min as Anderson et al. ({
discrepant results can hardly b
basis of different dose levels.
Opioids may inhibit central al. (419) infused a similar total dose of morphine over
min as Anderson et al. (9) infused over 2 h. The
screpant results can hardly be reconciled solely on the
sis of different dose levels.
Opioids may inhibit centrally s bam inatome and Y-metric present eigented parameter and the central its of a peripheral site of action. (419).

However, opioids may also affect acid secretion at a central site of action. Gastric acid secretion simulated

30 min as Anderson et al. (9) infused over 2 h. The discrepant results can hardly be reconciled solely on the basis of different dose levels.

Opioids may inhibit centrally stimulated gastric acid secretion by either perip discrepant results can hardly be reconciled solely on the basis of different dose levels.
Opioids may inhibit centrally stimulated gastric acid
secretion by either peripheral presynaptic inhibition of
acetylcholine release basis of different dose levels.

Opioids may inhibit centrally stimulated gastric acid

secretion by either peripheral presynaptic inhibition of

acetylcholine release or depressing the vagal center.

Meal-stimulated acid Opioids may inhibit centrally stimulated gastric accretion by either peripheral presynaptic inhibition acetylcholine release or depressing the vagal central Meal-stimulated acid secretion from the main stomac probably a re acetylcholine release or depressing the vagal center.
Meal-stimulated acid secretion from the main stomach,
probably a result of central vagal stimulation, was inhib-
ited by $[Met⁵]$ -enkephalin, while no significant e Meal-stimulated acid secretion from the main stomach,
probably a result of central vagal stimulation, was inhib-
ited by $[Met⁵]$ -enkephalin, while no significant effect
was observed at the same time in the denervated probably a result of central vagal stimulation, was inhibited by [Met⁵]-enkephalin, while no significant effect was observed at the same time in the denervated Heidenhain pouch (225). Although Shefner et al. (408; see se ited by [Met⁵]-enkephalin, while no significan
was observed at the same time in the denervated l
hain pouch (225). Although Shefner et al. (4
section IV B 3 b) found no such evidence, opioid re
and opioids have been sugg was observed at the same time in the denervated Heidenhain pouch (225). Although Shefner et al. (408; see
section IV B 3 b) found no such evidence, opioid receptors
and opioids have been suggested on immunohistochemi-
cal hain pouch (225). Although Shefner et al. (408; see
section IV B 3 b) found no such evidence, opioid receptors
and opioids have been suggested on immunohistochemi-
cal grounds to occur in the solitary nuclei of the brain
s section IV B 3 b) found no such evidence, opioid receptors
and opioids have been suggested on immunohistochemi-
cal grounds to occur in the solitary nuclei of the brain
stem and in the vagus nerve (245, 261). Penetration o and opioids have been suggested on immunohistochemical grounds to occur in the solitary nuclei of the brain stem and in the vagus nerve (245, 261). Penetration of neuropeptides through the blood-brain barrier may be poor, cal grounds to occur in the solitary nuclei of t
stem and in the vagus nerve (245, 261). Penet
neuropeptides through the blood-brain barrier
poor, but central effects of peripherally adm
opioids have nonetheless been repor em and in the vagus nerve (245, 261). Penetration of
uropeptides through the blood-brain barrier may be
or, but central effects of peripherally administered
ioids have nonetheless been reported (202).
Enhancement and inhib

neuropeptides through the blood-brain barrier may be
poor, but central effects of peripherally administered
opioids have nonetheless been reported (202).
Enhancement and inhibition of acid secretion by
opioids are probably poor, but central effects of peripherally administered
opioids have nonetheless been reported (202).
Enhancement and inhibition of acid secretion by
opioids are probably superimposed in the dog to varying
degrees, dependin opioids have nonetheless been reported (202).

Enhancement and inhibition of acid secretion by

opioids are probably superimposed in the dog to varying

degrees, depending on the experimental conditions which

may favor ei Enhancement and inhibition of acid secretion by
opioids are probably superimposed in the dog to varying
degrees, depending on the experimental conditions which
may favor either central or peripheral mechanisms. Kos-
tritsk opioids are probably superimposed in the dog to varying
degrees, depending on the experimental conditions which
may favor either central or peripheral mechanisms. Kos-
tritsky-Pereira et al. (225) demonstrated an inhibitio degrees, depending on the experimental conditions which
may favor either central or peripheral mechanisms. Kos-
tritsky-Pereira et al. (225) demonstrated an inhibition of
pentagastrin-induced acid secretion from the innerv

OPIOIDS AND CONTROL OF GASTROINTES
secretion from the denervated canine Heidenhain pouch (9
by intravenously infused [Met⁵]-enkephalin. These conopioing and contract of GASTRO
secretion from the denervated canine Heidenhain pouch
by intravenously infused [Met⁵]-enkephalin. These con-
trasting opioid effects were observed simultaneously in **OPIOIDS AND CONTROL OF GASTROINTEST**
secretion from the denervated canine Heidenhain pouch (9)
by intravenously infused $[Met⁵]$ -enkephalin. These con-
trasting opioid effects were observed simultaneously in DG-
the s secretion from the denervated canine Heidenhain pouch
by intravenously infused [Met⁵]-enkephalin. These con-
trasting opioid effects were observed simultaneously in
the same animals. It remains unclear why Konturek et
al secretion from the denervated canine Heidenhain pouch
by intravenously infused [Met⁵]-enkephalin. These con-
trasting opioid effects were observed simultaneously in I
the same animals. It remains unclear why Konturek et
 trasting opioid effects were observed simultaneously in
the same animals. It remains unclear why Konturek et
al. (215) found opioid enhancement of acid secretion
from both the main stomach and the Heidenhain pouch
under si

from both the main stomach and the Heidenhain pouce

under similar conditions.

e. POTENTIAL INFLUENCES ON SOMATOSTATIN, GA

TRIN, AND HISTAMINE RELEASE. Dependent on the nu

trient conditions, opioids might affect gastric where similar conditions.

e. POTENTIAL INFLUENCES ON SOMATOSTATIN, GAS-

TRIN, AND HISTAMINE RELEASE. Dependent on the nu-

trient conditions, opioids might affect gastric acid secre-

tion by either inhibiting or stimula e. POTENTIAL INFLUENCES ON SOMATOSTATIN, GAS-
TRIN, AND HISTAMINE RELEASE. Dependent on the nu-
trient conditions, opioids might affect gastric acid secre-
tion by either inhibiting or stimulating systemic release imp
of s TRIN, AND HISTAMINE RELEASE. Dependent on the nutrient conditions, opioids might affect gastric acid secretion by either inhibiting or stimulating systemic release of somatostatin, which in turn inhibits acid secretion. In trient conditions, opioids might affect gastric acid secre-
tion by either inhibiting or stimulating systemic release impaire
of somatostatin, which in turn inhibits acid secretion. In Heiden
the conscious dog, basal plas tion by either inhibiting or stimulating systemic release
of somatostatin, which in turn inhibits acid secretion. In
the conscious dog, basal plasma concentrations of so-
matostatin were reduced by various opioids (401). of somatostatin, which in turn inhibits acid secretion. In
the conscious dog, basal plasma concentrations of so-
matostatin were reduced by various opioids (401). A
similar inhibition was found with i.v. [Met⁵]-enkephali the conscious dog, basal plasma concentrations of so-
matostatin were reduced by various opioids (401). A sys
similar inhibition was found with i.v. [Met⁵]-enkephalin gas
during an i.v. background infusion of a glucose-a matostatin were reduced by various opioids (401). in similar inhibition was found with i.v. [Met⁵]-enkephaliduring an i.v. background infusion of a glucose-amin acid mixture (396), whereas i.v. beta-casein) (35, 211) sti similar inhibition was found with i.v. [Met⁵]-enkephaduring an i.v. background infusion of a glucose-am
acid mixture (396), whereas i.v. beta-casomorphin-5
opioid peptide derived from beta-casein) (35, 211) st
ulated som during an i.v. background infusion of a glucose-amino
acid mixture (396), whereas i.v. beta-casomorphin-5 (an
opioid peptide derived from beta-casein) (35, 211) stim-
ulated somatostatin release. In contrast to i.v. admini acid mixture (396), whereas i.v. beta-casomorphin-5 (an opioid peptide derived from beta-casein) (35, 211) stimulated somatostatin release. In contrast to i.v. administration, intragastric administration of $[Met^5]$ -enkeph opioid peptide derived from beta-casein) (35, 211) stim-
ulated somatostatin release. In contrast to i.v. adminis-
tration, intragastric administration of [Met⁵]-enkephalin
led to an enhancement of somatostatin release (ulated somatostatin release. In contrast to i.v. admin
tration, intragastric administration of [Met⁵]-enkepha
led to an enhancement of somatostatin release (39
while application of [Met⁵]-enkephalin to the vascu
perfus tration, intragastric administration of [Met⁸]-enkephalin tras
led to an enhancement of somatostatin release (396), Thi
while application of [Met⁸]-enkephalin to the vascular affe
perfusion medium of in vitro canine pa led to an enhancement of somatostatin release (396),
while application of $[Met^5]$ -enkephalin to the vascular
perfusion medium of in vitro canine pancreatic prepa-
rations (163) confirmed the inhibitory opioid effect on
so while application of [Met⁸]-enkephalin to the vascul
perfusion medium of in vitro canine pancreatic preprations (163) confirmed the inhibitory opioid effect
somatostatin release as observed by Schusdziarra et
(396, 401). perfusion medium of in vitro canine pancreatic preparations (163) confirmed the inhibitory opioid effect on somatostatin release as observed by Schusdziarra et al. (396, 401). The effect was glucose dependent. Correspondin rations (163) confirmed the inhibitory opioid effect on somatostatin release as observed by Schusdziarra et al. (396, 401). The effect was glucose dependent. Correspondingly, naloxone alone had either a stimulatory (394) o somatostatin release as observed by Schusdziarra et al. (396, 401). The effect was glucose dependent. Correspondingly, naloxone alone had either a stimulatory (394) or an inhibitory (395) effect on postprandial somatostati (396, 401). The effect was glucose dependent. Correspondingly, naloxone alone had either a stimulatory (394) or an inhibitory (395) effect on postprandial somatostatin release in the conscious dog. The particular effect wa (394) or an inhibitory (395) effect on postprandial sometostatin release in the conscious dog. The particular effect was again dependent on the nutrient situation. This was also found with regard to motilin-induced so-
ma (394) or an inhibitory (395) effect on postprandial so
matostatin release in the conscious dog. The particula
effect was again dependent on the nutrient situation
This was also found with regard to motilin-induced so
mato matostatin release in the conscious dog. The particula
effect was again dependent on the nutrient situation
This was also found with regard to motilin-induced so
matostatin release when i.v. glucose converted the inhi
biti effect was again dependent on the nutrient situation.
This was also found with regard to motilin-induced so-
matostatin release when i.v. glucose converted the inhi-
bition by naloxone to stimulation (379). This may indi-
 This was also found with regard to motiline
matostatin release when i.v. glucose conver
bition by naloxone to stimulation (379). T
cate contrasting endogenous opioid funct
view, see Schusdziarra and Schmid (398).
Since i.v atostatin release when i.v. glucose converted the inhi-
ition by naloxone to stimulation (379). This may indi-
te contrasting endogenous opioid functions. For re-
phew, see Schusdziarra and Schmid (398).
Since i.v. infusio

bition by naloxone to stimulation (379). This may indicate contrasting endogenous opioid functions. For review, see Schusdziarra and Schmid (398). fereview, see Schusdziarra and Schmid (398). fereview, in the dog, enhancem cate contrasting endogenous opioid functions. For review, see Schusdziarra and Schmid (398).
Since i.v. infusion of morphine slightly diminished the
serum gastrin concentration in the dog, enhancement of
acid secretion fro view, see Schusdziarra and Schmid (398).

Since i.v. infusion of morphine slightly diminished the

serum gastrin concentration in the dog, enhancement of

tacid secretion from the main stomach was obviously not

lue to gas Since i.v. infusion of morphine slightly diminished the serum gastrin concentration in the dog, enhancement of tacid secretion from the main stomach was obviously not have to gastrin release (224) . In contrast, Yamaguch acid secretion from the main stomach was obviously not
due to gastrin release (224). In contrast, Yamaguchi et
al. (490) found a fairly close correlation between volume
of basal gastric secretion and serum gastrin in the m acid secretion from the main stomach was obviously not
due to gastrin release (224). In contrast, Yamaguchi et
al. (490) found a fairly close correlation between volume
of basal gastric secretion and serum gastrin in the m due to gastrin release (224). In contrast, Yamaguchi et moral. (490) found a fairly close correlation between volume 4. of basal gastric secretion and serum gastrin in the mor-
phine/urethane-anesthetized dog. They conclud al. (490) found a fairly close correlation between volume
of basal gastric secretion and serum gastrin in the mor-
phine/urethane-anesthetized dog. They concluded that eff
an opioid-induced release of gastrin may be involv of basal gastric secretion and serum gastrin in the mor-
phine/urethane-anesthetized dog. They concluded that effer
an opioid-induced release of gastrin may be involved in of t
the opioid stimulation of gastric secretion. phine/urethane-anesthetized dog. They concluded that efference of pastric secretion. However, the interpretion of gastric secretion. However, the influence of morphine per se was not investigated, no 41 morphine-free contr an opioid-induced release of gastrin m
the opioid stimulation of gastric secret
influence of morphine per se was no
morphine-free controls were included
evidently inconclusive in this respect.
Opioids have been shown to re e opioid stimulation of gastric secretion. However, the fluence of morphine per se was not investigated, no orphine-free controls were included, so the study is idently inconclusive in this respect.
Opioids have been shown

influence of morphine per se was not investigated, no
morphine-free controls were included, so the study is
evidently inconclusive in this respect.
Opioids have been shown to release histamine (444,
144, 146, 429). Hence, morphine-free controls were included, so the study is
evidently inconclusive in this respect.
Opioids have been shown to release histamine (444,
144, 146, 429). Hence, peripheral histamine release and/
or direct stimulator evidently inconclusive in this respect.

Opioids have been shown to release histamine (4

144, 146, 429). Hence, peripheral histamine release a

or direct stimulatory modulation at the parietal cell (2

237, 375) may be th Opioids have been shown to release histamine (444, 144, 146, 429). Hence, peripheral histamine release and/
or direct stimulatory modulation at the parietal cell (238,
237, 375) may be the mechanism underlying the enhance-144, 146, 429). Hence, peripheral histamine release and
or direct stimulatory modulation at the parietal cell (238
237, 375) may be the mechanism underlying the enhance
ment of acid secretion from the denervated Heidenhaii

did not antagonize enkephalin inhibition of either 2-DG

trasting opioid effects were observed simultaneously in DG-stimulated acid secretion in the absence of exoge-
the same animals. It remains unclear why Konturek et nous opioids (9). In another study on dogs, naloxone
al. (2 ESTINAL MOTILITY AND SECRETION 143
(9) or peptone-meal-stimulated acid secretion (224).
However, a high dose of naloxone clearly decreased 2-ESTINAL MOTILITY AND SECRETION 143
(9) or peptone-meal-stimulated acid secretion (224).
However, a high dose of naloxone clearly decreased 2-
DG-stimulated acid secretion in the absence of exoge-ESTINAL MOTILITY AND SECRETION 1
(9) or peptone-meal-stimulated acid secretion (22-
However, a high dose of naloxone clearly decreased
DG-stimulated acid secretion in the absence of exog
nous opioids (9). In another study (9) or peptone-meal-stimulated acid secretion (224).
However, a high dose of naloxone clearly decreased 2-
DG-stimulated acid secretion in the absence of exoge-
nous opioids (9). In another study on dogs, naloxone
alone al (9) or peptone-meal-stimulated acid secretion (224).
However, a high dose of naloxone clearly decreased 2-
DG-stimulated acid secretion in the absence of exoge-
nous opioids (9). In another study on dogs, naloxone
alone al However, a high dose of naloxone clearly decreased 2-DG-stimulated acid secretion in the absence of exogenous opioids (9). In another study on dogs, naloxone alone also impaired acid secretion (212), again suggestive of st DG-stimulated acid secretion in the absence of exogenous opioids (9). In another study on dogs, naloxone alone also impaired acid secretion (212), again suggestive of stimulation by endogenous opioids. This is consistent w alone also impaired acid secretion (212) , again suggestive
of stimulation by endogenous opioids. This is consistent
with the proposition of superimposed stimulatory and
inhibitory opioid mechanisms in the control of gas alone also impaired acid secretion (212), again suggestive of stimulation by endogenous opioids. This is consistentify with the proposition of superimposed stimulatory are inhibitory opioid mechanisms in the control of gas of stimulation by endogenous opioids. This is consistent with the proposition of superimposed stimulatory and inhibitory opioid mechanisms in the control of gastracid secretion, although the interpretation is still hyperpe acid secretion, although the interpretation is still hypothetical. Since both naloxone and N-methyl-levallorphan
impaired pentagastrin-stimulated acid secretion from the
Heidenhain pouch and the innervated stomach in the inhibitory opioid mechanisms in the control of gastric
acid secretion, although the interpretation is still hypo-
thetical. Since both naloxone and N-methyl-levallorphan
impaired pentagastrin-stimulated acid secretion from acid secretion, although the interpretation is still hypothetical. Since both naloxone and N-methyl-levallorphan
impaired pentagastrin-stimulated acid secretion from the
Heidenhain pouch and the innervated stomach in the
a thetical. Since both naloxone and N-methyl-levallorphan
impaired pentagastrin-stimulated acid secretion from the
Heidenhain pouch and the innervated stomach in the
absence of exogenous opioids (419), an endogenous opioid
s impaired pentagastrin
Heidenhain pouch are
absence of exogenous
system is probably c
gastric acid secretion.
g. INVOLVEMENT

absence of exogenous opioids (419), an endogenous opioid
system is probably operative to peripherally enhance
gastric acid secretion.
g. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR
TYPES. Since morphine, a mu-agonist, enhance system is probably operative to peripherally enhagastric acid secretion.
g. INVOLVEMENT OF DIFFERENT OPIOID RECEF
TYPES. Since morphine, a mu-agonist, enhanced
[Met⁵]-enkephalin, a delta-agonist, impaired 2-DG-s
ulated a gastric acid secretion.

g. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOF

TYPES. Since morphine, a mu-agonist, enhanced and

[Met⁵]-enkephalin, a delta-agonist, impaired 2-DG-stim-

ulated acid secretion (9), the authors att g. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOI
TYPES. Since morphine, a mu-agonist, enhanced and
[Met⁵]-enkephalin, a delta-agonist, impaired 2-DG-stim
ulated acid secretion (9), the authors attributed the con
trasting eff System as procedure of peripheral period of periodic and Transmit periodic and TMet²]-enkephalin, a delta-agonist, impaired 2-DG-stim-
ulated increase morphine, a mu-agonist, impaired 2-DG-stim-
ulated acid secretion (9 ulated acid secretion (9), the authors attributed the con-
trasting effects to mu- and delta-receptors, respectively.
This might also explain why [Met⁵]-enkephalin failed to
affect bethanechol plus pentagastrin-induced a ulated acid secretion (9), the authors attributed the con-
trasting effects to mu- and delta-receptors, respectively.
This might also explain why [Met⁵]-enkephalin failed to
affect bethanechol plus pentagastrin-induced a trasting effects to mu- and delta-receptors, respectively.

This might also explain why [Met⁵]-enkephalin failed to

affect bethanechol plus pentagastrin-induced acid secre-

tion from both the main stomach and the Heid This might also explain why [Met⁵]-enkephalin failed to affect bethanechol plus pentagastrin-induced acid secretion from both the main stomach and the Heidenhain pouch (225) and bethanechol-induced acid secretion in the affect bethanechol plus pentagastrin-induced acid secretion from both the main stomach and the Heidenhain
pouch (225) and bethanechol-induced acid secretion in
the gastric fistula dog (9), whereas morphine and der-
morphin tion from both the main stomach and the Heidenhain
pouch (225) and bethanechol-induced acid secretion in
the gastric fistula dog (9), whereas morphine and der-
morphin enhanced bethanechol-induced acid secretion
from both (419). e gastric fistula dog (9), whereas morphine and der-
orphin enhanced bethanechol-induced acid secretion
om both the main stomach and the Heidenhain pouch
19).
As discussed earlier in this review, some reservation
pears to

morphin enhanced bethanechol-induced acid secretion
from both the main stomach and the Heidenhain pouch
(419).
As discussed earlier in this review, some reservation
appears to be appropriate when conclusions as to the
invo from both the main stomach and the Heidenhain pouch

(419).

As discussed earlier in this review, some reservation

appears to be appropriate when conclusions as to the

involvement of different receptor types solely base (419). As discussed earlier in this review, some reservation
appears to be appropriate when conclusions as to the
involvement of different receptor types solely based
differences in agonist actions are drawn. This is part
 As discussed earlier in this review, some reservation
appears to be appropriate when conclusions as to the
involvement of different receptor types solely based on
differences in agonist actions are drawn. This is partic
ul appears to be appropriate when conclusions as to the involvement of different receptor types solely based on differences in agonist actions are drawn. This is particularly true if the agonists are poorly selective like mor involvement of different receptor types solely based on differences in agonist actions are drawn. This is particularly true if the agonists are poorly selective like morphine and [Met⁵]-enkephalin. However, contrasting e differences in agonist actions are drawn. This is particularly true if the agonists are poorly selective like morphine and $[Met⁵]$ -enkephalin. However, contrasting effects were found (9), and the data are, overall, at ularly true if the agonists are poorly selective like morphine and [Met⁵]-enkephalin. However, contrasting effects were found (9), and the data are, overall, at least suggestive of different sites of action. Opioid mu-re phine and [Met⁵]-enkephalin. However, contrasting effects were found (9), and the data are, overall, at least suggestive of different sites of action. Opioid mu-receptors are activated by morphine, while [Met⁵]-enkepha fects were found (9), a
suggestive of different
tors are activated by m
has a higher affinity (
morphine (487, 494).
4. Man and monke ggestive of different sites of action. Opioid mu-recep-

rs are activated by morphine, while [Met⁵]-enkephalin

as a higher affinity to delta-receptors compared with

orphine (487, 494).

4. Man and monkey. a. DUAL OPIOI

237, 375) may be the mechanism underlying the enhance-
ment of acid secretion from the denervated Heidenhain
would nevertheless be consistent with data by other
pouch. The actual mechanism, however, is not known.
f. THE EF tors are activated by morphine, while $[Met⁵]$ -enkephalin
has a higher affinity to delta-receptors compared with
morphine $(487, 494)$.
4. Man and monkey. a. DUAL OPIOID EFFECTS. In
human studies, both stimulatory and has a higher affinity to delta-receptors compared with
morphine (487, 494).
4. Man and monkey. a. DUAL OPIOID EFFECTS. In
human studies, both stimulatory and inhibitory opioid
effects on gastric acid secretion have been pu morphine (487, 494).
4. Man and monkey. a. DUAL OPIOID EFFECTS. In
human studies, both stimulatory and inhibitory opioid
effects on gastric acid secretion have been published. All
of the studies were performed in healthy s 4. Man and monkey. a. DUAL OPIOID EFFECTS. In
human studies, both stimulatory and inhibitory opioid
effects on gastric acid secretion have been published. All
of the studies were performed in healthy subjects with
intact i human studies, both stimulatory and inhibitory opioid
effects on gastric acid secretion have been published. All
of the studies were performed in healthy subjects with
intact innervation of the stomach. Skov Olsen et al. (effects on gastric acid secretion have been published. All
of the studies were performed in healthy subjects with
intact innervation of the stomach. Skov Olsen et al. (413;
412) found enhancement of pentagastrin-stimulated of the studies were performed in healthy subjects with
intact innervation of the stomach. Skov Olsen et al. (413;
412) found enhancement of pentagastrin-stimulated acid
secretion by continuous i.v. infusion of FK 33-824, a intact innervation of the stomach. Skov Olsen et al. (413;
412) found enhancement of pentagastrin-stimulated acid
secretion by continuous i.v. infusion of FK 33-824, a
[Met⁵]-enkephalin analogue. Enhancement by a low
dos 412) found enhancement of pentagastrin-stimulated acid
secretion by continuous i.v. infusion of FK 33-824, a
[Met⁵]-enkephalin analogue. Enhancement by a low
dose, but fading of this effect at a higher dose (413), may
i secretion by continuous i.v. infusion of FK 33-824, a [Met⁵]-enkephalin analogue. Enhancement by a low dose, but fading of this effect at a higher dose (413), may indicate a dual stimulatory-inhibitory action, although [Met⁵]-enkephalin analogue. Enhancement by a low
dose, but fading of this effect at a higher dose (413), may
indicate a dual stimulatory-inhibitory action, although
some caution should be exercised considering that no
co dose, but fading of this effect at a higher dose (413), may
indicate a dual stimulatory-inhibitory action, although
some caution should be exercised considering that no
controls over time were demonstrated. Such a hypothes indicate a dual stimulatory-inhibitory action, although
some caution should be exercised considering that no
controls over time were demonstrated. Such a hypothesis
would nevertheless be consistent with data by other
worke some caution should be exercised considering that if controls over time were demonstrated. Such a hypothes would nevertheless be consistent with data by oth workers showing either no effect of i.v. beta-endorph (100) or in controls over time were demonstrated. Such a hypothesis
would nevertheless be consistent with data by other
workers showing either no effect of i.v. beta-endorphin
(100) or inhibition of basal acid secretion by i.m. pethiwould nevertheless be consistent with data by other
workers showing either no effect of i.v. beta-endorphin
(100) or inhibition of basal acid secretion by i.m. pethi-
dine (281), inhibition of morphine (101), inhibition
by

PHARMACOLOGICAL REVIEWS

144
of both basal and pentagastrin-stimulated acid secretion
by oral loperamide (51), inhibition of pentagastrin-stim-144
of both basal and pentagastrin-stimulated acid se
by oral loperamide (51), inhibition of pentagastri
ulated acid secretion by i.v. morphine (430), inl KROMI

144 KROMI

16 of both basal and pentagastrin-stimulated acid secretion

16 of pentagastrin-stimulated acid secretion

16 of both basal and pentagastrin-stimulated acid secretion

16 of both basal and pentagastrin-st of both basal and pentagastrin-stimulated acid secretion tiply oral loperamide (51), inhibition of pentagastrin-stim-
ulated acid secretion by i.v. morphine (430), inhibition last of both basal and pentagastrin-stimulated of both basal and pentagastrin-stimulated acid secretion tiply oral loperamide (51), inhibition of pentagastrin-stim-
ulated acid secretion by i.v. morphine (430), inhibition lase of both basal and pentagastrin-stimulated by oral loperamide (51), inhibition of pentagastrin-stim-
ulated acid secretion by i.v. morphine (430), inhibition
of both basal and pentagastrin-stimulated acid secretion
by s.c. [D-Ala², methyl-Phe⁴-(O)-ol]-enkephali ulated acid secretion by i.v. morphine (430), inhibition
of both basal and pentagastrin-stimulated acid secretion
by s.c. [D-Ala², methyl-Phe⁴-(O)-ol]-enkephalin (FK 33-
824) (431), or, finally, inhibition of basal, sh of both basal and pentagastrin-stimulated acid secretio
by s.c. [D-Ala², methyl-Phe⁴-(O)-ol]-enkephalin (FK 33
824) (431), or, finally, inhibition of basal, sham-feedin
or pentagastrin-stimulated acid secretion by cont by s.c. [D-Ala², methyl-Phe⁴-(O)-ol]-enkephalin (FK 33-
824) (431), or, finally, inhibition of basal, sham-feeding
or pentagastrin-stimulated acid secretion by continuous
i.v. infusion of [D-Ala², Met⁵]-enkephalin or pentagastrin-stimulated acid secretion by continuous
i.v. infusion of $[D-Ala^2$, Met⁵]-enkephalin (213). Simi-
larly, continuous i.v. infusion of both $[Met^5]$ -enkephalin
and $[D-Ala^2$, Met⁵]-enkephalin-amide impaired a or pentagastrin-stimulated acid secretion by continuou
i.v. infusion of [D-Ala², Met⁵]-enkephalin (213). Sim
larly, continuous i.v. infusion of both [Met⁵]-enkephali
and [D-Ala², Met⁵]-enkephalin-amide impaired a i.v. infusion of [D-Ala², Met
larly, continuous i.v. infusion
and [D-Ala², Met⁵]-enkephal
cretion in the conscious Rhee
gastric water loading (406).
b. THE EFFECT OF NALON

cretion in the conscious Rhesus monkey following intra-
gastric water loading (406).
b. THE EFFECT OF NALOXONE IN THE ABSENCE OF $e.g.$
EXOGENOUS OPIOIDS. A dual function of endogenous of topioids in the control of gastric gastric water loading (406).
b. THE EFFECT OF NALOXONE IN THE ABSENCE OF
EXOGENOUS OPIOIDS. A dual function of endogenous
opioids in the control of gastric acid secretion in man
could easily explain why naloxone, when admi b. THE EFFECT OF NALOXONE IN THE ABSENCE OF EXOGENOUS OPIOIDS. A dual function of endogenous opioids in the control of gastric acid secretion in man could easily explain why naloxone, when administered alone, had either no **EXOGENOUS OPIOIDS.** A dual function of endogenous opioids in the control of gastric acid secretion in man could easily explain why naloxone, when administered gas alone, had either no effect on acid secretion as stimulat popioids in the control of gastric acid secretion in man
could easily explain why naloxone, when administered g
alone, had either no effect on acid secretion as stimulated
by sham feeding (424), intragastric water load (4 alone, had either no effect on acid secretion as stimulated
by sham feeding (424), intragastric water load (406), and
pentagastrin (430, 412), or inhibited basal acid secretion
(101, 51, 213) and acid secretion stimulated by sham feeding (424), intragastric water load (406), and
pentagastrin (430, 412), or inhibited basal acid secretion
(101, 51, 213) and acid secretion stimulated by a meal
(101), by sham feeding (213), by pentagastrin, an pentagastrin (430, 412), or inhibited basal acid secretion

(101, 51, 213) and acid secretion stimulated by a meal

(101), by sham feeding (213), by pentagastrin, and by

histamine (51, 99). Both the negative and positive (101, 51, 213) and acid secretion stimulated by a meature (101), by sham feeding (213), by pentagastrin, and b histamine (51, 99). Both the negative and positive result with naloxone in the absence of exogenous opioids we (101), by sham feeding (213), by pentagastrin, and by
histamine (51, 99). Both the negative and positive results and
with naloxone in the absence of exogenous opioids were
obtained at different dose levels, which makes an histamine $(51, 99)$. Both the negative and positive results with naloxone in the absence of exogenous opioids were obtained at different dose levels, which makes an interpretation even more difficult. It might well be th with naloxone in the absence of exogenous opioids were
obtained at different dose levels, which makes an inter-
pretation even more difficult. It might well be that an
enhancement of acid secretion by endogenous opioids
pr obtained at different dose levels, which makes an interpretation even more difficult. It might well be that enhancement of acid secretion by endogenous opioid prevented any further enhancement by exogeno opioids, thereby p pretation even more difficult. It might well be that an enhancement of acid secretion by endogenous opioids prevented any further enhancement by exogenous opioids, thereby promoting the appearance of an inhibitory effect precation even more unit, it might went be that and
enhancement of acid secretion by endogenous opioids to speculate about a possible involvement of endogenous
opioids, thereby promoting the appearance of an inhibi-
tory e prevented any further enhancement by exogenopioids, thereby promoting the appearance of an inhitory effect at another site of action (see preceding sect IV B 4a). In that still hypothetical case, naloxone wo impair acid se opioids, thereby promoting the appearance of an inhiltory effect at another site of action (see preceding section IV B 4a). In that still hypothetical case, naloxone would, further, either antagonize or fail to antagonize tory effect at another site of action (see preceding section IV B 4a). In that still hypothetical case, naloxone would
impair acid secretion by blocking endogenous stimula-
tory opioid mechanisms. It would, further, either IV B 4a). In that still hypothetical case, naloxone would
impair acid secretion by blocking endogenous stimula-
tory opioid mechanisms. It would, further, either antag-
onize or fail to antagonize (431) acid inhibition by impair acid secretion by blocking endogenous stimulatory opioid mechanisms. It would, further, either antagonize or fail to antagonize (431) acid inhibition by exogenous opioids, depending on the balance between endogen tory opioid mechanisms. It would, further, either antagonize or fail to antagonize (431) acid inhibition by ex-
ogenous opioids, depending on the balance between en-
dogenous opioid stimulation and exogenous opioid ga
inhi

dogenous opioid stimulation and exogenous opioid
inhibition of acid secretion.
c. THE ROLE OF SOMATOSTATIN AND GASTRIN RE-
LEASE. As in the dog, contrasting opioid systems may
modulate somatostatin release in man. Morley e inhibition of acid secretion.

c. THE ROLE OF SOMATOSTATIN AND GASTRIN

LEASE. As in the dog, contrasting opioid systems in

modulate somatostatin release in man. Morley et

(296) found that hydrolyzed gluten produced a na c. THE ROLE OF SOMATOSTATIN AND GASTRIN RE-
LEASE. As in the dog, contrasting opioid systems may
modulate somatostatin release in man. Morley et al.
(296) found that hydrolyzed gluten produced a naloxone-
blockable increas LEASE. As in the dog, contrasting opioid systems may
modulate somatostatin release in man. Morley et al.
(296) found that hydrolyzed gluten produced a naloxone-
blockable increase in plasma somatostatin concentration
and modulate somatostatin release in man. Morley et al. (296) found that hydrolyzed gluten produced a naloxone
blockable increase in plasma somatostatin concentration
and ascribed this action to exorphins possibly release
from (296) found that hydrolyzed gluten produced a naloxo
blockable increase in plasma somatostatin concentrat
and ascribed this action to exorphins possibly relea
from gluten. By contrast, Schusdziarra et al. (393) de
onstrate blockable increase in plasma somatostatin concentration and ascribed this action to exorphins possibly release
from gluten. By contrast, Schusdziarra et al. (393) defonstrated an increase in postprandial plasma somat
stati and ascribed this action to exorphins possibly released
from gluten. By contrast, Schusdziarra et al. (393) dem-
onstrated an increase in postprandial plasma somato-
statin concentration upon naloxone administration,
which from gluten. By contrast, Schusdziarra et al. (393) demonstrated an increase in postprandial plasma somato-
statin concentration upon naloxone administration,
which suggests that endogenous opioids were operative
under the onstrated an increase in postprandial plasma somate statin concentration upon naloxone administratio which suggests that endogenous opioids were operatively under these conditions to inhibit somatostatin release Somatostat tion. ich suggests that endogenous opioids were operative
der these conditions to inhibit somatostatin release. I
matostatin is well known to depress gastric acid secre-
of i
n.
On the other hand, gastrin stimulates gastric acid

under these conditions to inhibit somatostatin release.
Somatostatin is well known to depress gastric acid secretion.
On the other hand, gastrin stimulates gastric acid
secretion. It should therefore be noted that morphine Somatostatin is well known to depress gastric acid secre-
tion.
On the other hand, gastrin stimulates gastric acid
precretion. It should therefore be noted that morphine
is (101) or $[D-Ala^2$, Met⁵]-enkephalin (213) enhan tion. $\begin{array}{c} \text{co} \\ \text{On the other hand, gastr is in the same set, and the number of the first set, and the$ secretion. It should therefore be noted that morphine (101) or [D-Ala², Met⁵]-enkephalin (213) enhanced the gastrin response to a meal and elevated serum gastrin concentration, while decreasing gastric acid secretion. secretion. It should therefore be noted that morphine is (101) or [D-Ala², Met⁵]-enkephalin (213) enhanced the mogastrin response to a meal and elevated serum gastrin an concentration, while decreasing gastric acid sec (101) or $[D-Ala^2$, Met⁵]-enkephalin (213) enhanced th
gastrin response to a meal and elevated serum gastric
concentration, while decreasing gastric acid secretion
Stimulation of acid secretion by gastrin was, under the

ER
tional significance. Feldman et al. (101) interpreted the
increase in serum gastrin concentration in terms of deincrease in serial and the seriangle increase in serum gastrin concentration in terms of de-
increase in serum gastrin concentration in terms of de-
layed gastric emptying caused by morphine, leading to a layed gastricance. Feldman et al. (101) interpreted the increase in serum gastrin concentration in terms of delayed gastric emptying caused by morphine, leading to a prolonged contact of the amino acid meal with antral provided a significance. Feldman et al. (101) interpreted the increase in serum gastrin concentration in terms of delayed gastric emptying caused by morphine, leading to a prolonged contact of the amino acid meal with antr tional significance. Feldman et al. (101) interpreted the increase in serum gastrin concentration in terms of delayed gastric emptying caused by morphine, leading to a prolonged contact of the amino acid meal with antral g increase in serum gastrin concentration in terms (layed gastric emptying caused by morphine, leadin prolonged contact of the amino acid meal with a gastrin cells. Naloxone alone, however, never afferum gastrin concentrati prolonged contact of the amir

gastrin cells. Naloxone alone,

serum gastrin concentrations (
 C. Pathophysiological Aspects

1. Potential opioid mechanis **1. Positial State External operator** alone, however, never affected
 1. Pathophysiological Aspects

1. Potential opioid mechanisms in gastroduodenal ul-

1. Potential opioid mechanisms in gastroduodenal ul-

action. It

b. THE EFFECT OF NALOXONE IN THE ABSENCE OF equipmental methods, see ref. 321) as well as physical stress,

b. THE EFFECT OF NALOXONE IN THE ABSENCE OF e.g., severe burns (351). In either case the pathogenesis
 EXOGENOUS alone, had either no effect on acid secretion as stimulated
by sham feeding (424), intragastric water load (406), and
pentagastrin (430, 412), or inhibited basal acid secretion
in gastrointestinal eicosanoids, or imbalanc **Example 101. cerations** (101, 99, 412, 213).
 C. Pathophysiological Aspects

1. Potential opioid mechanisms in gastroduodenal ul-

ceration. It is well known that gastroduodenal ulceration

can be produced by psycholo C. Pathophysiological Aspects
1. Potential opioid mechanisms in gastroduodenal
ceration. It is well known that gastroduodenal ulcerati
can be produced by psychological (for review of experimental methods, see ref. 321) as C. Pathophysiological Aspects
1. Potential opioid mechanisms in gastroduodenal ul-
ceration. It is well known that gastroduodenal ulceration
can be produced by psychological (for review of experi-
mental methods, see ref. 1. Potential opioid mechanisms in gastroduodenal ulceration. It is well known that gastroduodenal ulceration can be produced by psychological (for review of experimental methods, see ref. 321) as well as physical stress, ceration. It is well known that gastroduodenal ulceration
can be produced by psychological (for review of experi-
mental methods, see ref. 321) as well as physical stress,
e.g., severe burns (351). In either case the patho can be produced by psychological (for review of experimental methods, see ref. 321) as well as physical stress, e.g., severe burns (351). In either case the pathogenesis of the lesions is multifactorial and may involve a mental methods, see ref. 321) as well as physical stress,
e.g., severe burns (351). In either case the pathogenesis
of the lesions is multifactorial and may involve a decrease
in mucus and bicarbonate production, an increa e.g., severe burns (351). In either case the pathogenes of the lesions is multifactorial and may involve a decreas
in mucus and bicarbonate production, an increase is
gastric acid and pepsin secretion, hypotension, or loce of the lesions is multifactorial and may involve a decrease
in mucus and bicarbonate production, an increase in
gastric acid and pepsin secretion, hypotension, or local
blood stasis resulting in ischemic mucosal damage, al blood stasis resulting in ischemic mucosal damage, altergastric acid and pepsin secretion, hypotension, or local
blood stasis resulting in ischemic mucosal damage, alter-
ations in adrenal steroids and catecholamines as well as
in gastrointestinal eicosanoids, or imbalances bet blood stasis resulting in ischemic mucosal damage, alterations in adrenal steroids and catecholamines as well as
in gastrointestinal eicosanoids, or imbalances between
sympathetic and parasympathetic control mechanisms
and ations in adrenal steroids and catecholamines as well as
in gastrointestinal eicosanoids, or imbalances between
sympathetic and parasympathetic control mechanisms
and between gastrointestinal hormones. Since a detailed
ana in gastrointestinal eicosanoids, or imbalances between
sympathetic and parasympathetic control mechanisms
and between gastrointestinal hormones. Since a detailed
analysis of these factors is beyond the scope of this
articl sympathetic and parasympathetic control mechanisms

and between gastrointestinal hormones. Since a detailed

analysis of these factors is beyond the scope of this

article, the reader is referred to other sources $(74, 15$ analysis of these factors is beyond the scope of this article, the reader is referred to other sources $(74, 158, 116, 36, 37, 352, 283, 282, 210, 209, 351, 164)$. Opioids are known to affect several of these factors, so analysis of these factors is beyond the scope of this
article, the reader is referred to other sources (74, 158,
116, 36, 37, 352, 283, 282, 210, 209, 351, 164). Opioids are
known to affect several of these factors, so it article, the reader is referred to other sources (74, 158
116, 36, 37, 352, 283, 282, 210, 209, 351, 164). Opioids are
known to affect several of these factors, so it is tempting
to speculate about a possible involvement o 6, 36, 37, 352, 283, 282, 210, 209, 351, 164). Opioids are
nown to affect several of these factors, so it is tempting
speculate about a possible involvement of endogenous
ioids in the pathogenesis of gastroduodenal ulcerat known to affect several of these factors, so it is tempting
to speculate about a possible involvement of endogenous
opioids in the pathogenesis of gastroduodenal ulceration.
As with gastrointestinal motility and gastric ac

to speculate about a possible involvement of endogenous
opioids in the pathogenesis of gastroduodenal ulceration.
As with gastrointestinal motility and gastric acid se-
cretion, contrasting effects of opioids have been rep opioids in the pathogenesis of gastroduodenal ulceration.

As with gastrointestinal motility and gastric acid secretion, contrasting effects of opioids have been reported

by different authors. Selye (403) noted that morp As with gastrointestinal motility and gastric acid secretion, contrasting effects of opioids have been reported
by different authors. Selye (403) noted that morphine
was able to produce gastric mucosal lesions in the rat. cretion, contrasting effects of opioids have been reported
by different authors. Selye (403) noted that morphine
was able to produce gastric mucosal lesions in the rat. In
support of this, Ho et al. (170, 175) found that i by different authors. Selye (403) noted that morphine was able to produce gastric mucosal lesions in the rat. In support of this, Ho et al. (170, 175) found that i.p. morphine increased ulcer development in the stomach of was able to produce gastric mucosal lesions in the rat. In
support of this, Ho et al. (170, 175) found that i.p.
morphine increased ulcer development in the stomach of
the conscious rat with pyloric ligation but, at the sa support of this, Ho et al. (170, 175) found that i.p.
morphine increased ulcer development in the stomach of
the conscious rat with pyloric ligation but, at the same
time, also increased mucus production and decreased
gas morphine increased ulcer development in the stomac
the conscious rat with pyloric ligation but, at the s
time, also increased mucus production and decreas
gastric acid secretion. Thus, the ulcerogenic mechan
remained obscu the conscious rat with pyloric ligation but, at the sand time, also increased mucus production and decreases gastric acid secretion. Thus, the ulcerogenic mechanis remained obscure. Besides, hypoxaemia and hypercania, know time, also increased mucus production and decreased
gastric acid secretion. Thus, the ulcerogenic mechanism
remained obscure. Besides, hypoxaemia and hypercap-
nia, known side effects of morphine, did not cause ulcer-
atio gastric acid secretion. Thus, the ulcerogenic mechanism
remained obscure. Besides, hypoxaemia and hypercap-
nia, known side effects of morphine, did not cause ulcer-
ation per se (175). All three gastric effects of morphin remained obscure. Besides, hypoxaemia and hypercapnia, known side effects of morphine, did not cause ulcertation per se (175). All three gastric effects of morphine, however, were blocked by pretreatment with naloxone (170 ation per se (175). All three gastric effects of morphine, however, were blocked by pretreatment with naloxone (170, 174). Naloxone-precipitated morphine withdrawal had no influence on the severity of mucosal lesions (171) however, were blocked by pretreatment with naloxone however, were blocked by pretreatment with naloxone (170, 174). Naloxone-precipitated morphine withdrawal had no influence on the severity of mucosal lesions (171), but naloxone protected against indomethacin-induced ulcer (170, 174). Naloxone-precipitated morphine withdrawal
had no influence on the severity of mucosal lesions (171),
but naloxone protected against indomethacin-induced
ulcerations in the rat (461a) to indicate an ulcerogenic had no influence on the severity of mucosal lesions (171),
but naloxone protected against indomethacin-induced
ulcerations in the rat (461a) to indicate an ulcerogenic
function of endogenous opioids. The protective effect levels. cerations in the rat (461a) to indicate an ulcerogenic
nction of endogenous opioids. The protective effect of
loxone was accompanied by increased mucosal cAMP
vels.
Del Tacca et al. (83) confirmed the ulcerogenic effect
i.

function of endogenous opioids. The protective effect of naloxone was accompanied by increased mucosal cAMP
levels.
Del Tacca et al. (83) confirmed the ulcerogenic effect
of i.p. morphine in the pylorus ligated rat but fou naloxone was accompanied by increased mucosal cAMP
levels.
Del Tacca et al. (83) confirmed the ulcerogenic effect
of i.p. morphine in the pylorus ligated rat but found, in
contrast to Ho et al. (170, 175), a decrease in mu levels.

Del Tacca et al. (83) confirmed the ulcerogenic effect

of i.p. morphine in the pylorus ligated rat but found, in

contrast to Ho et al. (170, 175), a decrease in mucus

production using a similar technique. This Del Tacca et al. (83) confirmed the ulcerogenic effect
of i.p. morphine in the pylorus ligated rat but found, in
contrast to Ho et al. (170, 175), a decrease in mucus
production using a similar technique. This discrepancy
 of i.p. morphine in the pylorus ligated rat but found, in contrast to Ho et al. (170, 175), a decrease in mucus production using a similar technique. This discrepancy is still unresolved. Moreover, the ulcerogenic effect o contrast to Ho et al. (170, 175
production using a similar tech
is still unresolved. Moreover, t
morphine was weak, poorly do
antagonized by naloxone (83).
More compatible with increas production using a similar technique. This discrepancy
is still unresolved. Moreover, the ulcerogenic effect of
morphine was weak, poorly dose dependent, and not
antagonized by naloxone (83).
More compatible with increased is still unresolved. Moreover, the ulcerogenic effect of morphine was weak, poorly dose dependent, and not antagonized by naloxone (83).
More compatible with increased mucus and decreased acid secretion upon morphine admin

morphine was weak, poorly dose dependent, and not
antagonized by naloxone (83).
More compatible with increased mucus and decreased
acid secretion upon morphine administration are data
obtained in the conscious rat (105, 13

opioids and contract of GASTROINTES
found, after i.p. administration of morphine or of a stable
enkephalin analogue (FK 33-824), a reduction in the ex-
ulcer index following cold restraint stress. The effect of op-OPIOIDS AND CONTROL OF GASTROINTE
found, after i.p. administration of morphine or of a stable
enkephalin analogue (FK 33-824), a reduction in the
ulcer index following cold restraint stress. The effect of
morphine was anta found, after i.p. administration of morphine or of a sta
enkephalin analogue (FK 33-824), a reduction in t
ulcer index following cold restraint stress. The effect
morphine was antagonized by naloxone (138). A prot
tive opi found, after i.p. administration of morphine or of a stable
enkephalin analogue (FK 33-824), a reduction in the
ulcer index following cold restraint stress. The effect of
morphine was antagonized by naloxone (138). A prote enkephalin analogue (FK 33-824), a reduction in the exercise ulcer index following cold restraint stress. The effect of opprophine was antagonized by naloxone (138). A protective opioid effect against HCl- or NaOH-induced morphine was antagonized by naloxone (138). A protective opioid effect against HCl- or NaOH-induced lesions may be mediated by mucosal prostaglandins since it was impaired by indomethacin (105a). In the rat, morphine suppr tive opioid effect against HCl- or NaOH-induced lesions

tive opioid effect against HCl- or NaOH-induced lesions
may be mediated by mucosal prostaglandins since it was
impaired by indomethacin (105a).
In the rat, morphine suppressed acid secretion stimu-
lated by cold restraint may be mediated by mucosal prostaglandins since it was
impaired by indomethacin (105a). like
In the rat, morphine suppressed acid secretion stimu-
lated by cold restraint similarly to dexamethasone (10). pr
Since beta-endo impaired by indomethacin (105a).

In the rat, morphine suppressed acid secretion stimulated by cold restraint similarly to dexamethasone (10).

