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The effect of PGE_1 on peristalsis and on perivascular nerve inhibition of peristaltic activity in guinea-pig isolated ileum

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The effect of PGE_1 on peristalsis of guinea-pig isolated ileum was examined using a modified Trendelenburg method to evoke and record peristaltic activity. PGE_1 (14 nM, 0·11 μM and 0·56 μM) increased peristaltic activity of both longitudinal and circular muscle, mainly by increasing the amplitude of contraction. Preparations of ileum subjected to a 'minimal' peristaltic stimulus were more sensitive to the effects of PGE_1 than were preparations subjected to a 'just-maximal' peristaltic stimulus. The inhibition of peristaltic activity caused by perivascular nerve stimulation was antagonized by 0·56 μM PGE_1 but slightly increased by 14 nM PGE_1.

Prostaglandins (PGs) E_1 or E_2 enhance the peristaltic activity of the longitudinal muscle of guinea-pig isolated ileum (Bennett, Eley & Scholes, 1968a; Radmanović, 1972; Takai, Matsuyama & Yagasaki, 1974). Small concentrations of PGE_1 or PGE_2 may also increase the peristaltic activity of the circular muscle of the ileum (Radmanović, 1972; Takai & others, 1974), but higher concentrations of these PGs inhibit circular muscle peristaltic activity (Bennett & others, 1968a; Radmanović, 1972; Fontaine, Van Nueten & Reuse, 1977). The experiments presented here, using guinea-pig isolated ileum, examine the action of PGE_1 on varying degrees of peristaltic activity.

METHODS

Male guinea-pigs, ~400 g, were stunned and bled. Segments of terminal ileum, 4 to 5 cm long, were removed at least 8 cm from the caecum. The tissue was suspended as described by Trendelenburg (1917) in a 50 ml organ bath, under an initial load of 1 g; it was bathed with a modified Krebs solution (NaCl 118·6; $CaCl_2$ 2·7; KCl 4·7; KH_2PO_4 1·2; $MgSO_4$ 0·1; $NaHCO_3$ 25·0; dextrose 10·4 mM) maintained at 37° and bubbled with 5% CO_2 in oxygen.

Peristalsis was elicited for 45 s by increasing the intraluminal pressure from zero by 1 to 6 cm H_2O. Longitudinal muscle responses were measured using either an isotonic force-displacement transducer (SRI) or an isometric transducer (Grass Instrument Co. Ltd. FTO3C). A pressure transducer (Ether Ltd. UPI) measured intraluminal pressure as an indication of circular muscle activity. The response to perivascular nerve stimulation, was studied using a Grass S88 stimulator, two platinum ring-electrodes surrounding the nerve, and a stimulus isolation unit (Grass Instrument Co. Ltd. SIU5) to minimize stimulus artifact.

The pressures required to produce 'minimal' peristaltic responses (threshold and often transient), and 'just-maximal' peristaltic responses were determined in each experiment.

Measurements were made of longitudinal and circular muscle activity 15, 30 and 45 s after inducing peristalsis, by determining (1) the amplitude of peristaltic contractions, (2) the increased tone ('peristaltic tone') and (3) the number of peristaltic contractions during the 45 s period of peristalsis. Results were analysed using the two-tailed Wilcoxon Matched-pairs Signed-rank test. Where probability values are not given 'significant' means $P<0.05$.

RESULTS

PGE_1 added to the bath dose-dependently contracted the longitudinal muscle. When peristalsis was elicited the longitudinal muscle contractions were superimposed on this PGE_1-induced contraction, and the peristaltic activities of the longitudinal and circular muscle layers increased (Fig. 1). Fig. 2 illustrates the effect of PGE_1 on the amplitude of contraction and on 'peristaltic tone'. The results were similar with isotonic or isometric recordings of longitudinal activity, so only the isotonic responses are shown in Fig. 2.

