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The effect of mepyramine and ranitidine on the oestrogen and anti-oestrogen stimulated rat uterus

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1 The aims of this study were to elucidate further the role of histamine in the rat uterotrophic response and to investigate the differences between the oestrogen and the anti-oestrogen induced uterine responses.

2 The parameters examined were uterine blood flow (measured by the microsphere technique), uterine wet and dry weights.

3 17β-Oestradiol and the anti-oestrogen, tamoxifen, were used to stimulate the ovariectomised rat uterus and the antihistamines mepyramine (H_1) and ranitidine (H_2) were employed to modify these responses.

4 The uterine changes evoked by oestradiol proved to be more susceptible to modification by the antihistamines than the tamoxifen-stimulated responses.

5 The results suggest that histamine is involved in the early uterine response to oestradiol but histamine does not appear to play a major role in the uterine response to tamoxifen.

Introduction

The time lag which occurs between oestrogen administration and the onset of the early oestrogenic effects has led several investigators to postulate that oestrogen does not work directly but via a mediator or mediators. One proposed mediator is histamine (Spaziani & Szego, 1959; Phaily & Senior, 1978).

Observations which suggest a histaminic involvement in the response to oestrogen include a cyclical variation in uterine histamine content (Spaziani & Szego, 1959) and the ability of histamine to mimic certain other actions of oestrogen such as promoting water imbibition (Szego, 1965; Brandon, 1977) and causing oestrous-like vaginal smears (Oppo, 1956), coupled with the well established finding of mast cells in the uterus (Levier & Spaziani, 1966). More recently Wordinger *et al.* (1983) have presented evidence for a steroid responsive non-mast cell pool of uterine histamine in the mouse uterus. The studies of Szego & Sloan (1961) and Spaziani (1963) indicated that histamine promotes early uterine growth in the rat and it has been suggested that there is a positive correlation between uterine hyperaemia and growth (Spaziani, 1975).

In this study, oestradiol-17β and the non-steroidal anti-oestrogen, tamoxifen, which probably exerts its action (at least in part) via the oestrogen receptor system, were used in conjunction with mepyramine (H_1-receptor antagonist) and ranitidine (H_2-receptor antagonist) in an attempt to investigate any differences observed between oestrogen and anti-oestrogen in respect of the uterotrophic response. Initially in the rat tamoxifen responses are stimulatory in that uterine growth occurs but the responses to oestrogen are blocked and further stimulation is inhibited.

Methods

Mature virgin female rats of a CD-derived Sprague-Dawley random bred strain from the animal house, University of Bradford, were used throughout and were housed in light (07 h 00 min–19 h 00 min) and temperature (18°C) controlled rooms. Food and water were available *ad libitum*. All the animals used in this study were bilaterally ovariectomised at least 14 days before further experimentation and were randomly assigned to groups.

Measurement of blood flow

Blood flow was measured in rats, anaesthetized with sodium pentobarbitone (60 mg kg^{-1}), by the micro-

sphere technique described in previous work (Phaily & Senior, 1978). In the present experiments the microspheres had a mean diameter of 15 μm (NEN-Trac, New England Nuclear, Boston, MA, U.S.A.) and were uniformly labelled with ^{46}Sc and suspended in 10% (w/v) dextran containing 0.01% (w/v) Tween 80. Blood flows were calculated using wet weight of tissues. When dry weights are quoted the tissues were dried until the weight remained constant.

Drug administration

Oestradiol (oestra-1,3,5(10)-triene-3,17β-diol) (B.D.H., Poole) was dissolved in a 10% (v/v) solution of propylene glycol and administered intravenously (i.v.) at a dose of 0.5 $\mu g\,kg^{-1}$ into the tail vein of the conscious rat. Blood flow and uterine weight changes were measured 3 and 6 h after treatment. Tamoxifen (I.C.I., Macclesfield, Cheshire) was dissolved in absolute alcohol and dispersed in arachis oil before subcutaneous (s.c.) injection; with the anti-oestrogen treatment 24 h was allowed to elapse before other drugs were administered. This time lapse was to allow the full anti-oestrogenic effect to develop due to the long half-life of tamoxifen and its metabolites. Mepyramine maleate (May and Baker Ltd., Dagenham) and ranitidine hydrochloride (Glaxo Group Research Ltd., Hertfordshire) were dissolved in 0.9% (w/v) sodium chloride solution. Mepyramine was given by the intraperitoneal (i.p.) route at a dose of 5 $mg\,kg^{-1}$ and ranitidine was given i.v. at a dose of 1 $mg\,kg^{-1}$. The dosage schedules are given in the legends to the tables. The shorter half-life of ranitidine resulted in more frequent administration than that used for mepyramine. The solvents used did not have any effect on uterine blood flow or weight and these results have been grouped as controls.

