GASTROINTESTINAL PHARMACOLOGY

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Control of gastrointestinal function is accomplished by a diverse extrinsic autonomic innervation, a sophisticated intrinsic neural system, extramural humoral influences, and a plethora of hormones produced by the gastrointestinal organs themselves. Because drugs generally do not create new physiological or biochemical functions, they are useful only insofar as they modify ongoing processes. In the gastrointestinal tract, drugs modify mainly the various mechanisms that control secretion and motility. Unfortunately, often so little is known about the gastrointestinal tract that understanding of drug actions seems difficult or impossible and pharmacology is still presented in descriptive terms. While certainly the answers to the major problems in gastrointestinal pharmacology are not yet available, perhaps we can gain some satisfaction from the belief that at least the quality of the questions is improving.

GASTRIC SECRETION

Previous empirical approaches to the treatment of diseases in which decreased gastric acid secretion might offer benefit have been either ineffective because of inherent limitations in the drugs themselves or have been directed at the result, not the cause, of the disorder. The use of atropine, which is completely rational, is usually ineffective because of dosage limitations (1). We therefore rely heavily on neutralization of secreted acid; this approach completely ignores the control mechanisms involved in gastric secretion and in fact increases secretory stimuli (2).

The primary stimulus for gastric acid secretion is the gastrointestinal hormone, gastrin (3–6). Gastrin is present in the mucosa of the antrum of the stomach and, decreasing caudally, in the small intestine; it is also present in the pancreas (6). Gastrin occurs in several molecular forms. The forms isolated from antral mucosa are heptadecapeptides known as gastrins I and II (gastrin II differs from I only in

that the tyrosine residue in position 12 is sulfated), or frequently as the "little gastrins," with molecular weights of approximately 2,100. The principal molecular species of gastrin in the circulation, "big gastrin," has a molecular weight of approximately 7,000 (6). Big gastrin is a major component of gastrin extracted from intestinal mucosa. A third gastrin, delightfully called "big, big gastrin," has been isolated from serum and jejunal mucosa and has a molecular weight of approximately 20,000 (7). A "minigastrin" of 13 amino acid residues has also been identifed (3). A stimulating account of the discovery and identification of gastrin and other gastrointestinal hormones was published recently (3).

Stimuli for the release of gastrin include alkaline pH of the antral contents, mechanical distention of the antrum, neural acetylcholine, and the presence in the antrum of food, particularly proteins and amino acids (4). The acetylcholine released by vagal stimulation causes the release of antral gastrin and also has a direct stimulatory effect on the parietal cells. The negative feedback control that inhibits gastrin release is acid in the stomach antrum. The regulation of release of intestinal gastrin is less well understood (6).

Gastrin stimulates acid secretion by interacting with a gastrin receptor in the parietal cell. This receptor, but not receptors for acetylcholine or histamine, is blocked by secretin (8). Gastrin and other gastric secretagogues may stimulate acid secretion through activation of parietal cell adenylate cyclase with subsequent increases in intracellular cyclic adenosine monophosphate (cAMP). The arguments for and against a role of cAMP in gastric acid secretion are presented in the comprehensive review by Kimberg (9).

The logical points for pharmacological modification of gastric acid secretion are the control mechanisms for gastrin release, gastrin interaction with the parietal cell, and the events that lead to acid secretion subsequent to that interaction.

H_2 Receptor Blockers

The relative inability of conventional (H_1) antihistamines to block the gastric secretory and certain other effects of histamine is part of the treasured lore of pharmacology. In the belief that the non-H_1 effects of histamine represent actions on a second kind of histamine receptor, Black and his colleagues designed and tested hundreds of compounds for gastric antisecretory activity. The success of their effort (10) not only provided a valuable new class of pharmacological tools and potentially useful therapeutic agents, but also stands as a tribute to scientific perseverence and rational drug design. The gastric antisecretory actions of the H_2 receptor antagonists have recently been reviewed (11); only the significant studies that have appeared since that thorough review are discussed here.

Studies of H_2 receptor antagonists have focused on burimamide and metiamide. A third promising agent, cimetidine, was only recently described (12). The gastric antisecretory effects of burimamide and metiamide have been confirmed in animals and man (13–15). In addition to inhibition of acid secretion, burimamide and metiamide also reduce gastric mucosal blood flow. Since there is a close relation between acid secretion and gastric mucosal blood flow (16), the question arose whether the inhibition of histamine-induced acid secretion by the H_2 receptor antag-

