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Actions of prostaglandins A_2, E_1 and $F_{2\alpha}$ on cat skeletal muscle vascular bed

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The effects of prostaglandins (PG) A_2, E_1 and $F_{2\alpha}$ on the consecutive functional sections of the vascular bed of acutely denervated cat calf muscle were investigated. Male cats (n = 57), 2.5-3.2 kg, were anaesthetized with chloralose (46 mg/kg) and urethane (460 mg/kg) intramuscularly. The acutely denervated calf muscle was prepared according to the method described by Mellander (1966). The prostaglandins were given by infusion in doses ranging from 0.007 to 15 $\mu g\ kg^{-1}\ min^{-1}$ intra-arterially.

The results are given in Table 1. All three prostaglandins elicited dose-dependent decreases in peripheral resistance, indicating dilatation of the resistance vessels in the following order of potency: $PGE_1 > PGA_2 > PGF_{2\alpha}$. Whereas dilatation of the capacitance vessels was also observed during the infusion of PGA_2 and PGE_1, a dose-dependent constriction of the capacitance vessels was provoked by the infusion of $PGF_{2\alpha}$. A net increase in interstitial fluid was observed during the infusion of PGA_2 and PGE_1, however, only the effect of PGA_2 was dose-related. $PGF_{2\alpha}$ had no effect on transcapillary fluid filtration.

The effects of PGA_2, PGE_1 and $PGF_{2\alpha}$ on the peripheral vascular bed of cats appeared to be qualitatively similar to those reported for man (Robinson, Collier, Karim & Somers, 1973).

Table 1 Effects of prostaglandins A_2, E_1 and $F_{2\alpha}$ on the acutely denervated vascular bed of cat calf muscle

PG	Dose ($\mu g\ kg^{-1}\ min^{-1}$ i.a.)	n	% Resistance response ± s.e. mean (control = 100%)	Capacitance response ± s.e. mean (ml/100 g tissue)	Transcapillary fluid filtration ± s.e. mean ($ml\ min^{-1}\ 100\ g\ tissue^{-1}$)
A_2	0.062	4	97 ± 7	0.00	+0.03 ± 0.03
	0.187	5	86 ± 8	+0.09 ± 0.05	+0.10 ± 0.01
	0.560	5	77 ± 5	+0.12 ± 0.06	+0.19 ± 0.03
	1.67	4	77 ± 4	+0.23 ± 0.08	+0.19 ± 0.06
E_1	0.007	4	93 ± 1	0.00	+0.09 ± 0.05
	0.021	6	89 ± 2	+0.14 ± 0.03	+0.04 ± 0.03
	0.062	4	88 ± 5	+0.03 ± 0.03	+0.26 ± 0.06
	0.187	4	75 ± 4	+0.39 ± 0.13	+0.05 ± 0.05
	0.560	6	67 ± 3	+0.39 ± 0.12	+0.12 ± 0.05
$F_{2\alpha}$	1.67	6	92 ± 3	−0.17 ± 0.12	0.00
	5.0	4	90 ± 2	−0.32 ± 0.13	−0.05 ± 0.02
	15.0	5	89 ± 3	−0.39 ± 0.2	−0.04 ± 0.04

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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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