THE FALL OF BLOOD PRESSURE FOLLOWING INDUCTION OF DECIDUOMATA IN STEROID HYPERTENSIVE RATS RECEIVING PROGESTERONE

By
H. C. Moore, I. Cserhatי, and F. P. Biliczkiי

ABSTRACT
Experimental deciduomata and progesterone together lower the blood pressure in the steroid hypertensive rat from the 5th to 10th day of decidual growth i.e. from the 10th to 15th day of pseudopregnancy. This would suggest that the fall of blood pressure at an equivalent time of gestation in hypertensive pregnant rats could be due to the maternal decidua under the influence of progesterone. It is further considered that the metrial gland of the deciduoma is more likely to be responsible for the hypotensive effect and by comparison that the metrial gland is implicated in the hypotensive effect of pregnancy.

Progesterone alone also exerts a minor hypotensive effect in those animals in which a nephrectomy forms part of the hypertension regimen and indicates one way in which a maternal renal factor could influence blood pressure responses in hypertensive pregnant rats.

Hypertension, however caused, is not maintained in the pregnant rat (Moore & Biliczki 1968 a) but whether the fall of blood pressure is due to the influence of the foetus or the placenta has proved controversial. In further work Moore & Biliczki (1968 b) found that experimental deciduomata of 5 to 6 days duration in rats with steroid hypertension had no effect on the blood pressure and concluded that since experimental deciduomata have features in common with the maternal placenta (Krehbiel 1937), the fall of blood pressure during the first 10 or 11 days of pregnancy was not due to the maternal placenta.

The luminal decidual reaction in the pregnant rat, however, begins to regress at about the 12th or 13th day of gestation and declines both absolutely and

* of the 1st Department of Medicine, Medical University of Szeged, Hungary.
relatively until delivery (Duval 1891). Consequently in the present study the
effect of experimental deciduomata on the blood pressure was followed for a
longer period, for 10 days from induction, i.e. 15 days of pseudopregnancy.
This duration was selected because preliminary experiments had shown that
luminal decidual growth undergoes necrosis at about this time.

MATERIALS AND METHODS

Virgin Wistar Albino rats imported from a dealer and weighing between 142 and
180 g on receipt were used throughout. They were fed normal rat meal (M.R.C.
formula). At the beginning of the hypertension regimen their weights ranged between
142 and 218 g and there was no difference in range and mean between those test
animals which developed deciduomata and those which did not. 58 animals were used
and with the exception of three all gained weight but none was excluded on the
grounds of illness or loss of weight.

After a preliminary period of about 2 weeks during which time basal blood pressures
were determined the animals were subjected to one of two experimental procedures
designed to produce hypertension (Table 1).

Deoxycorticosterone acetate (Organon Ltd.) was given as a 100 mg nuchal implant
and cortisone (Adreson®, Organon Ltd.) daily intramuscularly in a dose of 1 mg per
100 g body weight. Left nephrectomy was carried out by a dorsal approach and saline
was given ad libitum as a 1 per cent solution by mouth.

The blood pressure was measured by the Friedman microphone technique (Friedman
& Freed 1949). The normal blood pressure in this laboratory ranges from 54 to 145
mm Hg with a mean of 104 mm Hg (S.D. ± 15). We accepted that readings of over
150 mm Hg represented hypertensive levels and only animals whose blood pressure
exceeded this at the time of oil instillation into the uterus are included here.

Induction of deciduoma

At about 14 days from the onset of the hypertension regimen all animals were placed
with vasectomized males in mating cages overnight. Mating when it occurred did so
between 17 and 45 days (mean 25 days) after the onset of the hypertension regimen
and this range and mean did not differ in any of the experimental groups. Mating was
determined each morning by the presence of a vaginal plug and the day on which
mating occurred was counted as Day 1. The course of pseudopregnancy in those that
mated was followed by daily vaginal swabbing.

At between 98 and 114 h after mating, a decidual reaction was induced in each
uterine horn by the method of Finn & Keen (1963) as detailed in an earlier report
(Moore & Biliczki 1968 b). In addition 5 mg progesterone (Organon) was given daily
by intramuscular injection from the time of oil instillation. Control animals were those
on the same hypertension regimen, which had received oil instillation but had not
developed a decidual reaction.

