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INHIBITION BY MORPHINE OF PROSTAGLANDIN-STIMULATED FLUID SECRETION IN RAT JEJUNUM

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1 Anaesthetized rats (225 to 300 g) were used to study the inhibitory effect of morphine on fluid secreted by the small intestine.

2 Small intestinal fluid secretion was stimulated by infusion of prostaglandin E_1 (PGE_1) into the aortic arch, the jejunum being more sensitive than the ileum. Infusion of PGE_1 2 μg/min caused maximal net fluid secretion in the jejunum but inhibited net fluid absorption in the ileum.

3 Morphine caused a dose-related inhibition of maximal PGE_1-stimulated fluid secretion in the jejunum. At the higher doses of morphine used (5 to 20 mg/kg) the fluid transporting function of the jejunum was restored almost to normal net absorption.

4 The inhibitory effect of morphine on PGE_1-stimulated fluid secretion was antagonized by naloxone. Naloxone caused a parallel shift to the right of the dose-response curve for morphine.

5 Two other narcotic analgesics were assayed relative to morphine and their descending order of potency was oxymorphone > morphine > pethidine.

6 It is suggested that the antisecretory effect of morphine in the small intestine may contribute to its efficacy as an anti-diarrhoeal drug. Further studies on the rat jejunum may show it to be a useful model for predicting narcotic drug activity and as such, may give some insight into the mechanisms of action of these drugs.

Introduction

The constipating actions of narcotic analgesics, such as morphine, have been a subject of investigation for many years. In most animals, including man, morphine inhibits gastric emptying, increases smooth muscle tone and inhibits propulsion of intestinal contents (Vaughan-Williams & Streeten, 1950; Daniel, Sutherland & Bogoch, 1959; Burks, 1976a). Additionally, morphine generally decreases gastric and pancreatic secretions and inhibits bile flow which further promotes concentration of gastrointestinal contents (Weinstock, 1971). There is evidence that part of the effect of morphine on the intestine is mediated by the release of 5-hydroxytryptamine (5-HT) (Burks & Long, 1967; Grubb, 1975) which stimulates acetylcholine release from intramural nerves (Daniel *et al.*, 1959). This appears to increase the tone and hence decrease the propulsive ability of the smooth muscle (Vaughan-Williams & Streeten, 1950).

Morphine is sometimes used to treat diarrhoea because of its constipating action (Martindale, 1972). Although in some cases diarrhoea results from increased gastrointestinal propulsion, it may also result from fluid secreted by the mucosa of the small intestine into the lumen. This fluid secretion is stimulated by many substances such as cholera enterotoxin and other bacterial toxins (Sladen, 1975), bile acids (Harries & Sladen, 1972), vasoactive intestinal peptide (Barbezat & Grossman, 1971) and prostaglandins (Greenough, Pierce, Al-Awqati & Carpenter, 1969). More recently, morphine has been shown to have antisecretory activity against the effect of crude cholera enterotoxin in rabbits and guinea-pigs (Valiulis & Long, 1973). This observation offers an explanation of the antidiarrhoel action of morphine in addition to its effect on muscle activity of the gut.

The purpose of the present investigation was to examine whether morphine inhibits the secretory rather than smooth muscle actions of prostaglandins, since prostaglandins may be released from the intestine in certain circumstances (Collier, 1974; Herman & Vane, 1975; Mennie, Dalley, Dinneen & Collier,

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1975) to produce a fluid diarrhoea (Mennie *et al.*, 1975). Furthermore, there have been a number of reports that morphine interacts with prostaglandins in some isolated tissues (Ehrenpreis, Greenberg & Belman, 1973; Collier & Roy, 1974; Traber, Fischer, Latzin & Hamprecht, 1975). If this is also the situation in the rat small intestinal mucosa then it may have some value as a model for exploring the actions of morphine. Prostaglandin E_1 (PGE_1) has been used since it has a direct action on the mucosa and its effects, in several species including man, have been relatively well documented (see Discussion). A preliminary determination was first made of the region of the small intestine most sensitive to PGE_1 as this had not previously been undertaken in the rat.