Statistical analysis

The results (expressed as mean ± s.e.mean) were compared using Student's t test (two tailed) (Snedecor & Cochran, 1979).

Results

In the absence of any exogenous oestradiol the two histamine antagonists in the doses used had no significant effect on uterine blood flow or weight (Tables 1 and 2).

Effect of histamine receptor antagonism on oestrogen stimulated uterine blood flow

Pretreatment with mepyramine had no effect on oestrogen stimulated uterine blood flow 3 h after oestrogen administration but when mepyramine was replaced by ranitidine in the treatment regimen a significant increase ($P < 0.005$) in blood flow was seen. However, the use of the two antihistamines together with oestradiol produced a similar effect on uterine blood flow to that seen with oestradiol alone 3 h after oestrogen treatment (Table 3). When uterine blood flow was measured 6 h after the oestrogen was given the histamine antagonist pretreatments had no effect on this parameter (Table 4).

None of the treatments had a significant effect on blood flow through the other organs investigated (kidney, stomach, duodenum and spleen) with the exception of the adrenal glands. Three hours after oestradiol administration pretreatment with ranitidine alone and in combination with mepyramine caused a decrease in adrenal blood flow ($P < 0.05$). When adrenal blood flow was measured 6 h after oestrogen administration, pretreatment with mepyramine increased adrenal blood flow ($P < 0.05$), pretreatment with ranitidine decreased adrenal blood flow ($P < 0.05$) and joint administration of the two antihistamines caused a decrease in flow ($P < 0.05$). In all cases blood flow between the adrenals and kidneys was balanced indicating a uniform distribution of microspheres. Cardiac output was unaffected by the treatments.

Effect of histamine receptor antagonism on uterine weight and water content in the oestrogen stimulated rat uterus

Pretreatment with mepyramine caused a decrease in uterine wet weight 3 h after oestrogen was given, this depression became more pronounced when ranitidine was substituted for or included with mepyramine. The fall in wet weight was accompanied by a decrease in uterine water content. Antihistamine pretreatment also caused a depression in uterine dry weight 3 h after oestradiol injection (Table 3).

Six hours after oestrogen injection uterine wet weight was not significantly affected by the antihistamines but mepyramine and mepyramine plus ranitidine produced a depression in uterine dry weight (Table 4).

Effect of histamine receptor antagonism on tamoxifen stimulated uterine blood flow

Twenty seven and 30 h after tamoxifen was given the administration of mepyramine had no significant effect on uterine blood flow, whereas ranitidine caused a significant decrease in this parameter (Tables 5 and 6).

None of the treatments had any significant effect on blood flow through the other organs investigated (kidney, stomach, duodenum, adrenals and spleen)

and cardiac output was also unaffected. Microsphere distribution was shown to be uniform; right and left kidney and adrenal blood flows were balanced.

Effect of histamine receptor antagonism on uterine weight and water content in the tamoxifen stimulated uterus

Twenty seven hours after tamoxifen was given neither mepyramine nor ranitidine had any effect on uterine wet or dry weight (Table 5). Thirty hours after tamoxifen administration a similar situation existed, except that after mepyramine administration the dry weight was significantly decreased (Table 6).

Discussion

Early uterine blood flow (that is, measurements made 3 h after oestradiol injection) was unaffected by antihistamine pretreatment, with the exception of the ranitidine (alone) pretreatment which produced a significant increase in blood flow. This treatment also depressed adrenal blood flow ($P < 0.05$); diminution in adrenal blood flow may, therefore, be contributing to the increase in uterine blood flow seen. Both histamine receptor antagonists suppressed the oestradiol-induced increases in wet and dry weight. However, subsequent measurement of these parameters (6 h after oestradiol administration) revealed that the effects of the histamine antagonists were on the whole short-lived.

