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Endogenous and Exogenous Opioids in the Control of Gastrointestinal Motility and Secretion

WOLFGANG KROMER

Byk Gulden Research Laboratories, Byk-Gulden-Straße 2, D-7750 Konstanz, Federal Republic of Germany

I. Introduction

THIS REVIEW will focus on possible physiological functions of endogenous opioids and, as far as data are available, on potential pathophysiological disturbances thereof in the control of gastrointestinal motility and secretion. The actions of exogenous opioids will also be 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 propulsive 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 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 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 desirable, specific compounds are named, but 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 opposed to opioids, either peptides or alkaloids, which were administered exogenously.

The different accentuation of the various chapters reflects their varying representation in the literature.

II. Distribution of Opioid Peptides and Opioid 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 the first identification 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 precursors: proopiomelanocortin; proenkephalin; and prodynorphin (for review see refs. 182, 191, 208, and 160). Endogenous opioids, present in high concentration among other neuropeptides in the intestinal wall, were detected by immunohistochemical and radioimmunological 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 project to the circular muscle. Orally directed processes may represent dendrites (117, 269) or axons (76a) of myenteric cell bodies.

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 myenteric plexus or in the guinea pig cecum after denervation (196). Nerve fibers containing immunoreactive [Met^5]-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 neuronal 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 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 gastrointestinal tract (315, 354) 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 [Met^5]-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 proopiomelanocortin.

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 neurons of the gastrointestinal wall of the guinea pig and rat (468, 460a,

* Abbreviations used are: ACTH, adrenocorticotropin; B_{max}, maximum binding capacity; CCK, cholecystokinin; CNS, central nervous system; CTP, D-Phe–Cys–Tyr–D-Trp–Lys–Thr–Pen–Thr–NH_2; DAGO, [D-Ala^2, N-methyl-Phe^4, Gly^5-ol]-enkephalin; dbcAMP, dibutyryl cyclic adenosine 3′,5′-monophosphate; 2-DG, 2-deoxy-D-glucose; DMPP, 1,1-dimethyl-4-phenyl-piperazinium; DPDPE, [D-Pen^2, D-Pen^5]-enkephalin; EC cells, enterochromaffin cells; EJPs, excitatory junction potentials; FK 33-824,[D-Ala^2,methyl-Phe^4-(O)-ol]-enkephalin; GIP, gastric inhibitory polypeptide; i.c., intracisternally; ICI 154,129, N,N-bisallyl-Tyr–Gly–Gly–ψ-(CH_2S)–Phe–Leu–OH; i.c.v., intracerebroventricularly; i.m., intramuscularly; K_d, dissociation constant; LES, lower esophageal sphincter; Leu, leucine; Met, methionine; MMC, migrating motility complex; MR 2034, [(−)-(1*R*, 5*R*, 9*R*, 2″*S*)-5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan]tartrate; alpha-MSH, alpha-melanocyte-stimulating hormone; NANC, nonadrenergic-noncho-linergic; PG, prostaglandin; PIA, N^6-phenylisopropyladenosine; PL 017, [methyl-Phe^3, D-Pro^4]-morphiceptin; Ro 15-1788, ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazole[1,5-a][1,4]benzodiazepine-3-carboxylate; RX 783006, Tyr–D–Ala–Gly–MePheNH$(CH_2)_2$OH; SKF 10.047, N-allyl-normetazocine; TRH, thyrotropin releasing hormone; TTX, tetrodotoxin; U50,488H, *trans*-(±)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzene-acedamide-methansulfonate; VIP, vasoactive intestinal polypeptide.

65a). In the rat, dynorphin-A(1–8) was detected in duodenal 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 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 intestinal wall contains [Met^5]-enkephalin immunoreactivity within neurons which again are preferentially localized within the myenteric plexus (88, 259). In a population of these neurons, substance P and [Met^5]-enkephalin may coexist within the same neuron, both in the feline (88) and guinea pig (449a) small intestine. In the cat, cell processes containing [Met^5]-enkephalin project to neurons of both the myenteric and the submucosal plexus, 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, 364, 103). Consistent with the high concentration of the proenkephalin-derived peptide [Met^5, Arg^6, Gly^7, Leu^8]-enkephalin in the muscle layer as opposed to the mucosa and submucosa, 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). In addition, the human vagus nerve has been found to contain [Met^5]-enkephalin-immunoreactive nerve fibers (261).

Some direct immunohistochemical comparisons were made between species concerning enkephalin immunoreactivity 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 pig, rat, and hamster gastrointestinal tract (256, 382). Keast et al. (204) demonstrated enkephalin-immunoreactive nerve fibers, though at a lower density compared with a variety of other neuropeptide-staining nerve fibers, in the mucosa and muscularis mucosae of the guinea pig, rat, dog, marmoset, and human gastrointestinal tract.

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 the duodenal mucosa. However, relative to other regions, a high concentration was confirmed in the stomach. These authors described in contrast to other species a large number of enkephalin neurons within the canine submucosal plexus. Despite other, subtle species differences, there was a surprisingly close similarity between the species. The wall of the lower esophagus of a variety of species inclusive of man also contained, particularly within the external muscle and the myenteric plexus, enkephalin nerve fibers and neurons (450 469a, 204).

Ferri et al. (104) extracted [Met^5, Arg^6, Gly^7, Leu^{-8}]-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 concentrations in the cardiac and ileocecal region. Enkephalin immunoreactivity was demonstrated by Aggestrup 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 [Met^5]-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 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 found, in human antropyloric mucosa and that of some other species, both gastrin and cholecystokinin cells stained by antibodies capable of reacting with [Met^5]-enkephalin congeners elongated at the COOH terminus. By the same group, opioid material which could not be distinguished from [Met^5]-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 immunoreactivity in extracts of human antral mucosa. Thus, human and rat antral G-cells are probably 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 particular 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 enterochromaffin (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 degrading enzymes, i.e., enkephalinases, in the stomach and intestine (257; for nomenclature, see ref. 165). This finding in the rat suggests a functional 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 longitudinal muscle and myenteric plexus has been demonstrated (71). This high affinity binding was reversible, saturable, and stereospecific. It correlated excellently with the pharmacological potency of a variety of opioids

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 Glasel et al. (136) who demonstrated specific opioid binding to a purified synaptosomal fraction from guinea pig ileum homogenates. 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, reversible, stereospecific, and sensitive to sodium concentration. Sensitivity to sodium is a well-recognized feature of opioid agonist binding (for review, see refs. 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, 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, binding was found in the submucosal and deep muscular 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 and enriched guinea pig parietal cells (238) or isolated intestinal epithelial cells from guinea pig small and large intestine (260). The latter binding sites were [Leu^5]-enkephalin selective and may differ from delta-type opioid receptors which have very recently been distinguished 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 found throughout the gastrointestinal tract in neuronal and endocrine cells with potential receptor sites on neuronal, smooth muscle, and mucosal cells. As expected for an intrinsic opioid system, specific degrading enzymes are also present.

III. The Role of Opioids in the Control of Gastrointestinal Motility

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. Nevertheless, the isolated guinea-pig ileum has received particular attention for in vitro investigation of gut motility as it permits, for instance in the experimental setup introduced by Trendelenburg (446), an accurate measurement of single propulsive circular muscle contractions. In this review, in vitro peristalsis is defined as phasic circular muscle contractions travelling down the intestinal segment, thereby expelling its contents from proximal 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 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 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 peristaltic reflex (373, 222, 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 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 unmask the physiological role of those receptors that had already been endogenously activated at the time of antagonist administration, whereas administration of exogenous opioids indiscriminately leads to simultaneous 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, at concentrations below 1 μmol/liter, provides a rather specific tool for such experiments, although nonspecific actions may be observed at higher concentrations (369). At concentrations of at least up to 1 μmol/liter, naloxone had no influence on the actions of noradrenaline, dopamine, serotonin, acetylcholine, histamine, or PGE_1 in the longitudinal muscle myenteric plexus preparation of the guinea-pig ileum (Kromer, unpublished results).

