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EFFECTS OF MORPHINE ON CANINE INTESTINAL ABSORPTION AND BLOOD FLOW

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1 Intestinal absorption and blood flow were determined in anaesthetized fed or fasted dogs following rapid intravenous injections of morphine (0.01, 0.1, 1 mg/kg).

2 ^3H_2O and ^{22}Na were used to determine the unidirectional fluxes of Na^+ and H_2O from saline perfused through the ileal lumen and the clearances of ^3H_2O were used to determine total and absorptive site blood flow.

3 Net Na^+ and H_2O absorption were increased at each dose of morphine in fed but not in fasted dogs, due primarily to increased absorptive fluxes.

4 Arterial pressure was decreased by morphine but mesenteric vein pressure was little affected. Absorptive site blood flow was increased by morphine due to decreased blood flow resistance but total blood flow resistance was little affected by morphine.

5 The absorptive fluxes of Na^+ and H_2O were correlated with absorptive site blood flow in both fed and fasted animals. The secretory fluxes of Na^+ and H_2O were correlated with estimated capillary pressure in fasted dogs but morphine decreased the secretory fluxes at a given capillary pressure in dogs which had been fed.

6 Naloxone (0.12 mg, i.v.) reversed the effects of morphine. The effects of morphine on the gut were reversed more slowly than on systemic blood pressure.

7 It was concluded that morphine can increase net absorption in fed dogs by a selective increase in intestinal absorptive site blood flow and thus increase absorptive fluxes by a washout effect but that there is also an epithelial effect, sensitized by feeding, which reduces the secretory fluxes of Na^+ and H_2O.

Introduction

Opiates have been used as anti-diarrhoeal agents for centuries and the gut is extremely sensitive (Jaffe & Martin, 1975). The mechanism of opiate anti-diarrhoeal action is thought to be due to slowing of intestinal propulsive motility. Binder (1977) states, 'There is no experimental evidence to date that drugs like codeine directly affect absorptive or secretory transport processes'. However, many diarrhoeal states involve active secretion (Powell, Binder & Curran, 1973) and slowing of propulsive activity *per se* would not reverse this secretion (Binder, 1977). Also, codeine has been shown to increase intestinal transport *in vitro* (Racusen, Binder & Dobbins, 1978). Therefore, the possibility that gut absorption could be directly increased by opiates was investigated as was the involvement of cardiovascular effects because of previous work showing that gut absorptive site blood flow or pressure could, in part, be responsible for changes in gut absorption due to hormones (MacFerran & Mailman, 1977; Mailman, 1978a).

Methods

Experimental procedures

The basic experimental procedure has been described in detail elsewhere (Mailman & Jordan, 1975). Isotonic saline containing ^3H_2O, [^{14}C]-inulin (as a volume marker) and ^{22}Na was perfused at a known rate ($\simeq 3$ ml/min) through ileal segments of dogs anaesthetized with pentobarbitone sodium. The dogs were either fed food and H_2O *ad libitum*, including the morning of the experiment, or deprived of food for at least 18 h. The effluent solution was collected from a cannula arranged so that a pressure of about 5 cm saline was exerted on the gut and allowed mixing of the intestinal contents due to peristalsis and respiratory movement. A femoral artery and a branch of the mesenteric vein draining the ileal segment were cannulated in order to obtain pressures and plasma samples. At the end of the experiment the gut segments were removed, drained and weighed; all pertinent data are expressed as 'per g gut'. Arterial and mesenteric venous pres-

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sures were determined by mercury and saline manometers, respectively. The gut effluent and plasma were analyzed for ^3H_2O, ^{14}C and ^{22}Na by liquid scintillation counting and Na^+ and K^+ by flame photometry. Femoral artery blood flow was determined by means of an electromagnetic flow meter (Carolina Medical Electronics). Transmural intestinal voltage was measured with 1 M KCl- 3% agar salt bridges in the peritoneal cavity (as zero reference) and gut lumen, and a high impedance electrometer (Keithley).

