Br. J. Pharmac. (1976), **57**, 335–340

INHIBITION OF PERISTALSIS IN GUINEA-PIG ISOLATED ILEUM AND COLON BY DRUGS THAT BLOCK PROSTAGLANDIN SYNTHESIS

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1 Methods of analysing peristaltic activity have been evaluated by the use of recordings of longitudinal and circular muscle activity and of propulsion in whole segments of guinea-pig ileum and colon.

2 Some prostaglandin synthesis inhibitors, and antagonists of prostaglandin action were tested for their suitability for studying the role of prostaglandins in peristalsis. Aspirin was suitable; at 10–200 μg/ml it had little effect on responses of longitudinal muscle strips of the guinea-pig ileum to acetylcholine (ACh), histamine, nicotine or prostaglandin E_2. Indomethacin (1–4 μg/ml) reduced responses to nicotine and prostaglandin E_2. The prostaglandin antagonists polyphloretin phosphate and SC-19220 reduced contractions of ileal longitudinal muscle caused by nerve excitation with either nicotine or transmural stimulation.

3 Aspirin (20–100 μg/ml) or indomethacin (1–4 μg/ml) applied serosally greatly inhibited all aspects of peristalsis in guinea-pig ileum and colon. Inhibition of peristalsis of the ileum by aspirin was antagonized by prostaglandin E_2 and that by indomethacin was removed by prostaglandin $F_{2\alpha}$ or ACh. Inhibition of colonic peristalsis by aspirin was antagonized by prostaglandin E_2 but rarely by ACh, and that by indomethacin by prostaglandin E_1 or E_2. Mucosal application of aspirin had little effect on either ileum or colon but indomethacin caused some inhibition.

4 These results support the supposition that prostaglandins contribute to peristaltic activity.

Introduction

Studies in various species have demonstrated prostaglandin-like material in the gastrointestinal tract which may contribute to muscle tone and activity (see reviews by Bennett & Fleshler, 1970; Bennett, 1972; 1976). The following discussion is restricted to guinea-pig intestine. Prostaglandin E_2- and $F_{2\alpha}$-like materials occur in the ileum (Ambache, Brummer, Rose & Whiting, 1966; and unpublished data). Low concentrations of prostaglandins E_1, E_2, $F_{1\alpha}$ or $F_{2\alpha}$ contract the longitudinal muscle of guinea-pig isolated intestine, apparently in part by direct action on the muscle cells, and partly by stimulating nerves. In the ileum the nerves stimulated are cholinergic irrespective of the prostaglandin but in the colon prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ stimulate cholinergic nerves, whereas prostaglandins E_1 and E_2 stimulate non-cholinergic excitatory nerves (Bennett, Eley & Scholes, 1968a; Harry, 1968; Bennett, Eley & Stockley, 1975a). In circular muscle of the intestine prostaglandins E and F seem to act directly on the muscle but whereas the F prostaglandins cause contraction, the E prostaglandins cause inhibition (Bennett *et al.*, 1968a; Fleshler & Bennett, 1969).

Prostaglandins may generate tone in the longitudinal muscle of guinea-pig isolated intestine (Bennett & Posner, 1971; Botting & Salzmann, 1974; Willis, Davison & Ramwell, 1974; Bennett *et al.*, 1975a) and may be necessary to maintain contractions to histamine and other substances (Eckenfels & Vane, 1972). By contrast, endogenous prostaglandin E may maintain relaxation of the circular muscle (Bennett *et al.*, 1975a). Prostaglandins E_1 or E_2 bathing the serosal surface of guinea-pig isolated ileum inhibit peristaltic activity (Bennett *et al.*, 1968b), but low concentrations (10–50 ng/ml) of prostaglandin E_1 first cause stimulation (Radmanović, 1972). Serosally applied prostaglandins E_1 or E_2 (0.3–0.5 μg/ml) in guinea-pig isolated colon, or prostaglandins $F_{1\alpha}$ or $F_{2\alpha}$ in the ileum (0.1–1 μg/ml) or colon (0.3–0.5 μg/ml) tend to stimulate circular muscle contractions when peristalsis is initiated by raising the intraluminal pressure (unpublished data). These results suggest that prostaglandins may be involved in peristalsis. Furthermore, prostaglandin E may modulate the response to cholinergic nerve stimulation (Ehrenpreis, Greenberg & Belman, 1973; Chong & Downing, 1974; Kadlec, Mašek & Šeferna, 1974; Bennett *et al.*, 1975b). We therefore studied the effects of drugs which inhibit prostaglandin synthesis (Ferreira, Moncada & Vane,