A different picture emerges when oestradiol is substituted by the triphenylethylene anti-oestrogen, tamoxifen. The antihistamines appear to have little effect on the uterine weight response to tamoxifen, with the exception of mepyramine treatment which caused a decrease in uterine dry weight when measured 7 h after the initial mepyramine injection. Ranitidine, however, had a more marked effect on the tamoxifen blood flow response, causing a significant reduction in this parameter.

From the oestradiol results it would seem that histamine does play a role in the early hyperaemic response, although its involvement would appear to be transitory. The importance of this role apparently depends upon the relative proportions of the 2 types of histamine receptor. These results suggest that the H_1 and H_2 receptors mediate opposing effects in relation to blood vessel tone. The vasodilatory effect of histamine being produced by H_1-receptor stimulation. In addition to this, Masini *et al.* (1982) have suggested that histamine may regulate its own secretion by means of a negative feedback mechanism, probably mediated via the H_2-receptor. Therefore, blockade of the latter by, for example, ranitidine, would presumably cause an increase in histamine secretion which would reinforce the hyperaemia.

In contrast to this, when tamoxifen replaced oestradiol in the regimen ranitidine caused a fall in uterine blood flow which persisted into the latter stage of the study. A possible explanation of this phenomenon could lie in the recent discovery by Brandes *et al.* (1985); they found, when studying an anti-oestrogen binding site selective compound, that the anti-oestrogen binding site may be a form of histamine receptor. If this is so then perhaps the histamine antagonists used in this study, notably ranitidine, alter the histamine receptor/anti-oestrogen binding site 'equilibrium' which in turn alters the distribution of tamoxifen (or its metabolites), thus affecting the ability of the anti-oestrogen to stimulate uterine blood flow.

Differences also become apparent between the two uterine stimulants, oestradiol and tamoxifen, when comparing the effects of the antihistamines on uterine weight. When oestradiol is used with the antagonists

Table 1 The effect of mepyramine and ranitidine, 4 h after initial administration, on uterine blood flow and weight in rats

Pretreatment	*No. of rats*	*Body weight* (g)	*Cardiac output* (ml min^{-1})	*Uterine blood flow* ml min^{-1}	ml min^{-1} $100\,g^{-1}$	*Uterine weight* (mg) *Wet*	*Dry*	*Water content of uterus* (mg)
None (control)	8	309 ± 9	107 ± 10	0.067 ± 0.01	72 ± 15	97 ± 5	20 ± 1	77.3
Mepyramine	6	313 ± 3	104 ± 11	0.041 ± 0.09	42 ± 11	99 ± 2	21 ± 0.8	78.0
Ranitidine	6	317 ± 5	122 ± 9	0.066 ± 0.02	74 ± 21	89 ± 3	18 ± 0.6	72.3
Mepyramine + ranitidine	6	321 ± 11	122 ± 8	0.097 ± 0.02	98 ± 21	97 ± 6	19 ± 1	77.2

Values are mean ± s.e.mean and are not significantly different from those of untreated control group. Mepyramine 5 mg kg^{-1} (i.p.) was administered 4 h before measurements were made and ranitidine 1 mg kg^{-1} (i.v.) was administered 1 h and 4 h before measurements were made.

Table 2 The effect of mepyramine and ranitidine, 7 h after initial administration, on uterine blood flow and weight in rats

Pretreatment	No. of rats	Body weight (g)	Cardiac output (ml min^{-1})	Uterine blood flow		Uterine weight (mg)		Water content of uterus (mg)
				ml min^{-1}	ml min^{-1} $100\,g^{-1}$	Wet	Dry	
None (control)	8	309 ± 9	107 ± 10	0.067 ± 0.01	72 ± 15	97 ± 5	20 ± 1	77.3
Mepyramine	6	311 ± 6	107 ± 7	0.092 ± 0.03	126 ± 51	89 ± 7	18 ± 1	70.9
Ranitidine	6	324 ± 4	93 ± 5	0.079 ± 0.02	69 ± 19	110 ± 5	23 ± 2	88.0
Mepyramine + ranitidine	6	307 ± 6	106 ± 12	0.090 ± 0.01	112 ± 20	97 ± 5	19 ± 2	77.4

Values are mean ± s.e.mean and are not significantly different from those of untreated control group. Mepyramine 5 mg kg^{-1} (i.p.) was administered 3.5 h and 7 h before measurements were made and ranitidine 1 mg kg^{-1} (i.v.) was administered 1 h, 4.5 h and 7 h before measurements were made.

