Ann. Rev. Pharmacol. Toxicol. 1985. 25:249–73

THE CENTRAL AND PERIPHERAL INFLUENCES OF OPIOIDS ON GASTROINTESTINAL PROPULSION

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INTRODUCTION

The constipating effects of extracts of the poppy plant *Papaver somniferum* are among the oldest known pharmacological actions, and their application as antidiarrheal remedies preceded the use of opium preparations for analgesia. However, we are still far from a thorough understanding of how opioids[1] influence the gut in spite of considerable recent advances, including the discovery of specific binding sites and their endogenous ligands (65). While the mechanism of pain relief by morphine-like natural alkaloids and related synthetic narcotic analgesics is currently assumed to involve exclusively the central nervous system (CNS), both their direct effects on the bowel and their centrally elicited actions are believed to account for constipation (66). Opioid receptors and endorphins are widely distributed in the CNS and throughout the gastrointestinal (GI) tract, implying possible participation of the endogenous opiate system at either level in the regulation of gut functions, including motility.

This article represents an effort to lay out a framework against which to assess the relative roles of central and peripheral opioid–specific mechanisms affecting gastrointestinal propulsion. Our sights have been kept on subjects of

[1]Throughout this paper, the word *opioid*, according to its currently prevailing use, is used interchangeably with morphine-like plant alkaloids, their synthetic analogues and animal peptides mimicking their effects.

0362-1642/85/415-0249$02.00

clinical significance, like the well-recognized selectivity of newer synthetic antidiarrheal agents for the gut (3) and the unwanted intestinal spasm and constipation that are virtually inevitable complications associated with pain relief by narcotic analgesics (85).

Space limitations do not permit exhaustive coverage of the available literature, so we concentrated on summarizing, correlating, and interpreting mostly recent and some older experimental studies selected primarily in terms of the above aim. Our reference to reviews, without necessarily endorsing the opinions expressed therein, is intended as a useful complement to the present compact overview.

EXPERIMENTAL CONDITIONS

Anyone wishing to provide a coherent picture of the imposing amount of data on gastrointestinal motility as affected by opioids is faced with the initial obstacle of variation in results depending on experimental conditions. These include animal species, techniques, and drugs.

Considerable species differences have long been known in the effects of morphine and similar drugs, excitation versus sedation, for example, and myosis versus mydriasis (66). To some extent this also applies to the gastrointestinal tract. The mode of opioid action on the motility of all intestinal portions of different animals and the related neurochemical factors have been reviewed elsewhere (21, 35, 36, 166). The variety of mechanisms, which range from inhibition of tone and acetylcholine release in the guinea pig ileum to spasmogenic action and increased release of serotonin and/or acetylcholine in most other species, all produce constipation in the mammalian gut. This is the key aspect in the present context, where slowing of the propulsion of intestinal contents is dealt with as the main functional consequence of altered gut movement by opioids.

The propulsive performance of the intestine in vivo is usually assessed by measuring the transit of nonabsorbable markers along the alimentary canal of animals (100) and man (16). Clearly, these relatively coarse techniques preclude any detailed analysis of opioid influences on distinct but integrated events underlying gastrointestinal motor function at different levels. Thus, myogenic and neural events are studied through mechanical or electrical recordings from isolated preparations either in situ or in vitro (36, 39). These kinds of studies have often been considered merely model systems to clarify typical problems of CNS opioid pharmacology like tolerance and dependence, but of course they also provide extensive evidence that specific responses to opioids can be elicited locally throughout the gut. However, several questions persist regarding the relevance of the responses observed in isolated gut preparations to the possible local functional role of endogenous opioids in animals under physio-

logical conditions or to the direct intestinal origin of the constipating action of morphine-like drugs, as seen in therapeutics. How does local application of substances compare to their reaching the gut through the bloodstream upon systemic administration or to neuronal release at discrete sites? Does removal of other controlling mechanisms as a consequence of isolation of preparations show up responses to opioids otherwise absent and/or of little or no significance in the interplay of the many factors concurring in gastrointestinal propulsion in the intact organism? Are anesthesia or other medications a source of artifacts?

These outstanding questions apart, this review considers mostly in vivo studies measuring transit along the intestine of intact animals, because it is essentially under such conditions that the balance between central and peripheral opioid specific mechanisms of constipation can best be assessed. Most available data have been produced by different laboratories using rats and mice and the long-established charcoal meal test (58) or related methods[2]; for review see (100). Some meaningful extrapolations to man should be possible judging from the results obtained with these animal models, which have been instrumental in the development of the newer, gut-selective, clinically effective antidiarrheal opioids (3). While these animal models essentially reflect the propulsive performance of the small intestine, in humans only about a quarter of the constipating action of morphine is believed to take place there, half being attributed to delayed gastric emptying and the remaining quarter to large intestine and anal sphincter spasms plus inattention to sensory stimuli for the defecation reflex (66).