Since beta-endorphin is coreleased with ACTH from the

rat pituitary during st In the rat, morphine suppressed acid secretion stimulated by cold restraint similarly to dexamethasone (10). P Since beta-endorphin is coreleased with ACTH from the stress riduced release may be involved in stress-induced lated by cold restraint similarly to dexamethasone (10). I
Since beta-endorphin is coreleased with ACTH from the
rat pituitary during stress (150) and endogenous opioids
may be involved in stress-induced corticosteroid rel Since beta-endorphin is coreleased with ACTH from the rat pituitary during stress (150) and endogenous opioids may be involved in stress-induced corticosteroid release in the mouse (131), the mechanism of opioid inhibition rat pituitary during stress (150) and endogenous opioi
may be involved in stress-induced corticosteroid relea
in the mouse (131), the mechanism of opioid inhibiti
of stress ulceration may be indirect. On the other har
redu may be involved in stress-induced corticosteroid release find
in the mouse (131), the mechanism of opioid inhibition con
of stress ulceration may be indirect. On the other hand, resp
reduction of stress-induced gastric le in the mouse (131), the mechanism of opioid inhibition concerns of stress ulceration may be indirect. On the other hand, respectively reduction of stress-induced gastric lesions by the antag-
endint naloxone was not assoc reduction of stress-induced gastric lesions by the antagonist naloxone was not associated with any change in serum corticosteroids in rats (75a). In conclusion, two contrasting opioid systems appear to modify the develreduction of stress-induced gastric lesions by the antaconist naloxone was not associated with any change serum corticosteroids in rats (75a). In conclusion, to contrasting opioid systems appear to modify the devopment of tions.

contrasting opioid systems appear to modify the devopment of mucosal lesions under still unknown con
tions.
2. Peripheral versus central opioid effects. Since b
i.p. administration of morphine methyliodide, a quater-
nary opment of mucosal lesions under still unknown condi-
tions.
2. Peripheral versus central opioid effects. Since both
i.p. administration of morphine methyliodide, a quater-
nary derivative which does not cross the blood-bra ions.

2. Peripheral versus central opioid effects. Since both

i.p. administration of morphine methyliodide, a quater-

nary derivative which does not cross the blood-brain

barrier, and i.c.v. injection of morphine or of 2. Peripheral versus central opioid effects. Since both i.p. administration of morphine methyliodide, a quaternary derivative which does not cross the blood-brain phenometric, and i.e.v. injection of morphine or of enkepha i.p. administration of morphine methyliodide, a quater-
nary derivative which does not cross the blood-brain phy-
barrier, and i.c.v. injection of morphine or of enkephalin his
analogues reduced the intensity of stress ul nary derivative which does not cross the blood-brain
barrier, and i.c.v. injection of morphine or of enkephalin
analogues reduced the intensity of stress ulcers in the
rat in a dose-dependent manner, both a peripheral and
 barrier, and i.c.v. injection of morphine or of enkeph
analogues reduced the intensity of stress ulcers in
rat in a dose-dependent manner, both a peripheral
central antiulcerogenic mode of opioid action was
gested (295, 10 analogues reduced the intensity of stress ulcers in the
rat in a dose-dependent manner, both a peripheral and
central antiulcerogenic mode of opioid action was sug-
gested (295, 105, 151). This is in line with naloxone-
b rat in a dose-dependent manner, both a peripheral and central antiulcerogenic mode of opioid action was suggested (295, 105, 151). This is in line with naloxone blockable inhibition of ulcer development, along with acid se central antiulcerogenic mode of opioid action was suggested (295, 105, 151). This is in line with naloxone-
blockable inhibition of ulcer development, along with
acid secretion in the pylorus ligated rat, by i.c.v. mor-
ph blockable inhibition of ulcer development, along with acid secretion in the pylorus ligated rat, by i.c.v. morphine (83). Endogenous opioids may physiologically exert antiulcerogenic effects within the CNS, since i.c.v. ad blockable inhibition of ulcer development, along with
acid secretion in the pylorus ligated rat, by i.c.v. mor-
phine (83). Endogenous opioids may physiologically exert
antiulcerogenic effects within the CNS, since i.c.v. acid secretion
phine (83). En
antiulcerogeni
ministration c
ulcers (151). By contrast ine (83). Endogenous opioids may physiologically exitulcerogenic effects within the CNS, since i.c.v.
inistration of naloxone alone enhanced stress-ind
cers (151).
By contrast, though ineffective upon i.c.v. admini
on, the

antiulcerogenic effects within the CNS, since i.c.v. administration of naloxone alone enhanced stress-induced
ulcers (151).
By contrast, though ineffective upon i.c.v. administra-
tion, the antagonist naltrexone reduced st ministration of naloxone alone enhanced stress-induced
ulcers (151).
By contrast, though ineffective upon i.c.v. administra-
tion, the antagonist naltrexone reduced stress ulcer de-
velopment after peripheral administratio ulcers (151).
By contrast, though ineffective upon i.c.v. administra-
tion, the antagonist naltrexone reduced stress ulcer de-
velopment after peripheral administration to the rat
(295). Morley et al. (295) suggested that By contrast, though ineffective upon i.c.v. administration, the antagonist naltrexone reduced stress ulcer development after peripheral administration to the rat (295). Morley et al. (295) suggested that endogenous opioid tion, the antagonist naltrexone reduced stress ulcer development after peripheral administration to the rat (295). Morley et al. (295) suggested that endogenous opioids might play a role in the pathogenesis of stress ulcer velopment after peripheral administration to the rat (295). Morley et al. (295) suggested that endogenous opioids might play a role in the pathogenesis of stress ulceration at a peripheral site of action. When naltrexone opioids might play a role in the pathogenesis of stress
ulceration at a peripheral site of action. When naltrexone
also enhanced mucosal blood flow, the authors concluded
that endogenous opioids might produce their periphe opioids might play a role in the pathogenesis of stres
ulceration at a peripheral site of action. When naltrexon
also enhanced mucosal blood flow, the authors conclude
that endogenous opioids might produce their periphera
 ulceration at a peripheral site of action. When naltrexone
also enhanced mucosal blood flow, the authors concluded
that endogenous opioids might produce their peripheral
ulcerogenic effect by causing vascular congestion. C also enhanced mucosal blood flow, the authors concluded
that endogenous opioids might produce their peripheral D .
ulcerogenic effect by causing vascular congestion. Con-
sistent with the antiulcerogenic effect of naltre that endogenous opioids independent offect by causaint with the antiulo (295), i.p. morphine enhappylorus-ligated rat (83). In summary, opioids mathematic cerogenic effect by causing vascular congestion. Constent with the antiulcerogenic effect of naltrexone 195), i.p. morphine enhanced ulcer development in the vlorus-ligated rat (83).
In summary, opioids may exert a dual ac

sistent with the antiulcerogenic effect of naltrexone (295), i.p. morphine enhanced ulcer development in the pylorus-ligated rat (83).
In summary, opioids may exert a dual action on stress ulcer formation, which only parti (295), i.p. morphine enhanced ulcer development in the pylorus-ligated rat (83) .
In summary, opioids may exert a dual action on stress ulcer formation, which only partially coincides with their impact on gastric acid se pylorus-ligated rat (83).
In summary, opioids may exert a dual as
ulcer formation, which only partially coinci
impact on gastric acid secretion. Both action
may be localized centrally and peripherally
3. The activity state In summary, opioids may exert a dual action on strecer formation, which only partially coincides with the pact on gastric acid secretion. Both action componently be localized centrally and peripherally.
3. The activity sta

ulcer formation, which only partially coincides with the
impact on gastric acid secretion. Both action componen
may be localized centrally and peripherally.
3. The activity state of endogenous opioids in ulce
related condi impact on gastric acid secretion. Both action components
may be localized centrally and peripherally.
3. The activity state of endogenous opioids in ulcer-
related conditions in man. Interestingly, duodenal acidi-
ficatio may be localized centrally and peripherally. \therefore in \therefore 3. The activity state of endogenous opioids in ulcer-
related conditions in man. Interestingly, duodenal acidi-
fication (as well as tetragastrin or a test meal) 3. The activity state of endogenous opioids in ulcer-
related conditions in man. Interestingly, duodenal acidination (as well as tetragastrin or a test meal) increase-
plasma beta-endorphin-like immunoreactivity in ma-
(2 related conditions in man. Interestingly, duodenal acidification (as well as tetragastrin or a test meal) increased plasma beta-endorphin-like immunoreactivity in man (276). The same group demonstrated release of beta-endo

found, after i.p. administration of morphine or of a stable mucosa in vitro upon acidification (277). Simple acidic
enkephalin analogue (FK 33-824), a reduction in the extraction cannot be ruled out in the latter case, as
 ESTINAL MOTILITY AND SECRETION 145
mucosa in vitro upon acidification (277). Simple acidic
extraction cannot be ruled out in the latter case, as ESTINAL MOTILITY AND SECRETION 145
mucosa in vitro upon acidification (277). Simple acidic
extraction cannot be ruled out in the latter case, as
opposed to the in vivo study. Nevertheless, these findings TESTINAL MOTILITY AND SECRETION 145
mucosa in vitro upon acidification (277). Simple acidic
extraction cannot be ruled out in the latter case, as
opposed to the in vivo study. Nevertheless, these findings
seem to be at var mucosa in vitro upon acidification (277). Simple acidic extraction cannot be ruled out in the latter case, as opposed to the in vivo study. Nevertheless, these findings seem to be at variance with the observation by Kuhn e mucosa in vitro upon acidification (277). Simple acidic extraction cannot be ruled out in the latter case, as opposed to the in vivo study. Nevertheless, these findings seem to be at variance with the observation by Kuhn e extraction cannot be ruled out in the latter copposed to the in vivo study. Nevertheless, these fi
seem to be at variance with the observation by K
al. (246) that patients with (mostly) duodenal ulc
ease showed a decreased opposed to the in vivo study. Nevertheless, these findings
seem to be at variance with the observation by Kuhn et
al. (246) that patients with (mostly) duodenal ulcer dis-
ease showed a decreased plasma level of beta-endor al. (246) that patients with (mostly) duodenal ulcer dis-
ease showed a decreased plasma level of beta-endorphin-
like immunoreactivity compared with healthy subjects.
The duodenum of duodenal ulcer patients, however, is
p al. (246) that patients with (mostly) duodenal ulcer disease showed a decreased plasma level of beta-endorphin-
like immunoreactivity compared with healthy subjects.
The duodenum of duodenal ulcer patients, however, is
pro ease showed a decreased plasma level of beta-endorphin
like immunoreactivity compared with healthy subject:
The duodenum of duodenal ulcer patients, however, i
probably exposed to an excess of gastric acid. Moreove
stress like immunoreactivity compared with healthy subjects.
The duodenum of duodenal ulcer patients, however, is
probably exposed to an excess of gastric acid. Moreover,
stress increases rather than decreases the release of beta The duodenum of duodenal ulcer patients, however, is
probably exposed to an excess of gastric acid. Moreover,
stress increases rather than decreases the release of beta-
endorphin from the pituitary (150). These discrepant probably exposed to an excess of gastric acid. Moreover,
stress increases rather than decreases the release of beta-
endorphin from the pituitary (150). These discrepant
findings deserve further research. Stenquist et al. stress increases rather than decreases the release of beta-
endorphin from the pituitary (150). These discrepant
findings deserve further research. Stenquist et al. (424)
concluded from the failure of naloxone to affect th endorphin from the pituitary (150). These discrepant
findings deserve further research. Stenquist et al. (424)
concluded from the failure of naloxone to affect the acid
response to sham feeding in duodenal ulcer patients findings deserve further research
concluded from the failure of nalc
response to sham feeding in duod
endogenous opioid systems are un
these pathophysiological events.
4. Potential role of opioid-hista Included from the failure of naloxone to affect the acceptome is the asponse to sham feeding in duodenal ulcer patients the dogenous opioid systems are unlikely to participate is ese pathophysiological events.
4. Potential response to sham feeding in duodenal ulcer patients that
endogenous opioid systems are unlikely to participate in
these pathophysiological events.
4. Potential role of opioid-histamine interactions. His-
tamine plays a key

2. Peripheral versus central opioid effects. Since both constraining interactions. His contrasting opioid systems appear to modify the devel-

tamine plays a key role in the physiological control of

opment of mucosal le endogenous opioid systems are unlikely to participate in
these pathophysiological events.
4. Potential role of opioid-histamine interactions. His-
tamine plays a key role in the physiological control of
gastric acid secret these pathophysiological events.
4. Potential role of opioid-histamine interactions. His-
tamine plays a key role in the physiological control of
gastric acid secretion and may, thus, be either a causative
or a sequential 4. Potential role of opioid-histamine interactions. Histamine plays a key role in the physiological control of gastric acid secretion and may, thus, be either a causative or a sequential factor in ulcer development (14, 32 tamine plays a key role in the physiological control gastric acid secretion and may, thus, be either a causat or a sequential factor in ulcer development (14, 32 Gastrointestinal mast cells, which are storage sites histami gastric acid secretion and may, thus, be either a causative
or a sequential factor in ulcer development (14, 322).
Gastrointestinal mast cells, which are storage sites for
histamine in man, are affected by a variety of pat or a sequential factor in ulcer development (14, 322).
Gastrointestinal mast cells, which are storage sites for
histamine in man, are affected by a variety of patho-
physiological events (252). In addition, both exogenous
 Gastrointestinal mast cells, which are storage sites for
histamine in man, are affected by a variety of patho-
physiological events (252). In addition, both exogenous
histamine (353, 92, 437) and pharmacologically released histamine in man, are affected by a variety of patho-
physiological events (252). In addition, both exogenous
histamine (353, 92, 437) and pharmacologically released
histamine in the rat (438) are able to produce duodenal
 physiological events (252). In addition, both exogenous
histamine (353, 92, 437) and pharmacologically released
histamine in the rat (438) are able to produce duodenal
or gastric mucosal lesions along with acid secretion. histamine (353, 92, 437) and pharmacologically released
histamine in the rat (438) are able to produce duodenal
or gastric mucosal lesions along with acid secretion. Since
opioids have been found to sensitize the parietal histamine in the rat (438) are able to produce duodenal
or gastric mucosal lesions along with acid secretion. Since
opioids have been found to sensitize the parietal cell to
histamine, and since endogenous opioids may exe or gastric mucosal lesions along with acid secretion.
opioids have been found to sensitize the parietal c
histamine, and since endogenous opioids may ex
similar role within the mucosa (237), opioids intrin
the gastric muco opioids have been found to sensitize the parietal cell t
histamine, and since endogenous opioids may exert
similar role within the mucosa (237), opioids intrinsic t
the gastric mucosa may participate in the pathophysiol
og histamine, and since endogenous opioids may exert a
similar role within the mucosa (237), opioids intrinsic to
the gastric mucosa may participate in the pathophysiol-
ogy of gastrointestinal ulceration. This hypothesis, ho similar role within the mucosa (237), opioids intrinsic to
the gastric mucosa may participate in the pathophysiol-
ogy of gastrointestinal ulceration. This hypothesis, how-
ever, requires further elucidation. A seasonal pe the gastric mucosa may participate in the pathophysiology of gastrointestinal ulceration. This hypothesis, how-
ever, requires further elucidation. A seasonal periodicity
of peptic ulcer disease (316) may correspond to pot ogy of gastrointestinal ulceration. This hypothesis, how-
ever, requires further elucidation. A seasonal periodicity
of peptic ulcer disease (316) may correspond to potential
seasonal variations in the activity of opioid (ever, requires further elucidation. A seasonal periodicity
of peptic ulcer disease (316) may correspond to potential
seasonal variations in the activity of opioid (237) as well
as other neuromodulator systems. Again, of peptic ulcer disease (316) may correspond to poten
seasonal variations in the activity of opioid (237) as
as other neuromodulator systems. Again, more wor
needed in this field. Halter et al. (153) demonstrate
higher sen seasonal variations in the activity of opioid (237) as well
as other neuromodulator systems. Again, more work is
needed in this field. Halter et al. (153) demonstrated a
higher sensitivity of duodenal ulcer patients to pen as other neuromodulator systems. Again, more work is
needed in this field. Halter et al. (153) demonstrated a
higher sensitivity of duodenal ulcer patients to pentagas-
trin as an acid stimulant, compared with controls. It needed in this field. Halter et al. (153) demonstrated a
higher sensitivity of duodenal ulcer patients to pentagas-
trin as an acid stimulant, compared with controls. It is
not known whether endogenous opioids modulate th higher sensitivity of du
trin as an acid stimula
not known whether e
susceptibility of the pa
that against histamine
 D Conclusions not known whether endogenous opioids modulate the
susceptibility of the parietal cell to gastrin similarly to
that against histamine.
D. Conclusions
In vitro studies in both guinea pig and rat isolated In example it is a seeptibility of the parietal cell to gastrin similarly to
at against histamine.
In vitro studies in both guinea pig and rat isolated
prietal cells demonstrate functional opioid receptors

partial cells demonstrate functional opioid receptors
which enhance stimulated acid secretion. The effect is
which enhance stimulated acid secretion. The effect is D. Conclusions
In vitro studies in both guinea pig and rat isolated
parietal cells demonstrate functional opioid receptors
which enhance stimulated acid secretion. The effect is
small and modulatory. It probably correspond D. Conclusions
In vitro studies in both guinea pig and rat isolated
parietal cells demonstrate functional opioid receptors
which enhance stimulated acid secretion. The effect is
small and modulatory. It probably correspond In vitro studies in both guinea pig and rat isolal parietal cells demonstrate functional opioid recep which enhance stimulated acid secretion. The effecs and and modulatory. It probably corresponds to a steneor cific effec parietal cells demonstrate functional opioid recep
which enhance stimulated acid secretion. The effect
small and modulatory. It probably corresponds to a s
ilar role of mucosal opioids as judged from the stereor
cific effe which enhance stimulated acid secretion. The effect is
small and modulatory. It probably corresponds to a sim-
ilar role of mucosal opioids as judged from the stereospe-
cific effect of the opioid antagonist naloxone alone

small and modulatory. It probably corresponds to a similar role of mucosal opioids as judged from the stereospecific effect of the opioid antagonist naloxone alone.
Superimposed on this excitatory opioid system is an inhib ilar role of mucosal opioids as judged from the stereospecific effect of the opioid antagonist naloxone alone.
Superimposed on this excitatory opioid system is an inhibitory one, which obviously predominates under in vivo cific effect of the opioid antagonist naloxone alone.
Superimposed on this excitatory opioid system is an
inhibitory one, which obviously predominates under in
vivo conditions in the rat. Opioid inhibition of gastric
acid Superimposed on this excitatory opioid system is an inhibitory one, which obviously predominates under in vivo conditions in the rat. Opioid inhibition of gastric acid secretion has central and peripheral components and pr inhibitory one, which obviously predominates under in
vivo conditions in the rat. Opioid inhibition of gastric
acid secretion has central and peripheral components
and probably involves, at least partially, an inhibitory
m vivo conditions in the rat. Opioid inhibition of gas
acid secretion has central and peripheral compone
and probably involves, at least partially, an inhibit
modulation of both vagal acetylcholine release and
postsynaptic a acid secretion has central and peripheral components
and probably involves, at least partially, an inhibitory
modulation of both vagal acetylcholine release and its
postsynaptic action. Little is known about the differen-

146
opioid mechanisms. In the rat, both central and perip
eral opioid mu-receptors inhibit, while peripheral kapp 146
opioid mechanisms. In the rat, both central and perip
eral opioid mu-receptors inhibit, while peripheral kapp
receptors stimulate gastric acid secretion. No role KROME
popioid mechanisms. In the rat, both central and periph-
seral opioid mu-receptors inhibit, while peripheral kappa-
receptors stimulate gastric acid secretion. No role of bi
delta-receptors was detected. In the dog, opioid mechanisms. In the rat, both central and peripleral opioid mu-receptors inhibit, while peripheral kappreceptors stimulate gastric acid secretion. No role delta-receptors was detected. In the dog, however, available opioid mechanisms. In the rat, both central and periph-
eral opioid mu-receptors inhibit, while peripheral kappa-
receptors stimulate gastric acid secretion. No role of bloc
delta-receptors was detected. In the dog, howeve eral opioid mu-receptors inhibit, while peripheral kappa
receptors stimulate gastric acid secretion. No role of
delta-receptors was detected. In the dog, however, avail
able data suggest inhibition by delta- and stimulatio receptors stimulate gastric acid se
delta-receptors was detected. In the
able data suggest inhibition by delta
mu-receptors, the former probably l
The issue requires further attention.
Complex opioid actions in the dog lta-receptors was detected. In the dog, however, avail-
le data suggest inhibition by delta- and stimulation by
u-receptors, the former probably located peripherally.
pe issue requires further attention.
Complex opioid act

able data suggest inhibition by delta- and stimulation by
mu-receptors, the former probably located peripherally.
The issue requires further attention.
Complex opioid actions in the dog and in man support
the notion of sup mu-receptors, the former probably located peripherally.
The issue requires further attention.
Complex opioid actions in the dog and in man support
the notion of superimposition of functionally contrasting
opioid systems in The issue requires further attention.
Complex opioid actions in the dog and in man support
the notion of superimposition of functionally contrasting
opioid systems in the control of acid secretion. Current
investigations, Complex opioid actions in the dog and in man support tall
the notion of superimposition of functionally contrasting me
opioid systems in the control of acid secretion. Current
investigations, in this respect, confirm and e the notion of superimposition of functionally contrasting me
opioid systems in the control of acid secretion. Current
investigations, in this respect, confirm and extend earlier gas
reports on a transient inhibition of aci opioid systems in the control of acid secretion. Current
investigations, in this respect, confirm and extend earlier
reports on a transient inhibition of acid secretion by high
doses followed by stimulation which can insta investigations, in this respect, confirm and extend earlier game
reports on a transient inhibition of acid secretion by high game
doses followed by stimulation which can instantly be Sin
seen after lower opioid doses in do reports on a transient inhibition of acid secretion by high doses followed by stimulation which can instantly be seen after lower opioid doses in dog and man. As opposed to the rat, however, the predominant opioid effect i doses followed by stimulation which can instantly be Sin
seen after lower opioid doses in dog and man. As opposed sec
to the rat, however, the predominant opioid effect in the oph
dog and in man appears to be stimulation, seen after fower option doses in dog and man. As opposed
to the rat, however, the predominant opioid effect in the
dog and in man appears to be stimulation, not inhibition.
An opioid-effected increase in mucosal blood flow dog and in man appears to be stimulation, not inhibition
An opioid-effected increase in mucosal blood flow may
contribute to the enhancement of acid secretion if stim
ulated exogenously. This may be mediated by an in
creas An opioid-effected increase in mucosal blood flow may par
contribute to the enhancement of acid secretion if stim-
ulated exogenously. This may be mediated by an in-
creased supply of the stimulant to the mucosa. Moreover ulated exogenously. This may be mediated by an increased supply of the stimulant to the mucosa. Moreover, a cooperative interaction between opioid receptors and secretagogue receptors seems probable. ated exogenously. This may be mediated by an in-
eased supply of the stimulant to the mucosa. Moreover,
cooperative interaction between opioid receptors and
cretagogue receptors seems probable.
Apparent discrepancies betwe

creased supply of the stimulant to the mucosa. Moreover,

a cooperative interaction between opioid receptors and $\overline{A} \overline{S}$

secretagogue receptors seems probable.

Apparent discrepancies between data from different
 a cooperative interaction between opioid receptors and
secretagogue receptors seems probable.
Apparent discrepancies between data from different
laboratories may be best explained by differences in
experimental conditions. secretagogue receptors seems probable.

Apparent discrepancies between data from different

laboratories may be best explained by differences in

experimental conditions. These include anesthesia ver-

sus consciousness, i Apparent discrepancies between data from different
laboratories may be best explained by differences in
experimental conditions. These include anesthesia ver-
sus consciousness, innervated main stomach versus de-
nervated laboratories may be best explained by differences in
experimental conditions. These include anesthesia versus
sus consciousness, innervated main stomach versus de-
nervated Heidenhain pouch, basal secretion versus ex-
ogen experimental conditions. These include anesthesia versus density consciousness, innervated main stomach versus density are nervated Heidenhain pouch, basal secretion versus ex-
ogenously stimulated secretion, different st sus consciousness, innervated main stomach versus derivated Heidenhain pouch, basal secretion versus expending
ogenously stimulated secretion, different stimulants and
ose levels, central versus peripheral stimulation, acc nervated Heidenhain pouch, basal secretion versus ex-
ogenously stimulated secretion, different stimulants and
dose levels, central versus peripheral stimulation, access
of the opioid to the CNS versus foreclosure by the b ogenously stimulated secretion, different stimulants and
dose levels, central versus peripheral stimulation, access
of the opioid to the CNS versus foreclosure by the blood-
functional states of endogenous opioid systems dose levels, central versus peripheral stimulation, accession of the opioid to the CNS versus foreclosure by the blood brain barrier, intact versus dissected antrum, and various functional states of endogenous opioid syste of the opioid to the CNS versus foreclosure by the blood-
brain barrier, intact versus dissected antrum, and various
functional states of endogenous opioid systems on which
the effects of exogenous opioids may be superimpo functional states of endogenous opioid systems on which
the effects of exogenous opioids may be superimposed.
The theory of superimposition of contrasting opioid ef-
fects gains strong support from the observation of si-
m functional states of endogenous opioid systems on which
the effects of exogenous opioids may be superimposed.
The theory of superimposition of contrasting opioid ef-
fects gains strong support from the observation of si-
m the effects of exogenous opioids may be superimpose
The theory of superimposition of contrasting opioid ϵ
fects gains strong support from the observation of ϵ
multaneous enhancement of acid secretion in the d
nervate The theory of superimposition of contrasting opioid effects gains strong support from the observation of simultaneous enhancement of acid secretion in the denervated Heidenhain pouch and inhibition in the innervated stoma fects gains strong support from the observation of si-
multaneous enhancement of acid secretion in the de-
nervated Heidenhain pouch and inhibition in the inner-
vated stomach by enkephalin in the same dog. The
stimulatory multaneous enhance
nervated Heidenhain
vated stomach by e
stimulatory effect of
to release of gastrin.
Inhibition of acid s rvated Heidenhain pouch and inhibition in the inner-
ted stomach by enkephalin in the same dog. The
mulatory effect of opioids does not appear to be due
release of gastrin.
Inhibition of acid secretion by naloxone alone h

vated stomach by enkephalin in the same dog. The
stimulatory effect of opioids does not appear to be due
to release of gastrin.
Inhibition of acid secretion by naloxone alone has been
demonstrated in the dog in vivo. Since stimulatory effect of opioids does not appear to be due
to release of gastrin. The
to release of gastrin. The
demonstrated in the dog in vivo. Since opioid agonists larly
predominantly stimulate acid secretion in the dog i to release of gastrin.

Inhibition of acid secretion by naloxone alone has be

demonstrated in the dog in vivo. Since opioid agonis

predominantly stimulate acid secretion in the dog

vivo, inhibition by naloxone alone sug Inhibition of acid secretion by naloxone alone has been
demonstrated in the dog in vivo. Since opioid agonists
predominantly stimulate acid secretion in the dog in
vivo, inhibition by naloxone alone suggests that endog-
e demonstrated in the dog in vivo. Since opioid agonis
predominantly stimulate acid secretion in the dog
vivo, inhibition by naloxone alone suggests that endo
enous opioids operate in a similar manner. The situatie
is compar predominantly stimulate acid secretion in the dog in oxivo, inhibition by naloxone alone suggests that endog-
enous opioids operate in a similar manner. The situation age
is comparable in man. On the other hand, since exo vivo, inhibition by naloxone alone suggests that endogenous opioids operate in a similar manner. The situation is comparable in man. On the other hand, since exogenous opioids predominantly inhibit acid secretion in the r enous opioids operate in a similar mainter. The situation
is comparable in man. On the other hand, since exoge-
mous opioids predominantly inhibit acid secretion in the
rat in vivo, stimulation by naloxone alone again poin us opioids predominantly inhibit acid secretion in the
t in vivo, stimulation by naloxone alone again points
a functional role of endogenous opioids similar to the
tion of exogenous opioids in this species.
Development of

rat in vivo, stimulation by naloxone alone again points
to a functional role of endogenous opioids similar to the
rent of exogenous opioids in this species.
the
Development of gastroduodenal ulceration under dif-
to the fe to a functional role of endogenous opioids similar to the action of exogenous opioids in this species.

Development of gastroduodenal ulceration under different conditions is likewise affected by opioids in a complex fashi action of exogenous opioids in this species.
Development of gastroduodenal ulceration under different conditions is likewise affected by opioids in a
complex fashion, yielding apparently contradictory re-
sults. In additio Development of gastroduodenal ulceration under dif-
ferent conditions is likewise affected by opioids in a
complex fashion, yielding apparently contradictory re-
sults. In addition to a peripheral dual effect, a central fe ferent conditions is likewise affected by opioids in a at a complex fashion, yielding apparently contradictory re-
sults. In addition to a peripheral dual effect, a central fect
action may be present with both an ulcerogen

ER
sound basis for relating those effects to defined mech
nisms of action, like changes in acid secretion or muco nisms of action, like changes effects to defined mechanisms of action, like changes in acid secretion or mucosal
blood flow. As discussed for opioid effects on gastric acid ER
sound basis for relating those effects to defined mecha-
nisms of action, like changes in acid secretion or mucosal
blood flow. As discussed for opioid effects on gastric acid
secretion, the discrepancies with respect t sound basis for relating those effects to defined mechanisms of action, like changes in acid secretion or mucoss blood flow. As discussed for opioid effects on gastric acise
cretion, the discrepancies with respect to opioi sound basis for relating those effects to defined mechanisms of action, like changes in acid secretion or mucosal
blood flow. As discussed for opioid effects on gastric acid
secretion, the discrepancies with respect to opi nisms of action, like changes in acid secretion or mucosal
blood flow. As discussed for opioid effects on gastric acid
secretion, the discrepancies with respect to opioid influ-
ences on mucosal ulceration may be caused by blood flow. As discussed for opioid effects on gastric secretion, the discrepancies with respect to opioid in ences on mucosal ulceration may be caused by differexperimental conditions. This refers particularly to chemical secretion, the discrepancies with respect to opioid influences on mucosal ulceration may be caused by differing experimental conditions. This refers particularly to the chemical stimulants and procedures used to experiment mechanisms. perimental conditions. This refers particularly to the emical stimulants and procedures used to experimen-
lly induce ulceration via central and/or peripheral
echanisms.
So far, no correlation has been established between

tally induce ulceration via central and/or peripheral
mechanisms.
So far, no correlation has been established between
gastroduodenal ulceration in man and disturbances of
gastrointestinal opioids or systemically released o tally induce ulceration via central and/or peripheral
mechanisms.
So far, no correlation has been established between
gastroduodenal ulceration in man and disturbances of
gastrointestinal opioids or systemically released o mechanisms.
So far, no correlation has been established between
gastroduodenal ulceration in man and disturbances of
gastrointestinal opioids or systemically released opioids.
Since histamine plays a key role in the contro So far, no correlation has been established betwee
gastroduodenal ulceration in man and disturbances of
gastrointestinal opioids or systemically released opioid
Since histamine plays a key role in the control of aci
secret gastroduodenal ulceration in man and disturbances of gastrointestinal opioids or systemically released opioids.
Since histamine plays a key role in the control of acid secretion and may produce mucosal lesions under pathop gastrointestinal opioids or systemically released opioids.
Since histamine plays a key role in the control of acid
secretion and may produce mucosal lesions under path-
ophysiological conditions, an enhancement of this his Since histamine plays a key role in the
secretion and may produce mucosal lesi
ophysiological conditions, an enhancen
tamine-stimulated acid secretion in gu
parietal cells deserves further attention. **IMPLE OPINTS INTERT CONTRETT:** The Role of Opioids in the Control of Intestinal

V. The Role of Opioids in the Control of Intestinal

Water and Electrolyte Secretion and Absorption **Example 3 and rational and act and the Secretion in guinea pig and rational varietal cells deserves further attention.

Electrolyte Secretion and Absorption**
 Water and Electrolyte Secretion and Absorption
 Computer S

**A Small Interior Christian Interior Interior Interior V. The Role of Opioids in the Control of Intestina
** *A Small Intestine: Guinea Pig; Rat; Rabbit; Dog; Pig;***
** *A Man***
** *A Man*

and Man

Vater and Electrolyte Secretion and Absorption
Small Intestine: Guinea Pig; Rat; Rabbit; Dog; Pig;
d Man
Evidence has accumulated in the past that opioids
mulate, as an important component of their antidi-A Small Intestine: Guinea Pig; Rat; Rabbit; Dog; Pig;
and Man
Evidence has accumulated in the past that opio
stimulate, as an important component of their anti
arrheal action, the net absorption of water and elect. A small intestine. Galled Γ is, that, habout, D og, Γ is, and Man
Evidence has accumulated in the past that opio
stimulate, as an important component of their anti
arrheal action, the net absorption of water and el Evidence has accumulated in the past that opioids
stimulate, as an important component of their antidi-
arrheal action, the net absorption of water and electro-
lytes in the small and large intestine in several species,
in Evidence has accumulated in the past that opioids
stimulate, as an important component of their antidi-
arrheal action, the net absorption of water and electro-
lytes in the small and large intestine in several species,
in stimulate, as an important component of their antidi-
arrheal action, the net absorption of water and electro-
lytes in the small and large intestine in several species,
including man. Most of the data do not allow the dis arrheal action, the net absorption of water and electro-
lytes in the small and large intestine in several species,
including man. Most of the data do not allow the dis-
tinction between proabsorbtive and antisecretory act lytes in the small and large interpreticle including man. Most of the date including man. Most of the date components so that both terms effects unless otherwise stated.
1. Guinea pig. a. THE EFFECT

Including man. Wost of the data do not allow the distriction between proabsorbtive and antisecretory action components so that both terms are used to mean net effects unless otherwise stated.

1. Guinea pig. a. THE EFFECTS effects unless otherwise stated.

1. Guinea pig. a. THE EFFECTS OF OPIOIDS AND NAL

OXONE IN VITRO. In the guinea pig, Kachur et al. (200

demonstrated that enkephalin analogues and etcrphine

but less so beta-endorphin, r 1. Guinea pig. a. THE EFFECTS OF OPIOIDS AND NAL-
OXONE IN VITRO. In the guinea pig, Kachur et al. (200)
demonstrated that enkephalin analogues and etorphine,
but less so beta-endorphin, reduced the short-circuit
current a OXONE IN VITRO. In the guinea pig, Kachur et al. (200)
demonstrated that enkephalin analogues and etorphine,
but less so beta-endorphin, reduced the short-circuit
current and reversed net chloride secretion to net ab-
sorp demonstrated that enkephalin analogues and etorphine,
but less so beta-endorphin, reduced the short-circuit
current and reversed net chloride secretion to net ab-
sorption in the ileal mucosa in vitro. The opioid effect
wa but less so beta-endorphin, reduced the short-circuit current and reversed net chloride secretion to net absorption in the ileal mucosa in vitro. The opioid effect was antagonized by naloxone, which, in a subsequent study current and reversed net chloride secretion to net absorption in the ileal mucosa in vitro. The opioid effect was antagonized by naloxone, which, in a subsequent study (199), slightly increased the short-circuit current ev sorption in the ileal mucosa in vitro. The opioid effect
was antagonized by naloxone, which, in a subsequent
study (199), slightly increased the short-circuit current
even when tested in the absence of exogenous opioids.
T was antagonized by naloxone, which, in a subsequen
study (199), slightly increased the short-circuit curren
even when tested in the absence of exogenous opioids
The antagonist diprenorphine, which has a high affinit
to bot study (199), slightly increased the short-circuit current
even when tested in the absence of exogenous opioids.
The antagonist diprenorphine, which has a high affinity
to both opioid mu- and delta-receptors, behaved simi-
 even when tested in the absence of exogenous opioids.
The antagonist diprenorphine, which has a high affinity
to both opioid mu- and delta-receptors, behaved simi-
larly, although it was more potent than naloxone. Nal-
oxo The antagonist diprenorphine, which has a high affinito both opioid mu- and delta-receptors, behaved similarly, although it was more potent than naloxone. Na oxone displays its highest affinity at mu-receptors. The may ind to both opioid mu- and delta-receptors, behaved similarly, although it was more potent than naloxone. Naloxone displays its highest affinity at mu-receptors. This may indicate that endogenous opioids, possibly delta-agonis larly, although it was more potent than naloxone. Naloxone displays its highest affinity at mu-receptors. This may indicate that endogenous opioids, possibly delta-agonists, were operative in the mucosal preparations. No f oxone displays its highes
may indicate that endo
agonists, were operative
firm statement as to rec
the basis of these data.
b. INVOLVEMENT OF firm statement as to receptor subtypes can be made on
the basis of these data.
b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR

agonists, were operative in the mucosal preparations. No
firm statement as to receptor subtypes can be made on
the basis of these data.
b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR
TYPES AND THEIR POTENTIAL LOCATIONS. By co firm statement as to receptor subtypes can be made on
the basis of these data.
b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR
TYPES AND THEIR POTENTIAL LOCATIONS. By comparing
the relative potencies of the above mentioned ago the basis of these data.

b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR

TYPES AND THEIR POTENTIAL LOCATIONS. By comparing

the relative potencies of the above mentioned agonists

to those of fentanyl and ketocyclazocine, wh b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR
TYPES AND THEIR POTENTIAL LOCATIONS. By comparing
the relative potencies of the above mentioned agonists
to those of fentanyl and ketocyclazocine, which were not
at all or far le TYPES AND THEIR POTENTIAL LOCATIONS. By comparing
the relative potencies of the above mentioned agonists
to those of fentanyl and ketocyclazocine, which were not
at all or far less active, Kachur et al. (200) concluded
tha the relative potencies of the above mentioned agonists
to those of fentanyl and ketocyclazocine, which were not
at all or far less active, Kachur et al. (200) concluded
that the peripheral antisecretory and proabsorptive e to those of fentanyl and ketocyclazocine, which were not This was supported by in vitro data from the same

laboratory (459), showing that a rather selective delta-
receptor antagonist (ICI 154,129) readily antagonized the OPIOIDS AND CONTROL OF GASTROINTES
laboratory (459), showing that a rather selective delta-
receptor antagonist (ICI 154,129) readily antagonized the nee
enkephalin effect. López-Ruiz and Prieto (260) found ap opions and contract of GASTROINTES
laboratory (459), showing that a rather selective delta-
receptor antagonist (ICI 154,129) readily antagonized the
nekephalin effect. López-Ruiz and Prieto (260) found ap
both high-affin laboratory (459), showing that a rather selective delta-
receptor antagonist (ICI 154,129) readily antagonized the
enkephalin effect. López-Ruiz and Prieto (260) found
both high-affinity $(K_d$ in the range of 0.1 to 2.0 nm laboratory (459), showing that a rather selective delta-
receptor antagonist (ICI 154,129) readily antagonized the
enkephalin effect. López-Ruiz and Prieto (260) found
both high-affinity $(K_d$ in the range of 0.1 to 2.0 nm receptor antagonist (ICI 154,129) readily antagonized the enkephalin effect. López-Ruiz and Prieto (260) fould both high-affinity (K_d in the range of 0.1 to 2.0 nmoliter) and low-affinity (K_d in the range of 10 to 70 both high-affinity $(K_d$ in the range of 0.1 to 2.0 nmol/ in
liter) and low-affinity $(K_d$ in the range of 10 to 70 nmol/ caliter) binding of $[^3H\textrm{-}Leu^6]$ -enkephalin to isolated enter-
ocytes in all parts of the guinea p liter) and low-affinity $(K_d$ in the range of 10 to 70 nmol/
liter) binding of $[^3H$ -Leu⁵]-enkephalin to isolated enter-
ocytes in all parts of the guinea pig small and large
intestine. Binding was saturable. Displacemen liter) binding of $[{}^{3}H$ -Leu⁵]-enkephalin to isolated enter-
ocytes in all parts of the guinea pig small and large stimula
intestine. Binding was saturable. Displacement was within
achieved specifically by [Leu⁵]-en ocytes in all parts of the guinea pig small and large intestine. Binding was saturable. Displacement was achieved specifically by [Leu⁵]-enkephalin with [Met⁵]-enkephalin analogues and naloxone displaying very low affi intestine. Binding was saturable. Displacement was
achieved specifically by [Leu⁶]-enkephalin with [Met⁶]-
enkephalin analogues and naloxone displaying very low
affinity. This would be consistent with a low antagonisti achieved specifically by $[Leu^6]$ -enkephalin with $[Met^6]$ -
enkephalin analogues and naloxone displaying very low (2
affinity. This would be consistent with a low antagonistic th
potency of naloxone in functional tests. Th enkephalin analogues and naloxone displaying very low
affinity. This would be consistent with a low antagonistic
potency of naloxone in functional tests. The biological
significance of this specific $[Leu⁵]$ -enkephali affinity. This would be consistent with a low antagonistic
potency of naloxone in functional tests. The biological
significance of this specific [Leu⁵]-enkephalin binding
site is still unclear. It should be recognized in potency of naloxone in functional tests. The biological pro
significance of this specific [Leu⁵]-enkephalin binding ins
site is still unclear. It should be recognized in this context (12
that membrane receptors may well significance of this specific [Leu^o]-enkephalin binding in
site is still unclear. It should be recognized in this context (1
that membrane receptors may well be altered upon cell tis
preparation. This may also explain th site is still unclear. It show
that membrane receptors
preparation. This may al
regard to negative bindin
enterocytes (see below).
Enterocytes are just on at membrane receptors may well be altered upon cell
eparation. This may also explain the discrepancy with
gard to negative binding data in rat and rabbit isolated
terocytes (see below).
Enterocytes are just one possible ta

preparation. This may also explain the discrepancy with
regard to negative binding data in rat and rabbit isolated
enterocytes (see below).
Enterocytes are just one possible target of endogenous
opioids in the control of i regard to negative binding data in rat and rabbit isolated
enterocytes (see below).
Enterocytes are just one possible target of endogenous
opioids in the control of intestinal secretion. Sato et al.
(368) demonstrated by e enterocytes (see below). in
Enterocytes are just one possible target of endogenous
opioids in the control of intestinal secretion. Sato et al.
(368) demonstrated by extracellular recording from sin-
gle neurons of the subm Enterocytes are just one possible target of endogenous appoids in the control of intestinal secretion. Sato et al. 3
(368) demonstrated by extracellular recording from sintigle neurons of the submucosal plexus of the guine opioids in the control of intestinal secretion. Sato et al. (368) demonstrated by extracellular recording from single neurons of the submucosal plexus of the guinea-pig tileum opioid inhibition of spontaneous neuronal acti (368) demonstrated by extracellular recording from single neurons of the submucosal plexus of the guinea-pig
ileum opioid inhibition of spontaneous neuronal activity
similar to alpha-adrenergic inhibition. Thus, inhibition ileum opioid inhibition of spontaneous neuronal activity
similar to alpha-adrenergic inhibition. Thus, inhibition
of acetylcholine release from the submucosal plexus,
which stimulates intestinal secretion, may be another
m similar to alpha-adrenergic inhibition. Thus, inhibition
of acetylcholine release from the submucosal plexus,
which stimulates intestinal secretion, may be another
mode of the antisecretory opioid action.
Although toleranc milar to alpha-adrenergic inhibition. Thus, inhibition
acetylcholine release from the submucosal plexus,
inch stimulates intestinal secretion, may be another
ode of the antisecretory opioid action.
Although tolerance to th

of acetylcholine release from the submucosal plexus, in which stimulates intestinal secretion, may be another position of the antisecretory opioid action. The antisecretory enkephaline constrated (460), no withdrawal sign which stimulates intestinal secretion, may be another perimode of the antisecretory opioid action. In min

Although tolerance to the antisecretory enkephalin createffect was demonstrated (460), no withdrawal sign was inte
 mode of the antisecretory opioid action. In antisecretory enkephalinery
Although tolerance to the antisecretory enkephalinery
effect was demonstrated (460), no withdrawal sign was
intellicted in the ileal mucosa by antagon Although tolerance to the antisecretory enkephalin creader effect was demonstrated (460), no withdrawal sign was intellectied in the ileal mucosa by antagonist application in may vitro. In fact, Warhurst et al. (465) noted effect was demonstrated (460), no withdrawal sign was
elicited in the ileal mucosa by antagonist application in
vitro. In fact, Warhurst et al. (465) noted that, in the
rat, the antagonist had to be administered in vivo in elicited in the ileal mucosa by antagonist application in
vitro. In fact, Warhurst et al. (465) noted that, in the
rat, the antagonist had to be administered in vivo in
order to induce withdrawal diarrhea. Similarly, Chang vitro. In fact, Warhurst et al. (465) noted that, in the orat, the antagonist had to be administered in vivo in a order to induce withdrawal diarrhea. Similarly, Chang et al. (56) found no change in sodium or chloride flux rat, the antagonist had to be administered in vivo in
order to induce withdrawal diarrhea. Similarly, Chang et
al. (56) found no change in sodium or chloride fluxes
upon naltrexone application in vitro to intestinal mucosa order to induce withdrawal diarrhea. Similarly, Chang et al. (56) found no change in sodium or chloride fluxes
upon naltrexone application in vitro to intestinal mucoss
from morphine-dependent rats, although it did elicit
 al. (56) found no change in sodium or chloride fluxes
upon naltrexone application in vitro to intestinal mucosa
from morphine-dependent rats, although it did elicit
withdrawal diarrhea in vivo. The situation is reminiscent upon naltrexone application in vitro to intestinal mucosa
from morphine-dependent rats, although it did elicit
withdrawal diarrhea in vivo. The situation is reminiscent
of the mouse vas deferens contractions. Here, again,
 from morphine-dependent
withdrawal diarrhea in vivo
of the mouse vas deferent
neurons which may develo
trinsic to the organ (390).
2. Rat. a. SPECIFICITY AN

neurons which may develop opioid dependence are ex-
trinsic to the organ (390).
2. Rat. a. SPECIFICITY AND LOCATION OF THE ANTISE-
CRETORY EFFECT OF OPIOIDS. In the rat, opioids not only
increased in vivo net absorption of trinsic to the organ (390).

