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# The Response of the Intestinal Mucosa to Prostaglandin $E_2$ during Withdrawal from Morphine

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**Abstract**—Experiments were designed to determine whether the diarrhoea characteristic of morphine withdrawal results from an enhanced sensitivity of the intestinal mucosa to $PGE_2$. Rats (250–300 g) were made morphine-dependent by subcutaneous injection of an emulsion releasing 300 mg morphine HCl over 48 h. In-vivo, the transintestinal potential difference (PD) responses to $PGE_2$ (4·6–46 $\mu g\ kg^{-1}$ i.v.), which reflect increased Cl secretion, were significantly larger in withdrawn (morphine emulsion, 10 mg $kg^{-1}$ naloxone s.c.) compared with non-dependent animals (emulsion only, naloxone s.c., $P < 0.05$). Muscle-stripped intestinal sheets from dependent animals incubated with naloxone ($10^{-5}$ mol $L^{-1}$) in-vitro did not demonstrate a greater electrical response (PD, short circuit current) to $PGE_2$ ($1.4 \times 10^{-6}$ mol $L^{-1}$) than sheets taken from non-dependent animals. In-vitro preparations from animals withdrawn in-vivo did not respond differently from tissue taken from non-dependent animals (naloxone 10 mg $kg^{-1}$ s.c., $10^{-4}$ mol $L^{-1}$ in medium, in both groups). This occurred in whole sheets of intestine as well as sheets without attached muscle. Jejunal fluid absorption in-vivo was lower in withdrawn animals than in non-dependent animals. However, the responses to intra-arterial infusion of $PGE_2$ were similar in both groups with 2 $\mu g\ min^{-1}$ inhibiting absorption and 4 $\mu g\ min^{-1}$ inducing secretion. In-vivo, $PGE_2$-induced Cl secretion appears to be enhanced during withdrawal although net fluid transport is not altered, suggesting different effects of the withdrawal process on the electrogenic Cl secretory and neutral NaCl absorptive mechanisms.

Abdominal cramping and diarrhoea are frequently reported by addicts as the most unpleasant symptoms of withdrawal from opiates. The diarrhoea and failure to maintain adequate fluid intake can lead to dehydration, weight loss and salt imbalance (Jaffe 1985). Until recently, increased intestinal motility was presumed to be the sole cause of morphine withdrawal diarrhoea. This was an assumption based on the fact that isolated segments of intestine from morphine-dependent rats and guinea-pigs display excessive spontaneous activity when suspended in morphine-free solution and actively contract when exposed to opioid antagonists (Kaymakcalan & Temelli 1964; Schulz & Herz 1976; Gintzler 1979; Huidobro-Toro & Way 1981). However, it is now well recognized that most diarrhoeal states are caused by a combination of changes in motor pattern together with pathophysiological disturbance in the mucosa resulting in intestinal fluid secretion. Fluid secretion occurs from the rat colon on antagonist-precipitated withdrawal from morphine and inhibition of fluid absorption occurs in the small intestine (Chang et al 1984; Warhurst et al 1984). These are classic withdrawal effects in that they are directly opposite to the acute effect of morphine on the intestinal mucosa (Lee & Coupar 1980; Warhurst et al 1983). During chronic exposure the mucosa adapts as shown by tolerance to the proabsorptive effects of morphine (Warhurst et al 1984) and on withdrawal from morphine the adaptive change is unmasked. Morphine may cause this disturbance in the mucosa at two sites. For example, it may exert its effect on the nerves that control the rate of intestinal fluid transport or on the epithelium. Support for a change in nerve activity comes from the finding that isolated ileum taken from morphine-dependent guinea-pigs is supersensitive to substances that stimulate enteric nerves such as 5-HT and nicotine but not to acetylcholine (Johnson et al 1978). The change in neuronal activity is finally manifested by exaggerated activity of cholinergic neurons (Collier et al 1981). Adaptation may also arise whereby a morphine-induced decrease in transmitter release causes denervation or misuse supersensitivity in the end organ in an analogous manner to the well-documented phenomenon occurring in skeletal muscle. Although many neurotransmitters, neuromodulators and gut hormones have been shown to affect intestinal fluid transport, the physiological control of the intestinal epithelium is still poorly understood. It is known that morphine inhibits intestinal fluid secretion induced by a variety of substances normally present in the gut (Awouters et al 1983). For example prostaglandin E (PGE) is formed throughout the length of the intestinal mucosa and its secretory effect is blocked by morphine (Coupar 1978; Peskar et al 1981). It has been suggested that prostaglandins are partly involved in the physiological control of intestinal absorption (Beubler & Juan 1977) but if released in excessive amounts are the underlying cause of a number of clinical diarrhoeal states (Rask-Madsen & Bukhave 1981). Prostaglandin $E_2$ is the major prostaglandin of the gut and is presumed from binding studies to act on receptors located on the membrane of intestinal epithelial cells (Tepperman & Soper 1981). The specific aim of the following study was to determine whether chronic morphine exposure leads to the development of supersensitivity to $PGE_2$ in the end tissue, namely the intestinal epithelium. If so, this would help to explain why diarrhoea is a symptom of withdrawal from morphine. Added encouragement to test this possibility