Experimental protocol

After three 20 min control periods, morphine sulphate (0.01, 0.1, 1 mg/kg) was injected rapidly intravenously (i.v. bolus) and gut absorption measured for three 20 min periods after each dose. Any changes with time were also studied in control animals. Both fed and fasted animals were used. Statistical analysis was by paired *t* test, in which the value for the average of the three 20 min control periods was subtracted from the value for each experimental period and the significance of the difference determined. Linear regression analysis was employed to determine the relationship between the variables. All values are given as mean ± s.e. mean.

After completion of the above series of experiments, the effects of the opiate antagonists naloxone hydrochloride (0.12 mg, i.v., Endo Laboratories) and nalorphine HCl (0.2 mg, i.v. Merck, Sharp & Dohme) on the morphine-induced changes was determined. After three 20 min control periods morphine was injected (1 mg/kg, i.v.) and, after 5 to 10 min, a 20 min period of gut absorption taken. Naloxone or nalorphine was injected after this period and then two 20 min periods carried out. Statistical analysis was carried out as above.

Calculations

Unidirectional Na^+ and H_2O fluxes were determined by the method of Berger & Steele (1958). Total blood flow (TBF) was calculated from the clearance of ^3H_2O as $TBF = {}^3H_2O_{ABS}/[{}^3H_2O]_V - [{}^3H_2O]_A$ and absorptive site blood flow (ASBF) as $ASBF = {}^3H_2O_{ABS}/[{}^3H_2O]_L - [{}^3H_2O]_A$; where $^3H_2O_{ABS}$ represents the amount of ^3H_2O absorbed from the lumen, $[{}^3H_2O]$ represents the concentration of ^3H_2O and V, A, L represent mesenteric vein, artery and lumen effluent, respectively. It should be pointed out that $^3H_2O_{ABS}$ in the formulae is not the same as the absorptive H_2O flux calculated from the flux equations.

Previous work (Mailman, 1978b) has suggested that this measurement of TBF provides an accurate measurement of a real blood flow to the gut. The calculation of ASBF is intrinsically valid as a measure of a virtual functional blood flow into which ^3H_2O reaches complete equilibrium between lumen and blood. In addition, ASBF seems to be a measure of a real blood flow rather than only a virtual flow (Mailman, 1978b). Blood flow resistance was determined from the A-V pressure difference and TBF or ASBF. Capillary pressure was estimated by the method of Pappenheimer & Soto-Rivera (1948). The control pre:post capillary resistance ratio was taken as 5:1 and any changes in total resistance were assumed to be pre-capillary (Folkow, 1967). It should be emphasized that this is an indirect measurement and only an approximation of capillary pressure.

Results

Control periods in fed or fasted dogs

There were no significant differences between fed and fasted dogs in the control periods (Table 1) but there were small but significant changes with time, particularly in fed control animals and, thus, these control groups are shown in the Figures.

Effect of morphine on Na^+ and H_2O fluxes

Morphine significantly increased net Na^+ absorption at each dose (Figure 1) in fed dogs but not in fasted dogs. At the two lowest doses in fed dogs the effect was transient, from 20 to 40 min, but was sustained for the entire 60 min period after 1 mg/kg morphine. Net Na^+ absorption in fasted dogs was significantly increased in only one period at the highest dose. There was little effect of morphine on the secretory flux of Na^+ in either fed or fasted dogs. Morphine significantly increased the absorptive flux of Na^+ only in the first 20 min following each dose in fed but not in fasted dogs. However, the absorptive Na^+ flux was increased to about the same extent in fed and fasted dogs at the highest dose of morphine even though net Na^+ absorptive was not. Also, net Na^+ absorption was increased significantly without significant increases in the absorptive Na^+ fluxes. Therefore, the difference between outflux and influx (the net flux) is more affected by morphine than is either unidirectional flux. This was also reflected in the absorptive: secretory Na^+ flux ratio which, in fed dogs was increased from 2.4 to 4.3 but unchanged in fasted dogs from 2.7 to 2.6 at 1 mg/kg morphine. Morphine had effects on the H_2O fluxes that were similar to those on the Na^+ fluxes (Figure 2). Net secretion of K^+ ($\mu Eq\ g^{-1}\ min^{-1}$) was little affected by morphine, changing from 0.061 ± 0.003 to 0.068 ± 0.005 in fasted dogs and from 0.046 ± 0.002 to 0.047 ± 0.003 in fed dogs from the control periods as compared to 1 mg/kg morphine.