Based on studies in electrically stimulated guinea-pig ileum, inhibition of acetylcholine release by opioid alkaloids (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 of acetylcholine in the longitudinal muscle myenteric plexus preparation of the guinea-pig ileum (467). Stereospecificity 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 high-frequency electrical stimulation (339). Thus, endogenous opioids may have inhibited electrically evoked release of acetylcholine, which was reversed by naloxone (467). Moreover, Van Nueten et al. (452) reported an "unexpected 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 haloperidol (452), the actions of these compounds were not prevented by naloxone (Kromer, unpublished data).

Therefore, the above mentioned antagonism was evidently 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 reversed fatigue of peristalsis but had no influence on "normal peristalsis." This interpretation, 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 also in vivo (42; for review, see refs. 361 and 470). Moreover, the isolated guinea-pig ileum is capable of producing 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 against their closed distal end, developed fatigue, although naloxone increased the number of peristaltic contractions in these segments by a percentage similar to that observed in segments allowed to expel their contents. Thus, endogenous opioids seem to control "normal peristalsis" rather than to protect the gut from becoming exhausted (i.e., producing "fatigue"). Kadlec 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 that, after cessation of this "stress" stimulus, peristalsis reappeared earlier under the influence of naloxone than 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 misinterpretation that a "stress" response rather than normal peristalsis was affected by naloxone.

Naloxone enhanced in vitro peristalsis to a higher degree when administered acutely into the organ bath (233) than after preexposure of the segments to naloxone (231). In the former case, the naloxone effect declined somewhat over time, although sufficient naloxone was still present to occupy all opioid receptors. These data suggest a compensatory mechanism (for potential causative agents, see refs. 65, 130, and 46).

3. Intestinal actions of opioids prior to parturition. Consistent with the presence of [Met^5]-enkephalin immunoreactivity in 18-day fetal tissue cultures of mouse intestine (381) or [Leu^5]-enkephalin immunoreactivity in human fetal intestinal tissue (248a), naloxone enhanced 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 taken from fetuses just prior to parturition, but significantly less so in preparations taken from adult guinea pigs (241). Therefore it appears that, just prior to parturition, either pituitary (229, 73) or gastrointestinal opioids produce some degree of intestinal opioid dependence. 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 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 did not introduce naloxone in order to search for a possible 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, alternately or simultaneously, (*a*) an increase in duration of individual periods of rhythmic peristaltic activity induced 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 frequency of peristaltic waves within periods of peristaltic activity (233). 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 inhibitory fashion, in the control of periodicity of peristalsis. 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 activity. The effects of naloxone on both fetal and adult intestinal tissues were stereospecific and observed at low concentrations (~100 nmol/liter), which makes nonspecific actions extremely unlikely. A possible modulation of mechanoreceptor sensitivity (318) by opioids cannot be ruled out as they increased the threshold of intraluminal pressure in the rat ileum necessary to elicit a decrease in systemic blood pressure. This effect of codeine was reduced by naloxone. It had an, albeit minor, peripheral action component since bilateral vagotomy increased the required codeine dose, but did not abolish its effect (64).

5. Intramural location of the intestinal opioid mechanism. 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 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 concentration 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, normorphine concentration dependently inhibited, while nal-

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 acetylcholine (236). This acetylcholine effect was TTX sensitive. Therefore, most likely opioid receptors and endogenous opioids also modulate, in addition to its release, the action of acetylcholine during induction of peristaltic activity. Kilbinger and Wessler (205) found that similar concentrations of acetylcholine inhibited the stimulation-evoked release of [^{3}H]acetylcholine from the myenteric plexus. It is therefore unlikely that, in the experiments of Kromer and Schmidt (236), exogenous acetylcholine induced additional release of endogenous acetylcholine, which release might have been modulated by opioid receptors. A ganglionic postsynaptic opioid inhibition of neurotransmission in this tissue is consistent with recent data of Beleslin et al. (17) showing that opioid inhibition of peristalsis in the isolated guinea-pig 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. These data are not inconsistent with opioid inhibition of acetylcholine-induced peristalsis, since both intestinal preparations display completely different functions due to their distinct structures.

6. Opioid tolerance/dependence and intestinal peristalsis. Consistent with the above interpretation, sensitivity of the peristaltic reflex in the intact segment to exogenous acetylcholine was increased in the morphine-tolerant 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 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 increase of peristaltic waves per min (242), suggesting that enhanced 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 review of recent developments in this field, see Wüster et al. (488). It should be noted in this context that elevations in intestinal tissue levels of distinct endogenous opioids brought 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 release of [Met^5]-enkephalin from the guinea-pig myenteric plexus in vitro (137), whereas this release from the morphine-tolerant/dependent preparation was transiently dependent on morphine (134). Subsequently, [Met^5]-enkephalin release from the morphine-withdrawn preparation was enhanced but again inhibited by reexposure 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; electrophysiological data. Opioids 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 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 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 action. In fact, Kromer et al. (235) demonstrated that enhancement of peristalsis by naloxone declined when the extracellular calcium concentration was stepwise increased. A similar depression of excitatory influence by naloxone was found upon 4-aminopyridine application (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 the alpha$_2$-agonist, clonidine, were likewise reduced by 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 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 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 calcium concentration (313, 314, 184, 185). Interestingly, high-frequency electrical stimulation of the guinea-pig ileum longitudinal muscle myenteric plexus preparation resulted in partially naloxone-sensitive inhibition of subsequent low-frequency stimulated contractions. This inhibition is probably caused by endogenous opioids and again antagonized by a rise in extracellular calcium concentration (314).

8. The opioid mechanism and spontaneous neuronal activity. The proposed opioid neurons which are operative in the gastrointestinal tract may be either spontaneously active or driven by pacemaker neurons in order to suppress, proximal to their location, peristaltic activity. 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 present in the myenteric plexus (483). Upon distension

of the intestinal wall by intestinal contents, this proposed, 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, both [Met^5]-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) demonstrated 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 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 majority of axons and nerve terminals present in the tissue, irrespective 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 functional significances. Thus, Donnerer et al. (89) found an increase in dynorphin release from isolated 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 control is once more underlined by recent findings of Glass et al. (137). They reported an increase in spontaneous [Met^5]-enkephalin release from the guinea-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 not enhanced by naloxone (230), suggesting a more significant role of reflex mechanisms under these conditions as discussed above.

9. Distribution of the opioid mechanism over the intestine. 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 earlier report showing that opioids are at their highest 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 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 phenomenon, from oral to aboral, of decreasing frequency of peristaltic waves and decreasing sensitivity to the distension stimulus.

10. Involvement of different opioid receptor types. Although multiple opioid receptor types, i.e., mu-, delta-, 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, 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 longitudinal 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-normetazocine (SKF 10.047). This opioid alkaloid inhibited the longitudinal muscle contraction in a naloxone reversible fashion, but enhanced both reflex peristalsis and 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 displayed 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 reservation is appropriate when extrapolating from one type of guinea-pig ileum preparation to another, with both respect to receptor populations and presynaptic versus postsynaptic actions.