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came from the findings that the cyclooxygenase inhibitors, indomethacin and diclofenac, both reduce morphine withdrawal diarrhoea in rats (Francis et al 1978) and that morphine withdrawal unmasks an increased sensitivity to the contractile response of guinea-pig isolated ileum to $PGE_1$ (Schultz & Herz 1976).

## Methods

Experiments were carried out on male Wistar rats, 250–300 g, obtained from the Sheffield Field Laboratories and allowed free access to food (diet 86, Oxoid, London) and water.

*Measurement of transintestinal potential difference in-vivo*

The transintestinal potential difference (PD) across rat intestine was measured in-vivo using the preparation described by Hardcastle & Eggenton (1973). Rats were anaesthetized with pentobarbitone (60 mg $kg^{-1}$ i.p.) and a 5 cm segment of mid small intestine was isolated by tying off at the distal end and inserting a cannula at the proximal end. A glass cannula was also inserted into the proximal colon. The intestinal segments and the peritoneal cavity were then filled with 154 mM NaCl. The PD was measured between two salt bridge electrodes, one in contact with the luminal fluid and the other in contact, via a wick electrode, with the peritoneal fluid. These electrodes were connected via calomel half-cells to an optoisolator connected to a Vibron electrometer (Electronic Instruments Ltd., model 33B-2) whose output was displayed on a Vitatron chart recorder (MSE Scientific Instruments, 2001 series). $PGE_2$ was administered through a cannula in the jugular vein at increasing doses at 5 min intervals.

*Measurement of intestinal electrical activity in-vitro*

The potential difference (PD), short-circuit current (SCC) and resistance were measured in-vitro using sheets of mid small intestine obtained from animals anaesthetized with pentobarbitone (60 mg $kg^{-1}$). The sheets were clamped between two Perspex chambers, incubated in Krebs bicarbonate saline and gassed with 5% $CO_2$ in $O_2$. Current was applied across the tissue using Ag/AgCl electrodes which made contact with mucosal and serosal solutions via wide bore salt bridges. When short-circuiting the tissue a correction was made for the resistance of the medium as described by Field et al (1971).

After they had been mounted, tissues were left for 10 min before readings were made. PD and SCC were measured every min for 5 min before and 10 min after the addition of $PGE_2$ to the serosal solution. The change in PD and SCC was taken as the difference between the maximum value in the presence of $PGE_2$ and the value immediately before its addition. When present, naloxone and morphine were added to the mucosal and serosal solutions as soon as the preparation was set up.

*Measurement of net water transport in-vivo*

Fluid absorption from, and secretion into, the lumen of the rat small intestine was measured by the method described by Coupar (1985). In brief, rats were anaesthetized with pentobarbitone (60 mg $kg^{-1}$) and a cannula introduced into the left common carotid artery for constant intra-arterial (i.a.) infusions of saline or $PGE_2$ in saline at a rate of 40 $\mu$L $min^{-1}$. Mean systemic blood pressure was recorded from a side-arm off the carotid cannula by means of a Statham pressure transducer connected to a Grass polygraph (Model 79C). A recirculation technique was used to measure the net amount of fluid transported by the jejunum. The perfusing solution (8 mL of an isosmotic solution containing NaCl 148, KCl 5, dextrose 5·5 and phenol red 0·05 mmol $L^{-1}$ as a non-absorbable marker) was recirculated through the intestinal loop (20 to 30 cm in length starting distal from the Ligament of Trietz) from a reservoir maintained at 37°C by gas-lift consisting of moistened 5% $CO_2$ in $O_2$.