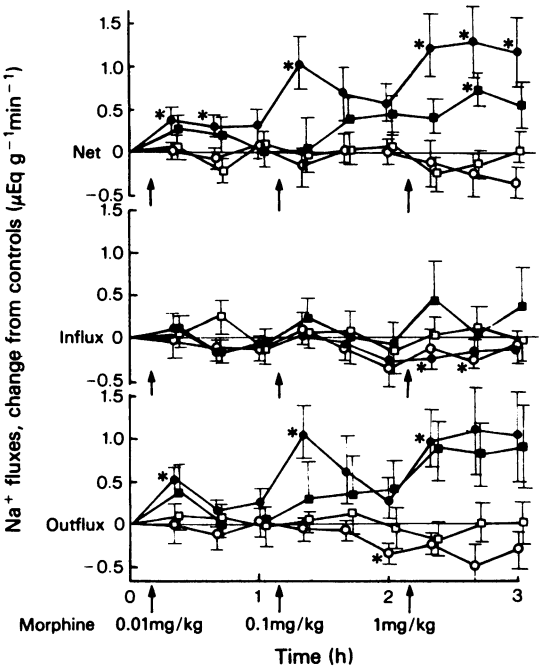

Figure 1 Effects of morphine (0.01, 0.1, 1 mg/kg i.v. bolus at ↑) on net, secretory (influx) and absorptive (outflux) fluxes of Na^+ across fed or fasted canine ileum. Open symbols: control, closed symbols: plus morphine; (○) fed (n = 7); (□) fasted (n = 7); (●) fed (n = 9); (■) fasted (n = 7). * represents a difference from control period values significant to at least the 5% level. Mean values are shown; vertical lines indicate s.e. mean.

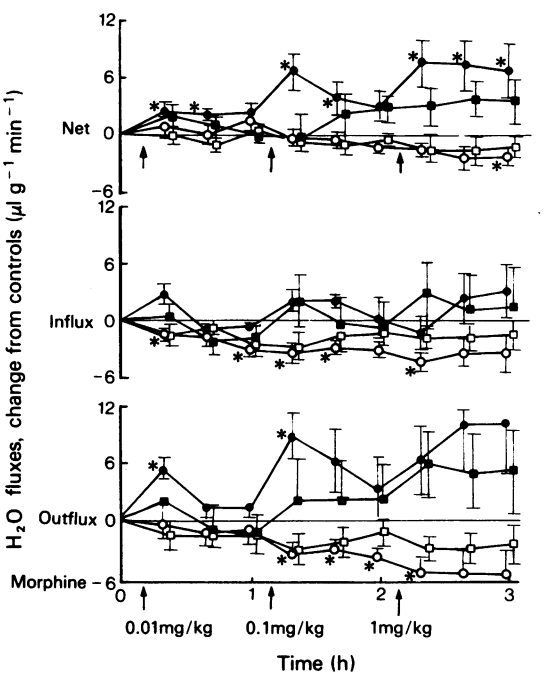

Figure 2 Effects of morphine (0.01, 0.1, 1 mg/kg i.v. bolus at ↑) on net, secretory (influx) and absorptive (outflux) fluxes of H_2O across fed or fasted canine ileum. Open symbols: control; closed symbols: plus morphine; (○) fed (n = 7); (□) fasted (n = 7); (●) fed (n = 9); (■) fasted (n = 7). * represents a difference from control period values significant to at least the 5% level. Mean values are shown; vertical lines indicate s.e. mean.