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 (guinea-pig 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 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 somatostatin which, in the isolated guinea-pig ileum, prolongs or shortens regular peristalsis-free intervals dependent on their length preceding drug application (243). An assessment of the functional significance of 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 an increase in the presence of atropine. Under 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 morphine reduced high spontaneous muscle tone, and increased muscle tone in a naloxone-reversible fashion when the circular muscle had been relaxed beforehand by hyoscine (445). Hence, both excitatory and inhibitory

opioid 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 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 naloxone stereospecifically enhanced propulsive peristaltic 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, unpublished observations). These opioid effects have been essentially confirmed by Beleslin and Terzić (16). However, the functional relationship of opioid-effected inhibition 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 in the guinea-pig and rabbit intestine, were inhibited by opioids in a stereospecific fashion (232). Naloxone alone, in some of the segments, stimulated peristalsis, which again suggests an inhibitory modulation of peristalsis by intestinal opioids. Dahl et al. (75) reported very recently that partial chemical ablation of myenteric neurons increased [Leu^5]-enkephalin concentrations in the rat jejunum. Thus, there may be a 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 peristalsis 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 correspond to an increased, decreased, or unchanged spike activity of extracellularly recorded cat myenteric neurons upon morphine application (97). Intracellular recordings, however, revealed naloxone-blockable hyperpolarization 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 inhibition of neurogenic peristalsis with no species differences observed at least with respect to electrophysiological findings, even in comparison with the guinea-pig. It should be noted that uniform hyperpolarization by opioids of either excitatory or inhibitory neurons may 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 observed (232). These effects were again stereospecific. In a number of experiments, on the other hand, opioids converted high-frequency but low-amplitude propulsive contractions of 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). 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 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 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 phasic contractions associated with release of serotonin into the vasculature (48, 44). Since TTX barely affected contractions elicited by [Met^5]-enkephalin, the authors discussed 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, beta-endorphin-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. It 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 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 opioid effects are observed. This may define species differences.

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 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 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 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 data are consistent with an inverse relationship between segmenting and peristaltic contractions (see also rabbit, section III B 1).

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 chemical 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 to lower morphine concentrations used in the latter study. In the rabbit, opioids enhanced EJPs in the proximal, 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, 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 concept on 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 contractions, morphine attenuated the electrically evoked release of [^{3}H]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 for relating these results to the effects of opioids on propulsive peristalsis.

D. In Vivo Data on Gastrointestinal Motility in Various 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 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 (108). Abbott and Pendergrass (1) concluded that morphine delayed gastric emptying at least partially by increasing 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 a decrease in gastric tone with superimposed transient phasic contractions (251). Interestingly, naloxone alone slightly increased both the frequency and amplitude of ruminal contractions in sheep (359, 264). This was only observed under well-defined feeding conditions (264), suggesting 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 enhance gastric emptying in man (288). Mittal et al. (288) speculated that this might be relevant at different dose levels or in patients suffering from delayed gastric emptying. Thus, endogenous opioids might play a role as 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 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 in mice. The effect was antagonized by the quaternary 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 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. 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 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 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 intestinal 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-Williams (455) stressed that opiates increase 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 not prevent transit by increasing resistance as assumed by early 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 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 found in the fasted or fed state (470), but the precise relationship is not known. Any statement on "contractile" or "relaxant" effects of opioids in the gastrointestinal tract is, therefore, only meaningful within the context of further 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 that in both man (1, 355) and dog (456) as well as in other species opioids exert a long lasting depression of propulsive activity of the small

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 lead to controversial interpretations of inhibitory versus stimulatory opioid actions. These publications may be consulted for further references to earlier publications.

c. DUAL OPIOID EFFECTS: CURRENT INVESTIGATIONS; 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 rat (427, 442, 441, 49, 107, 123, 124, 365, 426, 218, 273, 272, 139, 119), mouse (482, 332, 23, 481), and man (2), although Borody et al. (32) did not find any slowing 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 myoelectric complex) or mechanically (migrating motor complex; for review, see ref. 470). "Phase III activity" of the MMC 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 the 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 different routes of administration (360). Weisbrodt et al. (471) demonstrated a positive correlation between inhibition 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 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 case, the pattern of intestinal motility has a considerable impact on intestinal propulsion.

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 abolished by morphine. In addition to morphine (366b), [Met^5]-enkephalin (216) inhibited myoelectric activity in 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 Konturek et al. (216) found stimulation of interdigestive MMCs by morphine. Induction of a premature MMC cycle by morphine may correspond to the period of augmented propulsion followed by depression over an 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 by the observation that stimulation of myoelectrical activity in the canine small intestine by morphine was converted 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 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 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 radiopaque marker in the small intestine were also inhibited by an enkephalin analogue (474).

Most important, a dual stimulatory-inhibitory effect 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, although no information was provided on their 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 ACTIVITY STATE 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 sufficient dose, more or less all opioid receptor types irrespective of their location and functional significance, the alternating operation of opioid mechanisms of contrasting 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 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 loperamide. 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 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 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

naloxone alone had no effect upon transit time of myoelectrical 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 (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 different species and under different conditions.

e. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR 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 antagonistic potency of naloxone against different agonists, mu- and delta-, but not kappa-type receptors have been implicated in the opioid-effected contraction of the canine small intestine (458). Opioid receptors, which mediate the supraspinal (i.c.v.) and peripheral opioid inhibition of intestinal transit in mice and rats, probably belong to the mu-type (125, 334, 408a, 464). Shook et al. (408a) used, in their recent mouse studies, rather selective 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 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^5]-enkephalin after i.c.v. administration to the mouse that delta-type receptors were preferentially involved in supraspinal inhibition of intestinal transit. However, these agonists poorly discriminate between opioid receptor types. Apart from poor receptor selectivity, any conclusion based solely on agonist potencies is dangerous in view of possible differences in intrinsic activities of the tested opioids as well as in spare receptor pools of the test systems (285). Similar objections apply also to the conclusion of Culpepper-Morgan et al. (73a) that both kappa- and mu-type opioid receptors may slow down gastrointestinal transit in the guinea-pig, while the kappa-selective agonist U-50,488H was ineffective in the 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 to the relative importance of different sites of action, different receptor populations involved, and different motility measures affected, quantitative 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 of acetylcholine from the isolated guinea-pig ileum (325), but might have even stimulated this release in the rat and human intestine (78). However, Paton (325) actually 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. Mediation of the spasmogenic 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 muscarinic 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 serotonin 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 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 transient 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 authors 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 animal. It might turn out that these authors found a species 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 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 any definite statement on "basic" species differences in opioid actions on gut motility. Species differences may rather be of a quantitative nature due to superimposition of contrasting opioid effects observed in all species, however to varying degrees (see section III D 2 c).

3. Large Intestine. In the large intestine, a dual excitatory-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 investigated, the motility parameter looked at, the feeding conditions and thus the predrug motility pattern, the time interval 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 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 naloxone antagonism reported recently in the conscious dog.

Here morphine and the more specific mu-receptor agonist [D-Ala^2, N-methyl-Phe^4, Gly^5-ol]-enkephalin (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. administration were not. Interestingly, the increased colonic motility after i.c.v. administration was prevented by the benzodiazepine antagonist RO 15-1788, leading the authors to suggest that benzodiazepine, rather than opioid, receptors were involved in this central action on colonic motility. Alternatively, i.v. naloxone at the dose employed 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 antagonist may be functional. This interesting issue deserves further attention. On the other hand, Daniel et al. (76a) never observed excitatory responses to close intraarterial opioid injections in the canine colon but found transient inhibition of electrically induced contractions, as to be 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 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 stomach, the failure of naloxone alone to alter colonic motility patterns (371) may be related to a counterbalance between a blockade of inhibitory and excitatory 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, 33) may develop under certain conditions, which are not yet fully understood. Sun et al. (433) reported that the gastrocolonic response, i.e., a vagally mediated increase in distal colonic spiking activity after eating, was completely 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 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. pethidine induced phasic increases in gastroesophageal (rsp. LES) sphincter pressure (428). Potential blockade by naloxone was not tested. Howard et al. (178) reported that enkephalin reduced LES relaxation upon swallowing in healthy volunteers without any effect on LES pressure or peristalsis otherwise. They did not find any influence of naloxone alone on LES motility. Endogenous opioids might, therefore, not exert any major impact on LES function. Morphine slightly elevated LES pressure in man and also decreased LES relaxation upon swallowing (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, reports on just the opposite opioid effect, i.e., enhanced LES relaxation with an increased likelihood of gastroesophageal reflux in man and monkey (152, 166, 288). Again, systemic administration of the drug implied that 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 from in vivo experiments in the opossum that opioid mu- and kappa receptors, possibly located on the sphincter muscle, 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 a physiological relaxant role of endogenous opioids. In 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 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 stimulation of the vagus nerve or upon administration of exogenous opioids in the cat (93, 348). Both effects as well as 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 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 sphincter contractions in the cat and dog. This is consonant with data by Rattan and 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 effects were antagonized by naloxone. By contrast, 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 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 been demonstrated immunohistochemically in the anal sphincter, were probably inhibitory in these experiments. The data are at variance with those of Rattan and Culver (343) obtained in the opossum. In their experiments, loperamide inhibited internal anal sphincter relaxation

caused by sacral nerve stimulation, but not that caused 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 fibers. The issue awaits further clarification.

