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Methyl analogues of prostaglandin E_2 and gastro-intestinal function in the rat

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The 15-methyl and 16,16-dimethyl analogues of prostaglandin E_2 (PGE_2) are potent inhibitors of gastric secretion in the dog (Robert & Magerlein, 1973) and man (Karim, Carter, Bhana & Adaikan Ganesan, 1973; Robert, Nylander & Andersson, 1974). Since these analogues are of potential therapeutic value, we have compared their potency and selectivity of action with the parent prostaglandin.

Gastric acid secretion and mucosal blood flow (MBF) were determined in the urethane-anaesthetized rat (Main & Whittle, 1973a). During submaximal secretory stimulation with pentagastrin (0.3 $\mu g\ kg^{-1}\ min^{-1}$ i.v.), or histamine (30 $\mu g\ kg^{-1}\ min^{-1}$ i.v.), intravenous infusion of (15S)-15-methyl PGE_2 methyl ester or 16,16-dimethyl PGE_2 (2 μg/kg over 20 min) caused near-maximal inhibition of acid output. Secretory inhibition of comparable magnitude but of shorter duration was obtained with an infusion (60 μg/kg i.v.) of PGE_2 (see also Main & Whittle, 1973b). Increases in MBF per unit acid output during secretory inhibition and increases in resting MBF were observed with both prostaglandin analogues, indicating a primary effect on acid secretion. When infused intravenously in equivalent antisecretory doses, PGE_2 caused a maintained fall in systemic arterial blood pressure (B.P.), whereas 15-methyl PGE_2 caused only a small, transient fall in B.P. and 16,16-dimethyl PGE_2, a small increase in B.P. When administered by single i.v. injection (2-10 μg/kg), PGE_2 and the methyl analogues had similar vasodepressor activity.

In the unanaesthetized chronic fistula rat, administration of the methyl analogues (1.25-2.5 μg/kg s.c.) during resting acid secretion caused reflux of bile into the gastric lumen and the gastric output became alkaline. With higher doses (5-20 μg/kg), bile reflux was often accompanied by a profuse mucoid diarrhoea; the ED_{50} for the latter effect with 15-methyl PGE_2 was 7 μg/kg. Since these actions reflect altered gastro-intestinal motility, intraluminal pressure was recorded in the duodenum, jejunum and ileum of the anaesthetized rat. Both analogues (0.5-5 μg/kg i.v.) caused prolonged increases in intestinal tone and motility, and were at least 20 times more active than PGE_2. *In vitro*, the three prostaglandins were of similar potency in contracting gastro-intestinal segments.

Though these methyl analogues of PGE_2 have a selective action on gastric secretion as compared with the cardiovascular system in the rat, there is no marked degree of selectivity with respect to gastro-intestinal motility. Progress towards a more selective antisecretory prostaglandin, possibly a prostaglandin A analogue, would be facilitated by a better understanding of the mechanism of action of prostaglandins on the gastro-intestinal tract.

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