Table 1 Control period values in fed or fasted dogs

	Fed (n = 9)	*Fasted* (n = 7)
Na^+ fluxes	(μEq g^{-1} min^{-1})	
Net absorption	1.05 ± 0.29	1.23 ± 0.20
Secretory	0.77 ± 0.10	0.75 ± 0.17
Absorptive	1.82 ± 0.31	1.98 ± 0.75
H_2O fluxes	(μl g^{-1} min^{-1})	
Net absorption	6.06 ± 1.91	7.01 ± 1.64
Secretory	17.8 ± 2.2	19.5 ± 1.2
Absorptive	23.9 ± 3.3	26.6 ± 2.4
Blood pressure	(mmHg)	
Arterial	133 ± 5	132 ± 6
Mesenteric vein	7.2 ± 0.3	7.0 ± 0.7
Blood flow	(ml g^{-1} min^{-1})	
Total	0.82 ± 0.11	0.80 ± 0.13
Absorptive site	0.031 ± 0.005	0.034 ± 0.003
Resistance	(mmHg·g·min/ml)	
Total	194 ± 24	189 ± 22
Absorptive site	5070 ± 727	4322 ± 513

Values are mean ± s.e. mean.

Effect of morphine on cardiovascular parameters

Morphine had little effect on total blood flow (Figure 3) which decreased significantly in many periods in both control and morphine-injected dogs, both fed and fasted. Absorptive site blood flow was significantly increased in fed dogs for 20 min following the two lowest doses of morphine but, although relatively high, was not significantly increased above control periods at 1 mg/kg morphine (Figure 3). However, when compared to fed control animals, which had significant decreases in ASBF, the ASBF was significantly increased in all periods following 0.1 and 1 mg/kg morphine as determined by unpaired t test. Morphine had no significant effect on ASBF in fasted animals either in comparison to their own control periods or to fasted control animals except for an increase during the first 20 min after 1 mg/kg morphine by the latter comparison. Femoral artery blood flow was not consistently affected by morphine. Femoral artery blood flow was 32.6 (±3.7), 43.1 (±7.1), 37.6 (±6.6) and 57.8 (±10.0) in fed dogs and

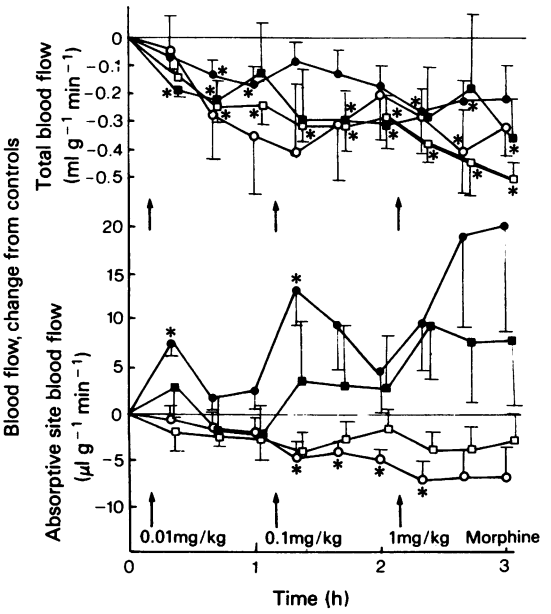

Figure 3 Effects of morphine (0.01, 0.1, 1 mg/kg i.v. bolus at ↑) on total and absorptive site blood flow through fed or fasted canine ileum. Open symbols: control; closed symbols: plus morphine; (○) fed (n = 7); (□) fasted (n = 7); (●) fed (n = 9); (■) fasted (n = 7). * represents a difference from control period values significant to at least the 5% level. Mean values are shown; vertical lines indicate s.e. mean.

