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Histamine H_2-receptor antagonists in the mouse isolated vas deferens

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Histamine inhibits the electrically stimulated twitch response of the mouse isolated vas deferens (Marshall, 1978). The inhibition was antagonized by cimetidine and not by mepyramine suggesting a histamine H_2-receptor was involved. Quantitative studies of the interaction between histamine H_2-receptor agonists and antagonists have now been completed.

Mice vasa deferentia were suspended in magnesium-free Krebs solution and responses to stimulation (0.2 Hz, 2.0 ms) recorded isometrically. For each preparation cumulative concentration-inhibition curves to histamine or selective histamine H_2-receptor agonists were obtained. After recovery the vas deferens was equilibrated with a single concentration of histamine H_2-receptor antagonist for 40 min before a second application of agonist.

Cimetidine (10, 30, 100, 300 and 1000 μM), burimamide (30, 100, 300, 1000 and 3000 μM) and metiamide (10, 30 and 100 μM) shifted the histamine-inhibition curve (control IC_{50}, concentration to inhibit the twitch by 50%, 4.76 ± 0.22 μM, mean ± s.e. mean) to the right with no change in the maximum inhibitory effect (greater than 95% twitch inhibition). Higher concentrations of metiamide (300 μM and 1 mM), unlike those of cimetidine, did not shift the curve for histamine, dimaprit (control IC_{50} 21.3 ± 2.2 μM) or 4-methyl histamine (control IC_{50} 49.8 ± 4.2 μM) further to the right but the maximum inhibition was unaltered. This 'ceiling effect' of metiamide was unaffected by a longer equilibration period (80 or 120 min). Metiamide and cimetidine appear to compete for a single receptor site because combinations of the two drugs (e.g. metiamide 300 μM with cimetidine 300 μM or 1 mM) produced dose ratio shifts of the histamine inhibition curve consistent with $DR_1 + DR_2 - 1$ (DR_1 and DR_2 are the dose ratio shifts produced separately by the two antagonists) (Paton & Rang, 1965).

From the dose ratios based on the IC_{50} in each experiment, pA_2 values were determined (Black, Duncan, Durant, Ganellin & Parson, 1972). When all five concentrations of either metiamide or cimetidine were used the slope of the plot of log (DR-1) against log molar concentration of antagonist was less than unity. However, when the three lowest concentrations of antagonist were used a slope not differing from unity was obtained with a pA_2 value for metiamide against histamine of 5.05 (3.97–5.72, 95% confidence limits; slope 0.91 ± 0.39, ±95% confidence limits) and a pA_2 value for cimetidine against histamine of 4.97 (3.94 – 5.61; slope 0.84 ± 0.34). These pA_2 values are similar to those reported for the mouse stomach (Angus, Black & Stone, 1978) and are significantly lower than those reported for the guinea-pig atrium and rat uterus (Brimblecombe, Duncan, Durant, Emmett, Ganellin & Parsons, 1975; Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973).

The results with the lower concentrations of antagonist suggest that the histamine receptor in the mouse vas deferens is of the H_2-type. Higher concentrations of antagonist appear to produce additional effects.

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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.