1971; Smith & Willis, 1971; Vane, 1971) on peristaltic activity in guinea-pig isolated ileum and colon. Since peristaltic activity is complex, we first evaluated various methods for quantitative assessment.

Methods

The ileum and colon were removed from freshly killed guinea-pigs, and 5–8 cm segments were cut from the mid-ileum or the colon approximately 10 cm from the anus. Peristalsis was studied by the method of Bennett *et al.* (1968a) with the following slight modifications: (1) the Marriotte bottle controlling the intraluminal pressure (zero pressure at rest to 1–5 cm water pressure) was raised at a constant rate by a linear motor for 1.5 min every 8 min (15 s to raise 4 cm, 15 s to lower); (2) in some experiments the Krebs solution expelled during peristalsis was collected in a vertical tube 25 cm long and 8 mm internal diameter, with a side-arm at the bottom to measure the hydrostatic head of pressure with a transducer. The waste outlet at the bottom of the collecting tube was closed by a relay before raising the intraluminal pressure and was opened after returning to zero pressure. This method allowed simultaneous recordings of the tone of the longitudinal muscle and the circular muscle (pressures were measured intraluminally by one or two fine polyethylene tubes) and of the propulsion of fluid. Drugs were either added to the Krebs solution bathing the serosol surface, or injected intraluminally over approximately 20 s in 1 ml 0.9% w/v NaCl (saline), usually 4 to 5 min before raising the pressure. The final concentration of intraluminally injected drugs is not known, and only the amounts injected have been stated. Control injections of saline or Krebs solution into the fluid bathing the serosol surface usually had little effect on the tissue. Control intraluminal injections sometimes variably affected peristaltic activity, so reducing the statistical significance of minor changes due to drugs.

The Krebs solution used had the following composition (g/l): NaCl 7.1, $CaCl_2.6H_20$ 0.55, KCl 0.35, KH_2PO_4 0.16, $MgSO_4.7H_2O$ 0.29, $NaHCO_3$ 2.1 and dextrose 1.0.

Tests for statistical significance

Responses to test substances were compared with controls and analysed by the median test, unless otherwise stated. All probability values refer to two-tailed tests.

Drugs

The following drugs were used: 1-acetyl-2-(8-chloro-10,11-dihydrodibenz (b,f)(1,4) oxazepine-10-carbonyl) hydrazine (SC-19220), acetylcholine perchlorate (ACh), acetylsalicyclic acid, histamine acid phosphate, 5-hydroxytryptamine creatinine sulphate (5-HT), (–)-hyoscine hydrobromide, indomethacin, nicotine hydrogen tartrate, polyphloretin phosphate (PPP), potassium chloride, prostaglandins E_1, E_2 and $F_{2\alpha}$ tromethamine salt. All concentrations of salts are expressed as base or free acid. The prostaglandins were dissolved in ethanol (0.1 ml per mg) and diluted with 0.9 ml sodium carbonate solution 0.2 mg/ml. Indomethacin 1 mg/ml and aspirin 10 mg/ml were added to saline and dissolved by adding solid sodium carbonate to pH7.

