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Comparison of various prostaglandins (PG's) on the *in vitro* longitudinal uterine smooth muscle of the rat and guinea-pig

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Prostaglandins of the E and F series stimulate the non-pregnant uteri of most animals both *in vivo* and *in vitro* (Bergström, Carlson & Weeks, 1968). This study compares the potencies of various PG's on the *in vitro* longitudinal uterine smooth muscle preparation from non-pregnant rats and guinea-pigs in an attempt to define some pharmacological characteristics of the receptors mediating these effects. Longitudinal uterine strips from rats (Sprague Dawley) in oestrus and guinea-pigs in di-oestrous were suspended in De Jalon's solution at 35°C and Van Dyke and Hasting's solution at 32°C respectively, and bubbled with 95% O_2 and 5% CO_2. Indomethacin (2.8×10^{-6} M) was present in the bathing fluids throughout the experiments. A resting tension of 1 g was imposed on the tissues and contractions were recorded isometrically and displayed on a Grass Polygraph. The PG's used were PGE_1, PGE_2, $PGF_{2\alpha}$, the $PGF_{2\alpha}$ analogue ICI81008, the analogue of PGH_2, (15S)-hydroxy-11α,9α-(epoxymethano)prosta-5Z, 13E-dienic acid (U46619) and prostacyclin (PGI_2).

The relative potencies of the PG's were determined by comparing the mean ($n = 4$–9) Molar EC_{50} of each PG to that of $PGF_{2\alpha}$ (assigned a potency = 1). The results are shown in Table 1. On the guinea-pig uterus the rank order of potency of the PG's was $E_2 \geqslant E_1 >$ U46619 $\geqslant I_2 \geqslant F_{2\alpha} \gg$ ICI81008. ICI81008 acted as a partial agonist on the guinea-pig uterus, its mean maximal response being 42% of that produced by $PGF_{2\alpha}$. The order of potency of the PG's on the rat uterus was ICI81008 $\gg F_{2\alpha} > E_1 \geqslant E_2 > I_2 >$ U46619. U46619 was only effective at high concentrations on the rat uterus, the responses when produced always being near or equivalent to the $PGF_{2\alpha}$ maximum response. The $PFG_{2\alpha}$ analogue ICI81008 has previously been described as a relatively selective luteolytic agent with very little uterine smooth muscle stimulating activity, this latter effect being determined by its action on the guinea-pig uterus (Dukes, Russell & Walpole, 1974). Our results also demonstrate a low potency for ICI81008 on the guinea-pig uterus, however, in contrast this PG was found to be very potent on the rat uterus, the effect being of long duration and difficult to wash off.

These results demonstrate a different rank order

Table 1 Relative potencies of various prostaglandins in stimulating contractions of *in vitro* longitudinal uterine smooth muscle of non-pregnant rats and guinea-pigs

Compound	*Rat uterus*	*Guinea-pig uterus*
ICI 81008	13.1	0.01
PG $F_{2\alpha}$	1.0 (assigned)	1.0 (assigned)
PG E_1	0.28	19.7
PG E_2	0.15	22.2
PG I_2	0.008	2.2
U46619	†	3.1

†—not determined.

of potency for the PG's studied on the isolated guinea-pig and rat uterus. This provides further evidence for the existence of different PG receptors mediating contractions of these two uterine smooth muscle preparations.

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Dose-dependent nature of the interaction of fibrinogen-degradation products and 5-hydroxytryptamine on various vascular smooth muscle preparations

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It has been shown that fibrin or fibrinogen degradation products (FDP's) can potentiate the effect of 5-hydroxytryptamine (5-HT) on various smooth muscle preparations (Buluk & Malofiejew, 1969). This study investigates further the interaction between FDP's and 5-HT on three vascular smooth muscle preparations: rabbit aortic strip (Rb.A); rat aortic strip (R.A.) and human basilar arterial strip (H.Ba). A crude preparation of FDP's was produced in the following way. Plasma from citrated blood of normal healthy human volunteers was thoroughly mixed with 2000 units of streptokinase and incubated for 90 min, after which time the reaction was stopped by the addition of 500 units/ml of aprotinin (Trasylol®). Aliquots of the incubate were then immediately deep frozen or kept cold until required.

A 90 min incubation period was chosen since we have recently shown that a standard 0.1 ml aliquot of incubate taken at this time produces a maximum potentiation of a response to a standard concentration of 5-HT on various vascular smooth muscles (Forster, Mohan & Whalley, 1979). R.A., Rb.A. and H.BA. strips were bathed in aerated Krebs-Henslett solution at 37°C and allowed to equilibrate for at least 2 hours. After full concentration effect curves to 5-HT were produced, the tissues were then challenged repeatedly with a threshold concentration of 5-HT, the contractions being recorded isometrically and displayed on a Grass Polygraph. When a constant threshold response was obtained, increasing volumes of the crude FDP sample were added to each bath, and left in contact for 1 min without washing out. The threshold concentration of 5-HT was then added. This procedure was repeated using an EC_{50} of 5-HT.

Small volumes of the FDP incubate (< 100 µl) exhibited no intrinsic activity on any of the tissues, however with larger volumes (100–800 µl) a dose-dependent slow-sustained contraction developed which was always preceded by a dose-dependent transient relaxation. Both the threshold concentration and EC_{50} of 5-HT were potentiated in a dose-dependent fashion by increasing volumes of the FDP sample. Citrated plasma or streptokinase added alone possessed neither intrinsic activity nor the ability to potentiate the responses to 5-HT on any of the preparations.

Tovi, Nilsson & Thulin (1973) have demonstrated that there are increased levels of FDP's in the cerebrospinal fluid (CSF) following subarachnoid haemorrhage in humans. It is suggested that FDP's in CSF following rupture of an intracranial aneurysm may play some role in the intense cerebral vasospasm which can often be the cause of morbidity in this condition.

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