The blood pressure in all animals was measured every second day until mating
from which time daily levels in both animals with deciduomata and without were
determined until death, or until the completion of the period of observation.

The animals were killed by bleeding under ether anaesthesia and the presence of
deciduomata determined histologically. The uteri with deciduomata of 10 days duration

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weighed between 0.2 and 4.17 g (mean 1.01 g) whereas normal uteri weighed between 0.2 and 0.5 g (mean 0.32 g); in only three of the animals with deciduomata did the weight of the uterus fall within the control range.

RESULTS

Of the 16 hypertensive animals in Group 1 (Table 1) and the 16 animals of Group 2 in which deciduomata were induced and which received progesterone, 14 in Group 1 animals and 13 in Group 2 showed a fall of blood pressure. With few exceptions this began after 3 to 5 days of decidual growth i.e. between Day 8 and Day 10 following mating. The fall of blood pressure was progressive reaching the lowest level at or just before Day 15 when the experiment concluded; the lowest levels of blood pressure were either at the upper limit of normal or slightly higher. Up to the time of the fall of blood pressure, that is, during pseudopregnancy after mating and for a few days after oil instillation the blood pressure was maintained at the previous high level or rose. Two animals of the 16 of Group 1 and 3 animals of Group 2 maintained the level of hypertension throughout.

Of those animals of the same groups in which deciduomas were not induced but progesterone given only two of the 15 animals of Group 1 and 3 of Group 2 showed a consistent fall of blood pressure similar to that described in the deciduoma bearing animals.

These results are summarised in Table 2.

Table 1.
The experimental groups: all received progesterone from the time of induction of deciduoma.

<table>
<thead>
<tr>
<th>Group</th>
<th>Experimental procedure to produce hypertension</th>
<th>Uterus: deciduoma present (D) or normal (N)</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>left nephrectomy + Administration of DOCA + Cortisone + Saline</td>
<td>D { N } 16</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>D { N } 15</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>--</td>
<td>D { N } 16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N 11</td>
<td></td>
</tr>
</tbody>
</table>

+ Done
— Not done
Table 2.
A comparison of the effect on the blood pressure of deciduomata with progesterone and progesterone alone in animals with steroid hypertension.

<table>
<thead>
<tr>
<th>Hypertension regimen</th>
<th>Uterus with deciduoma (D) or normal (N)</th>
<th>Number of animals</th>
<th>Number showing progressive fall of blood pressure</th>
<th>Number with maintained hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (unilateral nephrectomy, receiving DOCA and cortisone with saline to drink)</td>
<td>D</td>
<td>16</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Group 2 (receiving DOCA and cortisone with saline to drink)</td>
<td>D</td>
<td>16</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>11</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

The details of the blood pressures in all animals of both groups are given in Tables 3 and 4 and the significance of differences between those animals with deciduomata and those with normal uteri determined by Student's t test.

Table 3.
Effect of deciduomata and progesterone on blood pressure in all animals of hypertension group 1.

<table>
<thead>
<tr>
<th>Duration pseudopregnancy</th>
<th>Range and mean (in brackets) of blood pressure in hypertensive animals (mm Hg)</th>
<th>P (deciduoma – normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with deciduoma</td>
<td>with normal uterus</td>
</tr>
<tr>
<td>Day 1 (mating)</td>
<td>135–200 (171.8)</td>
<td>150–200 (176.8)</td>
</tr>
<tr>
<td>Day 5 (oil instillation)</td>
<td>155–215 (182.1)</td>
<td>155–210 (186.1)</td>
</tr>
<tr>
<td>Day 10 (5 days after oil instillation)</td>
<td>135–205 (167.1)</td>
<td>134–205 (178.5)</td>
</tr>
<tr>
<td>Day 15 (10 days after oil instillation)</td>
<td>100–190 (147.8)</td>
<td>95–210 (173.8)</td>
</tr>
</tbody>
</table>
Table 4.
Effect of deciduoma and progesterone on blood pressure in all animals of hypertension group 2.