Differences in constipating action among morphine-like drugs have been generally regarded as quantitative rather than qualitative (66). Narcotic analgesics reportedly less constipating than morphine include mixed agonists like pentazocine (17), nalbuphine (80), butorphanol (59) and buprenorphine (60). Mixed agonists are also relatively free from respiratory depression, a side effect of exclusively central origin. This suggests that a common factor possibly inherent in receptor mechanisms might account for the lower frequency of either undesirable action. Pethidine is also indicated from therapeutic experi-

[2]In these methods, transit along the small intestine of a nonabsorbable marker fed by stomach tube is generally measured from the percentage of the total length reached by the marker in a given time. The marker may be introduced through a duodenal cannula in chronically implanted animals (48, 145); the presence or absence of the marker in the cecum can be taken as an all-or-none response (101); the slope produced by linear regression analysis of the cumulative percentage of radioactive marker passing through each of several intestinal segments or the geometric center of the distribution of radioactivity throughout the intestine are the scored endpoints (96); cathartic-primed rather than normal animals may be used (145). Additional factors influencing the results are: observation times in relation to drug treatment and to marker progression kinetics (151); fasted versus freely feeding animals (58); drug administration routes and techniques, particularly intraperitoneal injection, which, at least in rats, might be regarded as local intestinal application (151).

ence as less constipating than morphine (97), this being consistent with precise animal findings that pethidine doses producing analgesia are lower than those required for inhibition of intestinal transit (58).

Whether differences exist between narcotic analgesics other than morphine in the extent to which central or local intestinal mechanisms underlie their constipating action does not seem to have been investigated; for a beginning see (110).

RECEPTOR ASPECTS OF THE INTESTINAL MOTOR EFFECTS OF OPIOIDS

Throughout the modern era of research on opioids, considerable efforts have been made to explain their action in terms of receptor pharmacology. The existence of specific opioid receptors was postulated in the mid-50s by Beckett & Casy, who formulated theoretical opiate receptor models based on stereochemical considerations for synthetic narcotic analgesics (5). The characterization of such receptors has since proceeded mainly by pharmacological and biochemical approaches in vitro in isolated tissue preparations and tissue homogenates.

In the gut, opioid receptors were first identified by classical pharmacological methods. After the pioneering work of Paton on the action of morphine on the electrically stimulated contraction of guinea pig ileum and associated acetylcholine-release inhibition (108), this in vitro preparation was extensively studied by Kosterlitz and his group (70). They found that the concentration-response relation of morphine and other narcotic agonists in the presence and absence of specific antagonists conformed to the law of mass action and calculated kinetic parameters for agonists and antagonists.

Biochemical evidence for opioid receptors was later provided by several investigators, who identified specific, stereoselective binding sites in isolated tissues by in vitro techniques using radiolabelled opioid agonists and antagonists as ligands (56, 111, 141, 156). With these techniques, the presence of opioid binding sites could be confirmed, not only in brain but also in intestinal tissues such as the myenteric plexus of the guinea pig (155) and, more recently, of the rat (98). The most convincing evidence that the guinea pig ileum binding sites represent pharmacological receptors comes from the close correlation between binding affinities and potencies in influencing electrically induced contraction for a variety of opioid drugs (33); it was also suggested that these receptors are similar to those located centrally, after comparison of the rank order of potencies of agonists and antagonists in this preparation and in the CNS (33).

Attempts to identify and characterize opioid receptors on the basis of pharmacological responses in vivo have also been described (90, 148, 149). Despite

the apparent difficulties of establishing precise, reliable receptor-kinetic constants (119, 150), the in vivo approach has the considerable advantage of correlating the pharmacological effects to receptor occupancy in an integrated system—the whole animal. As to the specific receptors involved in opioid constipation, several investigators have measured either dissociation constants for narcotic agonists or pA_2 values for antagonists in rodents treated by different administration routes. In mice injected subcutaneously, Takemori et al (148) found that the pA_2 value of naloxone for antagonism of morphine constipation (6.6) was lower than for antagonism of morphine analgesia (7.0) and even lower than that reported in the isolated guinea pig ileum (8.7) by Kosterlitz & Watt (70). These findings suggest that the receptors for analgesia and inhibition of intestinal motility may not be the same and that different mechanisms of inhibition of intestinal motility by morphine may apply in vitro and in vivo.

Opposite conclusions may be drawn from the results of Raffa et al, who measured the receptor dissociation constant (K_a) of morphine for inhibition of gastrointestinal transit in subcutaneously treated rats and found it similar to that for antinociception (124). However, from theoretical considerations, the authors excluded the applicability of the classical drug-receptor theory to their system. To obtain reliable pA_2 values from in vivo experiments, it has been recommended that antagonist concentrations at the sites of action should be determined; alternatively, the antagonist should be given by a route ensuring drug delivery in the proximity of the presumed loci of action (119). Accordingly, a pA_2 value of 8.8 was obtained for naloxone against morphine constipation in intraperitoneally treated rats (90), this being remarkably close to that (8.7) obtained in vitro on the guinea pig ileum (70). In contrast to a previous study in subcutaneously treated mice (148), this supports the notion of functional similarity of intestinal opioid receptors in vivo and in vitro. Since direct intracranial administration of morphine is known to induce constipation in rodents (see below), the estimated pA_2 for morphine-naloxone, both administered intracerebroventricularly to rats, yielded a value of 7.1, which agrees substantially with pA_2 values in various analgesia tests, but in systemically treated animals (107). Nonetheless, these results have led their authors to advocate the primary importance of centrally located receptors, similar to those inducing antinociception, for mediation of the effects of systemic morphine on the gut (107).

A recent different in vivo approach in localizing and characterizing opioid receptors involved in the constipating action of morphine consisted of monitoring the drug's intestinal effects and its tissue levels in the same rats; morphine levels in small intestine longitudinal muscle, but not in plasma or brain, presented a striking correlation with gastrointestinal transit inhibition scores as predicted by a currently accepted equation describing drug-receptor kinetics

(10). Consistently, narcotic antagonists antagonized morphine's antipropulsive action and under the same experimental conditions prevented in vivo labelling of binding sites in the gut with the radiolabelled opioid buprenorphine, further supporting the presence and relevance to motor function of specific receptor mechanisms in the rat intestine (11).