onists could be due to inhibition of mucosal vasodilatation through an effect on vascular H_2 receptors (17). Studies in dogs with gastric fistulas and Heindenhain pouches demonstrated that while metiamide decreased mucosal blood flow, the ratio of aminopyrine concentration in the gastric juice and blood plasma was not changed by metiamide (18). This result indicated that the reduction in gastric mucosal blood flow was secondary to the inhibition of gastric secretion induced by metiamide. In anesthetized cats with acute gastric fistulas, burimamide and metiamide reduced acid secretion more than they reduced gastric mucosal blood flow (19, 20). Finally, metiamide was shown to inhibit stimulated acid secretion in isolated gastric mucosa of frog and isolated stomach of rat, preparations in which blood flow was not a consideration (17). It now appears, therefore, that the basic effect of the H_2 receptor antagonists on gastric acid secretion is exerted directly on the acid secretory mechanisms in the gastric mucosa. An additional contributory effect of reduced gastric mucosal blood flow, however, cannot yet be ruled out. Some portion of the gastric antisecretory effect of burimamide, but not metiamide, may be attributable to release of catecholamines (19).

In their original study of the antisecretory effects of burimamide, Black et al (10) found it to be effective against gastric acid secretion induced by histamine, pentagastrin, and feeding, but not against secretion induced by reflex or direct vagal stimulation. It is now apparent, however, that metiamide inhibits also the gastric acid secretion induced by vagal stimulation, bethanechol, and methacholine (14, 18, 21–25). Acid output induced by pentagastrin, bethanechol, methacholine, reflex vagal stimulation, feeding and caerulein, but not by histamine, is antagonized also by atropine (18, 24, 25). These data indicate an anticholinergic component of metiamide action, a nonspecific gastric antisecretory effect, or some complicated interaction of H_2 receptors with those for acetylcholine and gastrointestinal hormones. Both cholinergic and histaminergic links in the acid secretory responses to food, vagal stimulation, and gastrin-like gastrointestinal hormones could be postulated. The histamine receptor would be more proximal to the secretory mechanism than the cholinergic receptor, thus explaining the ability of metiamide to antagonize all the stimuli tested and the ability of atropine (in dogs and cats) to inhibit all but the histamine stimulus. Grossman & Konturek (25) have proposed a far more provocative hypothesis to account for the data. According to this hypothesis, the parietal cell has separate receptors for histamine, acetylcholine, and gastrin. Blockade of one receptor may change the properties of one or both of the other two receptors. For example, blockade of the histamine receptor by metiamide, or blockade of the acetylcholine receptor by atropine, would change the properties of the gastrin receptor so that stimulation by pentagastrin would be less effective. This interesting hypothesis is worthy of testing by appropriate pharmacological techniques. One result of the studies with atropine and metiamide, as pointed out by Grossman & Konturek (25), is the conclusion that it is not necessary for a drug to be an effective antagonist of histamine for it to inhibit acid secretion in response to a meal. The reason that atropine has relatively little practical therapeutic value in depressing gastric acid secretion in patients with duodenal ulcer is not because it does not have a broad enough spectrum of stimulants against which it is effective. It is

therapeutically ineffective because it cannot be used in high enough doses to provide the desired degree of inhibition of acid secretion without intolerable side effects.

Prostaglandins

Despite their varied effects on the gastrointestinal tract, it is the actions of prostaglandins on gastric secretion where hope for therapeutic utility has largely focused. It has been known for several years that several prostaglandins (particularly E_1 and E_2) can inhibit gastric secretion (26). Studies in man were disappointing in that the natural prostaglandins exhibited no antisecretory activity when administered orally and produced undesirable side effects when administered intravenously. These effects of the prostaglandins have been reviewed extensively (27–30). The oral inactivity of the natural prostaglandins results from their breakdown by prostaglandin 15-hydroxydehydrogenase. Several prostaglandin analogs resistant to this enzyme have been developed (31). 15-Methyl-PGE_2-methyl ester (R and S isomers) and 16:16-dimethyl-PGE_2-methyl ester are active orally and are more potent than the natural prostaglandin E_2 (32). After intragastric administration in man, 15(S)-15-methyl-PGE_2-methyl ester, 16:16-dimethyl-PGE_2, and 16:16 dimethyl-PGE_2-methyl ester inhibited spontaneous and pentagastrin-induced gastric acid secretion (33, 34). When administered into the intestine, however, these compounds were considerably less effective than after intragastric administration (35). The 16:16 dimethyl-PGE_2 analogs were virtually inactive when given into any part of the human upper small bowel, yet 16:16 dimethyl-PGE_2 did inhibit dog Heidenhain pouch acid secretion following administration into the jejunum (32). The curious inactivity of the methyl prostaglandins after intraintestinal administration in man may indicate chemical instability in the intestinal environment or raises the possibility of a direct, local effect of these agents on the oxyntic glands. At high doses, the methyl prostaglandin derivatives can decrease stomach and intestinal motility (36). Three other synthetic prostaglandin analogs, 15-hydroxy-9-oxoprostanoic acid, 15-hydroxy-15-methyl-9-oxoprostanoic acid, and 15-hydroxy-15-methyl-9-oxoprostanoic acid methyl ester, inhibited gastric acid secretion when administered parenterally in rats, but the compound lacking a 15-methyl substitution was not effective when administered orally (37). The synthetic analogs of the prostaglandins may hold great promise as effective gastric antisecretory agents if they do not produce prostaglandin-like side effects, such as diarrhea, in further clinical trials.