2. Rat. a. SPECIFICITY AND LOCATION OF THE ANTISE-

CRETORY EFFECT OF OPIOIDS. In the rat, opioids not only

increased in vivo net absorption of water and ions but,

as an in vitro equivalent, 2. Rat. a. SPECIFICITY AND LOCATION OF THE ANTISE-CRETORY EFFECT OF OPIOIDS. In the rat, opioids not only increased in vivo net absorption of water and ions but, as an in vitro equivalent, decreased short-circuit current CRETORY EFFECT OF OPIOIDS. In the rat, opioids not only coincreased in vivo net absorption of water and ions but, ras an in vitro equivalent, decreased short-circuit current tiunder basal conditions (21, 85, 466, 113, 465 increased in vivo net absorption of water and ions but,
as an in vitro equivalent, decreased short-circuit current
under basal conditions (21, 85, 466, 113, 465), and after
stimulation by PGE_1 (66, 253, 22), VIP (21, 24 as an in vitro equivalent, decreased short-circuit curre
under basal conditions $(21, 85, 466, 113, 465)$, and aft
stimulation by PGE₁ $(66, 253, 22)$, VIP $(21, 249)$,
cholera toxin $(38, 39)$. The opioid effect was an under basal conditions (21, 85, 466, 113, 465), and afte stimulation by PGE_1 (66, 253, 22), VIP (21, 249), of cholera toxin (38, 39). The opioid effect was antagonized by naloxone or naltrexone. In contrast to levorphan stimulation by PGE₁ (66, 253, 22), VIP (21, 249), or la
cholera toxin (38, 39). The opioid effect was antagonized bi
by naloxone or naltrexone. In contrast to levorphanol, je
its (+)-enantiomer dextrorphan was inactive cholera toxin (38, 39). The opioid effect was antagonized by
hy naloxone or naltrexone. In contrast to levorphanol, jets (+)-enantiomer dextrorphan was inactive (21), indi-
cating stereospecificity as a characteristic prop by naloxone or naltrexone. In contrast to levorphanol, jejuits (+)-enantiomer dextrorphan was inactive (21), indi-
its (+)-enantiomer dextrorphan was inactive (21), indi-
cating stereospecificity as a characteristic proper its (+)-enantiomer dextrorphan was inactive (21), indicating stereospecificity as a characteristic property of opioid receptor-mediated events. However, inhibition of VIP-induced secretion by morphine was only found in the cating stereospecificity as a characteristic property of opioid receptor-mediated events. However, inhibition of VIP-induced secretion by morphine was only found in the intact rat (21), not in the tied-off jejunal loop (18 opioid receptor-mediated events. However, in
VIP-induced secretion by morphine was onle
the intact rat (21), not in the tied-off jejuna
It may, therefore, represent opioid inhibition
creatic (214) rather than intestinal se P-induced secretion by morphine was only found in sect
e intact rat (21) , not in the tied-off jejunal loop (18) . b
may, therefore, represent opioid inhibition of pan-
rypetic (214) rather than intestinal secretion.

both high-affinity $(K_d$ in the range of 0.1 to 2.0 nmol/ in carbachol action, as opposed to a postsynaptic mus-
liter) and low-affinity $(K_d$ in the range of 10 to 70 nmol/ carinic action of bethanechol. Also, the secretor ESTINAL MOTILITY AND SECRETION
carbachol was reduced by opioids, stimulation by beth
nechol was unaffected (21). The authors discussed th ESTINAL MOTILITY AND SECRETION 147
carbachol was reduced by opioids, stimulation by betha-
nechol was unaffected (21). The authors discussed this
apparent discrepancy in terms of a nicotinic component ESTINAL MOTILITY AND SECRETION 147
carbachol was reduced by opioids, stimulation by betha-
nechol was unaffected (21). The authors discussed this
apparent discrepancy in terms of a nicotinic component
in carbachol action, carbachol was reduced by opioids, stimulation by betha
nechol was unaffected (21). The authors discussed thi
apparent discrepancy in terms of a nicotinic componen
in carbachol action, as opposed to a postsynaptic mus
carin carbachol was reduced by opioids, stimulation by bethanechol was unaffected (21). The authors discussed this apparent discrepancy in terms of a nicotinic component in carbachol action, as opposed to a postsynaptic muscarin apparent discrepancy in terms of a nicotinic component in carbachol action, as opposed to a postsynaptic musin carbachol action, as opposed to a postsynaptic mus-
carinic action of bethanechol. Also, the secretory effect
of the laxative bisacodyl, which is thought to act via
stimulation of PGE biosynthesis at an unknown site
wit carinic action of bethanechol. Also, the secretory effect
of the laxative bisacodyl, which is thought to act via
stimulation of PGE biosynthesis at an unknown site
within the intestinal wall (19, 20), was impaired by
opioi of the laxative bisacodyl, which is thought to act via
stimulation of PGE biosynthesis at an unknown site
within the intestinal wall (19, 20), was impaired by
opioids, but not that of the osmotic compound mannitol
(21). A stimulation of PGE biosynthesis at an unknown site
within the intestinal wall (19, 20), was impaired by
opioids, but not that of the osmotic compound mannitol
(21). A presynaptic action would also be consistent with
the fa within the intestinal wall $(19, 20)$, was impaired by opioids, but not that of the osmotic compound mannitol (21) . A presynaptic action would also be consistent with the failure of morphine to affect PGE_2 -stimulated opioids, but not that of the osmotic compound mannitol (21). A presynaptic action would also be consistent with the failure of morphine to affect PGE₂-stimulated cAMP production by rat isolated enterocytes (157) and with (21). A presynaptic action would also be consistent w
the failure of morphine to affect PGE_2 -stimulated cAl
production by rat isolated enterocytes (157) and with
inability to demonstrate specific opioid binding on
(120) the failure of morphine to affect PGE₂-stimulated cAMP
production by rat isolated enterocytes (157) and with the
inability to demonstrate specific opioid binding on rat
(120) or rabbit (25; see below) enterocytes. The pr production by rat isolated enterocytes (157) and with the
inability to demonstrate specific opioid binding on rat
(120) or rabbit (25; see below) enterocytes. The proposi-
tion of a presynaptic action is, further, consonan inability to demonstrate specific opioid binding on rat (120) or rabbit (25; see below) enterocytes. The proposition of a presynaptic action is, further, consonant with opioid inhibition of acetylcholine release from the s (120) or rabbit (25; see below) enterocytes. The proposition of a presynaptic action is, further, consonant with opioid inhibition of acetylcholine release from the sub-
mucosal plexus of the rat colon (121). The rat smal tion of a presynaptic action is, further, consonant with opioid inhibition of acetylcholine release from the sub-
mucosal plexus of the rat colon (121). The rat small intestine contains opioid binding sites within the vill opioid inhibition of acetylcholine release from the
mucosal plexus of the rat colon (121). The rat s
intestine contains opioid binding sites within the
and submucosal plexus as shown by autoradiography
302). Their attribut mucosal plexus of the rat colon (121). The rat small
intestine contains opioid binding sites within the villi
and submucosal plexus as shown by autoradiography (79,
302). Their attribution, however, to mu- and delta-recepintestine contains opioid binding si
and submucosal plexus as shown by a
302). Their attribution, however, to n
tors (302) remains speculative due t
type selectivity of the ligands used.
The enkephalin analogue FK 33-8 d submucosal plexus as shown by autoradiography (79,
2). Their attribution, however, to mu- and delta-recep-
rs (302) remains speculative due to the poor receptor
pe selectivity of the ligands used.
The enkephalin analogue

302). Their attribution, however, to mu- and delta-receptors (302) remains speculative due to the poor receptor type selectivity of the ligands used.
The enkephalin analogue FK 33-824 inhibited PGE₁-effected increase in tors (302) remains speculative due to the poor receptor
type selectivity of the ligands used.
The enkephalin analogue FK 33-824 inhibited PGE₁-
effected increase in intestinal fluid volume in both the
intact conscious a type selectivity of the ligands used.
The enkephalin analogue FK 33-824 inhibited PGE₁-
effected increase in intestinal fluid volume in both the
intact conscious and the pithed rat (253). Moreover, the
peripherally acti The enkephalin analogue FK 33-824 inhibited PGE₁-
effected increase in intestinal fluid volume in both the
intact conscious and the pithed rat (253). Moreover, the
peripherally acting opioid loperamide (21) and i.c.v. a effected increase in intestinal fluid volume in both the
intact conscious and the pithed rat (253). Moreover, the
peripherally acting opioid loperamide (21) and i.c.v. ad-
ministered [D-Ala², Met⁵]-enkephalin-amide (3 intact conscious and the pithed rat (253) . Moreover, the peripherally acting opioid loperamide (21) and i.c.v. administered $[D-Ala²$, Met⁵]-enkephalin-amide (38) increased net fluid absorption in the rat. Henc and orientation of activity when the relation of activity of activity of activity of the rat colon (121). The rat small intestine contains opioid by the ratio and submucosal plexus as shown by autoradiography (79, 302). T after both peripheral and central administration (56). creased net fluid absorption in the rat. Hence, both and intestinal and a central site of antisecretory opioid action
may exist. This coincides with an antiabsorptive action
of quaternary naltrexone in the morphine-depende testinal and a central site of antisecretory opioid action
ay exist. This coincides with an antiabsorptive action
quaternary naltrexone in the morphine-dependent rat,
ter both peripheral and central administration (56).
Ha

2. Rat. a. SPECIFICITY AND LOCATION OF THE ANTISE-
 2. Rat. a. SPECIFICITY AND LOCATION OF THE ANTISE-
 CRETORY EFFECT OF OPIOIDS. In the rat, opioids not only components. It is an interesting observation that, in th may exist. This coincides with an antiabsorptive action
of quaternary naltrexone in the morphine-dependent rat,
after both peripheral and central administration (56).
Hardcastle et al. (156) explained the antisecretory
eff of quaternary naltrexone in the morphine-dependent rat,
after both peripheral and central administration (56).
Hardcastle et al. (156) explained the antisecretory
effect of loperamide by prevention of PGE-induced in-
hibit after both peripheral and central administration (56).

Hardcastle et al. (156) explained the antisecretory

effect of loperamide by prevention of PGE-induced in-

hibition of mucosal-to-serosal sodium movement, not

reduc Hardcastle et al. (156) explained the antisecretory
effect of loperamide by prevention of PGE-induced in-
hibition of mucosal-to-serosal sodium movement, not
reduction in PGE-stimulated chloride secretion. The
same group (effect of loperamide by prevention of PGE-induced in-
hibition of mucosal-to-serosal sodium movement, not
reduction in PGE-stimulated chloride secretion. The
same group (155) noted that loperamide, when applied
to the muco hibition of mucosal-to-serosal sodium movement, not
reduction in PGE-stimulated chloride secretion. The
same group (155) noted that loperamide, when applied
to the mucosal side, displayed in the rat small intestine
an anti reduction in PGE-stimulated chloride secretion. The
same group (155) noted that loperamide, when applied
to the mucosal side, displayed in the rat small intestine
an antiabsorptive action in addition to its antisecretory
a to the mucosal side, displayed in the rat small intestine to the mucosal side, displayed in the rat small intestine
an antiabsorptive action in addition to its antisecretory
action. Thus, the overall effect of loperamide may depend
on the actual balance between the two contrastin an antiabsorptive action in addition to its antisecreto:
action. Thus, the overall effect of loperamide may deper
on the actual balance between the two contrasting actio
components. It is an interesting observation that, i on the actual balance between the two contrasting action components. It is an interesting observation that, in the rat colon in vivo, loperamide suppressed net fluid secretion induced by cholera toxin but had no influence on the actual balance between the two contrasting actic components. It is an interesting observation that, in the rat colon in vivo, loperamide suppressed net fluid section induced by cholera toxin but had no influence the components. It is an interesting observation that, in the rat colon in vivo, loperamide suppressed net fluid secretion induced by cholera toxin but had no influence on the increase in mucosal cAMP concentration as stimulat rat colon in vivo, loperamide suppressed net fluid secretion induced by cholera toxin but had no influence on the increase in mucosal cAMP concentration as stimulated by cholera toxin (98). Since morphine, by contrast, blo tion induced by cholera toxin but had no influence of the increase in mucosal cAMP concentration as stim lated by cholera toxin (98). Since morphine, by contras blocked the PGE_1 -effected increase in cAMP in the r jejunu the increase in mucosal cAMP concentration as stimulated by cholera toxin (98). Since morphine, by contrast, blocked the PGE₁-effected increase in cAMP in the rat jejunum (22), the sites of action of morphine and loperam blocked the PGE₁-effected increase in cAMP in the rat jejunum (22), the sites of action of morphine and loperamide may be located before and beyond the cAMP link, respectively. There may, thus, be subtle differences beblocked the PGE₁-effected increase in cAMP in the rat jejunum (22), the sites of action of morphine and loper-
amide may be located before and beyond the cAMP link,
respectively. There may, thus, be subtle differences b is performance 122, the sites of action of morphine and loper-

incherencies may, thus, be subtle differences be-

tween the modes of action of different opioids. See also

section VA7.

b. INVOLVEMENT OF DIFFERENT OPIOID

tween the modes of action of different opioids. See a
section VA7.
b. INVOLVEMENT OF DIFFERENT OPIOID RECEPT
TYPES. A comparison between potencies of the mu-aq
nists morphine, RX 783006, and FK 33-824, the kapp
agonists et section VA7.
b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR
TYPES. A comparison between potencies of the mu-ago-
nists morphine, RX 783006, and FK 33-824, the kappa-
agonists ethylketocyclazocine and MR 2034, and the

148
delta-agonist [D-Ala², D-Leu⁵]-enkephalin led Coupar
(67) to conclude that, in contrast to the guinea pig, opioid KROMER

(67) to conclude that, in contrast to the guinea pig, opioid

(67) to conclude that, in contrast to the guinea pig, opioid

mu-receptors were involved in the net proabsorptive 148
delta-agonist $[D-Ala^2, D-Leu^5]$ -enkephalin led Coupar
(67) to conclude that, in contrast to the guinea pig, opioid
mu-receptors were involved in the net proabsorptive
action of opioids in the rat small intestine after i. delta-agonist [D-Ala², D-Leu⁵]-enkephalin led Coupar (67) to conclude that, in contrast to the guinea pig, opioid mu-receptors were involved in the net proabsorptive action of opioids in the rat small intestine after i delta-agonist [D-Ala², D-Leu⁹]-enkephalin led Coupar (67) to conclude that, in contrast to the guinea pig, opioid mu-receptors were involved in the net proabsorptive action of opioids in the rat small intestine after i (67) to conclude that, in contrast to the guinea pig, opioid
mu-receptors were involved in the net proabsorptive
action of opioids in the rat small intestine after i.v. to
administration. Fogel and Kaplan (113) stated tha mu-receptors were involved in the net proabsorptive 4.
action of opioids in the rat small intestine after i.v. to in
administration. Fogel and Kaplan (113) stated that nal-
oxone, whose affinity to mu-receptors is 20 to 3 action of opioids in the rat small intestine after i.v.
administration. Fogel and Kaplan (113) stated that nal-
oxone, whose affinity to mu-receptors is 20 to 30 times
that to delta-receptors (57, 58), antagonized (at 100 administration. Fogel and Kaplan (113) stated that nal-
oxone, whose affinity to mu-receptors is 20 to 30 times
that to delta-receptors (57, 58), antagonized (at 100 tiz
 μ mol/liter) the effect of morphine. Although [Doxone, whose affinity to mu-receptors is 20 to 30 times
that to delta-receptors (57, 58), antagonized (at 100
 μ mol/liter) the effect of morphine. Although [D-Ala²,
Met⁵]-enkephalin-amide, applied at 1 μ mol/liter that to delta-receptors (57, 58), antagonized (at 100 μ mol/liter) the effect of morphine. Although [D-Ala², Met⁶]-enkephalin-amide, applied at 1 μ mol/liter in the intraluminal perfusate, significantly increased μ mol/liter) the effect of morphine. Although [D-Ala², Met⁶]-enkephalin-amide, applied at 1 μ mol/liter in the intraluminal perfusate, significantly increased water absorption, this effect was antagonized only by Met^o]-enkephalin-amide, applied at 1 μ mol/liter in the
intraluminal perfusate, significantly increased water ab-
sorption, this effect was antagonized only by an ex-
tremely high dose of naloxone (1 mmol/liter). Howe intraluminal perfusate, significantly increased water absorption, this effect was antagonized only by an ex-
tremely high dose of naloxone (1 mmol/liter). However, fect
it was readily antagonized by diprenorphine (1 μ m sorption, this effect was antagonized only by an tremely high dose of naloxone (1 mmol/liter). However, it was readily antagonized by diprenorphine (1 μ) liter). Diprenorphine has a high affinity to both opmu- and delt tremely high dose of naloxone (1 mmol/liter). However,
it was readily antagonized by diprenorphine (1 μ mol/
liter). Diprenorphine has a high affinity to both opioid
mu- and delta-receptors (59). Thus, opioid delta-rece it was readily antagonized by diprenorphine $(1 \mu m \delta)$
liter). Diprenorphine has a high affinity to both opioi
mu- and delta-receptors (59). Thus, opioid delta-receptors may be involved in the rat as well, although no fin the operator of the opioid agons and the opioid delta-receptors (59). Thus, opioid delta-receptors may be involved in the rat as well, although no final conclusion can be drawn due to the poor receptor selectivity of the mu- and delta-receptors (59). Thus, opioid delta-recep-
tors may be involved in the rat as well, although no final
conclusion can be drawn due to the poor receptor selec-
tivity of the opioid agonists and antagonists used. conclusion can be drawn due to the poor receptor selectivity of the opioid agonists and antagonists used. The integral same limitation applies to another rat study. Here, [D. Ala², Met⁵]-enkephalin-amide reduced jejun tivity of the opioid agonists and antagonists used. The
same limitation applies to another rat study. Here, [D-
fou
hala², Met⁵]-enkephalin-amide reduced jejunal secretion
upon i.c.v. administration, whereas morphine Ala², Met⁵]-enkephalin-amide reduced jejunal secretion upon i.c.v. administration, whereas morphine i.c.v. had no detectable effect (39). Therefore, receptor types may differ between sites, but this awaits more detail sis.

rabbit. Opioids decreased serosa-to-mucosa chloride fluxes in vitro in a stereospecific fashion, although high the same in the fluxes in vitro in a stereospecific fashion, although high $\frac{1}{\sqrt{2}}$ differ between sites, but this awaits more detailed analy-
sis.
3. Rabbit. The situation is essentially the same in the
rabbit. Opioids decreased serosa-to-mucosa chloride
fluxes in vitro in a stereospecific fashion, alth sis.

3. Rabbit. The situation is essentially the same in the

rabbit. Opioids decreased serosa-to-mucosa chloride

fluxes in vitro in a stereospecific fashion, although high

concentrations of morphine and dextromoramide 3. Rabbit. The situation is essentially the same in the rabbit. Opioids decreased serosa-to-mucosa chloride fluxes in vitro in a stereospecific fashion, although high concentrations of morphine and dextromoramide (10 μ rabbit. Opioids decreased serosa-to-mucosa chloride
fluxes in vitro in a stereospecific fashion, although high
concentrations of morphine and dextromoramide (10
 μ mol/liter or more) were needed (280, 279). However, at
le fluxes in vitro in a stereospecific fashion, although high concentrations of morphine and dextromoramide (10 μ mol/liter or more) were needed (280, 279). However, at least consistent with the proposition of a functional μ mol/liter or more) were needed (280, 279). However, at
least consistent with the proposition of a functional
opioid delta-receptor in this tissue (see guinea pig, sec-
tion V A 1b), an enkephalin analogue was consider μ mol/liter or more) were needed (280, 279). However, at least consistent with the proposition of a functional copioid delta-receptor in this tissue (see guinea pig, section V A 1b), an enkephalin analogue was considera least consistent with the proposition of a functional red
opioid delta-receptor in this tissue (see guinea pig, sec-
tion V A 1b), an enkephalin analogue was considerably
more potent than morphine (280). All effects were
 opioid delta-receptor in this tissue (see guinea pig, it
ion V A 1b), an enkephalin analogue was consideration
more potent than morphine (280). All effects v
blocked by naloxone. The same group (279, 448) is
demonstrated more potent than morphine (280). All effects were
blocked by naloxone. The same group (279, 448) also
demonstrated opioid inhibition of PGE₂-, acetylcho-
line, or cholera toxin-induced net chloride secretion and
interpr blocked by naloxone. The same group $(279, 448)$ also
demonstrated opioid inhibition of $PGE₂$, acetylcho-
line, or cholera toxin-induced net chloride secretion and
interpreted in vitro data in terms of enhancement o blocked by naloxone. The same group $(279, 448)$ also $5.$
demonstrated opioid inhibition of PGE_2 -, acetylcholeration, or choleration induced net chloride secretion and interpreted in vitro data in terms of enhancement demonstrated opioid inhibition of PGE_2 -, acetylcholine, or cholera toxin-induced net chloride secretion and cromometry interpreted in vitro data in terms of enhancement of absorption plus inhibition of secretion. In con line, or cholera toxin-induced net chloride secretion and
interpreted in vitro data in terms of enhancement of
absorption plus inhibition of secretion. In contrast to
Racusen et al. (342), who found an increase in sodium
 interpreted in vitro data in terms of enhancement of ula
absorption plus inhibition of secretion. In contrast to net
Racusen et al. (342), who found an increase in sodium
absorption by high concentrations of codeine in th absorption plus inhibition of secretion. In conditions and a subsorption by high concentrations of codeinabilities in the match of the solution of the solution of sodium fluxes. Tetrodotoxin completely blocked the decreas acusen et al. (342), who found an increase in sodium
sorption by high concentrations of codeine in the
bbit ileal mucosa, McKay et al. (280) did not find any
mificant opioid influence on sodium fluxes.
Tetrodotoxin complet

absorption by high concentrations of codeine
rabbit ileal mucosa, McKay et al. (280) did not fi
significant opioid influence on sodium fluxes.
Tetrodotoxin completely blocked the decrease is
circuit current as caused by [D rabbit ileal mucosa, McKay et al. (280) did not find any tail experiment opioid influence on sodium fluxes.

Tetrodotoxin completely blocked the decrease in short ticincuit current as caused by $[D-Ala^2, Met^5]$ -enkephalin-

a significant opioid influence on sodium fluxes.
Tetrodotoxin completely blocked the decrease in short
circuit current as caused by $[D-Ala^2, Met^5]$ -enkephalin-
amide in the rabbit ileal mucosa in vitro (86, 25). These
data sug Tetrodotoxin completely blocked the decrease in short
circuit current as caused by $[D-Ala^2, Met^5]$ -enkephalin-
amide in the rabbit ileal mucosa in vitro (86, 25). These
data suggest a neuronal site of action within the sub-
 circuit current as caused by [D-Ala², Met³]-enkephalin-
amide in the rabbit ileal mucosa in vitro (86, 25). These
data suggest a neuronal site of action within the sub-
mucosal plexus, since the myenteric plexus was ob amide in the rabbit ileal mucosa in vitro $(86, 25)$. These expected by a failure of action within the sub-
mucosal plexus, since the myenteric plexus was obviously 24 has stripped off together with the longitudinal muscl data suggest a neuronal site of action within the sub-
mucosal plexus, since the myenteric plexus was obviously
stripped off together with the longitudinal muscle layer.
This conclusion is further supported by a failure to mucosal plexus, since the myenteric plexus was obviously
stripped off together with the longitudinal muscle layer.
This conclusion is further supported by a failure to
demonstrate any [Met⁵]-enkephalin binding sites on r stripped off together with the longitudinal muscle layer.
This conclusion is further supported by a failure to in
demonstrate any [Met⁵]-enkephalin binding sites on rab-
mit isolated enterocytes (25). However, this does This conclusion is further supported by a failure to inf
demonstrate any [Met⁵]-enkephalin binding sites on rab-
bit isolated enterocytes (25). However, this does not was
necessarily rule out their existence, as they mi demonstrate any [Met⁸]-enkephalin binding sites on rab-
bit isolated enterocytes (25). However, this does not w
necessarily rule out their existence, as they might have the
been lost during the isolation procedure. It sh bit isolated enterocytes (25). However, this does not necessarily rule out their existence, as they might have been lost during the isolation procedure. It should be noted in this context that the neuronal specificity of T

ER
secretion by $\mathrm{PGE_{1}}$ and VIP (68), which can also stimulate
enterocytes directly. ER
secretion by $\mathrm{PGE_{1}}$ and
enterocytes directly.
4. Dog. In the dog,

²
 4. Dog. In the dog, Mailman (266) found i.v. morphine
 4. Dog. In the dog, Mailman (266) found i.v. morphine

increase net absorption of ²²Na⁺ and water in a nalsecretion by PGE₁ and VIP (68), which can also stimulate
enterocytes directly.
4. Dog. In the dog, Mailman (266) found i.v. morphine
to increase net absorption of ²²Na⁺ and water in a nal-
oxone-reversible manner. T secretion by PGE₁ and VIP (68), which can also stimulate
enterocytes directly.
4. Dog. In the dog, Mailman (266) found i.v. morphine
to increase net absorption of ²²Na⁺ and water in a nal-
oxone-reversible manner. T enterocytes directly.
4. Dog. In the dog, Mailman (266) found i.v. morph
to increase net absorption of $2^{2}Na^{+}$ and water in a r
oxone-reversible-manner. This increase in absorpt
from the isolated perfused ileal segment 4. Dog. In the dog, Mailman (266) found i.v. morphine
to increase net absorption of ²²Na⁺ and water in a nal-
oxone-reversible manner. This increase in absorption
from the isolated perfused ileal segment in the anesth to increase net absorption of $^{22}Na^{+}$ and water in a na
oxone-reversible manner. This increase in absorptio
from the isolated perfused ileal segment in the anesthe
tized dog was positively correlated with an increase i from the isolated perfused ileal segment in the anesthe-
tized dog was positively correlated with an increase in
absorptive site blood flow as determined by ${}^{3}H_{2}O$ clear-
ance. This correlation held both in the fed a from the isolated perfused ileal segment in the anesthe-
tized dog was positively correlated with an increase in
absorptive site blood flow as determined by ${}^{3}H_{2}O$ clear-
ance. This correlation held both in the fed a tized dog was positively correlated with an increase in absorptive site blood flow as determined by ${}^{3}H_{2}O$ clearance. This correlation held both in the fed and fasted state, but fed animals displayed a more pronounce absorptive site blood flow as determined by ${}^{3}H_{2}O$ clear-
ance. This correlation held both in the fed and fasted
state, but fed animals displayed a more pronounced
response to morphine than fasted animals. Thus, in t ance. This correlation held both in the fed and fasted state, but fed animals displayed a more pronounced response to morphine than fasted animals. Thus, in the fed state, some unknown mechanism may sensitize the gut to th state, but fed animals displayed a more pronounced
response to morphine than fasted animals. Thus, in the
fed state, some unknown mechanism may sensitize the
gut to the effect of opioids on absorptive site blood flow.
As u response to morphine than fasted animals. Thus, in the fed state, some unknown mechanism may sensitize the gut to the effect of opioids on absorptive site blood flow.
As unidirectional fluxes were only determined for so-
d fed state, some unknown mechanism may sensit
gut to the effect of opioids on absorptive site blocks
As unidirectional fluxes were only determined
dium, nothing can be said about changes in c
fluxes which may, in fact, be t t to the effect of opioids on absorptive site blood flow.

Unidirectional fluxes were only determined for so-

um, nothing can be said about changes in chloride

uses which may, in fact, be the primary event.

Opioid mecha

and detectable effect (39). Therefore, receptor types may
differ between sites, but this awaits more detailed analy-
sis.
3. Rabbit. The situation is essentially the same in the
rabbit. Opioids decreased serosa-to-mucosa c As unidirectional fluxes were only determined for so-
dium, nothing can be said about changes in chloride
fluxes which may, in fact, be the primary event.
Opioid mechanisms both intrinsic and extrinsic to the
intestinal w dium, nothing can be said about changes in chloride
fluxes which may, in fact, be the primary event.
Opioid mechanisms both intrinsic and extrinsic to the
intestinal wall are likely to be involved. Morphine was
found to in fluxes which may, in fact, be the primary event.
Opioid mechanisms both intrinsic and extrinsic to t
intestinal wall are likely to be involved. Morphine w
found to increase net Na⁺ and water absorption relat
to controls Opioid mechanisms both intrinsic and extrinsic to the
intestinal wall are likely to be involved. Morphine was
found to increase net $Na⁺$ and water absorption relative
to controls after both luminal and intraarterial intestinal wall are likely to be involved. Morphine was
found to increase net Na⁺ and water absorption relative
to controls after both luminal and intraarterial admin-
istration in the anesthetized dog with intact innerv found to increase net Na⁺ and water absorption relative to controls after both luminal and intraarterial administration in the anesthetized dog with intact innervation of the ileal segment (267). In the denervated segmen fluxes which may, in fact, be the primary event.

Opioid mechanisms both intrinsic and extrinsic to the

interstinal wall are likely to be involved. Morphine was

from to increase net Na⁺ and water absorption relative
 istration in the anesthetized dog with intact innervation
of the ileal segment (267). In the denervated segment,
however, only luminal administration was effective. Mor-
phine may get access to the site of action related t of the ileal segment (267). In the denervated
however, only luminal administration was effect
phine may get access to the site of action relat
intrinsic mechanism only from the luminal sid
under these particular conditions wever, only luminal administration was effective. Mo
ine may get access to the site of action related to the
trinsic mechanism only from the luminal side, at lea
ider these particular conditions in the dog.
As in the rat,

phine may get access to the site of action related to the
intrinsic mechanism only from the luminal side, at least
under these particular conditions in the dog.
As in the rat, a central site of opioid action on intes-
tina intrinsic mechanism only from the luminal side, at least
under these particular conditions in the dog.
As in the rat, a central site of opioid action on intes-
tinal net fluid absorption has been demonstrated in the
dog (under these particular conditions in the dog.

As in the rat, a central site of opioid action on intes-

tinal net fluid absorption has been demonstrated in the

dog (336). [D-Ala², Met⁶]-enkephalin-amide was shown

t As in the rat, a central site of opioid action on intestinal net fluid absorption has been demonstrated in the dog (336) . [D-Ala², Met⁵]-enkephalin-amide was shown to slightly increase net water absorption and marke tinal net fluid absorption has been demonstrated in dog (336). [D-Ala², Met⁵]-enkephalin-amide was shot o slightly increase net water absorption and marke reduce cholera toxin-effected net secretion in the with a Thiry dog (336). [D-Ala², Met⁶]-enkephalin-amide was shown
to slightly increase net water absorption and markedly
reduce cholera toxin-effected net secretion in the dog
with a Thiry-Vella loop after i.c.v. but not i.v. admin to slightly increase net w
reduce cholera toxin-effect
with a Thiry-Vella loop at
tration. An additional p
nevertheless exist (266).
5. *Pig*. In the anesthet duce cholera toxin-effected net secretion in the dog
th a Thiry-Vella loop after i.c.v. but not i.v. adminis-
ation. An additional peripheral site of action may
vertheless exist (266).
5. *Pig*. In the anesthetized pig, co

with a Thiry-Vella loop after i.c.v. but not i.v. administration. An additional peripheral site of action may nevertheless exist (266) .
5. *Pig*. In the anesthetized pig, continuous luminal perfusion of isolated intesti tration. An additional peripheral site of action ma
nevertheless exist (266).
5. Pig. In the anesthetized pig, continuous lumina
perfusion of isolated intestinal loops in situ with a mi
cromolar concentration of morphine s nevertheless exist (266).
5. Pig. In the anesthetized pig, continuous luminal
perfusion of isolated intestinal loops in situ with a mi-
cromolar concentration of morphine significantly stim-
ulated net water and electrolyt 5. Pig. In the anesthetized pig, continuous lumin
perfusion of isolated intestinal loops in situ with a m
cromolar concentration of morphine significantly stin
ulated net water and electrolyte absorption and impair-
net se perfusion of isolated intestinal loops in situ with a micromolar concentration of morphine significantly stim-
ulated net water and electrolyte absorption and impaired
net secretion as stimulated by *Escherichia coli* heat tested. stable enterotoxin (5). Unfortunately, opioid specificity, as demonstrated by naloxone blockade, has not been tested.
6. Man. Schiller et al. (380) measured the concentra-

stable enterotoxin (5). Unfortunately, opioid specificity,
as demonstrated by naloxone blockade, has not been
tested.
6. Man. Schiller et al. (380) measured the concentra-
tion of a nonabsorbable marker after intraluminal as demonstrated by naloxone blockade, has not been
tested.
6. Man. Schiller et al. (380) measured the concentra-
tion of a nonabsorbable marker after intraluminal bolus
administration in healthy subjects under conditions o tested.
6. Man. Schiller et al. (380) measured the concentration of a nonabsorbable marker after intraluminal bolu
administration in healthy subjects under conditions experimental diarrhea induced by intragastric or inte
t 6. Man. Schiller et al. (380) measured the concentration of a nonabsorbable marker after intraluminal bolus administration in healthy subjects under conditions of experimental diarrhea induced by intragastric or intesti tion of a nonabsorbable marker after intraluminal bolus
administration in healthy subjects under conditions of
experimental diarrhea induced by intragastric or intes-
tinal infusion of a balanced electrolyte solution. Up t administration in healthy subjects under conditions of
experimental diarrhea induced by intragastric or intes-
tinal infusion of a balanced electrolyte solution. Up to
24 h following 30 mg of codeine i.m., the authors foun experimental diarrhea induced by intragastric or intestinal infusion of a balanced electrolyte solution. Up to 24 h following 30 mg of codeine i.m., the authors found a reduced cumulative stool volume under the opioid infl tinal infusion of a balanced electrolyte solution. Up to 24 h following 30 mg of codeine i.m., the authors found a reduced cumulative stool volume under the opioid influence. Since total marker output was decreased and mar 24 h following 30 mg of codeine i.m., the authors found
a reduced cumulative stool volume under the opioid
influence. Since total marker output was decreased and
marker concentration was not affected by codeine, but
was in a reduced cumulative stool volume under the opioinfluence. Since total marker output was decreased an marker concentration was not affected by codeine, but was increased by glucose solution, they concluded that the opioid influence. Since total marker output was decreased and marker concentration was not affected by codeine, but was increased by glucose solution, they concluded that the opioid decreased the transit rate through the intestin marker concentration was not affected by codeine, but was increased by glucose solution, they concluded that the opioid decreased the transit rate through the intestine but did not increase absorption. In their discussion, was increased by glucose solution, they concluded that
the opioid decreased the transit rate through the intes-
tine but did not increase absorption. In their discussion,
however, they also made a modified statement, i.e.,

PHARMACOLOGICAL REVIEWS

OPIOIDS AND CONTROL OF GASTROIS

contact time of luminal fluid with the mucosa. As their

data stand, they conflict with animal data (see above).

Schiller et al. (380) discussed this discrepancy in terms OPIOIDS AND CONTROL OF GASTROINT
contact time of luminal fluid with the mucosa. As their
data stand, they conflict with animal data (see above).
Schiller et al. (380) discussed this discrepancy in terms
of higher opioid do contact time of luminal fluid with the mucosa. As the data stand, they conflict with animal data (see abov Schiller et al. (380) discussed this discrepancy in term of higher opioid doses used in the animal studies, potenti contact time of luminal fluid with the mucosa. As their data stand, they conflict with animal data (see above). Schiller et al. (380) discussed this discrepancy in terms of higher opioid doses used in the animal studies, p data stand, they conflict with animal data (see above)
Schiller et al. (380) discussed this discrepancy in term
of higher opioid doses used in the animal studies, poten
tial receptor type selectivities of different opioids of higher opioid doses used in the animal studies, poten-
tial receptor type selectivities of different opioids used,
or high basal absorption rates under their experimental
or high basal absorption rates under their expe of higher opioid doses used in the animal studies, potential receptor type selectivities of different opioids used, or high basal absorption rates under their experimental conditions. Under conditions of luminal perfusion tial receptor type selectivities of different opioids used, or high basal absorption rates under their experimental conditions. Under conditions of luminal perfusion with balanced electrolyte solutions, codeine reduced net or high basal absorption rates under their experimental the conditions. Under conditions of luminal perfusion with balanced electrolyte solutions, codeine reduced net abovertion in the jejunum, the only region where transi conditions. Under conditions of luminal perfusion with tyled
alanced electrolyte solutions, codeine reduced net ab-
sorption in the jejunum, the only region where transit lut
time was increased. This casts some doubt on th balanced electrolyte solutions, codeine reduced net absorption in the jejunum, the only region where transi
time was increased. This casts some doubt on the above
interpretation and the biological significance of this kine sorption in the jejunum, the only region where transit
time was increased. This casts some doubt on the above
interpretation and the biological significance of this kind
of study using large volumes of luminal electrolyte time was increased. This casts some doubt on the above
interpretation and the biological significance of this kind
of study using large volumes of luminal electrolyte solu-
tion to induce "diarrhea." However, VIP-induced n interpretation and the biological significance of this kind
of study using large volumes of luminal electrolyte solu-
tion to induce "diarrhea." However, VIP-induced net
secretion was also unaffected by codeine. The autho of study using large volumes of luminal electrolyte solu-
tion to induce "diarrhea." However, VIP-induced net (85)
secretion was also unaffected by codeine. The authors deta
did not find any indication for the activity of tion to induce "diarrhea." However, VIP-induced net (8)
secretion was also unaffected by codeine. The authors de
did not find any indication for the activity of endogenous sta
opioids, since i.v. infusion of naloxone at 4 secretion was also unaffecedid not find any indication
opioids, since i.v. infusion h^{-1} had no detectable effection
jejunum and ileum (380).
Turnberg (448) adminis d not find any indication for the activity of endoger
ioids, since i.v. infusion of naloxone at $40 \mu g \times kg^1$
had no detectable effect on net absorption in
unum and ileum (380).
Turnberg (448) administered loperamide intra

opioids, since i.v. infusion of naloxone at $40 \mu g \times kg^{-1} \times$ cond

h⁻¹ had no detectable effect on net absorption in the inter-

jejunum and ileum (380). ques

Turnberg (448) administered loperamide intralumi-

condity b h^{-1} had no detectable effect on net absorption in the integral perfusion and ileum (380).

Turnberg (448) administered loperamide intralumicant connally by tube to healthy volunteers at a bolus dose of 4 kap mg followe jejunum and ileum (380). Turnberg (448) administered loperamide intralumically by tube to healthy volunteers at a bolus dose of 4 km mg followed by luminal perfusion of 3 mg/liter. He did cont find any influence on jejunal Turnberg (448) administered loperamide intralum
nally by tube to healthy volunteers at a bolus dose of
mg followed by luminal perfusion of 3 mg/liter. He
not find any influence on jejunal basal net absorption
water or elec nally by tube to healthy volunteers at a bolus dose of 4 mg followed by luminal perfusion of 3 mg/liter. He did not find any influence on jejunal basal net absorption of water or electrolytes, but noted a reduction of pros mg followed by luminal perfusion of 3 mg/liter. He didnot find any influence on jejunal basal net absorption of water or electrolytes, but noted a reduction of prostaglandin-induced secretion and, in half of the subjects, sented. rater or electrolytes, but noted a reduction of prostandin-induced secretion and, in half of the subjects, neversion to absorption. No detailed data were pre-
nted.
7. Possible mechanisms of antisecretory action. Several e

glandin-induced secretion and, in half of the subjects, wilconversion to absorption. No detailed data were pre-
sented.
7. Possible mechanisms of antisecretory action. Several of mediators of the antisecretory action of op conversion to absorption. No detailed data were pr
sented.
7. Possible mechanisms of antisecretory action. Sever
mediators of the antisecretory action of opioids ha
been proposed. Central opioid inhibition of cholera toxi
 we sented.

7. Possible mechanisms of antisecretory action. Several of

mediators of the antisecretory action of opioids have

meen proposed. Central opioid inhibition of cholera toxin-

induced intestinal fluid secretion 7. Possible mechanisms of antisecretory action. Several
mediators of the antisecretory action of opioids have
been proposed. Central opioid inhibition of cholera toxin-
induced intestinal fluid secretion in the rat was blo mediators of the antisecretory action of opioids have might been proposed. Central opioid inhibition of cholera toxintant pinduced intestinal fluid secretion in the rat was blocked shown by phentolamine or by pretreatment been proposed. Central opioid inhibition of cholera toxin-
induced intestinal fluid secretion in the rat was blocked
by phentolamine or by pretreatment with guanethidine
administered in order to deplete catecholamines from induced intestinal fluid secretion in the rat was blocked
by phentolamine or by pretreatment with guanethidine
administered in order to deplete catecholamines from
nerve terminals (39). It was suggested that the central
an by phentolamine or by pretreatment with guanethidine properties (10a). This may be an additional mode of administered in order to deplete catecholamines from antisecretory action, though at relatively high concentra-
nerve administered in order to deplete catecholamines from
nerve terminals (39). It was suggested that the central
antisecretory effect of opioids on the gut may be mediated
by stimulation of the sympathetic nervous system, whic nerve terminals (39). It was suggested that the central ti
antisecretory effect of opioids on the gut may be mediated
by stimulation of the sympathetic nervous system, which bli
is known to have antisecretory function. Thi antisecretory effect of opioids on the gut may be mediaty stimulation of the sympathetic nervous system, whis known to have antisecretory function. This is a ported by the findings of Coupar and Taylor (70) show that chemi by stimulation of the sympathetic nervous system, whicl
is known to have antisecretory function. This is sup
ported by the findings of Coupar and Taylor (70) showing
that chemical depletion of intestinal stores of noradren is known to have antisecretory function. This is sup-
ported by the findings of Coupar and Taylor (70) showing
that chemical depletion of intestinal stores of noradren-
aline and serotonin abolished or impaired, respective ported by the findings of Coupar and Taylor (70) showing pothat chemical depletion of intestinal stores of noradrencoline and serotonin abolished or impaired, respectively, by the antisecretory effect of i.v. morphine in t that chemical depletion of intestinal stores of noradren-
aline and serotonin abolished or impaired, respectively,
the antisecretory effect of i.v. morphine in the rat je-
junum. Likewise, the opioid effect was impaired by aline and serotonin abolished or impaired, respective
the antisecretory effect of i.v. morphine in the rat
junum. Likewise, the opioid effect was impaired by t
alpha-adrenoceptor antagonist phentolamine or the :
rotonin re senin. num. Likewise, the opioid effect was impaired by the pha-adrenoceptor antagonist phentolamine or the setonin receptor antagonists methysergide and ketan-
rin.
Though atropine failed to prevent the net antisecretory fect of

alpha-adrenoceptor antagonist phentolamine or the se-
rotonin receptor antagonists methysergide and ketan-
serin.
Though atropine failed to prevent the net antisecretory
effect of morphine in the rabbit isolated ileal muco Frotonin receptor antagonists methysergide and ketan-
serin.
Though atropine failed to prevent the net antisecretory enter
effect of morphine in the rabbit isolated ileal mucosa add
(280), it blocked the net secretory effe serin. misserin. Though atropine failed to prevent the net antisecretory enerfect of morphine in the rabbit isolated ileal mucosa ad (280), it blocked the net secretory effect of naloxone in age the rat in vivo (113). The Though atropine failed to prevent the net antisecrete
effect of morphine in the rabbit isolated ileal muc
(280), it blocked the net secretory effect of naloxone
the rat in vivo (113). The peripheral antisecretory opi
actio effect of morphine in the rabbit isolated ileal mucosa addition, Rozsa and Varro (358) found that the delta-
(280), it blocked the net secretory effect of naloxone in agonist $[D-Met^2$, NleS⁵]-enkephalin-amide enhanced,
t the rat in vivo (113). The peripheral antisecretory opioid 466). This probably depends on the particular expeniaction components may be discussed in terms of presynaptic inhibition of acetylcholine release and inhibition of adenylate cyclase stimulated by prostaglandins (22, 121, 466). This probably depends on the particular experi aptic inhibition of acetylcholine release and inhibition of adenylate cyclase stimulated by prostaglandins (22, 121, 466). This probably depends on the particular experimental conditions employed. Although opioids did not adenylate cyclase stimulated by prostaglandins (22, 121, 466). This probably depends on the particular experimental conditions employed. Although opioids did not influence PG-stimulated adenylate cyclase in isolated rat en 466). This probably depends on the particular experimental conditions employed. Although opioids did not the influence PG-stimulated adenylate cyclase in isolated rat in enterocytes (157), this still leaves the possibility

contact time of luminal fluid with the mucosa. As their once more be noted that TTX blocked the decrease in data stand, they conflict with animal data (see above). short-circuit current by $[D-Ala^2$, Met⁵]-enkephalin-Schi ESTINAL MOTILITY AND SECRETION 149
once more be noted that TTX blocked the decrease in
short-circuit current by [D-Ala², Met⁵]-enkephalin-ESTINAL MOTILITY AND SECRETION
once more be noted that TTX blocked the decrea
short-circuit current by [D-Ala², Met⁵]-enkeph
amide in the rabbit ileal mucosa in vitro (86, 25). ESTINAL MOTILITY AND SECRETION
once more be noted that TTX blocked the decreas
short-circuit current by $[D-Ala^2$, Met⁵]-enkeph
amide in the rabbit ileal mucosa in vitro (86, 25).
Since opioids are believed to decrease in

Since opioids are believed to decrease intracellular free once more be noted that TTX blocked the decrease in short-circuit current by $[D-Ala^2, Met^5]$ -enkephalinamide in the rabbit ileal mucosa in vitro (86, 25).
Since opioids are believed to decrease intracellular free calcium (s short-circuit current by $[D-Ala^2, Met^6]$ -enkephalin-
amide in the rabbit ileal mucosa in vitro (86, 25).
Since opioids are believed to decrease intracellular free
calcium (see section III A 7), there may be a link between
t amide in the rabbit ileal mucosa in vitro $(86, 25)$.
Since opioids are believed to decrease intracellular free
calcium (see section III A 7), there may be a link between
this effect and impaired release of the secretagog Since opioids are believed to decrease intracellular free calcium (see section III A 7), there may be a link between this effect and impaired release of the secretagogue acetylcholine within the intestinal wall. Both the calcium (see section III A 7), there may be a link between
this effect and impaired release of the secretagogue ace-
tylcholine within the intestinal wall. Both the calcium
channel blocker verapamil and a Ca^{2+} -free bat this effect and impaired release of the secretagogue ace-
tylcholine within the intestinal wall. Both the calcium
channel blocker verapamil and a Ca^{2+} -free bathing so-
lution produced an increase in sodium and chloride tylcholine within the intestinal wall. Both the calcium
channel blocker verapamil and a Ca^{2+} -free bathing so-
lution produced an increase in sodium and chloride ab-
sorption in the rabbit intestine in vitro (85). Consi channel blocker verapamil and a Ca^{2+} -free bathing solution produced an increase in sodium and chloride absorption in the rabbit intestine in vitro (85). Consistent with the above hypothesis, $[D-Ala^2, Met^5]$ -enkephalin did lution produced an increase in sodium and chloride absorption in the rabbit intestine in vitro (85). Consistent
with the above hypothesis, [D-Ala², Met⁵]-enkephalin did
not further increase absorption under these condi sorption in the rabbit intestine in vitro (85). Consistent
with the above hypothesis, [D-Ala², Met⁵]-enkephalin did
not further increase absorption under these conditions
(85). Unfortunately, neither experimental condi with the above hypothesis, $[D-Ala^2, Met^5]$ -enkephalin did
not further increase absorption under these conditions
(85). Unfortunately, neither experimental conditions nor
detailed data have been reported in support of these
s not further increase absorption under these conditions (85). Unfortunately, neither experimental conditions nor detailed data have been reported in support of these statements. They do not allow any final assessment or con (85). Unfortunately, neither experimental conditions nor
detailed data have been reported in support of these
statements. They do not allow any final assessment or
conclusion as to the site, i.e., the cell type, within th detailed data have been reported in support of these
statements. They do not allow any final assessment or
conclusion as to the site, i.e., the cell type, within the
intestinal preparation where the calcium channel in
ques statements. They do not allow any final assessment or
conclusion as to the site, i.e., the cell type, within the
intestinal preparation where the calcium channel in
question may be located. Werz and MacDonald (473a)
conclu conclusion as to the site, i.e., the cell type, within the
intestinal preparation where the calcium channel in
question may be located. Werz and MacDonald (473a)
concluded from electrophysiological data that opioid
kappa-r intestinal preparation where the calcium channel in question may be located. Werz and MacDonald (473a) concluded from electrophysiological data that opioid kappa-receptors in mouse dosal root ganglion cells are coupled to question may be located. Werz and MacDonald (473a)
concluded from electrophysiological data that opioid
kappa-receptors in mouse dosal root ganglion cells are
coupled to a voltage-dependent calcium channel to de-
crease ca concluded from electrophysiological data that opioid
kappa-receptors in mouse dosal root ganglion cells are
coupled to a voltage-dependent calcium channel to de-
crease calcium-dependent action potential duration. This
eff kappa-receptors in mouse dosal root ganglion cells
coupled to a voltage-dependent calcium channel to
crease calcium-dependent action potential duration. T
effect might add to that of opioid mu- and delta-recept
which may i coupled to a voltage-dependent calcium channel to decrease calcium-dependent action potential duration. This effect might add to that of opioid mu- and delta-receptors which may increase potassium conductance to hyperpolar crease calcium-dependent action potential duration. This
effect might add to that of opioid mu- and delta-receptors
which may increase potassium conductance to hyperpo-
larize the cell membrane. It is tempting to speculate effect might add to that of opioid mu- and delta-receptors
which may increase potassium conductance to hyperpo-
larize the cell membrane. It is tempting to speculate
whether such opioid mechanisms explain similar effects
o which may increase potassium conductance to hyper
larize the cell membrane. It is tempting to specula
whether such opioid mechanisms explain similar effect
of verapamil and opioids in complex mucosal tissues.
might be note larize the cell membrane. It is tempting to speculate
whether such opioid mechanisms explain similar effects
of verapamil and opioids in complex mucosal tissues. It
might be noted that loperamide, which displays surfac-
ta whether such opioid mechanisms explain similar effects
of verapamil and opioids in complex mucosal tissues. It
might be noted that loperamide, which displays surfac-
tant properties and acts peripherally (486a), has been
s of verapamil and opioids in complex mucosal tissues. It
might be noted that loperamide, which displays surfac-
tant properties and acts peripherally (486a), has been
shown to inhibit calmodulin independently of its opioid
 might be noted that loperamide, which displays surfant properties and acts peripherally (486a), has lest above to inhibit calmodulin independently of its or properties (10a). This may be an additional mod antisecretory act shown to inhibit calmodulin independently of its opioid
properties (10a). This may be an additional mode of
antisecretory action, though at relatively high concentra-
tions.
Contrasting effects of opioids on canine intesti

properties (10a). This may be an additional mode of antisecretory action, though at relatively high concentra-
tions.
Contrasting effects of opioids on canine intestinal
blood flow have been described. Morphine may increas antisecretory action, though at relatively high concentra-
tions.
Contrasting effects of opioids on canine intestinal
blood flow have been described. Morphine may increase
or decrease intestinal blood flow, the increase be tions.
Contrasting effects of opioids on canine intestin
blood flow have been described. Morphine may increase
or decrease intestinal blood flow, the increase beir
possibly produced by a release of histamine (449). Vase
co Contrasting effects of opioids on canine intestinal
blood flow have been described. Morphine may increase
or decrease intestinal blood flow, the increase being
possibly produced by a release of histamine (449). Vaso-
const blood flow have been described. Morphine may increase
or decrease intestinal blood flow, the increase being
possibly produced by a release of histamine (449). Vaso-
constriction by larger doses of morphine was prevented
by or decrease intestinal blood flow, the increase beipossibly produced by a release of histamine (449). Valconstriction by larger doses of morphine was prevent by phentolamine and was attributed to adrenaline release from th possibly produced by a release of histamine (449). Vaso-
constriction by larger doses of morphine was prevented
by phentolamine and was attributed to adrenaline release
from the adrenal medulla. However, presynaptic inhibi constriction by larger doses of morphine was prevented
by phentolamine and was attributed to adrenaline release
from the adrenal medulla. However, presynaptic inhibi-
tion, not facilitation, of noradrenaline release has be by phentolamine and was attributed to adrenaline release
from the adrenal medulla. However, presynaptic inhibi-
tion, not facilitation, of noradrenaline release has been
attributed to opioid delta-receptor activation in th from the adrenal medulla. However, presynaptic inhibition, not facilitation, of noradrenaline release has been attributed to opioid delta-receptor activation in the rab bit ear artery (188). In fact, $[Met^5]$ -enkephalin, a tion, not facilitation, of noradrenaline release has been
attributed to opioid delta-receptor activation in the rab-
bit ear artery (188). In fact, [Met⁵]-enkephalin, an ago-
nist at opioid delta- and mu-receptors, incr attributed to opioid delta-receptor activation in the ral
bit ear artery (188). In fact, [Met⁵]-enkephalin, an ag
nist at opioid delta- and mu-receptors, increased me
enteric blood flow in the anesthetized dog (327). I
a bit ear artery (188). In fact, [Met⁵]-enkephalin, an agonist at opioid delta- and mu-receptors, increased mes-
enteric blood flow in the anesthetized dog (327). In
addition, Rozsa and Varro (358) found that the delta-
ag nist at opioid delta- and mu-receptors, increased
enteric blood flow in the anesthetized dog (32'
addition, Rozsa and Varro (358) found that the
agonist [D-Met², NleS⁶]-enkephalin-amide enha
and the mu- plus delta-agon enteric blood flow in the anesthetized dog (327).
addition, Rozsa and Varro (358) found that the delt
agonist [D-Met², NleS⁶]-enkephalin-amide enhance
and the mu- plus delta-agonist [D-Met², Pro⁸]-enkeph
lin-amide addition, Rozsa and Varro (358) found that the delta-
agonist [D-Met², NleS⁵]-enkephalin-amide enhanced,
and the mu- plus delta-agonist [D-Met², Pro⁵]-enkepha-
lin-amide inhibited the flow-increasing effect of chol agonist $[D-Met^2, NleS^5]$ -enkephalin-amide enhanced,
and the mu- plus delta-agonist $[D-Met^2, Pro^5]$ -enkepha-
lin-amide inhibited the flow-increasing effect of chole-
cystokinin-octapeptide (CCK-8) in the arteria ileocolica
of t and the mu- plus delta-agonist $[D-Met^2, Pro^5]$ -enkepha-
lin-amide inhibited the flow-increasing effect of chole-
cystokinin-octapeptide (CCK-8) in the arteria ileocolica
of the anesthetized dog. CCK-8 is known to release
ace lin-amide inhibited the flow-increasing effect of cholcystokinin-octapeptide (CCK-8) in the arteria ileocolic of the anesthetized dog. CCK-8 is known to releasetylcholine within the myenteric plexus (461). The there may be cystokinin-octapeptide (CCK-8) in the arteria ileocolic
of the anesthetized dog. CCK-8 is known to release
acetylcholine within the myenteric plexus (461). Thus
there may be superimposition of delta-receptor-mediate
inhibi acetylcholine within the myenteric plexus (461). Thus, there may be superimposition of delta-receptor-mediated inhibition of noradrenaline and mu-receptor-mediated inhibition of acetylcholine release in the intestinal wall

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cosal blood flow. This attribution of opioid receptor type
to hypothetical functions in this particular tissue requires further investigation.
8. The effect of naloxone in the absence of exogenous
opioids in vivo. Intralu to hypothetical functions in this particular tissue requires further investigation.
8. The effect of naloxone in the absence of exogenous
opioids in vivo. Intraluminal perfusion of rat small intes-
tinal loops by naloxone quires further investigation.