Opioid receptors are currently classified as several subtypes [for review, see (93, 140)] whose relative importance in influencing gastrointestinal function is still uncertain. Most work on this subject has been carried out in vitro on isolated intestinal segments, where the presence of a given receptor subtype may be inferred from the different sensitivity of the preparation to various agonists and antagonists presumably selective with regard to postulated multiple opioid receptors. Thus, the GI tract was shown to contain the putative receptor subtypes μ, κ, and δ, but their distribution along the gut presented broad variability depending on the species and intestinal segment considered (105). Only a few in vivo studies have so far attempted to ascribe opioid effects on intestinal propulsion and/or mechanical activity to activation of a particular receptor subtype. Based on the effects of several opioid-agonists injected in the esophageal branch of the left gastric artery in anesthetized opossums, it was concluded that the lower esophageal sphincter (LES) contains μ, κ, σ, and δ opioid receptors (126). In order to identify and localize the receptor subtypes involved in inhibition of intestinal transit in mice, Ward & Takemori (162) utilized β-funaltrexamine (β-FNA) as a specific, irreversible μ antagonist, and morphine, D-Ala^2 D-Leu^5 enkephalin (DADL) and nalorphine as selective agonists for μ, δ, and κ sites respectively. A full dose-response curve was obtained with morphine given either intracerebroventricularly or subcutaneously, while DADL and nalorphine only partially inhibited transit. Since β-FNA antagonizes morphine and DADL but not nalorphine, the authors supported the existence of central and peripheral μ-mediated components and of a peripheral κ component accounting for limited inhibition of GI transit; furthermore, from the outcome of the combined administration of agonists and antagonists by the intracerebroventricular and/or subcutaneous routes, they concluded that the effects of subcutaneous morphine are mediated predominantly at peripheral sites. Whether there are any κ receptors instrumental in the slowing of GI transit by opioids in rodents is doubtful in view of the inconsistent results in intact rats (54, 153) with benzomorphans or other compounds proposed as acting on κ sites in vitro. Porreca et al (118) found that ketazocines, considered κ agonists, slow intestinal transit in both mice and rats when administered subcutaneously, but, unlike morphine, not when injected intracerebroventricularly; they suggested an anatomically distinct distribution of μ and κ sites mediating intestinal function. However, the intestinal activity of ketazocines in rodents is likely to consist of poor discrimination between μ and κ receptors, since cross tolerance between ethylketocyclazocine and morphine

on the intestine has been reported (117). In the anesthetized dog, the contractions of duodenum circular muscle are increased by normorphine and Met-enkephalin but not by the putative κ agonists dynorphin 1-13, bremazocine, and U-50,488H, which shows that in these conditions, too, no κ component of intestinal action can be detected (158). Data supporting the involvement of enkephalin (δ) receptors in the constipating action of opioids have been presented by Cowan & Gmerek, who showed intestinal transit inhibition in mice by the opioid peptide metkephamid and its prevention by the reportedly selective antagonist ICI 154,129 (32). Likewise, in anesthetized cats, Met-enkephalin was a hundred times more potent than morphine in inducing phasic ileal contractions associated with ileocecal sphincter closure (106). In addition, based on in vitro findings, it has been suggested that a δ opioid receptor might mediate permeability changes across the guinea pig ileal mucosa and thereby account for antidiarrheal action consisting of an antisecretory effect more than actual inhibition of propulsive activity (67).

CNS-ELICITED OPIOID INFLUENCES ON GUT MOTILITY

Evidence for central opioid-sensitive sites of inhibition of gastrointestinal transit comes primarily from animal studies consisting of administering morphine-like drugs or endogenous peptides directly into the CNS. This approach can be traced back to the work of Margolin (91), who reported delay in the transit of a charcoal suspension through the small intestine of unanesthetized mice given intracranial (subdural) morphine at doses considerably lower than the intravenous ones required to produce comparable constipation; this author reported similar findings in rats and guinea pigs. Subsequent observations by different laboratories in mice (8, 137, 162), rats (51, 53, 58, 89, 107, 137, 143, 145), guinea pigs (137), ewes (19), and cats (144) have provided more adequate evidence that morphine applied intracranially with several techniques produces centrally initiated intestinal motor responses.

Very little is known of the precise cerebral sites involved in these intestinal responses. Conceivably, morphine could more easily, via the circulating cerebrospinal fluid, reach the periventricular regions currently indicated as the loci of CNS-mediated analgesia (66). The periaqueductal gray matter has been consistently associated with inhibition of gastrointestinal propulsion in rats (133). A nervous (vagal) pathway seems to link central opioid–specific mechanisms to the gut (44, 145). The original suggestion by Margolin et al postulating release by morphine from the brain of an unknown humoral agent that inhibits gastrointestinal propulsion through the circulation (92, 113) has been recently reexamined in the light of its possible opioid peptidergic nature, but the results are not compatible with this hypothesis (137).

