THE EFFECT OF MESTRANOL AND LYNOESTRENOl ON UTERINE HISTAMINE IN THE RAT

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Shelesnyak (1959) first suggested that histamine might be the inducing factor for decidualization and that it might be involved in the process of implantation in the rat (Shelesnyak & Kraicer, 1964). Treatment with oestrogen results in histamine depletion from the rat uterus (Szego, 1966; McKercher, Van Orden, Bhatnagar & Burke, 1973), and it was suggested that histamine might be involved in the hyperaemia and oedema stimulated by oestrogen (Szego, 1966). Recently, it has been reported that treatment with the contraceptive steroids, mestranol and lynoestrenol, alone or in combination, resulted in a decrease in histamine content per ovary in the rat (Abdel-Aziz, Ghazel & Daabees, 1974). The present work was undertaken to study the effect of mestranol and lynoestrenol on the histamine content of the rat uterus.

Fifty-six virgin female albino rats with a mean body weight of 112±5 g were allocated equally to four groups. The animals selected showed regular oestrous cycles. The contraceptive steroids were administered orally and were suspended in 0·5% carboxymethylcellulose (CMC). Treatment was started when the animals were in natural oestrus and was continued for 12 consecutive days, the daily dose being suspended in 0·2 ml CMC. Animals in the first group received 0·08 mg mestranol/rat/day, in the second group 2·5 mg lynoestrenol/rat/day, in the third group 0·08 mg mestranol+2·5 mg lynoestrenol/rat/day and in the fourth group corresponding volumes of 0·5% CMC to serve as controls. Histamine extraction was carried out as described by Parrat & West (1957) and histamine bioassay was performed as described by Barsoum & Gaddum (1935). In each group, seven sets of pooled uteri, each from two animals, were extracted for histamine. The uterine histamine content was expressed in terms of µg histamine/g uterus and /uterus.

For microscopic examination, histological sections were prepared, and stained with haematoxylin and eosin. Unna's method (1968) was used for differential staining of mast cells. Mast cells were counted per section in the mesometrial triangle, the myometrium and the endometrium.

The effect of contraceptive steroids on uterine histamine is shown in Table 1. Treatment with mestranol alone or in combination with lynoestrenol

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Table 1. Effect of treatment with mestranol and lynoestrenol, alone and in combination, on rat uterine histamine

<table>
<thead>
<tr>
<th>Uterine histamine</th>
<th>Controls</th>
<th>Mestranol</th>
<th>Lynoestrenol</th>
<th>Mestranol + lynoestrenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/g µg/uterus</td>
<td>µg/g µg/uterus</td>
<td>µg/g µg/uterus</td>
<td>µg/g µg/uterus</td>
<td></td>
</tr>
<tr>
<td>2.82 ± 0.4</td>
<td>0.699 ± 0.06</td>
<td>1.71 ± 0.21*</td>
<td>0.542 ± 0.04*</td>
<td>1.79 ± 0.24*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.56 ± 0.2**</td>
<td>0.429 ± 0.04**</td>
<td></td>
</tr>
</tbody>
</table>

The uterine histamine values are expressed as Mean ± S.E.M.

* P < 0.05; ** P < 0.01. The P values indicate the level of significance of differences between the means of control and treated animals. For number of rats and number of uteri, see text.

resulted in a significant increase in uterine weight in mg per 100 g body weight (P < 0.05), while lynoestrenol treatment resulted in a non-significant increase (P > 0.05). Treatment with mestranol and lynoestrenol alone or in combination resulted in a significant decrease in uterine histamine when expressed in terms of µg histamine/g uterine tissue or uterus.

