Histamine involvement in the regulation of uterine blood flow in the rat

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Oestrogen has been shown by several workers to increase both uterine blood flow and blood volume in the rat (Spaziani, 1975). In a previous study we have shown the possible involvement of histamine as one of the mediators in the oestrogenic-induced increase in uterine blood flow (UBF) in the ovariectomized rat (Phaily & Senior, 1978). Blood flow was measured using radioactive microspheres (15 μm diameter) in the sodium pentobarbitone anaesthetized animal (50 mg/kg i.p.).

From an initial study in the ovariectomized rat the increase in uterine blood flow evoked by oestradiol-17β (0.5 μg/kg i.v.) was significantly ($P < 0.001$) reduced from 680 ± 70 ml min^{-1} 100 g^{-1} to 300 ± 60 ml min^{-1} 100 g^{-1} if the animals were pretreated with mepyramine maleate (5 mg/kg i.p.). Cimetidine (0.5 mg kg^{-1} min^{-1} i.v.) over 30 min did not affect the oestrogen induced uterine hyperaemia.

Following the initial study histamine was infused intravenously, 20 μg kg^{-1} min^{-1} for 15 min then 80 μg kg^{-1} min^{-1} for 3 min, into the demedullated ovariectomized rat. This treatment produced a significant ($P < 0.001$) increase in uterine blood flow from 28 ± 5 ml min^{-1} 100 g^{-1} (saline infused control group) to 520 ± 43 ml min^{-1} 100 g^{-1} in the histamine infused animals. Cardiac output was significantly reduced by the histamine infusion. This effect of histamine on UBF was antagonized by pretreatment with either mepyramine or cimetidine.

In the 21–22 day (non parturient) pregnant rat treatment with mepyramine did not affect uterine, ovarian or placental blood flows. Infusion of cimetidine intravenously resulted in a significant ($P < 0.05$) reduction in uterine (29 ± 5 to 12 ± 2 ml min^{-1} 100 g^{-1}) and placental (63 ± 8 to 33 ± 3 ml min^{-1} 100 g^{-1}) blood flows but ovarian blood flow was not significantly reduced (587 ± 159 to 387 ± 53 ml min^{-1} 100 g^{-1}). Treatment with both mepyramine and cimetidine produced a similar effect on these blood flows to that seen with cimetidine alone.

Cardiovascular responses to histamine have been shown to involve both histamine H_1 and H_2 receptors (Flynn, Johnston & Owen, 1977). From this study using antagonists it is concluded that the type of histamine receptor involved in regulating UBF is hormonally dependant. In the ovariectomized rat H_1 and H_2 are present, pretreatment with oestrogen results in H_1 predominance but in the pregnant rat near term H_2 receptors only have been shown to be involved.

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The biphasic inotropic response of guinea-pig isolated atria to histamine receptor agonists.

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The positive chronotropic responses of the heart to histamine are mediated via H_2-receptors, as are the positive inotropic responses of guinea-pig ventricles (Verma & McNeill, 1977). However, the positive inotropic response of the left atrium is mediated via H_1-receptors (Reinhardt, Wagner & Schümann, 1974; Steinberg & Holland, 1975). We have previously shown that only part of the latter response is due to H_1-receptor stimulation, the shift of the dose-response curves by mepyramine being limited (Broadley & Wilson, 1977). Furthermore, biphasic inotropic responses are exhibited by sequentially administered histamine. The present study extends the qualitative assessment of the inotropic response using other histamine receptor agonists.

The tension responses were obtained from the isolated paced left atria (2.0 Hz) of guinea-pigs and the rate responses were recorded from the spontaneous right atria, both set up in Krebs-bicarbonate solution at 38°C as described previously (Broadley & Lumley,

Table 1 Comparison between the ability of a series of histamine receptor agonists to produce biphasic inotropic responses and their activity on H_1- and H_2-receptors relative to histamine

Agonist	*Concentration for biphasic inotropic response*	*Relative H_1-receptor activity (guinea-pig ileum)*	*Relative H_2-receptor activity (guinea-pig right atrium)*
Histamine	$\sim 2 \times 10^{-6}$M	100	100
N,N-dimethylhistamine	$\sim 5 \times 10^{-6}$M	~43[a]	~50[a]
2-methylhistamine	$\sim 5 \times 10^{-6}$M	16.5[a]	4.4[a]
2-pyridylethylamine	$\sim 2 \times 10^{-4}$M*	5.6[b]	~0.2 [b]†
3-methylhistamine	$\sim 5 \times 10^{-4}$M	~1[a]	~0[a]
4-methylhistamine	$\sim 5 \times 10^{-4}$M	0.2[a]	43[a]
dimaprit	no response	<0.0001[c]	70.7[c]

[a] Black, Duncan, Durant, Ganellin & Parsons (1972).
[b] Durant, Ganellin & Parsons (1975).
[c] Parsons, Owen, Ganellin & Durant (1977).
* In reserpine pretreated guinea-pig atria.
† On rat gastric acid secretion.

1977). All agonists were examined by sequential addition of single doses. They were compared in each preparation with a submaximal dose of histamine producing the biphasic response and are considered in groups based upon their known classification as H_1-receptor selective (2-methylhistamine, 3-methylhistamine and 2-pyridylethylamine (2-PEA)), H_2-receptor selective (4-methylhistamine and dimaprit) and non-selective (N,N-dimethylhistamine and histamine itself).

All agonists tested, except dimaprit, if given in sufficient concentration produced a biphasic tension response. However, 2-PEA required preparations from reserpine-pretreated animals (2.5 mg/kg i.p. 24 h before use) to do so, since it was found also to exhibit indirect β-adrenoceptor stimulation. The ability of the agonists to produce biphasic responses correlated well with their documented order of potency on H_1-receptors (Table 1). H_2-receptor selective agonists were approximately equipotent with histamine on rate, but produced biphasic tension responses only with much higher concentrations (4-methylhistamine, 5×10^{-4}M) or failed to do so at any concentration examined (dimaprit). Biphasic responses were therefore associated with H_1-receptor activity. Furthermore, they were converted to monophasic responses by mepyramine (10^{-7}M), the residual component being resistant to both H_1- and H_2-receptor antagonism.

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