Although there are differences in degree of inhibition, prostaglandin E_1 has a broad spectrum of inhibitory activity against several secretagogues, including carbachol, direct and reflex vagal stimulation, histamine, pentagastrin, and food (11). Since their antisecretory activity appears not to result from changes in mucosal blood flow (38), the prostaglandins may act by interfering with events that couple parietal cell stimulation to acid secretion. Prostaglandins could alter activity of adenylate cyclase or membrane permeability to ions, or act as feedback inhibitors (9, 11, 28). Whether or not prostaglandin derivatives will ever serve as useful therapeutic antisecretory agents, understanding their mechanism of action will represent a major advance in gastrointestinal pharmacology.

Gastrointestinal Hormones

Perhaps the most promising method for control of gastric secretion will occur as a result of advances in knowledge about the physiology and biochemistry of the endogenous gastrointestinal hormones. There are three generally recognized gastrointestinal hormones: gastrin, secretin, and cholecystokinin (CCK). There are also a number of what Grossman (39) has called "candidate hormones." The candidate hormones include chymodenin, gastric inhibitory peptide, motilin, vasoactive intestinal peptide, coherin, urogastrone, gastrone, bulbogastrone, duocrinin, enterocrinin, enterogastrone, enteroglucagon, incretin, and villikinin. The list could be extended by including potential hormones postulated on the basis of physiological evidence but for which chemical evidence is so far absent.

A great deal is known about the effects of the three established hormones on gastrointestinal function and on processes elsewhere in the body. Some of these effects are summarized in Table 1. In the table, no distinction is made between low-dose and high-dose effects of the hormones. The effects of gastrin on release of insulin and on intestinal contractions, for example, may be observed only with high doses and may not represent physiological actions (3). Since the gastrointestinal hormones exhibit such a variety of effects, there is frequent disagreement about "physiological" and "pharmacological" effects. One of the more interesting controversies concerns the potential role of gastrin in maintenance of tone in the lower esophageal sphincter (49–52).

The role of gastrin in acid secretion is reviewed above. CCK is a 33 amino acid polypeptide hormone that has been prepared in pure form from duodenal mucosa (44). The major stimulus for release of CCK is entry of peptides, amino acids, and especially fats into the small bowel. CCK shares many of the physiological properties of gastrin and can be considered a member of the gastrin family of hormones (3). In the rat and cat, CCK is a full agonist at parietal cell gastrin receptors and

Table 1 Effects of gastrointestinal hormones on selected functions of the gastrointestinal tract

	Gastrin	Cholecystokinin	Secretin
Secretion			
Gastric			
H+	increase (3)	partial agonist (3)	decrease (3, 48)
Pepsin	increase (3)	none (3)	increase (3, 48)
Intestine	increase (3)	increase (39)	increase (3)
Pancreas	increase (3)	increase (3)	increase (3)
Bile flow	increase (3)	increase (44)	increase (3)
Insulin release	increase (3)	increase (45)	increase (3, 45)
Motility			
Lower esophageal sphincter	contraction (3)	relaxation (46)	relaxation (3)
Gastric			
Contractions	increase (40)	decrease (44)	decrease (48)
Emptying	delayed (41)	delayed (44)	delayed (3, 48)
Intestinal contractions	increase (3, 4, 42)	increase (47)	decrease (3, 42, 47)
Gastrointestinal blood flow	increase (43)	increase (43)	increase (3, 48)

can stimulate gastric acid secretion as strongly as gastrin (3). In dog and man, CCK is a partial agonist; given alone it evokes only a small response and, given in conjunction, it inhibits the response to gastrin (3). Caerulein, a decapeptide, has physiological activity almost identical with the C-terminal octapeptide of CCK.

Secretin is a 27 amino acid polypeptide hormone present in high concentration in the upper portion of the small bowel (4). While products of fat and protein digestion may stimulate secretin release, the major stimulus for its release is the presence of hydrochloric acid within the proximal small bowel (4). Secretin induces the secretion of water and electrolytes by the pancreas. As the volume increases, so does the bicarbonate concentration. In addition to providing the alkaline pancreatic juice that neutralizes the acid gastric contents as they pass into the duodenum, secretin also inhibits the action of gastrin on the parietal cell, as mentioned above, and inhibits the release of gastrin from the stomach antrum (3).