Narcotic drugs other than morphine may not all share its ability to affect gastrointestinal transit after central administration. Thus, putative κ agonists ketazocines slowed transit of a suitable marker through the small intestine of rodents when administered subcutaneously, but not by the intracerebroventricular route, whereas phenazocine, a benzomorphan supposedly acting at μ receptors, delayed marker transit after intracerebroventricular injection (118) and so did heroin and etorphine (112). Likewise, different results have been obtained by intraventricular injection to rats (castor oil–primed) of opioid peptides: β-endorphin and [D-Ala^2, Met^5] enkephalinamide reduced transit along the small intestine of intraduodenally administered radiochromium, but [D-Ala^2, Leu^5] enkephalinamide and dynorphin 1–13 did not (52). Other opioid peptides with constipating action when injected intracerebroventricularly to mice tested with the charcoal meal procedure are Leu-enkephalin and Met-enkephalin (31) and the enkephalin-like pentapeptide FK 33824 (137).

The results of studies showing effects on enteric functions of opioids directly administered into the CNS are of considerable interest for supporting specific action sites, therein influencing the gut. However, this does not justify assigning a definite role in gastrointestinal physiology to central endogenous opioids. In addition, an essential caveat is that centrally elicited effects on the bowel of narcotic drugs directly injected into the CNS are by no means a precise reflection of their mechanism of intestinal action on systemic administration. On these questionable grounds, in fact, a primarily central component affecting gut peristalsis has been attributed to parenterally administered morphine (107, 137). Yet the following important aspects seriously undermine this conclusion. Because of possible biotransformation and different distribution kinetics, generally great caution is required in extrapolating the responses evoked by local application of drugs to the effects presumably associated with their reaching the same site via the general circulation. With intracranial morphine, the delivered amounts that produce constipation in rats largely exceed the lower than microgram per gram brain concentrations[3] recovered even after a subtoxic intravenous dose (88). Therefore, not surprisingly: (*a*) in the early report by Green describing rats given morphine intracisternally, the dose-response curves for charcoal meal intestinal transit inhibition and respiratory depression were superposable and stood to the right of that for antinociception (58); (*b*) later studies clarified that test meal transit inhibition in rats by a standard intracerebroventricular morphine dose was constantly associated with severe catatonia that persisted in naloxone subcutaneously pretreated animals whose transit had fully recovered to control values (89). More importantly, a lower

[3]Regional distribution of morphine in the rat brain is reportedly fairly uniform (20, 34), which makes it unlikely that drug concentrations are higher at cerebral sites involved in the constipating action of opioids.

dose of morphine that substantially slowed gastrointestinal transit when injected intraperitoneally failed to do so upon intracerebroventricular administration, although it produced sustained catatonia in all treated rats (151).

Since only small amounts of systemically administered morphine pass the blood brain barrier (66), reasonable doses cannot be expected to have a predominantly central component of intestinal action (see below).

An apparently less questionable approach to ascertaining whether systemically administered opioids have central effects on the gut consists in checking their reversibility in animals given a narcotic antagonist intracerebroventricularly. Naloxone, the best tolerated,[4] is more readily diffusible across the blood brain barrier than is morphine, thus requiring careful titration of the intracerebral dose plus adequate controls of its exclusively local effectiveness. Several narcotic analgesics were compared at subcutaneous doses producing about 50% inhibition of gastrointestinal transit in rats; intracerebroventricular naloxone failed to antagonize morphine but fully antagonized etorphine and pethidine and partly antagonized heroin and methadone (110). These results are reinforced by the outcome of a twin experiment in which intracerebroventricular naloxone was replaced by intraperitoneally administered, peripherally selective quaternary ammonium antagonists (see below) and suggest that, unlike morphine, other narcotics act largely, if not exclusively, in the brain to affect the gut (110).

Recently, the spinal cord, which is currently indicated as an important site for pain relief by narcotic analgesics (78, 170), has been considered a potential locus of opioid action in the production of gastrointestinal motor effects. Morphine and some of a number of narcotic analgesics and opioid peptides directly administered (intrathecally) in the spinal cord of mice effectively inhibit the passage of a radiolabel maker through the gastrointestinal tract (116, 120, 121), but a similar study including rats did not confirm spinally elicited constipating effects in this species (159). In this connection, the rat may be a more predictive model for humans than mice, because constipation does not seem to occur in patients receiving spinal analgesia with morphine (28, 171).

THE LOCAL INTESTINAL MOTOR EFFECTS OF OPIOIDS

The presence throughout the gastrointestinal tract of opioid receptors whereby specific responses can be elicited in a variety of isolated gut preparations strongly suggests that in vivo, too, the intestinal motor effects of systemically

[4]Quaternary narcotic antagonists (see below) given intracranially may cause animals to convulse (24, 55).

administered morphine-like drugs may be initiated locally. However, undisputed evidence for CNS-originated inhibition of gut peristalsis following intracranial application of opioids (see above) poses the question of whether and to what extent this central component of intestinal action contributes to the effects produced in intact animals treated by a systemic route. Different approaches can be taken to answer this question.

Since resection of the vagus nerve in rats abolished the antidiarrheal action of intracerebroventricular but not of subcutaneous morphine, the latter action was considered free of any central component (145).

