Effects of prostacyclin (PGI_2), PGI_1 and 6-oxo-$PGF_{1\alpha}$ on the rat gastric mucosa

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Prostacyclin (PGI_2) is an unstable potent vasodilator, which can be formed by vascular tissue and the rat stomach (Gryglewski, Bunting, Moncada, Flower & Vane, 1976). We have now investigated the effects of PGI_2, its stable degradation product 6-oxo-$PGF_{1\alpha}$, and 6β-PGI_1, a 5,6-dihydro prostacyclin (Johnson, Lincoln, Thompson, Nidy, Mizsak & Axen, 1977) on the rat gastric mucosa.

The inhibition of pentagastrin (0.5 μg $kg^{-1}min^{-1}$)-induced gastric acid secretion and the change in mucosal blood flow (MBF) in the urethane-anaesthetised rat was determined as previously described (Main & Whittle, 1973). PGI_2 (0.25–5 μg $kg^{-1}min^{-1}$ i.v.) caused a dose-dependant fall in systemic arterial blood pressure and inhibition of acid output; the ID_{50} (dose causing 50% inhibition) was 0.5 μg $kg^{-1}min^{-1}$ (infused i.v. for 30 min) compared with an ID_{50} of 1 μg $kg^{-1}min^{-1}$ for PGE_2. Subcutaneous administration of PGI_2 (50–200 μg/kg) likewise inhibited acid output (ID_{50}, 100 μg/kg, s.c.). 6-oxo-$PGF_{1\alpha}$ had little effect on acid output in doses up to 50 $\mu g^{-1}kg^{-1}min$ i.v. for 30 minutes. However, the stable prostacyclin analogue, PGI_1 inhibited acid secretion (ID_{50}, 4 μg $kg^{-1}min^{-1}$ i.v.) and in these antisecretory doses, it was less active than PGI_2 as a vasodepressor.

During the inhibition of acid secretion by PGI_2, the ratio of MBF to acid output increased. Furthermore, PGI_2 (0.5 $\mu g^{-1}kg^{-1}min$, i.v.) increased resting MBF, indicating a direct vasodilator action on the mucosa.

In the isolated perfused whole rat-stomach preparation (Bunce & Parsons, 1976), PGI_2 added to the serosal solution (pH 7.6, 37°C) inhibited histamine (5×10^{-5} M)-induced acid output with an ID_{50} of 6×10^{-6}M. Although PGI_2 appeared less active than PGE_2 (ID_{50}, 10^{-6} M) in this preparation, this may well result from the rapid breakdown of PGI_2 under these *in vitro* conditions; the stable analogue, PGI_1, showed marked antisecretory activity (ID_{50}, 1.0×10^{-6} M).

The inhibition of gastric mucosal erosions was assessed 3 h after administration of indomethacin (20 mg/kg s.c.) as previously described (Whittle, 1976). Repeated subcutaneous administration of PGI_2, PGI_1 and 6-oxo-$PGF_{1\alpha}$ reduced the incidence and severity of the lesions, with an ID_{50} of 35, 30 and 500 μg $kg^{-1}h^{-1}$ respectively. Likewise, a single subcutaneous injection of PGI_2 and PGI_1 immediately prior to indomethacin, inhibited the erosions, with an ID_{50} of 350 and 200 μg/kg s.c. respectively compared to 450 μg/kg s.c. for PGE_2. 6-oxo-$PGF_{1\alpha}$ had little activity in single doses up to 500 μg/kg s.c.

The present findings indicate that prostacyclin exhibits many of the actions previously ascribed to PGE_2, being a potent mucosal vasodilator, an inhibitor of gastric acid secretion and an inhibitor of erosion formation in the rat. The interaction and relative roles of PGI_2 and PGE_2 in the gastric mucosa remains to be clarified.

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The renal haemodynamic and excretory actions of prostacyclin (PGI_2) in anaesthetized dogs

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Prostacyclin (PGI_2) is a newly discovered arachidonic acid metabolite synthesized in vascular walls of different species including man. PGI_2 relaxes a variety of vascular muscle strips *in vitro* (Bunting, Gryglewski, Moncada & Vane, 1976) and is a strong hypotensive in rabbits and rats (Armstrong, Lattimer, Moncada & Vane, 1977).

As prostaglandins have profound stimulatory actions on renal haemodynamics and excretion in a variety of species (McGiff & Itskovitz, 1973) we have measured the renal actions of PGI_2 in anaesthetized dogs.

