Effect of Estrone- and Estriol-3-methyl Ether on Progesterone in Decidual Development

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The ovariectomized rats were used. After estrogen-priming for six days, a thread was placed into the lumen of one uterine cornu, the contralateral untreated cornu served as a control. The animals were then injected with progesterone and test compounds for five days. Total of 10 mg of progesterone effected a 336% increase over the contralateral untreated cornu. However, when various doses of estrogen-3-methyl ether were given with 10 mg of progesterone, the effect on decidual development was significantly weaker than that due to progesterone alone. In a dose of 1.0 mg, percent inhibition to the effect of progesterone was 97 by estrone-3-methyl ether and 64 by estriol-3-methyl ether. The results indicate that estrone- and estriol-3-methyl ether are capable of inhibiting the decidual response to progesterone.

Evidence has accumulated that estrogen tends to inhibit the decidual growth. In a review on the antagonistic interaction of estrogen-progesterone in the uterus, Velardo and Hisaw provided information on the determination of quantitative relationship of estrogen and progesterone in the inhibitory process and mentioned that the development of the decidual tissue was, as a rule, proportional to the dosage of progesterone administered, and in response to the combined estrogen-progesterone treatment, a typical fall of decidual reaction was observed, the degree being characteristic of graded doses of estrogen. In this point of view, it would be expected that the antagonistic effect of synthetic estrogen, namely estrone- and estriol-3-methyl ether, on the decidual action of progesterone might be established quantitatively.

This investigation was made in an attempt to elucidate how estrone- and estriol-3-methyl ether affect the increased decidual tissue formation producible by progesterone.

METHODS

Experiments were performed on female albino rats weighing approxi-
mately 200 g. All of the animals were ovariectomized under ether anesthesia about 30 days prior to experiments. According to common procedures to produce deciduomata for the ovariectomized animal, the rats were primed with subcutaneous injection of 1 \( \mu \text{g} \) estradiol once daily for six days. After this period, a thread was placed into the lumen of the left uterine cornu, by inserting a needle through the tubal sphincter beneath the oviduct down to cervix. The contralateral untreated cornu served as a control. The animals were then injected subcutaneously with progesterone and test compounds once daily for five days. A standard total dosage of progesterone was 10 mg and test compounds were given in amounts ranging from 0.1 mg to 1.0 mg per animal. All steroids were dissolved in sesame oil and all injections were contained in either 0.1 or 0.2 cc of vehicle.

At 24 hours after the last injection, the rats were sacrificed by breaking a head and by cutting the carotid artery. The uteri were removed and bisected at the cervical junction and weighed on a torsion balance.

**RESULTS**

In these experiments, the ovariectomized rats were given with total of 10 mg of progesterone by subcutaneous injection. The results are summarized in Table 1. A total of 10 mg of progesterone induced an appreciable increase in the production of decidual tissue, an increase of

<table>
<thead>
<tr>
<th>Group</th>
<th>Series of hormone</th>
<th>Dose (mg/animal)</th>
<th>No. of rats</th>
<th>Increase, %</th>
<th>Percent inhibition**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sesame oil</td>
<td>0 0</td>
<td>4</td>
<td>70 ± 2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Progesterone</td>
<td>10.0 0</td>
<td>5</td>
<td>336 ± 19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Estrone-3-methyl ether  + Progesterone</td>
<td>10.0 1.0</td>
<td>5</td>
<td>77 ± 9</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>Estriol-3-methyl ether  + Progesterone</td>
<td>10.0 0.1</td>
<td>5</td>
<td>231 ± 28</td>
<td>39</td>
</tr>
</tbody>
</table>

*: Increase, % = \( \frac{\text{wt. of traum. horn} - \text{wt. control horn}}{\text{wt. control horn}} \times 100 \)

**:Percent inhibition = \( \frac{\text{Rp} - \text{Re}}{\text{Rp} - \text{C}} \times 100 \); Rp = Increased decidual response to progesterone alone; Re = Increased decidual response to combination of progesterone and estrogen; C = Control level.
336% over the contralateral untreated cornu being observed. Hereupon, the decidual responses to 10 mg of progesterone with and without estrogen-3-methyl ether were compared.

As is evident from Table 1, when estrogens were given a total of 1.0 mg per animal along with progesterone, estrogen effected a substantial decrease, only a 77% increase in estrone-3-methyl ether and a 165% in estriol-3-methyl ether in contrast to the control figure of a 336%. Percent inhibition to the full effect of progesterone was 97 by estrone-3-methyl ether and 64 by estriol-3-methyl ether. Likewise, a total of 0.1 mg appeared unequivocally to prevent the effect of 10 mg of progesterone, but it was not so pronounced as in a dose of 1.0 mg, causing a 39% inhibition by estrone-3-methyl ether and a 46% by estriol-3-methyl ether.

DISCUSSION

The observation, in the experiments described here, suggests that estrone- and estriol-3-methyl ether are effective in inhibiting the decidual response to progesterone. There is, however, significant difference between estrone- and estriol-3-methyl ether in antagonizing progesterone. Estriol-3-methyl ether seems to be somewhat less effective than estrone-3-methyl ether in the potency, if the comparison is made.

Concerning inhibitory abilities of estrone- and estriol-3-methyl ether on progesterone in the endometrial carbonic anhydrase, the previously reported work\(^6\) provided quantitative evidence on inhibition by estrone- and estriol-3-methyl ether. The results were obtained that estriol-3-methyl ether seems to have approximately 1/10 the potency of estrone-3-methyl ether, if given systemically. When VELARDO and HISAW\(^{42}\) made comparisons as to the abilities of six estrogens to inhibit the action of progesterone in the induction of decidual development, it was found that estrone is approximately 100 to 200 times more effective than estriol as an inhibitor of progesterone. Considering from these results, it is of interest that the discrepancy in inhibiting abilities of synthetic estrogens employed in the present investigation is not so pronounced as the naturally occurring estrogen, only by reason of methylation at position three.

We have not at present any conclusive evidence which indicates the site of the inhibitory action of estrogen. In this point, COURRIER\(^{35}\) and COURRIER and POUMEAU-DELLLE\(^{37}\) demonstrated the antagonistic relations between systemic progesterone and intra-uterine estradiol benzoate in castrated rabbits. A marked inhibition of progestational development by systemic progesterone was formed only in a part of the uterus where the estradiol was injected. This was followed by a few experiments of HEATH, HÖHN and ROBSON,\(^{35}\) Hereupon it seems that
estrogen-progesterone antagonism takes place, as a rule, in the uterus. However, it might be expected another possible site of antagonism if given systemically, such as inactivation or neutralization of progesterone in blood or some tissue.

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**References**