'Minimal' peristalsis. PGE_1 tended to increase the amplitude of contraction of both muscle layers in an approximately dose-dependent manner, but these

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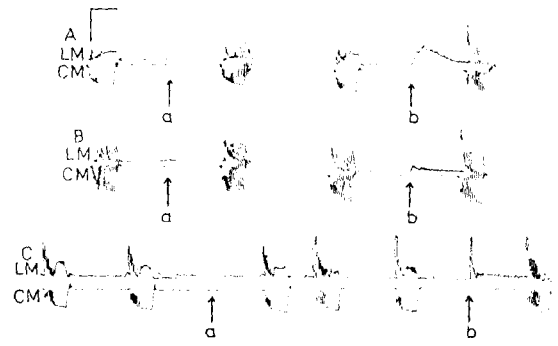

FIG. 1. Typical records illustrating the effect of 14 nM (a) and 0·56 μM PGE_1 (b) on (A) 'minimal'; (B) 'just-maximal' peristalsis and (C) 'minimal' peristalsis with perivascular nerve stimulation at 0·8 Hz. LM, longitudinal muscle; CM, circular muscle recordings. Periods of perivascular nerve stimulation (1 min) are indicated by the horizontal bars below the trace, beginning 15 s before peristalsis was initiated by raising the intraluminal pressure. PGE_1 was added 2 min before the peristaltic reflex was induced. The vertical calibration shows longitudinal muscle tension (3 g).

changes were not significant (except for circular muscle with 0·56 μM PGE_1 30 s after peristalsis was elicited). The longitudinal muscle 'peristaltic tone' was significantly increased with 14 nM PGE_1 15 and 30 s after inducing peristalsis, indicating incomplete relaxation after each peristaltic contraction. However, this increase was not significant with 0·11 μM PGE_1, and 0·55 μM PGE_1 tended to reduce longitudinal muscle 'peristaltic tone' (only significant 30 s after peristalsis was elicited; $P = 0{\cdot}002$). The effect of PGE_1 on 'peristaltic tone' contrasts with the tendency for PGE_1 to cause a dose-dependent increase in contraction amplitude. PGE_1 did not significantly affect circular muscle 'peristaltic tone' except with 0·56 μM PGE_1 30 s after peristalsis was elicited, where there was a significant reduction of 'peristaltic tone' ($P = 0{\cdot}04$). As a percentage of control, the number of peristaltic contractions with 14 nM, 0·11 μM and 0·56 μM PGE_1 were respectively 92 ± 12% ($P = 0{\cdot}165$), 147 ± 21% ($P = 0{\cdot}099$) and 142 ± 21% ($P = 0{\cdot}010$).

'Just-maximal' peristalsis. This was less-effectively increased by PGE_1. Longitudinal muscle contractions were not significantly increased (except with 14 nM PGE_1 30 s after peristalsis was elicited), and 0·56 μM PGE_1 appeared less effective than 0·11 μM PGE_1. Circular muscle contractions tended to increase with 14 nM or 0·11 μM PGE_1, but the effect was not significant. PGE_1 0·56 μM did not significantly increase circular muscle contractions 15 and 30 s after peristalsis was elicited, but significantly reduced the contraction after 45 s peristalsis ($P = 0{\cdot}021$). Longitudinal muscle 'peristaltic tone' was not significantly affected by PGE_1, while circular muscle 'peristaltic tone' was significantly increased with 0·11 μM PGE_1 but not by 14 nM or 0·56 μM PGE_1. As a percentage of control, the number of peristaltic contractions with 14 nM, 0·11 μM and 0·56 μM PGE_1 were respectively 107 ± 4% ($P = 0{\cdot}280$), 108 ± 5% ($P = 0{\cdot}142$) and 105 ± 5% ($P = 0{\cdot}222$).