both uterine wet and dry weights are depressed, the pretreatment combining both histamine H_1- and H_2-antagonists producing the most marked suppression. Once again this effect tended to be transient. The inhibition of dry weight, which represents 'true' uterine growth, could be a result of some obstruction in the genomic response and/or an indirect effect of the inhibition of wet weight. Leroy *et al.* (1977) have shown that uterine distension, as a result of oestradiol-induced oedema, stimulates uterine cell division. Thus a decrease in water imbibition could, to some extent, suppress the increase in dry weight which usually accompanies oestrogen priming.

Replacement of oestradiol with tamoxifen in the treatment regime produced a significant depression of uterine weight only when mepyramine held down uterine dry weight 6 h after pretreatment. The reduction of the effect of mepyramine and ranitidine on uterine weight when used with tamoxifen could be attributable to tamoxifen blocking the intracellular oestrogen receptor site and so preventing the histamine antagonists from exerting their inhibitory influence through this site, assuming that stimulation of uterine weight can be ascribed to activation of the classical oestrogen receptor pathway. Indeed, preliminary experiments in this laboratory have revealed that mepyramine and ranitidine are capable of altering oestrogen receptor dynamics (Marshall & Senior, unpublished observation).

Therefore, it would seem that tamoxifen is at least much less dependent on the release of histamine as a mediator to produce its uterotrophic response. Possibly tamoxifen is less able to elicit histamine release. Pankova *et al.* (1983) have suggested that after oestradiol is accepted by the nuclei of target cells it induces the synthesis of histidine decarboxylase and

Table 3 The effect of mepyramine and ranitidine, used separately and together, on uterine blood flow and weight in rats 3 h after a single intravenous injection of 0.5 μg kg^{-1} oestradiol

Pretreatment	No. of rats	Body weight (g)	Cardiac output (ml min^{-1})	Uterine blood flow		Uterine weight (mg)		Water content of uterus (mg)
				ml min^{-1}	ml min^{-1} $100\,g^{-1}$	Wet	Dry	
None (control)	8	321 ± 7	104 ± 11	0.94 ± 0.10	735 ± 66	128 ± 7	35 ± 2	93.0
Mepyramine	9	317 ± 9	100 ± 9	0.94 ± 0.12	916 ± 136	106 ± 5*†	24 ± 1††	79.4
Ranitidine	7	315 ± 4	124 ± 11	1.0 ± 0.10	1183 ± 117††	93 ± 3††	24 ± 1††	69.0
Mepyramine + ranitidine	6	321 ± 11	118 ± 11	0.72 ± 0.12	866 ± 168	85 ± 4†††	21 ± 1††	64.3

Values are mean ± s.e.mean. Mepyramine 5 mg kg^{-1} (i.p.) was administered 1 h before oestradiol injection, and ranitidine 1 mg kg^{-1} (i.v.) was administered 1 h before and 2 h after oestradiol injection.
†$P < 0.05$, ††$P < 0.005$, †††$P < 0.001$, values are significantly different from those of oestradiol alone group.
*$P < 0.05$, values are significantly different from those of mepyramine + ranitidine group.

Table 4 The effect of mepyramine and ranitidine, used separately and together, on uterine blood flow and weight in rats 6 h after a single intravenous injection of 0.5 μg^{-1} oestradiol

Pretreatment	*No. of rats*	*Body weight* (g)	*Cardiac output* (ml min^{-1})	*Uterine blood flow* ml min^{-1}	*Uterine blood flow* ml min^{-1} $100\,g^{-1}$	*Uterine weight* (mg) *Wet*	*Uterine weight* (mg) *Dry*	*Water content of uterus* (mg)
None (control)	8	306 ± 5	90 ± 5	0.56 ± 0.07	394 ± 46	144 ± 8	27 ± 1	116.6
Mepyramine	6	313 ± 8	125 ± 11	0.44 ± 0.04	388 ± 57	122 ± 14	21 ± 2†	100.7
Ranitidine	6	308 ± 6	106 ± 9	0.56 ± 0.06	436 ± 49	129 ± 5	27 ± 1*	102.0
Mepyramine + ranitidine	6	303 ± 10	94 ± 10	0.45 ± 0.08	340 ± 50	132 ± 13	22 ± 2†	109.2

Values are mean ± s.e.mean.
Mepyramine 5 mg kg^{-1} (i.p.) was administered 1 h before and 2.5 h after oestradiol injection. Ranitidine 1 mg kg^{-1} (i.v.) was administered 1 h before and 2.5 h and 5 h after oestradiol injection.
†$P < 0.05$, values significantly different from those of oestradiol alone group. *$P < 0.05$, value significantly different from those of mepyramine and mepyramine + ranitidine group.