Uteri from rats treated with mestranol showed pronounced histological changes reflecting the oestrogenic effect of this steroid, while uteri from rats treated with lynoestrenol showed less marked oestrogenic manifestations. The combination of mestranol and lynoestrenol resulted in uterine histological changes which reflected the predominance of oestrogenic activity. The effect of contraceptive steroids on uterine mast cells is shown in Table 2. The greatest number of mast cells in the rat uterus occurred in the mesometrial triangle and in the myometrium near the blood vessels, with few cells in the endometrium. Treatment with contraceptive steroids increased the number of mast cells in

Table 2. Effect of treatment with mestranol and lynoestrenol, alone and in combination, on mast cell counts in the different parts of the rat uterus

<table>
<thead>
<tr>
<th>Group</th>
<th>Mesometrial triangle</th>
<th>Myometrium</th>
<th>Endometrium</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (12)</td>
<td>7.4 ± 1.20</td>
<td>7.3 ± 1.30</td>
<td>1.08 ± 0.34</td>
<td>15.8 ± 2.28</td>
</tr>
<tr>
<td>Mestranol (13)</td>
<td>4.7 ± 0.98</td>
<td>6.5 ± 0.94</td>
<td>0.31 ± 0.24</td>
<td>11.5 ± 1.55</td>
</tr>
<tr>
<td></td>
<td>P &gt; 0.05</td>
<td>P &gt; 0.05</td>
<td>P &gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Lynoestrenol (11)</td>
<td>3.2 ± 0.91</td>
<td>5.3 ± 1.08</td>
<td>0</td>
<td>8.5 ± 1.84</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.01</td>
<td>P &gt; 0.05</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Mestranol + lynoestrenol (9)</td>
<td>5.7 ± 1.52</td>
<td>9.0 ± 2.28</td>
<td>1.00 ± 2.29</td>
<td>15.7 ± 3.20</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.05</td>
<td>P &gt; 0.05</td>
<td>P &gt; 0.05</td>
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</tr>
</tbody>
</table>

The uterine mast cell counts are expressed as Means ± S.E.M. The P values indicate the level of significance of differences between the means of control and treated animals. The numbers in parentheses indicate the number of uteri examined.
the mesometrial triangle. This decrease was significant after treatment with 
lynoestrenol alone or in combination with mestranol, while mestranol treat-
ment resulted in a non-significant decrease. The number of mast cells in the 
myometrium did not change significantly after any of the hormonal treatments. 
Only lynoestrenol treatment resulted in a significant decrease in the number 
of mast cells in the endometrium and also in the total number of mast cells 
in the uterus.

The reduction in uterine histamine following treatment with the synthetic 
oestrogen, mestranol, was parallel with that reported after treatment with 
natural oestrogen (Szego, 1966; McKercher et al., 1973). It was not expected, 
however, that treatment with lynoestrenol, a dominant progestational steroid, 
would also result in reduction of uterine histamine. The weak oestrogenic 
activity reported for lynoestrenol (Overbeek, Madjerek & Divisser, 1962; 
Okada, Amatsu, Ishihara & Tokuda, 1964; Paulsen, 1965) has also been 
shown by the effect of this steroid on the vaginal smear (Abdel-Aziz et al., 
1974) and the histological changes in the uterus observed in the present work. 
The reduction in uterine histamine observed after treatment with lynoestrenol 
might thus be mediated through its oestrogenic action or through its progesta-
tional and oestrogenic actions.

It has recently been reported that treatment with oestradiol-17β resulted 
in a reduction in uterine and 5-hydroxytryptamine which was consistent with 
a reduction in uterine mast cell count (McKercher et al., 1973). In the present 
study, an attempt was made to investigate the effect of treatment with contra-
ceptive steroids on uterine mast cells. Such treatment resulted in a reduction in 
the number of mast cells in the mesometrial triangle. Besides containing the 
highest number of mast cells, the mesometrial triangle may play an important 
rôle in the regional regulation of uterine vascularity and permeability (De 
Feo, 1967). In view of the evidence provided by Schayer (1962) concerning 
the rôle of histamine in regulation of the microcirculation, it is possible that 
histamine depletion in the uterus, particularly from the mesometrial triangle, 
following treatment with contraceptive steroids, may be one of the factors 
contributing to the antifertility action of these steroids in the rat. The signi-
ficant reduction in uterine histamine observed after all hormonal treatment, 
but with a parallel significant decrease in the total cell count only after treat-
ment with lynoestrenol, indicates that this decrease in uterine histamine may 
be mainly from non-mast cell sites.

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