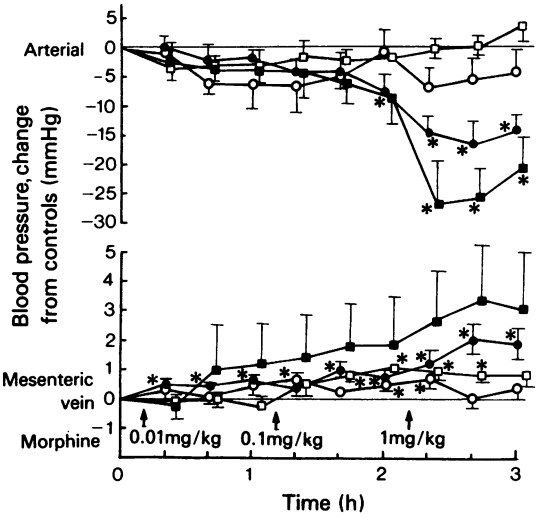

Figure 4 Effects of morphine (0.01, 0.1, 1 mg/kg i.v. bolus at ↑) on arterial and mesenteric venous pressure in fed or fasted dogs. Open symbols: control; closed symbols: plus morphine; (○) fed (n = 7); (□) fasted (n = 7); (●) fed (n = 9); (■) fasted (n = 7). * represents a difference from control period values significant to at least the 5% level. Mean values are shown; vertical lines indicate s.e. mean.

37.3 (±4.5), 36.2 (±6.7), 43.5 (±9.6) and 29.8 (±5.2) in fasted dogs for the four consecutive hour periods, respectively.

Morphine decreased arterial pressure in both fed and fasted animals only at 1 mg/kg (Figure 4). Mesenteric venous pressure was little affected by morphine although it tended to increase (Fig. 4). However, small but significant increases in mesenteric venous pressure were present in controls and the largest increases, which were in fasted animals injected with morphine, were not significant.

Total blood flow resistance tended to increase following morphine but the increase was less than in control animals (not shown) and may be indicative of a relative decrease in resistance due to morphine (Figure 5). In contrast, ASBF resistance was decreased by morphine in both fed and fasted dogs although the decrease was greater in fed dogs. Control dogs had steady increases in ASBF resistance with a final value about 20% above their first hour.

Correlation between fluxes and cardiovascular parameters

The absorptive fluxes of Na^+ and H_2O were correlated with ASBF (Figure 6) with no differences in the relationship between fed or fasted dogs. However, the points from fasted dogs tended to be distributed toward the lower portion of the line. Estimated capillary pressures (the average over the entire hour periods) were 28.1, 31.5, 35.2 and 41.2 in fed dogs and 27.8, 28.7, 31.4 and 36.0 in fasted dogs for control, 0.01, 0.1 and 1 mg/kg morphine periods, respectively. The secretory fluxes of both Na^+ and H_2O were significantly correlated with estimated capillary pressure in fasted dogs injected with morphine (Figure 7). The secretory fluxes of H_2O were also significantly correlated with estimated capillary pressure in fed dogs given morphine but for any given capillary pressure the secretory H_2O fluxes were less in fed than in fasted animals. The secretory Na^+ flux was not significantly correlated with capillary pressure following morphine injection in fed dogs and, as with H_2O, the secretory Na^+ flux was less in fed than in fasted dogs as capillary pressure increased.

Effects of opiate antagonists

The data presented above indicated that 1 mg/kg i.v. morphine, following lower doses of morphine, caused changes in gut transport and blood flow which lasted for at least 60 min. The effects of naloxone (n = 9) and nalorphine (n = 4) were determined 20 min after

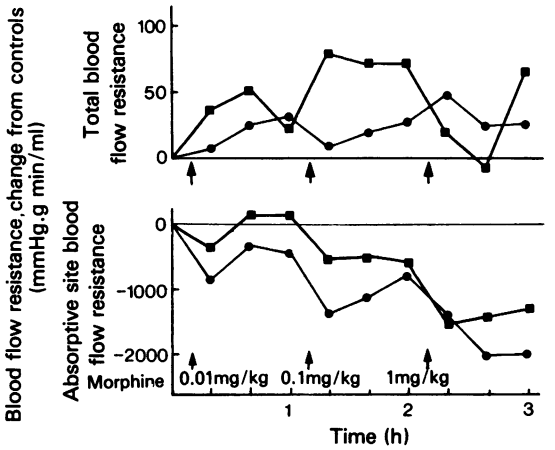

Figure 5 Effects of morphine (0.01, 0.1, 1 mg/kg i.v. bolus at ↑) on blood flow resistance (based on average values of blood pressure and flow) in fed or fasted canine ileum. (●) Fed plus morphine (n = 9); (■) fasted plus morphine (n = 7).