Two candidate gastrointestinal hormones, gastric inhibitory peptide (GIP) and vasoactive intestinal peptide (VIP), share several actions of secretin and can be thought of as members of the secretin family (3). GIP is a 43 amino acid polypeptide obtained from duodenal mucosa (3, 53). GIP is effective in inhibiting gastric acid secretion stimulated by pentagastrin, histamine, and reflex vagal stimulation (53). VIP is a 28 amino acid polypeptide isolated from hog intestine (54). Although it shares some physiological actions with secretin, such as ability to inhibit both histamine- and pentagastrin-induced acid secretion, VIP also has properties unlike those of secretin. For example, VIP is a potent vasodilator and it inhibits gastric pepsin secretion (53). The hormonal role of VIP is in doubt because it is largely inactivated in passing through the liver (55). Other candidate gastrointestinal hormones capable of inhibiting gastric acid secretion have been postulated (39).

A recent arrival on the gastrointestinal hormone scene is growth hormone–release inhibitory hormone (GH–RIH) or somatostatin. It is a 14 amino acid polypeptide first isolated from hypothalamic nuclei but now known to be present in rat pancreas and stomach (56). Evidence to date indicates that GH–RIH inhibits release of growth hormone, thyroid-stimulating hormone, insulin, glucagon, and gastrin. In dogs, cats, and humans, GH–RIH inhibited gastric acid secretion in response to histamine, pentagastrin, and feeding (57, 58). The inhibitory effect was most pronounced with food-induced acid secretion and was least prominent against histamine. Although conclusions must await establishment of dose-response relationships, the efficacy against food-stimulated acid secretion could be due to a combined effect on release of gastrin and on the parietal cell.

Directions for the Future

It would appear that several means exist by which gastric acid secretion should be subject to modification by drugs. Endogenous substances, such as secretin and GH–RIH, are capable of inhibiting release of gastrin and thereby reducing the primary stimulus for acid secretion. Secretin, gastric inhibitory peptide, vasoactive intestinal peptide, GH–RIH, and H_2 receptor antagonists may decrease acid secretion by interference with the ability of gastrin and other secretagogues to interact effectively with their parietal cell receptors. Certain natural prostaglandins and their

synthetic derivatives appear to decrease acid secretion by virtue of actions on secretory mechanisms that are distal to parietal cell receptor activation.

All three of these approaches to prevention of acid hypersecretion call for a greater investment by pharmacologists in analysis of the control mechanisms responsible for gastric secretion. The likely dividends may include highly selective and effective drugs for precise modulation of specific secretory events.

MOTILITY

The primary myogenic control of gastrointestinal motility results from the electrical slow waves generated in the longitudinal layer of smooth muscle. Neurogenic control is exerted primarily via the neurons of the myenteric plexus and determines whether spike potentials will be initiated by the depolarization phase of the slow waves. Spike potentials are associated with muscle contractions (59, 60). Excitatory stimuli, such as release of acetylcholine from myenteric nerves, raise the level of excitability of the muscle and promote spike bursts and contractions. The distribution in time and space of contractions is determined by the slow wave or control electrical activity (59). Propulsion of intestinal contents requires an aboral net pressure gradient (59) and results from the sum of many separate events. These events require neural, muscular, and temporal integration for proper regulation of flow. The integration occurs over long periods of time and across large distances. The dimensions differ considerably from the rapid events of the cardiac cycle or the short distances of the capillary.

Extrinsic Control

Neural control of gastrointestinal motility occurs primarily from the activity of the intrinsic nerves which are subject to modulation by the extrinsic innervation. Electrical stimulation of vagal or sympathetic nerves or local field stimulation can provoke both excitatory and inhibitory effects in the stomach and intestine (61–65). Signals over the extrinsic nerves originate in the central nervous system after appropriate afferent input. Perhaps the most striking example of extrinsic modulation of motility is the intestinal interdigestive myoelectric complex, first described by Szurszewski (66). The complex consists of distinct bands of electrical burst activity and segmenting contractions that migrate aborally in a cyclic fashion in fasted animals. Each band is approximately 25–35 cm long and requires 5–7 min (depending on part of intestine involved) to pass a point in the bowel. The bowel is quiet after passage of a complex; activity increases again as the subsequent complex develops. As one complex reaches the ileum, another develops in the duodenum (66). The complex is under extrinsic control, mediated probably over sympathetic nerves, since Thiry-Vella loops of bowel taken out of continuity still display the characteristic pattern at the appropriate time in the passage of the activity down the remainder of the small intestine (67). The interdigestive myoelectric complex has implications for drug studies of intestinal motility. Ideally, the effects of drugs on motility should be characterized in unanesthetized animals against defined backgrounds of fed or fasting motility patterns.