At the end of the 20 min perfusion the fluid from the loop was recovered and peak absorbance in samples diluted with buffer was measured at 560 nM as well as 520 and 600 nM to correct for non-specific interferences as described by Miller & Schedl (1972). Results are expressed as the net amount of water absorbed (+) or secreted (−) per gram wet weight of jejunum during the 20 min perfusion.

*Induction of physical dependence and withdrawal*

Morphine HCl was formulated as a slow-release emulsion as described by Warhurst et al (1984). Physical dependence was induced by administering 300 mg $kg^{-1}$ of morphine HCl over 2 days in a total volume of 10 mL $kg^{-1}$. 25% of the dose was injected s.c. on the morning and then afternoon of the first day and the remaining 50% on the morning of the second day. Control animals received emulsion only. Dependent and control animals were used on the third day. Abrupt withdrawal from morphine was induced by injecting morphine-treated animals with naloxone (10 mg $kg^{-1}$ s.c.) In a group of conscious morphine-tolerant animals this caused the characteristic signs of morphine withdrawal comprising of head shakes, escape attempts, teeth chattering, urination, ejaculation and notably, diarrhoea. Hard pellets tended to be passed during the first 10 min following naloxone injection but changed to fluid diarrhoea after this time. Animals were anaesthetized with pentobarbitone (60 mg $kg^{-1}$ i.p.) in all subsequent experiments. Naloxone was administered 20 min before tissues were removed or in-vivo PD and net fluid transport determinations began.

*Drugs*

Morphine hydrochloride (M & B), naloxone hydrochloride (Sigma), pentobarbitone sodium (Abbott), prostaglandin $E_2$ (Upjohn).

*Statistics*

Results are expressed as means ±1 s.e.m.. The effect of treatments on grouped means was assessed by analysis of variance and the significance of treatments on individual pairs of means was assessed by multiple comparison analysis. Means were considered statistically different if $P < 0.05$.

## Results

*Transintestinal potential difference in-vivo*

In the in-vivo preparation the mid small intestine and colon generated a transmural PD serosa positive. There was no significant difference between the resting transintestinal PD

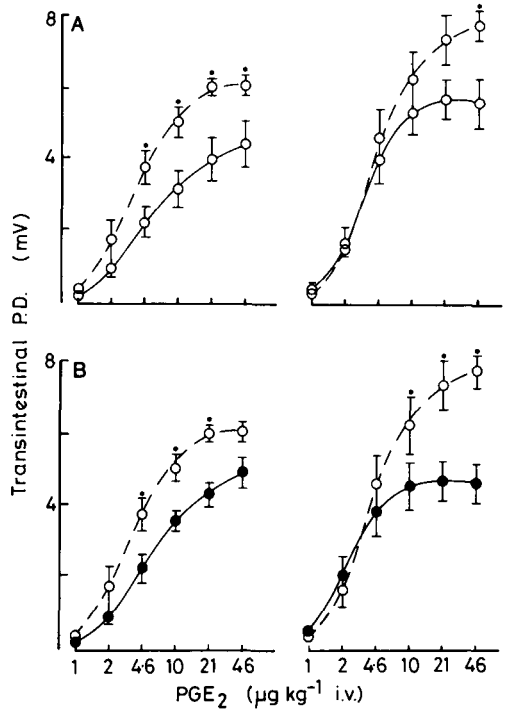


FIG. 1. Rise in transintestinal PD in response to $PGE_2$ in the mid small intestine (left panels) and colon (right panels). A. Comparison between the rise in transintestinal PD recorded from a group of non-dependent (continuous dose-response-curve, open symbols) and a separate group of withdrawn animals (hatched curve, open symbols). Both groups received naloxone (10 mg $kg^{-1}$ s.c., 20 min before measurements). * Indicates the responses to $PGE_2$ in the intestine of withdrawn animals are larger than from non-dependent ($P<0.05$, n=6, for each group unpaired $t$-test). B. Comparison between the rise in transintestinal PD in a group of morphine-dependent animals before (continuous curve, filled symbols) and after inducing withdrawal (hatched curve, open symbols). * Indicates responses are significantly greater during withdrawal than dependence ($P<0.05$, n=6, paired $t$-test). Bars in this and the following figures represent the s.e.means.