<table>
<thead>
<tr>
<th>Duration pseudopregnancy</th>
<th>Range and mean (in brackets) of blood pressure in hypertensive animals (mm Hg)</th>
<th>$P$ (deciduoma – normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with deciduoma</td>
<td>with normal uterus</td>
</tr>
<tr>
<td>Day 1 (mating)</td>
<td>120–205 (156.8)</td>
<td>130–187 (154.7)</td>
</tr>
<tr>
<td>Day 5 (oil instillation)</td>
<td>156–220 (176.9)</td>
<td>154–205 (171)</td>
</tr>
<tr>
<td>Day 10 (5 days after oil instillation)</td>
<td>145–190 (168.1)</td>
<td>125–205 (162.3)</td>
</tr>
<tr>
<td>Day 15 (10 days after oil instillation)</td>
<td>130–196 (151.5)</td>
<td>144–200 (171)</td>
</tr>
</tbody>
</table>

In both groups the lowering of blood pressure by deciduomata together with progesterone is highly significant at Day 15 i.e. after 10 days of decidual growth, whereas there is no effect at Day 10 following mating i.e. 5 days of decidual growth. Fig. 1 shows the typical pattern of the fall of blood pressure in deciduoma bearing animals compared with the maintenance of blood pressure in those animals with normal uteri.

From the data in Tables 3 and 4 it is found that in the control animals of Group 2 without deciduomata and receiving progesterone there is no significant fall of blood pressure during the experimental period. In the control animals of Group 1, however, the blood pressure at Day 15 following mating is lower than the pressure in the same group at Day 10 and the difference reaches a level of significance ($P < 0.05$).

**DISCUSSION**

The finding that experimental deciduomata supported by progesterone lower the blood pressure in steroid hypertensive rats suggests that the fall of blood pressure in hypertensive pregnant rats at equivalent times of gestation, from the 10th to 15th day, is related to maternal decidual function.

The present paper shows that the role of parenteral progesterone is two-
The fall of blood pressure in 5 animals (—) of Group 1 hypertension (Table 1) with deciduomata and progesterone compared with the blood pressure in 3 animals (-----) of the same group without deciduomata. The eight animals were matched as near as possible for weight, for the time after onset of hypertensive regimen at which they mated and for the level of blood pressure at the time of oil instillation into the uterus.

This finding is in agreement with that of Armstrong (1959) who reported that progesterone lowers the blood pressure in rats with renal hypertension. The absence of such an effect in intact animals without deciduomata suggests that the hypotensive action of progesterone is dependent on a disturbed renal function and indicates one way the maternal kidney could influence blood pressure responses in the pregnant animal. We have no data to support the view of Armstrong (1959) that the hypotensive effect of progesterone follows an increase in sodium excretion.

The second role of progesterone concerns the maintenance of the experimental deciduoma. In a previous paper (Moore & Biliczki 1968b) we concluded that deciduomata without parenteral progesterone and of 7 to 20 days
duration did not lower the blood pressure in hypertensive animals. Consequently the hypotensive effect in the present experiments is either a combined effect of parenteral progesterone and deciduomata or an effect solely of deciduomata which are maintained for a longer period by progesterone, as has been stated to occur in the mouse (Atkinson 1944). Furthermore, since experimental deciduomata cannot be induced in the absence of progesterone (Lobel et al. 1965) the effect of parenteral progesterone in animals with intact ovaries could be purely quantitative.

The precise relationship, however, between progesterone, deciduoma formation, and other hormones particularly the oestrogens, in producing the hypotensive effect must wait on further experiments.

An experimental deciduoma is a complex structure and consists of 3 parts, a mesometrial and antimesometrial decidual growth within the uterine lumen and the metrial gland of the mesometrial triangle (Velardo et al. 1953). At 10 days from the induction of deciduomata the whole of the antimesometrial deciduoma and much of the mesometrial deciduoma is necrotic and the luminal deciduoma consists only of a thin rim of mesometrial decidual cells. The granular cells, however, of the metrial gland are actively proliferating and form a nodule. The development of the metrial gland begins at about Day 7 or 8 and reaches a peak at Day 14 following mating i.e. from the onset of pseudopregnancy. The time of growth and maintenance of the metrial gland coincides therefore with the time at which the blood pressure falls suggesting that the metrial gland itself is more likely to be implicated in the hypotensive effect than the luminal deciduoma. In normal pregnancy in the rat the metrial gland is prominent at term and by comparison with the present findings it is possible that the pregnancy metrial gland is implicated in the hypotensive effect of pregnancy.

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REFERENCES

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