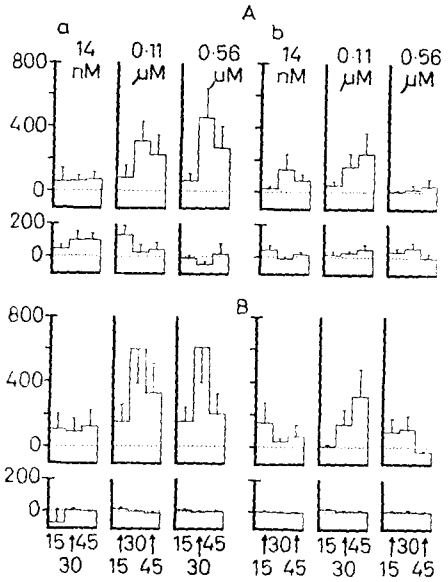

FIG. 2. Percentage effects ± s.e.m. of PGE_1 on longitudinal (A) and circular muscle (B) activity during 'minimal' (a) and 'just-maximal' (b) peristalsis, calculated 15, 30 and 45 s after the initiation of peristalsis (n = 20). Upper row, changes in the amplitude of peristaltic contractions; lower row, 'peristaltic tone'. Ordinate: % change. Abscissa: Duration of peristalsis (s).

Perivascular nerve stimulation

Continuous perivascular nerve stimulation was applied at 8, 16 or 32 Hz (8 experiments each) at just-maximal voltage (10–30 V) and a pulse duration of 0·5 ms starting 15 s before the peristaltic response was elicited so that the preparatory phase of the peristaltic reflex was maximally inhibited.

Where PGE_1 contracted the muscle, perivascular nerve stimulation reduced, or usually prevented, this contraction.

Measurements of peristaltic activity during perivascular nerve stimulation with and without addition of PGE_1 were compared with the unstimulated control. The effects of PGE_1, expressed as the difference between these percentage changes, were plotted on a

scattergram against the percentage change with perivascular nerve stimulation alone. Figs 3 and 4 show the results obtained for the longitudinal and circular muscle after 15 s 'minimal' peristalsis. Apart from a slightly greater scatter of observations, the results were similar with longer peristalsis.

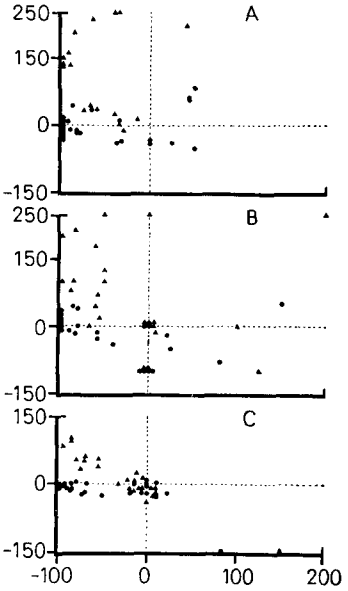

FIG. 3. Effect of PGE_1 on the inhibition by perivascular nerve stimulation of longitudinal muscle peristaltic activity induced by a 'minimal' peristaltic stimulus, after 2 min exposure to PGE_1 14 nM (●) or 0·56 μM (▲). Points occupying the upper left-hand quadrant represent antagonism by PGE_1 of the perivascular nerve-induced inhibition of peristalsis, while those in the lower left-hand quadrant represent an increased sympathetic effect with PGE_1. Points occupying the rt-hand quadrants represent the effect of PGE_1 on occasions when perivascular nerve stimulation increased the peristaltic response. A: Amplitude; B: Peristaltic tone; C: Total peristaltic contractions during 45 s. Ordinate: Change in perivascular nerve effect with PGE_1. Abscissa: % change with perivascular stimulation.

PGE_1 14 nM produced small increases in all aspects of the nerve-stimulated inhibition of peristalsis (significant only for the number of peristaltic contractions), except the circular muscle 'peristaltic tone' where PGE_1 significantly antagonized the sympathetic effect. PGE_1 0·56 μM did, however, antagonize the response to perivascular nerve stimulation, and this was significant for the contraction amplitude and 'peristaltic tone' of both muscle layers but the increase in the number of peristaltic contractions was not statistically significant ($P = 0·103$). A similar pattern of responses with PGE_1 was observed during 'just-maximal' peristalsis.