8. The effect of naloxone in the absence of exogeno

opioids in vivo. Intraluminal perfusion of rat small int

tinal loops by naloxone (100 μ mol/liter) or diprenorph

(1 μ mol/liter) de 8. The effect of naloxone in the absence of exogenous ant opioids in vivo. Intraluminal perfusion of rat small intes-
tinal loops by naloxone (100 μ mol/liter) or diprenorphine chlore (1 μ mol/liter) decreased basal w opioids in vivo. Intraluminal perfusion of rat small intes
tinal loops by naloxone $(100 \mu \text{mol/liter})$ or diprenorphin
 $(1 \mu \text{mol/liter})$ decreased basal water and ion net absorption in vivo (113) . Diprenorphine at $10 \mu \text{mol/liter}$ (1 μ mol/liter) decreased basal water and ion net absorption in vivo (113). Diprenorphine at 10 μ mol/liter also decreased basal water absorption in the rat colon. Lembeck and Beubler (253) found a small net secretory (1 μ mol/liter) decreased basal water and ion net absorp-colo
tion in vivo (113). Diprenorphine at 10 μ mol/liter also they
decreased basal water absorption in the rat colon. Lem-late
beck and Beubler (253) found a sm tion in vivo (113). Diprenorphine at 10 μ mol/liter also
decreased basal water absorption in the rat colon. Lem-
beck and Beubler (253) found a small net secretory effect
of s.c. naloxone in the conscious rat under PGE decreased basal water absorption in the rat colon. Lembeck and Beubler (253) found a small net secretory effect Ra of s.c. naloxone in the conscious rat under PGE_1 or VIP tio stimulation. These results may indicate toni beck and Beubler (253) found a small net secretory effect Racches of s.c. naloxone in the conscious rat under PGE₁ or VIP tion stimulation. These results may indicate tonic inhibition muot net fluid secretion by intestin of s.c. naloxone in the conscious rat under PGE_1 or VIP stimulation. These results may indicate tonic inhibition m
of net fluid secretion by intestinal opioids, although Lee m
and Coupar (249) or Chang et al. (56) were stimulation. These results may indicate tonic inhibition
of net fluid secretion by intestinal opioids, although Lee
and Coupar (249) or Chang et al. (56) were not able to
demonstrate any net secretory effect of s.c. naloxo of net fluid secretion by intestinal opioids, although Lee
and Coupar (249) or Chang et al. (56) were not able to
demonstrate any net secretory effect of s.c. naloxone or
naltrexone, respectively. When Fogel and Kaplan (11 and Coupar (249) or Chang et al. (56) were not able to
demonstrate any net secretory effect of s.c. naloxone or
naltrexone, respectively. When Fogel and Kaplan (113)
found that i.v. atropine prevented the net secretory eff demonstrate any net secretory effect of s.c. naloxone or
naltrexone, respectively. When Fogel and Kaplan (113)
found that i.v. atropine prevented the net secretory effect
of naloxone, but not that of diprenorphine, they su naltrexone, respectively. When Fogel and Kaplan (113) un
found that i.v. atropine prevented the net secretory effect ever
of naloxone, but not that of diprenorphine, they sug-
to gested that different receptors and mechani found that i.v. atropine prevented the net secretory effect evoluding the naloxone, but not that of diprenorphine, they sug-
gested that different receptors and mechanisms were nativated by the respective endogenous agoni of naloxone, but not that of diprenorphine, they sug-
gested that different receptors and mechanisms were na
activated by the respective endogenous agonists in the
rat. Although naloxone and diprenorphine in fact display gested that different receptors and mechanisms were
activated by the respective endogenous agonists in the
rat. Although naloxone and diprenorphine in fact display
different affinity profiles at opioid receptor types, the
 activated by the respective endogenous agonists in the
rat. Although naloxone and diprenorphine in fact display
different affinity profiles at opioid receptor types, the
above suggestion remains highly speculative consider rat. Although naloxone and diprenorphine in fact display
different affinity profiles at opioid receptor types, the
above suggestion remains highly speculative considering
that the differences in receptor type selectivity i different affinity profiles at opioid receptor types, the
above suggestion remains highly speculative considering
that the differences in receptor type selectivity is quite
small and solely due to naloxone (328a). It is o above suggestion remains highly speculative considering
that the differences in receptor type selectivity is quite
small and solely due to naloxone (328a). It is of particular
interest that enkephalinase inhibitors, thiorp that the differences in receptor type selectivity is quite
small and solely due to naloxone (328a). It is of particular
interest that enkephalinase inhibitors, thiorphan and
acetorphan, decreased castor oil-induced diarrh small and solely due to naloxone $(328a)$. It is of particular
interest that enkephalinase inhibitors, thiorphan and
acetorphan, decreased castor oil-induced diarrhea in the
rat in a naloxone-blockable fashion $(273a)$. T interest that enkephalinase inhibitors, thiorphan and
acetorphan, decreased castor oil-induced diarrhea in the
rat in a naloxone-blockable fashion (273a). This may
indicate a low degree of activation of endogenous opioids
 acetorphan, decreased castor oil-induced diarrhea in the
rat in a naloxone-blockable fashion (273a). This may
indicate a low degree of activation of endogenous opioids
and may correspond to the observation of Dobbins et al rat in a naloxone-blockable fashion (273a). This may distal to Brunner's glands. Contribution of pancreatic indicate a low degree of activation of endogenous opioids secretion was precluded by their technique. Maximum and and may correspond to the observation of Dobbins et al.
(86) that naloxone alone only occasionally caused a dramatic increase in short-circuit current in the isolated rabbit ileal mucosa.
B. Large Intestine (86) that naloxone alone only occasionally caused a dra-

Fabbit ileal mucosa.
 $B. Large Intestine$
 $[Leu⁵] -enkephalin specific binding on isolated guir
pig enterocytes from cecum and colon has been demc
strated (260). The capacity of both the low- and the high$ B. Large Intestine
[Leu⁶]-enkephalin specific binding on isolated guine
pig enterocytes from cecum and colon has been demon
strated (260). The capacity of both the low- and the high-
affinity site is lower in the large i B. Large Intestine with example in the large intervals in the large intervoytes from cecum and colon has been demon-
pig enterocytes from cecum and colon has been demon-
strated (260). The capacity of both the low- and the [Leu⁶]-enkephalin specific binding on isolated guinearing enterocytes from cecum and colon has been demonstrated (260). The capacity of both the low- and the high-affinity site is lower in the large intestine than in th g enterocytes from cecum and colon has been demon-
rated (260). The capacity of both the low- and the high-
finity site is lower in the large intestine than in the
all intestine. The functional significance is unknown.
In

strated (260). The capacity of both the low- and the high-
affinity site is lower in the large intestine than in the
small intestine. The functional significance is unknown. in
In the tied-off colon of the anesthetized rat affinity site is lower in the large intestine than in the small intestine. The functional significance is unknown. in the tied-off colon of the anesthetized rat, opioids rhad no effect on basal net water absorption but imp small intestine. The functional significance is unknown.
In the tied-off colon of the anesthetized rat, opioids
had no effect on basal net water absorption but impaired
stereospecificly the secretory influence of the laxat In the tied-off colon of the anesthetized rat, opioids
had no effect on basal net water absorption but impaired
stereospecificly the secretory influence of the laxative
bisacodyl (21). Naloxone alone had no effect. Bisacod had no effect on basal net water absorption but impaired
stereospecificly the secretory influence of the laxative
bisacodyl (21). Naloxone alone had no effect. Bisacodyl
is thought to stimulate intestinal prostaglandin syn stereospecificly the secretory influence of the laxative R
bisacodyl (21). Naloxone alone had no effect. Bisacodyl nalo
is thought to stimulate intestinal prostaglandin synthesis tric
(19, 20). In extension of these experi is thought to stimulate intestinal prostaglandin synthesis (19, 20). In extension of these experiments, Beubler et al. (18a) demonstrated that naloxone administration to the morphine-dependent rat did not affect mucosal cA is thought to stimulate intestinal prostaglandin synthesis tries

(19, 20). In extension of these experiments, Beubler et enl

al. (18a) demonstrated that naloxone administration to bic

the morphine-dependent rat did not (19, 20). In extension of these experiments, Beubler et al. (18a) demonstrated that naloxone administration to l
the morphine-dependent rat did not affect mucosal cAMP levels but resulted in an enhanced release of both ve al. (18a) demonstrated that naloxone administration to
the morphine-dependent rat did not affect mucosal
cAMP levels but resulted in an enhanced release of both
serotonin and PGE_2 into the colonic lumen. These events the morphine-dependent rat did not affect mucosal olar cAMP levels but resulted in an enhanced release of both was serotonin and PGE_2 into the colonic lumen. These events delt were accompanied by a reversal of net fluid cAMP levels but resulted in an enhanced release of bosecrotonin and PGE_2 into the colonic lumen. These ever
were accompanied by a reversal of net fluid absorptic
to net fluid secretion. The latter effect was prevented
s were accompanied by a reversal of net fluid absorption centrations. This may point to the involvement of opioid
to net fluid secretion. The latter effect was prevented by delta-receptors, but no firm conclusion can be dra to net fluid secretion. The latter effect was prevented by cluded, therefore, that opioid withdrawal might release

ER
serotonin, which in turn stimulates PGE_2 synthesis with
subsequent net fluid secretion. The converse may apply ER
serotonin, which in turn stimulates PGE_2 synthesis with
subsequent net fluid secretion. The converse may apply
to opioid agonists. ER
serotonin, which in
subsequent net flu
to opioid agonists.
Inhibition of ade Infidence and the intermulates PGE_2 synthesis with be equent net fluid secretion. The converse may apply opioid agonists.
Inhibition of adenylate cyclase as a mechanism of the tisecretory opioid action is controversial.

subsequent net fluid secretion. The converse may apply
to opioid agonists.
Inhibition of adenylate cyclase as a mechanism of the
antisecretory opioid action is controversial. Warhurst et
al. (466) reported that morphine en subsequent net fluid secretion. The converse may apply
to opioid agonists.
Inhibition of adenylate cyclase as a mechanism of the
antisecretory opioid action is controversial. Warhurst et
al. (466) reported that morphine en to opioid agonists.

Inhibition of adenylate cyclase as a mechanism of the

antisecretory opioid action is controversial. Warhurst et

al. (466) reported that morphine enhanced net water and

chloride absorption under basa Inhibition of adenylate cyclase as a mechanism of the
antisecretory opioid action is controversial. Warhurst et
al. (466) reported that morphine enhanced net water and
chloride absorption under basal conditions in the rat
 antisecretory opioid action is controversial. Warhur
al. (466) reported that morphine enhanced net water
chloride absorption under basal conditions in the
colon. In general agreement with Beubler et al. (
they found no inh al. (466) reported that morphine enhanced net water and
chloride absorption under basal conditions in the rat
colon. In general agreement with Beubler et al. (18a),
they found no inhibition by morphine of PGE₂-stimu-
lat colon. In general agreement with Beubler et al. (18
colon. In general agreement with Beubler et al. (18
they found no inhibition by morphine of PGE_2 -stim
lated colonic adenylate cyclase activity. In contra
Rachmilewitz colon. In general agreement with Beubler et al. (18a),
they found no inhibition by morphine of PGE₂-stimu-
lated colonic adenylate cyclase activity. In contrast,
Rachmilewitz et al. (341) found almost complete inhibi-
ti they found no inhibition by morphine of PGE₂-stimu-
lated colonic adenylate cyclase activity. In contrast,
Rachmilewitz et al. (341) found almost complete inhibi-
tion by opioids added in vitro to the human colonic
mucos lated colonic adenylate cyclase activity. In contrast,
Rachmilewitz et al. (341) found almost complete inhibi-
tion by opioids added in vitro to the human colonic
mucosal homogenate. Aside from this potential opioid
mechan Rachmilewitz et al. (341) found almost complete inhibition by opioids added in vitro to the human colonic mucosal homogenate. Aside from this potential opioid mechanism in the human colonic mucosa, inhibition of acetylchol tion by opioids added in vitro to the human colonic mucosal homogenate. Aside from this potential opioid mechanism in the human colonic mucosa, inhibition of acetylcholine release from the submucosal plexus of the colon ma mucosal homogenate. Aside from this potential opioion
mechanism in the human colonic mucosa, inhibition o
acetylcholine release from the submucosal plexus of the
colon may be another mechanism possibly operating
under diff mechanism in the human colonic mucosa, inhibition of acetylcholine release from the submucosal plexus of the colon may be another mechanism possibly operating under different conditions in the rat (121). So far, however, t acetylcholine release from the submucosal plexus of the colon may be another mechanism possibly operating under different conditions in the rat (121). So far, how-
ever, this hypothesis lacks support, since atropine failed colon may be another mechanism possibly operating
under different conditions in the rat (121). So far, how-
ever, this hypothesis lacks support, since atropine failed
to counteract net fluid secretion in the rat colon due under different conditions in the rat (121). So far, how-
ever, this hypothesis lacks support, since atropine failed
to counteract net fluid secretion in the rat colon due to
naloxone-precipitated morphine withdrawal (18a) to counteract net fluid secretion in the rat colon due to
naloxone-precipitated morphine withdrawal (18a), al-
though it prevented the net secretory effect of naloxone
in the rat small intestine in vivo (113).
C. Bicarbona *C.* Bicare-precipitated morthough it prevented the net in the rat small intestine in C. *Bicarbonate Secretion* Flemström et al. (111, 11

B. Large Intestine

[Leu⁵]-enkephalin specific binding on isolated guinea

[Leu⁵]-enkephalin specific binding on isolated guinea

pig entercovers from cecum and colon has been demon-

estingly, naloxone alone did not a ough it prevented the net secretory effect of naloxon
the rat small intestine in vivo (113).
Bicarbonate Secretion
Flemström et al. (111, 112) demonstrated in the anes-
etized rat in situ that morphine, beta-endorphine in the rat small intestine in vivo (113).

C. Bicarbonate Secretion

Flemström et al. (111, 112) demonstrated in the ant

thetized rat in situ that morphine, beta-endorph

[Met⁵]-enkephalin, and [Leu⁵]-enkephalin i.v. C. Bicarbonate Secretion

Flemström et al. (111, 112) demonstrated in the ant

thetized rat in situ that morphine, beta-endorph

[Met⁵]-enkephalin, and [Leu⁵]-enkephalin i.v. stimuted bicarbonate secretion from the duo C. Bicarbonate Secretion

Flemström et al. (111, 112) demonstrated in the anes-

thetized rat in situ that morphine, beta-endorphin,

[Met⁵]-enkephalin, and [Leu⁵]-enkephalin i.v. stimu-

lated bicarbonate secretion f Flemström et al. $(111, 112)$ demonstrated in the anes-
thetized rat in situ that morphine, beta-endorphin,
[Met⁵]-enkephalin, and [Leu⁵]-enkephalin i.v. stimu-
lated bicarbonate secretion from the duodenal mucosa
dis thetized rat in situ that morphine, beta-endorphin,

[Met⁵]-enkephalin, and [Leu⁵]-enkephalin i.v. stimu-

lated bicarbonate secretion from the duodenal mucosa

distal to Brunner's glands. Contribution of pancreatic
 [Met⁵]-enkephalin, and [Leu⁵]-enkephalin i.v. stimulated bicarbonate secretion from the duodenal mucosa
distal to Brunner's glands. Contribution of pancreatic
secretion was precluded by their technique. Maximum
stimula lated bicarbonate secretion from the duodenal mucosa
distal to Brunner's glands. Contribution of pancreatic
secretion was precluded by their technique. Maximum
stimulation was 100% above controls and blocked by
naloxone. A distal to Brunner's glands. Contribution of pancreatic
secretion was precluded by their technique. Maximum
stimulation was 100% above controls and blocked by
naloxone. Although [D-Ala², D-Leu⁵]-enkephalin failed
to inf stimulation was 100% above controls and blocked by
naloxone. Although [D-Ala², D-Leu⁵]-enkephalin failed
to influence bicarbonate secretion, no conclusion as to
the involvement of opioid receptor types can be drawn
fro naloxone. Although [D-Ala², D-Leu⁵]-enkephalin failed
to influence bicarbonate secretion, no conclusion as to
the involvement of opioid receptor types can be drawn
from these results, since all of the above agonists bi to influence bicarbonate secretion, no conclusion as the involvement of opioid receptor types can be draw
from these results, since all of the above agonists bir
with high affinity to both delta- and mu-receptors (3288
Thi from these results, since all of the above agonists bind
with high affinity to both delta- and mu-receptors (328a).
This discrepancy remains therefore unexplained. Inter-
estingly, naloxone alone did not affect basal bica from these results, since all of the above agonists bin
with high affinity to both delta- and mu-receptors (328a
This discrepancy remains therefore unexplained. Inter
estingly, naloxone alone did not affect basal bicarbona with high affinity to both delta- and mu-receptors (328a).
This discrepancy remains therefore unexplained. Inter-
estingly, naloxone alone did not affect basal bicarbonate
secretion, but impaired secretion induced by brief This discrepancy remains therefore unexplained. Inter-
estingly, naloxone alone did not affect basal bicarbonate
secretion, but impaired secretion induced by brief expo-
sure of the duodenal mucosa to low pH (112). This ma estingly, naloxone alone did not affect basal bicarbonate
secretion, but impaired secretion induced by brief expo-
sure of the duodenal mucosa to low pH (112). This may
indicate a possible role of endogenous opioids in the secretion, but impaired secretion induced
sure of the duodenal mucosa to low pH (
indicate a possible role of endogenous
mediation of acid-stimulated duodenal l
cretion as a means of mucosal protection
Rees et al. (346) fo re of the duodenal mucosa to low pH (112). This may
dicate a possible role of endogenous opioids in the
ediation of acid-stimulated duodenal bicarbonate se-
etion as a means of mucosal protection.
Rees et al. (346) found n

indicate a possible role of endogenous opioids in the
mediation of acid-stimulated duodenal bicarbonate se-
cretion as a means of mucosal protection.
Rees et al. (346) found no influence of opioids or
naloxone on bicarbona mediation of acid-stimulated duodenal bicarbonate se-
cretion as a means of mucosal protection.
Rees et al. (346) found no influence of opioids or
naloxone on bicarbonate secretion from amphibian gas-
tric mucosa in vitro. cretion as a means of mucosal protection.

Rees et al. (346) found no influence of opioids or

naloxone on bicarbonate secretion from amphibian gas-

tric mucosa in vitro. However, morphine and $[Met⁵]-$

enkephalin Rees et al. (346) found no influence of opioids
naloxone on bicarbonate secretion from amphibian g
tric mucosa in vitro. However, morphine and [Me
enkephalin significantly stimulated amphibian duode
bicarbonate secretion a naloxone on bicarbonate secretion from amphibian gas-
tric mucosa in vitro. However, morphine and [Met⁵]-
enkephalin significantly stimulated amphibian duodenal
bicarbonate secretion at concentrations in the microm-
olar tric mucosa in vitro. However, morphine and [Met⁵]-
enkephalin significantly stimulated amphibian duodenal
bicarbonate secretion at concentrations in the microm-
olar range by roughly 30% over basal levels. The effect
wa enkephalin significantly stimulated amphibian duodenabicarbonate secretion at concentrations in the micromolar range by roughly 30% over basal levels. The effect was blocked by naloxone and by the relatively selective delt bicarbonate secretion at concentrations in the microm-
olar range by roughly 30% over basal levels. The effect
was blocked by naloxone and by the relatively selective
delta-receptor antagonist ICI 154,129, albeit at high c olar range by roughly 30% over basal levels. The effect
was blocked by naloxone and by the relatively selective
delta-receptor antagonist ICI 154,129, albeit at high con-
centrations. This may point to the involvement of o was blocked by naloxone and by the relatively selective delta-receptor antagonist ICI 154,129, albeit at high condelta-receptors, but no firm conclusion can be drawn on centrations. This may point to the involvement of opioidelta-receptors, but no firm conclusion can be drawn of
the basis of these data. The opioid effect was also blockee
by tetrodotoxin, suggesting that the relevant opioi delta-receptors, but no firm conclusion can be drawn on
the basis of these data. The opioid effect was also blocked
by tetrodotoxin, suggesting that the relevant opioid re-
ceptors are located on neurons not mucosal cells.

OPIOIDS AND CONTROL OF GASTROINTESTINAL MOTILITY AND SECRETION ¹⁵¹

OPIOIDS AND CONTROL OF GASTROINT
effect to manifest itself, although Coupar (68) questioned
the neuronal selectivity of tetrodotoxin. OPIOIDS AND CONS
effect to manifest itself, although Coup
the neuronal selectivity of tetrodotoxin.
Replacement in the nutrient soluti

OPIOIDS AND CONTROL OF GASTROIN

fect to manifest itself, although Coupar (68) questioned

e neuronal selectivity of tetrodotoxin.

Replacement in the nutrient solution of bicarbonate

the impermeable anion 4-(2-hydroxyeth effect to manifest itself, although Coupar (68)
the neuronal selectivity of tetrodotoxin.
Replacement in the nutrient solution of b
by the impermeable anion 4-(2-hydroxyethyl
zineethanesulfonic acid (HEPES), removal o effect to manifest itself, although Coupar (68) questioned
the neuronal selectivity of tetrodotoxin.
Replacement in the nutrient solution of bicarbonate
by the impermeable anion 4-(2-hydroxyethyl)-1-pipera-
zineethanesulfo the neuronal selectivity of tetrodotoxin. The control of the impermeable anion 4-(2-hydroxyethyl)-1-piperation eximethanesulfonic acid (HEPES), removal of chloride, in or addition of furosemide inhibited the stimulation of Replacement in the nutrient solution of bicarbonate
by the impermeable anion 4-(2-hydroxyethyl)-1-pipera-
zineethanesulfonic acid (HEPES), removal of chloride,
or addition of furosemide inhibited the stimulation of
amphibi by the impermeable anion 4-(2-hydroxyethyl)-1-pipera-
zineethanesulfonic acid (HEPES), removal of chloride,
or addition of furosemide inhibited the stimulation of
amphibian duodenal bicarbonate secretion by morphine
(346). zineethanesulfonic acid (HEPES), removal of chloride,
or addition of furosemide inhibited the stimulation of
amphibian duodenal bicarbonate secretion by morphine
(346). The mechanism operated by the opioid receptor
may, th or addition of furosemide inhibited the stimulation of site amphibian duodenal bicarbonate secretion by morphine anti (346) . The mechanism operated by the opioid receptor min may, therefore, be an electroneutral Cl^-/HCO_3 amphibian duodenal bicarbonate secretion by morphine
 (346) . The mechanism operated by the opioid receptor minay, therefore, be an electroneutral Cl^-/HCO_3^- exchange. m

This would be consistent with a failure of opioid (346). The mechanism operated by the opioid receptom may, therefore, be an electroneutral Cl^-/HCO_3^- exchange. This would be consistent with a failure of opioids to affect the open-circuit potential difference across the may, therefore, be an electroneutral Cl^-/HCO_3^- exchange. must in this would be consistent with a failure of opioids to see affect the open-circuit potential difference across the change of an unidentified ion flux elevat affect the open-circuit potential difference across the mucosal tissue. The proposed mechanism is reminiscent of an unidentified ion flux elevated by morphine in the isolated rabbit ileal mucosa, which was tentatively at-
 affect the open-circuit potential difference across the mucosal tissue. The proposed mechanism is reminiscent of an unidentified ion flux elevated by morphine in the lisolated rabbit ileal mucosa, which was tentatively att mucosal tissue. The proposed mechanism is reminiscent sec
of an unidentified ion flux elevated by morphine in the
isolated rabbit ileal mucosa, which was tentatively at-
tributed to increased bicarbonate secretion in excha of an unidentified ion flux elevated by morphine in the
isolated rabbit ileal mucosa, which was tentatively at-
tributed to increased bicarbonate secretion in exchange
for absorbed chloride (280). Opioid mechanisms may
the isolated rabbit ileal mucosa, which was tentatively attributed to increased bicarbonate secretion in exchange
for absorbed chloride (280). Opioid mechanisms may
therefore be similar in amphibian and mammalian mu-
cosal tis tributed to increased bicarbonate secretion in exchange
for absorbed chloride (280). Opioid mechanisms may
therefore be similar in amphibian and mammalian mu-
cosal tissue with adherent submucosal plexus. However,
it is no for absorbed chloride (280). Opioid mechanisms m
therefore be similar in amphibian and mammalian n
cosal tissue with adherent submucosal plexus. Howev
it is not clear why Barbezat and Reasbeck (12), in stud
on dog jejunum, therefore be similar in amphibian and mammalian mu-
cosal tissue with adherent submucosal plexus. However,
it is not clear why Barbezat and Reasbeck (12), in studies
on dog jejunum, found increased net bicarbonate absorp-
 enkephalin. It has become increasingly evident in the past that and electrolyte absorption by $\frac{1}{2}$ pro

D. Conclusions

enkephalin. of ii

D. Conclusions app

It has become increasingly evident in the past that an $\frac{1}{100}$

enhancement of net water and electrolyte absorption by protopioids in both the small and large intestine may be a D. Conclusions

It has become increasingly evident in the past that an $\frac{1}{10}$

enhancement of net water and electrolyte absorption by pro

opioids in both the small and large intestine may be a

major component of the major conclusions
It has become increasingly evident in the past that an
enhancement of net water and electrolyte absorption by
popioids in both the small and large intestine may be a
major component of their antidiarrheal It has become increasingly evident in the past that an enhancement of net water and electrolyte absorption by opioids in both the small and large intestine may be a major component of their antidiarrheal (227) as oppose enhancement of net water and electrolyte absorption by
opioids in both the small and large intestine may be a
major component of their antidiarrheal (227) as opposed
to constipating (84) effect. The latter may be determine provides in both the small and large intestine may be a major component of their antidiarrheal (227) as opposed to constipating (84) effect. The latter may be determined predominantly by motility changes, but the effects m major component of their antidiarrheal (227) as opposed
to constipating (84) effect. The latter may be determined
predominantly by motility changes, but the effects most
probably act in concert, as already discussed by Kru to constipating (84) effect. The latter may be determined
predominantly by motility changes, but the effects most
probably act in concert, as already discussed by Krueger
(244). The intestinal net antisecretory action of o predominantly by motility changes, but the effects most by probably act in concert, as already discussed by Krueger net (244). The intestinal net antisecretory action of opioids sy is observed in all species tested so far, probably act in concert, as already discussed by Kruege (244). The intestinal net antisecretory action of opioid
is observed in all species tested so far, including man
Both basal net water and electrolyte fluxes and thos
 (244). The intestinal net antisecretory action of opioid
is observed in all species tested so far, including man
Both basal net water and electrolyte fluxes and those
stimulated by various secretagogues like PGE, VIP, chol is observed in all species tested so far, including man. rolled to basal net water and electrolyte fluxes and those timulated by various secretagogues like PGE, VIP, chologera toxin, E . coli heat-stable toxin, carbachol Both basal net water and electrolyte fluxes and the
stimulated by various secretagogues like PGE, VIP, ch
era toxin, E. coli heat-stable toxin, carbachol, or bis
codyl may be affected by opioids, but this depends on t
spec stimulated by various secretagogues like PGE, VIP, chol-
era toxin, E. coli heat-stable toxin, carbachol, or bisa-
codyl may be affected by opioids, but this depends on the
respecies and experimental conditions. The opioid era toxin, E . coli heat-stable toxin, carbachol, or bisacodyl may be affected by opioids, but this depends on the species and experimental conditions. The opioid mechanism is stereospecific and blocked by naloxone, whic species and experimental conditions. The opioid mecha-
nism is stereospecific and blocked by naloxone, which is
suggestive of a receptor-mediated action.
Aside from a peripheral mechanism, a central opioid
mechanism exists

nism is stereospecific and blocked by naloxone, which is
suggestive of a receptor-mediated action.
Aside from a peripheral mechanism, a central opioid
mechanism exists, which also results in an increase in
water and electr suggestive of a receptor-mediated action.
Aside from a peripheral mechanism, a central opioi
mechanism exists, which also results in an increase i
water and electrolyte net absorption. This central effec
may be mediated by Aside from
mechanism
water and el
may be medi
ous system.
Opioid del echanism exists, which also results in an increase in alter and electrolyte net absorption. This central effect
ay be mediated by stimulation of the sympathetic nerv-
bs system.
Opioid delta-receptors may be involved in th water and electrolyte net absorption. This central effect
may be mediated by stimulation of the sympathetic nerv-
ous system.
Opioid delta-receptors may be involved in the guinea
copia at peripheral and in the rat at centr

may be mediated by stimulation of the sympathetic nerv-
ous system.
Opioid delta-receptors may be involved in the guinea
pig at peripheral and in the rat at central and possibly
peripheral sites. In addition, rat data indi ous system.

Opioid delta-receptors may be involved in the guinea

pig at peripheral and in the rat at central and possibly

peripheral sites. In addition, rat data indicate participa-

tion of mu-receptors. In the isolate Opioid delta-receptors may be involved in the guinea
pig at peripheral and in the rat at central and possibly
peripheral sites. In addition, rat data indicate participa-
tion of mu-receptors. In the isolated tissue, releva plexus, as evidenced and in the rat at central and possibly
peripheral sites. In addition, rat data indicate participa-
ion of mu-receptors. In the isolated tissue, relevant
preceptors are probably located within the submu peripheral sites. In addition, rat data indicate participation of mu-receptors. In the isolated tissue, relevant receptors are probably located within the submucosal plexus, as evidenced by sensitivity of the opioid effect receptors are probably located within the submucosal
plexus, as evidenced by sensitivity of the opioid effects
to tetrodotoxin. Enterocytes may additionally carry func-
tional opioid receptors, but this needs further clari tion. exus, as evidenced by sensitivity of the opioid effects part
tetrodotoxin. Enterocytes may additionally carry func-
incomal opioid receptors, but this needs further clarifica-
each
m.
Whether peripheral action involves an to tetrodotoxin. Enterocytes may additionally carry func-
tional opioid receptors, but this needs further clarifica-
ion.
Whether peripheral action involves an impairment in
adenylate cyclase activity stimulated by, e.g.,

tional opioid receptors, but this needs further clarifica-
tion.
Whether peripheral action involves an impairment in
adenylate cyclase activity stimulated by, e.g., PGE, is
controversial. Opioid inhibition of acetylcholine

FINAL MOTILITY AND SECRETION 151
from the submucosal plexus may also be involved under
certain conditions, although atropine failed to prevent ESTINAL MOTILITY AND SECRETION 151
from the submucosal plexus may also be involved under
certain conditions, although atropine failed to prevent
the opioid effect as far as reported. The net secretory TESTINAL MOTILITY AND SECRETION 151
from the submucosal plexus may also be involved under
certain conditions, although atropine failed to prevent
the opioid effect as far as reported. The net secretory
effect of naloxone, from the submucosal plexus may also be involved under
certain conditions, although atropine failed to prevent
the opioid effect as far as reported. The net secretory
effect of naloxone, however, was prevented by atropine
i from the submucosal plexus may also be involved under
certain conditions, although atropine failed to prevent
the opioid effect as far as reported. The net secretory
effect of naloxone, however, was prevented by atropine
i certain conditions, although atropine failed to prevent
the opioid effect as far as reported. The net secretory
effect of naloxone, however, was prevented by atropine
in the rat in vivo. Moreover, an increase in absorptive the opioid effect as far as reported. The net secreto-
effect of naloxone, however, was prevented by atropin
in the rat in vivo. Moreover, an increase in absorpti-
site blood flow by opioids has been implicated in the
anti effect of naloxone, however, was prevented by atropine
in the rat in vivo. Moreover, an increase in absorptive
site blood flow by opioids has been implicated in their
antisecretory action. The feeding state seems to detersite blood flow by opioids has been implicated in their
antisecretory action. The feeding state seems to deter-
mine this action component. The final outcome, at the
mucosal level, is predominantly a decrease in chloride
s site blood flow by opioids has been implicated in their
antisecretory action. The feeding state seems to deter-
mine this action component. The final outcome, at the
mucosal level, is predominantly a decrease in chloride
s antisecretory action. The feeding state seems to determine this action component. The final outcome, at the mucosal level, is predominantly a decrease in chloride secretion. Since chloride is probably electroneutrally exch mine this action component. The final outcome, at the mucosal level, is predominantly a decrease in chloride secretion. Since chloride is probably electroneutrally exchanged for bicarbonate, this results in decreased net s mucosal level, is predominantly a decrease in chloride
secretion. Since chloride is probably electroneutrally ex-
changed for bicarbonate, this results in decreased net
secretion of chloride and in increased net secretion secretion. Since chloride is probably electroneutrally ex-
changed for bicarbonate, this results in decreased net
secretion of chloride and in increased net secretion of
bicarbonate. The latter effect has been demonstrated changed for bicarbonate, this results in decreased net
secretion of chloride and in increased net secretion of
bicarbonate. The latter effect has been demonstrated in
rat and amphibian duodenal mucosa, is blocked by nal-
o secretion of chloride and in increased net secretion of
bicarbonate. The latter effect has been demonstrated in
rat and amphibian duodenal mucosa, is blocked by nal-
oxone, and is sensitive to tetrodotoxin, pointing to neu rat and amphibian duodenal mucosa, is blocked by nal-
oxone, and is sensitive to tetrodotoxin, pointing to neu-
ronal mediation.
Data on the influence of opioid antagonists on fluid
and electrolyte secretion in the small a

oxone, and is sensitive to tetrodotoxin, pointing to neu-
ronal mediation.
Data on the influence of opioid antagonists on fluid
and electrolyte secretion in the small and large intestine
are controversial, but under partic ronal mediation.

Data on the influence of opioid antagonists on fluid

and electrolyte secretion in the small and large intesting

are controversial, but under particular circumstance

inhibition of net absorption by nalo Data on the influence of opioid antagonists on fluid
and electrolyte secretion in the small and large intestine
are controversial, but under particular circumstances
inhibition of net absorption by naloxone seems to indi-
 and electrolyte secretion in the small and large intestine
are controversial, but under particular circumstances
inhibition of net absorption by naloxone seems to indi-
cate that endogenous opioids are functional in the co are controversial, but under particular circumstances
inhibition of net absorption by naloxone seems to indi-
cate that endogenous opioids are functional in the control
of intestinal secretion. Endogenous opioids, for exam inhibition of net absorption by naloxone seems to indicate that endogenous opioids are functional in the control
of intestinal secretion. Endogenous opioids, for example,
appear to participate in the enhancement of bicarbo cate that endogenous opioids are functional in the control
of intestinal secretion. Endogenous opioids, for example,
appear to participate in the enhancement of bicarbonate
secretion effected by exposure of the duodenal m of intestinal secretion. Endogenous opicappear to participate in the enhancement
secretion effected by exposure of the
to low pH and may, thus, be involved
protective mechanisms of the mucosa.
VI General Conclusions and We participate in the emanitement of bicarbon
on effected by exposure of the duodenal muo
pH and may, thus, be involved physiologicall
ive mechanisms of the mucosa.
VI. General Conclusions and Outlook
endogenous opioids an low pH and may, thus, be involved physiologically in
otective mechanisms of the mucosa.
VI. General Conclusions and Outlook
Both endogenous opioids and opioid receptors have
en found within the gastrointestinal wall, the e

dyl may be affected by opioids, but this depends on the respect to physiological functions of endogenous opioids,
ecies and experimental conditions. The opioid mecha-
although many unresolved questions and contradictory
sm mal mediation.

Data on the influence of opioid antagonists on fluid

electrolyte secretion in the small and large intestine

e controversial, but under particular circumstances

hibition of net absorption by naloxone see protective mechanisms of the mucosa.

VI. General Conclusions and Outlook

Both endogenous opioids and opioid receptors have

been found within the gastrointestinal wall, the extrinsic

nerve fibers innervating the gut, an VI. General Conclusions and Outlook
Both endogenous opioids and opioid receptors have
been found within the gastrointestinal wall, the extrinsic
nerve fibers innervating the gut, and the central nervous
system. Since vario VI. General Conclusions and Outlook
Both endogenous opioids and opioid receptors have
been found within the gastrointestinal wall, the extrinsic
nerve fibers innervating the gut, and the central nervous
system. Since vario Both endogenous opioids and opioid receptors
been found within the gastrointestinal wall, the extr
nerve fibers innervating the gut, and the central ner
system. Since various neurotransmitter as well as
rohormonal systems been found within the gastrointestinal wall, the extrinsic
nerve fibers innervating the gut, and the central nervous
system. Since various neurotransmitter as well as neu-
rohormonal systems are known to modulate gastroint nerve fibers innervating the gut, and the central nervous
system. Since various neurotransmitter as well as neu-
rohormonal systems are known to modulate gastrointes-
tinal functions, physiological involvement of endogenou system. Since various neurotransmitter as well as neurohormonal systems are known to modulate gastrointes-
tinal functions, physiological involvement of endogenous
opioids and pathophysiological disturbances thereof are
to rohormonal systems are known to modulate gastrointes-
tinal functions, physiological involvement of endogenous
opioids and pathophysiological disturbances thereof are
to be anticipated. This forecast has been confirmed wit tinal functions, physiological involvement of endogenous
opioids and pathophysiological disturbances thereof are
to be anticipated. This forecast has been confirmed with
respect to physiological functions of endogenous opi opioids and pathophysiological disturbances thereof at to be anticipated. This forecast has been confirmed wi
respect to physiological functions of endogenous opioial
though many unresolved questions and contradict
results to be anticipated. This forecast has been confirmed with
respect to physiological functions of endogenous opioids,
although many unresolved questions and contradictory
results await further attention. As to potential path although many unresolved questions and contradictory able. sults await further attention. As to potential patho-
ysiological states which might involve imbalances in
dogenous opioid systems, no conclusive data are avail-
le.
Only opioid effects on intestinal water, electrolyte, an

physiological states which might involve imbalances in
endogenous opioid systems, no conclusive data are avail-
able.
Only opioid effects on intestinal water, electrolyte, and
bicarbonate secretion are unequivocal. By cont endogenous opioid systems, no conclusive data are available.

Only opioid effects on intestinal water, electrolyte, and

bicarbonate secretion are unequivocal. By contrast, dual

effects on gastric acid secretion were obse able.

Only opioid effects on intestinal water, electrolyte, and

bicarbonate secretion are unequivocal. By contrast, dual

effects on gastric acid secretion were observed under

certain experimental conditions, even simu Only opioid effects on intestinal water, electrolyte, and
bicarbonate secretion are unequivocal. By contrast, dual
effects on gastric acid secretion were observed under
certain experimental conditions, even simultaneously bicarbonate secretion are unequivocal. By contrast, dual
effects on gastric acid secretion were observed under
certain experimental conditions, even simultaneously in
the same animal. Similarly conflicting data have been
r effects on gastric acid secretion were observed under
certain experimental conditions, even simultaneously in
the same animal. Similarly conflicting data have been
reported with respect to opioid influences on various
para certain experimental conditions, even simultaneously in
the same animal. Similarly conflicting data have been
reported with respect to opioid influences on various
parameters of gastrointestinal motility. At a close look,
 the same animal. Similarly conflicting data have been reported with respect to opioid influences on various parameters of gastrointestinal motility. At a close look, it appears that contrasting opioid effects are observed reported with respect to opioid influences on various
parameters of gastrointestinal motility. At a close look,
it appears that contrasting opioid effects are observed in
parallel within each species rather than separately parameters of gastrointestinal motility. At a close look, it appears that contrasting opioid effects are observed in parallel within each species rather than separately in different species and occur at varying ratios rela it appears that contrasting opioid effects are observed in parallel within each species rather than separately in different species and occur at varying ratios relative to each other. The relative significance of these con parallel within each species rather than separately in different species and occur at varying ratios relative to each other. The relative significance of these contrasting opioid effects may then define species differences different species and occur at varying ratios relative to each other. The relative significance of these contrasting opioid effects may then define species differences. Hence, these appear quantitative rather than qualitat each other. The relative significance of these contrasting
opioid effects may then define species differences. Hence,
these appear quantitative rather than qualitative in na-
ture. They might wrongly be considered qualitat

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animal species are compared. The reason for the occur-
rence of contrasting opioid effects on one physiological KR
animal species are compared. The reason for the occur-
rence of contrasting opioid effects on one physiologica
system and in one species may be that opioids are inhibs
animal species are compared. The reason for the occurence of contrasting opioid effects on one physiologic
system and in one species may be that opioids are inhi
itory neuromodulators with functional roles at multip itory animal species are compared. The reason for the occurrence of contrasting opioid effects on one physiological functional roles at multiple is itory neuromodulators with functional roles at multiple is sites. Inhibiti animal species are compared. The reason for the occurrence of contrasting opioid effects on one physiological
system and in one species may be that opioids are inhib-
itory neuromodulators with functional roles at multiple rence of contrasting opioid effects on one physiological
system and in one species may be that opioids are inhib-
itory neuromodulators with functional roles at multiple
sites. Inhibition of excitatory functions results in itory neuromodulators with functional roles at multiple
sites. Inhibition of excitatory functions results in final
inhibition, inhibition of inhibitory functions in final
excitation, i.e., desinhibition.
There is close int For neuromodulators with functional roles at multions. Inhibition of excitatory functions results in hibition, inhibition of inhibitory functions in citation, i.e., desinhibition.
There is close interdependence between gas

sites. Inhibition of excitatory functions results in final
inhibition, inhibition of inhibitory functions in final
excitation, i.e., desinhibition.
There is close interdependence between gastrointes-
tinal motility, blood inhibition, inhibition of inhibitory functions in final
excitation, i.e., desinhibition.
There is close interdependence between gastrointes-
tinal motility, blood flow, acid secretion, bicarbonate
secretion, water, and ele excitation, i.e., desinhibition. who

There is close interdependence between gastrointes-

tinal motility, blood flow, acid secretion, bicarbonate work

secretion, water, and electrolyte secretion (345, 203, 329, tric

145 There is close interdependence between gastroint
tinal motility, blood flow, acid secretion, bicarbon
secretion, water, and electrolyte secretion (345, 203, 3
145). Motility and secretion occur simultaneously
many instance tinal motility, blood flow, acid secretion, bicarbonate
secretion, water, and electrolyte secretion (345, 203, 329,
145). Motility and secretion occur simultaneously in
many instances. For example, distension of the gastro secretion, water, and electrolyte secretion (345, 203, 329, 145). Motility and secretion occur simultaneously in many instances. For example, distension of the gastrointestinal wall, vagal activation, acetylcholine, histam 145). Motility and secretion occur simultaneousl
many instances. For example, distension of the gastr
testinal wall, vagal activation, acetylcholine, histan
gastrin, bile salts, or cholera toxin elicit both contra
and secr many instances. For example, distension of the gastroin-
testinal wall, vagal activation, acetylcholine, histamine, of ϵ
gastrin, bile salts, or cholera toxin elicit both contractile tor,
and secretory responses. On th testinal wall, vagal activation, acetylcholine, histamine
gastrin, bile salts, or cholera toxin elicit both contractil
and secretory responses. On the other hand, noradrena
line inhibits gastrointestinal motility, gastric gastrin, bile salts, or cholera toxin elicit both contractile
and secretory responses. On the other hand, noradrena-
line inhibits gastrointestinal motility, gastric acid, and
intestinal secretion. There are exceptions lik and secretory responses. On the other hand, noradrena-
line inhibits gastrointestinal motility, gastric acid, and
intestinal secretion. There are exceptions like the pros-
of taglandins, which stimulate motility as well a line inhibits gastrointestinal motility, gastric acid, and
intestinal secretion. There are exceptions like the pros-
taglandins, which stimulate motility as well as intestinal
fluid and electrolyte secretion, but inhibit intestinal secretion. There are exceptions like the prostaglandins, which stimulate motility as well as intestinal fluid and electrolyte secretion, but inhibit gastric acid secretion. As a general rule, secretagogues incre taglandins, which stimulate motility as well as intestinal
fluid and electrolyte secretion, but inhibit gastric acid me:
secretion. As a general rule, secretagogues increase and (22
antisecretory compounds decrease mucosa fluid and electrolyte secretion, but inhibit gastric acid
secretion. As a general rule, secretagogues increase and
antisecretory compounds decrease mucosal blood flow,
but there are again exceptions, as prostaglandins and
 secretion. As a general rule, secretagogues increase antisecretory compounds decrease mucosal blood fl
but there are again exceptions, as prostaglandins a
beta-adrenoceptor agonists increase mucosal blood fl
but inhibit ac antisecretory compounds decrease mucosal blood flow,
but there are again exceptions, as prostaglandins and
beta-adrenoceptor agonists increase mucosal blood flow,
but inhibit acid secretion. Obviously, complex intereac-
ti beta-adrenoceptor agonists increase mucosal blood flow,
beta-adrenoceptor agonists increase mucosal blood flow,
but inhibit acid secretion. Obviously, complex intereac-
diffuns occur between these functions, but there is n beta-adrenoceptor agonists increase mucosal blood flow,
but inhibit acid secretion. Obviously, complex intereac-
tions occur between these functions, but there is no strict
stroughing. The mechanisms by which these functio but inhibit acid secretion. Obviously, complex intereac-
tions occur between these functions, but there is no strict
coupling. The mechanisms by which these functions are
interrelated may comprise parallel innervation of t tions occur between these functions, but there is no strict
coupling. The mechanisms by which these functions are
interrelated may comprise parallel innervation of the
different structures by the same extrinsic nerves, lea coupling. The mechanisms by which these functions are
interrelated may comprise parallel innervation of the
different structures by the same extrinsic nerves, leading
to simple coincidences, as well as sequential relations different structures by the same extrinsic nerves, leading
to simple coincidences, as well as sequential relationships
brought about by mechanical, hormonal, and neuronal
links (for review, see ref. 145).
Opioids are well to simple coincidences, as well as sequential relationships
brought about by mechanical, hormonal, and neuronal
links (for review, see ref. 145).
Opioids are well known to affect all of these functions.
For example, opioid

to simple coincidences, as well as sequential relationship
brought about by mechanical, hormonal, and neurona
links (for review, see ref. 145).
Opioids are well known to affect all of these functions
For example, opioids h brought about by mechanical, hormonal, and neuronal
links (for review, see ref. 145).
Opioids are well known to affect all of these functions.
For example, opioids have specific effects on postprandial
gastrointestinal hor links (for review, see ref. 145).

