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Progesterone Is Not Responsible for the Blood Pressure Fall in Late-Pregnant New Zealand Genetically Hypertensive Rats (41846)

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Abstract. In various models of experimental and genetic hypertension in rats, blood pressure is markedly reduced during late pregnancy. The period during which the blood pressure reduction occurs is also the period when plasma progesterone is maximally elevated, and administration of progesterone to renal hypertensive rats has been reported to reduce blood pressure (J. Armstrong, 1959, *Proc. Soc. Exp. Biol. Med.* **102**:452–455). To test the possibility that elevated plasma progesterone is responsible for the blood pressure reduction in late pregnancy, on Day 14 of pregnancy a group of New Zealand genetically hypertensive (NZGH) rats was ovariectomized and implanted with progesterone-filled capsules, to maintain plasma progesterone at low levels just sufficient to maintain pregnancy, and compared with intact, pregnant NZGH. Ovariectomy did not alter the characteristic course of blood pressure reduction seen in late-pregnant intact NZGH rats. In addition, daily administration of progesterone (15 mg/kg, sc) for 14 days did not alter blood pressure of either nonpregnant NZGH rats or New Zealand normotensive rats with chronic 1-kidney, 1-clip hypertension. It is concluded that blood pressure of NZGH rats is reduced to near normotensive levels in late pregnancy, as reported for other models of rat hypertension, but that elevated plasma progesterone levels are not requisite for that reduction and do not reduce blood pressure of renal hypertensive rats.

In genetically hypertensive rats of the Okamoto (SH) strain, and in rats with other forms of experimental hypertension, blood pressure falls progressively during the last week of pregnancy to nearly normotensive levels, remains reduced through parturition, and then returns rapidly to prepregnancy hypertensive levels by the first or second day postparturition (1–5). Also during the last week of pregnancy in the rat, plasma progesterone levels rise, reaching a sustained peak at a time coinciding with the reduction of blood pressure, and then fall rapidly, returning to prepregnancy levels at a time coinciding with the return of blood pressure to hypertensive levels (4, 6). In addition to these temporally coincident patterns of inverse changes in blood pressure and plasma progesterone levels, Armstrong (7) has reported that daily administration of progesterone, at a dose similar to the amount produced by late-pregnant rats (8), reduced blood pressure of 1-kidney, 1-clip hypertensive rats. From these various findings, investigation of the possibility that elevations in plasma progesterone levels contribute to the reduction of blood pressure in late-pregnant hypertensive rats appeared to be warranted.

The effect of pregnancy on blood pressure of the New Zealand strain of genetically hypertensive (NZGH) rat has not been reported. We noted in preliminary studies of pregnant NZGH rats that blood pressure was decreased just prior to parturition. The present studies were carried out to document fully the effect of pregnancy on blood pressure in NZGH rats, a model of genetic hypertension not previously studied in this regard, and to investigate the possibility of a causal relationship between changes in plasma progesterone levels and changes in blood pressure in late-pregnant genetically hypertensive rats.

Materials and Methods. Rats used in this study were from the colony of New Zealand normotensive (NZNR) and genetically hypertensive (NZGH) rats maintained at this institution. Rats were housed in group cages, with three to five rats per cage, in a room with controlled temperature (24°C) and humidity (50%), illuminated from 6:00 AM to 6:00 PM, and received tap water and standard rat chow (Purina No. 5001; sodium 174, potassium 282 meq/kg) *ad libitum*. Systolic blood pressure was measured by tail sphygmomanometry after warming the rats for 10 min at 37°C.

Studies in pregnant NZGH. Rats were mated overnight and Day 1 of pregnancy was

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determined from vaginal smears and/or the presence of a cervical plug. At two to five-day intervals before, during, and after pregnancy, blood pressure was determined and the rats were lightly anesthetized with halothane to permit sampling of blood (0.2 ml) from the tail for determination of plasma progesterone. On Day 14 of pregnancy, one group of rats was ovariectomized and implanted with progesterone-filled Silastic capsules (1.5 × 40 mm), to maintain low progesterone levels just sufficient to prevent spontaneous abortion.

Studies in nonpregnant NZGH. Systolic blood pressure of virgin female NZGH rats was measured before, during and after treatment with progesterone. Rats received daily subcutaneous injections of either progesterone (Sigma, 15 mg/kg/day) or peanut oil vehicle (1 ml/kg) for a period of 14 days.

Studies in 1-kidney, 1-clip hypertensive NZNR. Fourteen-week-old female NZNR were anesthetized with halothane; the right kidney was removed and a silver clip, 0.2 mm i.d., was placed on the left renal artery (9). Six weeks later, after the rats had developed stable hypertension, daily injections of progesterone (Progesterone injection, USP; Eli Lilly Co.; 15 mg/kg) or vehicle were given for a period of 14 days; blood pressure was measured two or three times a week.