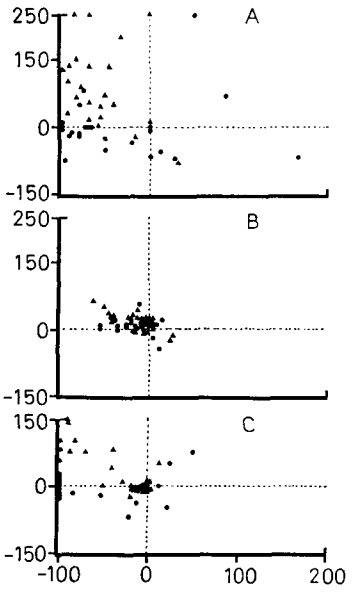

FIG. 4. Effect of PGE_1 on the inhibition by perivascular nerve stimulation of circular muscle peristaltic activity induced by a 'minimal' peristaltic stimulus, after 2 min exposure to PGE_1 14 nM (●) or 0·56 μM (▲). Points occupying the upper left-hand quadrant represent antagonism by PGE_1 of the perivascular nerve-induced inhibition of peristalsis, while those in the lower left-hand quadrant represent an increased sympathetic effect of PGE_1. Points occupying the rt-hand quadrants represent the effect of PGE_1 on occasions when perivascular nerve stimulation increased the peristaltic response. A, B, C, ordinate and abscissa as for Fig. 3.

DISCUSSION

The results for the longitudinal muscle support those of Bennett & others (1968a), Radmanović (1972) and Takai & others (1974), and show in addition that stimuli which cannot consistently induce peristalsis may be made more effective by low concentrations of PGE_1. This agrees with the findings of Mukhopadhyay, Weisbrodt & Copeland (1974), who reported that PGE_2 increased the electrical activity of the canine small intestine during fasting, but had little effect after feeding. The action of PGE_1 on longitudinal muscle peristaltic activity may therefore depend on the existing electrical activity of the muscle membrane (Miyazaki, Ishizawa & others, 1967), perhaps exerting its effect by facilitating the excitation-contraction coupling mechanism (Clegg, Hall & Pickles, 1966).

In the present experiments, stimulation of the peristaltic activity of the ileal circular muscle by PGE_1 supports the observations of Radmanović (1972) using 28-140 nM PGE_1. However, it contrasts

with the findings of inhibition of circular muscle activity by 0·28–2·8 μM PGE_1 (Bennett & others, 1968a; Radmanović, 1972), and the inhibition by PGE_1 or E_2 of circular muscle strips (Bennett, Eley & Scholes, 1968b; Harry, 1968; Bennett, Eley & Stockley, 1975), or electrically stimulated circular muscle in segments of guinea-pig ileum (Kottegoda, 1969). The Krebs solution used in our experiments differed in composition from that used by Bennett & others (1968a) or by Radmanović (1972), and this may explain the different results on peristalsis.

Low concentrations of PGE_1 stimulate circular muscle peristaltic activity in cat isolated ileum (Turker & Onur, 1971) and guinea-pig isolated colon (Ishizawa & Miyazaki, 1973a, b; Eley, Bennett & Stockley, 1977). This may be due to a primary action on the circular muscle or its nerve supply, or, as suggested by Eley & others (1977), it may be an effect secondary to increased intraluminal pressure of the closed Trendelenburg system due to longitudinal muscle contraction. However, we obtained increased circular muscle activity with both isotonic and isometric preparations of ileum; longitudinal muscle shortening therefore does not have an important role in the circular muscle response to PGE_1, although changes in longitudinal tension or electrical activity might still affect intraluminal pressure changes.

The inhibition of peristaltic activity caused by perivascular nerve stimulation was slightly increased by 14nM PGE_1, but greatly reduced by 0·56 μM PGE_1. Low PGE_1 concentrations also enhanced the effect of sympathomimetics on the rat gastric fundus strip or colon (Clegg, 1966a, b), whereas PGE_1 antagonized the inhibitory effect of perivascular nerve stimulation on the guinea-pig taenia caecum (Sakato, 1975). In the guinea-pig ileum, 0·56 μM PGE_1 may antagonize the sympathetic response partly by acting on the perivascular nerves, and partly by stimulating peristaltic activity by an action on muscles.

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