Anaesthesia was induced with thiopentone (30–40 mg/kg i.v.) and maintained with chloralose (25–35 mg/kg i.v.) and pentobarbitone (7.5–10.5 mg/kg i.v.). The dogs were artificially ventilated; arterial pO_2 was maintained above 90 mm Hg and pCO_2 in the range 25–40 mm Hg. A loading dose of creatinine (50 mg/kg in 0.9% w/v saline i.v.) was followed by a maintenance infusion (0.42 $mg/kg^{-1}min^{-1}$ in 0.9% saline at 0.25 $ml/kg^{-1}min^{-1}$) via a cannulated femoral vein. Arterial (BP) and venous (VP) blood pressures were measured from brachial vessels with pressure transducers connected to a chart recorder. Heart rate (HR) was recorded by integrating the arterial pulse. An electromagnetic flow probe (2–4 mm diameter) was fitted to the left renal artery to measure renal blood flow (RBF). The ureters were cannulated and urine flow (UV) from the left kidney recorded by integrating the signal from a photo-electric drop counter.

Renal arterial (i.a.) infusions of PGI_2 (30–300 ng/min for 15–30 min in 5 dogs) caused dose dependent increases in RBF, UV and sodium excretion ($U_{Na}V$), $U_{Cl}V$, $U_{Osm}V$, and reductions in calculated renal vascular resistance (RVR) and filtration fraction (FF) without altering BP or HR. Qualitatively similar responses to PGI_2 (1000–3000 ng/min i.a.) were associated with hypotension and tachycardia. VP and creatinine clearance (C_{Cr}) were unaffected.

Intravenous infusion of PGI_2 (30–300 ng/min in 3 dogs) tended to increase RBF but reduced $U_{Na}V$, $U_{Cl}V$, $U_{Osm}V$, while BP, HR, C_{Cr}, FF, UV and U_KV were unaltered. Larger doses (1000–3000 ng/min i.v.) caused pronounced hypotension accompanied by further elevations of RBF and HR, but reductions in all other variables. The stable metabolite of prostacyclin, 6-oxo-$PGF_{1\alpha}$ (10,000 ng/min) had no effect by either i.v. or i.a. routes.

After meclofenamate (2.5 mg/kg i.v. in 2 dogs), RBF was unchanged, though the increase in RBF to PGI_2 (300 ng/min i.a.) was enhanced.

As glomerular filtration rate (C_{Cr}) was unaltered by sub-hypotensive doses (i.a.) of PGI_2, the reduction in calculated FF could be explained by efferent arteriolar dilatation (Bolger, Eisner, Ramwell & Slotkoff, 1976). Similarly, the increased $U_{Na}V$ and $U_{Cl}V$ resulted from reductions in tubular Na^+ and Cl^- reabsorption, rather than through increases in their filtered loads. Endogenous PGI_2 synthesized by kidney vessels may influence renal function.

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Disappearance of prostacyclin (PGI_2) in the circulation of the dog

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Prostacyclin (PGI_2) is a potent endogenous vasodilator in dogs (Armstrong, Chapple, Dusting, Hughes, Moncada & Vane, 1977a; Dusting, Moncada & Vane, 1977) rats and rabbits (Armstrong, Lattimer, Moncada & Vane, 1977b). Prostaglandin E_2 (PGE_2) is less potent as a hypotensive agent when given intravenously rather than intra-arterially because of extensive pulmonary metabolism (Ferreira & Vane, 1967), but prostacyclin is of similar potency when given by either route (Armstrong *et al.*, 1977a, b). We have now examined the stability of prostacyclin in blood, and its removal by various vascular beds of the dog.

Prostacyclin was detected by direct bioassay in blood continuously withdrawn from the arterial circulation of chloralose anaesthetized dogs (Vane, 1964). The vascular bioassay tissues (spiral strips of rabbit coeliac artery, RbCA; bovine coronary artery, BCA) were relaxed by prostacyclin (threshold 2–5 ng/ml), whereas gastro-intestinal bioassay tissues (rat stomach strip, RSS; rat colon, RC) were contracted by prostacyclin (threshold above 10 ng/ml). All bioassay tissues were insensitive to 6-oxo-$PGF_{1\alpha}$ (up to 100 ng/ml).

To measure the stability of prostacyclin in blood, a coil of silicone tubing was interposed between the blood supply and the bioassay tissues such that a transit time of up to 5 min could be achieved. Prostacyclin infusions (20–80 ng/ml) were made at different points in the coil and their effect compared with infusions of prostacyclin close to the assay tissues. From the disappearance of the activity on RbCA, BCA or RSS the half-life in blood was calculated to be 3.1 ± 0.4 min (6 experiments). This probably reflects chemical rather than enzymic breakdown for the half-life of prostacyclin in buffer at 37°C and pH 7.5 is about 3 minutes.