Presumptions of extrinsic control over specific motility patterns frequently are shown to be unfounded. Such may be the case with esophageal peristalsis. Because the peristaltic wave in the esophagus travels over a relatively long distance and requires several integrated events in the musculature of the esophagus and the lower esophageal sphincter, it was thought to represent an extrinsically controlled, preordained motility pattern (68). The idea of medullary control over the mechanical events of swallowing was based primarily on studies in dogs and other species whose esophagi are composed of striated muscle. Recent studies in the opossum, in which, like the human, the distal two thirds of the esophagus is composed of smooth muscle, refute the classical view of central control (69). These studies demonstrate that electrical stimulation of the distal end of the divided vagus nerve induced fully coordinated, propagated peristaltic contractions in the body of the esophagus. The results indicate that esophageal peristalsis is under the control of local intrinsic mechanisms rather than the central nervous system. In order to avoid cardiac responses to vagal stimulation, the animals in this experiment were treated with 0.1 mg/kg of atropine. This may indicate that the local control mechanisms are noncholinergic.

Intrinsic Control

The most familiar intrinsic neural reflex of the intestine is the peristaltic reflex. This reflex requires simultaneous ascending contraction and descending inhibition of the circular muscle (70). The neural basis for descending inhibition has been established by intracellular recordings from the myenteric plexus (63). In the cat colon, atropine can impair propulsion by selective blockade of the descending inhibition (71), which thus seems to contain muscarinic cholinergic receptor links. The descending inhibition associated with propulsion in the large intestine appears to involve a nonadrenergic inhibitory system (71).

Extracellular recordings from ganglion cells in cat small intestine myenteric and submucous plexuses before and after exposure to drugs suggested the presence of cholinergic excitatory neurons, tonic inhibitory neurons, and adrenergic fibers that synapse with nonadrenergic inhibitory neurons (72). Excitatory myenteric neural pathways with transmitters other than ACh or 5-hydroxytryptamine (5-HT) may exist (73). Tonic inhibition of gut circular muscle can be revealed by tetrodotoxin even during blockade of cholinergic and adrenergic receptors (74, 75). The hypothesis has been put forward that adenosine triphosphate or related nucleotides may be the transmitters released by the nonadrenergic inhibitory neurons (76).

Humoral Control

The gastrointestinal hormones deserve special attention as potential physiological modulators that are subject to pharmacological intervention. They may also be important as mediators of some indirect actions of existing gastrointestinal drugs. The actions of catecholamines on gastrointestinal motility have been reviewed previously (77).

In addition to its effects on gastric secretion, gastrin has effects on gastrointestinal motor activity. Gastrin can increase tone of the lower esophageal sphincter (78);

increase antral slow wave activity; increase force of antral contractions, yet delay gastric emptying (41); and, in relatively high doses, increase spike bursts and contractile activity of intestine (42). The effect of gastrin on tone of the lower esophageal sphincter is particularly noteworthy. Gastrin release during the gastric phase of digestion may help tighten the sphincter against esophageal reflux. Also, the role of antacids in treating esophageal reflux may be not only to neutralize acid, but to strengthen the sphincter by inducing the release of endogenous gastrin (79).

Secretin reduces gastric motility, delays gastric emptying, decreases intestinal motility, and causes relaxation of the lower esophageal sphincter (4, 42). As in the case of gastric acid secretion, secretin appears to be a competitive inhibitor of the stimulant effect of gastrin on the lower esophageal sphincter (78).

Cholecystokinin (CCK), caerulein, and the C-terminal octapeptide of CCK exhibit essentially identical diverse actions on gastrointestinal motility. Like secretin, CCK produces dose-related decreases in lower esophageal sphincter pressure (46). Upper small bowel activity in humans was stimulated by CCK and inhibited by secretin (47). The motility effects of the two hormones were mutually antagonistic, but too few dose levels were tested to allow conclusions about mechanisms. In isolated ileum of rabbit, caerulein increased spike bursts associated with contractions of the circular muscle (80). The effect of caerulein on spike bursts and muscle contraction was abolished by tetrodotoxin. When administered to mice, caerulein enhanced transit through the intestine, but delayed gastric emptying (81).

