Possible involvement of prostaglandins in the contractile action of bradykinin on rat terminal ileum

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There is an increasing body of evidence suggesting a relation between prostaglandins and bradykinin in several systems. Bradykinin affects the release of prostaglandins from dog kidney (McGiff, Terragno & others, 1972), dog spleen *in vitro* and *in vivo* (Moncada, Ferreira & Vane, 1972; Ferreira, Moncada & Vane, 1973), and isolated guinea-pig lungs (Palmer, Piper & Vane, 1973). Aspirin-like drugs, which inhibit prostaglandin synthesis (Vane, 1971), antagonize several pharmacological responses to bradykinin. These include renal vasodilation and diuresis (McGiff, 1975), bronchoconstriction (Collier, Holgate & others, 1960), hypotension (Collier & Shorley, 1960) and vascular smooth muscle relaxation (Aiken, 1974), and Vane & Ferreira (1975) suggested that such antagonism, indicates involvement of prostaglandin. The present experiments suggest that prostaglandin participates in the contractile action of bradykinin on the longitudinal muscle of rat isolated terminal ileum.

Male Wistar rats, 200–300 g, were killed by a blow on the head after an overnight fast, and sections of terminal ileum, 2·5 cm long, were suspended under a load of 1 g in a 20 ml organ bath containing aerated Tyrode solution at 30°. Doses of the agonists used were chosen to produce contractions approximately 50% of maximum and the responses were recorded using Devices isotonic transducers and M2 electronic recorders.

Aspirin (610 μM) significantly reduced contractions to bradykinin (56·0 $\pm$ 7·2% (s.e.), (n = 14, $P < 0{\cdot}001$, Student's *t*-test for paired data) after 50 min but responses to acetylcholine were not affected (102 $\pm$ 6·2% of controls; n = 13). Indomethacin 2·8 or 28·0 μM reduced the responses to bradykinin, after 50 min incubation, to 74·4 $\pm$ 7·3% (n = 9) and 42·8 $\pm$ 7·3% (n = 13) respectively ($P < 0{\cdot}001$) but responses to acetylcholine were not significantly affected (119·8 $\pm$ 7·2%, n = 10; and 105·9 $\pm$ 5·1%, n = 13 respectively). After the removal of aspirin or indomethacin from the bathing medium the contractile responses to bradykinin returned gradually to control levels over a period of 2 h.

The prostaglandin antagonist polyphloretin phosphate (Eakins, Karim & Miller, 1970) was incubated with the tissue at a concentration of 10 μg ml^{-1} for 2 min before the addition of acetylcholine, bradykinin or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). The responses to bradykinin and $PGF_{2\alpha}$ were reduced to 64·8 $\pm$ 5·8% (n = 8) and 37·1 $\pm$ 6·0% (n = 11) respectively ($P < 0{\cdot}001$) while acetylcholine-induced contractions were not significantly affected (94·5 $\pm$ 3·6%; n = 10).

Since aspirin, indomethacin or polyphloretin phosphate antagonize the contractile action of bradykinin at concentrations which do not significantly alter the response to acetylcholine, prostaglandin may participate in the contractile action of bradykinin on the longitudinal muscle of rat isolated terminal ileum.

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REFERENCES

AIKEN, J. W. (1974). *Pharmacologist*, **16**, 295.

COLLIER, H. O. J., HOLGATE, J. A., SCHACTER, M. & SHORLEY, P. G. (1960). *Br. J. Pharmac.*, **15**, 290–297.

COLLIER, H. O. J. & SHORLEY, P. G. (1960). *Ibid.*, **15**, 601–610.

EAKINS, K. E., KARIM, S. M. M. & MILLER, J. D. (1970). *Ibid.*, **39**, 556–563.
FERREIRA, S. H., MONCADA, S. & VANE, J. R. (1973). *Ibid.*, **49**, 86–97.
MCGIFF, J. C. (1975). *Life Sci.*, **16**, 805.
MCGIFF, J. C., TERRAGNO, N. A., MALIK, K. U. & LONIGRO, A. J. (1972). *Circ. Res.*, **31**, 36–43.
MONCADA, S., FERREIRA, S. H. & VANE, J. R. (1972). Abstr. Vth Int. Congress Pharmac. San Francisco, 160.
PALMER, M. A., PIPER, P. J. & VANE, J. R. (1973). *Br. J. Pharmac.*, **49**, 226–242.
VANE, J. R. (1971). *Nature New Biol.*, **231**, 232–235.
VANE, J. R. & FERREIRA, S. H. (1975). *Life Sci.*, **16**, 804.

Passage of intravenously administered pethidine into gastric juice in man

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Pethidine is eliminated in animals and man mainly after biotransformation to metabolites which are excreted in urine (Burns, Berger & others 1955; Plotnikoff, Elliott & Way, 1952; Plotnikoff, Way & Elliott, 1956). In their studies of tissue distribution of the ^{14}C label following parenteral administration of [^{14}C]pethidine to rats, Plotnikoff & others (1952) noted significant amounts of radioactivity in the gastrointestinal tract. They concluded "The radioactive material in all probability represents metabolic products of the parent compound." We wish to report that irrespective of any possible excretion of metabolites of pethidine via bile and/or gastrointestinal tract, pethidine itself can appear in the tract after parenteral administration by passing into the gastric juice. The process also involves concentration of the drug to levels one to two orders of magnitude greater than those in plasma.

We studied four patients who received pethidine potentiated nitrous oxide-oxygen anaesthesia. Preoperative medication was 10 mg of diazepam. The amount of pethidine each patient received in divided doses ranged from 225 to 600 mg (i.v.). Curare was the relaxant drug in doses from 15 to 22 mg. Gastric samples along with simultaneous blood samples were obtained before and from 10 min up to 4 h after the last dose of pethidine. All samples were analysed for pethidine by gas chromato-

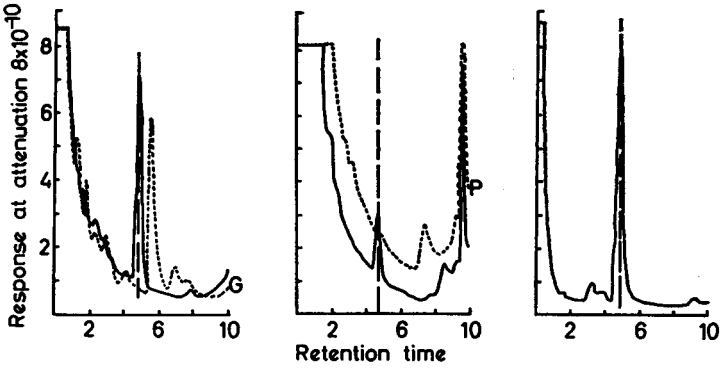

FIG. 1. Identification of pethidine in gastric juice and plasma of a patient administered pethidine intravenously. Left panel: gas chromatograms of extracts of gastric juice; broken line—zero time sample, i.e. before administration of pethidine; solid line–sample taken 75 min after administration of pethidine. Right panel: gas chromatogram of authentic pethidine sample. Middle panel: gas chromatograms of extracts of plasma; broken line–zero time sample; solid line–sample taken 75 min after administration of pethidine.