Opioids are well known to affect all of these functif

For example, opioids have specific effects on postprandial

gastrointestinal hormone secretion. This is exemplif

by the postprandia Opioids are well known to affect all of these functions.
For example, opioids have specific effects on postprandial
gastrointestinal hormone secretion. This is exemplified
by the postprandial increase in serum gastrin conc For example, opioids have specific effects on postprandial gastrointestinal hormone secretion. This is exemplified by the postprandial increase in serum gastrin concentration which, in man, was prolonged by morphine (55). gastrointestinal hormone secretion. This is exemplified
by the postprandial increase in serum gastrin concentra-
tion which, in man, was prolonged by morphine (55).
Inhibition of acetylcholine release from the myenteric
an by the postprandial increase in serum gastrin concentra-
tion which, in man, was prolonged by morphine (55).
Inhibition of acetylcholine release from the myenteric
and submucosal plexus by opioids indicates a neuronal
sit **Inhibition of acetylcholine release from the myenteric** 1370-1375, 1986.
 and submucosal plexus by opioids indicates a neuronal
 EXECUTE ACCESTRUP, S., UDDMAN, R., JENSEN, ST. L., SUNDLER, F., SCHAPPAL-
 EXECUTE ACC and submucosal plexus by opioids indicates a neuronal and submucosal plexus by opioids indicates a neuronal
site, where different gastrointestinal functions may be
linked to each other. In the first example, both motility
and gastric secretion may be enhanced, although confli site, where different gastrointestinal functions may be linked to each other. In the first example, both motility and gastric secretion may be enhanced, although conflicting data were reported in different species. Both mo example. d gastric secretion may be enhanced, although confl
g data were reported in different species. Both moti
d secretion, however, will be impaired in the sec
ample.
It is difficult to assess whether opioids affect gastro
stin

ing data were reported in different species. Both motility and secretion, however, will be impaired in the second example.
It is difficult to assess whether opioids affect gastroin-
testinal motility, secretion, and mucosa and secretion, however, will be impaired in the second
example.
It is difficult to assess whether opioids affect gastroin-
testinal motility, secretion, and mucosal integrity at sim-
ilar dose levels, since data are mostl example.
It is difficult to assess whether opioids affect gastroin-
testinal motility, secretion, and mucosal integrity at sim-
ilar dose levels, since data are mostly incomparable due
to considerable differences in experi It is difficult to assess whether opioids affect gastroin-
testinal motility, secretion, and mucosal integrity at sim-
ilar dose levels, since data are mostly incomparable due
to considerable differences in experimental c testinal motility, secretion, and mucosal integrity at similar dose levels, since data are mostly incomparable due
to considerable differences in experimental conditions.
This important question could possibly be answered filar dose levels, since data are mostly incomparable due
to considerable differences in experimental conditions.
This important question could possibly be answered in
dogs with chronically implanted gastric and intestina This important question could possibly be answered in dogs with chronically implanted gastric and intestinal fistulas as well as electrodes or strain gauges, fixed to the intestinal serosa. Under these conditions, the diff This important question could possibly be answered in
dogs with chronically implanted gastric and intestinal
fistulas as well as electrodes or strain gauges, fixed to
the intestinal serosa. Under these conditions, the diff dogs with chronically implanted gastric and intestinal
fistulas as well as electrodes or strain gauges, fixed to
the intestinal serosa. Under these conditions, the differ-
ent parameters may be determined simultaneously in fistulas as well as electrodes or strain gauges, fixed to
the intestinal serosa. Under these conditions, the differ-
ent parameters may be determined simultaneously in the
same animal by constructing dose-response curves. the intestinal serosa. Under these cond
ent parameters may be determined simi
same animal by constructing dose-respo
attention should be given to this prob
periments, though the task is difficult.

poside that the controlling and modulating these the opioid receptors controlling and modulating these actions are located both centrally and peripherally, FUNCTURE
THE Opioid receptors controlling and modulating thes
functions are located both centrally and peripherally
probably comprising different mechanisms and resultin FR

Opioid receptors controlling and modulating these

functions are located both centrally and peripherally,

probably comprising different mechanisms and resulting

in different effects at different sites. It is not poss Dpioid receptors controlling and modulating these
functions are located both centrally and peripherally,
probably comprising different mechanisms and resulting
in different effects at different sites. It is not possible, a Opioid receptors controlling and modulating these
functions are located both centrally and peripherally,
probably comprising different mechanisms and resulting
in different effects at different sites. It is not possible, a functions are located both centrally and peripherally,
probably comprising different mechanisms and resulting
in different effects at different sites. It is not possible, at
present, to relate specific mechanisms and effec probably comprising different mechanisms and result
in different effects at different sites. It is not possible
present, to relate specific mechanisms and effects to e
other in order to build up a comprehensive picture of
 in different effects at different sites. It is not possible, at present, to relate specific mechanisms and effects to each other in order to build up a comprehensive picture of the whole opioid system involved in the contr present, to relate specific mechanisms and effects to each
other in order to build up a comprehensive picture of the
whole opioid system involved in the control of gastroin-
testinal functions. This is a great challenge fo other in order to build up a comprehensive picture of the whole opioid system involved in the control of gastroin testinal functions. This is a great challenge for future work. Diminished acid secretion (90) plus impaired whole opioid system involved in the control of gastroin-
testinal functions. This is a great challenge for future
work. Diminished acid secretion (90) plus impaired gas-
tric motility might increase the risk of bacterial o work. Diminished acid secretion (90) plus impaired gas-
tric motility might increase the risk of bacterial over-
growth in the stomach. It might be speculated therefore
that, under special circumstances, the antimotility e of endogenous opioids may go along with the acid secretric motility might increase the risk of bacterial over-
growth in the stomach. It might be speculated therefore
that, under special circumstances, the antimotility effect
of endogenous opioids may go along with the acid s growth in the stomach. It might be speculated therefore
that, under special circumstances, the antimotility effect
of endogenous opioids may go along with the acid secre-
tory effect. Hibernation may exemplify a particular that, under special circumstances, the antimotility effect
of endogenous opioids may go along with the acid secre-
tory effect. Hibernation may exemplify a particular stage
in animal life where endogenous opioids possibly of endogenous opioids may go along with the acid secre-
tory effect. Hibernation may exemplify a particular stage
in animal life where endogenous opioids possibly play
some physiological role (228) and where a combination
 tory effect. Hibernation may exemplify a particular stain animal life where endogenous opioids possibly popen physiological role (228) and where a combination antimotility with a minimum acid secretory opioideffect would m in animal life where endogenous opioids possibly play
some physiological role (228) and where a combination
of antimotility with a minimum acid secretory opioid
effect would make biological sense. Although involve-
ment of some physiological role (228) and where a combination
of antimotility with a minimum acid secretory opioid
effect would make biological sense. Although involve-
ment of endogenous opioids in hibernation was suggested
(228) of antimotility with a minimum acid secretory opioid
effect would make biological sense. Although involve-
ment of endogenous opioids in hibernation was suggested
(228) and has been supported by recent findings (39a), it
s speculative. ent of endogenous opioids in hibernation was suggested
28) and has been supported by recent findings (39a), it
ould once more be noted that these notions are still
eculative.
Since different opioid systems may be equipped

should once more be noted that these notions are still
speculative.
Since different opioid systems may be equipped with
different opioid receptor types, future pharmacological
studies may well unravel the complex and somet should once more be noted that these notions are still
speculative.
Since different opioid systems may be equipped with
different opioid receptor types, future pharmacological
studies may well unravel the complex and somet speculative.
Since different opioid systems may be equipped with
different opioid receptor types, future pharmacological
studies may well unravel the complex and sometimes
contradictory opioid actions, to put them to clini *Acknowledgments.* Careful typing of the manuscript by Mrs. I. Here, is gratefully acknowledged.

contradictory opioid a
Ac*knowledgments*. Caref
zog is gratefully acknowled_!

REFERENCES

- 1. ABBOTT, W. O., AND PENDERGRASS, E. P.: Intubation studies of the human

1. ABBOTT, W. O., AND PENDERGRASS, E. P.: Intubation studies of the human

small intestine. V. The motor effects of single clinical doses of morphi REFERENCES
Sulphate in normal subjects. Am. J. R. Intubation studies of the human
small intestine. V. The motor effects of single clinical doses of morphine
sulphate in normal subjects. Am. J. Roentgenol. Radium Ther. 35: **299, 1936.** 2. ADLER, H. F., AND PENDERGRASS, E. P.: Intubation studies of the human small intestine. V. The motor effects of single clinical doses of morphine sulphate in normal subjects. Am. J. Roentgenol. Radium Ther.
- colon of man. Arch. Internet med. Supplementations of man. Archives and phate in normal subjects. Am. J. Roentgenol. Radium Ther. 35: 289-
299, 1936.
2. ADLER, H. F., ATKINSON, A. J., AND IVY, A. C.: Effect of morphine and
- EDLER, H. F., ATKINSON, A. J., AND IVY, A. C.: Effect of morphine and dilaudid on the ileum and of morphine, dilaudid, and atropine on the colon of man. Arch. Intern. Med. 69: 974–985, 1942.
GGESTRUP, S., UDDMAN, R., JENSE dilaudid on the ileum and of morphine, dilaudid, and atropine on the
colon of man. Arch. Intern. Med. **69:** 974-985, 1942.
3. AGGESTRUP, S., UDDMAN, R., JENSEN, ST. L., HAKANSON, P.: Regulatory
F., SCHAFFALITZKY DE MUCKADE 4. AGGESTRUP, S., UDDMAN, R., JENSEN, ST. L., HAKANSON, R., SUNDLER,
F., SCHAFFALITZKY DE MUCKADELL, O., AND EMSON, P.: Regulatory
peptides in lower esophageal sphincter of pig and man. Dig. Dis. Sci. 31:
1370–1375, 1986.

- peptides in lower esophageal sphincter of pig and man. Dig. Dis. Sci. 31:
320–1375, 1986.
GESTRUP, S., UDDMAN, R., JENSEN, ST. L., SUNDLER, F., SCHAFFAL-
GESTRUP, S., UDDMAN, R., JENSEN, ST. L., SUNDLER, F., SCHAFFAL-
TTZK 1370–1375, 1986.

4. AGGESTRUP, S., UDDMAN, R., JENSEN, ST. L., SUNDLER, F., SCHAPPAL-

TZKY DE MUCKADELL, O., HOLST, J. J., HAKANSON, R., EKMAN, R., AND

SØRENSEN, H. R.: Regulatory peptides in the lower esophageal sphinc
-
- phenylephrine, and morphine on intestinal secretion mediated by *Escherinia coli* heat-stable enterotoxin in pig jejunum. Can. J. Physiol. Phar-
macol. 60: 1680-1685, 1982.
LESCHER, H. D., SCHUSDZIARRA, V., WEIGERT, N., AN Interaction between endogenous opioids, cholinergic and adrenergic mechanisms during vagally-induced gastrin release in rats. Neuropeptides 9:
309–323, 1987.
ALUMETS, J., ALM, P., FALKMER, S., HAKANSON, R., LJUNGBERG, O.,

- Interaction between endogenous opioids, cholinergic and adrenergic ranisms during vagally-induced gastrin release in rats. Neuropeptic
309–323, 1987.
LUMETS, J., ALM, P., FALKMER, S., HAKANSON, R., LJUNGBER
MARTENSSON, H., anisms during vagally-induced gastrin release in rats. Neuropeptides 9:
309–323, 1987.
LUMETS, J., ALM, P., FALKMER, S., HAKANSON, R., LJUNGBERG, O.,
MARTENSSON, H., SUNDLER, F., AND TIBBLIN, S.: Immunohistochemical
eviden (Phila.) **48: 2409-2415, 1981.** 7a. ALUMETS, J., HAKANSON, R., SUNDLER, F., AND CHANG, K.-J.: Leu-
- MARTENSSON, H., SUNDLER, F., AND TIBBLIN, S.: Immunohistochemical
evidence of peptide hormones in endocrine tumors of the rectum. Cancer
(Phila.) 48: 2409–2415, 1981.
LLUMETS, J., HAKANSON, R., SUNDLER, F., AND CHANG, K.-J (Phila.) 48: 2409-2415, 1981.

7a. ALUMETS, J., HAKANSON, R., SUNDLER, F., AND CHANG, K.-J.: Leu-

enkephalin-like material in nerves and enterochromaffin cells in the gut.

An immunohistochemical study. Histochemistry 56 Ta. ALUMETS, J., HAKANSON, R., SUNDLER, F., AND CHANG, K.-J.: Leu-
enkephalin-like material in nerves and entercochromaffin cells in the gut.
An immunohistochemical study. Histochemistry 56: 187-196, 1978.
8. ALVAREZ, W. C
-
- LVAREZ, W. C., AND STARKWEATHER, E.: The metabolic gradient underlying intestinal peristalsis. Am. J. Physiol. 46: 186–208, 1918.
NDERSON, W., MOLINA, E., RENTZ, J., AND HIRSCHOWITZ, B. I.: Analysis
of the 2-deoxy-d-glucos University of the Shannon Delta Band Deristalism. Am. J. Physiol. 46: 186-208, 1918.

9. ANDERSON, W., MOLINA, E., RENTZ, J., AND HIRSCHOWITZ, B. I.: Analysis

of the 2-deoxy-d-glucose-induced vagal stimulation of gastric
-
-

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COPIOIDS AND CONTROL OF GASTROINT

cology of antidiarrheal drugs. Annu. Rev. Pharmacol. Toxicol. **23: 279-**

301, 1983.

ADO, A., CHICAU-CHOVET, M., APPIA, F., DUBRASQUET, M., LECOMTE, J.

- **11. BADO, A., CHICAU-CHOVET, M., APPIA, F., DUBRASQUET, M., LECOMTE, J.**

11. BADO, A., CHICAU-CHOVET, M., APPIA, F., DUBRASQUET, M., LECOMTE, J.

11. BADO, A., CHICAU-CHOVET, M., APPIA, F., DUBRASQUET, M., LECOMTE, J.

1 cology of antidiarrheal drugs. Annu. Rev. Pharmacol. Toxicol. 23: 279-301, 1983.

11. BADO, A., CHICAU-CHOVET, M., APPIA, F., DUBRASQUET, M., LECOMTE, J.

11. BADO, A., CHICAU-CHOVET, M., APPIA, F., DUBRASQUET, M., LECOMTE
- 11. BADO, A., CHICAU-CHOVET, M., APPIA, T., LUBRARQUET, M., LECOMTE, J.

M., AND ROZE, C.: Acetorphalin and enkephalinase inhibitor, decreases

gastric secretion in cata. Peptides 8: 89-93, 1987.

12. BARBEZAT, G. O., AND
- **EXECULT:** G. O., AND REASBECK, P. G.: Effects of bombesin, calcitonin, and enkephalin on canine jejunal water and electrolyte transport. Dig. Dis. Sci. 28: 273-277, 1983.
REDON, T., AND RUCKEBUSCH, Y.: Comparative effects
-
- 329–334, 1985.

RRON, J. H.: Current views on pathogenesis of peptic ulcer. Scand. J.
 Gastroenterol. 17 (suppl. 80): 1-10, 1982.
 ARTHO, L., SEBOK, B., AND SZOLCSANYI, J.: Indirect evidence for the inhibition of enteri 14. BARON, J. H.: Current views on pathogenesis of peptic ulcer. Scand. J. Gastroenterol. 17 (suppl. 80): 1-10, 1982.
15. BARTHO, L., SEBOK, B., AND SZOLCSANYI, J.: Indirect evidence for the inhibition of enteric substance 16. BARTHO, L., SEBOK, B., AND SZOLCSANYI, J.: Indirect evidence for the inhibition of enteric substance P neurones by opiate agonists but not by capsain, D. B., AND TERZIC, B.: Inhibition by enkephalins of peristaltic act
- RRTHO, L., SEBOK, B., AND SZOLCSANYI, J.: Indirect evidence for the inhibition of enteric substance P neurones by opiate agonists but not by capeaicin. Eur. J. Pharmacol. 77: 273-279, 1982.
ELESLIN, D. B., AND TERZIC, B.:
- 17. BELESLIN, **D. B.,** TERZIC, **B., AND SMARDZIC, R.: The effect of leucine-** enkephalin on the peristaltic reflex of the isolated guinea-pig ileum. Acta activity of the rabbit ileum and its reversal by naloxone. J. Pharm.
Pharmacol. 34: 738-739, 1962.
ELESLIN, D. B., TERZIC, B., AND SMARDZIC, R.: The effect of leucine-
enkephalin on the peristaltic reflex of the isolated g **flux and cyclic adenosine 3'**, AND SMARDZIC, R.: The effect of leucine-
enkephalin on the peristatic reflex of the isolated guinea-pig ileum. Acta
Physiol. Hung. **69:** 105-114, 1987.
EUBLER, E.: Influence of vasoactive in
- 18. BEUBLER, E.: Influence of vasoactive intestinal polypeptide on net water
- enkephalin on the peristatic reflex of the isolated guinea-pig ileum. Acta

Physiol. Hung. 69: 105-114, 1987.

18. BEUBLER, E.: Influence of vasoective intestinal polypeptide on net water

flux and cyclic adenosine 3',5'-m to diarrhea due to morphine withdrawal in the rat. Gastroenterology **87:** Business, E., Business, and *B*-hydroxytryptamine may contribute to diarrhea due to morphine withdrawal in the rat. Gastroenterology 87:
1042-1048, mediated by prostaglandin E₂ and 5-hydroxytryptamine may contribute
to diarrhea due to morphine withdrawal in the rat. Gastroenterology 87:
1042–1048, 1984.
90. BEUBLER, E., AND JUAN, H.: PGE-mediated laxel) 34: 386-387,
-
- **laxatives. Naunyn-Schmiedeberg's** Arch. Pharmacol. **305: 241-246, 1978.**
- 19. BEUBLER, E., AND JUAN, H.: Is the effect of diphenolic laxatives mediated
via release of prostaglandin E? Experientia (Basel) 34: 386-387, 1978.
20. BEUBLER, E., AND JUAN, H.: PGE-mediated laxative effect of diphenoli
-
- 21. BEUBLER, E., AND LEMBECK, F.: Inhibition of stimulated fluid secretion in
the rat small and large intestine by opiste ageonists. Naunyn-Schmiede-
berg's Arch. Pharmacol. 306: 113-118, 1979.
22. BEUBLER, E., AND LEMBEC 22. BEUBLER, E., AND LEMBECK, F.: Inhibition by morphine of prostaglandin E_1 -stimulated secretion and cyclic adenosine $3', 5'$ -monophosphate formation in the rat jejunum in vivo. Br. J. Pharmacol. 68: 513–518, 1980.
23
- morphine withdrawal diarrhea and juelective opioid antagonist SR 58002 C
ckel., M., ALPERMANN, H.-G., ROCH
LENN, H.-J.: Pharmacology of a gut mo
logue. Drug Res. 9: 1417-1426, 1985.
NDER, H. J., LAURENSON, J. P., AN
- **24. BICKEL, M., ALPERMANN, H.-G., ROCHE, M., SCHEMANN, M., AND EHR.**

24. BICKEL, M., ALPERMANN, H.-G., ROCHE, M., SCHEMANN, M., AND EHR.

LEIN, H.-J.: Pharmacology of a gut motility stimulating enkephalin ana-

logue. Dr
- comptor in regulation of enkephalin stimulation of active sodium and
chloride absorption. Am. J. Physiol. 247: G432-G436, 1984.
26. BISHOP, A. E., POLAK, J. M., LAKE, B. D., BRYANT, M. G., AND BLOOM,
S. R.: Abnormalities o
-
- receptors in regulation of enkephalin stimulation of active solium and

chioride absorption. Am. J. Physiol. 247: G433.-G436, 1984.

26. BisHoP, A. E., POLAK, J. M., LAKE, B. D., BRYANT, M. G., AND BLOOM,

S. R.: Abnormali morphine on spontaneous electrical activity and on junction potentials
elicited by parasympathetic nerve stimulation in cat and rabbit colon. Br.
J. Pharmacol. 77: 419-429, 1982.
29. BODYCOTE, I. J., AND CHESHER, G. B.: Na
-
-
-
- 29. BODYCOTR, I. J., AND CHESHER, G. B.: Naloxone-induced contracture of
ileum from stressed guinea pigs. Eur. J. Pharmacol. 57: 259-261, 1979.
30. BOLTON, T. B.: On the nature of the oscillations of the membrane potential **32. BORODY, T. J., QUIGLEY, E. M. M., PHILLIPS, S. F., WIENBECK, M., TUCKER, R. L., HADDAD, A., AND ZINSMEISTER, A. R.: Effects of morphine on** endtropine on morphine J. C., NAUDY, B., AND SALDUCCI, J.: Effects of morphi
- **153-161,** 1987.
- 34. BOUVIER, M., KIRSCHNER, G., AND GONELLA, J.: Actions of morphine and
- morphine on electrical activity in the rectum in man. J. Physiol. 388:

153-161, 1987.

34. BOUVIER, M., KIRSCHNER, G., AND GONELLA, J.: Actions of morphine and

enkephalins on the internal anal sphincter of the cat: relev **Example 1211-1216, 1979.** The Seyler's *Z. Physiological role of opiates.* J. Auton. Nerv. Syst. 16: 219-232, 1986.
36. BRANTL, V., TESCHEMACHER, H., HENSCHEN, A., AND LOTTSPEICH, F.: Novel opioid peptides derived in the
- 35. BRANTL, V., TESCHEMACHER, H., HENSCHEN, A., AND LOTTSPEICH, F.
Novel opioid peptides derived from casein (β -casomorphins). Hoppe-
Seyler's Z. Physiol. Chem. 360: 1211-1216, 1979.
36. BRODIE, D. A., AND HANSON, H. M. production of gastric ulcers by the restraint technique. Gastroenterology
38: 353-360, 1960.
37. BRODIE, D. A., MARSHALL, R. W., AND MORENO, O. M.: Effect of restraint
on gastric acidity in the rat. Am. J. Physiol. 202: 81
-
-

-
- **ESTINAL MOTILITY AND SECRETION** 153

action of $[Met^1]$ enkephalinamide on the rat intestine. Eur. J. Pharmacol.

90: 441-444, 1983.

39. BROWN, D. R., AND MILLER, R. J.: Adrenergic mediation of the intestinal

antisecret anusecretory action of opiates administered into the central nervous
system. J. Pharmacol. Exp. Ther. 231: 114-119, 1984.
BRUCE, D. S., Cope, G. W., ELAM, T. R., RUT, K. A., OELTGEN, P. R.,
AND SU, T.-P.: Opioids and hiber
-
- 13. BARDON, T., AND RUCKERUSCH, Y.: Comparative effects of opiate agonists

on proximal and distal colonic motility in dogs. Eur. J. Pharmacol. 110:

329–334, 1985.

239–334, 1985.

239–334, 1985.

14. BARON, J. H.: Curren AND SO, 1.-F.: Uploas and niormation. I. Enects or national
HIT's depression of guinea pig ileum contractility and on induction of
summer hibernation in the ground squirrel. Life Sci. 41: 2107-2113, 1987.
40. BUENO, L., AN mvolved in the effects of morphine on colonic motility in dog. Eur. J.
 Pharmacol. 82: 147-153, 1982.
 41. BUENO, L., FIONDANOTTI, J., HONDÉ, C., FARGEAS, M. J., AND PRIMI, M.
 P.: Central and peripheral control of ga
	-
	- F.: Central and peripheral control of gastrointestinal and colonic motility
by endogenous opiates in conscious dogs. Gastroenterology 88: 549–556,
1985.
42. BOLBRING, E., AND CREMA, A.: The release of 5-hydroxytryptamine i **Metriculant Argpheric Phalin Argpheric Phalin Argentian Argpheric Phalin Argpheric Argpheric Metrical and the station of Metric Lange and Stronten and the metric morphine stimulant Metric Metric Phe⁷. J. Histochem. Cyto** U'LOCK, A. J., VAILLANT, C., AND DOCKRAY, G. J.: Immunohistochemics
studies on the gastrointestinal tract using antisera to Met-enkephalin and
Met-enkephalin Arg^oPhe⁷. J. Histochem. Cytochem. 31: 1356–1362, 1983
URKS,
	- **45. BURKS, T. F.: Mediation Argeleric effects of morphine on rat intestinal motility. Eur. J. Pharmac 44. BURKS, T. F.: Mediation by 5-hydroxytryptamine of morphine stimulations in dog intestine. J. Pharmacol. Exp. Ther. 185: 530–539, 1974.
45. BURKS, T. F.: Acute effects of morphine on rat intestinal motility. Eurepharma**
	- actions in dog intestine. J. Pharmacol. Exp. Ther. 185: 530-539, 1973.
45. BURKS, T. F.: Acute effects of morphine on rat intestinal motility. Eur. J. Pharmacol. 40: 279-283, 1976.
45a. BURKS, T. F.: Central sites of actio
	-
	- Pharmacol. 40: 279–283, 1976.

	SURKS, T. F.: Central sites of action of gastrointestinal drugs. Gastroen-

	terology 74: 322–324, 1978.

	URKS, T. F.: Actions of drugs on gastrointestinal motility. In Physiology

	of the Gast terology 74: 322-324, 1978.

	46. BURKS, T. F.: Actions of drugs on gastrointestinal motility. In Physiology

	of the Gastrointestinal Tract, ed. by L. R. Johnson, ed. 2, pp. 723-743,

	Raven Press, New York, 1987.

	47. BURKS of the Gastrointestinal Tract, ed. by L. R. Johnson, ed. 2, pp. 723-743,
Raven Press, New York, 1987.
47. BURKS, T. F., HIRNING, L. D., GALLIGAN, J. J., AND DAVIS, T. P.: Motility
effects of opoid periods in dog intestine.
	-
	-
	- Raven Press, New York, 1987.

	47. BURKS, T. F., HIRNING, L. D., GALLIGAN, J. J., AND DAVIS, T. P.: Motility

	effects of opioid peptides in dog intestine. Life Sci. 31: 2237-2240, 1982.

	48. BURKS, T. F., AND LONG, J. P.: R
	- morphine reduces intestinal propulsion in rats partly by a central action.
Eur. J. Pharmacol. 75: 283–287, 1981.
50. BURLEIGH, D. E., AND TROUT, S. J.: Morphine attenuates cholinergic nerve
activity in human isolated colon
	- EUR. J. Pharmacol. 76: 283-287, 1981.

	50. BURLEIGH, D. E., AND TROUT, S. J.: Morphine attenuates cholinergic nerve

	activity in human isolated colonic muscle. Br. J. Pharmacol. 88: 307-313,

	1986.

	51. CALDARA, R., CAMBIE
	- activity in human isolated colonic muscle. Br. J. Pharmacol. 88: 307-313,
1986.

	51. CALDARA, R., CAMBIELLI, M., MASCI, E., GUSLANDI, M., BARBIERI, C., AND

	FERRARI, C.: Effect of loperamide and naloxone on gastric acid se in healthy man. Gut 22: 72

	MILLERI, M., MALAGELAD,

	R., KAO, P. C., AND LI, C. 1

	endorphin and naloxone on

	251: 147-154, 1986.

	NIVIELD, S. P., AND SPENC 52. CAMILLERI, M., MALAGELADA, J.-R., STANGHELLINI, V., ZINSMEISTER, A.

	R., KAO, P. C., AND LI, C. H.: Dose-related effects of synthetic human β-

	endorphin and naloxone on fed gastrointestinal motility. Am. J. Physiol.

	- 251: 147-154, 1986.

	53. CANFIELD, S. P., AND SPENCER, J.: The action of morphine and naloxone

	on acid secretion by the rat isolated stomach. Eur. J. Pharmacol. 71: 135-

	138, 1981.

	54. CARENSAS, H. L., AND ROSS, D. H.:
	-
	- 138, 1981.
 REDENAS, H. L., AND ROSS, D. H.: Calcium depletion of synaptosomes
 ARAFION, M. C., SULLIVAN, S. N., BLOOM, S. R., ADRIAN, T. E., AND
 CHRISTOFIDES, N. D.: The effects of naloxone and morphine on postpran-55. CHAMPION, M. C., SULLIVAN, S. N., BLOOM, S. R., ADRIAN, T. E., AND CHRISTOFIDES, N. D.: The effects of naloxone and morphine on postprandial gastrointestinal hormone secretion. Am. J. Gastroenterol. 77: 617-620, 1982.

	-
	- HANG, E. B., BROWN, D. R., FIELD, M., AND MILLER, R. J.: An antisorptive basis for precipitated withdrawal diarrhee in morphine-dependents. J. Pharmacol. Exp. Ther. 228: 364-369, 1984.
HANG, K. J., Cooper, B. R., HAZUM, E. rats. J. Pharmacol. Exp. Ther. 228: 364-369, 1984.

	57. CHANG, K. J., COOPER, B. R., HAZUM, E., AND CUATRECASAS, P.: Multiple

	opiate receptors: different regional distribution in the brain and differ-

	oniat receptors: di
	-
- and atropine on motility and transit in the human ileum. Gastroenterology

39: 562-570, 1985.

33. BOUVIER, M., GRIMAUD, J. C., NAUDY, B., AND SALDUCCI, J.: Effects of

33. BOUVIER, M., GRIMAUD, J. C., NAUDY, B., AND SALDU ential binding of opiates and opioid peptides. Mol. Pharmacol. 16: 91-
104, 1979.
58. CHANG, K. J., AND CUATRECASAS, P.: Multiple opiate receptors. J. Biol.
58. CHANG, K. J., AND CUATRECASAS, P.: Possible role of distinct
 Chem. 254: 2610–2618, 1979.
HANG, K. J., HAZUM, E., AND CUATRECASAS, P.: Possible role of distinct
morphine and enkephalin receptors in mediating actions of benzomorphan
drugs (putative kappa and sigma agonists). Proc. Nat 69. CHANG, K. J., HAZUM, E., AND CUATRECASAS, P.: Possible role of distinct morphine and enkephalin receptors in mediating actions of benzomorphan drugs (putative kappa and sigma agonists). Proc. Natl. Acad. Sci. USA 77: 4
	- HAVKIN, C., AND GOLDSTEIN, A.: Demonstration of a specific dynameter of the match of a specific dynameter of the HAVKIN, C., AND GOLDSTEIN, A.: Reduction in opiate receptor reset morphine tolerant guinea pig ilea. Life Sci
	- 693, 1981.
61. CHAVKIN, C., AND GOLDSTEIN, A.: Reduction in opiate receptor reserve in
morphine tolerant guinea pig ilea. Life Sci., 31: 1687–1690, 1982.
62. CHIBA, T., TAMINATO, T., KADOWAKI, S., INOUE, Y., MORI, K., SEIN
	- receptor in guinea-pig ileum myenteric plexus. Nature (Lond.) 291: 591-
593, 1981.
61. CHAVKIN, C., AND GOLDSTEIN, A.: Reduction in opiate receptor reserve in
morphine tolerant guinea pig ilea. Life Sci., 31: 1687–1690, 19 morphine tolerant guinea pig ilea. Life Sci., 31: 1687-1690, 1982.
62. CHIBA, T., TAMINATO, T., KADOWAKI, S., INOUE, Y., MORI, K., SEINO, Y., ABE, H., CHIHARA, K., MATSUKURA, S., FUJITA, T., AND GOTO, Y.: Effects of variou
	- docrinology 106: 145-149, 1980.

	63. CLARK, S. J., AND SMITH, T. W.: Peristalsis abolishes the release of methionie-enkephalin from guinea-pig ileum in vitro. Eur. J. Pharmacol.

	70: 421-424, 1981.

	64. CLARK, S. J., AND S 63. CLARK, S. J., AND SMITH, T. W.: Peristalsis abolishes the release of
	-

spet

 $\, \mathbb G \,$

PHARM
REV

- deberg's Arch. Pharmacol. 330: 179-183, 1985.
08TA, M., AND FURNESS, J. B.: The peristaltic reflex: an analysis of the nerve pathways and their pharmacology. Naunyn-Schmiedeberg's Arch. 654

distension reflex by peripheral and central mechanisms. Naunyn-Schmie-

deberg's Arch. Pharmacol. 330: 179–183, 1985.

65. Costa, M., AND FURNESS, J. B.: The peristaltic reflex: an analysis of the

nerve pathways and deberg's Arch. Pharmacol. 330: 179–183, 1985.

65. Costa, M., AND FURNESS, J. B.: The peristaltic reflex: an analysis of the

nerve pathways and their pharmacology. Naunyn-Schmiedeberg's Arch.

Pharmacol. 294: 47–60, 1976.
- ophioning neurons in the guinea-pig intestine. Neuropeptides 5:
 Exameneo. 294: 47-60, 1976.
 **COSTA, M., FURNESS, J. B., AND CUELLO, A. C.: Separate populations of

opioid containing neurons in the guinea-pig intestine.** Sec. COSTA, M., FURNESS, J. B., AND CUELLO, A. C.: Separate populations of opioid containing neurons in the guinea-pig intestine. Neuropeptides 5: 445-448, 1985.
66. COUPAR, I. M.: Inhibition by morphine of prostaglandine-
-
- 440–448, 1980.

66. Courag, I. M.: Inhibition by morphine of prostaglandine-stimulated fluid

67. Courag, I. M.: Characterization of the opiate receptor population mediating

67. Courag, I. M.: Characterization of the opi
-
-
- EXECUTE BET ALIFER SCI. AND TATA CONTROLLATION IN THE SECTION OF ALIFER SCI. THE SCI. COUPAR, I. M.: Tetrodotoxin inhibits directly acting stimulants of intestinal fluid secretion. J. Pharm. Pharmacol. 38: 553-555, 1986.
 fluid secretion. J. Pharm. Pharmacol. 38: 553-555, 1986.

69. COUPAR, I. M.: Opioid action on the intestine: the importance of the

intestinal mucosa. Life Sci. 41: 917-925, 1987.

70. COUPAR, I. M.. AND TAYLOR, D. A.: Evi rat jejunum. J. Pharm. Pharmacol. 39: 363-369, 1987.
To Couran, I. M.: Opposite Sci. 41: 917-925, 1987.
To Couran, I. M., AND TaYLOR, D. A.: Evidence for tryptaminergic anoradrenergic involvement in the antisecretory actio JUPAR, I. M., AND TAYLOR, D. A.: Evidence for tryptaminergic and noradrenergic involvement in the antisecretory action of morphine in the rat jejunum. J. Pharm. Pharmacol. 39: 363-369, 1987.
REESS., I., AND SNYDER, S. H.:
- 71. CREESS., I., AND SNYDER, S. H.: Receptor binding and pharmacological
271. CREESS., I., AND SNYDER, S. H.: Receptor binding and pharmacological
activity of opiates in the guinea-pig intestine. J. Pharmacol. Exp. Ther.
2
- activity of opiates in the guinea-pig intestine. J. Pharmacol. Exp. Ther.
194: 205-219, 1975.
72. CREMA, A., DEL TACCA, M., FRIGO, G. M., AND LECCHINI, S.: Presence of
a non-adrenergic inhibitory system in the human colon.
-
- 194: 205-219, 1975.

72. CREMA, A., DEL TACCA, M., FRIGO, G. M., AND LECCHINI, S.: Presence of

a non-adrenergic inhibitory system in the human colon. Gut 9: 633-637,

1968.

73. CSONTOS, K., RUST, M., HOLLT, V., MAHR, W. women and their neonates. Life Sci. 20: 830–844, 1979.

73a. CULFEPPER-MORGAN, J., KREEK, M. J., HOLT, P. R., LAROCHE, D., ZHANG, J., AND O'BRYAN, L.: Orally administered kappa as well as mu opiate agonists delay gastroint ZHANG, J., AND O'BRYAN, L.: Orally administered kappa as well as mu opiate agonists delay gastrointestinal transit time in the guinea pig. Life Sci. 42: 2073-2077, 1988.
74. CURLING, T. B.: On acute ulceration of the duode
-
-
-
- 75a. DAI, S., AND CHAN, M. Y.: Effects of naloxone on serum corticosterone and gastric lesions in stressed rats. Pharmacology 27: 180-184, 1983.
76. DANIEL, E. E.: Pharmacology of the gastrointestinal tract. In Handbook of
- Effect of chemical ablation of myenteric neurons on neurotransmitter
levels in the rat jejunum. Gastroentrology 92: 338-344, 1987.
To Dal, S., AND CHAN, M. Y.: Effects of naloxone on serum corticosterone
and gastric lesion
-
- **and other draws on Mother drugs on Mondaying on Michael Substance P and Met²-enkephalin in dog ileum. Can. J. Physiol. Pharmacol. 60:** 830–840, 1982.
mmcol. 60: 830–840, 1982.
ANISL. E. E., SUTHERLAND, W. H., AND BO
-
- Endorphin and its metabolites stimulate motility of the dog small intes-Bur. J. Pharmacol. 107: 267-269, 1985.

80. DAVIS, T. P., CULLING, A. J., SCHOEMAKER, H., AND GALLIGAN, J. J.: β -

Endorphin and its metabolites stimulate motility of the dog small intes.

tine. J. Pharmacol. Exp. The. **bowel malignancy and is metabolites stimulate motility of the dog small intestine. J. Pharmacol. Exp. Ther. 227: 499-507, 1983.

B1. Davis, W. G., TORMEY, W. P., AND DELANEY, P. V.: Enkephalins in large bowel malignancy**
-
- tine. J. Pharmacol. Exp. Ther. 227: 499-507, 1983.

81. DAVIS, W. G., TORMEY, W. P., AND DELANEY, P. V.: Enkephalins in large

bowel malignancy and in acute appendicitis. Gut 20: 865-867, 1979.

82. DEBAS, H. T.: Periphera
- Secretion in the University of the Gastrointestinal Tract, ed. by L. R. Johnson, ed. 2, pp. 931⁻¹
Raven Press, New York, 1987.
83. **DEL TACCA, M., BERNARDINI**, C., CORSANO, E., SOLDANI, G., AND RC.
C.: Effects of morphin
- 83. DEL TACCA, M., BERNARDINI, C., CORSANO, E., SOLDANI, G., AND ROZE, C.: Effects of morphine on gastric ulceration, barrier mucus, and acid secretion in pylorus-ligated rats. Pharmacology 35: 174–180, 1987.

84. DEVROEDE C.: Effects of morphine on gastric ulceration, barrier mucus, and acid

secretion in pylorus-ligated rats. Pharmacology 35: 174-180, 1987.

84. DEVROEDE, G.: Constipation: mechanisms and management. In Gastroin-

testinal
-
- testinal Disease. Pathophysiology, Diagnosis, Management, ed. by M. H.
Sleisenger and J. S. Fordtran, pp. 288-308, Saunders, Philadelphia, 1983.

26. DOBSINS, J., DHARMSATHAPHORN, K., RACUSEN, L., AND BINDER, H. J.:

The e
- onine enkephalin amide on ion transport in rabbit ileum. J. Clin. Invest.
66: 19-28, 1980.
87. DoCKRAV, G. J.: Physiology of enteric neuropeptides. In Physiology of the
Gastrointestinal Tract, ed. by L. R. Johnson, ed. 2,
- SUCKRAY, G. J.: Physiology of enteric neuropeptides. In Physiology of the Gastrointestinal Tract, ed. by L. R. Johnson, ed. 2, pp. 41–66, Raven
Press, New York, 1987.
DMOTO, T., GONDA, T., OKI, M., AND YANAIHARA, N.: Coexi 88. DOMOTO, T., GONDA, T., OKI, M., AND YANAIHARA, N.: Coexistence of substance P- and methionine⁸enkephalin-like immunoreactivity in nervells of the myenteric ganglia in the cat ileum. Neurosci. Lett. 47: 9-1: 1984.
198 solls of the myenteric ganglia in the cat ileum. Neurosci. Lett. 47: 9-13,
1984.
89. DONNERER, J., HOLZER, P., AND LEMBECK, F.: Release of dynorphin.
somatostatin, and substance P from the vascularly perfused small intes-
-

tine of the guinea-pig during peristalsis. Br. J. Pharmacol. 83: 919-925, 1984.

- 90. Donown⁷z, L. G., PAGE, M. C., MILEUR, B. L., AND GUENTHNER, S. H.: Alteration of normal gastric flora in critical care patients receiving antacid
and cimetidine therapy. Infect. Control 7: 23–26, 1986.
- The or the guinea-pig curing peristalists. Br. J. Pharmacol. 83: 919–925,
1984.
90. DONOWITZ, L. G., PAGR, M. C., MILEUR, B. L., AND GUENTHNER, S. H.:
Alteration of normal gastric flora in critical care patients receiving Alteration of normal gastric flora in critical care patients reand cimetidine therapy. Infect. Control 7: 23-26, 1986.

DWLATSHAHI, K., EVANDER, A., WALTHER, B., AND SK

Influence of morphine on the distal oesophagus and t and cimetidine therapy. Infect. Control 7: 23-26, 1986.

91. DOWLATSHAHI, K., EVANDER, A., WALTHER, B., AND SKINNER, D. B.:

Influence of morphine on the distal cesophages and the lower oesophageal

sphincter—a manometric
- Influence of morphine on the distal oesophagus and the lower oesophageal
sphincter—a manometric study. Gut 26: 802-806, 1985.
29. EAGLETON, G., AND WATT, J.: The selective production of gastric and
duodenal ulceration usin Influence of morphine on the distal desophs
sphincter—a manometric study. Gut 26: 8
(GLETON, G., AND WATT, J.: The selection
diodenal ulceration using histamine. In Pepp.
9.34–44, Lippincott, Philadelphia, 1971.
DIN, R., L **92. EAGLETON, G., AND WATT, J.: The selective production of gastric and duodenal ulceration using histamine. In Peptic Ulcer, ed. by C. J. Pfeiffer, pp. 34–44, Lippincott, Philadelphia, 1971.

93. EDIN, R., LUNDBERG, J.,**
-
- Chir. Forum Exp. Klin. Forum Exp. Klin. Form Exp. Solution Exp. 23. EDIN, R., LUNDBERG, J., DAHLSTROM, A., HOKFELT, T., TERENIUS, L.,
AND AHLMAN, H.: The peptidergic neural control of the feline pylorus.
Chir. Forum Exp. K AND AHLMAN, H.: The peptidergic neural control of the feline pylorus.
Chir. Forum Exp. Klin. Forschung. 233–237, 1980.
DIN, R., LUNDBERG, J., TERENIUS, L., DAHLSTRÓM, A., HÖKFELT, T.,
KEWENTER, I., AND AHLMAN, H.: Evidence **94. EDIN, R., LUNDBERG, J., TERENIUS, L., DAHLSTROM, A., HÖKFELT, T.**
 **KEWENTER, I., AND AHLMAN, H.: Evidence for vagal enkephalinergic

neural control of the feline pylorus and stomach. Gastroenterology 78.

492-497, 19**
- Insural control of the feline pylon
192–497, 1980.
192–497, 1980.
U.S. Res. 28: 293–296, 1980.
U.S. Surg. Res. 28: 293–296, 1980.
L. MUNSHID, H. A., HÅKANSON, 1
- 85. EXECT., 1980.

95. EXECT., SCHULTE, W. J., CONDON, R. E., WOODS, J. H., AND COWLES,

V.: Effects of narcotic analgesics on bowel motility in subhuman primates.

J. Surg. Res. 28: 293-296, 1980.

96. EL MUNSHID, H. A., 96. EL MUNSHID, H. A., HAKANSON, R., LIEDBERG, G., UND SUNDLER, F.: Effects of various gastrointestinal peptides on parietal cells and endocrine cells in the oxyntic mucosa of rat stomach. J. Physiol. 305: 249–265, 1980.
 Effects of various gastrointestinal peptides on parietal cells and endocrine
cells in the oxyntic mucosa of rat stomach. J. Physiol. 305: 249–265,
1980.
RAWIN, D. N., NONCHOJI, T., AND WOOD, J. D.: Effects of morphine on
e
-
- 1980.

97. ERWIN, D. N., NONCHOJI, T., AND WOOD, J. D.: Effects of morphine on

electrical activity of single myenteric neurons in cat small bowel. Eur. J.

Pharmacol. 47: 401–405, 1978.

98. FARACK, U. M., KAUTZ, U., AND intestinal secretion but not the mucosal cAMP accumulation induced by
choleratoxin. Naunyn-Schmiedeberg's Arch. Pharmacol. 317: 178-179,
1981.
ELDMAN, M., AND COWLEY, Y. M.: Effect of an opiate antagonist (nalox-one) on t
-
- choleratorin. Naunyn-Schmiedeberg's Arch. Pharmacol. 317: 178-179,
1981.
Standard Mac Cowt. Effect of an opiate antagonist (nalox-
one) on the gastric acid secretory response to sham feeding, pentagastrin,
and histamine in
- and histamine in man. Dig. Dis. Sci. 27: 308-310, 1982.

100. **FELDMAN, M.**, AND LI, C. H.: Effect of β -endorphin on gastric acid secretion

and serum gastrin concentration in humans. Regul. Pept. 4: 311-315,

1982.

1 and serum gastrin concentration in humans. Regul. Pept. 4: 311-315, 1982.

101. FELDMAN, M., WALSH, J. H., AND TAYLOR, I. L.: Effect of naloxone and

morphine on gastric acid secretion and on serum gastrin and pancreatic
 101. FELDMAN, M., WALSH, J. H., AND TAYLOR, I. L.: Effect of naloxone and
morphine on gastric acid secretion and on serum gastrin and pancreatic
polypeptide concentrations in humans. Gastroenterology 79: 294–298,
102. FERR
- morphine on gastric acid secretion and on serum gastrin and pancreations polypeptide concentrations in humans. Gastroenterology 79: 294–294
1980.
1980.
IRRI, G. L., BOTTI, P., BILIOTTI, G., REBECCHI, L., BLOOM, S. R
TONELL polyophide concentrations in numans. Gastroenterology 79: 294–298,
102. FRRRI, G. L., BOTTI, P., BILIOTTI, G., REBECCHI, L., BLOOM, S. R.,
TONELLI, L., LABO, G., AND POLAK, J. M.: VIP-, substance P-, and Met-
enkephalin-im
- mucosa and Brunner's glands. Gut 25: 948-952, 1984.

103. FERRI, G. L., MORREALE, R. A., AND DOCKRAY, G. J.: Met⁸-enkephalin-

Arg⁸-Gly⁷-Leu⁸ immunoreactivity in the human gut. Peptides 7: 735-739,

1986.

104. FER
- 103. FERRI, G. L., MORREALE, R. A., AND DOCKRAY, G. J.: Met⁵-enkephalin-
Arg⁴-Gly⁷-Leu⁴ immunoreactivity in the human gut. Peptides 7: 735-739,
1986.
104. FERRI, G. L., MORREALE, R. A., SOIMERO, L., BILIOTTI, G., A
- macol. 300-340, 1982.

78. DANIER, G. J.; BILIOTIT, G., AND DOCKRAY,

78. DANIERO, L., BILIOTIT, G., AND DOCKRAY,

28. SOLUENCI, G. AND TRIGGENT (G. AND DOCKRAY, and Cold in the stress of morphine and other chrome of morp G. J.: Intramural distribution of Met⁺-enkephalin-Arg^e-Gly⁷-Leu^e in sphincter regions of the human gut. Neurosci. Lett. 74: 304-308, 1987. SPERNI, S., ARNIGO-REINA, R., CANDELETTI, S., COSTA, G., MURARI, G., SPERNO sphincter regions of the human
RRRI, S., ARRIGO-REINA, R., G.
SPERONI, E., AND SCOTO, G.:
the protective effect of opioi
Commun. 15: 409–418, 1983.
"ERRI, S., SPERONI, E., CANDE 105. FERRI, S., ARRIGO-KEINA, K., CANDELETTI, S., COSTA, G., MURARI, G., SPERONI, E., AND SCOTO, G.: Central and peripheral sites of action for
the protective effect of opioids of the rat stomach. Pharmacol. Res.
Commun. 1
	- less commun. 15: 409-418, 1983.

	Commun. 15: 409-418, 1983.

	105a. FERRI, S., SPERONI, E., CANDELETTI, S., CAVICCHINI, E., ROMUALDI, P., Govoni, P., Govoni, P., Govoni, P., Govoni, P., and Decletini, M.: Protection by opio
	-
	- 105a. FERRI, S., SPERONI, E., CANDELETTI, S., CAVICCHINI, E., ROMUALDI, P.,

	GOVONI, P., AND MARCHINI, M.: Protection by opioids against gastric

	lesions caused by necrotizing agents. Pharmacology 36: 140-144, 1988.

	106. tion of Met-enkephalin-immuno reactivity in gastroenteropancreatic tis-
sues of the rat. Life Sci. 39: 1909-1915, 1986.
107. FIOCCHI, R., BIANCHI, G., PETRILLO, P., TAVANI, A., AND MANARA, L.:
Morphine inhibits gastrointes Morphine inhibits gastrointestinal transit in the rat primarily by impairing propulsive activity of the small intestine. Life Sci. 31: 2221-2223, 1982.