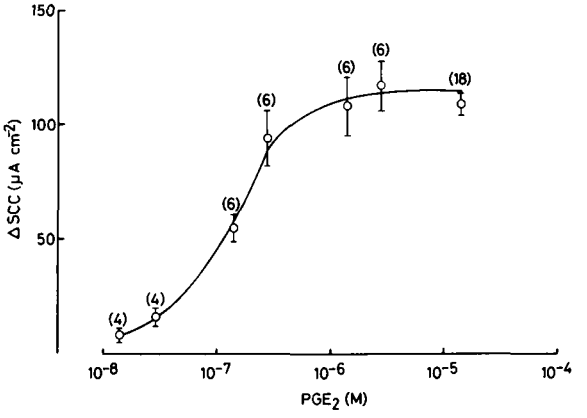


FIG. 2. Concentration-dependence of the rise in SCC induced by $PGE_2$ in stripped sheets of rat mid-intestine. Each determination was carried out on a separate sheet and $PGE_2$ was added to the serosal solution. Each point represents the mean ± 1 s.e. of the mean of the number of observations indicated.

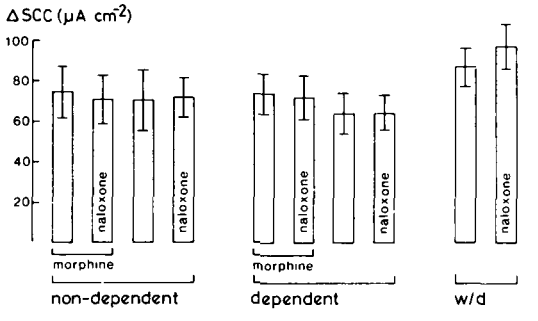


FIG. 3. Rise in SCC induced by $PGE_2$ ($1.4\times10^{-6}$ mol $L^{-1}$ serosal bathing solution) in muscle stripped sheets of mid small intestinal mucosa. Tissues from non-dependent and dependent animals were incubated with morphine ($10^{-4}$ mol $L^{-1}$), naloxone ($10^{-5}$ mol $L^{-1}$) or morphine ($10^{-4}$ mol $L^{-1}$) plus naloxone ($10^{-5}$ mol $L^{-1}$) in serosal and mucosal solutions. Two groups of animals were also withdrawn in-vivo (naloxone, 10 mg $kg^{-1}$ s.c. for 20 min). Tissues from one group were incubated in Krebs solution only, the other in Krebs solution plus naloxone ($10^{-4}$ mol $L^{-1}$ in serosal and mucosal solutions). None of the means differed significantly (analysis of variance, $P=0.57$, n=8 for each mean).

of control (emulsion + naloxone) or withdrawn animals in either the small intestine or colon. (Small intestine 6·5 ± 0·6 non-dependent, 6·18 ± 1·27 mV withdrawn, $P>0.05$, colon 14·25 ± 1·19 non-dependent, 15·25 ± 1 mV withdrawn, $P>0.05$, n=6 in all cases). Subcutaneous injection of naloxone did not change transintestinal PD in non-dependent or dependent groups. Intravenous injection of $PGE_2$ caused a dose-dependent increase in transintestinal PD. In both small intestine and colon the responses peaked by approximately 1 min and fully returned to resting levels by 5 min. The responses of the intestine to $PGE_2$ in withdrawn animals were greater than in non-dependent animals, particularly at the higher doses. Responses to $PGE_2$ were also compared in dependent animals and in the same animals during withdrawal. Supersensitivity to $PGE_2$ was again apparent especially at high doses (Fig. 1).