Methods

Male hooded rats (225 to 300 g) were kept for 1 week in wire bottomed cages and before experiments were allowed no food overnight but had access to drinking water. They were anaesthetized with a subcutaneous injection of pentobarbitone sodium (8 mg/100 g body weight) 1 h before experiments were started. The animals were placed on an electrically heated pad (approximately 35°C) and the trachea cannulated. A second cannula was introduced into the left common carotid artery and pushed down until its tip lay near the junction with the aorta for constant infusion of either 0.9% w/v NaCl solution (saline) or PGE_1 into the aortic arch from a constant infusion pump (C.F. Palmer London Ltd). Mean arterial blood pressure was recorded from the site of infusion with a pressure transducer connected to a polygraph.

Comparison of jejunum and ileum

A gravimetric method was used to determine the region of the small intestine most sensitive to the effect of PGE_1 on net water transport. Two groups of rats were used. In each the abdomen was opened and 2 segments of small intestine exposed, one approximately 20 cm distal from the ligament of Treitz (jejunum) and the other approximately 20 cm proximal to the ileo-coecal region (ileum). Infusion was then started in each of either saline or PGE_1 at 2 μg/min via the cannula in the carotid artery. The loops of intestine were washed with warm saline and emptied by gentle squeezing along their lengths. A ligature was placed at one end of each loop and tied; 5 min after starting infusion, the jejunum was filled with approximately 5 ml of isosmotic solution containing (g/l), NaCl 8.57, KCl 0.37 and dextrose 1.0, by the use of a blunt ended needle attached to a 5 ml syringe. The segment of ileum was filled in a similar manner with isosmotic solution containing (g/l), NaCl 8.74 and KCl 0.37. Both loops were tied off with a second ligature and returned to the abdominal cavity for a further 20 min while either the saline or PGE_1 continued to be infused (total volume 0.9 ml). The loops were then removed, carefully blotted with tissue paper, weighed, opened along the mesenteric border, blotted and weighed again. The syringes were also weighed before and after filling the segments. The differences in weights of the loops when first instilled with saline, and then again after 20 min was taken as an estimate of net water transport as has been used previously by Harries & Sladen (1972).

Jejunum

In the remainder of experiments net fluid transported by the jejunum was measured by a recirculation technique. The composition of the fluid was the same as that used in the closed loops of jejunum but contained additionally phenolsulphonphthalein (PSP) 20 mg/l to act as a non-absorbable marker for water transport. The solution was initially at pH 5.3 and approximately 10 ml was recirculated through the loop, from a glass reservoir (maintained at 37°C), by a gas lift consisting of a mixture of moistened 5% CO_2 in O_2. The height of the fluid in the reservoir was approximately 10 cm above the midpoint of the loop. At the end of the 20 min perfusion animals were killed by bleeding, the fluid from the loop was recovered and centrifuged; the net amount of water transported by the loop was estimated by measurement of the PSP concentration in a spectrophotometer by means of the triple wavelength correction method of Miller & Schedl (1972).

Results are expressed as the net amount of water absorbed (+) or secreted (−) per g wet weight of jejunum or ileum during the 20 min perfusion. The data obtained were subjected to analysis of variance and the significance of differences between control and treatment means assessed by Dunnetts' t test. Pairs of log dose-response curves were compared for estimation of dose-ratios, slope and curvature by use of a 3 + 3 bioassay design (Colquhoun, 1971). For all experiments results were considered to be significantly different when $P < 0.05$.

Drugs

Prostaglandin E_1 (PGE_1) (Upjohn Pty. Ltd.) was dissolved at a concentration of 10 mg/ml in absolute ethanol and stored at −20°C. On the day of experiments a sample of this was diluted to 1 mg/ml with 0.2 mol/l phosphate buffer ($NaH_2PO_4.H_2O$ 11 g/l and $Na_2HPO_4.7H_2O$, 8.45 g/l) and further diluted with saline to permit the required infusion rate. All other drugs were given subcutaneously.

