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The role of accelerated colonic transit in prostaglandin-induced diarrhoea and its inhibition by prostacyclin

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1 Rats treated with subcutaneous 16,16-dimethyl prostaglandin E_2 (16,16-dimethyl PGE_2, 100 $\mu g\,kg^{-1}$) exhibited diarrhoea even when their ileo-caecal junctions were tied, thereby eliminating contributions from small intestinal transit or fluid accumulation (enteropooling).

2 The origin of the watery stool appeared to be the caecum, since tying the caecal-colonic junction eliminated it.

3 The acceleration of colonic transit is likely to be a primary mechanism of PGE_2-induced diarrhoea in the rat, since both normal animals and those with tied ileo-caecal junctions exhibited almost the same incidence of diarrhoea.

4 Subcutaneous prostacyclin (PGI_2) (2 $mg\,kg^{-1}$ every 60 min) suppressed 16, 16-dimethyl PGE_2-induced diarrhoea in normal rats and in those with tied ileo-caecal junctions.

5 Colonic transit measured in rats with cannula preimplanted in their proximal colon indicated that 16, 16-dimethyl PGE_2 enhanced colonic transit and PGI_2 suppressed this increase. Thus, PGI_2 can inhibit diarrhoea in the rat caused by 16, 16-dimethyl PGE_2 by suppressing colonic transit exclusive of its effects on small intestinal transit and enteropooling.

Introduction

A common side effect of prostaglandin administration is diarrhoea, which has been attributed to the eteropooling properties of these compounds (Robert *et al.*, 1976). This increase in small intestinal fluids occurs with most protaglandins and has been recently shown to be inhibited by various antidiarrhoeal agents [prostacyclin (PGI_2, Robert *et al.*, 1979); loperamide (Karim & Adaikan, 1977)]. However, this study presents evidence that prostaglandin-induced acceleration of colonic transit can produce diarrhoea in the rat even when contributions from enteropooling are excluded. Furthermore, PGI_2 is able to inhibit this diarrhoea by suppressing prostaglandin-induced increases in colonic transit.

Methods

Diarrhoea

Unfasted male Upjohn rats (200–220 g) were used. They received either no surgical intervention or were laparotomized under methoxyflurane anaesthesia during which time their ileo-caecal or caecal-colonic junctions were tied with surgical silk. They were then restrained in metal tubes and administered subcutaneous vehicle (0.2 M carbonate buffer, pH 10.5) or PGI_2 sodium salt (2 $mg\,kg^{-1}$). Subcutaneous 16,16-dimethyl prostaglandin E_2 (16, 16-dimethyl PGE_2) (100 $\mu g\,kg^{-1}$) was administered 10 min later. Rats were observed for 2 h after 16, 16-dimethyl PGE_2 (dm PGE_2) treatment for appearance of diarrhoea (defined as passage of watery, unformed stool). PGI_2 was given a second time 60 min after its first injection to maintain biological activity.

Both drugs were given in 1 ml of vehicle. 16, 16-dimethyl PGE_2 was solubilized in ethanol and then diluted with saline to make a 2% ethanol-saline mixture; PGI_2 was dissolved in 0.1 M carbonate buffer, pH 10. Control groups were given vehicle at the appropriate times to match the experimental groups. Each group consisted of 10 animals.

The number of animals displaying diarrhoea within a treatment group was expressed as a proportion of those treated and related to the two experimental design factors, surgery or PGI_2 administration, by a linear statistical model (Grizzle *et al.*, 1969) in a fashion similar to analysis of variance.

Colonic transit

Rats were preimplated with colonic cannula as previously described (Ruwart *et al.*, 1979) and fasted for 48 h before use. They were then treated with subcutaneous vehicle (Groups 1a and 2a) or 2 mg kg^{-1} PGI_2 (Groups 1b and 2b) followed 10 min later by subcutaneous vehicle (Group 1a and 2a), or 100 $\mu g\,kg^{-1}$ dm PGE_2 (Group 2a and 1b). A colonic transit marker was injected into the cannula at this time also. Forty-five min later, rats were killed by CO_2 asphyxiation. Colonic transit (CT) was expressed as the percentage of intestinal length travelled by the distal edge of the marker. Wilcoxon's Ranksum test was used for statistical comparisons. Use of this test over the more common Student *t* test was supported by an analysis of variance.