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 effect, but elicited strong withdrawal contractions 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). Naloxone alone had no effect. Whether endogenous opioids 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. 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 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) nor did it alter tissue concentrations of immunoreactive [Met^5]-enkephalin in any part of the rat gastrointestinal tract (106). Vagal input appears, therefore, not necessary 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 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 antagonized by naloxone. It may have some physiological significance for acetylcholine release at these synapses, considering that Schultzberg et al. (384) found enkephalin-immunoreactive nerve fibers and neurons in guinea-pig and rat sympathetic ganglia. Aside from acetylcholine, a number of additional neurotransmitters may be indirectly involved in this complex system, both in relation to acetylcholine release and independent thereof. 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 (219, 76, 223, 130, 46, 87, 470). Both ATP and, more recently, VIP have been ascribed the properties of a "nonadrenergic" inhibitory neurotransmitter in the gut, although this issue is still far from being settled (470). A similar inhibitory system may be operative in the human gut (72). Enkephalins inhibited nonadrenergic-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 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, 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 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 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 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 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 excitatory neurotransmitter like acetylcholine by the opioid. This possibility was then discarded, since atropine 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 turn, inhibited by endogenous opioids (15). This was concluded from experiments showing that naloxone 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 dependently impaired by an enkephalin analogue. A smaller contraction by naloxone following CCK-8 was 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 [Met^5]-enkephalin coexist within a subpopulation of myenteric neurons (88, 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 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 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

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, unpublished data).

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 vitro (122). In the canine stomach in vivo, [Met^5]-enkephalin decreased the frequency of pacesetter potentials recorded serosally. However, as both naloxone and indometacin prevented and PGE_2 partially mimicked this inhibitory opioid effect, its mediation by local prostaglandins was suggested (206). Thus, opioids may interact with prostaglandins at different sites.

Inhibition of electrically induced acetylcholine release and consequent twitch of the longitudinal muscle myenteric 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 neurotensin and an inhibition of spontaneous pendular activity by dynorphin was observed (187).

The situation is even more complex in vivo, exemplified by bombesin, which delays intestinal transit in the rat (140). Although the opiate antagonist naltrexone did 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 gastrointestinal motility is motilin (for 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 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 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 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 notion, recent data (115c) indirectly support its first part.

5. Catecholamines and serotonin. The well-known inhibition of acetylcholine release by activation of both opioid and alpha$_2$-receptors on nerve terminals in the guinea-pig myenteric plexus (374, 326, 220, 423, 476) may explain why the alpha$_2$-receptor-antagonist yohimbine functionally antagonized the antitransit effect of morphine in the mouse in vivo (480), i.e., under conditions where the extrinsic sympathetic gut innervation is operative. This is in line with data by Stewart (425) 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 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 opioid effect. The other way round, Majeed et al. (268) suggested, on the basis of decreased tissue concentrations of immunoreactive dynorphin, that activation of sertonin receptors may stimulate the release of dynorphin from the rat myenteric plexus. How these data relate to intestinal peristalsis is not known.

Indirect pharmacological evidence suggests that biosynthesis and release of myenteric opioids may be under the inhibitory control of receptors activated by dopamine (453, 454); these data have been obtained with electrically stimulated preparations, and there is no information 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 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 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 waves) of the membrane potential of the smooth muscle 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 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 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 duodenum 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-insensitive 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 not present their data in detail and did not show any controls, claimed a direct inhibitory influence of opioids on chemically induced smooth muscle contractions in the guinea-pig ileum. These data could not be reproduced (Kromer, unpublished data).

Both hyperpolarization (probably related to relaxa-

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 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 [Met^5]-enkephalin was hardly affected by TTX, suggesting 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-neurotransmitter interactions.

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 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 technique predominantly detecting circular muscle activity, 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 ineffective in preventing opioid-induced contractile activity. 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 relaxation of longitudinal muscle tone in the guinea-pig colon in vitro using concentrations of morphine (1 μmol/liter) similar to those that produced longitudinal muscle contraction 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). Opioid-induced longitudinal contractions of isolated colonic tissue 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) demonstrated that TTX counteracted tonic intraluminal pressure changes, induced by opioids in the whole (undissected) 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 muscle may be released from tonic neuronal inhibition (483) by opioids and TTX to produce rhythmic contractions. The relationship of this opioid-effected desinhibition to inhibition of reflex peristalsis is still unsolved and needs further investigation.

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 suffering from hypertrophic pyloric stenosis, a nonselective loss of [Met^5]-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 immunoreactivity was found within the myenteric plexus. Enkephalin contracts the pylorus (94, 348). A pathophysiological role of a potentially elevated tonic enkephalinergic 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) investigating children suffering from Hirschsprung's disease found 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 [Met^5]-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 disappearance of enkephalin-immunoreactive neurons and nerve fibers in the aganglionic segment. Moreover, Lolova et al. (258) reported that substance P-, serotonin-, and [Met^5]-enkephalin-immunoreactive nerve fibers were diminished in the aganglionic segment, speculating on the 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 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. 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 rat pituitary, first demonstrated by Guillemin et al. (150). However, naloxone failed to antagonize intestinal hypomotility in rats submitted to surgical stress (179). In fact, opioid agonists increased the frequency of migrating motor complexes in the duodenum, not the stomach, 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 unclear. Shah et 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 emptying and "purposeful" intestinal motility in their patients. There is, however, no indication as to a possible involvement of endogenous opioids in the mechanism underlying hypomotility following surgery.

Central stimuli such as hypothermia or labyrinthine stimulation elevated the plasma beta-endorphin concentration and suppressed antral motility in healthy subjects. The latter effect was prevented by naloxone (421a).

Under particular conditions, therefore, endogenous opioids might be released to inhibit gastrointestinal motility. On the other hand, an enkephalin analogue has been suggested as a drug to treat paralyzing ileus (24). Although the opioid may stimulate canine jejunal digestive 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 and the 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 naloxone-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 gastric emptying in patients with duodenal dyskinesia (298). It 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 treatment in one patient who had unsuccessfully undergone subtotal colectomy. The above case reports should of course not be overvalued.

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 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 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 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 intraluminal pressures than in unaffected intestinal segments (319).

Immunocytochemical data of Sjölund et al. (411) suggest 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 both the nonafflicted and afflicted ileum, but not in controls not suffering from Crohn's disease. The pathophysiological 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, respectively, displayed an opioid withdrawal-like contracture 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 compared with nonstressed controls (Kromer and Steigemann, unpublished results). These withdrawal-like phenomena 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, plasma levels of beta-endorphin in pregnant women undergoing labor and parturition were elevated (73), which may also relate to a stressful condition.