Assuming no major differences, as allowed in the light of current knowledge, between centrally and peripherally located opioid receptors influencing bowel movements, clearly pharmacokinetic factors (i.e. the drug distribution in the CNS and gut after systemic treatment) should account mainly for the central and/or peripheral modes of the constipation action of any given opioid drug (89, 110). This is best demonstrated with agents that are virtually completely excluded from the CNS like the peripherally selective opioids and antagonists (see below), but conceivably morphine-like drugs poorly passing the blood-brain barrier may also act primarily, or perhaps even solely, at local intestinal opioid receptors. Thus, in mice the constipating intravenous dose of the stabilized enkephalin derivative FK 33824 amounts to only 2% of the corresponding analgesic dose, but the drug is equipotent in producing analgesia and constipation when given intracerebroventricularly; on these grounds, it was inferred that the drug has considerable direct action on the intestine (137). In rats pretreated with a dose of naloxone sufficient to completely prevent analgesia by intravenous FK 33824, its inhibition of gastrointestinal transit is consistently only slightly relieved (47).

Only small amounts of morphine pass the blood-brain barrier after systemic administration (10, 66). Moreover, the clinical notion that "it requires considerably less morphine to affect the gut than to produce analgesia" (66) agrees with experimental animal data. As an example, the rat subcutaneous ED_{50} for morphine analgesia (14) is about four times[5] that for reduction of charcoal meal gastrointestinal transit (47, 110) and the difference for the oral route is much larger (89). The latter difference seems particularly to suggest the local intestinal nature of the constipating side effects of oral morphine in pain therapy of terminal patients, a currently recommended measure (2).

[5]The ratio between subcutaneous analgesic and constipating doses of morphine found by Green in rats is also very close to four (58). Subcutaneous morphine doses (5–10 mg/kg) considerably larger than those slowing the progression of a charcoal meal in normal rats have been required in the work of Stewart et al to antagonize castor oil diarrhea (145), but clearly this is a less sensitive model for prediction of clinical constipation as a side effect of narcotic analgesia. However, about 20 times less morphine is needed to antagonize castor oil diarrhea than to produce analgesia in orally treated mice (100).

Recently, the intraperitoneal route was reported as by far the most effective for producing morphine inhibition of the progression of a stomach tube fed charcoal meal along the rat small intestine (10, 89, 90, 151). Reasons have been presented (151) for previous failures (107, 137) to show the remarkable potency of the constipating action by intraperitoneal morphine under mostly comparable conditions (7, 151), and it has been clarified that this exclusively local intestinal action (90) consists of inhibition of small bowel propulsion rather than a direct effect on the stomach, delaying gastric emptying (48). More interestingly, comparison of morphine tissue levels and the effects on charcoal meal transit of intraperitoneally and intravenously dosed rats shows that higher intestinal morphine concentrations account for greater potency with the former injection route (10). These concentrations, irrespective of different doses, administration routes, and observation times, largely exceeded those in brain and, contrary to the latter, were closely correlated with the observed constipating effects so as to fit computer-generated curves described by equations complying with the receptor occupation theory of drug response (10). All together, these recent observations in rats, starting from pharmacokinetic considerations, render the animal model consistent with a primary role of a gut-located action site in morphine-induced constipation.

Peripherally Selective Opioids and Antagonists

In principle, opioids unable to pass through the blood-brain barrier offer an ideal means for acting selectively on their specific receptors outside the CNS, thereby revealing in vivo peripherally elicited effects.

QUATERNARY AMMONIUM COMPOUNDS Foster et al pioneered this approach[6] and showed that morphine and its N-methyl quaternary derivative given at the same intravenous dose to mice had comparable constipating effects scored as frequency of scybala output (49). Limitations of this early study for supporting an exclusively local intestinal action of morphine include the absence of dose-response analysis; the assumption that N-methyl morphine was unable to penetrate the CNS because of its failure to produce antinociception in a different experimental protocol (intraperitoneally dosed rats); the lack of control of the opioid-specific nature of the constipating effect based on reversal by a narcotic antagonist.

More recently, a growing number of studies have focused on quaternary ammonium salts of narcotic antagonists as a tool for differentiation between the central and peripheral components of opioid effects on the gut.

The N-allyl quaternary analog of nalorphine [diallylnormorphine (DANM)],

[6]As early as 1933, N. B. Eddy demonstrated the ability of quaternarized morphine and codeine to depress motility of the rabbit intestine in vivo [quoted in (49)].

unlike its parent tertiary amine and consistent with previous in vitro results (69), behaves like a pure narcotic antagonist, since by itself it does not slow gastrointestinal transit of a charcoal test meal fed to rats. Unlike naloxone, DANM does not reduce in vivo binding of buprenorphine in cerebrum, nor does it prevent gastrointestinal transit inhibition by intracerebroventricular morphine. DANM under comparable conditions substantially relieves the constipating action of a supramaximal analgesic dose of intravenous morphine, preserving at least part of its antinociceptive action in the same rats (89, 152). Other investigators have observed partial antagonism of the inhibition of intestinal propulsion of radioactive chromium after subcutaneous morphine in rats given an intracerebroventricular dose of DANM that had no such effect when given intravenously (24). In spite of apparent discrepancies due to different test conditions, these and an additional study with DANM in rats (12) agree in supporting a major, locally elicited component of slowing of intestinal transit by systemic morphine given even at larger than analgesic doses. However, DANM completely prevents the marked inhibition of gastrointestinal transit produced in rats by lower systemic doses of morphine (89).