morphine was injected immediately following the control periods. If the opiate antagonists were not given after 20 min then the significantly changed fluxes and ASBF became even larger and were 70 to

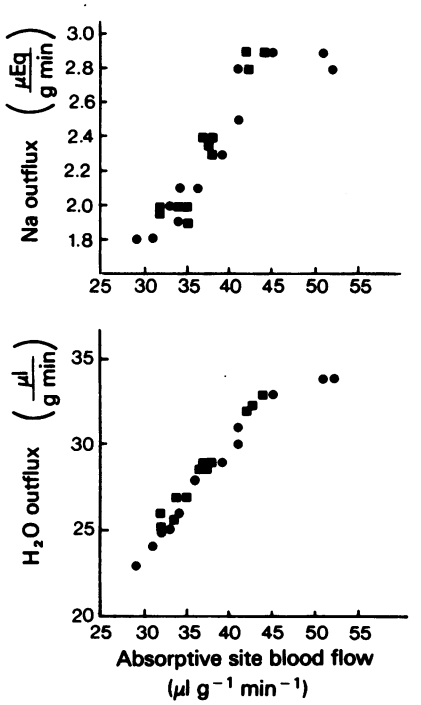

Figure 6 The relationship between average Na^+ and H_2O absorptive flux (outflux) and absorptive site blood flow in fed (●) or fasted (■) canine ileum following morphine injection.

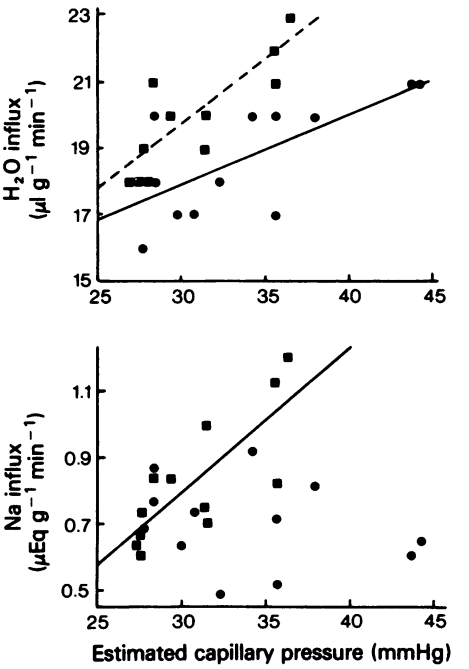

Figure 7 The relationship between average Na^+ and H_2O secretory flux (influx) and estimated capillary pressure in fed (●) or fasted (■) canine ileum following morphine injection. Lines represent significant (r at least 0.7; $P < 0.01$) linear regression equations.

100% greater in the 40 to 60 min period than in the 0 to 20 min period (data not included). In contrast, naloxone reversed the effects of morphine beginning within the first 20 min and all values became not significantly different from control within the next 20 min (Table 2). As in the previous experiments, net Na^+ and H_2O absorption were increased by morphine due to significant increases in the unidirectional absorptive fluxes and associated with increased ASBF. There was no effect of morphine on transmural voltage. The time course of the effect of naloxone was different for arterial blood pressure as compared to the gut effects. Naloxone returned blood pressure to control levels within a few minutes and blood pressure was slightly greater than control 40 min after naloxone, but the absorptive fluxes of Na^+ and H_2O were still significantly above control in the 20 min following naloxone and, in general, none of the values had returned completely to control levels within 40 min. ASBF, although not significantly different from control, was slightly greater after naloxone than after morphine. The relatively lower dose of nalorphine (0.2 mg i.v.) reversed the effect of morphine only for 20 min but the values returned to the same level as with morphine alone during the following 20 min period (data not included).