6. Gastrointestinal tumors and inflammation. Beta-endorphin- and [Met^5]- as well as [Leu^5]-enkephalin-like 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 opioid activity. There were, however, no evident clinical signs of gastrointestinal disturbances related to an altered functional state of endogenous opioids. Davis et al. (81) found increased tissue concentrations of [Met^5]-enkephalin in adenocarcinomas of the colon and in the inflamed appendix. The authors speculated that constipation, 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 distended guinea-pig ileum observed by van Nueten et al. (452) in vitro.

7. Possible biological significance of exorphins. A physiological aspect possibly related to particular stages in life may be influenced by exorphins like beta-casomorphins. 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-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 protect the irritable infantile gut from frequent diarrhea. While Petrilli et al. (328) were unable to demonstrate any in vitro cleavage of buffalo beta-casein to beta-casomorphins by various peptidases and by intestinal brush border enzymes, Hamel et al. (154) showed the generation of beta-casomorphin-like immunoreactivity from cow's milk by caseolytic bacteria. The identity of the material was characterized by gel chromatography. These exciting aspects may stimulate future work in this field.

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 exogenous opioids. Since administration of exogenous agonists causes activation of receptors at different locations, of different functional significances, different functional states, and of different types simultaneously, the outcome of this

experimental approach may well distort the true picture of endogenous opioid functions. In fact, distinct opioid mechanisms, which might be operative at different functional stages of gastrointestinal motility, probably have to be activated at the proper time relative to each other 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 receptor type selective, opioid functions mediated by distinct receptor types will not be distinguished. This may be 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 opioid receptors should be manifest as functional deficits, even this strategy might, to some extent, obscure true physiological functions. The reason is that during prolonged 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 peristalsis has emerged in several species. In the guinea-pig, it appears that the periodicity of 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 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 small intestine. It is antagonized by calcium ions, causes hyperpolarization of myenteric neurons, and modulates not only the release, but also the action of acetylcholine. Spontaneously active neurons within the myenteric 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 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 versus the propulsive circular muscle contraction. Actually, the contrasting effects of N-allyl-normetazocine (i.e., inhibition *versus* excitation) can only be explained by distinct receptor types, provided one takes into account that other opioids exert consistent effects in both intestinal preparations.

The opioid mechanism is subject to partial functional counterregulation and development of tolerance/dependence. Dependence on the body's own opioids probably develops in the fetal intestine just prior to parturition.

In all species tested, opioids seem to exert a dual excitatory-inhibitory effect in the small and large intestine. In the guinea-pig small intestine, the inhibitory component prevails, while the excitatory component is 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 response in a 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 release of serotonin within the intestinal wall, although other endogenous compounds like substance P or motilin might also be involved. Aside from 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 species, including man, inhibition of propulsive and 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 different methodological approaches should receive greater attention in the future to define the propulsive versus the segmenting nature of any motility parameter investigated. 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 to 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 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 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 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 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 unequivocally unmask any physiological role of endogenous opioids in gastrointestinal motility. This does not mean, however, that such opioid function 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 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 sphincter, the pylorus, and the anal sphincter. The conclusion of early investigators that opioids produce, at

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 enhancing segmentations in the duodenum and colon, still appears to be valid. The guinea pig may be an exception as stimulatory opioid action components probably do not contribute to the constipating effect. This may define one extreme of the spectrum obtained by 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 have been described. Their significance in the control of intestinal peristalsis 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 inhibited by opioids but motilin, and CCK alike, may itself stimulate the release of opioids. Similarly, serotonin may be released by opioids but may itself stimulate opioid release. These conclusions on interrelations between gastrointestinal neurotransmitter systems are to some extent hypothetical and need confirmation, extension, and finally conceptual integration in the future.

Attempts to define malfunctions of endogenous opioid 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 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 Acid Secretion

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 components (349, 176). These early and current in vivo investigations will be discussed later on. In vitro studies on the opioid influence on acid secretion at the parietal cell level were performed recently in order to reduce the 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% with parietal cells by counterflow centrifugation. Secretion of HCl into the tubulovesicular system of suspended parietal cells was determined indirectly by accumulation of [^{14}C]aminopyrine, a weak base which freely penetrates the cell membrane at neutral pH, but becomes protonated and thus entrapped in an acidic environment. The enkephalin analogue [D-Ala^2, D-Leu^5]-enkephalin did not affect basal acid secretion, but further enhanced histamine-stimulated acid secretion by roughly 20%. This effect was blocked by naloxone. A homogenate of enriched 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 effect on acid secretion in this parietal cell system turned out to be stereospecific (237). Most interestingly, naloxone stereospecifically impaired histamine-stimulated 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 secretion. 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 naloxone 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 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 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, although nanomolar opioid concentrations were effective, no clear-cut concentration-response relationship 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 secretion by both (−)- and (+)-naloxone at concentrations above 10 μmol/liter, whereas (−)-naloxone at lower concentrations specifically antagonized the effects of opioids. It should be noted, however, that the inhibitory effect of (−)-naloxone alone, in guinea pig parietal cells (237), was observed at concentrations of 1 μmol/liter and below and was stereospecific, which is indicative of a receptor-mediated effect. 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 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 observations 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 histamine- or bethanechol-stimulated acid secretion in the isolated rat gastric mucosa. However, they used concen-

trations of both the secretagogues and morphine greater than 100 μmol/liter. At those high concentrations, opioids are to be expected to exert nonspecific inhibitory effects which might be superimposed on specific stimulatory actions. Moreover, supramaximal stimulation of acid output by histamine or bethanechol might have 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 Canfield and Spencer (53) who preincubated isolated rat stomachs in the presence of 1 μmol/liter of morphine or naloxone for 1 h and stimulated acid secretion thereafter by various secretagogues. Under these conditions, development of acute tolerance to morphine may be expected.

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 in a calcium-dependent manner. Although it is 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. Somatostatin inhibits and bombesin stimulates gastric 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 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 reproduced though it appeared from that publication (397) that such an effect was not definitely precluded. An inhibition by exogenous acetylcholine of somatostatin release in the isolated rat stomach may be caused by endogenously released opioids, since naloxone prevented 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). Moreover, in the presence of naloxone, [Leu^5]-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 bombesin-like immunoreactivity was enhanced by [Leu^5]-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 preliminary 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 effect of naloxone alone, endogenous opioids contributed little to the vagally stimulated noncholinergic gastrin 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 indicates facilitation by endogenous opioids under these conditions. Again, opioid systems opposing each other may be superimposed, the overall outcome possibly determined by their actual balance.

B. In Vivo Studies in Rat, Cat, Dog, Monkey, and Man

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, 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 administration, and after pyloric ligation. Pyloric ligation is known to vagally stimulate acid secretion (151a, 451a). These inhibitory opioid effects on acid secretion were blocked by naloxone, indicating receptor-mediated actions. Acid secretion was reduced by morphine and atropine 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 vagal 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 stimulus parameters. 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 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 stimulated acid secretion by morphine in terms of a central as 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-precipitated morphine withdrawal did not significantly change gastric secretion (171).

b. OPIOID EFFECTS ON ACETYLCHOLINE AND HISTAMINE 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 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 acid secretion, i.c.v. dermorphin was ineffective against histamine-stimulated acid secretion in the rat (190). Since opioid receptors, probably located on parietal cells, en-

hance histamine-stimulated acid production (238, 237, 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 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 comparison between the effects of i.v. and i.c.v. administered receptor type-selective opioids and by introducing the quaternary naltrexone-methylbromide that central and possibly peripheral mu-receptors (selectively activated by PL 017 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 mechanisms may be involved in inhibition of gastric acid secretion (357, 105, 115) in addition to stimulatory, peripheral sites of action (115, 238, 237, 375). Detection of 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 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-stimulated acid secretion but not basal acid secretion, while beta-endorphin did just the opposite, and [D-Ala^2, Met^5]-enkephalin impaired both basal and TRH-stimulated acid secretion (294). These confusing and partially conflicting data need further clarification.

d. THE EFFECTS OF OPIOID ANTAGONISTS IN THE ABSENCE 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 preliminary publication that, in the anesthetized rat, 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. (138) 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 above basal values was achieved. Fifty mg/kg of naloxone, 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 mechanisms 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 interpreted with caution. Even a failure of opioids to affect acid secretion may result from superimposition of functionally opposite action components.