	1082.

	10RAMONTI, J., FARGEAS, M. J., AND BUENO, L.: Comparative effe
	-
	- Morphine inhibits gastrointestinal transit in the rat primarily by impair-
ing propulsive activity of the small intestine. Life Sci. 31: 2221-2223,
1982.
108. FIORAMONTI, J., FARGEAS, M. J., AND BUÉNO, L.: Comparative effe
	- Arch. Int. Pharmacodyn. 270: 141-150, 1984.

	109. FIORAMONTI, J., FARGRAS, M. J., AND BUÉNO, L.: Different targets for i.v.

	vs. i.c.v. administered morphine for its effect on colonic motility in dogs.

	Eur. J. Pharmacol. 110. **FIORAMONTI**, J., FARGEAS, M. J., AND BUENO, L.: Reversal of the effects of
centrally-administered morphine on colonic motility in dogs by the ben-
zodiazepine receptor antagonist RO 15-1788. Life Sci. 41: 1449–1455,

	- centrally-administered morphine on colonic motility in dogs by the ben-
zodiazepine receptor antagonist RO 15-1788. Life Sci. 41: 1449–1455,
1987.
EMSTRÔM, G., JEDSTEDT, G., AND NYLANDER, O.: Effects of some opiates
and va 49-53, 1985. 111. **FLEMSTROM,** G., JEDSTEDT, G., AND NYLANDER, O.: Effects of some opiates and vasoactive intestinal peptide (VIP) on duodenal surface epithelial bicarbonate secretion in the rat. Scand. J. Gastroenterol. **20** (suppl.
	- vivo. G., JEDSTEDT, G., AND NYLANDER, O.: β-Endorphin and enkephalins stimulate duodenal mucosal alkaline secretion in the rat in vivo. Gastroenterology 90: 368-372, 1986. Touch, R., AND KAPLAN, R. B.: Role of enkephalins
	-

ARMACOLO

spet

ARMACOLO

spet

 $\overline{\mathbb{O}}$

PHARM
REV

intestinal water and ion absorption in the rat. Am. J. Physiol. **246:** G386- **G392,** 1984.

- **114. Fontained water and ion absorption in the rat. Am. J. Physiol. 246: G386-6392, 1984.

414. FONTAINE, J., AND REUSE, J.: Contractor responses of the isolated colon of**

the mouse to morphine and some opioid peptides.
- G392, 1984.

114. FONTAINE, J., AND REUSE, J.: Contractor responses of the isolated colon of

the mouse to morphine and some opioid peptides. Br. J. Pharmacol. 85:

861-867, 1985.

115. Fox, D. A., AND BURKS, T. F.: Roles 861–867, 1985.

115. Fox, D. A., AND BURKS, T. F.: Roles of central and peripheral mu, delta,

and kappa opoioid receptors in the mediation of gastric acid secretory

effects in the rat. J. Pharmacol. Exp. Ther. 244: 456–4
-
- **253: G179-G188, 1987.**
 253: G179-G188, 1988.
 263: G179-G188, POX, J. E. T., AND DANIEL, E. E.: Exogenous opiates: their local mechanisms of action in the canine small intestine and stomach. Am. J. Physiol.

263: G17
- 115b. Fox, J. E. T., AND DANIEL, E. E.: Exogenous opiates: their local mechanisms of action in the canine small intestine and stomach. Am. J. Physiol.
253: G179-G188, 1987.
263: 279-G188, 1987.
115c. Fox, J. E. T., AND DAN
-
- Am. J. Physiol. 253: G189-G194, 1987.
116. FRIESEN, S. R.: The genesis of gastroduodenal ulcer following burns. Surgery
28: 123-158, 1950.
117. FURNESS, J. B., COSTA, M., AND MILLER, R. J.: Distribution and projections
of interiors. Neuroscience 8: 653-664, 1983.

118. FRIESEN, S. R.: The genesis of gastroduodenal ulcer following burns. Surge

28: 123-158, 1950.

117. FURNESS, J. B., COSTA, M., AND MILLER, R. J.: Distribution and projection
- IRNESS, J. B., COSTA, M., AND MILLER, R. J.: Distribution and projections
of nerves with enkephalin-like immunoreactivity in the guinea-pig small
intestine. Neuroscience 8: 653-664, 1983.
RUKAWA, K., TONOUE, T., AND NOMOTO Intestine. Neuroscience 8: 653-664, 1983.

118. FURUKAWA, K., TONOUE, T., AND NOMOTO, T.: Postnatal change in rectivity for methionine⁴-enlephalin in rat duodenum: transition from rogenic to myogenic receptivity. Eur. J. 118. FURUKAWA, K., TONOUE, T., AND NOMOTO, T.: Postnatal change in receptivity for methionine⁸-enkephalin in rat duodenum: transition from neurogenic to myogenic receptivity. Eur. J. Pharmacol. 82: 161-166, 1982.
119. GA
-
- 119. GAGINELLA, T. S., BERTKO, R. J., AND KACHUR, J. F.: Effect of dextrome-
thorphan and levomethorphan on gastric emptying and intestinal transit
in the rat. J. Pharmacol. Exp. Ther. 240: 388-391, 1987.
120. GAGINELLA, T
- in the rat. J. Pharmacol. Exp. Ther. 240: 388-391, 1987.

120. GAGINELLA, T. S., RIMELE, T. J., AND WIETECHA, M.: Studies on rat

14 intestinal epithelial cell receptors for serotonin and opiates. J. Physiol.

335: 101-111
- 121. GAGINELLA, T. S., AND WU, Z. C.: [D-Ala^x,D-Met⁹NH₃]-enkephalin inhibits
acetylcholine release from the submucosal plexus of rat colon. J. Pharm.
Pharmacol. 35: 823-825, 1983.
122. GAION, R. M., AND TRENTO, M.: T
- MON, R. M., AND TRENTO, M.: The role of adrenergic, purinergic, and opiate receptors in the control of prostacyclin-induced contraction in the guinea-pig ileum. Arch. Int. Pharmacodyn. 271: 33-44, 1984.

MLIGAN, J. J., AND quinea-pig ileum. Arch. Int. Pharmacodyn. 271: 33-44, 1984.

123. GALLIGAN, J. J., AND BURKS, T. F.: Inhibition of gastric and intestinal motility by centrally and peripherally administered morphine. Proc. West.

Pharmacol 123. GALLIGAN, J. J., AND BURKS, T. F.: Inhibition of gastric and intestinal
motility by centrally and peripherally administered morphine. Proc. West.
Pharmacol. Soc. 25: 307-311, 1982.
124. GALLIGAN, J. J., AND BURKS, T.
-
- motility by centrally and peripherally administered morphine. Proc. West.

Pharmacol. Soc. 25: 307-311, 1982.

124. GALLIGAN, J. J., AND BURKS, T. F.: Opioid peptides inhibit intestinal transit

in the rat by a central mec LLLIGAN, J. J., AND BURKS, T. F.: Opioid peptides inhibit intestinal transit
in the rat by a central mechanism. Eur. J. Pharmacol. 85: 61-68, 1982.
LLIGAN, J. J., MOSBERG, H. I., HURST, R., HRUBY, V. J., AND BURKS,
T. F.: in the rat by a central mechanism. Eur. J. Pharmacol. 88
ALLIGAN, J. J., MOSBERG, H. I., HURST, R., HRUBY, V.
T. F.: Cerebral delta opioid receptors mediate analge
intestinal motility effects of intracererbroventricular
op 125. GALLIGAN, J. J., MOSBERG, H. I., HURST, R., HRUBY, V. J., AND BURKS,
T. F.: Cerebral delta opioid receptors mediate analgesia but not the
intestinal motility effects of intracerebroventricularly administered
opioids.
-
- ulcerative colitis after opiate administration. Gastroenterology 53: 93-100, 1967.

127. GARZÓN, J., HÖLLT, V., AND HERZ, A.: Cholecystokinin octapeptide activates an opioid mechanism in the guinea-pig ileum: a possible ro
- 128. GARZÓN, J., HÖLLT, V., SÁNCHEZ-BLÁZQUEZ, P., AND HERZ, A.: Neural activation of opioid mechanisms in guinea pig ileum by excitatory pep-
- tides. J. Pharmacol. Exp. Ther. 240: 642-649, 1987.
ASCOIGNE, A. D., HIRST, B. H., THE LATE REED, J. D., AND SHAW, B.:
Effects of thyrotrophin-releasing hormone, and methionine-enkephalin **129. GAR2ÓN, J., HOLLT, V., SÁNCHEZ-BLÁZQUEZ, P., AND HERZ, A.: Neural**
 129. GAR2ÓN, J., HOLLT, V., SÁNCHEZ-BLÁZQUEZ, P., AND HERZ, A.: Neural
 219. GASCOIGNE, A. D., HIRST, TB. H., THE LATE REED, J. D., AND SHAW, B.: on gastric acid and pepsin secretion in guinea pig ileum by excitatory peptides. J. Pharmacol. Exp. Ther. 240: 642-649, 1987.
ASCOIGNE, A. D., HIRST, B. H., THE LATE REED, J. D., AND SHAW, B.:
Effects of thyrotrophin-rel 129. GASCOIGNE, A. D., HIRST, B. H., THE LATE REED, J. D., AND SHAW, B.:
Effects of thyrotrophin-releasing hormone, and methionine-enkephalin
on gastric acid and pepsin secretion in the cat. Br. J. Pharmacol. 69: 527-
534,
-
- opiate receptor agonists and antagonists on the stress-induced secretion Castroenterology 80: 1571-1594, 1981.

131. GIBSON, A., GINSBURG, M., HALL, M., AND HART, S. L.: The effects of 15

opiate receptor agonists and antagonists on the stress-induced secretion

of corticosterone in mice. Br. J
- B8ON, A., GINSBURG, M., HALL, M., AND HART, S. L.: The effects of
opiate receptor agonists and antagonists on the stress-induced secretion
of corticosterone in mice. Br. J. Pharmacol. 65: 139–146, 1979.
ILBERT, R. J., SARN Solar Suppler againsts and antagonists on the stress-induced secretion
of corticosterone in mice. Br. J. Pharmacol. 65: 139–146, 1979.
132. GILBERT, R. J., SARNA, S. K., AND HARDER, D. R.: Effect of morphine on
alectrophys on Controversion in mac. 21. The manneuver of responses to the morphine electrophysiological properties of circular and longitudinal muscles. *A*
 periodic 252: G333-G338, 1987.
 periodic on the motility and responses o
- J. Physiol. 252: G333-G338, 1987.
133. GILLAN, M. G. C., AND POLLOCK, D.: Acute effects of morphine and opioid
peptides on the motility and responses of rat colon to electrical stimula-
tion. Br. J. Pharmacol. **68:** 381–39
- **ELAN, M. G. C., AND POLLOCK, D.: Acute effects of morphine and opiperides on the motility and responses of rat colon to electrical stime ion. Br. J. Pharmacol. 68: 381–392, 1980.

ion. Br. J. Pharmacol. 68:** 381–392, 198 peptides on the motility and responses of rat colon to electrical stime. Br. J. Pharmacol. 68: 381–392, 1980.

NATZLER, A. R., CHAN, W. C., AND GLASS, J.: Evoked release of methior

enkephalin from tolerant/dependent enter 134. GINTZLER, A. R., CHAN, W. C., AND GLASS, J.: Evoked release of methionine tissues. Scand. J. Gastroenterol. 22 (suppl. 130): 27–46, 1987.

enkephalin from tolerant/dependent enteric ganglia: paradoxical depend-

ence
- **INTZLER, A. R., CHAN, W. C., AND GLASS, J.: Evoked release of methionine**
enkephalin from tolerant/dependent enteric ganglia: paradoxical depend-
ence on morphine. Proc. Natl. Acad. Sci. USA 84: 2537–2539, 1987.
INTZLER, ence on morphine. Proc. Natl. Acad. Sci. USA 84: 2537-2539, 1987.
135. GINTZLER, A. R., ROTHMAN, T. P., AND GERSHON, M. D.: Ontogeny of
opiate mechanisms in relation to the sequential development of neurons
known to be com opiate mechanisms in relation to the sequential development of neurons 136. GINTZLER, A. R., ROTHMAN, T. P., AND GERSHON, M. D.: Ontogeny of opiate mechanisms in relation to the sequential development of neurons known to be components of the guinea pig's enteric nervous system. Brain Res. 189
-
- 137. GLASS, **J., CHAN, W. C., AND GINTZLER, A. R.: Direct analysis ofthe release Res. 189: 31–48, 1980.**
LASEL, J. A., BRADBURY, W. M., AND VENN, R. F.: Opiate binding to
subcellular fractions from guinea pig ileum. Life Sci. 34: 345–351, 1984.
LASS, J., CHAN, W. C., AND GINTZLER, A. R.: Direct analys 239: 742-747, 1986. 1997. The magnificant product of methionine-enkephalin from guinea pig myenteric plexus: modulation of methionine-enkephalin from guinea pig myenteric plexus: modulation by endogenous opioids and exogen
- by endogenous opioids and exogenous morphine. J. Pharmacol. Exp. Ther. 165. HERSH, L. B.: Nomenclature for enkephalin degrading peptidases. Life Sci.

239: 742-747, 1986.

138. GLAVIN, G. B., KIERNAN, K., HNATOWICH, M. R.,
-

peripheral mediation of morphine-induced inhibition of gastrointestinal transit in rats. J. Pharmacol. Exp. Ther. 236: 8-13, 1986.
140. GMEREK, D. E., RYAN, J. P., AND COWAN, A.: Cross-tolerance between

- ESTINAL MOTILITY AND SECRETION 155
peripheral mediation of morphine-induced inhibition of gastrointestinal
transit in rats. J. Pharmacol. Exp. Ther. 236: 8-13, 1986.
140. GMEREK, D. E., RYAN, J. P., AND COWAN, A.: Cross-to MEREK, D. E., RYAN, J. P., AND COWAN, A.: Cross-tole
morphine- and bombesin-induced inhibition of intestinal
Eur. J. Pharmacol. 114: 175-180, 1985.
DLDSTEIN, A., AND JAMES, I. F.: Multiple opioid receptor
identification an morphine- and bombesin-induced inhibition of intestinal transit in rats.

Eur. J. Pharmacol. 114: 175-180, 1985.

141. GOLDSTEIN, A., AND JAMES, I. F.: Multiple opioid receptors. Criteria for

identification and classifica
-
-
- Eur. J. Pharmacol. 114: 175-180, 1985.

141. GOLDSTEIN, A., AND JAMES, I. F.: Multiple opioid receptors. Criteria for

identification and classification. TIPS 5: 503-505, 1984.

142. GOLDSTEIN, A., AND SCHULZ, R.: Morphine nism of gastric secretion induced by morphine and reservince in the mechanism of gastric secretion induced by morphine and reserpine. Farmakol.
Toksikol. 31: 450, 1968. 1450, 1968. 1450, 1968. 1450, 1968. 1450, 1968. 1450,
-
-
- **testinal motility and secretion. Am. J. Physiol. 252: G1-G7,** 1987. **145a. GRIDER, J. R., AND MAKHLOUF, G. M.: Role of opioid neurons in the**
- Toksikol. 31: 450, 1968.

1450, 1968.

1450, 1968.

1450, 1968.

1450, 1968.

1450, 1968.

1450, 1968.

1460, 1968.

1460. GREENWOOD, B., AND DAVISON, J. S.: The relationship between gastroin-

1460. GRIDER, J. R., AND MAK Agents Actions 11: 196-203, 1981.
 Agents Actions 11: 196-2031, 1987.
 Agents Actions 11: 196-203, 1981.
 Agents Actions 11: 196-203, 1981.
 Agents Actions 11: 196-203, 1981.
 Agents Actions 11: 196-203, 1981.

- ROSMAN, N.: Histamine release from isolated rat mast cells: effection of Agents Actions 11: 196-203, 1981.
Agents Actions 11: 196-203, 1981.
JARBAA, L. A., ORDONEZ, N. G., DEL JUNCO, G. W., AND LUNA, M
Gangliocytic paragan morphine and related drugs and their interaction with compound 48-80.
Agents Actions 11: 196-203, 1981.
147. GUARDA, L. A., ORDONEZ, N. G., DEL JUNCO, G. W., AND LUNA, M. A.:
6 angliocytic paraganglioma of the duodenum: an 147. GUARDA, L. A., ORDONEZ, N. G., DEL JUNCO, G. W., AND LUNA, M. A.:

Gangliocytic paraganglioma of the duodenum: an immunocytochemical

study. Am. J. Gastroenterol. 78: 794–798, 1983.

148. GUERRERO. Munoz, F., DE LourD
- Gangliocytic paraganglioma of the duodenum: an immunocytochemical
study. Am. J. Gastroenterol. 78: 794-798, 1983.
148. GUERRERO-MUNOZ, F., DE LOURDES GUERRERO, M., AND WAY, E. L.;
Effect of morphine on calcium uptake by ly
- UERRERO-MUNOZ, F., DE LOURDES GUERRERO, M., AND WAY, E. L.:
Effect of morphine on calcium uptake by lysed synaptosomes. J. Phar-
macol. Erp. Ther. 211: 370–374, 1979.
UERRERO-MUNOZ, F., DE LOURDES GUERRERO, M., WAY, E. L. macol. Exp. Ther. 211: 370–374, 1979.
149. GUERRERO-MUNOZ, F., DE LOURDES GUERRERO, M., WAY, E. L., AND L.,
C. H.: Effect of β -endorphin on calcium uptake in the brain. Science
(Wash. DC) 206: 89–91, 1979.
150. GUILLEMI
- UERRERO-MUNOZ, F., DE LOURDES GUERRERO, M., WAY, E. L., AND LI, C. H.: Effect of β-endorphin on calcium uptake in the brain. Science (Wash. DC) 2068: 89-91, 1979.

ULLEMIN, R., VARGO, T., ROSSIER, J., MINICK, S., LING, N. C. H.: Effect of β -endorphin on calcium uptake in the brain. Science (Wash. DC) 206: 89-91, 1979.
UILLEMIN, R., VARGO, T., ROSSIER, J., MINICK, S., LING, N., RIVIER, C., VALE, W., AND BLOOM, F.: β -Endorphin and adren (Wash. DC) 2003: 89-91, 1979.

150. GUILLEMIN, R., VARGO, T., ROSSIER, J., MINICK, S., LING, N., RIVIER, C., V., L., AND BLOOM, F.: *β*-Endorphin and adrenocorticotropin are

secreted concomitantly by the pituitary gland. UMLE, W., AND BLOOM, F.: β -Endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. Science (Wash. DC) 197: 1367–1369, 1977.
1367–1369, 1977.
UPTA, M. B., GUPTA, G. P., AND BHARGAVA, K. P.:
- 151. GUPTA, M. B., GUPTA, G. P., AND BHARGAVA, K. P.: Role of opioid receptors
in stress induced gastric ulceration in rats. Indian J. Med. Res. 83: 532-
535, 1986.
151a. HAKANSON, R., HEDENBRO, J., LIEDBERG, G., SUNDLER,
-
- 152. HALL, A. W., MOOSSA, A. R., CLARK, J., COOLEY, G. R., AND SKINNER, D.
B.: The effects of premedication drugs on the lower esophageal high
pressure zone and reflux status of Rhesus monkeys and man. Gut 16:
347-352. 197 B.: The effects of premedication drugs on the lower esophageal high 347-352, 1975. HALL, A. W., Moosa, A. R., CLARK, J., COLEY, G. R., AND SKINNER, D.

B.: The effects of premedication drugs on the lower esophageal high

pressure zone and reflux status of Rhesus monkeys and man. Gut 16:

3
- pressure zone and reflux status of Rhesus monkeys and man. Gut 16:

347-352, 1975.

153. HALTER, F., BANGERTER, U., HACKI, W. H., SCHLUP, M., VARGA, L.,

WYDER, S., ROTZER, A., AND GALEAZZI, R.: Sensitivity of the parietal
-
-
- on gastric acid and pepsin secretion in the cat. Br. J. Pharmacol. 69: 527-

534, 1986.

130. GERSHON, M. D., AND ERDE, S. M.: The nervous system of the gut.

156. HARDCASTLE, J., HARDCASTLE, P. T., READ, N. W., AND ERDEN, **no direct effect on PGE,**-stimulated cyclic AMP production in the rest on of loperamide in inhibiting prostaglandin-induced intestinal secretion in the rat. Br. J. Pharmacol. 74: 563-569, 1981.
157. HARDCASTLE, J., HARDCA
	- The action of loperamide in inhibiting proctaglandin-induced intestinal
secretion in the rat. Br. J. Pharmacol. 74: 563-569, 1981.
157. HARDCASTLE, J., HARDCASTLE, P. T., AND REDFERN, J. S.: Morphine has
no direct effect o
	-
	- 159. Hauter effect on PGE_T-stimulated cyclic AMP production by rat isolated
enterocytes. J. Pharm. Pharmacol. 34: 68, 1982.
159. HAUTEFEUILLE, M., Acute ulcer of the duodenum (Curling's ulcer) as a
complication of burns; 158. HARKINS, H. N.: Acute ulcer of the duodenum (Curling's ulcer) as a complication of burns; relation to sepais. Surgery 3: 608-641, 1938.

	159. HAUTEFEUILLE, M., BRANTL, V., DUMONTIER, A.-M., AND DESJEUX, J.-F.:

	In vit
	-
	-
	-
	- 160. HEDNER, T., AND CASSUTO, J.: Opicids and opicid receptors in peripheral
tissues. Scand. J. Gastroenterol. 22 (suppl. 130): 27–46, 1987.
161. HELLSTRÖM, P. M.: Pharmacological analysis of the mechanism of action
for co nervous system. Br. Med. Bull. 39: 59–64, 1983.

	163. HERMANSEN, K.: Enkephalins and the secretion of pancreatic somatostatin

	and insulin in the dog: studies in vitro. Endocrinology 113: 1149–1154,

	1983.

	164. HERNANDEZ, and insulin in the dog: studies in vitro. Endocrinology 113: 1149–1154,
1863.
164. HERNANDEZ, D. E.: Neuroendocrine mechanisms of stress ulceration: focus
on thyrotropin-releasing hormone (TRH). Life Sci. 39: 279–296, 1966
	-
	- 38: 1151-1153, 1986.
	- 164. HERNANDEZ, D. E.: Neuroendocrine mechanisms of stress ulceration: focus
on thyrotropin-releasing hormone (TRH). Life Sci. 39: 279–296, 1986.
165. HERSH, L. B.: Nomenclature for enkephalin degrading peptidases. Life Sc 166. HEY, V. M. F., OSTICK, D. G., MAZUMDER, J. K., AND LORD, W. D.: Pethidine, metoclopramide, and the gastro-oesophageal sphincter. Anaesthesia 36: 173-176. 1981.
	-

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

-
- agonists induce contractions of the canine small intestine ex vivo. Eur. J.
Pharmacol. 109: 49-54, 1985.
169. HIRSCHOWITZ, B. I., AND SACHS, G.: Vagal gastric secretory stimulation by
2-deoxy-D-glucose. Am. J. Physiol. 209
- Pharmacol. 109: 49-54, 1985.

168. HIRSCHOWITZ, B. I., AND SACHS, G.: Vagal gastric secretory stimulation by

2-deoxy-D-glucose. Am. J. Physiol. 209: 452-460, 1965.

169. HIRST, B. H.: Opiates and acid secretion. Gastroent
-
- 169. HIRST, B. H.: Opiates and acid secretion. Gastroenterology 78: 1124, 1980.
170. Ho, M. M., Dal, S., AND OGLE, C. W.: Decreased acid secretion and gastric lesion production by morphine in rats. Eur. J. Pharmacol. 102: 251-257, 1987. in morphine-dependent rats. Pharmacology 30: 301-307, 1985. 1988. JONSSON, A.-C.: Occurrence of met-enkephalin, met-enkephalin-Arg⁴-Phe⁷
172. Ho, M. M., Dai, S., AND OGLE, C. W.: Morphine reduces vagal-stimulated
251-2
- secretion by the isolated rat gastric mucosa. Pharmacol. Res. Commun. 17: 855-864. 1985. gastric acid secretion through a central action. Eur. J. Pharmacol. 139:
251-257, 1987.
173. Ho, M. M., OGLE, C. W., AND DAI, S.: The influence of morphine on acid
secretion by the isolated rat gastric mucosa. Pharmacol. R synthesis in rats. Eur. J. Pharmacol. The influence of morphine on accertaion by the isolated rat gastric mucosa. Pharmacol. Res. Commu 17: 855-864, 1985. The M. M., OGLE, C. W., AND DAI, S.: Morphine enhances gastric muco
-
- 17: 855-864, 1985.

0, M. M., OGLE, C. W., AND DAI, S.: Morphine enhances gastric mucus

synthesis in rats. Eur. J. Pharmacol. 122: 81-86, 1986.

0, M. M., OGLE, C. W., AND DAI, S.: Effects of morphine, hypoxaemia,

and hy synthesis in rats. Eur. J. Pharmacol. 122: 81-86, 1986.
175. Ho, M. M., OGLE, C. W., AND DAI, S.: Effects of morphine, hypoxaemia,
and hypercapnia on the rat stomach. Eur. J. Pharmacol. 126: 103-109,
1986.
176. HoLSTI, H.:
-
-
- **reflex. Naunyn Schmiedeberg's** Arch. Pharmacol 307: 257-264, 1979.
 reflex. Pharmacol 2018. 1-16, 1903.
 Pharmacol 307: 257-264, P., AND LEMBECK, F.: Effect of neuropeptides on the peristaltic reflex. Naunyn Schmiedebe des Magensattes. Z. klin. Med. 49: 1-16, 1903.

177. HOLZER, P., AND LEMBECK, F.: Effect of neuropeptides on the peristaltic

reflex. Naunyn Schmiedeberg's Arch. Pharmacol. 307: 257-264, 1979.

178. HOWARD, J. M., BELSHEIM
-
-
-
-
- nor. Home, Bullet and School and School and School and School and School and School and Transmission in the human colon. Eur. J. Pharmacol. 131: 159-160, 1986.
181. HUGHES, J.: Peripheral opiate receptor mechanisms. TIPS 2 tapeptides from the brain with potent opinions. Br. Med. Bull. 39: 17-24, 1983.

HUGHES, J., SMITH, T. W., KOSTERLITZ, H. W., FOTHERGILL, L. A., MORGAN, B. A., AND MORRIS, H. R.: Identification of two related pentapeptides MORGAN, B. A., AND MORRIS, H. R.: Identification of two related properties from the brain with potent opiate agonist activity. Natt (Lond.) 258: 577-579, 1975.
ULOBRO-TORO, J. P., HU, J., AND WAY, E. L.: Calcium antagonism
- **and 185.** (Lond.) 258: 577-579, 1975.
 AND 185. 1879. 1876. IL: Calcium antagonism of 20.
 184. HuIDOBRO-TORO, J. P., HU, J., AND WAY, E. L.: Calcium antagonism of the inhibitory effect of normorphine on the ileum of
- normorphine and *B*-endorphine on the giunea pig ileum. Atl. Instead and nontolerant guinea pig *J*. Pharmacol. Exp. Ther. 218: 84-91, 1981.

Alt. HuIDOBRO-TORO, J. P., HU, J., AND WAY, E. L.: Interaction of Ca⁺⁺ with

- 185. HUIDOBRO-TORO, J. P., HU, J., AND WAY, E. L.: Interaction of Ca⁺⁺ with
normorphine and β -endorphine no the guinee pig ileum. Natl. Inst. Drug
Abuse Res. Monogr. Ser. 41: 148-157, 1982.
186. HUIDOBRO-TORO, J. P.,
- and related opioid alkaloids, β -endorphin, and methionine enkephalin on
the isolated colon from Long Evans rats. Br. J. Pharmacol. 74: 681-694,
187. HUIDOBRO-TORO, J. P., AND YOSHIMURA, K.: Pharmacological character-
i opioid receptors in the rabbit ear artery. **Life** Sci. 33: 307-310, 1983. 189. **ILLE5, P., AND THESLEFF,** 5.: 4-Aminopyridine and evoked transmitter
-
- release from motor nerve endings. Br. J. Pharmacol. **64:** 623-629, 1978.
- teric plexus preparation. Br. J. Pharmacol. 80: 645-653, 1983.

188. ILLES, P., PTEIFTER, N., LIMBERGER, N., AND STARKE, K.: Presynaptic

opioid receptors in the rabbit ear artery. Life Sci. 33: 307-310, 1983.

189. ILLES,
- release from motor nerve endings. Br. J. Pharmacol. 64: 623-629, 1978.

190. IMPROTA, G., BROCCARDO, M., LISI, A., AND MELCHIORRI, P.: Neural

regulation of gastric scid secretion in rats: influence of dermoprhin. Regul.
 191. INURA, H., NAKAI, Y., NAKAO, K., OKI, S., TANAKA, I., JINGAMI, H

YOSHIMASA, T., TSUKADA, T., IKEDA, Y., SUDA, M., AND SAKAMOTO, M

Biosynthesis and distribution of opioid peptides. J. Endocrinol. Invest. 6

139–149,
-
- 139-149, 1983.

192. INGRAM, D. M., AND.CATCHPOLE, B. N.: Effect of opiates on gastroduodenal

motility following surgical operation. Dig. Dis. Sci. **26:** 989-992, 1981.

193. IPP, E., DOBBS, R., AND UNGER, R. H.: Morphin the secretion of the secretion of the endocrine pancreas. Nature 2013. IPP, E., DoBBS, R., AND UNGER, R. H.: Morphine and *β*-endorphin influence
the secretion of the endocrine pancreas. Nature (Lond.) 276: 190-191, 1978.
- **P. E., DOBBS, R., AND UNGER, R. H.: Morphine and** *β***-endorphin influence
the secretion of the endocrine pancreas. Nature (Lond.) 276: 190-191,
1978.
TO, S., TAKAI, K., SHIBATA, A., MATSUBARA, Y., AND YANAIHARA, N.:
Met-en** 193a. ITO, S., TAKAI, K., SHIBATA, A., MATSUBARA, Y., AND YANAIHARA, N.:

Met-enkephalin-immunoreactive and gastrin-immunoreactive cells in the

human and canine pyloric antrum. Gen. Comp. Endocrinol. 38: 238-245,

194. IW
- human and canine pyloric antrum. Gen. Comp. Endocrinol. 38: 238–245,
1979.
KAMOTO, E. T.: Locomotor activity and antinociception after putative mu,
kappa, and sigma opioid receptor agonists in the rat: influence of dopa-
m 194. IWAMOTO, E. T.: Locomotor activity and antinociception after putative mu,

kappa, and sigma opioid receptor agonists in the rat: influence of dopa-

minergic agonists and antagonists. J. Pharmacol. Exp. Ther. 217: 451
-
- minergic agonists and antagonists. J. Pharmacol. Exp. Ther. 217: 451-460, 1981.
195. JANOWSKA, E., LUNDBERG, A., RUDOMIN, P., AND SYKOVA, E.: Effects of 4-aminopyridine on transmission in excitatory and inhibitory synapses
- agonists induce contractions of the canine small intestine ex vivo. Eur. J. 196a. JIAN, R., JANSSENS, J., VANTRAPPEN, G., AND CECCATELLI, P.: Influence

Pharmacol. 109: 49-54, 1985.

HIRSCHOWITZ, B. I., AND SACHS, G.: Vaga of metenkephalin analogue on motor activity of the gastrointestinal tract.
Gastroenterology 93: 114-120, 1987. Of metenkephalin analogue on motor activity of the gastrointestinal tract.
of metenkephalin analogue on motor activity of the gastrointestinal tract.
Gastroenterology 93: 114-120, 1987.
197. JOHNSON, E. E.: Morphine: a dua
	-
	- 196a. JIAN, R., JANSSENS, J., VANTRAPPEN, G., AND CECCATELLI, P.: Influence
of metenkephalin analogue on motor activity of the gastrointestinal tract.
Castroenterology 93: 114-120, 1987.
1973. JOHNSON, E. E.: Morphine: a d Fration of guinea-pig ileum. Naunyn-Schmiedeberg's Arch. Pharmacol.

	Inhibitory effects of opioids in a circular muscle-myenteric plexus preparation of guinea-pig ileum. Naunyn-Schmiedeberg's Arch. Pharmacol.
 336: 419-4
	- **and met-enkephalin-Arg⁴-Gly⁷-Leu⁴ in gastrin cells of hog antral mucosa.** Cell Tissue Res. 240: 361-365, 1985.
Cell Tissue Res. 240: 361-365, 1985.
Cell Tissue Res. 240: 361-365, 1985.
XACHUR, J. F., AND MILLER,
	-
	- 198. JONSSON, A.-C.: Occurrence of met-enkephalin, met-enkephalin-Arg^a-Phe⁷
and met-enkephalin-Arg^a-Gly⁻¹-Leu^s in gastrin cells of hog antral mucosa.
Cell Tissue Res. 240: 361-365, 1985.
199. KACHUR, J. F., AND M 2753-2756, 1980. 200. KACHUR, J. F., MILLER, R. J., AND FIELD, M.: Control of guinea pig
intestinal electrolyte secretion by a delta-opiate receptor. Cell Biol. 77:
2753-2756, 1980.
201. KADLEC, O., AND HORACEK, J.: Inhibition of peristalt
	- ACHUR, J. F., MILLER, K. J., AND FIELD, M.: Control of guinea pig
intestinal electrolyte secretion by a delta-opiate receptor. Cell Biol. 77:
2753–2756, 1980.
ADLEC, O., AND HORÁCEK, J.: Inhibition of peristaltic activity intestinal electrolyte secretion by a delta-opiate receptor. Cell Biol. 77:
201. KADLEC, 0., AND HORÁCEK, J.: Inhibition of peristaltic activity in the
guines-pig ileum by specific stress stimulus; its reversal by nalorone quinea-pig ileum by specific stress stimulus; its reversal by naloxone and
indomethacin. Life Sci. 27: 1557-1562, 1980.
202. KAUFIN, A. J., OLSON, R. D., SCHALLY, A. V., AND COY, D. H.: CNS effects
of peripherally administ
	-
	- 202. KASTIN, A. J., OLSON, R. D., SCHALLY, A. V., AND COY, D. H.: CNS effects
of peripherally administered brain peptides. Life Sci. 25: 401-414, 1979.
203. KAUFFMAN, G. L.: Blood flow and gastric secretion. Fed. Proc. 41:
	- of peripherally administered brain peptides. Life Sci. 25: 401-414, 1979.

	203. KAUTTMAN, G. L.: Blood flow and gastric secretion. Fed. Proc. 41: 2080-

	2083, 1982.

	204. KEAST, J. R., FURNESS, J. B., AND COSTA, M.: Distri 203. KAU**FFMAN, G. L.: Biood flow and gastric secretion. Fed. Proc. 41: 2080-2083, 1982.**
2043. M. Character Mammalian species. J. Comp. Neurol. 236: 403-422, 1985.
peptide-containing nerve fibres and endocrine cells in th
	- to inhibit pervice-containing nerve fibres and endocrine cells in the gastrointestinal mucosa in five mammalian species. J. Comp. Neurol. 236: 403-422, 1985.

	204a. KENNEDY, C., AND KRIER, J.: [Met^s]enkephalin acts via
	- to inhibit pelvic nerve-evoked contractions of cat distal colon. Br. J.

	205. KILBINGER, H., AND WESSLER, I.: Inhibition by acetylcholine of the stim-

	ulation-evoked release of [*H]acetylcholine from the guinea-pig myente 205. KILBINGER, H., AND WESSLER, I.: Inhibition by acetylcholine of the stim-
ulation-evoked release of [³H]acetylcholine from the guinea-pig myenteric
plexus. Neuroscience 5: 1331-1340, 1980.
206. KIM, C. H., ZINSMEISTE
	-
	- **pates in the contractile response to morphine in the rat isolated colon.**
	-
	- 208. KITCHEN, I.: Endogenous opioid nomenclature: light at the end of the tunnel.
Gen. Pharmacol. 16: 79–84, 1985.
209. KIVILAAKSO, E., BRAZILAI, A., SCHIESSEL, R., FROMM, D., AND SILEN, W.:
Experimental ulceration of rabb Experimental ulceration of rabbit antral mucosa. Gastroenterology 80:

	Gen. Pharmacol. 16: 79-84, 1986.

	209. KIVILAAKS0, E., BRAZILAI, A., SCHIESSEL, R., FROMM, D., AND SILEN, W.:

	Experimental ulceration of rabbit antral
	- atin and intramural pH of gastric mucosa during hemorrhagic shock.
Surgery 84: 70-78, 1978.
211. KOCH, G., WIEDEMANN, K., AND TESCHEMACHER, H.: Opioid activities of Surgerimental ulceration of rabbit antral mucosa. Gastroenterology 80:

	77-83, 1981.

	210. KIVILAAKSO, E., FROMM, D., AND SILEN, W.: Relationship between ulcer-

	ain and intramural pH of gastric mucosa during hemorrhagic s
	- FROMM, D., AND SILEN, W.: Relationship between ulceratin and intramural pH of gastric mucosa during hemorrhagic shock.
Surgery 84: 70-78, 1978.
211. KOCH, G., WIEDEMANN, K., AND TESCHEMACHER, H.: Opioid activities of
huma
	- OCH, G., WIEDEMANN, K., AND TESCHEMACHER, H.: Opioid activities of human β -casomorphins. Naunyn-Schmiedeberg's Arch. Pharmacol. 331:
351–354, 1985.
351–354, 1985.
ONTUREK, S. J., JAWOREK, J., BIELAÑSKI, W., CIESZKOWSKI, 606, 1982. 213. Kontugal, M., AND COY, D. H.: Comparison of enkephalin and atropine
in the inhibition of vagally stimulated gastric and pancreatic secretion
and gastrin and pancreatic polypeptide release in dogs. Peptides 3: 601-
606
	- and gastrin and pancreatic polypeptide release in dogs. Peptides 3: 601-606, 1982.

	606, 1982.
 ONTUREK, S. J., KWIECIEŃ, N., OBTULOWICZ, W., SWIERCZEK, J., BIELAŃSKI, W., OLEKSY, J., AND COY, D. H.: Effect of enkephalin LAŃSKI, W., OLEKSY, J., AND COY, D. H.: Effect of enkephalin and
naloxone on gastric acid and serum gastrin and pancreatic polypeptide
concentrations in humans. Gut 24: 740-745, 1983.
214. KONTUREK, S. J., PAWLIK, W., WALU
	- mucosal blood flow. Proc. Soc. Exp. Biol. Med. 158: 156-160, 1978.
214a. KONTUREK, S. J., TASLER, J., CIESZKOWSKI, M., JAWOREK, J., COY, D.
	- concentrations in humans. Gut 24: 740-745, 1983.

	214. KONTUREK, S. J., PAWLIK, W., WALUS, K. M., COY, D. H., AND SCHALLY,

	A. V.: Methionine-enkephalin stimulates gastric secretion and gastric

	mucosal blood flow. Proc. S
	- KONTUREK, S. J., TASLER, J., CIESZKOWSKI, M., JAWOREK, J., COV, D.
H., AND SCHALLY, A. V.: Inhibition of pancreatic secretion by enkephalin
and morphine in dogs. Gastroenterology 74: 851-855, 1978.
AND SCHALLY, A. V.: Comp and morphine in dogs. Gastroenterology 74: 261-255, 1978.

	215. KONTUREK, S. J., TASLER, J., CIESZKOWSKI, M., MIKOS, E., COY, D. H.,

	AND SCHALLY, A. V.: Comparison of methionine-enkephalin and mor-

	phine in the stimulati
	- phine in the stimulation of gastric acid secretion in the dog. Gastroenter-

	216. KONTUREK, S. J., THOR, P., KRÓL, R., DEMBIŃSKI, A., AND SCHALLY, A.

	V.: Influence of methionine-enkephalin and morphine on myoelectric

	act SONTUREK, S. J., THOR, P., KRÓL, R., DEMBIŃS
V.: Influence of methionine-enkephalin and ractivity of small bowel. Am. J. Physiol. 238: G3
OPPANYI, T., AND MURPHY, W. S.: The effect
sphincters. Science (Wash. DC) 78: 14, 19
	-
	- V.: Influence of methionine-enkephalin and morphine on myoelectric
activity of small bowel. Am. J. Physiol. 238: G384–G389, 1980.
217. Koppanyn, T., AND MURPHY, W. S.: The effect of morphine on the anal
sphincters. Science **Phincers. Science (Wash. DC) 78: 11e effect of morphine on the anal

	sphincers. Science (Wash. DC) 78: 14, 1933.

	R. Kosto, R. J., VAUGHT, J. L., COWAN, A., GMEREK, D. E., AND PORRECA,

	F.: Intrathecal morphine slows gast**
	-
	- 220. Kosten, *H. W., AND LRES, G. M.: Pharmacological analysis of intrinsic intestinal reflexes. Pharmacol. Rev. 16: 301–339, 1964.
219. Kosten, H. W., AND LRES, G. M.: Pharmacological analysis of intrinsic intestinal ref* adrenoceptors in the longitudinal muscle of the guinea-pig ileum. Br. J. intestinal reflexes. Pharmacol. Rev. 16: 301-339, 1964.

	220. KOSTERLITZ, H. W., LYDON, R. J., AND WATT, A. J.: The effects of adrenaline, noradrenaline, and isoprenaline on inhibitory alpha- and β -

	adrenaceptors in th adrenaline, noradrenaline, and isoprenaline on inhibitory alpha- and β -
	- of the peristaltic reflex in the isolated guinea-pig ileum. J. Physiol. 133: 681-694, 1956.

ARMA

spet

- 222. KOSTERLITZ, **H. W., AND ROBINSON, J. A.: Inhibition of the peristaltic**
- **OPIOIDS AND CONTROL OF GASTROIN**
222. KOSTERLITZ, H. W., AND ROBINSON, J. A.: Inhibition of the peristaltic
reflex of the isolated guinea-pig ileum. J. Physiol. 136: 249–262, 1957.
223. KOSTERLITZ, H. W., AND WATT, A. J.:
- **pp. 391-401, Plenum Press, New York, 1975.**

223. KOSTRELITZ, H. W., AND WATT, A. J.: The peristatic reflex. In Methods

in Pharmacology, ed. by E. E. Daniel and D. M. Paton, vol. 3, chap. 21,

pp. 391-401, Plenum Press, in Pharmacology, ed. by E. E. Daniel and D. M. Paton, vol. 3, chap. 21, pp. 391-401, Plenum Press, New York, 1975.
224. KOSTRITSKY-PEREIRA, A., WOUSSON-COLLE, M. C., AND DE GRAEP, J.:
Effects of morphine, enkephalins, and Physiol. Pienum Press, New York, 1975.
224. KOSTRITSKY-PEREIRA, A., WOUSSON-COLLE, M. C., AND DE GRAEF, J.:
Effects of morphine, enkephalins, and naloxone on postprandial gastric
acid secretion, gastric emptying, and gastr
- Effects of morphine, enkephalins, and naioxone on postprandial gastric acid secretion, gastric emptying, and gastrin release in dogs. Arch. Int. 25 Physiol. Biochim. 92: 19-26, 1984.
 OSTRITSKY-PEREIRA, A., WOUSSEN-COLLE, bethanechol, or a meal. IN. 1992. 19-26, 1984.

225. KOSTRITSKY-PEREIRA, A., WOUSSEN-COLLE, M. C., AND DE GRAEF, J.

Effect of Met-enkephalin on acid secretion from gastric fistulas and

heidenhain pouches in dogs stimulat Effect of Met-enkephalin on acid secretion from gastric fistulas a
Heidenhain pouches in dogs stimulated by pentagastrin, pentagastrin pi
bethanechol, or a meal. Int. J. Tissue Reac. 6: 167-173, 1984.
REEK, M. J., SCHAEFER
-
- 226. KREK, M. J., SCHAEFER, R. A., HAHN, E. F., AND FISHMAN, J.: Naloxone,
226. KREK, M. J., SCHAEFER, R. A., HAHN, E. F., AND FISHMAN, J.: Naloxone,
237. KREK, G. J., AND FORDTRAN, J. S.: Diarrhea. *In* Gastrointestinal D S. Fordtran, pp. 257-280, Saunders, Philadelphia, 1983.

227. KREJS, G. J., AND FORDTRAN, J. S.: Diarrhea. *In* Gastrointestinal Disease.

Pathophysiology, Diagnosis, Management, ed. by M. H. Sleisenger and J.

S. Fordtran 227. KREJS, G. J., AND FORDTRAN, J. S.: Diarrhea. In Gastrointestinal Disease.

Pathophysiology, Diagnosis, Management, ed. by M. H. Sleisenger and J.

S. Fordtran, pp. 257–280, Saunders, Philadelphia, 1983.

228. KROMER,
-
-
- 230. KROMER, W., HÖLLT, V., SCHMIDT, H., AND HERZ, A.: Release of immu-ROMER, W., HOLLT, V., SCHMIDT, H., AND HERZ, A.: Release of immunoreactive-dynorphin from the isolated guinea pig small intestine is reduced during peristaltic activity. Neurosci. Lett. 25: 53-5-56, 1981.
ROMER, W., AND PR
-
- **EXECUTE:** 231. **KROMER, W., AND PRETZLAFF, W.:** In vitro evidence for the participation of intestine. Naunyn-Schmiedeberg's Arch. Pharmacol. 309: 153-157, 1979. 232. **KROMER,** W., PRETZLAFF, W., AND SCHEIBLHUBER, E.: In v ROMER, W., AND PRETZLAFF, W.: In vitro evidence for the participation of intestinal opioids in the control of peristalsis in the guinea pig small intestine. Naunyn-Schmiedeberg's Arch. Pharmacol. 309: 153-157, 1979. ROMER of intestinal opioids in the control of peristalsis in the guinea pig small
intestine. Naunyn-Schmiedeberg's Arch. Pharmacol. 309: 153–157, 1979.
ROMER, W., PRETZLAFF, W., AND SCHEIBLIUBER, E.: In vitro evidence
for an inv
- nists, ed. by E. L. Way, pp. 337-340, Pergamon Press, New York, 1980.
233. KROMER, W., PRETZLAFF, W., AND WOINOFF, R.: Opioids modulate perio-
dicity rather than efficacy of peristaltic waves in the guinea pig ileum in
vit views. Photogenous and Exogenous Opiate Agonists and Antagonists, ed. by E. L. Way, pp. 337-340, Pergamon Press, New York, 1980.
233. **KROMER, W., PRETZLAFF, W., AND WOINOFF, R.: Opioids modulate periodicity rather than ef**
- 233. KROMER, W., PRETZLAFF, W., AND WOINOFF, K.: Opioids modulate periodicity rather than efficacy of peristalic waves in the guinea pig ileum in
virto. Life Sci. 26: 1867-1865, 1980.
234. KROMER, W., PRETZLAFF, W., AND WO
- an opioid mechanism in the guinea-pig isolated intestine. J. Pharm.

Pharmacol. 33: 96-101, 1961.

235. KROMER, W., SCHEIBLHUBER, E., AND ILLES, P.: Functional antagonism

by calcium of an intrinsic opioid mechanism in the an opioid mechanism in the guinea-pig isolated intestine. J. Pharm.
Pharmacol. 33: 98-101, 1981.
235. **KROMER, W., SCHEIBLHUBER, E., AND ILLES, P.: Functional antagonism**
by calcium of an intrinsic opioid mechanism in the
- **a site of action additional to the modulation** in the guinea-pig isolated ileum. Neuropharmacology 19: 839-843, 1980.
ROMER, W., AND SCHMIDT, H.: Opioids modulate intestinal peristalsis at a site of action additional to
- EXECUTE: HERO MAND SCHENDT, H.: Opioids modulate intestinal peristalsis at 26 a site of action additional to that modulating acetylcholine release. J.
 Pharmacol. Exp. Ther. 223: 271-274, 1982.

237. KROMER, W., SCHENDTR a site of action additional to that modulating acetylcholine release. J.

237. KROMER, W., SCHRODER, P., AND NETZ, S.: Stereospecific inhibition by

naloxone of histamine-stimulated acid secretion in isolated guinea pig

p
- natoxone of histamine-stimulated acid secretion in isolated guinea pig
 RENOMER, W., SKOWRONEK, B., STARK, H., AND NETZ, S.: Modulation of

acid secretion from enriched guinea pig parietal cells by opioid receptors.

Pha
-
- acid secretion from enriched guinea pig parietal cells by opioid receptors.

Pharmacology 27: 298-304, 1983.

XROMER, W., AND STEIGEMANN, N.: Opiate tolerance/dependence in the

isolated guinea pig ileum is associated with **bergth. Pharmacology 25: 294–296, 1982.**

240. KROMER, W., STEIGEMANN, N., AND SHEARMAN, G. T.: Differential effects of SKF 10,047 (N-allyl-normetazocine) on peristalsis and longitud muscle contractions of the isolated gu
- muscle contractions of the isolated guinea-pig ileum. Naunyn-Schmiede-
berg's Arch. Pharmacol. 321: 218-222, 1982.
241. KROMER, W., AND TESCHEMACHER, H.: An opiate withdrawal-like phenom-
enon in the fetal guinea pig ileum muscle contractions of the isolated guinea-pig ileum. Naunyn-Schmiede-266. 1

berg's Arch. Pharmacol. 321: 218-222, 1982.