The mechanisms by which the gastrointestinal hormones produce their motility effects are not established, but progress in that direction is being made. The experiments of Lecchini & Gonella (80), for example, suggest that intrinsic nerves participate in motor responses to caerulein. This suggestion has been confirmed in other experiments. The guinea pig ileum contractor effects of CCK, CCK-octapeptide, caerulein, and pentagastrin were virtually abolished by tetrodotoxin (82). There seems to be a difference between the modes of CCK stimulation of intestine and gall bladder. Contractions of guinea pig ileum induced by purified CCK were blocked by low concentrations of atropine, but even at 500 times higher concentration, atropine failed to block CCK-induced contractions of gall bladder strips (83). CCK-induced contractions of guinea pig ileum were not blocked by hexamethonium. The contracting effect of CCK on gall bladder appears to be a direct effect, that on intestine an indirect effect. Vizi et al (84) examined the mechanism of stimulatory action of caerulein, CCK-octapeptide, gastrin, and pentagastrin on longitudinal muscle (with myenteric plexus) of guinea pig ileum. The contractor effects of all four peptides were blocked by atropine, tetrodotoxin, and morphine. The peptides were found to release acetylcholine, confirming the involvement of cholinergic nerves in the response. Norepinephrine, presumably by a presynaptic action, decreased responses to the peptides. This suggested that the neural pathway activated by the peptides contains ganglia, but the peptide effects were not blocked by hexamethonium. The intestinal effect of CCK and related peptides seems similar in some respects to those of 5-HT, which may act upon intramural cholinergic ganglia by activation of a receptor distinct from the nicotinic cholinergic receptor (85). This mechanism was subsequently confirmed in a model set of experiments (86). Guinea

pig ileum longitudinal muscle was stimulated by CCK-octapeptide, caerulein, nicotine, and dimethylphenylpiperazinium (DMPP). All four agents were found to release acetylcholine, and their contractor effects were blocked by atropine. Nicotine and DMPP contractions were blocked by hexamethonium; contractions induced by CCK-octapeptide and caerulein were not. Participation of 5-HT in the responses to the peptides was ruled out by 5-HT receptor desensitization experiments. Responses to the peptides were prevented by ganglionic depolarization with large concentrations of nicotine. To demonstrate that the blocking effect of nicotine was due to depolarization, the action of nicotine was prevented by prior administration of hexamethonium. In the presence of hexamethonium and nicotine, CCK-octapeptide exerted its usual effects. The author concludes from these experiments that parasympathetic ganglion cells in the myenteric plexus contain receptors for CCK and related peptides. While this is certainly the most likely explanation, the experiments do not rule out another mode of action involving ganglionic transmission but not nicotinic cholinergic receptors.

Indirect evidence was presented recently that some intestinal effects of *cis*–fatty acids could be due to release of CCK (87). The fatty acids, including *cis*-ricinoleic acid, caused initial stimulation, then prolonged inhibition, of upper small bowel motility. Intravenous CCK-octapeptide produced similar effects. The stimulatory effects of ricinoleic acid (the active ingredient of castor oil) and CCK-octapeptide were both blocked by atropine (because atropine alone inhibited motility, the inhibitory phase of ricinoleic acid or of CCK-octapeptide action could not be observed after atropine). This report is almost surely the first of many that will implicate gastrointestinal hormones as participants in responses to drugs.

Narcotic Drugs

The intestinal effects of narcotics have been studied primarily from two different points of view: (*a*) as a model system to understand actions of narcotics in the central nervous system and (*b*) as a means of improving understanding of gastrointestinal pharmacology and physiology with the aim of perfecting therapeutic modalities in humans. The guinea pig ileum, for better or worse, has frequently been the object of investigations intended for extrapolation to the central nervous system. Morphine and related narcotic drugs decrease release of acetylcholine from guinea pig lieum and thus decrease responses of the preparation to 5-HT and electrical field stimulation (88). It would be easy to attribute the constipating effect of morphine to a decrease in intestinal motility. In mammalian species other than the guinea pig, however, morphine in fact increases intestinal contractile activity and, except sometimes in high doses (89), does not block responses to 5-HT (90, 91). The increase in intestinal tone and motility induced by morphine retards propulsion through the bowel (92), increases resistance to flow of bile through the choledochoduodenal junction (93), and contributes to a delay in gastric emptying (89, 94).

The mechanisms by which morphine and related opiates produce their intestinal effects are becoming clarified. In isolated segments of dog small intestine perfused via the vasculature with a physiological salt solution (95), morphine and similar narcotics produce tonic and phasic contractions essentially identical with those recorded in situ. This demonstrates that the major component of morphine con-

tractile activity results from a direct effect on the intestine. The contractions produced by the opiates were associated with release of 5-HT (96). Narcotic-induced contractions and release of 5-HT were dose related, stereospecific (97), and blocked by naloxone (98). The stimulatory effects of narcotics in dog intestine appear to be due largely to mobilization of endogenous 5-HT (85). The 5-HT released by morphine stimulates intestinal smooth muscle directly and by activation of intramural cholinergic neural elements. Tetrodotoxin, atropine, methoxamine, and bufotenidine block the neural component of the response (85, 99–101). Although 5-HT does not stimulate nicotinic cholinergic receptors, the neural pathway acted upon by 5-HT contains ganglia (85, 102). Isoproterenol, prostaglandin E_1, and theophylline selectively inhibit intestinal responses to 5-HT and morphine (99, 101). This observation led to a proposal that the direct component of 5-HT action on intestinal smooth muscle results from interference with cAMP tonic inhibition.