2. Cat. Continuous i.v. infusion of [Met^5]-enkephalin 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-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 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 hypothetical opioid mechanisms would influence acid secretion in an 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 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 pentagastrin, histamine, or 2-DG by 40 to 60% (11). The effect was prevented by naloxone. In this study on cats, endogenous 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 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 inhibited and then stimulated acid secretion. The stimulatory effect in the dog was abolished by atropine 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 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 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 secretion in a chambered stomach preparation by close intraarterial infusion of [Met^5]-enkephalin. The 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 [Met^5]-enkephalin and morphine also augmented histamine-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 subsequent 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^5]-enkephalin and morphine

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 blood flow was increased, but no change in serum gastrin concentration was observed. Opioids, however, inhibited the release of somatostatin from the isolated 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 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 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 stimulatory 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 under these particular conditions. Consistent 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 recordings from the infranodose vagus nerve in vitro. An opioid influence on vagal function may nevertheless contribute 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 et al. (212) also reported an inhibition of sham feeding-induced gastric acid secretion in the gastric fistula dog by similar doses of [Met^5]-enkephalin administered by continuous i.v. infusion. Similarly, i.v. [Met^5]-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. 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 opioid systems. Naloxone not only blocked the opioid effect but inhibited, when administered alone, acid secretion as compared to controls (212). Thus, opioid receptors stimulating 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 gastric acid secretion by i.v. infusion of [Met^5]-enkephalin (275), whereas inhibition of pentagastrin- or 2-DG-stimulated acid secretion in the gastric fistula dog by i.c.v. beta-endorphin (255, 254), i.v. gamma-endorphin, or beta-casomorphin-5 (415) was antagonized by naloxone.

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 fistula dog, dermorphine and morphine increased basal acid secretion after i.v. administration. This effect was blocked by naloxone as well as naltrexone methylbromide 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 morphine and dermorphin in the denervated Heidenhain pouch, and by dermorphin in the innervated main stomach with gastric fistula (419). This effect was blocked by both naloxone and N-methyl-levallorphan, again pointing 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 stomach (419). This effect of morphine was not antagonized by the peripherally acting quaternary 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 clear why Magee (265) and Soldani et al. (419) found 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. (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. 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 peripheral presynaptic inhibition of acetylcholine release or depressing the vagal center. Meal-stimulated acid secretion from the main stomach, probably a result of central vagal stimulation, was inhibited by [Met^5]-enkephalin, while no significant effect 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 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, 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, depending on the experimental conditions which may favor either central or peripheral mechanisms. Kostritsky-Pereira et al. (225) demonstrated an inhibition of pentagastrin-induced acid secretion from the innervated main stomach as opposed to an enhancement of acid

secretion from the denervated canine Heidenhain pouch by intravenously infused [Met^5]-enkephalin. These contrasting 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 similar conditions.

e. POTENTIAL INFLUENCES ON SOMATOSTATIN, GASTRIN, 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 the conscious dog, basal plasma concentrations of somatostatin were reduced by various opioids (401). A similar inhibition was found with i.v. [Met^5]-enkephalin 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) stimulated somatostatin release. In contrast to i.v. administration, intragastric administration of [Met^5]-enkephalin led to an enhancement of somatostatin release (396), while application of [Met^5]-enkephalin to the vascular 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. Correspondingly, naloxone alone had either a stimulatory (394) or an inhibitory (395) effect on postprandial somatostatin release in the conscious dog. The particular effect was again dependent on the nutrient situation. This was also found with regard to motilin-induced somatostatin release when i.v. glucose converted the inhibition by naloxone to stimulation (379). This may indicate 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 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 morphine/urethane-anesthetized dog. They concluded that an opioid-induced release of gastrin may be involved in the opioid stimulation of gastric secretion. However, the 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, peripheral histamine release and/or direct stimulatory modulation at the parietal cell (238, 237, 375) may be the mechanism underlying the enhancement of acid secretion from the denervated Heidenhain pouch. The actual mechanism, however, is not known.

f. THE EFFECT OF NALOXONE IN THE ABSENCE OF EXOGENOUS OPIOIDS. In the gastric fistula dog, naloxone did not antagonize enkephalin inhibition of either 2-DG (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 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 with the proposition of superimposed stimulatory and inhibitory opioid mechanisms in the control of gastric 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 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, enhanced and [Met^5]-enkephalin, a delta-agonist, impaired 2-DG-stimulated acid secretion (9), the authors attributed the contrasting effects to mu- and delta-receptors, respectively. This might also explain why [Met^5]-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 gastric fistula dog (9), whereas morphine and dermorphin 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 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 [Met^5]-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 [Met^5]-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 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. (413; 412) found enhancement of pentagastrin-stimulated acid secretion by continuous i.v. infusion of FK 33-824, a [Met^5]-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 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. pethidine (281), inhibition of meal-stimulated acid secretion by continuous i.v. infusion of morphine (101), inhibition

of both basal and pentagastrin-stimulated acid secretion by oral loperamide (51), inhibition of pentagastrin-stimulated acid secretion by i.v. morphine (430), inhibition of both basal and pentagastrin-stimulated acid secretion by s.c. [D-Ala^2, methyl-Phe^4-(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-Ala^2, Met^5]-enkephalin (213). Similarly, continuous i.v. infusion of both [Met^5]-enkephalin and [D-Ala^2, Met^5]-enkephalin-amide impaired acid secretion in the conscious Rhesus monkey following intragastric 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 administered 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 a meal (101), by sham feeding (213), by pentagastrin, and by 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 that an enhancement of acid secretion by endogenous opioids prevented any further enhancement by exogenous opioids, thereby promoting the appearance of an inhibitory 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 stimulatory opioid mechanisms. It would, further, either antagonize or fail to antagonize (431) acid inhibition by exogenous opioids, depending on the balance between endogenous opioid stimulation and exogenous opioid inhibition of acid secretion.

c. THE ROLE OF SOMATOSTATIN AND GASTRIN RELEASE. 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 ascribed this action to exorphins possibly released from gluten. By contrast, Schusdziarra et al. (393) demonstrated an increase in postprandial plasma somatostatin concentration upon naloxone administration, which suggests that endogenous opioids were operative 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 (101) or [D-Ala^2, Met^5]-enkephalin (213) enhanced the gastrin response to a meal and elevated serum gastrin concentration, while decreasing gastric acid secretion. Stimulation of acid secretion by gastrin was, under the experimental conditions used, evidently of minor functional 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 gastrin cells. Naloxone alone, however, never affected serum gastrin concentrations (101, 99, 412, 213).

C. Pathophysiological Aspects

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, 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 increase in gastric acid and pepsin secretion, hypotension, or local 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 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, 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 of endogenous 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 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 the conscious rat with pyloric ligation but, at the same time, also increased mucus production and decreased gastric acid secretion. Thus, the ulcerogenic mechanism remained obscure. Besides, hypoxaemia and hypercapnia, known side effects of morphine, did not cause ulceration 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), but naloxone protected against indomethacin-induced ulcerations in the rat (461a) to indicate an ulcerogenic 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 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 of 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, 138). Both groups

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 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 suppressed acid secretion stimulated by cold restraint similarly to dexamethasone (10). 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 of stress ulceration may be indirect. On the other hand, 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 development of mucosal lesions under still unknown conditions.