*Short-circuit in-vitro*

$PGE_2$ caused a concentration-related increase in SCC, the maximal effect occurring at $1.4\times10^{-6}$ mol $L^{-1}$ (Fig. 2). Morphine ($10^{-4}$ mol $L^{-1}$), naloxone ($10^{-5}$ mol $L^{-1}$) and morphine ($10^{-4}$ mol $L^{-1}$) plus naloxone ($10^{-5}$ mol $L^{-1}$) did not alter the increase in SCC induced by $PGE_2$ ($1.4\times10^{-6}$ mol $L^{-1}$) in the serosal bathing solution in stripped sheets of small intestinal mucosa from non-dependent animals. To test whether withdrawal in-vitro results in supersensitivity to $PGE_2$, a comparison was made between the responses of sheets incubated with naloxone ($10^{-4}$ mol $L^{-1}$) from non-dependent animals and from sheets incubated with morphine ($10^{-4}$ mol $L^{-1}$) plus naloxone ($10^{-5}$ mol $L^{-1}$) from dependent animals. However, there was no significant difference in the $PGE_2$-induced increases in SCC and the tissue resistances at peak responses ($P>0.05$). Similarly in-vitro preparations from animals withdrawn in-vivo did not respond differently from tissues taken from non-dependent animals (naloxone, 10 mg $kg^{-1}$ s.c., $10^{-5}$ mol $L^{-1}$ in medium in both groups, $P>0.05$, Fig. 3).

In unstripped sheets of small intestine the rise in SCC in response to $PGE_2$ ($1.4\times10^{-5}$ mol $L^{-1}$) in the serosal bathing solution was not significantly different in tissue taken from animals withdrawn in-vivo and tissues from non-dependent

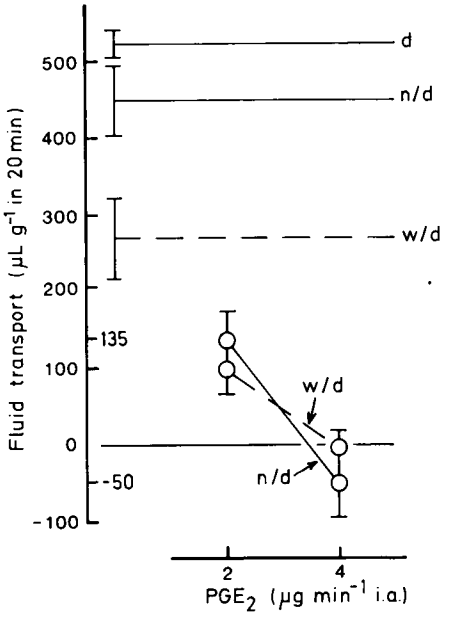


FIG. 4. The net rate of fluid absorption from the jejunum in withdrawn animals (naloxone, 10 mg $kg^{-1}$ s.c. hatched line) compared with either separate groups of non-dependent ($P<0.05$) or dependent animals ($P<0.01$, unpaired $t$-test, upper continuous line). Open symbols are responses to i.a. infusion of $PGE_2$ in non-dependent animals (continuous lines) and morphine withdrawn animals (hatched line). n = 5 for all groups.

animals (naloxone, 10 mg $kg^{-1}$ s.c., $10^{-5}$ mol $L^{-1}$ in medium in both groups, $62 \pm 14$ vs $42 \pm 5$ $\mu A\ cm^{-2}$, $P>0.05$, n = 8).

*Net fluid transport in-vivo*

The rates of net water absorption from the jejunum of non-dependent and dependent animals were $449 \pm 46$ and $524 \pm 19$ $\mu L\ g^{-1}$ in 20 min, respectively. This difference was not statistically significant, but net absorption was significantly reduced to $270 \pm 53$ $\mu L\ g^{-1}$ in 20 min in withdrawn animals ($P<0.05$ compared with the absorption rate in non-dependent animals). In non-dependent animals intra-arterial infusion of $PGE_2$ at 2 $\mu g\ min^{-1}$ reduced absorption and at 4 $\mu g\ min^{-1}$ induced a small net secretion of fluid.

The absolute values for the net fluid transport in withdrawn animals infused with $PGE_2$ were not significantly different from those in the non-dependent groups ($P>0.05$). When the basal value of fluid absorption is taken into account, $PGE_2$ appears to induce a smaller change in fluid transport in withdrawn compared with non-dependent animals. There was however, no significant difference between $PGE_2$-induced fluid secretion in the two groups of animals ($P>0.05$ for both infusion rates of $PGE_2$, Fig. 4).

