A STUDY OF ANTI-OVULATORY ACTIVITY OF HALOPERIDOL IN RABBITS

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Abstract—The effect of haloperidol (2.5 mg/kg i.v.) was studied on the ovulation induced by progesterone (1 mg/kg s.c.); copper acetate (5 mg/kg i.v.) and coitus in adult female rabbits. Progesterone induced ovulation was blocked by prior treatment with haloperidol. On the other hand, it was found to have no effect on copper acetate induced ovulation. Treatment of rabbits with haloperidol before coitus resulted in loss of receptivity in all the rabbits tested. The results of this study indicate that central adrenergic or dopaminergic mechanisms are involved in progesterone induced ovulation and copper acetate may be acting directly at median eminence to bring about the release of LHRF. The precoital administration of haloperidol in female rabbits resulted in loss of receptivity.

There is now ample evidence for the role of central catecholamines in ovulation (1–6). Furthermore, both reflex and spontaneous ovulation in rabbits and mice respectively have been reported to be adrenergically mediated through the central alpha adrenoceptors (7). In rabbits, ovulation can also be induced by other procedures e.g. administration of progesterone, dopamine (8) and copper acetate (9). Whether or not ovulation induced by progesterone and copper acetate is adrenergically mediated, is not yet clear. It was, therefore, thought worthwhile to study the effect of haloperidol (a tranquillizer, known to block both alpha adrenoceptors and dopaminergic receptors) on the ovulation induced by progesterone, copper acetate and coitus.

MATERIALS AND METHODS

The study was conducted on mature female rabbits weighing from 2 to 3.5 kg. The animals were housed in separate cages for a period of 33 days in order to exclude previous ovulation and pregnancy. They were given the diet of soaked gram and green vegetables. Water was given ad lib. All animals were pretreated with oestradiol dipropionate (100 µg s.c. for 2 days) prior to ovulating procedure. The oestrogen treated rabbits were divided into different groups. One male and one female rabbit were kept in each cage for mating purposes. Haloperidol 2.5 mg/kg was injected in the marginal ear vein of rabbits one hr before the administration of progesterone (1 mg/kg s.c.) or copper acetate (5 mg/kg i.v.) or coitus. Coitus was confirmed by the presence of motile spermatozoa in the vaginal flushings with normal saline on microscopic examination.

All rabbits were laparotomized under ether anaesthesia 24 hr after the ovulation in-
ducing procedure. The abdomen was incised and both ovaries were visualized for the presence of haemorrhagic spots indicating ovulation. The abdominal cavity was closed and the rabbits were allowed to recover.

RESULTS

The results of this study are summarized in Table I. It can be observed from the Table that only the rabbits on oestradiol and saline did not ovulate. The administration of progesterone (1 mg/kg s.c.) to oestrogen treated rabbits induced ovulation in five out of seven rabbits. This progesterone induced ovulation could be completely blocked by prior administration of haloperidol (2.5 mg/kg i.v.). On the other hand, haloperidol given similarly to rabbits on copper acetate (5.0 mg/kg iv.) as an ovulation inducing agent, failed to block ovulation.

The successful mating (confirmed by the presence of spermatozoa in the vaginal flushings) induced ovulation in nine out of ten rabbits. The administration of haloperidol (2.5 mg/kg i.v.) prior to mating resulted in loss of receptivity in all the eight female rabbits. These rabbits were sedated and were lying on the floor of the cages. The male rabbits co-habiting with these females made several attempts to mount but the females did not cooperate. No spermatozoa could be observed in the vaginal flushings of these rabbits. On laparotomy, none of the rabbits showed the presence of haemorrhagic spots on the ovaries.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Ovulation inducing procedure</th>
<th>Blocking agent (i.v. 1 hr before)</th>
<th>Number of rabbits</th>
<th>% of rabbits ovulating</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Saline</td>
<td></td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Progesterone (1.0 mg/kg s.c.)</td>
<td>Saline (1 ml)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>Progesterone (1.0 mg/kg s.c.)</td>
<td>Haloperidol (2.5 mg/kg)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>Copper acetate (5.0 mg/kg i.v.)</td>
<td>Saline (1 ml)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>V</td>
<td>Copper acetate (5.0 mg/kg i.v.)</td>
<td>Haloperidol (2.5 mg/kg)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>VI</td>
<td>Coitus</td>
<td>Saline (1 ml)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>VII</td>
<td>Coitus</td>
<td>Haloperidol (2.5 mg/kg)</td>
<td>8</td>
<td>Not receptive</td>
</tr>
</tbody>
</table>

DISCUSSION

The induction of ovulation by a single dose of progesterone is presumably due to action on the hypothalamus. Docke and Dorner (10) have reported that progesterone advances ovulation in the cyclic rat and stimulates it in the prepuberal rat by acting on the ventromedial arcuate region of hypothalamus. The ovulation induced by progesterone in rabbits as observed in the present study was found to be blocked by a prior treatment
with haloperidol. This observation suggests that the central adrenergic mechanism is involved in ovulation induced by progesterone in rabbits. The involvement of the noradrenergic system in progesterone induced ovulation in rats has been reported (11).

Haloperidol, on the other hand, was found to have no blocking effect on copper acetate induced ovulation in rabbits. Gupta et al. (12) have recently reported that prior administration of reserpine or phenoxybenzamine did not have any blocking effect on copper acetate induced ovulation. These observations provide further evidence in favour of the non-involvement of adrenergic or dopaminergic mechanisms in copper acetate induced ovulation. It appears that copper salts act directly at median eminence to bring about the release of the luteinizing hormone releasing factor (LHRF).

The administration of haloperidol 2.5 mg/kg i.v. one hr before coitus resulted in loss of receptivity in all rabbits tested, indicating that central dopaminergic mechanisms may play an important role in oestrous behaviour. This possibility is further supported by the fact that administration of oestrogen causes a significant increase in the level of brain dopamine in ovariectomized rats (13). Furthermore, it has been reported that haloperidol and pimozide (a specific dopaminergic receptor blocking agent) blocked the oestrogen progesterone induced oestrous behaviour in ovariectomized rats (14).

Thus, in conclusion, it may be stated that ovulation induced by progesterone requires an adrenergic link in the central nervous system, whereas, ovulation induced by copper acetate appears to be attributed to a direct effect on the median eminence. The results of this study suggest the role of central dopaminergic mechanism in oestrous behaviour in rabbits.

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