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Reversal by prostaglandin E_2 of the inhibitory effect of indomethacin on contractions of guinea-pig ileum induced by angiotensin

One of the putative roles for prostaglandins is in the modulation of neurohumoral transmission and hormone action (Hedqvist, 1970; Horton, 1969). It is possible that some of the multiplicity of angiotensin actions could be due to the interaction of prostaglandins and angiotensin. We have recently shown (Chong & Downing, 1973) that contractions of a variety of smooth muscle preparations induced by angiotensin II could be inhibited by indomethacin, which is a potent prostaglandin biosynthesis inhibitor (Vane, 1971). Indomethacin has also been shown to inhibit electrically-induced contractions of the guinea-pig ileum and the inhibition could be reversed by prostaglandins (Ehrenpreis, Greenberg & Belman, 1973). Further evidence is now presented for the involvement of prostaglandins in the contraction of the guinea-pig ileum by angiotensin II.

Segments of guinea-pig ileum 20–30 mm in length were suspended in aerated Tyrode solution in a 15 ml organ bath maintained at 34 ± 1°. Contractile responses were recorded by means of an isometric transducer. Prostaglandin E_2 (PGE_2) solutions (1 mg ml^{-1}) were prepared in 25% ethanol and kept frozen, dilutions were made in distilled water immediately before use. Indomethacin solution was prepared by dissolving it in a slight excess of sodium carbonate solution, making up to the desired volume with Tyrode solution and adjusting to pH 7·3, just before use.

Indomethacin ($5{\cdot}6 \times 10^{-5}$M) caused 46·1 ± 4·7% and 52·8 ± 6·4% reductions of the fast and slow components respectively of the submaximal contractile response

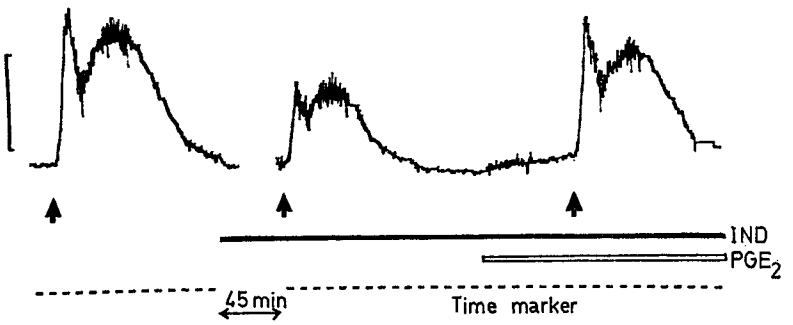

FIG. 1. Contractile responses of guinea-pig isolated ileum to $5{\cdot}0 \times 10^{-8}$M angiotensin for 60 s (arrows). Solid horizontal bar represents the presence of $5{\cdot}6 \times 10^{-5}$M indomethacin (IND), the open horizontal bar represents the presence of $1{\cdot}2 \times 10^{-8}$M prostaglandin E_2 (PGE_2). Vertical bar = 2 g tension. Time marker at 10 s intervals.

to angiotensin II. PGE_2 ($2{\cdot}8 \times 10^{-9}$M to $2{\cdot}8 \times 10^{-8}$M) added to the bath restored subsequent contractile responses to angiotensin II (Fig. 1). PGE_2 ($1{\cdot}2 \times 10^{-8}$M) restored the fast component to $95{\cdot}4 \pm 5{\cdot}5\%$ and the slow component to $88{\cdot}2 \pm 5{\cdot}7\%$ ($n = 6$) of the initial angiotensin II response. Removal of PGE_2 resulted in the recurrence of the indomethacin inhibition. Exposure to indomethacin for more than 2 h or increasing the concentration of indomethacin to $2{\cdot}3 \times 10^{-4}$M, reduced the reversal by exogenous PGE_2.

PGE_2 also potentiated submaximal contractions by angiotensin II in preparations which were not treated with indomethacin. This potentiation was less marked and was seen with lower concentrations of PGE_2 ($5{\cdot}6 \times 10^{-10}$M to $2{\cdot}8 \times 10^{-9}$M). Furthermore, the potentiation of the fast component was more marked than that of the slow component. For contractions of angiotensin around 50% of maximum PGE_2 ($2{\cdot}8 \times 10^{-9}$M) caused a $35{\cdot}2 \pm 8{\cdot}6\%$ potentiation of the fast component and a $26{\cdot}7 \pm 3{\cdot}6\%$ potentiation of the slow component. The same concentration of PGE_2 also caused a small potentiation ($15{\cdot}4 \pm 2{\cdot}1\%$) of acetylcholine contractions.

These results add further support to the idea presented earlier (Chong & Downing, 1973) that the inhibition of angiotensin II by indomethacin results from a failure of prostaglandin synthesis. On the basis of these limited findings, we tentatively suggest that some component of the contractile action of angiotensin II on the guinea-pig ileum involves the release of prostaglandins.

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