The quaternary N-methyl analog of naloxone given intraperitoneally to mice at doses presumably lacking CNS action, as indicated by the lack of effect on morphine analgesia, antagonizes the constipating action of the peripherally acting opioid loperamide, but not that of intravenous morphine (137). Doses of N-methyl naloxone higher than those preventing morphine antinociception do antagonize its slowing action on gastrointestinal transit when given systemically to mice (38, 137). Conversely, in rats quaternary naloxone restores gastrointestinal transit, nearly blocked by intravenous morphine, to about 70% of drug-free controls with no detectable impairment of analgesia tested concurrently in the same animals (12, 47). Near-maximal inhibition of gastrointestinal transit after either morphine or the enkephalin-like peptide FK 33824 given intraperitoneally to rats is virtually fully prevented by N-methyl naloxone at doses about one tenth those with no effect on morphine analgesia under comparable conditions (47). In rats given any of several narcotic analgesics subcutaneously at approximately equipotent doses inhibiting gastrointestinal transit by about 50%, intraperitoneal quaternary naloxone fails to antagonize etorphine and pethidine but fully antagonizes morphine and partly antagonizes heroin and methadone (110). Therefore, central and peripheral inhibition of gastrointestinal transit seems to differ depending on the narcotic tested, which may act at one or both levels.

Russel et al (132) showed that the N-methyl quaternary analog of naltrexone, at doses well below those that failed to precipitate behavioral signs (central) in morphine-dependent dogs, attenuates morphine-induced spike potentials recorded from chronically implanted canine duodenum. In the same study (132), intraperitoneal quaternary naltrexone in mice reversed antinociception by morphine but not its attenuation of prostaglandin-diarrhea, while in rats anti-

nociception was not reversed and diarrhea attentuation was only inconsistently prevented. Gmerec et al (55) reported full antagonism of gastrointestinal transit inhibition by subcutaneous morphine in rats given quaternary naltrexone subcutaneously that only slightly attenuated the constipating action of intracerebroventricular morphine.

The N-methyl quaternary analogs of nalorphine, naloxone, and naltrexone, and DANM, all given subcutaneously over a wide dose range, were compared by rating their abilities to prevent antinociception and gastrointestinal transit inhibition in individual rats receiving morphine intravenously. All four quaternary antagonists proved gut-selective when given shortly before morphine and started to antagonize antinociception only at doses up to 60 times those restoring test meal transit to 50% of drug-free controls. However, a time factor proved critical for peripheral selectivity, which was virtually lost within 80 minutes in the case of the most selective compound, quaternary naltrexone (12). Different laboratories have confirmed the short-lived peripheral selectivity of N-methyl naltrexone (18, 125).

These limitations of the available quaternary antagonists have prompted the search for better compounds. The first one tested was N-allyl levallorphan bromide (CM 32191). In mice treated subcutaneously, it did not interfere with morphine analgesia at a dose five times that reducing constipation by 50%, and its peripheral selectivity did not decrease with time; a 1.7 ratio between the anti-analgesic and anticonstipating doses was found for N-methyl naloxone tested in the same way (8). In rats, extensive tests over a range of doses and time intervals have shown that CM 32191 selectively prevented morphine's antipropulsive action and buprenorphine's in vivo binding in the intestine without impairing CNS binding and analgesia (11).

Despite its superiority over similar compounds in terms of peripheral selectivity, CM 32191 still presented the shortcoming of limited potency. Further efforts to clarify the stereochemical requirements at the chiral nitrogen for in vitro and in vivo activity of quaternary narcotic antagonist (9) yielded levallorphan methyl iodide (SR 58002), currently the best available peripheral antagonist (38).

These recent developments are providing more reliable research tools for characterizing opioid effects outside the CNS, including those arising locally in the gut. In addition, newer peripheral antagonists may yet render clinically applicable the dissociation of morphine analgesia from its direct intestinal side effects, as has already been done successfully in animal models (12, 47, 89, 152).

GUT-SELECTIVE ANTIDIARRHEAL OPIOIDS The potential of gut-located action sites for the production of clinically important opioid constipating effects is best illustrated by the recently developed antidiarrheal agents selective for the intestine. These agents, including diphenoxylate (157), loperamide (101, 102),

and SC 27166 (83, 102), reportedly have little or no analgesic or euphoriant action at doses largely exceeding those required for constipation and have been extensively reviewed (3, 36, 157). Here we will only briefly mention just a few aspects of special interest and/or closer relevance to the present context.

The selectivity of newer antidiarrheal opioids for the gut is proposed as a significant advance in therapeutics compared to previously available related agents that might produce central side effects, like analgesia, if not acute poisoning (respiratory depression) or physical dependence on repeated use (3). Gut selectivity apparently does not involve different drug-opioid receptor interactions in the CNS and at local intestinal sites (84), but simply reflects the drug's virtual inability to reach the CNS (61).

Loperamide, the most selective antidiarrheal opioid currently available for clinical use (160), has been shown to have narcotic antagonist reversible constipating action in that it delays the transit of a test meal along the gastrointestinal tract of normal animals (137) and man (4), like the traditional remedy codeine (123). This is the principal aspect for discussion here, because it stands as unequivocal evidence of an important, exclusively local, antipropulsive opioid action. However, interest is growing in alternative interpretations of the mechanism whereby antidiarrheal opioids are therapeutically effective (122, 134).

Abnormalities of intestinal water and electrolyte transport besides motility alterations are recognized factors in the pathophysiology of diarrhea (122, 134). The classic view has been that inhibition of muscle propulsive activity by opioids holds back the intestinal content, allowing more efficient absorption (13). Data supporting direct stimulation of intestinal water and electrolyte absorption by opioids have recently attracted more attention (45, 67, 94, 95, 163). Representative data (67) and concern about smooth muscle paralysis as a potentially dangerous complication when using opioids to treat secretory diarrhea have even led researchers to envisage the development of synthetic opioids specific for epithelial ion transport (27). Yet recent clinical studies with loperamide indicate that it relieves diarrhea by influencing motor function rather than the rate of absorption by intestinal mucosal cells (135). Therefore, at the moment this is only a challenging area for future research that inter alia must be addressed in any case to clarify the relationship between intestinal motility, blood flow, and absorption of luminal content as affected by opioids (6, 29, 41, 79, 86, 109, 161).