2. Peripheral versus central opioid effects. Since both i.p. administration of morphine methyliodide, a quaternary 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 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. morphine (83). Endogenous opioids may physiologically exert 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. administration, 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 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. Consistent 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 partially coincides with their 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 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-endorphin-like immunoreactivity from human duodenal 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 et 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 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. (424) concluded from the failure of naloxone to affect the acid 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. 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, 322). Gastrointestinal mast cells, which are storage sites for histamine in man, are affected by a variety of pathophysiological 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. Since opioids have been found to sensitize the parietal cell to histamine, and since endogenous opioids may exert a similar role within the mucosa (237), opioids intrinsic to the gastric mucosa may participate in the pathophysiology of gastrointestinal ulceration. This hypothesis, however, 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, more work is needed in this field. Halter et al. (153) demonstrated a higher sensitivity of duodenal ulcer patients to pentagastrin as an acid stimulant, compared with controls. It is 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 parietal cells demonstrate functional opioid receptors which enhance stimulated acid secretion. The effect is 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 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 modulation of both vagal acetylcholine release and its postsynaptic action. Little is known about the differential involvement of opioid receptor types in the different

opioid mechanisms. In the rat, both central and peripheral opioid mu-receptors inhibit, while peripheral kappa-receptors stimulate gastric acid secretion. No role of delta-receptors was detected. In the dog, however, available 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 superimposition of functionally contrasting 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 instantly be seen after lower opioid 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 may contribute to the enhancement of acid secretion if stimulated 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.

Apparent discrepancies between data from different laboratories may be best explained by differences in experimental conditions. These include anesthesia versus consciousness, innervated main stomach versus denervated Heidenhain pouch, basal secretion versus exogenously stimulated secretion, different stimulants and dose levels, central versus peripheral stimulation, access 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 superimposed. 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 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 opioid agonists predominantly stimulate acid secretion in the dog in 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 rat in vivo, stimulation by naloxone alone again points 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 fashion, yielding apparently contradictory results. In addition to a peripheral dual effect, a central action may be present with both an ulcerogenic and antiulcer component in the rat. At present, there is no 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 opioid influences on mucosal ulceration may be caused by differing experimental conditions. This refers particularly to the chemical stimulants and procedures used to experimentally 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 opioids. Since histamine plays a key role in the control of acid secretion and may produce mucosal lesions under pathophysiological conditions, an enhancement of this histamine-stimulated acid secretion in guinea pig and rat parietal cells deserves further attention.

V. The Role of Opioids in the Control of Intestinal Water and Electrolyte Secretion and Absorption

A Small Intestine: Guinea Pig; Rat; Rabbit; Dog; Pig; and Man

Evidence has accumulated in the past that opioids stimulate, as an important component of their antidiarrheal action, the net absorption of water and electrolytes in the small and large intestine in several species, including man. Most of the data do not allow the distinction 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 OF OPIOIDS AND NALOXONE 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 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 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 similarly, 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 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 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 effects of opioids in vitro were mediated by opioid delta-receptors as opposed to mu- and kappa-type receptors. 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 enkephalin effect. López-Ruiz and Prieto (260) found both high-affinity (K_d in the range of 0.1 to 2.0 nmol/liter) and low-affinity (K_d in the range of 10 to 70 nmol/liter) binding of [^{3}H-Leu^5]-enkephalin to isolated enterocytes in all parts of the guinea pig small and large intestine. Binding was saturable. Displacement was achieved specifically by [Leu^5]-enkephalin with [Met^5]-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 [Leu^5]-enkephalin binding site is still unclear. It should be recognized in this context that membrane receptors may well be altered upon cell 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 intestinal secretion. Sato et al. (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 of acetylcholine release from the submucosal plexus, which stimulates intestinal secretion, may be another mode of the antisecretory opioid action.

Although tolerance to the antisecretory enkephalin 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 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 from morphine-dependent rats, although it did elicit withdrawal diarrhea in vivo. The situation is reminiscent of the mouse vas deferens contractions. Here, again, neurons which may develop opioid dependence are extrinsic to the organ (390).

2. Rat. a. SPECIFICITY AND LOCATION OF THE ANTISECRETORY 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 under basal conditions (21, 85, 466, 113, 465), and after stimulation by PGE_1 (66, 253, 22), VIP (21, 249), or cholera toxin (38, 39). The opioid effect was antagonized by naloxone or naltrexone. In contrast to levorphanol, 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 intact rat (21), not in the tied-off jejunal loop (18). It may, therefore, represent opioid inhibition of pancreatic (214) rather than intestinal secretion.

Whereas the increase in intestinal fluid volume by 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 muscarinic 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 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 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 proposition of a presynaptic action is, further, consonant with opioid inhibition of acetylcholine release from the submucosal 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-receptors (302) remains speculative due to the poor receptor type selectivity of the ligands used.

The enkephalin analogue FK 33-824 inhibited PGE_1-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. administered [D-Ala^2, Met^5]-enkephalin-amide (38) increased net fluid absorption in the rat. Hence, both an intestinal and a central site of antisecretory opioid action 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 effect of loperamide by prevention of PGE-induced inhibition 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 antiabsorptive action in addition to its antisecretory action. Thus, the overall effect of loperamide may depend 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 increase in mucosal cAMP concentration as stimulated by cholera toxin (98). Since morphine, by contrast, blocked the PGE_1-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 between the modes of action of different opioids. See also section VA7.

b. INVOLVEMENT OF DIFFERENT OPIOID RECEPTOR TYPES. A comparison between potencies of the mu-agonists morphine, RX 783006, and FK 33-824, the kappa-agonists ethylketocyclazocine and MR 2034, and the

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.v. administration. Fogel and Kaplan (113) stated that naloxone, whose affinity to mu-receptors is 20 to 30 times that to delta-receptors (57, 58), antagonized (at 100 μmol/liter) the effect of morphine. Although [D-Ala^2, Met^5]-enkephalin-amide, applied at 1 μmol/liter in the intraluminal perfusate, significantly increased water absorption, this effect was antagonized only by an extremely high dose of naloxone (1 mmol/liter). However, it was readily antagonized by diprenorphine (1 μmol/liter). Diprenorphine has a high affinity to both opioid mu- and 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 opioid agonists and antagonists used. The same limitation applies to another rat study. Here, [D-Ala^2, Met^5]-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 detailed analysis.

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 μmol/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, section V A 1b), an enkephalin analogue was considerably more potent than morphine (280). All effects were blocked by naloxone. The same group (279, 448) also demonstrated opioid inhibition of PGE_2-, acetylcholine, 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 absorption by high concentrations of codeine in the rabbit ileal mucosa, McKay et al. (280) did not find any 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 suggest a neuronal site of action within the submucosal 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 [Met^5]-enkephalin binding sites on rabbit 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 TTX is not entirely clear, since it inhibited in vivo jejunal secretion by PGE_1 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 $^{22}Na^+$ and water in a naloxone-reversible manner. This increase in absorption from the isolated perfused ileal segment in the anesthetized dog was positively correlated with an increase in absorptive site blood flow as determined by ^3H_2O clearance. 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 the effect of opioids on absorptive site blood flow. As unidirectional fluxes were only determined for sodium, 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 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 segment, however, only luminal administration was effective. Morphine 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 intestinal net fluid absorption has been demonstrated in the dog (336). [D-Ala^2, Met^5]-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. administration. An additional peripheral site of action may nevertheless exist (266).

5. Pig. In the anesthetized pig, continuous luminal perfusion of isolated intestinal loops in situ with a micromolar concentration of morphine significantly stimulated net water and electrolyte absorption and impaired net secretion as stimulated by *Escherichia coli* heat-stable enterotoxin (5). Unfortunately, opioid specificity, as demonstrated by naloxone blockade, has not been tested.