241. KROMER, W., AND TESCHEMACHER, H.: An opiate withdrawal-like phenom-267. 1

enon in the fetal g
- 241. KROMER, W., AND TESCHEMACHER, H.: An opiate withdrawal-like phenom
enon in the fetal guinea pig ileum upon naloxone challenge. Eur. J
242. KROMER, W., AND WOINOFF, R.: Peristalsis in the isolated guinea-pig ileum
duri
- during opiate withdrawal. Naunyn-Schmiedeberg's Arch. Pharmacol.
314: 191–193, 1980.
243. KROMER, W., AND WOINOFF, R.: Dual action of somatostatin upon peri-
stalsis in the guinea pig isolated ileum. Neuroendocrinology 33: **243. KROMER, W., AND WOINOFF, R.: Dual action of somatostatin upon peristalsis in the guinea pig isolated ileum. Neuroendocrinology 33: 136-139, 1981.

244. KRUEGER, H.: The action of morphine on the digestive tract. Phy** 245. **KUHAR, M. U.: Histochemical localization** of somaloscalin upon periodicitals in the guinea pig isolated ileum. Neuroendocrinology 33: 136-139,

244. KRUEGER, H.: The action of morphine on the digestive tract. Physiol
-
-
- 244. KRUEGER, H.: The action of morphine on the digestive tract. Physiol. Rev.
17: 618–645, 1937.
246. KUHAR, M. U.: Histochemical localization of opiate receptors and opioid
peptides. Fed. Proc. 37: 153–157, 1978.
246. K UHAR, M. U.: Histochemical localization of opiate receptors and opioid
peptides. Fed. Proc. 37: 153-157, 1978.
UHN, E., LODIN, Z., LOVACKY, S., TAUBER, O., ZIZKOVSKY, V., DVORAK,
P., SRAJER, S., AND SKALA, I.: Plasma *ß*-e peptides. Fed. Proc. 37: 153-157, 1978.
UHN, E., LODIN, Z., LOVACKY, S., TAUBER, O., ZIZKOVSKY, V., DVORAK, P., SRAJER, S., AND SKALA, I.: Plasma β -endorphin immunoreactivity (PL- β -ED-ir) in patients with ulcer dise 247. KUPERMAN, D. A., SNINSKY, C. A., AND LYNCH, D. F.: Myoelectric activity (PL- β -ED-ir) in patients with ulcer disease and its management by acute and chronic administration of gastrozepin. Hepatogastroenterology 33:

- rats. Am. J. Physiol. 252: G562-G567, 1987.
247. KUPERMAN, D. A., SNINSKY, C. A., AND LYNCH, D. F.: Myoelectric of the small intestine during morphine dependence and with rats. Am. J. Physiol. 252: G562-G567, 1987.
248. LA
-
-

of peptide-containing neurones in human gut-an immunocytochemical study. Regul. Pept. 17: 243-256, 1987.

- STINAL MOTILITY AND SECRETION
of peptide-containing neurones in human gut—an immunocytochem
study. Regul. Pept. 17: 243–256, 1987.
248b. LARSSON, L.-T., MALMFORS, G., AND SUNDLER, F.: Peptidergic inne
tion in Hirschsprung' of peptide-containing neurones in human gut—an immunocytochemical
study. Regul. Pept. 17: 243–256, 1987.
LARSSON, L.-T., MALMFORS, G., AND SUNDLER, F.: Peptidergic innerva-
tion in Hirschsprung's disease. Peptiderge Innerv of peptide-containing neurones in human gut—an immunocytochemical
study. Regul. Pept. 17: 243–256, 1987.
248b. LARSSON, L.-T., MALMFORS, G., AND SUNDLER, F.: Peptidergic innerva-
tion in Hirschsprung's disease. Peptiderge
-
- Hirschsprung. Z. Kinderchir. 38: 301-304, 1983.

249. LEE, M. K., AND COUPAR, I. M.: Opiate receptor-mediated inhibition of rat

jejunal fluid secretion. Life Sci. 27: 2319-2325, 1980.

250. LEERWRE, A. A., BOGAERT, M. G.,
- **and vomiting by apomorphine, morphine, and fentanyl in the conscious** ergic innervation in the cat stomach. J. Pharm. Pharmacol. 38: 35–39,
1986.
251. LEFEBVRE, R. A., WILLEMS, J. L., AND BOGAERT, M. G.: Gastric relaxation
and vomiting by apomorphine, morphine, and fentanyl in the conscious

-
- 252. **LEMANSKE, R. F., JR., ATKINS, F. M., AND METCALFE, D. D.: Gastrointes**

tinal mast cells in health and disease. Part II. J. Pediatr. 103: 343-351

1983.

253. **LEMBECK, F., AND BEUBLER, E.: Inhibition of PGE₁-induc**
-
- tissue stimulate endorphin release from anterior pituitary in vitro. Neu-

noci. Lett. 8: 259–263, 1978.

RIVIER, J. E., AND BROWN, M. R.: Inhibition of gastric acid secretion by

ROMER, W. HOLLT, V., SCHMIDT, H., AND HERZ tinal mast cells in health and disease. Part II. J. Pediatr. 103: 343-351,
1983. LEMBECK, F., AND BEUBLER, E.: Inhibition of PGE₁-induced intestinal
secretion by the synthetic enkephalin analogue FK 33-824. Naunyn-
Schm endorphin on gastric acid secretion. Brain Res. 413: 1-9, 1987.

255. LENZ, H. J., KLAPDOR, R., HESTER, S. E., WEBB, V. J., GALYEAN, F.

RIVIER, J. E., AND BROWN, M. R.: Inhibition of gastric acid secretic

partin-peptides RIVIER, J. E., AND BROWN, M. R.: Inhibition of gastric acid secretion by brain peptides in the dog. Role of the autonomic nervous system and gastrin. Gastroenterology 91: 905-912, 1986.
LIBERGE, M., RIVIERE, P. M. J., AND
	- gastrin. Gastroenterology 91: 905-912, 1986.

	255a. LIBERGE, M., RIVIÈRE, P. M. J., AND BUÉNO, L.: Influence of enkephalinase inhibitors on gastric emptying in mice depends on the nature of the meal. Life Sci. 42: 2047-205 255a. LIBERGE, M., KIVIERE, P. M. J., AND BUENO, L.: Influence of enkephalinase inhibitors on gastric emptying in mice depends on the nature of the meal. Life Sci. 42: 2047-2053, 1988.

	256. LINNOILA, R. I., AND DI AUGUSTI
	-
	- organs. Eur. J. C.: Enkephalinase activity in rat peripheral
257. LLORENS, C., AND SCHWARTZ, J. C.: Enkephalinase activity in rat peripheral
258. LOLOVA, I., DAVIDOFF, M., ITZEV, D., AND APOSTOLOV, A.: Histochemical,
immun
- intestine. In Endogenous and Exogenous Opiate Agonists and Antago-
nists, ed. by E. L. Way, pp. 337-340, Pergamon Press, New York, 1980.
ROMER, W., PRETZLAFF, W., AND WOINOFF, R.: Opioids modulate perio-
immunocytochemical immunocytochemical, and units and units of the innervation of the innervations, C., AND SCHWARTZ, J. C.: Enkephalinase activity in rat peripheral organs. Eur. J. Pharmacol. 69: 113-116, 1981.
DLOVA, I., DAVIDOFF, M., ITZEV Physiol. Phanmacol. **89:** 113-116, 1981.

258. LoLOVA, I., DAVIDOFF, M., ITZEV, D., AND APOSTOLOV, A.: Histochemical,

immunocytochemical, and ultrastructural data on the innervation of the

smooth muscle of the large inte
	- mooth muscle of the large intestine in Hirschsprung's disease. Acta

	Physiol. Pharmacol. Bulg. 12: 55-62, 1986.

	259. LOLOVA, I., ITZEV, D., AND DAVIDOFF, M.: Immunocytochemical localization

	of substance P, methionine-enk
	- of substance P, methionine-enkephalin, and somatostatin in the cat

	260. LóPEz-Ruiz, M. P., AND PRIETO, J. C.: Specific binding of Leu-enkephalin

	to small and large intestinal epithelial cells from guinea-pig. Comp.

	Bioc
	- to small and large intestinal epithelial cells from guinea-pig. Comp.

	Biochem. Physiol. 85C: 215-218, 1986.

	LUNDEREC, I. M., HOKFELT, T., KEWENTER, I., PETTERSSON, G., AHLMAN,

	H., EDIN, R., DAHLSTROM, A., NILSSON, G., T
	- guantity in the human vagus nerve. Gastroenterology 77: 468-262. LUNDH, H., AND THESLEFF, S.: The mode of action of 4-aminopyridine and guanidine on transmitter release from motor nerve terminals. Eur. J.
Pharmacol. 42: 41
	- 263. MAAS, C. L.: Opiate antagonists stimulate ruminal motility of conscious goats. Eur. J. Pharmacol. 77: 71-74, 1982.
264. MAAS, C. L., AND LEEK, B. F.: Central and local actions of opioids upon reticulo-ruminal motility
	- **Pharmacol. 42: 411-412, 1977.**
263. MAAS, C. L.: Opiate antagonists stimulate ruminal motility of conscious goats. Eur. J. Pharmacol. 77: 71-74, 1982.
264. MAGE, C. L., AND LEEK, B. F.: Central and local actions of opioid gasts. Eur. J. Pharmacol. 77: 71-74, 1982.

	264. MAAS, C. L., AND LEEK, B. F.: Central and local actions of opioids upon

	reticulo-ruminal motility in sheep. Vet. Res. Commun. 9: 89-113, 1985.

	265. MAGEE, D. F.: Action of
	-
	-
	- reticulo-ruminal motility in sheep. Vet. Res. Commun. 9: 89-113, 1985.

	265. MAGEE, D. F.: Action of morphine sulphate on stimulated gastric secretion

	266. MAILMAN, D.: Effects of morphine-no canine intestinal absorption
	- and blood flow. Br. J. Pharmacol. 81: 263-270, 1984.

	266. MAILMAN, D.: Effects of morphine on canine intestinal absorption and blood flow. Br. J. Pharmacol. 81: 263-270, 1984.

	263. MAILMAN, D.: Morphine-neural interactio phine content in the ration of the brain content interactions of cantrie intestinal absorption
and blood flow. Br. J. Pharmacol. 81: 263–270, 1984.
268. MAJEED, N. H., LASON, W., PREEWLOCKA, B., AND PREEWLOCKI, R.:
Seroton in the gut. TIPS 6: 214-218, 1985. The guidary of the brain and gut beta-endorphin and dynor-
phin content in the rat. Pol. J. Pharmacol. Pharm. 37: 909-918, 1985.
269. MAKHLOUP, G. M.: Enteric neuropeptides: role in neuro
	-
	-
	- phin content in the rat. Pol. J. Pharmacol. Pharm. 37: 909-918, 1985.

	269. MAKHLOUP, G. M.: Enteric neuropeptides: role in neuromuscular activity

	in the gut. TIPS 6: 214–218, 1985.

	270. MALMFORS, G., AND SUNDLER, F.: Pe 270. MALMFORS, G., AND SUNDLER, F.: Peptideric innervation in infantile
hypertrophic pyloric stenosis. J. Pediatr. Surg. 21: 303-306, 1986.
271. MANARA, L., AND BIANCHETTI, A.: The central and peripheral influences of
opio
	- IANARA, L., AND BIANCHETTI, A.: The central and peripheral influences of opioids on gastrointestinal propulsion. Annu. Rev. Pharmacol. Toxicol.
25: 249–273, 1985.
IANARA, L., BIANCHI, G., FERRETTI, P., AND TAVANI, A.: Inhi 273. MANARA, L., BIANCHI, G., FERRETTI, P., AND TAVANI, A.: Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites. J. Pharmacol. Exp. Ther. 237: 945-949, 1
- (PL- β -ED-ir) in patients with ulcer disease and its management by acute
and chronic administration of gastrozepin. Hepatogastroenterology 33: 273. MANARA, L., BIANCHI, G., FIOCCHI, R., NOTARNICOLA, A., PERACCHIA, F.,
2 drug action on gut opioid sites. J. Pharmacol. Exp. Ther. 237: 945-949,
1986.
273. MANARA, L., BIANCHI, G., FIOCCHI, R., NOTARNICOLA, A., PERACCHIA, F.,
AND TAVANI, A.: Inhibition of gastrointestinal transit by morphine an
- related peptides in antropylonic gastrin cells. J. Histochem. Cytochem. 29: 1088-1098, 1981. 2484. LARSSON, L.-T., **HELM,** G., **MALMFORS,** G., **AND SUNDLER,** F.: Ontogeny naloxone and its N-methyl quaternary analog. Life Sci. 31: 1271-1274,
1982.

273a. MARCAIS-COLLADO, H., UCHIDA, G., COSTENTIN, J., SCHWARTZ, J.-C.,

AND LECOMTE, J.-M.: Naloxone-reversible antidiarrheal effects of en-

kep
	-

ARMACOLO

KROME
GILBERT, P. E.: The effects of morphine- and nalorphine-like drugs in
the nondependent and morphine-dependent chronic spinal dog. J. Phar-KI
GILBERT, P. E.: The effects of morphine- and nalorphine-like drugs
the nondependent and morphine-dependent chronic spinal dog. J. Pha
macol. Exp. Ther. 197: 517-532, 1976.
ATERIA, A., JAFFE, B. M., MODLIN, I. M., SANK,

- GILBERT, P. E.: The effects of morphine- and nalorphine-like drugs in
the nondependent and morphine-dependent chronic spinal dog. J. Phar-
macol. Exp. Ther. 197: 517-532, 1976.
275. MATERIA, A., AND ALBERT, D.:
Effect of m
- macol. Exp. Ther. 197: 517-532, 1976.

275. MATERIA, A., JAFFE, B. M., MODLIN, I. M., SANK, A., AND ALBERT, D.:

Effect of methionine-enkephalin and naloxone on bombesin-stimulated

gastric acid secretion, gastrin, and pan 276. MATSUMURA, M., FUKUDA, N., SAITO, S., AND MORI, H.: Effect of a test 302. 1 meal, duodenal acidification, and tetragastrin on the plasma concentration of β -endorphin-like immunoreactivity in man. Regul. Pept. 4: 17 meal, duodenal acidification, and tetragastrin on the plasma concentration
of β -endorphin-like immunoreactivity in man. Regul. Pept. 4: 173-181,
1982.
277. MATSUMURA, M., SAITO, S., AND FUJINO, M.: Effects of solution o
- of β -endorphin-like immunoreactivity in man. Regul. Pept. 4: 173-181,
1982.
277. MATSUMURA, M., SAITO, S., AND FUJINO, M.: Effects of solution of low pH
and taurocholate on release of β -endorphin-like immunoreactivit
- **ATSUMURA, M., SAITO, S., AND FUJINO, M.: Effects of solution of low pand taurocholate on release of** β **-endorphin-like immunoreactivity from an ododenal motosa in virto. Regul. Pept. 3: 173-181, 1982.
CINTOSH, C. H. S.,** and taurocholate on release of *B*-endorphin-like immunoreactivity from
human duodenal mucosa in vitro. Regul. Pept. 3: 173–181, 1982.
CINTOSH, C. H. S., KWOK, Y. N., MORDHORST, T., NISHIMURA, E.,
PEDERSON, R. A., AND BROW 278. McINTOSH, C. H. S., KWOK, Y. N., MORDHORST, T., NISHIMURA, E.,
PEDERSON, R. A., AND BROWN, J. C.: Enkephalinergic control of somatorial secretion from the perfused rat stomach. Can. J. Physiol. Pharmacol. 61: 657–663
- **Example 1982.**
 Example 1982.
 enterology 82: 667–663, 1983.
 EXAY, J. S., LINAKER, B. D., HIGHT AND START OF the antisectrory servives of the antisectron services
 EXAY, J. S., LINAKER, B. D., ANCERT AND START AND macol. 61: 657-663, 1983.

279. McKAY, J. S., LINAKER, B. D., HIGGS, N. B., AND TURNBERG, L. A.: Studies

of the antisecretory activity of morphine in rabbit ileum in vitro. Gastro-

enterology 82: 243-247, 1982.

220. McK
-
-
-
- 284, 1981.

Allen, J.C., FERNANDEZ, G. G., AND GAON, D.: Potent reduction of

basel acid output produced by meperidine. Dig. Dis. 23: 696-698, 1978.

282. MENGUY, R., DESBAILLETS, L., AND MASTERS, Y. F.: Mechanism of stres ulcer: influence of hypovolemic shock on energy metabolism in the gastric
mucosa. Gastroenterology 66: 46-55, 1974.
ENGUY, R., AND MASTERS, Y. F.: Mechanism of stress ulcer. III. Effects
of hemorrhagic shock on energy meta 283. MENGUY, R., AND MASTERS, Y. F.: Mechanism of stress ulcer. III. Effects of hemorrhagic shock on energy metabolism in the mucosa of the antrum, corpus, and fundus of the rabbit stomach. Gastroenterology 66: 1188-1176,
- 284. MILLER, G. H., AND PLANT, O. H.: Effect of morphine and some other
- corpus, and fundus of the rabbit stomach. Gastroenterology 66: 1168-
1176, 1974.
284. MILLER, G. H., AND PLANT, O. H.: Effect of morphine and some other
opium alkaloids on the muscular activity of the alimentary canal. J.

-
- activity to the action of opioids in vitro. Br. J. Pharmacol. 87: 595-601,
1986.
288. MILLER, R.: How do opistes act? TINS 7: 184-185, 1984.
287. MILLIKAN, L., CHEY, W. Y., KIM, M. S., LEE, K. Y., AND COY, D. H.: Effect
of 1986.
 ABLER, R.: How do opiates act? TINS 7: 184–185, 1984.

287. MILLIKAN, L., CHEV, W. Y., KIM, M. S., LEE, K. Y., AND COY, D. H.: Effect

of met-enkephalin on gastric acid secretion and gastrin release in dogs.
 Cas
- of met-enkephalin on gastric acid secretion and gastrin release in dogs.

Gastroenterology 80: 1233, 1981.

288. MITTAL, R. K., FRANK, E. B., LANGE, R. C., AND MCCALLUM, R. W.:

Effects of morphine and nalozone on esophage
- ITTAL, R. K., FRANK, E. B., LANGE, R. C., AND MCCALLUM, R. W.:
Effects of morphine and naloxone on esophageal motility and gastric
emptying in man. Dig. Dis. Sci. 31: 936-942, 1986.
ITTANGG, P., DOMSCHKE, W., SPROGEL, W., Effects of morphine and naloxone on esophageal motility and gastric
emptying in man. Dig. Dis. Sci. 31: 936-942, 1986.
289. MITZNEGG, P., DOMSCHKE, W., SPRÜGEL, W., DOMSCHKE, S., SUBRAMAN-
LAN, N., WÜNSCH, E., MORODER, L., 289. MITINEGG, P., DOMSCHKE, W., SPRÜGEL, W., DOMSCHKE, S., SUBRAMAN-
-
- 291. MORITA, K., AND NORTH, R. A.: Opiates and enkephalin reduce the excit-
ability of neuronal processes. Neuroscience 6: 1943-1951, 1981.
- ability of neuroscience 6: 1943-1951.

290. MONFERINI, E., STRADA, D., AND MANARA, L.: Evidence for opiate receptor

291. MORITA, K., AND NORTH, R. A.: Opiates and enkephalin reduce the excit-

292. MORITA, K., AND NORTH, binding in rat small intestine. Life Sci. 29: 595-602, 1981.

291. MoRTA, K., AND NORTH, R. A.: Opiates and ankephalin reduce the excit-

ability of neuronal processes. Neuroscience 6: 1943–1951, 1981.

292. MORTA, K., AND
-
- 150, 1982.

293. MoRLEY, J. E.: Food peptides. A new class of hormones? JAMA 247: 2379-2380, 1982.

294. MoRLEY, J. E., LEVINE, A. S., AND SILVIS, S. E.: Endogenous opiates inhibit

gastric acid secretion induced by centra
-
- 294. MORLEY, J. E., LEVINE, A. S., AND SILVIS, S. E.: Endogenous opiates inhibit gastric acid secretion induced by central administration of thyrotropin-
releasing hormone (TRH). Life Sci. 29: 293-297, 1981.
295. MORLEY, J **295. MORLEY, J. E., LEVINE, A. S., AND SILVIS, S. E.: Endogenous opiates and stress ulceration. Life Sci. 31: 693–699, 1982.**
296. MORLEY, J. E., LEVINE, A. S., YAMADA, T., GEBHARD, R. L., PRIGGE, W. F., SHAFER, R. B., G ology **84:** 1517-1523, 1983.
- Action of enkephalinergic neurons on the gastrointestinal motility. Jpn. J. Smooth Muscle Res. 21 (suppl): 103-109, 1985.
- 298. NARDUCCI, F., BASSOTTI, G., GRANATA, M. T, GABURRI, M., FARRONI, F., PALUMBO, R., AND MORELLI, A.: Functional dyspepsia and chronic idiopathic gastric stasis. Arch. Intern. Med. 146: 716-720, 1986.
- Action of enkephalinergic neurons on the gastrointestinal motility. Jpn.

1. Smooth Musicle Res. 21 (suppl): 103-109, 1985.

298. NARDUCCI, F., BASSOTTI, G., GRANATA, M. T, GABURRI, M., FARRONI, F.,

PALUMBO, R., AND MOREL PALUMBO, R., AND MORELLI, A.: Functional dyspepsia and chronic idi-

opathic gastric stasis. Arch. Intern. Med. 146: 716-720, 1986.
 ORENT SERVER SET AND MOREL AND SERVER SERVER SERVER SERVER SERVER SERVER SERVER SERVER S
- and of chronically streased Wistar-Kyoto (WKY)-rats. Biomed. Biochim.
Acta 44: 773–778, 1985.
IHEI, K., IWANAGA, T., YANAIHARA, N., MOCHIZUKI, T., AND FUJITA, T.:
Preproenkephalin A occurs in the enterochromaffin (EC) cell **Preproenkephalin A occurs in the enterochromaffin (EC) cells of the**
porcine intestine: an immunocytochemical study using antisera to Met-
enkephalin-Arg^a-Gly⁷-Leu^s and to serotonin. Biomed. Res. 4: 393-398,
1983. W enkephalin-Arg⁴-Gly⁷-Leu^s and to serotonin. Biomed. Res. 4: 393-398,
-

tion of Opioids, ed. by J. M. van Ree and L. Terenius, pp. 179-180, North Holland, Amsterdam, 1978. **Holland, Amsterdam, 1978.
Holland, Amsterdam, 1978.
Jishi, S., Skino, Y., Kitan**

- ELA

tion of Opioids, ed. by J. M. van Ree and L. Terenius, pp. 179–180, North

Holland, Amsterdam, 1978.

301a. Nishi, S., SEINO, Y., KITANO, N., SENO, M., TSUJI, K., KUROSE, T.,

TAMINATO, T., TSUDA, K., YANAHARA, C., YA Holland, Amsterdam, 1978.
KISHI, S., SEINO, Y., KITANO, N., SENO, M., TSUJI, K., KUROSE, T., TAMINATO, T., TSUDA, K., YANAHARA, C., YANAHARA, N., AND IMURA,
H.: Effects of naloxone on basal and vagus nerve-induced secretio **302. NISHIMURA, C., VANAHARA, C., VANAHARA, N., AND IMURA,**
H.: Effects of naloxone on basal and vagus nerve-induced secretions of
GRP, gastrin, and somatostatin from the isolated perfused rat stomach.
Life Sci. 41: 1787-
- H.: Effects of naloxone on basal and vagus nerve-induced secretions of GRP, gastrin, and somatostatin from the isolated perfused rat stomach. Life Sci. 41: 1787-1793, 1987.

ISHIMURA, E., BUCHAN, A. M. J., AND MCINTOSH, C 302. NISHIMURA, E., BUCHAN, A. M. J., AND MCINTOSH, C. H. S.: Autoradiographic localization of μ - and delta-type opioid receptors in the gastrointestinal tract of the rat and guinea pig. Gastroenterology 91: 1084-1094,
- immunoreactivity from the isolated perfused rat stomach. Eur. J. Phar-
macol. 124: 43-49, 1986.
304. NoRTH, R. A.: Effects of morphine on myenteric plexus neurones. Neuro-
pharmacology 15: 719-721, 1976.
-
- 903. NISHIMURA, E., AND MCINTOSH, C. H. S.: Kelease of [Leu^olenkephalin immunereactivity from the isolated perfused rat stomach. Eur. J. Pharmacology 12: 719-721, 1976.

904. NORTH, R. A.: Effects of morphine on myenteri 165: 67-77, 1979.

165: 67-78-721, 1976.

205. NORTH, R. A., KATAYAMA, Y., AND WILLIAMS, J. T.: On the mechanism

205. NORTH, R. A., KATAYAMA, Y., AND WILLIAMS, J. T.: On the mechanism

and site of action of enkephalin on 305. NORTH, R. A., KATAYAMA, Y., AND WILLIAMS, J. T.: On the mechanism
and site of action of enkephalin on single myenteric neurons. Brain Res.
165: 67-77, 1979.
306. NORTH, R. A., AND TONINI, M.: The mechanism of action o
-
-
- of heroin: direct action on opiate receptors. But all the receptors. Action on opiate release? TINS 6: 337-339, 1983.

2008. NORTHWAY, M. G., AND WILLIAMS, J. T.: Indirect intestinal stimulatory effects of heroin: direct a
- **address** in the guinear streaments of heroin: direct action on opiate receptors. Eur. J. Pharmacol. 59: 237-248, 1979.
 add, 1979.
 2009. OHKAWA, H.: Cholinergic modulation and effects of dynorphin on the non-adrenergi 1930. OHKAWA, H.: Cholinergic modulation and effects of dynorphin on the non-
adrenergic inhibitory potentials in the guinea-pig duodenum. Jpn. J.
Physiol. 36: 693-9-711, 1986.
1980. OKA, T.: Enkephalin receptor in the rab
-
- Physiol. 36: 699–711, 1986.
KA, T.: Enkephalin receptor in the rabbit ileum. Br. J. Pharmacol. 68:
193–195, 1960.
KAMOTO, T., KURAHASHI, K., TSUBOMURA, T., AND FUJIWARA, M.: Ef-
fects of morphine on hexamethonium-sensitive r. T.: Enkephalin receptor in the rabbit ileum. Br. J. Pharmacol. 68:
193–195, 1960.
KAMOTO, T., KURAHASHI, K., TSUBOMURA, T., AND FUJIWARA, M.: Ef-
fects of morphine on hexamethonium-sensitive and -resistant excitatory
re 311. ORAMOTO, T., KURAHASHI, K., TSUBOMURA, T., AND FUJIWARA, M.: Effects of morphine on hexamethonium-sensitive and -resistant excitatory responses of stomach to stimulation of vagal trunk in cats. Life Sci. 39:
147-153,
- ileum in vitro and in vivo. Life Sci. 27: 2393-2400, 1980.
 Example 15. 27: 2393-2400, 1980.
 Example in viron and in vivo. Life Sci. 27: 2393-2400, 1980.
 **Example in viron and in vivo. Life Sci. 27: 2393-2400, 1980. action in vitro and in vitro by calcium. Example treatment of guinea-pig elemm in vitro and in vivol. Life Sci. 27: 2393-2400, 1980.

313. OPMEER, F. A., AND VAN REE, J. M.: Competitive antagonism of morphine action in v**
-
- acute **and in vivo. Life Sci. 27: 2393-2400, 1980.**
 action in vitro by calcium. Exp. J. M.: Competitive antagonism of morphine
 action in vitro. by calcium. Eur. J. Pharmacol. 53: 395-397, 1979.

314. OPMEER, F. A., A 314. OPMERR, F. A., AND VAN RER, J. M.: Differential involvement of calcium in acute and chronic opioid action in the guinea-pig ileum in vitro. J. Pharmacol. Exp. Ther. 213: 188-195, 1980.
315. ORWOLL, E. S., AND KENDALL,
-
-
- 316. ØSTENSEN, H., GUDMUNDSEN, T. E., BURHOL, P. G., AND BONNEVIE, O.:
Seasonal periodicity of peptic ulcer disease. A prospective radiologic study.
Scand. J. Gastroenterol. 20: 1281-1284, 1985.
317. OUYANG, A., CLAIN, C. THE, 1000.

THENSEN, H., GUDMUNDSEN, T. E., BURHOL, P. G., AND BONNEVIE,

Seasonal periodicity of peptic ulcer disease. A prospective radiologic stus

Scand. J. Gastroenterol. 20: 1281–1284, 1985.

UVANG, A., CLAIN, C. J., Seasonal periodicity of peptic ulcer disease. A prospective radiologic study.
Seasonal periodicity of peptic ulcer disease. A prospective radiologic study.
Scand. J. Gastroenterol. 20: 1281-1284, 1985.
317. OUYANG, A., CLA
-
-
- ter. J. Clin. Invest. 69: 507-515, 1962.

318. PAINTAL, A. S.: Effects of drugs on vertebrate mechanoreceptors. Pharma-

col. Rev. 16: 341-380, 1964.

319. PAINTER, N.S., AND TRUELOVE, S. C.: Part II. The effect of morphin col. Rev. 16: 341–380, 1964.
 col. Rev. 16: 341–380, 1964.
 colon: comparison of in vivo and in vitro studies. Life Sci. 35: 1653–1658,
 colon: comparison of in vivo and in vitro studies. Life Sci. 35: 1653–1658,
 1 320. PARET, M., AND FROEDOVE, C. C. PERSONAL TRESS INCORPORATION.
320. PARET, M., AND RUCKEBUSCH, Y.: Opioid receptor agonists in the rabbit
colon: comparison of in vivo and in vitro studies. Life Sci. 35: 1653-1658,
321. **Bull. 5: 73-79, 1980.**
 Bull. 5: 1159-1164, 1985.
 Bull. 26: 1159-11
-
-
- 321. PARS, W. P.: Psychological studies of stress ulcer in the rat. Brain Res.
Bull. 5: 73–79, 1980.
322. PARSONS, M. E.: Histamine and the pathogenesis of duodenal ulcer disease.
Gut 26: 1159–1164, 1985.
322a. PASCAUD, X. Bull. 5: 73–79, 1980.

READI. 5: 73–79, 1980.

Gut 26: Histamine and the pathogenesis of duodenal ulcer disease.

Gut 26: 1159–1164, 1985.

PASCAUD, X. B., GENTON, M. G., REMOND, G., AND VINCENT, M.: Antral

to colonic mot 323. PASTERNAK, G. W., AND WOOD, P. J.: Minieview: multiple mu opiate receptors. Life Sci. 38: 1889-1898, 1986.
232. PASTERNAK, G. W., AND WOOD, P. J.: Minireview: multiple mu opiate receptors. Life Sci. 38: 1889-1898, 19 receptors. Life Sci. 38: 1889-1898, 1986.

Receptors. Life Sci. 38: 1889-1898, 1986.

23. PASS-RERNAK, G. W., AND Wood, P. J., Minireview: multiple mu opiate

323. PATERSON, S. W., AND WOOD, P. J.: Minireview: multiple mu
-
-
- **of opioid receptors. Br. Med. Bull. 39: 31-36, 1980.**
 S23. PASTERNAK, G. W., AND WOOD, P. J.: Minireview: multiple mu opiate
 receptors. Life Sci. 38: 1889–1898, 1986.
 S24. PATERNAK, G. W., RDB NOOD, L. E., AND KOS receptors. Life Sci. 38: 1889-1898, 1986.

324. PATERSON, S. J., ROBSON, L. E., AND KOSTERLITZ, H. W.: Classification

of opioid receptors. Br. Med. Bull. 39: 31-36, 1983.

325. PATON, W. D. M.: The action of morphine and 924. PATERBON, S. J., ROBSON, L. E., AND KOSTERLITZ, H. W.: Classification of opioid receptors. Br. Med. Bull. 39: 31-36, 1983.

325. PATON, W. D. M.: The action of morphine and related substances on contraction and on ace
- Archives on acetylcholine output of coaxially stimulated guines
pig ileum. Br. J. Pharmacol. 11: 119-127, 1957.
pig ileum. Br. J. Pharmacol. 11: 119-127, 1957.
and adrenaline on acetylcholine output by guinea-pig ileum lon
- 328. PATON, W. D. M., AND VIZI, E. S.: The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal muscle strip. Br. J. Pharmacol. 35: 10–28, 1969.
327. PawLIK, W. W. W. W
- Soc. Exp. Biol. Med. 165: 26-31, 1980. 327. Pharmacol. 35: 10-28, 1969.

The W.K., W., W.A.U.B, K. M., AND FONDACARO, J. D.: Effects of methionine-enkephalin on intestinal circulation and oxygen consumption. Proc.

Soc. Ex 328. PETRILLI, P., PICONE, D., CAPORALE, C., ADDEO, F., AURICCHIO, S., AND
-

binding sites with the use of a computerized curve-fitting technique. Mol. Pharmacol. 21: 266-271, 1982.

- **PHOIDS AND CONTROL OF GASTROI**
binding sites with the use of a computerized curve-fitting technique. Mol.
Pharmacol. 21: 266-271, 1982.
329. PHILLIPS, S. F.: Relationships among intestinal motility, transit, and ab-
sorpt binding sites with the use of a computerized curve-fitting technique. Mol.
Pharmacol. 21: 266–271, 1982.
HILLIPS, S. F.: Relationshipe among intestinal motility, transit, and absorption. *In* Mechanisms of Gastrointestinal
- Pharmacol. 21: 266-271, 1982.

Pharmacol. 21: 266-271, 1982.

329. PHILLIPS, S. F.: Relationships among intestinal motility, transit, and absorption. In Mechanisms of Gastrointestinal Motility and Secretion, ed.

by A. Ben by A. Bennett, pp. 239–258, New York, 1984.

330. PINNINGTON, J., AND WINGATE, D. L.: In vivo modulation of small bowel

motility by morphine and D-Ala²-D-Leu⁴ enkephalin. Life Sci. 31: 2217–

2219, 1982.

DLAK, J. M.,
- mothity by morphine and D-Ala⁻-D-Leu^r enkephalin. Life Sci. 31: 2217-
2219, 1982.
 201.AK, J. M., SULLIVAN, S. N., BLOOM, S. R., FACER, P., AND PEARSE, A.

G. E.: Enkephalin-like immunoreactivity in the human gastroi
- **OLAK, J. M., SULLIVAN, S. N., BLOOM, S. R., FACER, P., AND PEARSE, A.** G. E.: Enkephalin-like immunoreactivity in the human gastrointestinal tract. Lancet, 1: 972-974, 1977. The spinal cord as a site of opioid effects on tract. Lancet, 1: 972-974, 1977.

232. PORRECA, F., AND BURKS, T. F.: The spinal cord as a site of opioid effects

on gastrointestinal transit in the mouse. J. Pharmacol. Exp. Ther. 227:

22-27, 1983.

20RRECA, F., GALLIGA
-
- on gastrointestinal transit in the mouse. J. Pharmacol. Exp. Ther. 227:

22-27, 1983.

333. PORRECA, F., GALLIGAN, J. J., AND BURKS, T. F.: Central opioid receptor

involvement in gastrointestinal motility. TIPS 7: 104-10 mediation of gastrointestinal transit effects and hot-plate analgesia in the mouse. J. Pharmacol. Exp. Then. 230: 341-348, 1984. 335. PRIMI, M. P., AND BUENO, L.: Effects of centrally administered naloxone on gastrointesti
- r.: rotes or mu, certa, and asppe optour receptors in spinal and suprasinal
mediation of gastrointestinal transit effects and hot-plate analgesia in the
mouse. J. Pharmacol. Exp. Ther. 230: 341-348, 1984.
335. PRIMI, M. P.
-
-
- 338. Pauses and stimulated water and ion transport by endogenous opiates in dogs. Dig. Dis. Sci. 31: 172-176, 1986.
337. PROSSER, C. L.: Rhythmic potentials in intestinal muscle. Fed. Proc. 37: 2153-2157, 1978.
338. Paurrr dogs, cats, and monkeys. Eur. Haythmic potentials in intestinal muscle. Fed. Proc. 3
2153-2157, 1978.
338. PRUITT, D. B., GRUBB, M. N., JAQUETTE, D. L., AND BURKS, T.
Intestinal effects of 5-hydroxytryptamine and morphine
-
- Intestinal effects of 5-hydroxytryptamine and morphine on guinea pigs,
dogs, cats, and monkeys. Eur. J. Pharmacol. 26: 298-305, 1974.
339. PUIG, M. A., GASCON, P., CRAVISO, G. L., AND MUSACCHIO, J. M.: Endog-
enous opiate enous opate receptor ugang: electrically induced release in the guines pig
ioun. Science (Wash. DC) 195: 419-420, 1977.
340. QUIGLEY, J. P., HiGHSTONE, W. H., AND IVY, A. C.: Action of morphine,
papaverine, atropine, piloc
- papaverne, atropine, pilocarpine, pituitrin, pitocin, and pitressin on il
bolus method. J. Pharmacol. Exp. Ther. 51: 308–320, 1934.
hcHMILEWITZ, D., KARMELI, F., CHOREV, M., AND SELINGER, Z.: Effe
of opiates on human colon **93:** 169-173, 1983. **341. RACHMILEWITZ, D., KARMELI, F., CHOREV, M., AND SELINGER, Z.: Effect** of exogenous on human colonic adenylate cyclase activity. Eur. J. Pharmacol.
932. RACUSEN, L. C., BINDER, H. J., AND DOBBINS, J. W.: Effects of ex
-
- of opiates on human colonic adenyiate cyclase activity. Eur. J. Pharmacol.

98: 169-173, 1983.

24. RACUSEN, L. C., BINDER, H. J., AND DOBBINS, J. W.: Effects of exogenous

and endogenous opiate compounds on ion transport time in normal and μ -opioid receptor deficient (CXBK) mice
central (ICV) administration of μ - and δ -opioid agonists. Life
2229–2234, 1987.
ATTAN, S., AND CULVER, P.J.; Influence of loperamide on the interphincter
-
- **344. RATTAN, S., AND CULVER, P.J.; Influence of loperamide on the internal anal 23229–2234, 1987.**
 **343. RATTAN, S., AND CULVER, P.J.; Influence of loperamide on the internal anal 344. RATTAN, S., AND GOYAL, R.K.: Identi THAN, S., AND CULVER, P.J.; Inisphincter in the opossum. Gastriantly, S., AND GOYAL, R.K.: 1
THAN, S., AND GOYAL, R.K.: 1**
Tecptors in the opossum lower (Ther. 224: 391–397, 1983
RAD, N.W.:The relationship bet sphincter in the opossum. Gastroenterology93: 121-128, 1987.

344. RATTAN, S., AND GOYAL, R.K.: Identification and localization of opioid

receptors in the opossum lower esophageal sphincter. J. Pharmacol. Exp.

Ther. 224:
-
- 344. KATTAN, S., AND GOYAL, K.K..: Identification and localization of opioid
receptors in the oposeum lower esophageal sphincter. J. Pharmacol. Exp.
Ther. 224: 391-397, 1983
345. READ, N.W.:The relationship between intesti EAD, N.W.:The relationship between itransport. Clin. Res. Rev. 1 (suppl. 1):
EES, W. D. W., Grasons, L. C., AND TUD
on alkali secretion by amphibian gastroenterology 90: 323-327, 1986.
EES, W. D. W., SHARPE, G. R., CHRISTN
- **346. REES, W. D. W., GIBBONS, L. C., AND TURNBERG, L. A.: Influence of opiates**

on alkal secretion by amphibian gastric and duodenal mucosa in vitro.
 347. REES, W. D. W., SHARPE, G. R., CHRISTOFIDES, N. D., BLOOM, S. R on alkali secretion by amphibian gastric and duodenal mucosa in vitro.

Gastroenterology 90: 323-327, 1986.

347. REES, W. D. W., SHARPE, G. R., CHRISTOFIDES, N. D., BLOOM, S. R., AND

TURNERG, L. A.: The effects of an opi
-
-
- 349. RIEGEL, F.: Uber den Ennitus des Morphiums auf die Magensattsecretion.

Z. Klin. Med. 40: 347-368, 1900.

250. ROBERT, A.: Effect of drugs on gastric secretion. In Physiology of the

Gastrointestinal Tract, ed. by L.
- Disease. Pathophysiology, Diagnosis, Management, ed. by M. H. Sleisenger and J. S. Fordtran, pp. 612–625, Sanders, Philadelphia, 1983.
352. ROBERT, A., NORTHAM, J. I., NEZAMIS, J. E., AND PHILLIPS, J. P.: Exertion uclers i
- Disease. Pathophysiology, Diagnosis, Management, ed. by M. H. Sieisen-
ger and J. S. Fordtran, pp. 612–625, Sanders, Philadelphia, 1983.
352. ROBERT, A., NORTHAM, J. I., NEZAMIS, J. E., AND PHILLIPS, J. P.: Exertion
ulcers
-
- **352. ROBERT, A., NORTHAM, J. I., NEZAMIS, J. E., AND PHILLIPS, J. P.: Exertion**

ulcers in the rat. Dig. Dis. 15: 497-507, 1970.
 553. ROSENQING in Alternation is present in active and inactive forms in rat gastric antr
- 553. ROBERT, A., STOUT, T. J., AND DALE, J. E.: Production by secretagogues of
dodenal ulcers in the rat. Gastronetrology 59: 95-102, 1970.
AROSENQUIST, G. L., MARUTHAINAR, K., AND SMYTH, D. G.: β -Endorphin
is present i balloon kymograph recording of the comparative action of morphine and placebos on the motility of the upper small intestine in man. Surg. Gynecol. Obstet. 91: 129-137, 1950.
356. Rozż, C., DUBRASQUET, M., CHARIOT, J., AND
-

NAL MOTILITY AND SECRETION 159
tion of basal pancreatic and gastric secretions by β -endorphin in rats.
Gastroenterology 79: 659–664, 1980. NAL MOTILITY AND SECRET
tion of basal pancreatic and gastric s
Gastroenterology 79: 659-664, 1980.
oz£, C., DUBRASQUET, M., CHARIOT,

- ESITINAL MUTILITY AND SECRETION 100
tion of basal pancreatic and gastric secretions by β -endorphin in rats.
Gastroenterology 79: 659-664, 1980.
357. Rozz, C., DUBRASQUET, M., CHARIOT, J., AND VAILLE, C.: Methadone
inhi inhibition of vagally induced pancreatic and gastric secretions in rats:
central and peripheral sites of action. Eur. J. Pharmacol. 78: 271-278,
358. RozsA, Z., AND VARRO, V.: Mechanism of action of cholecystokinin on
inte central and peripheral sites of action. Eur. J. Pharmacol. 78: 271-278,
- intestinal blood flow; interactions with opioid peptides and vasoactive
- 359. RUCKEBUSCH, Y., BARDON, T., AND PAIRET, M.: Opioid control of the ruminant stomach motility: functional importance of μ , kappa, and delta receptors. Life Sci. 35: 1731–1738, 1984. receptors. Interactions with opiod peptides and vasoactive
intestinal blood flow; interactions with opiod peptides and vasoactive
intestinal peptide. Neuropeptides 6: 71-81, 1985.
RUCKEBUSCH, Y., BARDON, T., AND PAIRET, M
- JCKEBUSCH, Y., BARDON, T., AND PAIRET, M.: Uptoid control of the ruminant stomach motility: functional importance of μ , kappa, and delta receptors. Life Sci. 35: 1731–1738, 1984.
JCKEBUSCH, Y., FERRE, J. P., AND DU, C. 360. Ruckkeusch, Y., FERRE, J. P., AND DU, C.: In vivo modulation of intestinal motility and sites of opioid effects in the rat. Regul. Pept. 9: 109-117, 1984.

1861. Ruppin, H.: Current aspects of intestinal motility and motility and sites of opioid effects in the rat. Regul. Pept. 9: 109-117, 1984.
UPPIN, H.: Current aspects of intestinal motility and transport. Klin.
Wochenschr. 63: 679-688, 1985.
WAN, J. P., BHOJWANI, A., AND WANG, M. B
- 361. RUPPIN, H.: Current aspects of intestinal motility and transport. Klin.
- 362. RYAN, J. P., BHOJWANI, A., AND WANG, M. B.: Effect of pregnancy on gastric motility in vivo and in vitro in the guinea pig. Gastroenterology 93: 29-34, 1987. **93.** 29-34, 1987. **BARFOURI, B., 2017** 683. **BARFOURI, B., DEPART (1998)**
 9362. RYAN, J. P., BHOWWANI, A., AND WANG, M. B.: Effect of pregnancy on gastric motility in vivo and in vitro in the guinea pig. Gastroenterolo
- peptides and alkaloids on gastrin and somatostatin secretion in vitro.
Gastroenterology 80: 1267, 1981.
364. SAKAMOTO, M., NAKAO, K., YOSHIMASA, T., IKEDA, Y., SUDA, M., TAKASU, Gastroenterology 80: 1267, 1981.

S63. SAFFOURI, B., DUVAL, J. W., AND MAKHLOUF, G. M.: Effect of opiate

peptides and alkabids on gastrin and somatostatin secretion in vitro.

Gastroenterology 80: 1267, 1981.

364. SAKAMO
- Prount, B., DUVAL, J. W., AND MAKHLOUF, G. M.: Effect of opiate
peptides and alkaloids on gastrin and somatostatin secretion in vitro.
Gastroenterology 80: 1267, 1981.
KAMOTO, M., NAKAO, K., YOSHIMASA, T., IKEDA, Y., SUDA, 364. SAKAMOTO, M., NAKAO, K., YOSHIMASA, T., IKEDA, Y., SUDA, M., TAKASU,
K., SHIMBO, S., YANAIHARA, N., AND IMURA, H.: Occurrence of methio-
nine-enkephalin-Arg^a-Gly⁷-Leu⁴ with methionine-enkephalin, and methionine-
- enous opiate receptor ligand receptor (Wash, D.C.) 1965. ALLA, M., PAROLARO, D., CREMA, G., SPAZZI, L., GIAGNONI, G., CESANA, Intestinal effects of 5-hydroxytryptamine and morphine on guinea pigs, and monkeys. Eur. J. Phar nine-enkephalin-Arg^s-Gly'-Leu^e with methionine-enkephalin, leucine-en-
kephalin, and methionine-enkephalin-Arg⁴-Phe⁷ in human gastric an-
trum. J. Clin. Endocrinol. Metab. 56: 202-204, 1983.
LA, M., PAROLARO, D., C 1983.

2014, 1983.

202-204, 1983.

202-204, 1983.

202-204, 1983.

R., AND GORI, E.: Involvement of periaque-ductal gray matter in intestities

effect of centrally administered morphine. Eur. J. Pharmacol. 91: 21

254, 19 R., AND GORI, E.: Involvement of periaque-ductal gray matter in intestinal
effect of centrally administered morphine. Eur. J. Pharmacol. 91: 251-
254, 1983.
366. SARNA, S. K., AND CONDON, R. E.: Morphine-initiated migratin
	-
	- G217-G220, 1983. tric complexes in the fed state in dogs. Gastroenterology 86: 662-669, 1984.

	366a. SARNA, S. K., CONDON, R. E., AND COWLES, V.: Morphine versus motilin

	in the initiation of migrating myoelectric complexes. Am. J. Physiol
	- in the initiation of migrating myoelectric complexes. Am. J. Physiol. 245:

	G217-G220, 1983.

	366b. SARNA, S. K., AND LANG, I. M.: Dose- and time-dependent biphasic

	response to morphine on intestinal migrating myoelectric In the initiation of migrating myoelectric complexes. Am. J. Physiol. 245:

	G217-G220, 1983.

	366b. SARNA, S. K., AND LANG, I. M.: Dose- and time-dependent biphasic

	response to morphine on intestinal migrating myoelectric
	- MANA, S. K., AND LANG, I. M.: Dose- and time-dependent biphasic response to morphine on intestinal migrating myoelectric complex. J. Pharmacol. Exp. Ther. 234: 814-820, 1985.
REARMA, S., NORTHCOTT, P., AND BELBECK, L.: Mec
	- 1983. Satholary 1982. Then actional migrating myoelectric complex. J.

	24: S14-820, 1985.

	267. SARNA, S., NORTHCOTT, P., AND BELBECK, L.: Mechanism of cycling of

	1982. G588-G595, 1982.

	24: G688-G595, 1982.

	268. SATO, T migrating myoelectric complexes: effect of morphine. Am. J. Physiol.

	368. SATO, T., TAKAYANAGI, I., AND TAKAGI, K.: Pharmacological properties of

	electrical activities obtained from neurons in Auerbach's plexus. Jpn. J.
 370. Schange and activities obtained from neurons in Auerbach's pleyus. Jpn. J.
Pharmacol. 23: 665-671, 1973.
389. SAWYNOK, J., PINSKY, C., AND LA BELLA, F. S.: On the specificity of
nalozone as an opiste antagonist. Life
	-
	- Pharmacol. 23: 665–671, 1973.
WYNOK, J., PINSKY, C., AND LA BELLA, F. S.: On the specificity of
naloxone as an opiate antagonist. Life Sci. 25: 1621–1632, 1979.
PHANG, J. C., AND DEVROEDE, G.: Beneficial effects of naloxon naloxone as an opiate antagonist. Life Sci. 25: 1621-1632, 1979.