Pentobarbitone sodium (B. Vet. C.) was available

as Nembutal (Abbott Laboratories). This preparation contains 60 mg pentobarbitone sodium per ml of vehicle containing 10% ethanol and 40% propylene glycol in water for injection. Indomethacin (Merck, Sharp & Dohme (Australia) Pty. Ltd.) was dissolved directly in the Nembutal. Pentobarbitone sodium or the pentobarbitone sodium plus indomethacin mixture were given 1 h before perfusion of the jejunum. Morphine hydrochloride B.P. (Macfarlan Smith Ltd.), oxymorphone hydrochloride hydrate (Endo Laboratories) and pethidine hydrochloride B.P. (Endo Laboratories) were dissolved in saline and were given 30 min before perfusion of the jejunum. Naloxone hydrochloride (Bristol Myers Co.) was dissolved with morphine in saline and the mixture given 30 min before perfusion of the jejunum. All doses of drugs either separately or combined were given in volumes of 0.1 ml/100 g of body weight. Where drugs were available as hydrochlorides or hydrochloride hydrate (oxymorphone) their doses are expressed as the hydrochloride.

Results

Mean arterial blood pressure

The mean arterial blood pressure in the group pretreated with indomethacin was not significantly different from the control group (measured 15 min after starting saline infusion). Infusion of PGE_1 into the aortic arterial blood supply caused an infusion-related depressor response which was fully developed within 2 min (Table 1). Morphine did not affect the reduced arterial blood pressure that resulted from infusion of PGE_1 2 μg/min ($P > 0.05$).

Comparison of jejunum and ileum

Control animals, infused with saline into the aortic blood supply, absorbed 160 ± 60 μl/g of water from the closed loop of jejunum in 20 min ($n = 8$). On infusion of PGE_1 2 μg/min, instead of saline, the jejunum secreted −120 ± 50 μl/g of water in 20 min ($n = 8$). The 2 means were significantly different ($P < 0.05$).

The ileum of control animals absorbed 170 ± 10 μl/g ($n = 8$) which was a similar amount to that absorbed by the jejunum ($P > 0.05$). However, rather than reverse net water transport, as in the jejunum, PGE_1 2 μg/min only reduced net water absorption to 20 ± 40 μl/g ($n = 8$). This was significantly different from the control mean ($P < 0.05$).

The effect of the PGE_1 infusion on the jejunum was significantly greater than on the ileum ($P < 0.005$).

Jejunum

In the continuous perfusion of the jejunum experiments there was slightly, though not significantly ($P > 0.05$), greater net water absorption in the group pretreated with indomethacin (10 mg/kg) compared to the control group (Table 1). PGE_1 reduced net water absorption at low infusion rate and reversed it to net secretion at higher infusion rates. The effect was maximal at 2 μg/min since no further secretion occurred on infusing 8 μg/min (Table 1).

Morphine

In groups of rats pretreated with indomethacin, increasing doses of morphine caused a progressive inhi-

Table 1 Effect of prostaglandin E_1 (PGE_1) infusion on mean arterial blood pressure and net water transport.

Treatment			
Infusion	*s.c. injection*	*Arterial BP (mmHg)*	*Net water transport (μl/g in 20 min absorbed (+) or secreted (−))*
Saline	—	131 ± 7	+200 ± 70
Saline	Indomethacin (10 mg/kg)	153 ± 8 NS	+270 ± 40 NS
PGE_1 (μg/min)			
0.5	—	113 ± 9 NS	+70 ± 100 NS
2	—	91 ± 4*	−220 ± 40*
8	—	86 ± 4*	−140 ± 50*

Values are mean ± s.e. mean; $n = 6$.
* Mean differing significantly from its control mean ($P < 0.01$).
NS = not significant ($P > 0.05$). As indomethacin was dissolved in the anaesthetic vehicle the appropriate control for this treatment was an injection of Nembutal. Mean arterial blood pressure was measured 15 min after starting infusion.

