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Gastric acidity and the mechanisms by which prostaglandins prevent indomethacin-induced gastric erosions

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Antisecretory prostaglandins inhibit the formation of gastric ulcers and erosions induced by several techniques (Robert, Nezamis & Phillips, 1968). In the present study, the relationship between inhibition of gastric acid secretion and the prevention of indomethacin-induced mucosal erosions by several prostaglandins has been investigated in the rat.

Indomethacin (5-30 mg/kg s.c.) caused the formation of rat gastric mucosal erosions within 1-6 h, the incidence and severity depending on the dose and duration of administration. Prostaglandin E_2 (PGE_2) and its methyl analogues, which are potent inhibitors of rat gastric secretion (Main & Whittle, 1975), reduced erosion formation in a dose and time-dependent manner. The dose reducing the erosion 'score' by 50% (ED_{50}) observed 3 h after indomethacin (15 mg/kg s.c.), was 220, 250, 0.54 and 0.50 μg/kg s.c. for PGE_2, PGA_2, (15S)-15 methyl E_2 and 16, 16, dimethyl E_2 respectively. However, the H_2-receptor antagonist metiamide, in doses which inhibited gastric secretion, also reduced indomethacin erosions; the ED_{50} was 13 mg/kg s.c. The ratio of the ED_{50} for prevention of erosions to the ED_{50} for inhibition of gastric acid secretion in the chronic fistula rat (see Main & Whittle, 1975) was 1.6 for PGE_2 and 0.4 for its methyl analogues, showing a variable relationship. Furthermore, the (15S) methyl analogue of $PGF_{2\alpha}$ also prevented erosion formation (ED_{50} 20 μg/kg s.c.).

The mechanism by which prostaglandins inhibit erosions was further studied by perfusing acidic saline (pH 1-2; 100-10 mM HCl) through the gastric lumen of the urethane-anaesthetized rat. Indomethacin (5-20 mg/kg s.c.) induced a low incidence of erosion formation within 3 h at pH 1.2-2.0, but this effect was greatly potentiated, accompanied by mucus secretion, when the bile salt sodium taurocholate (0.2-5.0 mg/ml) was perfused simultaneously. The time-course and degree of erosion formation, which was followed more closely by enclosing the exteriorized stomach in a transparent chamber (Mersereau & Hinchey, 1973), depended on the acid and taurocholate concentrations and the dose of indomethacin. Administration of the PGE_2 methyl analogues (5 $\mu g\ kg^{-1}\ h^{-1}$ s.c.) prevented indomethacin (20 mg/kg s.c.)-induced erosions during gastric perfusion of taurocholate (1 mg/ml; 2 mM) at pH 1.3 (76 ± 9% inhibition of erosions, n = 4; mean ± s.e.mean) and pH 1 (53 ± 12%, n = 4) for 3 h, and the mucosa appeared hyperaemic. The loss of titratable acid from the gastric lumen, which followed indomethacin administration with taurocholate and acid perfusion, was also reduced by the PGE_2 methyl analogues (20 ± 5% reduction, n = 8).

These results indicate that the formation of indomethacin-induced gastric erosions in the rat depends on the acid concentration in the gastric lumen, and that antisecretory agents such as prostaglandins and metiamide can inhibit their formation. However, the ability of prostaglandins to prevent erosion formation in the presence of exogenous acid indicates that other mechanisms may also be involved. It is not yet known how such mechanisms are related to changes in local blood flow or mucosal permeability.

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The effect of prostaglandin E_1 and E_2 on drug-induced release of [^{3}H]-noradrenaline from rat mesenteric arteries

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The release of [^{3}H]-noradrenaline ([^{3}H]-NA) from sympathetic nerve endings by nerve stimulation is inhibited in the presence of prostaglandin E_1 and E_2 (Hedqvist, 1973). Prostaglandin E_1 and E_2 also inhibit the action of noradrenaline on a number of tissues (Bergstrom, Carlson & Weeks, 1968).

To investigate the effects of prostaglandins E_1 & E_2 on ^{3}HNA release by sympathomimetics, the rat mesenteric artery preparation was perfused with (−)-noradrenaline-[7-^{3}H] and carrier (−)-noradrenaline diluted with normal Krebs to give a final concentration of 4.2×10^{-9} Ci/ml [^{3}H]-(−)-noradrenaline and 200 ng/ml noradrenaline respectively as previously described (George & Leach, 1972). The mesentery was perfused with this solution for 60 min after which it was then perfused with normal, tracer free Krebs solution and the spontaneous release of [^{3}H]-NA measured over a further 60 min period as described, (George & Leach, 1975). The effect, of perfusion with prostaglandin E_1 and E_2 (1-100 ng/ml) on the spontaneous release of [^{3}H]-NA was measured. Finally, the effects of perfusion with prostaglandin E_1 and E_2 on [^{3}H]-NA release caused by injection of NA 200 ng, metaraminol 20 μg, octopamine 50 μg and tyramine 100 μg were studied and the results for prostaglandin E_1 are summarized in Table 1.

These results show that prostaglandin E_1 at each of the perfusion concentrations used has an inhibitory effect on the release of [^{3}H]-NA by sympathomimetic amines but no effect on the spontaneous release of [^{3}H]-NA in the absence of the sympathomimetic amines. Prostaglandin E_2 caused a similar though smaller inhibition. It appears that prostaglandins of the E series could have some role in the drug induced release of [^{3}H]-NA from sympathetic nerve endings.

Table 1 The mean increase in ^{3}H-noradrenaline outflow ± s.e. following injection of each of the amines during perfusion with normal Krebs in the presence or absence of prostaglandin.

Perfusate composition	*Mean spontaneous ^{3}HNA release d min^{-1} ml^{-1}*	*Total mean increase in [^{3}H]-noradrenaline outflow (d min^{-1} ml^{-1}) ± s.e. following injection of each of the amines in the presence or absence of prostaglandin*			
		Noradrenaline 200 ng	*Octopamine 50 μg*	*Metaraminol 20 μg*	*Tyramine 100 μg*
Normal	1901	920 ± 101	2370 ± 210	3261 ± 332	2522 ± 241
Prostaglandin E_1 1ng/ml	2004	877 ± 88	1782 ± 177	2817 ± 226	1593 ± 184
Prostaglandin E_1 10 ng/ml	1986	735 ± 72	1211 ± 120	1872 ± 163	1009 ± 116
Prostaglandin E_1 100 ng/ml	1899	710 ± 73	1089 ± 110	1377 ± 124	725 ± 93

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