The 5-HT hypothesis of morphine action on the dog intestine does not explain why morphine is constipating and 5-HT generally is not. The intestinal pressure gradient required for aboral flow through the gut results primarily from the gradient of circular muscle contractions at frequencies determined by electrical slow wave activity (59, 60, 103). Yet morphine, 5-HT, and cholinergic drugs produce grossly similar spike bursts and circular muscle contractions (104, 105). Close examination, however, often reveals slightly different patterns of circular and markedly different patterns of longitudinal muscle contractions induced by morphine and bethanecol (85, 105, 106). The interactions between longitudinal and circular muscle layers are still controversial (107–109), but differential drug effects on the two muscle layers could account for some of their different effects on intestinal flow. Only the intestinal stimulatory effect of morphine may be due to 5-HT release, and even this hypothesis should be questioned if a treatment blocks the intestinal stimulatory effect of 5-HT without reducing responses to morphine.

The inhibitory effect of opiates on guinea pig ileum results from inhibition of release of acetylcholine. Nicotine-, caerulein-, pentagastrin-, and 5-HT-induced increases in neuronal firing rate in myenteric plexus of guinea pig ileum were blocked by morphine (110, 111). The site of action of morphine appears to be on the postganglionic nerve fibers that secrete acetylcholine toward the muscle (112, 113). Indomethacin also can inhibit twitches in electrically stimulated guinea pig ileum. Ehrenpreis et al (114) have postulated that morphine and indomethacin interfere with an essential prostaglandin link in secretion of acetylcholine from intramural postganglionic nerve fibers. According to this theory, indomethacin inhibits prostaglandin synthesis, and morphine acts as a prostaglandin antagonist at a neural receptor. Evidence has been presented, however, that the indomethacin inhibition of contractions results from indirect effects (disinhibition) on intramural inhibitory adrenergic nerves (115). Morphine does not alter release of norepinephrine from guinea pig ileum myenteric plexus (116).

Tolerance to Narcotics

Tolerance to the intestinal effects of morphine and related opiates has been demonstrated often in guinea pig ileum (117–121). The mechanism by which tolerance to morphine develops in guinea pig ileum has been pursued in a series of related

investigations (120, 121). These investigations were based on the knowledge that opiates decrease acetylcholine release from electrically stimulated guinea pig ileum (88, 122) as well as the striking similarity of potency rank order of several opiates in this preparation as compared to their central narcotic agonist and antagonist activity (123). Goldstein & Schulz (121) prepared myenteric plexus–longitudinal muscle strips from control guinea pigs or animals that had been implanted subcutaneously with 300 mg of morphine base. Contractions of the strips were induced by supramaximal electrical field stimulation at a frequency of 0.1 Hz. Strips taken from the morphine-implanted animals were less sensitive than control strips to the depressant effects of morphine added to the bath. Tolerance was observed within 24 hr after morphine pellet implantation and became maximal 3–6 days after implantation. Maximum twitch tension and contractile responses to acetylcholine were not altered by tolerance to morphine. Interestingly, the depressant effects of epinephrine, isoproterenol, and dopamine were reduced considerably in strips from morphine-tolerant animals. A parallel study by the same authors (120) indicated that ileal strips from morphine-tolerant animals are supersensitive to the contracting effects of 5-HT. The authors proposed that tolerance to morphine results from an increase in the number or intrinsic sensitivity of 5-HT receptors. While this interpretation would account simultaneously for tolerance to morphine and catecholamines, a 5-HT link in ileal responses to field stimulation has not been demonstrated. Moreover, continuous interruption of neural activity, such as treatment with ganglion-blocking drugs, can cause supersensitivity in guinea pig ileum (124). The proposal by Schulz & Goldstein (120), however, is strengthened by the specificity of the supersensitivity to 5-HT during morphine tolerance. Van Neuten & Lal (125) found that ileal segments from morphine-tolerant guinea pigs were more sensitive (larger contractions with lower intensities of stimulation) to coaxial stimulation than strips from control animals. Interpretation of this observation is difficult because the experiments involved submaximal stimulation; the effect of morphine treatment could have been to decrease stimulus threshold in the intramural excitatory nerves.