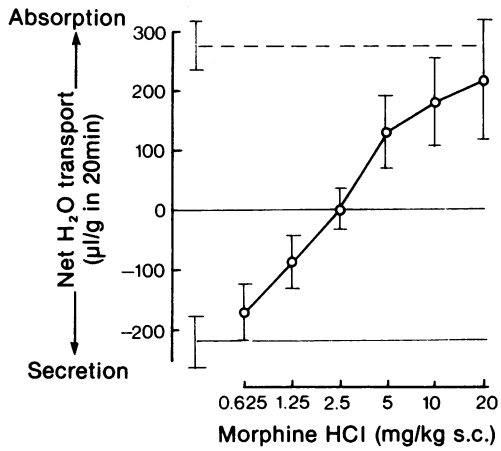

Figure 1 The inhibition by morphine of prostaglandin E_1 (PGE_1)-stimulated fluid secretion in the jejunum. The bottom continuous line represents the mean maximal fluid secretion stimulated by PGE_1 2 µg/minute. The top broken line represents the mean value of net fluid absorption in the control group infused with saline into the carotid artery and pretreated with indomethacin (10 mg/kg s.c. 1 h before). The vertical bars indicate s.e. mean (n = 6, from Table 1). Morphine reversed fluid secretion towards normal absorption in the groups injected with the higher doses. Bars indicate s.e. mean (n = 7 at each dose).

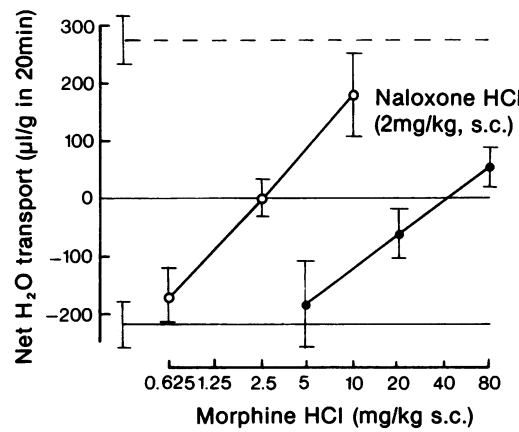

Figure 2 Inhibition by naloxone of the antisecretory effect of morphine. Bottom continuous line and top broken line as in Figure 1. Vertical bars represent the s.e. mean (n = 7 at each point). (○) Morphine alone; (●) morphine and naloxone mixture.

bition of maximal (2 µg/min) PGE_1-stimulated fluid secretion. The effect occurred over a range of doses from 1.25 to 20 mg/kg. At the higher doses of morphine the fluid transporting function of the jejunum was returned from net secretion almost to the normal control net absorptive value (Figure 1). The ED_{50} for morphine hydrochloride was 1.5 mg/kg (95% confidence limits 10.4 – 0.1 mg/kg) (Figure 1).

Morphine and naloxone

The inhibitory effect of morphine on PGE_1-stimulated fluid secretion was in turn inhibited by naloxone. The dose-response line of morphine given together with 2 mg/kg naloxone was significantly shifted to the right of the dose-response line of morphine alone ($P < 0.05$). The dose-ratio was 17 (95% confidence limits 50 – 10). There was significant regression in the lines ($P < 0.005$) but no significant differences between slopes or curvatures ($P > 0.05$) (Figure 2).

Potencies of oxymorphone and pethidine relative to morphine

Two other narcotic analgesics were assayed relative to morphine for ability to inhibit PGE_1-stimulated fluid secretion. Oxymorphone and pethidine both showed activity, the decreasing order of potency being oxymorphone > morphine > pethidine. Oxymorphone was 29 times more potent than morphine (95% confidence limits 100 – 9). There was significant regression in the lines ($P < 0.05$) but no significant differences between slopes or curvature ($P > 0.05$). Pethidine had only 0.1 times the activity of morphine (95% confidence limits 0.6 – 0.02). There was significant regression in the lines ($P < 0.05$) but no significant differences between slopes or curvature ($P > 0.05$) (Figure 3).