Table 2 Effects of morphine (1 mg/kg i.v. bolus) followed by naloxone (0.12 mg, i.v. bolus) on fed canine gut transport and blood flow

	Morphine + min 0–20	*Naloxone 20–40*	*40–60*
Na^+ fluxes		(μEq g^{-1} min^{-1})	
Net	0.92 ± 0.21**	0.56 ± 0.23*	0.37 ± 0.20
Secretory	−0.16 ± 0.12	0.08 ± 0.08	0.15 ± 0.15
Absorptive	0.76 ± 0.23**	0.64 ± 0.25*	0.52 ± 0.28
K secreted	0.011 ± 0.006	0.013 ± 0.005*	0.011 ± 0.005
H_2O fluxes		(μl g^{-1} min^{-1})	
Net	5.4 ± 1.3**	3.4 ± 1.5	2.4 ± 1.2
Secretory	2.8 ± 2.1	4.8 ± 2.5	4.1 ± 2.2
Absorptive	8.2 ± 2.5**	8.3 ± 3.6*	6.5 ± 3.2
Blood flow			
ASBF	11.9 ± 4.0*	12.4 ± 5.9 (ml min^{-1})	9.7 ± 5.2
Femoral	3.3 ± 5.4	2.6 ± 5.2	5.0 ± 4.8
Blood pressure		(mmHg)	
Arterial	−22.6 ± 6.2**	−1.8 ± 3.4	4.6 ± 5.9
Mesenteric vein	1.00 ± 0.70	0.46 ± 0.22	0.76 ± 0.36
		(mmHg·g·min/ml)	
ASBF resistance	−2244 ± 470***	−1278 ± 610	−948 ± 646
		(mV)	
Transmural voltage	−0.55 ± 0.67	−0.23 ± 0.57	0.02 ± 0.59

Change from control, mean ± s.e. mean.
*, **, *** represent changes from control, significant at the 5%, 1% and 0.1% level respectively. $n = 9$.

Discussion

Motility is known to be increased or decreased by morphine or other opiates depending on the species (Ehrenpreis, 1975; Grubb & Burks, 1975). Motility changes have been considered to be the sole explanation for the anti-diarrhoeal activity but the results from the present experiments suggest that, in addition, morphine can alter gut transport and blood flow. Motility or tonus changes with consequent possible effects on mucosal surface area or transit time could not account for the effect obtained here because this would result in proportional changes in all fluxes. Instead, it was found that absorptive and secretory fluxes could change in opposite directions and also the secretion of K^+, which is mainly passive, was unchanged by morphine.

Morphine increases proportionally ASBF and the absorptive Na^+ and H_2O fluxes in both fed and fasted dogs. ASBF resistance is decreased by morphine but TBF resistance is little affected. This suggests that morphine has a relatively specific cardiovascular effect on some component of villus blood flow but not on muscularis or submucosal flow. The absorptive fluxes of Na^+ and H_2O are probably increased due to increased washout by the elevated ASBF, as suggested in other experiments (Winne, 1972; Mailman, 1978a).

The greater increase in net Na^+ and H_2O absorption in fed dogs relative to fasted dogs is primarily due to the quantitatively greater decrease in ASBF resistance and relatively smaller decrease in blood pressure in fed dogs which results in a larger increase in ASBF. The larger increase in ASBF results in greater washout of the absorptive fluxes which will tend to increase net absorption more in fed dogs than in fasted dogs. However, the proportionality between ASBF and absorptive fluxes is the same in fed and fasted dogs. This suggests that any processes which affect the efficiency of washout (e.g., pumping rate, surface area) are not changed by morphine. Changes in efficiency of washout have been observed with other agents (Mailman, 1978a); therefore, the identity of the proportionality between ASBF and the absorptive fluxes is not obligatory. Increased net absorption in fed dogs also had a smaller and only relative contribution from a reduction in the efficiency with which the greater capillary pressure in fed dogs could increase the secretory fluxes into the lumen. The effect of morphine in decreasing the secretory fluxes of Na^+ and H_2O with respect to estimated capillary pressure, is sensitized by feeding. The action of morphine on the secretory fluxes in fed dogs opposes the simultaneous tendency for the secretory flux to increase as capillary pressure increases (Mailman & Jordan, 1975) and thus allows net absorption to increase