Results

Evaluation of methods to quantitate peristaltic activity

During peristaltic activity there were phasic contractions of the longitudinal and circular layers and propulsion of fluid. At least two consistent responses were obtained before a drug was added; its effect was determined by comparison with these controls and sometimes with the response after washing out the drug. Although it was clear from the trace when a drug had an effect, it was not always obvious how to express each change quantitatively. For example, reduced peristaltic activity might be accompanied by fewer but bigger circular muscle contractions, or *vice-versa*. Exact measurements of all the changes, including for example the number and height of spikes, apart from being tedious would sometimes have been difficult to evaluate (Figure 1). For example, how should sustained circular muscle contraction with no superimposed phasic activity be interpreted? Precise measurement of three traces showed reasonable correlation between separate assessments of peristaltic activity, based on the number of phasic muscle contractions, the summed heights of contraction, the mean height of contraction, the total length of pen travel in each response, and propulsion of fluid; the trends with each measurement were always in the same direction although the percentage change depended on the method of measurement and was not always consistent. In the subsequent studies we therefore measured the amount of fluid propelled and estimated changes in muscle contractility from approximate measurements of the traces.

The selectivity of drugs for studying peristalsis

Prostaglandin synthetase inhibitors. Aspirin (100–200 μg/ml) had no significant effect on submaximal contractions caused by ACh 4–10 ng/ml, histamine 10 ng/ml, nicotine, 1–20 μg/ml, or prostaglandin E_2 25–300 ng/ml ($n=6$, 1, 6 and 9 respectively). In 6 other experiments, aspirin (10–100 μg/ml) had no significant effect on responses to electrical field stimulation at 0.1 to 64 Hz. Indomethacin 1–4 μg/ml reduced contractions induced by

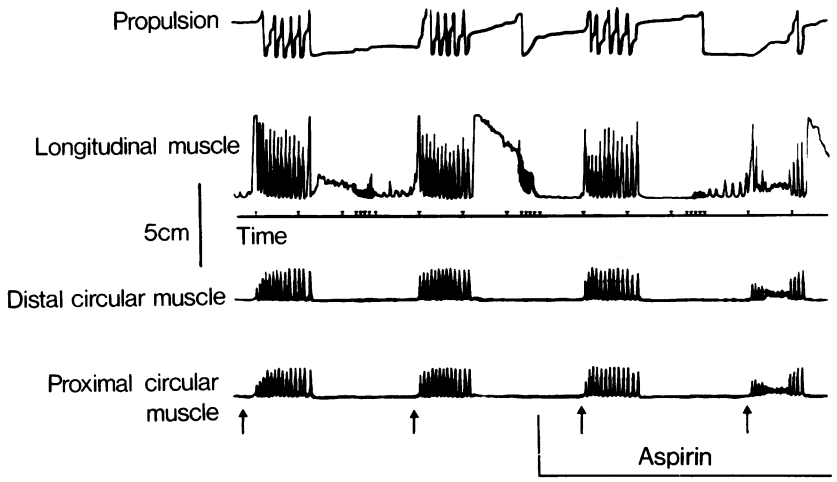

Figure 1 Peristalsis in a segment of guinea-pig isolated ileum induced by raising the intraluminal pressure from zero to 4 cm water pressure (↑). Aspirin 100 μg/ml bathing the serosal surface greatly reduced the responses in the second cycle after its administration. (In the middle of the last response there were many small contractions that are not clearly differentiated in the record). Measurement of propulsion in this experiment was by the original method of Bennett *et al.* (1968a) in which each peak represents 1 ml. Time trace, min.

prostaglandin E_2 ($n=12$) or nicotine ($n=18$) but had no significant effect on responses to ACh. With indomethacin at 1 μg/ml the reduction of the responses to nicotine was 10% (7 to 14) and of that to prostaglandin E_2 36% (32 to 44) (medians and semiquartile ranges). With indomethacin 4 μg/ml the reductions were 10% (7 to 16) for nicotine and 50% (30 to 57) for prostaglandin E_2. By comparison with saline controls the inhibitory effect was statistically significant ($P<0.03$ in every case; $n=4$ to 7; Mann Whitney U test).