Results and Discussion

The results of various surgical and drug treatments are summarized in Table 1. 16, 16-dimethyl PGE_2 produced diarrhoea in rats with or without tied ileal-caecal junctions. Fewer rats with surgical intervention had diarrhoea ($P<0.05$), but this difference was small, suggesting that the major mechanism of dm PGE_2-induced diarrhoea was still present. Thus, when the effects of dm PGE_2 on enteropooling and small intestinal transit were eliminated, diarrhoea was still prevalent. The origin of this diarrhoea was probably the caecum, since occluding the caecal-colonic junction completely eliminated it (Table 2). Furthermore, the caecal contents of vehicle-treated rats were of a watery consistency, while the colonic contents were solid at autopsy. After dm PGE_2 treatment, no formed stool was found in the colon and the caecum was frequently empty. Since colonic transit (CT) is normally longer than 3 h (Ruwart *et al.*, 1979), and most rats (80%) exhibited diarrhoea in the first hour, these data indicate that caecal contents are propelled through the colon at a much faster rate than normally occurs.

Table 1 Effect of 16, 16-dimethyl prostaglandin E_2 (dm PGE_2) and prostacyclin (PGI_2) on diarrhoea and colonic transit in rats

Group No.	*Drug treatment*	*Diarrhoea*		*CT*
		Tied IC[a]	*Normal*[b]	
1a	Vehicle + Vehicle	0/10	0/10	42.3 ± 3.2
1b	PGI_2 + Vehicle	0/10	0/10	43.1 ± 4.6
2a	Vehicle + dmPGE_2	8/10*	10/10*	85.5 ± 9.6*
2b	PGI_2 + dmPGE_2	2/10	5/10*	51.5 ± 10.2

* Indicates a value significantly different ($P<0.05$) from Group 1a.
[a] Tied ileal-caecal junction.
[b] No surgical intervention.

Table 2 Effect of 16, 16-dimethyl prostaglandin E_2 (dm PGE_2) on rats undergoing caecal-colonic junction ligation

Drug treatment	*Surgical treatment*	*Diarrhoea*
Vehicle	None	0/10
dm PGE_2	None	10/10*
Vehicle	Sham	0/10
dm PGE_2	Sham	10/10*
Vehicle	Ligation	0/10
dm PGE_2	Ligation	0/10

* Indicates a value significantly different ($P<0.01$) from first group.

Our assay does not distinguish between the contributions of accelerated caecal contraction and colonic propulsion. Normally, however, rat CT = 50% 3 h after a marker is placed in the proximal colon (Ruwart *et al.*, 1979) so that accelerated CT measured herein must include enhanced colonic propulsion and may also have a component due to caecal contraction.

This hypothesis was confirmed by measuring CT in rats with preimplanted colonic cannula. CT was enhanced by treatment with dm PGE_2, but this increase was prevented by PGI_2 pretreatment (Table 1). PGI_2 alone had no measureable effect, although earlier studies indicate that small intestinal transit in rats and dogs is inhibited by this compound (Ruwart *et al.*, 1980).

Acceleration of CT by dm PGE_2 has been reported previously in laparotomized rats (Ruwart *et al.*, 1978) but whether this is a result of direct stimulation of colonic propulsion or stimulation caused by enhanced small intestinal transit and the resulting increased movement of fluids into the colon was not determined. These results indicate that accelerated transit of caecal and colonic contents present as diarrhoea in rats when enteropooling and small intestinal transit effects are exluded; thus direct stimulation of colonic propulsion represents a major mechanism of dm PGE_2-induced diarrhoea in rats.

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