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 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 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 intestine but did not increase absorption. In their discussion, however, they also made a modified statement, i.e., that codeine may increase net absorption by increasing the

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, potential 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 absorption 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 solution to induce "diarrhea." However, VIP-induced net secretion was also unaffected by codeine. The authors did not find any indication for the activity of endogenous opioids, since i.v. infusion of naloxone at 40 $\mu g \times kg^{-1} \times h^{-1}$ had no detectable effect on net absorption in the jejunum and ileum (380).

Turnberg (448) administered loperamide intraluminally 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 prostaglandin-induced secretion and, in half of the subjects, conversion to absorption. No detailed data were presented.

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 blocked by phentolamine or by pretreatment with guanethidine 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, which is known to have antisecretory function. This is supported by the findings of Coupar and Taylor (70) showing that chemical depletion of intestinal stores of noradrenaline and serotonin abolished or impaired, respectively, the antisecretory effect of i.v. morphine in the rat jejunum. Likewise, the opioid effect was impaired by the alpha-adrenoceptor antagonist phentolamine or the serotonin receptor antagonists methysergide and ketanserin.

Though atropine failed to prevent the net antisecretory effect of morphine in the rabbit isolated ileal mucosa (280), it blocked the net secretory effect of naloxone in the rat in vivo (113). The peripheral antisecretory opioid action 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 experimental conditions employed. Although opioids did not influence PG-stimulated adenylate cyclase in isolated rat enterocytes (157), this still leaves the possibility of inhibition elsewhere within the neuronal plexus. It should 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 (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 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 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 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-receptors in mouse dosal root ganglion cells are 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 hyperpolarize 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 surfactant properties and acts peripherally (486a), has been shown to inhibit calmodulin independently of its opioid properties (10a). This may be an additional mode of antisecretory action, though at relatively high concentrations.

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). Vasoconstriction by larger doses of morphine was prevented by phentolamine and was attributed to adrenaline release from the adrenal medulla. However, presynaptic inhibition, not facilitation, of noradrenaline release has been attributed to opioid delta-receptor activation in the rabbit ear artery (188). In fact, [Met^5]-enkephalin, an agonist at opioid delta- and mu-receptors, increased mesenteric blood flow in the anesthetized dog (327). In addition, Rozsa and Varro (358) found that the delta-agonist [D-Met^2, NleS^5]-enkephalin-amide enhanced, and the mu- plus delta-agonist [D-Met^2, Pro^5]-enkephalin-amide inhibited the flow-increasing effect of cholecystokinin-octapeptide (CCK-8) in the arteria ileocolica of the anesthetized dog. CCK-8 is known to release 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 as well as stimulation of adrenaline release from the

adrenal medulla, resulting in contrasting effects on mucosal blood flow. This attribution of opioid receptor types 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 intestinal loops by naloxone (100 μmol/liter) or diprenorphine (1 μmol/liter) decreased basal water and ion net absorption in vivo (113). Diprenorphine at 10 μmol/liter also decreased basal water absorption in the rat colon. Lembeck and Beubler (253) found a small net secretory effect of s.c. naloxone in the conscious rat under PGE_1 or VIP 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. 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 suggested 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 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, 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 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

[Leu^5]-enkephalin specific binding on isolated guinea pig 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 the 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 laxative bisacodyl (21). Naloxone alone had no effect. Bisacodyl 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 cAMP levels but resulted in an enhanced release of both serotonin and PGE_2 into the colonic lumen. These events were accompanied by a reversal of net fluid absorption to net fluid secretion. The latter effect was prevented by serotonin receptor blockade by ketanserin or by inhibition of PG synthesis by indometacin. Enhanced PGE_2 release was inhibited by ketanserin. The authors concluded, therefore, that opioid withdrawal might release serotonin, which in turn stimulates PGE_2 synthesis with 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 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 PGE_2-stimulated colonic adenylate cyclase activity. In contrast, 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 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, this hypothesis lacks support, since atropine failed to counteract net fluid secretion in the rat colon due to naloxone-precipitated morphine withdrawal (18a), although it prevented the net secretory effect of naloxone in the rat small intestine in vivo (113).

C. Bicarbonate Secretion

Flemström et al. (111, 112) demonstrated in the anesthetized rat in situ that morphine, beta-endorphin, [Met^5]-enkephalin, and [Leu^5]-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 stimulation was 100% above controls and blocked by naloxone. Although [D-Ala^2, D-Leu^5]-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 bind with high affinity to both delta- and mu-receptors (328a). This discrepancy remains therefore unexplained. Interestingly, naloxone alone did not affect basal bicarbonate secretion, but impaired secretion induced by brief exposure of the duodenal mucosa to low pH (112). This may indicate a possible role of endogenous opioids in the mediation of acid-stimulated duodenal bicarbonate secretion as a means of mucosal protection.

Rees et al. (346) found no influence of opioids or naloxone on bicarbonate secretion from amphibian gastric mucosa in vitro. However, morphine and [Met^5]-enkephalin significantly stimulated amphibian duodenal bicarbonate secretion at concentrations in the micromolar 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 concentrations. This may point to the involvement of opioid 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 receptors are located on neurons not mucosal cells. Neuronal activity may indeed be necessary for the opioid

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-piperazineethanesulfonic 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, 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 mucosal tissue. The proposed mechanism is reminiscent of an unidentified ion flux elevated by morphine in 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 mucosal tissue with adherent submucosal plexus. However, it is not clear why Barbezat and Reasbeck (12), in studies on dog jejunum, found increased net bicarbonate absorption instead of secretion upon i.v. infusion of [Met^5]-enkephalin.

D. Conclusions

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 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 Krueger (244). The intestinal net antisecretory action of opioids 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, cholera 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, 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 electrolyte net absorption. This central effect may be mediated by stimulation of the sympathetic nervous 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 participation of mu-receptors. In the isolated tissue, relevant receptors are probably located within the submucosal plexus, as evidenced by sensitivity of the opioid effects to tetrodotoxin. Enterocytes may additionally carry functional opioid receptors, but this needs further clarification.

Whether peripheral action involves an impairment in adenylate cyclase activity stimulated by, e.g., PGE, is controversial. Opioid inhibition of acetylcholine release 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 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 determine 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 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 naloxone, and is sensitive to tetrodotoxin, pointing to neuronal mediation.

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 indicate 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 mucosa to low pH and may, thus, be involved physiologically in 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, and the central nervous system. Since various neurotransmitter as well as neurohormonal systems are known to modulate gastrointestinal 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 opioids, although many unresolved questions and contradictory results await further attention. As to potential pathophysiological states which might involve imbalances in 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 observed under 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, 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 contrasting opioid effects may then define species differences. Hence, these appear quantitative rather than qualitative in nature. They might wrongly be considered qualitative if only the extremes of the whole spectrum of laboratory

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 inhibitory 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 interdependence between gastrointestinal 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 gastrointestinal wall, vagal activation, acetylcholine, histamine, gastrin, bile salts, or cholera toxin elicit both contractile and secretory responses. On the other hand, noradrenaline inhibits gastrointestinal motility, gastric acid, and 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 increase and 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 intereactions 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, 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 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 concentration which, in man, was prolonged by morphine (55). Inhibition of acetylcholine release from the myenteric 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 conflicting 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 gastrointestinal 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 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 different parameters may be determined simultaneously in the same animal by constructing dose-response curves. More attention should be given to this problem in future experiments, though the task is difficult.

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, 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 control of gastrointestinal functions. This is a great challenge for future work. Diminished acid secretion (90) plus impaired gastric motility might increase the risk of bacterial overgrowth in the stomach. It might be speculated therefore that, under special circumstances, the antimotility effect of endogenous opioids may go along with the acid secretory effect. Hibernation may exemplify a particular stage 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 involvement of endogenous opioids in hibernation was suggested (228) and has been supported by recent findings (39a), it 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 sometimes contradictory opioid actions, to put them to clinical use.

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