Discussion

Infusion of PGE_1 into the aortic blood stimulated fluid secretion in the jejunum and inhibited fluid absorption in the ileum. Because of the greater sensitivity of the jejunum to PGE_1, experiments were confined to this region. Prostaglandins are probably not normally involved in the control of fluid transport by the small intestine but injury caused by mechanical compression stimulates PGE-like release from rat intestine (Collier, 1974). For this reason the prostaglandin synthetase inhibitor, indomethacin, was used in an attempt to reduce any possible background prostaglandin effects caused by release during the operative procedure.

In the jejunum there was a large difference between the amount of fluid normally absorbed and that secreted in response to infusion of PGE_1 into the aortic blood. Between this range morphine exerted a dose-related antisecretory effect on maximal PGE_1-stimu-

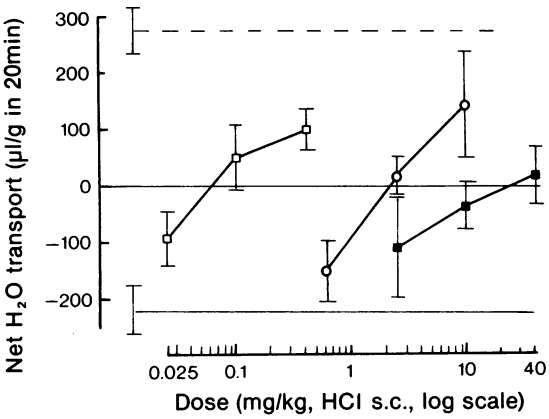

Figure 3 Relative potencies of 3 narcotic analgesics: (□) oxymorphone; (○) morphine; (■) pethidine. Bottom continuous line and top broken line as in Figure 1. The descending order of potency was oxymorphone > morphine > pethidine. Vertical bars show s.e. mean (n = 6 at each point).

lated fluid secretion, returning function almost to normal (Figure 1).

Experiments with isolated sheets of small intestinal mucosa have shown that prostaglandins act directly to stimulate electrolyte secretion. This involves inhibition of Na^+ absorption and possibly stimulation of Cl^- secretion (Al-Awqati & Greenough, 1972). Morphine must therefore act on the mucosa either directly or indirectly by liberating an intermediate. For example, morphine has been shown to cause circular muscle spasm in rat intestine *in vivo* by local release of endogenous 5-HT (Burks, 1976b). However, local 5-HT release cannot explain the antisecretory effect of morphine since 5-HT is a stimulant rather than an inhibitor of intestinal fluid secretion (Donowitz, Charney & Heffernan, 1977).

There is evidence that morphine acts directly on the mucosal cells. In a preliminary report (Collier & Roy, 1974) it was shown that morphine inhibited PGE_1-stimulated rise in cyclic 3',5'-adenosine monophosphate (cyclic AMP) formation in rat intestinal homogenate. This should be treated with some reservation since the effect may have been one on nerves or smooth muscle also present in the homogenate. However, cyclic AMP does appear to be the final common mediator of electrolyte and hence fluid secretion in the intestinal mucosa of the guinea-pig, rabbit and rat (Kimberg, Field, Johnson, Henderson & Gershon, 1971).