Prostaglandin antagonists. Polyphloretin phosphate (PPP) 40–100 μg/ml reduced contractions of the longitudinal muscle of guinea-pig ileum induced by nicotine (1–20 μg/ml) or prostaglandin E_2 (2–200 ng/ml) but had little effect on responses to ACh (10–100 ng/ml). The highest concentration of PPP (100 μg/ml) reduced submaximal responses to prostaglandin E_2, nicotine, ACh and responses to transmural electrical stimulation (1 ms, 0.5–4.0 Hz, 3.4 V/cm for 20 s) by 90% (69 to 100) $n=7$, 70% (54 to 86) $n=6$, 5% (0 to 20) $n=8$ and 13 to 64% $n=3$ respectively. SC-19220 (4–10 μg/ml) was also non-selective: 5 μg/ml reduced submaximal contractions of the longitudinal muscle of guinea-pig ileum to prostaglandin E_2, nicotine, ACh and transmural electrical stimulation by 90% (84 to 93) $n=6$, 72% (45 to 84) $n=7$, 12% (4 to 43) $n=7$ and 19 to 54% $n=4$, respectively. Because of the depression of nerve-mediated responses, these drugs were not used to study prostaglandins in peristalsis.

Effect of prostaglandin synthesis inhibitors on peristalsis

Guinea-pig isolated ileum. Longitudinal muscle tone is slight or absent in guinea-pig isolated ileum and was slightly reduced by aspirin in only 8 out of 21 trials. Aspirin (20 to 100 μg/ml) applied serosally usually depressed peristaltic contractions of the circular and longitudinal muscles and reduced propulsion (Figure 1, Table 1). However, in 4 out of the 21 studies, the inhibition by aspirin lasted only one 8 min cycle (see Methods section) even when aspirin was still present, and even when in one experiment its concentration was increased to 1 mg/ml. The drug was usually ineffective when given after prostaglandin E_2 (0.1–0.5 μg/ml) had been added to the bath and then washed out (5 out of 6 trials in 5 experiments), and a long-lasting inhibition caused by aspirin was antagonized by adding prostaglandin E_2 (0.3–0.5 μg/ml; 4 experiments). Indomethacin (1–4 μg/ml) applied serosally acted like aspirin but inhibited peristalsis more consistently (Table 1). Longitudinal muscle tone was reduced on 2 out of 22 occasions. Unlike aspirin, indomethacin caused inhibition even when prostaglandin E_2 had previously been applied serosally and then washed out (3 experiments), but the effect of indomethacin was lost or reduced after addition of prostaglandin $F_{2\alpha}$ (0.3–0.5 μg/ml; 3 experiments), ACh (0.3–1 μg/ml; 3 experiments), or histamine (0.1 μg/ml, 1 experiment).

When injected intraluminally in a volume of 1 ml aspirin (100 μg–10 mg) had no significant effect on

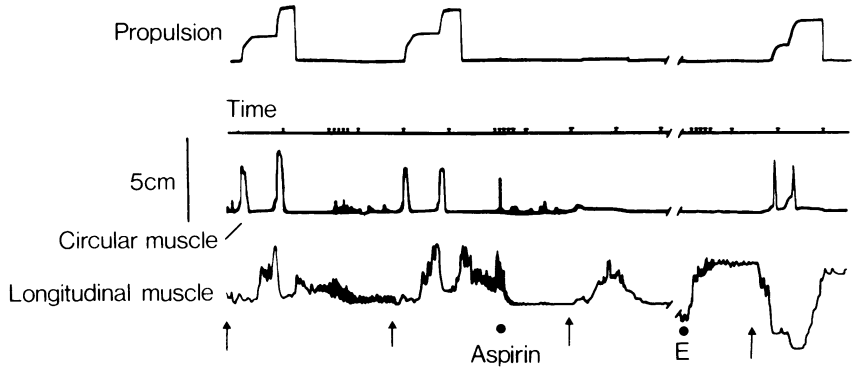

Figure 2 Peristalsis in guinea-pig isolated colon induced by raising the intraluminal pressure from zero to 5 cm water (↑). The gap in the record represents 200 minutes. During this time addition of histamine 0.2 μg/ml, 5-hydroxytryptamine 0.3 μg/ml or acetylcholine 0.2 μg/ml, after a single dose of aspirin, did not restore peristalsis, but subsequent administration of 0.3 μg/ml prostaglandin E_2 (E) antagonized the inhibition. Propulsion, 1 cm = 1 ml.

the ileum whereas indomethacin (10 or 100 μg in 1 ml) usually reduced peristaltic muscle activity and propulsion (Table 1). Longitudinal muscle tone fell with indomethacin 100 μg in 4 out of 12 experiments.