Table 5 The effect of mepyramine and ranitidine on uterine blood flow and weight in rats 27 h after pretreatment with a single subcutaneous dose (1 mg kg^{-1}) of tamoxifen

Pretreatment	*No. of rats*	*Body weight* (g)	*Cardiac output* (ml min^{-1})	*Uterine blood flow* ml min^{-1}	*Uterine blood flow* ml min^{-1} $100\,g^{-1}$	*Uterine weight* (mg) *Wet*	*Uterine weight* (mg) *Dry*	*Water content of uterus* (mg)
None (control)	6	312 ± 14	106 ± 12	0.88 ± 0.20	649 ± 117	129 ± 9	29 ± 2	99.6
Mepyramine	6	303 ± 12	85 ± 11	0.70 ± 0.06	547 ± 72	132 ± 7	29 ± 1	102.8
Ranitidine	6	316 ± 7	96 ± 10	0.35 ± 0.08*	281 ± 65*	130 ± 8	27 ± 3	102.5

Values are mean ± s.e.mean.
Mepyramine 5 mg kg^{-1} (i.p.) was given 4 h before the measurements were made. Ranitidine 1 mg kg^{-1} (i.v.) was given 1 h and 4 h before measurements were made.
*$P < 0.05$, values significantly different from those of tamoxifen alone group.

Table 6 The effect of mepyramine and ranitidine on uterine blood flow in rats 30 h after pretreatment with a single subcutaneous dose (1 mg kg^{-1}) of tamoxifen

Treatment	*No. of rats*	*Body weight* (g)	*Cardiac output* (ml min^{-1})	*Uterine blood flow* ml min^{-1}	*Uterine blood flow* ml min^{-1} $100\,g^{-1}$	*Uterine weight* (mg) *Wet*	*Uterine weight* (mg) *Dry*	*Water content of uterus* (mg)
None (control)	6	320 ± 12	86 ± 15	1.10 ± 0.19	848 ± 152	132 ± 4	29 ± 2	103.7
Mepyramine	6	330 ± 17	89 ± 7	0.87 ± 0.29	460 ± 164	120 ± 6	21 ± 2*	98.7
Ranitidine	6	335 ± 8	85 ± 8	0.42 ± 0.11*	309 ± 82*	138 ± 7	28 ± 3	110.5

Values are mean ± s.e.mean.
Mepyramine 5 mg kg^{-1} (i.p.) was given 3.5 h and 7 h before measurements were made. Ranitidine 1 mg kg^{-1} (i.v.) was given 7, 3.5 and 1 h before measurements were made.
*$P < 0.05$, values significantly different from those of tamoxifen alone group.

consequently histamine synthesis. If this is the case then perhaps tamoxifen or the tamoxifen-receptor complex formed is aberrant in some way and unable to induce enzyme synthesis.

Alternatively, the differences between the responses to histamine receptor blockade in the oestradiol and tamoxifen stimulated uteri may be indicative of a divergence in the mechanisms of action of these two agents, perhaps with tamoxifen the emphasis is switched from the intracellular genomic pathway to that of a non-genomic pathway. Lee (1982) surmised that there are in fact two oestrogen receptor systems operating in the rat uterus: one mediating the intracellular events of the genomic response and the other being concerned with non-genomic responses such as uterine oedema. To substantiate this other mechanism in part, Webster *et al.* (1984a, b) found that other treatments can mimic some of the oestrogenic uterine responses, e.g. cholera toxin – which seems unlikely to cause nuclear receptor accumulation. Tchernitchin (1979, 1983) has postulated that water imbibition is the result of eosinophilia. Galand *et al.* (1984) also found that the anti-oestrogen nafoxidine (also a tripheylethylene derivative) is capable of inducing eosinophil migration. Therefore, perhaps tamoxifen exerts some of its action via this mechanism, which may be separate from the genomic response.

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