From experiments using guinea-pig isolated small intestine, Jaques (1969) has suggested that the antidiarrhoeal action of morphine may result from its ability to inhibit smooth muscle contraction induced by PGE_1. The finding that morphine inhibits fluid secreted by the mucosa of the small intestine may offer an additional explanation for the efficacy of morphine as an antidiarrhoeal drug. The ED_{50} of morphine for inhibition of maximal PGE_1-stimulated fluid secretion (1.5 mg/kg) is similar to its ED_{50} in rat antinociceptive tests. The ED_{50} (mg/kg) for morphine sulphate, 30 min after subcutaneous injection, has been estimated as 2.9 by the tail pressure method (Blane, Boura, Fitzgerald & Lister, 1967) and 3.9 by the tail flick method (Wei, 1973). This suggests that morphine would be antisecretory, and hence antidiarrhoeal, at similar doses to those causing analgesia. The assumption is made here that prostaglandins are involved in the pathogenesis of diarrhoea or, if not, that morphine blocks the final common pathway of fluid secretion. Although prostaglandins can be released from the intestine and cause fluid secretion there is not yet enough evidence to substantiate whether they are mediators in the pathogenesis of fluid diarrhoea. For example, early studies with crude cholera enterotoxin implicated prostaglandins as intermediates since prostaglandin synthetase inhibitors were shown to be effective inhibitors of fluid secretion (Finck & Katz, 1972; Jacoby & Marshall, 1972). While there now appears to be more evidence refuting the involvement of prostaglandins in cholera, Bennett (1976) argues that much of this is not yet proven. It remains to be seen whether prostaglandin release causes the fluid secretion stimulated by other enterotoxins such as those produced by some strains of *E. coli*, *Staph. aureus* and *Cl. perfringens* (Sladen, 1975). Prostaglandins appear to be the cause of fluid diarrhoea in some patients receiving radiation therapy (Mennie *et al.*, 1975) and also in some patients with aminepeptide secreting tumours (Williams, Karim & Sandler, 1968). The observation that rat jejunum is more sensitive than ileum is interesting in relation to Collier's (1974) finding that rat jejunum can release more PGE-like material than ileum. This correlation suggests a possible function for prostaglandins of the E-type in the upper small intestinal mucosa although it has not been established what this might be. The finding that rat jejunum is more sensitive than ileum to cholera enterotoxin is also interesting (Strombeck, 1972). Whether this reflects release of prostaglandin by the toxin or just a general difference in sensitivity of the mucosa to all secretagogues remains to be determined.

The present experiments have not established site of action of morphine although the evidence cited suggests a direct one on the mucosal cells. This could be through occupation of a prostaglandin receptor or inhibition at a more distal site. The problem could be resolved by the use of other agonists such as vasoactive intestinal peptide which is a potent agonist in the rat jejunum (Coupar, 1976). Wherever morphine's site of action is located it appears to be

mediated through an opiate receptor since the effect of morphine was inhibited by the competitive opiate antagonist, naloxone. In these experiments naloxone may have acted competitively since the dose-response curve for morphine was moved to the right in a parallel manner (Figure 2). Further evidence implying that morphine interacts with an opiate receptor in rat mucosa was obtained from the relative potencies of two other narcotic analgesics. Oxymorphone was more potent while pethidine was less potent than morphine (Figure 3), a relationship that is the same as their relative potencies clinically as analgesics (Jaffe & Martin, 1975).

There are other instances where morphine inhibits the effect of prostaglandins in peripheral tissues. For example PGE_1 and PGE_2 reverse the inhibitory effect of morphine on electrically-induced contractions of guinea-pig isolated ileum (Ehrenpreis *et al.*, 1973). Also morphine inhibits the rise in cyclic AMP stimulated by PGE_1 in certain tumour cells from rodents (Traber *et al.*, 1975). As in these cells and the rat jejunum, morphine also exerts an inhibitory action on the production of cyclic AMP in brain cells. In rat brain, morphine decreases cyclic AMP especially in the hypothalamus, medulla and cerebellum (Clouet, Gold & Iwatsubo, 1975). Collier & Roy (1974) have shown, that morphine inhibits the rise in cyclic AMP stimulated by PGE_1 and PGE_2 in rat brain homogenate. In reviewing the effects of morphine, prostaglandins and cyclic AMP, they conclude that inhibition by morphine of prostaglandin-stimulated cyclie AMP may account at a biochemical level for the central effects of morphine (Collier & Roy, 1974; Collier, Francis, McDonald-Gibson, Roy & Saeed, 1975). Further studies of the effect of morphine on rat intestinal mucosa as well as helping to explain its antidiarrhoeal effect may also yield some valuable information on the actions of morphine. The mucosa may also be a useful model for predicting the constipating and analgesic activity of new narcotic analgesics.

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