## Discussion

This study confirms earlier observations (Beubler et al 1984; Chang et al 1984) that abrupt, antagonist-precipitated withdrawal from morphine dependence results in a decrease in the rate of fluid absorption from the intestine and associates this effect with an increased electrical response of withdrawn tissue to $PGE_2$. The increased transintestinal PD in-vivo induced by $PGE_2$ reflects the stimulation of net Cl secretion induced by this prostanoid (Hardcastle et al 1981). Morphine dependence did not alter the dose-response curve to $PGE_2$ significantly, but when dependent animals were withdrawn, there was a significant increase in the maximum response to the prostanoid. This suggests that the Cl secretion stimulated by $PGE_2$ is enhanced by morphine withdrawal. The basal PD was not affected by any of the experimental procedures and so it is unlikely that prostaglandins play a major role in the generation of basal electrical activity. To determine whether the increased sensitivity of the secretory response to $PGE_2$ on morphine withdrawal was an effect exerted at the level of the intestine, animals were withdrawn in-vivo and their intestines incubated in-vitro in the presence of naloxone. However, there was no increase in the responses of these tissues to a maximal concentration of $PGE_2$ when compared with control tissues. Thus the changes observed in-vivo must be initiated at some site outside the intestinal tract. This could alter background neural activity or lead to a change in the level of a substance within the gut that modifies its sensitivity to prostaglandins. Removal of the intestine from the animal would eliminate extrinsic neural activity and any modifying substance could diffuse out of the tissue or be inactivated in-vitro. This central site for the initiation of the withdrawal responses is in agreement with the findings of Warhurst et al (1984), although Chang et al (1984) found that methylnaltrexone, which does not readily pass the blood-brain barrier, decreased absorption in the jejunum and colon, but not in the ileum of dependent rats. This implies that a peripheral action was involved, but a central action was suggested in addition since administration of methylnaltrexone into the cerebral ventricles also decreased fluid absorption in dependent animals.

The net movement of fluid across the intestine is determined by the magnitude and direction of net solute transport (Hendrix & Bayless 1970). As well as stimulating net Cl secretion in the crypts, prostaglandins also inhibit the neutral absorption of NaCl by the villi (Al-Awqati & Greenough 1972; Frizzell & Schultz 1979), and these two actions constitute a co-ordinated secretory response. Since the inhibition of neutral NaCl absorption is electrically silent (Frizzell et al 1979), changes in its activity cannot be detected using an electrical technique. They will, however, contribute to alterations in net fluid transport that occur on prostaglandin challenge. When fluid movement was determined in-vivo, a significant decrease in net absorption occurred when $PGE_2$ was administered. In withdrawn animals basal fluid absorption was reduced, in agreement with the study of Warhurst et al (1984) who showed that this effect was due to an inhibition of Na and Cl absorption. However, the withdrawal process did not enhance the reduction in fluid transport induced by $PGE_2$. This is in contrast to the in-vivo PD response to $PGE_2$ which is increased under these conditions. If this represents increased net Cl secretion, then the discrepant in-vivo results could be resolved if $PGE_2$ was less effective in inhibiting NaCl absorption during withdrawal, so that Cl secreted at the crypts was reabsorbed at the villi. Although NaCl absorption is inhibited during withdrawal (Warhurst et al 1984) it is not abolished and there may be sufficient remaining activities to take up the Cl secreted in response to $PGE_2$ stimulation. This would explain why enhanced Cl secretion is not translated into increased fluid secretion.

The mechanisms involved in the withdrawal process are

unclear. The gut may adapt to the prolonged action of morphine on the epithelium by either an increased production or release of secretagogues or an alteration in the sensitivity to existing secretagogue levels. A cholinergic mechanism is thought to be involved in the jejunum, but not in the colon (Beubler et al 1984; Chang et al 1984), where there is evidence that during withdrawal 5-HT is released which in turn increases prostaglandin synthesis (Beubler et al 1984). The present study has shown an enhanced sensitivity of the electrogenic Cl secretory mechanism to $PGE_2$, but this is not translated into a detectable increase in the fluid transport response. Small changes in ion transport can result in a measurable electrical response without a significant alteration in ion fluxes being detected (Hardcastle et al 1984). A change in net fluid movement is a more functional response and will only result from marked alterations in ion transport and this difference in sensitivity could provide an explanation for the contrasting observations in-vivo. As $PGE_2$-stimulated fluid movement is not enhanced on withdrawal, any increased sensitivity of the electrogenic Cl secretory mechanism is unlikely to contribute to the diarrhoea experienced on morphine withdrawal unless other areas of the intestine are affected in a more pronounced manner.

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