ENDOGENOUS OPIOIDS AND GASTROINTESTINAL PROPULSION

Endogenous opioid peptides originally isolated from the CNS (65) are present throughout the gastrointestinal tracts of several animal species and man, as

demonstrated by immunocytochemical and radioimmunological methods; for reviews see (104, 115, 129). Met-enkephalin and Leu-enkephalin immunoreactive-like material has been localized mainly in the neurons of the myenteric plexus (1, 114), but it has also been detected in the endocrine cells of the gut (1, 77). More recently, substances immunoreactive to dynorphin antibodies have been found in intestinal tissues (74, 164).

If the gut contains these opioid peptides plus their precursors (87) and putative inactivating enzymes (81), they should play a role in gastrointestinal physiology, inasmuch as specific intestinal receptors have already been identified (see above). Indeed, exogenously administered enkephalins and β-endorphin influence gastrointestinal motility and other gut functions and mimic the action of morphine-like drugs in several in vitro and in vivo conditions, as reviewed (68). These are pharmacological actions of endogenous opioid peptides. In the search for better evidence for their postulated natural function in the bowel: (*a*) the observed effects of pure opioid antagonists like naloxone may be tentatively attributed to the suppression of a physiological tonic action of endogenous opioid peptides; (*b*) biochemical events pertaining to endorphins (e.g. release) may be detected and monitored at the same time as functional recordings in order to assess the underlying relationship.

This dual approach has been followed to ascertain whether endogenous opioids are involved in the modulation of peristalsis. In guinea pig isolated ileal segments, Kromer & Pretzlaff (75) found that naloxone significantly increases the frequency of peristaltic waves and concluded that intestinal-borne opioids, whose release from myenteric plexus was reported (138), participate in the control of peristalsis. These authors with the same in vitro technique showed that periodicity rather than efficacy of peristaltic waves (76) may be under the control of an endogenous opioid mechanism located in the intestinal wall. By a different in vivo method, in the anesthetized guinea pig, Clark & Smith (30) demonstrated that blockade of opioid receptors by naloxone facilitates induction of the peristaltic reflex evoked by luminal infusion of saline. However, several investigators have shown that naloxone had no effect on intestinal propulsion when given intravenously (152), subcutaneously (12) or intraperitoneally (107) to conscious rats, intraperitoneally to conscious mice (137), and intravenously to anesthetized dogs (84). Thus, we still do not know whether peristalsis might be inhibited by endogenous opioids under more physiological experimental conditions.

As regards the upper GI tract, various findings suggest either involvement or no participation of endogenous opioids in the regulation of gastric emptying, depending on the species studied and the experimental conditions. Edin et al (42) found that the atropine-resistant contraction of the pyloric sphincter induced by vagal stimulation in the anesthetized cat is blocked by naloxone dose-dependently. Considering that local intra-arterial injection of enkephalins

also elicits pyloric contraction and gastric relaxation, the authors proposed the existence of a vagal control of the pylorus and stomach mediated via enkephalinergic neurons in the cat. It has, in fact, been recently reported that in the same species pyloric contraction in response to duodenal acidification involves local neural pathways that may be mediated through an opioid peptide (128). Evidence for endogenous opioid involvement in digestive motility has also been obtained in ruminants. Maas (82) reported that intravenous injection of naltrexone and naloxone to conscious goats significantly increases the frequency of ruminal contractions, possibly by unmasking an inhibitory opioid system controlling forestomach motility. Identification of these mechanisms is important with a view to improving physiological functions or correcting pathological alterations in veterinary pharmacology with opioid antagonists (130, 131).

Other studies did not support a function of endorphins in the upper GI tract. For instance, Shea-Donohue et al (139) found that in conscious primates doses of naloxone sufficient to prevent the effects of exogenously administered opioid peptides on the stomach do not affect gastric emptying; these authors were thus led to assume that endogenous opioids play no major role in this connection. In humans, too, unequivocal evidence that endogenous opioids intervene as physiological mediators of the normal motricity of the GI tract is currently lacking. Feldman et al (46) found that intravenous infusion of naloxone to healthy subjects has no effect on the rate of gastric emptying of a liquid meal, even though gastric emptying is significantly reduced by morphine (46) or exogenously administered opioid peptides (146). Conversely, in recent experiments on healthy volunteers by different research groups, naloxone infusion was found to reduce antroduodenal contractile activity (127) and to inhibit the gastrocolonic response to eating (147).

Since specific receptors are present in the gastrointestinal tract along with their endogenous opioid ligands, their physiological function, whatever it is, should be primarily local. However, because of intestinal motor effects after direct intracranial application of opioid peptides (see above), and considering the good bioavailability of parenteral naloxone to the brain, its aforementioned effects might be interpreted as supporting an unidentified central endogenous opioid mechanism of gastrointestinal regulation. A related aspect is that of presumed peptidergic-mediated neural connections between gut and brain, supported by recent work in rats showing the modulation of central representation of gastric mechanoreceptor activity on application of opioid peptides or naloxone to the dorsal vagal nucleus (44).