	370. SCHANG, J. C., AND DEVROEDE, G.: Beneficial effects of naloxone in a

	patient with intestinal pseudoobstruction. Am. J. Gastroenterol. 80: 407-

	411, 1
	- morphine work on colonic motility? An electromyographic study in the human left and sigmoid colon. Life Sci. 38: 671-676, 1986.
372. SCHAUMANN, O.: Some new aspects of the action of morphine-like analge-
	- ileum. Br. J. Pharmacol. 10: 456-461, 1955.

	372. SCHAUMANN, O.: Some new aspects of the action of morphine-like analgesics. Br. Med. J. Nov 10: 1091-1093, 1956.

	373. SCHAUMANN, W.: The paralysing action of morphine on th
	- sics. Br. Med. J. Nov 10: 1091-1093, 1956.
373. SCHAUMANN, W.: The paralysing action of morphine on the guinea-pig
ileum. Br. J. Pharmacol. 10: 456-461, 1955.
	-
	- 373. SCHAUMANN, W.: The paralysing action of morphine on the guinea-pig
ileum. Br. J. Pharmacol. 10: 456–461, 1955.
374. SCHAUMANN, W.: Inhibition by morphine of the release of acetylcholine
from the intestine of the guine
- SAS. REYNOLDS, J. C., OUYANG, A., AND COHEN, S.: Evidence for an opiate-

mediated pyloric sphincter reflex. Am. J. Physiol. 246: G130-G136, 1984.

376. SCHEUERMANN, D. W., AND STACH, W.: NADH-dehydrogenase reaction in

2. 974. SCHAUMANN, W.: Inhibition by morphine of the release of acetylcholine
form the intestine of the guinea-pig. Br. J. Pharmacol. 12: 115-118, 1987.
SCHEPP, W., SCHUERDERR, J., SCHUSDZIARRA, V., AND CLASSEN, M.: Natu-
ral rally occurring opiod peptides modulate H⁻-production by isolated rat
parietal cells. Peptides 7: 885–890, 1986.
CHEURENAANN, D. W., ANDH-dehydrogenase reaction in
combination with immunoperoxidase (PAP) staining for lig of the pig. Acta Anat. 124: 31-34, 1985.

SCHEURERMANN, D. W., AND STACH, W.: NADH-dehydrogenase reaction in

combination with immunoperoxidase (PAP) staining for light microscopic

observation on the interneuronal relatio
	-
	- commuteur was unually constant of the enteric nervous system
observation on the interneuronal relations of the enteric nervous system
of the pig. Acta Anat. 124: 31-34, 1985.
377. SCHEURER, U., DRACK, E., AND HALTER, F.: C THE SCHEURER, U., DRACK, E., VARGA, L., AND HALTER, F.: Morphine-like
action of enkephalin analog FK 33-824 on motility of the isolated rat
colon. J. Pharmacol. Exp. Ther. 219: 534-539, 1981.
379. SCHILLER, AND SCHILSDELAR
	-
	- FORDTRAN, I. S.: STUDIES OF THE MECHAN, V.: Modulation of motilin-induced soma-
tostatin release in dogs by naloxone. Peptides 6: 861-864, 1985.
SCHILLER, L. R., DAVIS, G. R., SANTA ANA, C. A., MORAWSKI, S. G., AND
FORDTRA
	- XETTLER, L. R., DAVIS, G. R., SANTA ANA, C. A., MORAWSKI, S. G., AND FORDTRAN, I. S.: Studies of the mechanism of the antidiarrheal effect of codeine. J. Clin. Invest. 70: 999-1008, 1982.
PHILIER, L. R., DRAYPUS, C. F., GE FORDTRAN, I. S.: Studies of the mechanism of the antidiarrheal effect of codeine. J. Clin. Invest. 70: 999-1008, 1982.

	HULTZBERG, M., DREYFUS, C. F., GERSHON, M. D., HOKFELT, T., ELDE,

	R. P., NILSSON, G., SAID, S., AND G tissue cultures. Brain Has. 155: 239-248, 1978. 382. **SCHULTZBERG, M., HOKFELT, T., NILSSON, G., TERENIU5, L., REHFELD,**
	-

spet

J. F., **BROWN,** M., **ELDE,** R., **GOLDSTEIN,** M., **AND SAID,** S.: Distribution]
J. F., BROWN, M., ELDE, R., GOLDSTEIN, M., AND SAID, S.: Distribut
of peptide- and catecholamine-containing neurons in the gastro-intest
tract of rat and guinea-pig: immunohistochemical studies with antiser J. F., BROWN, M., ELDE, R., GOLDSTEIN, M., AND SAID, S.: Distribution
of peptide- and catecholamine-containing neurons in the gastro-intestinal
tract of rat and guinea-pig: immunohistochemical studies with antisera to
subs Fract of rat and guinea-pig: immunohistochemical studies with antisera to
substance P, vasoactive intestinal polypeptide, enkephalins, somatostatin,
gastrin/cholecystokinin, neurotensin, and dopamine β-hydroxylase. Neu-
r

- **Fastrin/cholecystokinin, neurotensin, and dopamine** *ß***-hydroxylase. Neurotence 5: 689-744, 1980.**
roscience 5: 689-744, 1980.
HULTZBERG, M., HOKFELT, T., OLSON, L., ALUND, M., NILSSON, G.,
TRERNIUS, L., ELDE, R., GOLDSTEI roacience 5: 689-744, 1980.

HULTZBERG, M., HOKFELT, T., OLSON, L., ALUND, M., NILSSON, G., TERENIUS, L., ELDE, R., GOLDSTEIN, M., AND SAID, S.: Substance P., VIR, enkephalin, and somatoetatin immunoreactive neurons in in TERENIUS, L., ELDE, R., GOLDSTEIN, M., AND SAID, S.: Substance P.,
VIP, enkephalin, and somatostatin immunoresctive neurons in intestinal
tissue transplanted to the anterior eye chamber. J. Auton. Nerv. Syst. 1:
291–308, 1 TERENIUS, L., ELDE, R., GOLDSTEIN, M., AND SAID, S.: Substance P.
VIP, enkephalin, and somatostatin immunoreactive neurons in intestinal
tissue transplanted to the anterior eye chamber. J. Auton. Nerv. Syst. 1:
291–308, 19
- tissue transplanted to the anterior eye chamber. J. Auton. Nerv. Syst. 1:
291–308, 1980.
HULTZERRG, M., HÖKFELT, T., TERENIUS, L., ELFVIN, L. G., LUNDBERG,
J. M., BRANDT, J., ELDE, R. P., AND GOLDSTEIN, M.: Enkephalin im-
 guinea, 1980.

291-308, 1980.

384. SCHULTZBERG, M., HOKFELT, T., TERENIUS, L., ELFVIN, L. G., LUNDBERG,

J. M., BRANDT, J., ELDE, R. P., AND GOLDSTEIN, M.: Enkephalin im-

muoreactive news fibres and cell bodies in sympat J. M., BRANDT, J., ELDE, R. P., AND GOLDSTEIN, M.: Enkephalin im-
munoreactive nerve fibres and cell bodies in sympathetic ganglia of the
guinea-pig and rat. Neuroacience 4: 249–270, 1979.
HULZ, R., AND CARTWRIGHT, C.: Eff
- guinea-pig and rat. Neuroscience 4: 249-270, 1979.
385. SCHULZ, R., AND CARTWRIGHT, C.: Effect of morphine on serotonin release
from myenteric plexus of the guinea pig. J. Pharmacol. Exp. Ther. 190:
420-430, 1974.
386. SCH
- S86. SCHULZ, R., AND CARTWRIGHT, C.: Effect of morphine on serotonin release
from myenteric plexus of the guinea-pig. J. Pharmacol. Exp. Ther. 190:
386. SCHULZ, R., AND GOLDSTEIN, A.: Morphine tolerance and supersensitivit
-
- 386. SCHULZ, R., AND GOLDSTEIN, A.: Morphine tolerance and supersensitivity
to 5-hydroxytryptamine in the myenteric plexus of the guinea-pig. Nature
(Lond.) 244: 168-170, 1973.
387. SCHULZ, R., AND HERZ, A.: Aspects of opi
- Arch. Pharmacol. 308: 261-386, 1986.

2008. SCHULZ, R., WUSTER, M., AND HERZ, A.: Centrally and peripherally mediated inhibition of intestinal motility by opioids. Naunyn-Schmiedeberg's

Arch. Pharmacol. 308: 255-260, 1979
- diated inhibition of intestinal motility by opions. Naunyn-Schmiedeberg's
Arch. Pharmacol. 308: 255-260, 1979.
SCHULZ, R., WÜSTER, M., KRENSS, H., AND HERZ, A.: Selective develop-
ment of tolerance without dependence in mu
-
- **plexus of selective tolerance development. J. Pharmacol. Exp. Ther. 219: 547-550, 1981.**
 plexus of the guinear of
- Electrically stimulated release of opiate-like material from the myenteric
plexus of the guinea pig ileum. Eur. J. Pharmacol. 41: 347-348, 1977.
393. SCHUSDZIARRA, V., HOLLAND, A., MAIER, V., AND PTEITTER, E. F.: Effect
of
-
- of naloxone on pancreatic and gastric endocrine function in response to
carbohydrate and fat-rich test meals. Peptides 5: 65-71, 1984.
394. SCHUSDZIARRA, V., REWES, B., LENZ, N., MAIER, V., AND PTEIFTER, E. F.:
Carbohydrat Carbohydrates modulate opiate receptor mediated mechanisms during
postprandial endocrine function. Regul. Pept. 7: 243-252, 1983.
396. SCHUSDZIARRA, V., REWES, B., LENZ, N., MAIER, V., AND PEEIFFER, E. F.:
Evidence for a r Evidence for a role of endogenous opiates in postprandial somatostatin
-
- In dogs. Endocrinology 112: 1948-1951, 1984-1951, 1994-1951, 1994-1951, 1994-1958. 398. SCHUSDZIARRA, V., SCHICK, R., DE LA FUENTE, A., HOLLAND, A., BRANTL, V., AND PTEITTER, E. F.: Effect of β-casomorphins on somatostati in dogs. Endocrinology 112: 1948-1951, 1983.

397. SCHUSDZIARRA, V., AND SCHMID, R.: Interaction between opiates and

somatostatin and their role in vagally-induced acid secretion. Klin. Woch-

enschr. 64 (suppl. 7): 112-1 **397. SCHUSDZIARRA, V., AND SCHMID, R.: Interaction between opiates and somatostatin and their role in vagally-induced acid secretion. Klin. Wochenschr. 64** (suppl. 7): 112–115, 1986.
 398. SCHUSDZIARRA, V., AND SCHMID,
- enachr. 64 (suppl. 7): 112-115, 1986.

398. SCHUSDZIARRA, V., AND SCHMID, R.: Physiological and pathophysiological

aspects of somatostatin. Scand. J. Gastroenterol. 21 (suppl. 119): 29-41,

1986.

399. SCHUSDZIARRA, V., S
- HUSDEIARRA, V., AND SCHMID, K.: Physiological and pathophysiological
aspects of somatostatin. Scand. J. Gastroenterol. 21 (suppl. 119): 29–41,
1986.
HUSDEIARRA, V., SCHMID, R., AND CLASSEN, M.: Effect of insulin on
secreti
- rat stomach in response to acetylcholine, VIP, and leucine-enkephalin.
Neuropeptides 7: 51-62, 1986.
400. SCHUSDZIARRA, V., SCHMID, R., AND CLASSEN, M.: Modulatory glucose
effect on bombesin-like immunoreactivity and gastr
- rat stomach in response to acetylcholine, VIP, and leucine-enkephalin.

Neuropeptides 7: 51-62, 1986. 423.

400. SCHUSDZIARRA, V., SCHMID, R., AND CLASSEN, M.: Modulatory glucose

effect on bombesin-like immunoreactivity a
- 138: 32, 1936. 402. SERIYA, K., FUNAKOSHI, A., NAKANO, I., NAWATA, H., KATO, K., AND

138: 32, 1936. 138: 344-348, 1986.

138: 32, 1936. 403. SELYE, H.: A syndrome produced by diverse nocuous agents. Nature (Lond.)

138: 3
-
- plasma motilin. Gastroenterol. Jpn. 21: 344–348, 1986.

403. SELYE, H.: A syndrome produced by diverse nocuous agents. Nature (Lond.)

138: 32, 1936.

404. SHAH, M., ROSEN, M., AND VICKERS, M. D.: Effect of premedication w
- 428P-429P, 1979. surgery. Br. J. Anassth. 56: 1235-1238, 1984.
405. SHAW, J. S.: Characterization of opiate receptors in the isolated rat rectum.
In Proceedings of the British Pharmacological Society, 17th-20th July,
428P-429P, 1979.
406
- In Proceedings of the British Pharmacological Society, 17
428P-429P, 1979.
REA-DONOHUE, P. T., ADAMS, N., ARNOLD, J., AND DUBO
of Met-enkephalin and naloxone on gastric emptying and
of Met-enkephalin and naloxone on gastri 428P-429P, 1979.
406. SHEA-DONOHUE, P. T., ADAMS, N., ARNOLD, J., AND DUBOIS, A.: Effects
of Met-enkephalin and naloxone on gastric emptying and secretion in
thesus monkeys. Am. J. Physiol. 245: G196-G200, 1983.
407. SHEAR
-

action with different opiate receptors. J. Pharmacol. Exp. Ther. 221: 735-739. 1982.

- IER

action with different opiate receptors. J. Pharmacol. Exp. Ther. 221:

735–739, 1982.

408. SHEPNER, S. A., NORTH, R. A., AND ZUKIN, R. S.: Opiate effects on rabbit
 vagus nerve: electrophysiology and radioligand bi action with different opiate receptors. J. Pharmacol. Exp. Ther. 221:

735-739, 1982.

408. SHEFNER, S. A., NORTH, R. A., AND ZUKIN, R. S.: Opiate effects on rabbit

vagus nerve: electrophysiology and radioligand binding.
-
-
- **408a.** SHOOK, J. E., PELTON, J. T., HRUBY, V. J., AND BURKS, T. F.: Peptide

opioid antagonis separates peripheral and central opioid antitransit ef-

fects. J. Pharmacol. Exp. Ther. 243: 492-500, 1987.

409. SIMON, E. J. MON, E. J., AND HILLER, J. M.: The opiate receptors. Annu. Rev. Pharmacol. Toxicol. 18: 371–394, 1978.
VAM, S. P., AND Ho, I. K.: Antinoccieptive and gastrointestinal effects opiates: an analysis of the nature of the invol macol. Toxicol. 18: 371-394, 1978.

410. SIVAM, S. P., AND HO, I. K.: Antinociceptive and gastrointestinal effects of

opiates: an analysis of the nature of the involvement of mu and delta

receptors of the central nervous opiates: an analysis of the nature of the involvement of mu and delifications of the central nervous system in morphine-tolerant and notolerant mice. Neuropharmacology 23: 105–108, 1984.
Colerant mice. Neuropharmacology 23
-
- receptors of the central nervous system in morphine-tolerant and non-
tolerant mice. Neuropharmacology 23: 105-108, 1984.
411. SJOLUND, K., SCHAFFALITZKY DE MUCKADELL, O. B., FAHRENKRUG, J.,
HÄKANSON, R., PETERSON, B. G.,
- server fibres in the gut wall in Chrohn's disease. Gut 24: 724-733, 1983.

112. SKOV OLSEN, P., KIRKEGAARD, P., PETERSEN, B., AND CHRISTIANSEN, J.:

Effect of naloxone on Met-enkephalin induced gastric acid secretion and
 Effect of naloxone on Met-enkephalin-induced gastric acid secretion and
serum gastrin in man. Gut 23: 63-65, 1982.
413. SKOV OLSEN, P., KIRKEGAARD, P., PETERSEN, B., LENDORF, A., AND
CHRISTIANSEN, J.: The effect of a synth **BULGAKOV,** S. A., **AND SHATALOV,** V. N.: Inhibitory action of methionine-
- **encephalin and morphine on pentagastrin-stimulated gastric Secretion and secretion in** man. Scand, **A. G., A. G., A. G., A. A. BELGAKOV**, V. **S. A., AND SHATALOV, V. N.: Inhibitory action of methionine-enkephalin an**
- BULGAKOV, S. A., AND SHATALOV, V. N.: inhibitory action of methionine-
enkephalin and morphine on pentagastrin-stimulated gastric secretion in
dogs. Byulleten' Eksperimental' noi Biologii i Meditsiny 92: 526-528,
1981.
415 **416. SMAGIN, V. G., TITOV, M. I., SHATALOV, V. M., VINOGRADOV, V. A., TEPLYUK, S. G., AND BULGAKOV, S. A.: Ability of ligands of opiate receptors (endorphiums and exorphiums) to inhibit gastric juice secretion in dogs. Bu**
- **auf die Magensekretion bei nochternen Hunden. Z. Ges. Exp. Bull. Exp. Bull. Exp. Bull. Med. 95:** 78-80, 1983.
 416. SMIRNOW, A. I., AND SCHIROKLI, W. F.: Über den Einfluß des Morphiums auf die Magensekretion bei nüchter
- **392. SCHULLA, R., WOSTER, M., SIMANYOV, R., SNYDER, S., AND HERZ, A.:** 417. SMITH, T. W., HUGHES, J., KOSTERLITZ, H. W., AND SOSA, R. P.: Enkeph-

Electrically stimulated release of opiate-like material from the myenteric MRNOW, A. 1., AND SCHIROKIJ, W. F.: Uber den Einfluß des Morphiums
auf die Magensekretion bei nüchternen Hunden. Z. Ges. Exp. Med. 57:
324–336, 1927.
MTH, T. W., HUGHES, J., KOSTERLITZ, H. W., AND SOSA, R. P.: Enkeph-
alin auf die Magensekretion bei nuchternen Hunden. Z. Ges. Exp. Me
1324–336, 1927.
MrH, T. W., HuGHES, J., KOSTERLITZ, H. W., AND SOSA, R. P.: E.
alins: isolation, distribution, and function. *In Opiates* and Endo_l
Opioid Pep 324–336, 1927.

A17. SMTH, T. W., MOSTERLITZ, H. W., AND SOSA, R. P.: Enkephanins: isolation, distribution, and function. In Opiates and Endogenous

Opioid Peptides, ed. by H. W. Kosterlitz, pp. 57–62, Elsevier/North-Holl
	-
	- Holland Biomedical Press, Amsterdam, 1976.
NYDER, S. H., AND CHILDERS, S. R.: Opiate receptors and opioid peptides.
Annu. Rev. Neurosci. 2: 35-64, 1979.
DLDANI, G., DEL TACCA, M., MENGOZZI, G., BERNARDINI, C. AND BAR-
TOL A. P., D. P., *A. R. P., MCKNIGHT, A. T.*, *MENGOZZI*, G., *BERNARDINI*, C. *AND BARTOLINI*, D.: Central and peripheral involvement of μ receptors in gastric secretory effects of opioids in the dog. Eur. J. Pharmacol. 1
	- **420.** SOBA, R. P., MCKNIGHT, A. T., HUGHES, J., AND KOSTERLITZ, H. W.:

	Incorporation of labelled amino acids into the enkephalins. FEBS. Lett.
 4421. STACHER, G., STEINNERIC of the synthetic enkephalin analogue FK 33-8
	-
	- Incorporation of labelled amino acids into the enkephalins. FEBS. Lett.
 421. STACHER, G., STEINENBER, H., AND SCHMIERER, G.: Stimulatory effects

	of the synthetic enkephalin analogue FK 33-824 on colonic motor activity
 of the synthetic enkephalin analogue FK 33-824 on colonic motor activity
antagonized by nalozone. Hepatogastroenterology 28: 110-115, 1981.
FranchellLINI, V., MALAGELADA, J. R., ZINSMEISTER, A. R., Go, V. L.
W., AND KAO, P 421a. STANGHELLINI, V., MALAGELADA, J. R., ZINSMEISTER, A. R., GO, V. L.
W., AND KAO, P. C.: Effect of opiate and adrenergic blockers on the gut
motor response to centrally acting stimuli. Gastroenterology 87: 1104-
1113,
- 1986.

Neuropeptides 7. 1999. SCHUSDZIARRA, V., SCHMID, R., AND CLASSEN, M.: Effect of insulin on

secretion of bombesin-like immunoreactivity and gastrin from the isolated

rat stomach in response to acetylcholine, VIP, a during vagally induced gastric acid secretion in rats. Can. J. Physiol.
Pharmacol. 64 (suppl.): 108, 1986.
423. STARKE, K.: Regulation of noradrenaline release by presynaptic receptor
systems. Rev. Physiol. Biochem. Pharma M.: Endogenous opioids inhibit adrenergic and cholinergic meduring vagally induced gastric acid secretion in rats. Can. J. Pharmacol. 64 (suppl.): 106, 1986.
KARKER, K.: Regulation of noradrenaline release by presynaptic
K during vagally induced gastric acid secretion in rats. Can. J. Physiol.
 423. STARKE, K.: Regulation of noradrenaline release by presynaptic receptor
 423. STARKE, K.: Regulation of noradrenaline release by presynaptic
	-
	- **OLBE, E.: Dog enception** of noradrenaline release by presynaptic receptor systems. Rev. Physiol. Biochem. Pharmacol. 77: 1–124, 1977.
 EXAMELY: D.: D.: D.: HAGLUND, U., HOLEN, J. J., REHPELD, J. F., AND
 CLBE, L.: Do e secretion in man? Hagulation of northernaline release by presynaptic receptor
systems. Rev. Physiol. Biochem. Pharmacol. 77: 1-124, 1977.
424. STENQUIST, B., LIND, T., HAGLUND, U., HOLST, J. J., REHFELD, J. F., AND
OLBB, L OLBE, L.: Do enkephalins participate in vagal activation of gastric acid
secretion in man? Regul. Pept. 17: 1-7, 1987.
425. STEWART, J. J.: Interactions of reserpine and morphine on rat intestinal
transit. J. Pharmacol. Ex
	-
	-
	- **Pharmacology 29: 47-55, 1984.**
 Pharmacology 29: 47-55, THEN. 205: 2008. 1.1. Temporal effects of morphine on rat intestinal trans

	Pharmacology 29: 47-55, 1984.
 Then. 205: 547-555, 1978.
 Then. 205: 547-555, 1978.
 Then. 205: 547-555, 1978.
 PARROLD, D.: Effects of a
	- **MEPERIDING, J. J., WEISBRODT, N. W., AND BURKS, T. F.: Central and peripheral actions of morphine on intestinal transit. J. Pharmacol. Exp.
Ther. 2005: 547-555, 1978.
428. STROMBECK, D. R., AND HARROLD, D.: Effects of at** meperidine, and xylazine on gastroesophageal sphincter pressure in the dog. Am. J. Vet. Res. 46: 963-965, 1985.

	429. SUCNMA, K., AND FURUTA, H.: Histamine release induced by dynorphin(1-13) from rat mast cells. Jpn. J. Ph
	-
	- monetating, and xylazine on gastroesophageal sphincter pressure in the dog. Am. J. Vet. Res. 46: 963-965, 1985.
429. SUGIYAMA, K., AND FURUTA, H.: Histamine release induced by dynorphin(1-13) from rat mast cells. Jpn. J. P AM. J. GASTROMA, N., AND FURUTA, H.: Histamine release induced by dynorphin(1-
13) from rat mast cells. Jpn. J. Pharmacol. 35: 247–252, 1984.
430. SULLIVAN, S. N., CHAMPION, N., CORKE, M., AND DARWISH, R.: Effect of
morphi
	- stimulated gastric acid secretion by an enkephalin of basal and
stimulated gastric acid secretion by an enkephalin analogue. Am. J.
Gastroenterol. 77: 360-362, 1982.
432. SUMMERS, R. W., HELM, J., AND CHRISTENSEN, J.: Inte
	-

ARMACOLO

spet

spet

in the dog. Its relation to food intake and the migratory myoelectric complex. Gastroenterology 70: 753-758, 1976.

- **CONTROL OF GASTROINT**

in the dog. Its relation to food intake and the migratory myoelectric

complex. Gastroenterology 70: 753-758, 1976.

433. SUN, E. A., SNAPE, W. J., JR., COHEN, S., AND RENNY, A.: The role of

opiate in the dog. Its relation to food intake and the migratory myoelectric
complex. Gastroenterology 70: 753–758, 1976.
433. SUN, E. A., SNAPE, W. J., JR., COHEN, S., AND RENNY, A.: The role of
opiate receptors and cholinergic
- Fass. SUN, E. A., SNAPE, W. J., J.R., COHEN, S., AND RENNY, A.: Ine role of about receptors and cholinergic neurons in the gastrocolonic response.

Gastroenterology 82: 689–693, 1982.

434. TACHÉ, Y., VALE, W., RIVIER, J.,
- gastric secretion: influence of neuropeptides. Proc. Natl. Acad. Sci. USA
77: 5515-5519, 1980.
435. TACHIBANA, S., ARAKI, K., OHYA, S., AND YOSHIDA, S.: Isolation and
structure of dynorphin, an opioid peptide, from porcine 435. TACHIBANA, S., ARAKI, K., OHYA, S., AND YOSHIDA, S.: Isolation and structure of dynorphin, an opioid peptide, from porcine duodenum. Nature (Lond.) 295: 339-340, 1982.
436. TAKEMORI, A. E., AND PORTOGHESE, P. S.: Rece
-
- **437. TAKEUCHI, K., FURUKAWA, O., TANAKA, H., AND OKABE, S.: A new model of duodenal ulcers induced in rats by indomethacin plus histamine.**
Gastroenterology **90:** 636-645, 1986.
- Gastroenterology 90: 636-645, 1986. TAKENGRI, K., FURUKAWA, O., TANAKA, H., AND OKABE, S.: A new model
437. TAKEUCHI, K., FURUKAWA, O., TANAKA, H., AND OKABE, S.: A new model
of duodenal ulcers induced in rats by indometha of duodenal ulcers induced in rats by indomethacin plus histamine.

Gastroenterology 90: 636-645, 1986.

438. TAKEUCHI, K., OHTSUKI, H., NOBUHARA, Y., AND OKABE, S.: Mechanisms

of irritative activity of compound 48/80 on
- of irritative activity of compound 48/80 on rat gastric mucosa. Digestion 33: 34–44, 1986.
 IMURA, H.: Presence of immunoreactive gamma-melanocyte-stimulating

IMURA, H.: Presence of immunoreactive gamma-melanocyte-stimu hormone, adrenocorticotropin, and β -endorphin in human gastric antral 33: 34–44, 1986.

439. TANKA, Y., NAKAO, K., OKI, S., MASAKI, N., OHTSUKI, H., AND

IMURA, H.: NAKAI, Y., NAKAO, K., OKI, S., MASAKI, N., OHTSUKI, H., AND

IMURA, H.: Presence of immunoreactive gamma-melanocyte-stimulatin
- mucosa. J. Clin. Endocrinol. Metab. 54: 392-396, 1982.
440. TARI, A., MIYACHI, Y., HIDE, M., SUMII, K., KAJIYAMA, G., TAHARA, E., TANAKA, K., AND MIYOSHI, A.: Beta-endorphinlike immunoreactivity and
somatostatinlike immuno
- TANAKA, K., AND MIYOSHI, A.: Beta-endorphininke immunoreactivity and
somatostatinlike immunoreactivity in normal gastric mucosa, muscle
layer, and adenocarcinoma. Gastroenterology 88: 670–674, 1985.
441. TAVANI, A., BIANC
- effective on gastrointestinal propulsion in rats by intraperitoneal route:
evidence for local action. Life Sci. 27: 2211-2217, 1980.
442. TAVANI, A., BIANCHI, G., AND MANARA, L.: Morphine no longer blocks
gastrointestinal
- VANI, A., BIANCHI, G., AND MANARA, L.: Morphine no longer blogastrointestinal transit but retains antinociceptive action in diallylne
mophine-pretreated rate. Eur. J. Pharmacol. 59: 151-154, 1979.
ELTORD, G. L., HOSHMONAI, gastrointestinal transit but retains antinociceptive action in dially inor-
mophine-pretreated rats. Eur. J. Pharmacol. 59: 151-154, 1979.
443. TELFORD, G. L., HOSHMONAI, M., MOSES, A. J., AND SZURSZEWSKI, J. H.
morphine i
- Morphine initiates migrating myoelectric complexes by acting on peripheral opioid receptors. Am. J. Physiol. 249: G557-G562, 1985.
444. THOMPSON, W. L., AND WALTON, R. P.: Elevation of plasma histamine levels in the dog fo **CREMA, A.: D., A.C., A.: Depression by morphine of the excitability of interests in the dog following administration of muscle relaxants, opinited and macromolecular polymers. J. Pharmacol. Exp. Ther. 143: 131-13
1964.
CR**
- itony neurons in the guinea-pig colon. Eun. J. Pharmacol. Exp. Ther. 143: 131-136, 1964.
1964.
NNNN, M., ONORI, L., PERUCCA, E., MANZO, L., DE PONTI, F., AND
CREMA, A.: Depression by morphine of the excitability of intrins 446. TONINI, M., ONORI, L., PERUCCA, E., MANZO, L., DE PONTI, F., AND
CREMA, A.: Depression by morphine of the excitability of intrinsic inhib-
itory neurons in the guinea-pig colon. Eur. J. Pharmacol. 115: 317-320,
1985.

- CREMA, A.: Depression by morphine of the excitability of intrinsic inhibitory neurons in the guinea-pig colon. Eur. J. Pharmacol. 115: 317–320, 1985.
1985.
RENDELENBURG, P.: Physiologische und pharmakologische Versuche übe itory neurons in the guinea-pig
1985.
RENDELENBURG, P.: Physiologis
die Dünndarmperistaltik. Nau
Pharmakol. 81: 55–129, 1917.
30TO, T., OKAMURA, H., FUKUI, 1980.
446. TRENDELENBURG, P.: Physiologische und pharmakologische Versuche übe
die Dünndarmperistaltik. Naunyn-Schmiedeberg's Arch. Exp. Pathol
147. TSUTO, T., OKAMURA, H., FUKUI, K., OBATA-TSUTO, H. L., TERUBAYASHI
H., YA
- Pharmakol. 81: 55-129, 1917.

447. TSUTO, T., OKAMURA, H., FUKUI, K., OBATA-TSUTO, H. L., TERUBAYASHI,

H., YANAGHARA, J., IWAI, N., N., N., N., N., N., N., N.

Y.: Immunohistochemical investigations of gut hormones in the
-
-
- H., YANAGIHARA, J., IWAI, N., MAJIMA, S., YANAIHARA, N., AND IBATA,

Y.: Immunohistochemical investigations of gut hormones in the colon of

patients with Hirscheprung's disease. J. Pediatr. Surg. 20: 266-270, 1985.

448. of fentanyl and morphine on intestinal circulation. Anseth. Analg. 64:
577-584, 1985.
449a. UCHIDA, T., KOBAYASHI, S., AND YANAIHARA, N.: Occurrence of Met-
enkephalin-Arg⁴-Gly⁷-Leu⁶ neurons in the guinea pig duodenu
- Peptidergic (enkephalin) innervation of the mammalian esophagus. Gas-
- 450. UDDMAN, R., ALUMETS, J., HÄKANSON, R., SUNDLER, F., AND WALLES, B.:
Peptidergic (enkephalin) innervation of the mammalian esophagus. Gas-
troenterology 78: 732–737, 1980.
451. UEDA, H., HARADA, H., NOZAKI, M., AND TAK **Poptidergic (enkephalin) innervation of the mammalian esophagus. Gastroenterology 78: 732-737, 1980.**

451. UEDA, H., HARADA, H., MISAWA, H., NOZAKI, M., AND TAKAGI, H.: Purified

opioid μ-receptor is of a different mole
- ext. Subs. Scand. J. Gastroenterol. 18: 491-496, 1984.

Scanding Preceptors. Neurosci. Lett. 75: 339-344, 1987.

451a. VALLGREN, S., EL MUNSHID, H. A., HEDENBRO, J., REHFELD, J. F., AND

HAKANSON, R.: Mechanism of gastric
- reversal effects of neurosing the guineal on the guinea pig ileum. H.A., HERPELD, J. F., AND
HAKANSON, R.: Mechanism of gastric acid response to pylorus ligation:
effects of nephrectomy. Scand. J. Gastroenterol. 18: 491–49
- existence for the existence of interactions between dopaminergic and

Pharmacological Pharmacological Pharmacological Pharmacological Pharmacological Pharmacological Pharmacological existence of the existence of interactio reversal effects of naloxone on the gunea pig ileum. Life Sci. 18: 803-

810, 1976.

453. VARGAS, M. L., MARTINEZ, J. A., AND MILANÉS, M. V.: Pharmacological

evidence for the existence of interactions between dopaminergic
- pig ileum. Gen. Pharmacol. 128: 259–263, 1986.

454. VARGAS, M. L., MARTNEZ, M., AND MILANEZ, M. V.: Effects of droperido

45. VARGAS, M. L., MARTNEZ, J. A., AND MILANEZ, M. V.: Effects of droperido

on the biosynthesis an on the biosynthesis and release of endogenous opioid peptides in guinea-
pig ileum. Gen. Pharmacol. 18: 283–286, 1987.
455. VAUGHAN WILLIAMS, E. M.: The mode of action of drugs upon intestinal
motility. Pharmacol. Rev. 6:
-
- on the biosynthesis and release of endogenous opiod peptides in guinea-
pig ileum. Gen. Pharmacol. 18: 283–286, 1987.
455. VAUGHAN WILLIAMS, E. M.: The mode of action of drugs upon intestinal
motility. Pharmacol. Rev. 6: 1
-

- SCRETION 161
slowing effect of intrathecal morphine on gastrointestinal transit. Eur. J.
Pharmacol. 94: 181-184, 1983.
458. VAUGHT, J. L., COWAN, A., AND JACOBY, H. J.: μ and delta, but not kappa,
opioid agonists induce c slowing effect of intrathecal morphine on gastrointestinal transit. Eur. J.
Pharmacol. 94: 181-184, 1983.
AUGHT, J. L., COWAN, A., AND JACOBY, H. J.: μ and delta, but not kappa,
opioid agonists induce contractions of t Eur. J. Pharmacol. 94: 181-184, 1983.
 Eur. J. L., COWAN, A., AND JACOBY, H. J.: μ and delta, but not kappa,

opioid agonists induce contractions of the canine small intestine in vivo.

Eur. J. Pharmacol. 109: 43-48, 19
- selective delta-opioid antagonist. Eur. J. Pharmacol. 94: 159-161, 1983.
- 459. VINAYEK, R., BROWN, D. R., AND MILLER, R. J.: Inhibition of the antise-
cretory effects of [D-Ala²,D-Leu²]-enkephalin in the guinea-pig ileum by a
selective delta-opioid antagonist. Eur. J. Pharmacol. 94: 159-161, cretory effects of $[D-Ala^2,D-Leu^6]$ -enkephalin in the guinea-pig ileum by a selective delta-opioid antagonist. Eur. J. Pharmacol. 94: 159–161, 1983.
460. VINAYEK, R., BROWN, D. R., AND MILLER, R. J.: Tolerance and cross-tol
-
- INCENT, S. R., DALSGAARD, C.-J., SCHULTZBERG, M., HÖKFELT, T., CHRISTENSSON, J., AND TERENIUS, L.: Dynorhpin-immunoreactive neurons in the autonomic nervous system. Neuroscience 11: 973–987, 1984.
21, E. S.: Acetylcholine Form in the autonomic nervous system. Neuroscience 11: 973-967, 1964.
461. Vizi, E. S.: Acetylcholine release from guinea-pig ileum by parasympathetic ganglion stimulants and gastrin-like polpeptides. Br. J. Pharmacol. 47: **2461. Vizi, E. S.: Acetylcholine release from guinea-pig ileum by parasympathetic ganglion stimulants and gastrin-like polpeptides. Br. J. Pharmacol. 47: 765–777, 1973.
WAISMAN, Y., DINARI, G., MARCUS, H., LIGUMSKY, M., R**
- ganguon stimulants and gastrin-like polpeptudes. Br. J. Pharmacol. 47:

765-777, 1973.

461a. WAISMAN, Y., DINARI, G., MARCUS, H., LIGUMSKY, M., ROSENBACH, Y., ZAHAVI, I., AND NITZAN, M.: Naloxone is protective against ind
- induced intestinal ulceration in the rat. Gastroenterology 89: 86-91, 1985.
462. WALUS, K. M., PAWLIK, W., KONTUREK, S. J., AND SCHALLY, A. V.: Effect
of Met-enkephalin and morphine on gastric secretion and blood flow.
Act **Acts Physiol. Politically, A. V.: Effect** of Met-enkephalin and morphine on gastric secretion and blood flow.
Acta Physiol. Pol. 32: 383-392, 1981.
463. WARD, S. J., Lo PRESTI, D., AND JAMES, D. W.: Activity of mu- and d
- of Met-enkephalin and morphine on gastric secretion and blood flow.
Acta Physiol. Pol. 32: 383-392, 1981.
VARD, S. J., LO PRESTI, D., AND JAMES, D. W.: Activity of mu- and delta-
selective opioid agonists in the guinea pi
- 464. WARD, S. J., AND TAKEMORI, A. E.: Relative involvement of receptor subtypes in opioid-induced inhibition of intestinal motility in mice. Life Sci. 31: 1267-1270, 1982.
- 465. WARHURST, G., SMITH, G. S., HIGGS, N., TONGE, A., AND TURNBERG, L.: Influence of morphine tolerance and withdrawal on intestinal salt and macol. Exp. Ther. 238: 625-631, 1986.

464. WARD, S. J., AND TAKEMORI, A. E.: Relative involvement of receptor

subtypes in opioid-induced inhibition of intestinal motility in mice. Life

Sci. 31: 1267-1270, 1982.

465. WA
- water transport in the rat in vivo and in vitro. Gastroenterology 87: 1035-1041, 1984.

ARHURST, G., SMITH, G. S., TONGE, A., AND TURNBERG, L.: Effects of

morphine on net water absorption, mucosal adenylate cyclase activi 466. WARHURST, G., SMITH, G. S., TONGE, A., AND TURNBERG, L.: Effects of morphine on net water absorption, mucosal adenylate cyclase activity, and PGE₂ metabolism in rat intestine. Eur. J. Pharmacol. 86: 77–82, 1983. WAT
- and macromolecular polymers. J. Pharmacol. Exp. Ther. 143: 131-136,
1964. WATANABE, K., YANO, S., AND MINAKAWA, Y.: Morphine inhibits the
1964. TONINI, M., ONORI, L., PERUCCA, E., MANZO, L., DE PONTI, F., AND
CREMA, A.: De morphine on net water absorption, mucosal adenyiate cyclase activity,

and PGE₂ metabolism in rat intestine. Eur. J. Pharmacol. 86: 77-82,

1983.

466a. WATANABE, K., YANO, S., AND MINAKAWA, Y.: Morphine inhibits the

ga
	- narcotic antagonists of evoked acetylcholine output in guinea-pig ileum. Life Sci. 16: 1787-1792, 1975.
467. WATERFIELD, A. A. AND KOSTERLITZ, H. W.: Stereospecific increase by
narcotic antagonists of evoked acetylcholine
- THE SCI. 10: 1761–1792, 1975.

die Dünndarmperistaltik. Naunyn-Schmiedeberg's Arch. Exp. Pathol.

The SCI. 10: 1761–1792, 1970.

The SCI. 10: 1792, 1970.

The SCI. 10: 1792, 1970.

Dimmunocytochemical localization in brain ATERFIELD, A. A., AND KUSTERLITZ, H. W.: Stereospecinc increase by
narcotic antagonists of evoked acetylcholine output in guinea-pig ileum.
Life Sci. 16: 1787-1792, 1975.
ATSON, S. J., AKIL, H., GHAZAROSSIAN, V. E., AND GO 469. WATSON, S. J., AKIL, H., GHAZAROSSIAN, V. E., AND GOLDSTEIN, A.:

Dynorphin immunocytochemical localization in brain and peripheral

nervous system: preliminary studies. Proc. Natl. Acad. Sci. USA 78:

1260–1263, 1981
	- nervous system: preliminary studies. Proc. Natl. Acad. Sci. USA 78:

	1260-1263, 1981.

	469. WATTCHOW, D. A., CASS, D. T., FURNESS, J. B., COSTA, M., O'BRIEN, P.

	E., LITTLE, K. E., AND PITKIN, J.: Abnormalities of peptide-**92: 443-469.** WATTCHOW, D. A., CASS, D. T., FURNESS, J. B., COSTA, M., O'BRIEN, P.

	E., LITTLE, K. E., AND PITKIN, J.: Abnormalities of peptide-containing

	nerve fibers in infantile hypertrophic pyloric stenosis. Gastroen
	-
	- 169. WATTCHOW, D. A., FURNESS, J. B., COSTA, M., O'BRIEN, P. E., AND

	PEACOCK, M.: Distributions of neuropeptides in the human esophagus.

	Gastroenterology 93: 1363-1371, 1987.

	170. WEISBRODT, N. W.: Motility of the small Peacock, M.: Dist
Gastroenterology 9
EISBRODT, N. W.:
Gastrointestinal Ti
New York, 1987.
EISBRODT, N. W.,
	- 470. WEISBRODT, N. W.: Motility of the small intestine. In Physiology of the Gastrointestinal Tract, ed. by L. R. Johnson, pp. 631–663, Raven Press, New York, 1987.
471. WEISBRODT, N. W., SUSSMAN, S. E., STEWART, J. J., AN 471. Weisbrodt, N. W., Sussman, S. E., Stewart, J. J., and Burks, T. F.: 471. WEISBRODT, N. W., SUSSMAN, S. E., STEWART, J. J., AND BURKS, T. F.:
Effect of morphine sulfate on intestinal transit and myoelectric activity
of the small intestine of the rat. J. Pharmacol. Exp. Ther. 214: 333-338,
1
	-
	- Tolerance to the effects of morphine on intestinal motility of unanea-
thetized dogs. J. Pharmacol. Exp. Ther. 215: 515-521, 1980.
473. WERZ, M. A., AND MACDONALD, R. L.: Opioid peptides decrease calcium-
dependent action
	-
	- in cell culture. Brain Res. 239: 315-321, 1982.
WERZ, M. A., AND MACDONALD, R. L.: Dynorphin reduces calcium-
dependent action potential duration by decreasing voltage-dependent
calcium conductance. Neurosci. Lett. 46: 185 calcium conductance. Neurosci. Lett. 46: 185-190, 1984.
474. WIENBECK, M., AND BLASBERG, M.: Effects of an enkephalin analog on
motility of the small and large intestine in the cat. Z. Gastroenterologie
42: 179-187, 1986.

	- 475. WIENBECK, M., AND KARAUS, M.: The effects of deoxycholic and ricinoleic acid on the isolated circular muscle of the cat colon are modified by leucine-enkephalin. Z. Gastroenterologie 21: 365-372, 1983. mothity of the small and large intestine in the cat. Z. Gastroenterologie 24: 179-187, 1986.

	475. WIKBERCK, M., AND KARAUS, M.: The effects of deoxycholic and ricinoleic acid on the isolated circular muscle of the cat col
	- RENBECK, M., AND KARAUS, M.: The effects of deoxycholic and ricinoleic
ecid on the isolated circular muscle of the cat colon are modified by
leucine-enkephalin. Z. Gastroenterologie 21: 365-372, 1983.
IKBERG, J.: Localisat acia on the isolated circular muscleucine-enkephalin. Z. Gastroenterol
|KBERG, J.: Localisation of adrenergy
|KBERG, J.: Localisation of adrenergy
|Thysiol. Scand. 99: 190-207, 1977.
|OLTER, H. J.: Dynorphin-A(1-8) an eucine-enkephain. *L*. Gastroenterologie 21: 365-372, 1983.
476. WIKBERG, J.: Localisation of adrenergic receptors in guinea pig ileum and
rabbit jejunum to cholinergic neurons and to smooth muscle cells. Acta
Physiol. Sca
	- rabbit jejunum to cholinergic neurons and to smooth muscle cells. Acta

	Physiol. Scand. 99: 190-207, 1977.

	477. WOLTER, H. J.: Dynorphin-A(1-8) and gamma-melanotropin exist within

	different myenteric plexus neurons of r 477. WOLTER, H. J.: Dynorphin-A(1-8) and gamma-melanotropin exist within
	-

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-
- 162

RRC

nervous system of rat duodenum. Biochem. Biophys. Res. Commun. 117:

568-573, 1983.

479. WOLTER, H. J.: Co-existence of the enkephalinergic system and the melan-

otropinergic system in the rat duodenum shown b
- try. Life Sci. 41: 717-721, 1987.

481. Wond, C. L.: The possible involvement of adrenoceptors in the intestinal

effect of morphine in mice. Clin. Exp. Pharmacol. Physiol. 11: 605-610,

1984.

Wond, C. L.: Central and per 1984.

481. Wowe, C. L.: Central and peripheral inhibitory effects of morphine on

1482. Wowe, C. L., ROBERTS, M. B., AND WAI, M. K.: Effect of morphine and

1986.

482. Wowe, C. L., ROBERTS, M. B., AND WAI, M. K.: Effect **nalone on intestinal transit in mice. Meth. Find. Exp. Clin. Pharmacol. 8: 479–483, 1986.**
 naloxone on intestinal transit in mice. Meth. Find. Exp. Clin. Pharmacol. 8: 479–483, 1980.
 naloxone on intestinal transit in
- 1986.

482. Wowe, C. L., ROBERTS, M. B., AND WAI, M. K.: Effect of morphine and

naloxone on intestinal transit in mice. Eur. J. Pharmacol. 64: 289–295,

1980.

483. Woon, J. D.: Neurophysiology of Auerbach's plexus and co naloxone on intestinal transit in mice. Eur. J. Pharmacol. 64: 289–295, 1980.

1000, J.D.: Neurophysiology of Auerbach's plexus and control of intestinal

motility. Physiol. Rev. 55: 307-324, 1975.

55: 307-324, 1975.

100
-
- 1880. Wood, J. D.: Neurophysiology of Auerbach's plexus and control of intestinal motility. Physiol. Rev. 55: 307-324, 1975.
484. Woop, J. D.: Neurophysiology of Auerbach's plexus and control of intestinal motility. Physio 1980.

con, J. D.: Neurophysiology of Auerbach's plexus and control of intestinal

motility. Physiol. Rev. 55: 307–324, 1975.

con, J. D.: Intracellular study of effects of morphine on electrical activity

of myenteric neu motility. Physiol. Rev. 55: 307-324, 1975.
484. Woon, J. D.: Intracellular study of effects of morphine on electrical activity
of myenteric neurons in cat small intestine. Gastroenterology 79: 1222-
1230, 1980.
485. Woon,
- 484. WOOD, J. D.: Intracentular sculp of errects of morphine on electrical sculvity
of myenter neurons in cat small intestine. Gastroenterology 79: 1222-
1230, 1980.
485. Woon, P. L., CHARLESON, S. E., LANE, D., AND HUDGI
-

analogue on cholecystokinin octapeptide-stimulated gallbladder emptying. **Am.** J. Gastroenterol. 77:509-511,1982.

- IER

analogue on cholecystokinin octapeptide-stimulated gallbladder emptying.

Am. J. Gastroenterol. 77: 509-511, 1982.

486a. W08TER, M., AND HERZ, A.: Opiste agonist action of antidiarrheal agents

in vitro and in vivo—f
-
-
- Schmiedeberg's Arch. Pharmacol. 301: 187-194, 1978.

487. WOSTER, M., SCHULZ, R., AND HERZ, A.: Multiple opiate receptors in

peripheral tissue preparations. Biochem. Pharmacol. 30: 1883-1887, 1981.

488. WOSTER, M., SCHUL
- 489. YAMADA, S., SASANO, N., AND NAKAMURA, T.: Immunohistochemical localization of brain-gut hormones in gastric carcinoma with relation to argyrophil cells. Tohoku J. Exp. Med. 143: 1-15, 1984.
490. YAMAGUCHI, I., FUKE, H neurons: functional difference between some between some between spatric secretion and serum gastrin levels in dogs anesthetized with morphine and urethane. Jpn. J. Pharmacol. 28: 521-526, 1978.
NU, W. M., DORSETT, J. A.,
-
- with morphine and urethane. Jpn. J. Pharmacol. 28: 521-526, 1978.

491. YAU, W. M., DORSETT, J. A., AND YOUTHER, M. L.: Inhibitory peptidergic

neurons: functional difference between somatostatin and enkephalin in

myenter **492. YOSHIMURA, K., HUIDOBRO-TORO, J. P., AND WAY, E. L.: Potency of three** opiate antagonists to reverse the inhibitory activity of dynorphin, enkephalins, and opioid all. **84:** 17-24, 1982.
84: 17-24, 1982.
80: EUR 494. ZUITING 7: 160-164, 1984.
 49. 204.
-
-

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HARMACOLOGI