Guinea-pig colon. Aspirin 100 μg/ml bathing the serosal surface usually reduced longitudinal muscle tone and always reduced propulsion and muscle peristaltic activity. Similarly, in most preparations, indomethacin 1 or 2 μg/ml applied serosally reduced longitudinal muscle tone, muscle peristaltic activity and propulsion (Table 1).

Intraluminal administration of aspirin 50 to 100 μg in 1 ml fluid had no significant effect on peristalsis; 1 mg lowered circular muscle peristaltic activity but a tendency to reduce propulsion was not statistically significant (Table 1). Indomethacin (0.5–1 μg) administered intraluminally reduced longitudinal muscle tone in 5 out of 10 experiments and inhibited propulsion, but a tendency to reduce muscle peristaltic activity was not statistically significant.

Inhibition by serosally applied aspirin was lost or reduced after addition of prostaglandin E_2 (0.15–0.3 μg/ml; 9 experiments; Figure 2), but not by addition of ACh (0.15–0.3 μg/ml) in 5 of 6 experiments, 5-HT (0.15–0.3 μg/ml) in 3 of 4 experiments, or histamine (0.15–0.3 μg/ml) in 4 experiments. The inhibition by indomethacin was removed by addition of prostaglandin E_1 or E_2 (0.3 μg/ml) in 5 experiments.

Table 1 The effects of aspirin (ASA) and indomethacin (INDO) on percentage changes in propulsion and peristaltic activity in guinea-pig isolated intestine

						Muscle peristaltic activity %	
Tissue	*No. Expts.*	*Drug*	*Amount*	*Route*	*Propulsion*	*Circular*	*Longitudinal*
Ileum	17/12	ASA	100 μg/ml	Serosal	−33(0 to −52)*	−15(0 to −60)*	−40(0 to −70)*
	8/6	INDO	3 μg/ml	Serosal	−48(−26 to −55)*	−35(−16 to −50)*	−25(−5 to −55)*
	9/4	ASA	1 mg	Mucosal	0(0 to −12)	−10(0 to −16)	0(0 to −15)
	12/6	INDO	100 μg	Mucosal	−23(−8 to −53)†	−30(0 to −75)†	−30(0 to −60)†
Colon	14/10	ASA	100 μg/ml	Serosal	−100(−99 to −100)*	−99(−67 to −100)*	−95(−30 to −100)*
	9/8	INDO	1 μg/ml	Serosal	−100(−65 to −100)*	−90(0 to −100)*	−50(0 to −100)*
	6/4	ASA	1 mg	Mucosal	−33 (0 to −58)	−84(−74 to −90)†	−15(0 to −90)
	9/5	INDO	1 μg	Mucosal	−40 (−14 to −67)†	−72(0 to −100)	0(0 to −50)

The number of experiments represents the number of observations/number of tissues. The changes shown are medians and semiquartile ranges. Serosally applied aspirin or indomethacin significantly reduced peristaltic activity and propulsion. Londitudinal muscle tone was reduced significantly only with aspirin or indomethacin applied serosally to the colon ($P < 0.05$).

*$P < 0.01$; †$P < 0.05$ compared with saline or Krebs solution controls.

Discussion

The selectivity of drugs for the study of peristalsis

Prostaglandin synthetase inhibitors. Previous studies with guinea-pig ileum in Krebs solution (Bennett *et al.*, 1975b) indicate that indomethacin at concentrations up to 3.6 μg/ml had no significant effect on contractions of the longitudinal muscle induced by ACh, and caused at most a small depression of contractions to electrical field stimulation at 4 Hz. However, indomethacin 20 μg/ml (Chong & Downing, 1974) or 40 μg/ml (Bennett *et al.*, 1975b) caused non-selective depression. The present experiments indicate a small inhibitory effect of indomethacin 1–4 μg/ml on responses to nicotine, a greater inhibition of responses to prostaglandin E_2, but no effect on those to ACh. Aspirin 100–200 μg/ml did not significantly depress the responses to any of these drugs or to transmural stimulation. At the concentrations used, both drugs seem sufficiently free of unwanted effects to validate their use as tools to study the role of prostaglandins in peristalsis.