If available information is still largely inadequate for assigning endogenous opioid peptides a definite physiological regulatory role in the enteric system, even less can be said of their involvement in gastrointestinal disease. Inhibition of ileal peristalsis in rats after laparotomy and cecum ablation was considered an experimental model representative of paralytic ileus in humans after intesti-

nal surgery (64); naloxone did not reverse peristaltic inhibition, so no support was obtained for increased release of endorphins under surgical stress as a causative factor in decreased intestinal motility. Subcutaneous administration of the enkephalin analog FK 33824 to human volunteers inhibited relaxation of the lower esophageal sphincter (LES), this inhibition being abolished by naloxone, which, given alone, had no influence on normal LES function; it was speculated that nonetheless naloxone might improve acalasia as a possible endogenous opioid–mediated disorder (63). Concurrent elevations in plasma β-endorphin (immunoreactive-material) and norepinephrine in healthy volunteers submitted to cold pain and labyrinthine stimulation suggest that these substances may be involved in stress-induced gastroduodenal motor disturbances (142). On the basis of two case-histories, Kreek and colleagues reported chronic constipation in humans to benefit from naloxone treatment (73), which implies that this condition might be sustained by hyperactivity of the endogenous opiate system; interestingly enough, naloxone relieved constipation even when given orally, its negligible central bioavailability upon oral administration suggesting an exclusively local intestinal mode of action. Improvement in eight aged constipated subjects after four days of treatment with oral naloxone, but not with placebo, on a double-blind, random, crossover protocol, has now been preliminarily reported by the same group (72). In this connection, food-derived opioid-like peptides (exorphins) may be mentioned for their potential effects on bowel movements, as suggested by the finding that hydrolyzed gluten prolongs intestinal transit time in man, this action being antagonized by concomitant oral naloxone (99). Quite recently, low doses of intracerebroventricular naloxone inactive intravenously were seen to prevent the inhibitory effect of *Escherichia coli* endotoxin on forestomach and antro-duodenal motility in ewes, and it was therefore suggested that a central endogenous opioid mechanism might account for the intestinal troubles (40), but whether this merely depends on the reversal of cardiovascular shock by naloxone (62) has not been clarified.

ADDITIONAL ASPECTS AND CONCLUSIONS

The effects of opioids on gut motility are still incompletely understood. While highlighting current developments in this area, we intend as well to call attention to some aspects of the gastrointestinal pharmacology of opioids that seem worthy of further work.

The recent significant advance in therapeutic utility consisting of the availability of gut-selective antidiarrheal agents without undesirable central actions clearly indicates that this kind of work can be highly rewarding, in terms of practical application among other things. These synthetic antidiarrheals unequivocally attest that local intestinal opioid-specific mechanisms are largely

sufficient for the production of important drug-induced motor effects in animals and man. The same local mechanisms have been classically advocated as the only ones accounting for morphine's constipating action (57), which, after the updated analysis presented in this review, can still be regarded as primarily if not exclusively peripheral. If the above holds for man, the undesirable constipation complicating morphine pain relief could be prevented by concurrent administration of a peripherally selective opioid antagonist, as already demonstrated in animal models (12, 47, 89, 152). This is reminiscent of the quite successful therapeutic combination of levodopa and a decarboxylase inhibitor unable to enter the CNS for treating Parkinson's disease, with lower incidence of peripheral side effects (25). Constipation as a troublesome complication of methadone maintenance in heroin addicts (37, 71) could possibly be managed by coadministration of suitable peripherally selective opioid antagonists, whose additional clinical potential might include replacement of naloxone for emergency reversal of delay in gastric emptying by narcotic analgesics during the induction of anesthesia (50, 103).

The pharmacological relevance of specific sites in the CNS inhibiting gut peristalsis, as evidenced by direct intracranial application of opioids, needs to be clarified. Narcotic analgesics such as etorphine that, unlike morphine (10), seem to be more readily available to the brain than to the gut (154), might act predominantly if not exclusively in the CNS to produce constipation (110). But information on distribution in intestinal tissues and CNS is scanty for most opioid drugs. Currently we are witnessing a boom in opioid receptor research, mostly in vitro, although the pharmacokinetic aspects of these agents appear to be somewhat neglected. Yet one of the most meaningful recent therapeutic examples of selectivity in opioid action, loperamide, is accounted for only pharmacokinetically, a factor that was fully considered in the sound in vivo pharmacological tests instrumental in developing this drug (157). Whether opioid receptor subtypes subserve any specific function affecting gut motility may well be ascertained in the light of future experiments.

The paucity of reports on in vivo studies on bowel function as affected by repeated administration of opioids [for representative work, see (22, 23, 26, 112, 117, 136, 154, 165, 167–169)] does not enable us to attempt an evaluation of the involvement of central and peripheral mechanisms in the development of intestinal tolerance and dependence.

Most of the arguments in favor of a role for endogenous opioids in gastrointestinal physiology are based on observations following either their administration or their presumed blockade by naloxone, with all the limitations of these approaches in studying gastrointestinal or other body systems (15). Better research tools—and we hope that newer, peripherally selective narcotic antagonists will provide some—are certainly needed for improving our knowledge of endogenous opioid function. However, this, like any other area of research, relies on critical attitudes of investigators as well as more sharply honed tools.

ACKNOWLEDGMENTS

We are grateful to Judy Baggott for style editing and to Monique Bibou for editorial assistance and for typing the manuscript.

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