because of the increased washout of the absorptive fluxes. This secretory effect could be due to a direct effect on the epithelial cell secretory NaCl pump or tissue conductance (Schultz, Frizzel & Nellans, 1974; Sheerin & Field, 1977). However, the increase in the absorptive: secretory flux ratio in the absence of significant changes in transmural voltage suggests that active epithelial transport could also be increased. The *in vivo* preparation does not allow these possibilities to be easily distinguished.

It was of interest that, of the fasted dogs (all of which had the amount of intestinal contents noted) the three which had significant intestinal contents remaining, responded to morphine more like fed dogs than did the remainder of the fasted dogs. For example, average net Na^+ absorption increased 1.13 vs 0.10 μEq g^{-1} min^{-1} in the three dogs with intestinal contents vs those without during the last period following 1 mg/kg morphine injection. These findings suggest that the different effects of morphine in fed compared to truly fasted dogs may be even larger than observed.

Feeding also may alter the systemic cardiovascular sensitivity relative to the intestinal sensitivity. The decrease in blood pressure in fasted dogs was about 50% greater than in fed dogs suggesting a larger decrease in peripheral resistance. The decrease in absorptive site resistance, however, was greater in fed dogs and even total blood flow resistance in the fed dogs was generally less than in the fasted dogs.

The effects of morphine on gut Na^+ and H_2O transport were reversed by opiate antagonists indicating that the effects involve opiate receptors. However, the time course of the reversal was faster for systemic arterial pressure than for the intestinal effects suggesting that either the receptors mediating these effects may be different (Jacquet, Klee, Rice, Ijima & Minamikawa, 1977; Lord, Waterfield, Hughes & Kosterlitz, 1977) or that morphine initiates a slowly reversible process which in turn mediates the observed effects on the intestine. Morphine is known to modulate the release and/or effects of neurotransmitters or humoral agents and two possible substances which may be involved in the intestinal response are the release of histamine or the inhibition of release of acetylcholine (Bhattacharya & Lewis, 1956; Gyang & Kosterlitz, 1966) although there is little histamine released by morphine in the dog (Burks & Long, 1967). Histamine is not likely to be involved because previous work has shown that histamine has effects opposite to those of morphine on absorptive fluxes and ASBF (MacFerran & Mailman, 1977). Other investigators also concluded that morphine-induced histamine release is not involved in morphine effects on intestinal smooth muscle (Burks & Long, 1967). If inhibition of acetylcholine release by morphine is involved then atropine should mimic the effect of morphine. Atropine does increase the absorptive fluxes of Na^+ and H_2O and ASBF but also increases secretory fluxes (unpublished observations). Therefore, although inhibition of acetylcholine may be partially involved in the effects of morphine, it is not the sole effect.

The findings in the intestine observed here are analogous to the effect of morphine and enkephalins observed in the stomach (Konturek, Pawlik, Walus, Coy & Schally, 1978). Both morphine and methionine-enkephalin (as little as 4 nmol kg^{-1} h^{-1} intra-arterially) increased mucosal blood flow in resting and secreting stomach but increased HCl secretion only in secreting stomach. Intravenous infusions gave the same effects but about a ten fold greater infusion dose was required. Naloxone, a specific opiate antagonist, reversed the effects of both morphine and enkephalin. The authors suggested that opiates might increase gastric secretion by an effect on the mucosal microcirculation.

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