Prostaglandin antagonists. The prostaglandin antagonists PPP and SC-19220 were not suitable for evaluation of the role of prostaglandins in peristalsis, because concentrations required to antagonize prostaglandin effects also reduced nerve-mediated responses that may be essential for peristaltic activity. Consequently a non-selective neuronal effect might occur. On the other hand the drugs might perhaps reduce the modulation by prostaglandins of cholinergic nerve excitation (see Introduction) and this could be a common effect of drugs that selectively inhibit a neuronal action of prostaglandins.

Effects of prostaglandin synthesis inhibitors on peristalsis

Serosally applied aspirin or indomethacin reduced peristaltic activity in guinea-pig ileum and colon, but the effect of aspirin on guinea-pig ileum was sometimes temporary, despite its continued presence. Addition of prostaglandin E_2 usually prevented the effect on the ileum of aspirin but not of indomethacin, possibly suggesting the involvement of a prostaglandin pathway which was more affected by indomethacin than by aspirin. Perhaps the greater effectiveness of indomethacin is related to its ability to reduce contractions of the longitudinal muscle of guinea-pig ileum to prostaglandin E_2. The involvement of prostaglandins in peristalsis is again suggested by their ability to reverse established inhibition caused by aspirin or indomethacin. Although acetylcholine, 5-HT or histamine could also produce reversal in the ileum, they were rarely effective in the colon.

The role of prostaglandins in peristaltic activity

The above data are consistent with a role for prostaglandins in peristalsis. It is not clear whether prostaglandin E_2 and/or $F_{2\alpha}$ are important; both are thought to be present (Ambache *et al.*, 1966). They might act in various ways (as indicated in the Introduction) by modulation of intrinsic nerve activity or responses to intrinsic substances, or by maintenance of muscle tone. The inhibitory effect of added prostaglandin E_1 or E_2 in guinea-pig isolated ileum presumably represents an overwhelming action directly on the circular muscle (Bennett *et al.*, 1968b); a lower concentration of prostaglandin E_1 initially causes stimulation (Radmanović, 1972).

That some peristaltic activity occurs in the presence of aspirin or indomethacin suggests that prostaglandins are unlikely to be essential. However, it is not known if small amounts of prostaglandin synthesis occurring in the presence of the inhibitors is sufficient to allow peristalsis to occur and if peristalsis would cease if all prostaglandin synthesis or action were stopped. Nor is it known if the drugs penetrate to all parts of the tissue or are able to inhibit all biosynthetic pathways for prostaglandins. Poor penetration might explain the tendency for the synthetase inhibitors to be less active intraluminally and might account for the 30–90 min contact time required for maximal effects in isolated strips (Bennett *et al.*, 1975a). The sensitivities of prostaglandin synthesizing enzymes to indomethacin in different rabbit tissues differ over a range of 1100-fold (Bhattacherjee & Eakins, 1974). If enzymes in the gut show a spectrum of sensitivities, drugs might not inhibit prostaglandin synthesis at all sites.

Although it seems unlikely that prostaglandins are essential for peristaltic activity in guinea-pig isolated intestine, it nevertheless seems that they are needed for full activity in the colon, and possibly in the ileum. As in other sites, prostaglandins might play a modulatory role.

We thank the Wellcome Trust for support (H.L.S.), Dr J.E. Pike, Upjohn Company Ltd., U.S.A. for prostaglandins, Dr J.H. Sanner, Searle Ltd., U.S.A. for SC-19220, Dr B. Högberg, Leo Research Laboratories, Sweden, for polyphloretin phosphate, and Merck, Sharpe and Dohme for indomethacin.

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(Received September 16, 1975. Revised January 13, 1976.)