In contrast to the above studies, Shoham & Weinstock (126) observed enhancement of responses of guinea pig ileum to acetylcholine during acute tolerance produced by addition of morphine to the bath fluid for 90 min. The increased sensitivity to acetylcholine was accompanied by a diminished effect of morphine on twitch height (contractions induced by supramaximal field stimulation). During the acute tolerance to morphine, there was no change in the ability of morphine to inhibit release of acetylcholine. It thus appeared that morphine had altered the smooth muscle acetylcholine receptors to cause supersensitivity. The acute tolerance to morphine in this case, and the enhanced responsiveness to acetylcholine, may in fact be due to the anticholinesterase property of morphine. After the twitch of coaxially stimulated guinea pig ileum was depressed by low concentrations of morphine, both dextrorphan and levorphanol were effective in restoration of the contractions (127). Dextrorphan and levorphanol differ considerably in narcotic agonist potency, but were about equally active as cholinesterase inhibitors in homogenates of the test preparation. Also, physostigmine in low concentrations restored the

twitch that had been depressed by morphine. Acute tolerance of the guinea pig ileum to morphine cannot be explained in terms of the proposed negative feedback neural inhibitory control of acetylcholine release (128), because the effect of morphine on acetylcholine release is undiminished during acute tolerance (126). The same consideration would argue against an inhibitory effect of morphine on a neural acetylcholine uptake site (129).

Tolerance to morphine has been demonstrated also in the small intestine of dog (130), in which morphine is stimulatory and, acting presumably through release of 5-HT, increases release of acetylcholine (85). Tolerance to the stimulatory effect of morphine in situ and in vitro was not associated with significant changes in dose-response curves for 5-HT or for bethanechol. The results indicated that in the dog, at least, intestinal tolerance to morphine does not occur as a consequence of changes in transmitter receptor sensitivity. Similar conclusions were prompted by a study of acute tolerance to opiates in dog intestine (98). Perfusion of intestinal segments with morphine nearly abolished responses to intraarterial bolus doses of morphine, but did not decrease responses to bethanechol, DMPP, or 5-HT. Levorphanol and morphine showed cross-tolerance; responses to morphine (but not responses to bethanechol, DMPP, or 5-HT) were blocked by naloxone. 5-HT receptor desensitization did not alter responses to bethanechol or DMPP, but caused a considerable reduction in responses to morphine. While the specific mechanisms of acute and chronic tolerance of the dog intestine to morphine may be quite different, both kinds of experiments indicate that tolerance reflects events at the opiate receptor or on 5-HT release, not events at 5-HT or cholinergic receptors.

ANTIDIARRHEAL AND CATHARTIC DRUGS

Selectivity of drug action is a principal goal in pharmacology. The opiates are our most effective antidiarrheal drugs, but their actions are not limited to the gastrointestinal tract. It may, however, be possible to separate the intestinal and the central effects of the opiates. Promising agents such as loperamide demonstrate significant antidiarrheal activity in animals and man without notable central actions (131–135). Behavioral tests in rats trained to discriminate between fentanyl and saline indicated that fentanyl, morphine, codeine, and diphenoxylate produced narcotic cues, but loperamide was completely inactive in this test (135). Bass and his colleagues (136) subjected a novel indoline derivative, coded Cl-750, to rigorous pharmacological testing. Cl-750 was shown to have minimal central narcotic agonist activity, but produced narcotic-like constipation in rats and monkeys. The gastrointestinal motor effects of the compound were similar to those produced by morphine. Unlike morphine, however, its actions were only partially antagonized even by high concentrations of naloxone. It was not established whether the naloxone-insensitive actions of Cl-750 contribute to its constipating effects. If the intestinal and central opiate receptors are identical, selective opiate actions on the intestine can be achieved only by preventing entry of the opiate drug into the central nervous system. It is quite important, therefore, that all new antidiarrheal agents be tested in the absence and presence of naloxone to determine whether their constipating effects are blocked by

naloxone. If they are blocked, the intestinal effect can be attributed to interaction with a conventional opiate receptor.

The constipating actions of narcotics can occur as a troublesome side effect of analgesic or narcotic addict maintenance therapy. Coadministration of cyproheptadine, a 5-HT antagonist, decreased the spasmogenic effect of methadone in dog intestine (137). Cyproheptadine also diminished the antipropulsive effect of methadone in mice, but did not alter the lethal dose of methadone.

Although little or no experimental evidence exists, "irritant" cathartics have been generally thought to stimulate intestinal smooth muscle. Stewart et al (138) performed a careful study of the effects of castor oil and magnesium sulfate on dog gastrointestinal contractile activity in vivo. Circular muscle activity, measured with extraluminal strain gages, was characterized during fed motility patterns and after twenty hours of fasting in the unanesthetized animals. Both laxative agents produced diarrhea when administered during the fasted state, but only mild laxation when administered after food. Both cathartics decreased motility, particularly in the ileum, especially when given during the interdigestive period. This interesting study provides support for the contention that increased circular muscle activity is obstructive and that some optimal decrease in activity might be associated with increased flow (136, 139). It is also noteworthy that castor oil and a saline cathartic, magnesium sulfate, had similar effects on both motility and absorption of water from the intestine (138).

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