Analytical and statistical methods. Progesterone in plasma was measured by radioimmunoassay using a commercially available kit (Coat-A-Count Progesterone, Diagnostics Products Corp., Los Angeles). Values are expressed in the text, figures, and tables and group means ± the standard error of the mean. Statistical significance was determined by Student's *t* test for unpaired values, or by analysis of variance followed by Neuman–Keuls test for multiple variables, as appropriate (10); a *P* value of less than 0.05 was taken to indicate statistical significance.

Results. As shown in Fig. 1, in intact pregnant NZGH rats plasma progesterone increased from prepregnancy levels of 20 ng/ml to 70 ng/ml on Days 17 and 20; systolic blood pressure remained constant at prepregnancy levels of 160–170 mm Hg until Day 14, then declined steadily to a minimum value of 135 mm Hg on the last day of pregnancy. After parturition, blood pressure rose rapidly, returning to prepregnancy levels by the second

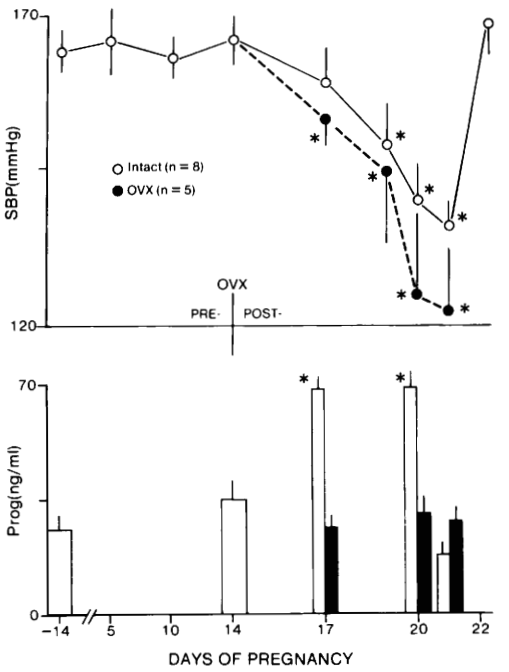

FIG. 1. Systolic blood pressure (SBP, upper panel) and plasma progesterone concentration (PROG, lower panel) in pregnant NZGH rats. Intact rats are indicated by open circles and bars; rats that were ovariectomized and implanted with progesterone capsules on Day 14 of pregnancy are indicated by solid circles and bars. * Indicates $P < 0.05$ compared with prepregnancy values.

day postparturition. In rats that were gonadectomized and implanted with progesterone-filled capsules on Day 14 of pregnancy, plasma progesterone did not exhibit the characteristic late-pregnancy increase, but remained instead at levels similar to those seen in nonpregnant rats. Despite prevention of the characteristic rise in plasma progesterone, blood pressure of the gonadectomized rats fell during late pregnancy as did that of intact rats, beginning about Day 14 and reaching a minimum value of 125 mm Hg on Day 21 of pregnancy. The gonadectomized rats were unable to deliver successfully and were sacrificed on Day 23 of pregnancy; blood pressure remained reduced until the rats were killed.

NZNR female rat blood pressures, shown in Fig. 2, rose progressively after renal artery constriction and contralateral uninephrectomy, from a control level of 125 mm Hg, to 220 mm Hg by the fourth week after clipping, and did not change thereafter. Daily injections

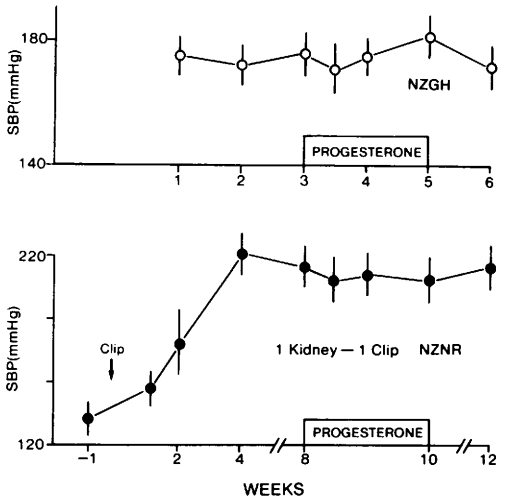

FIG. 2. Systolic blood pressure (SBP) of New Zealand genetically hypertensive rats (NZGH, upper panel) and of New Zealand normotensive strain rats with chronic 1-kidney, 1-clip hypertension (lower panel) before, during, and after daily administration of progesterone (15 mg/kg, sc) for 14 days.

of progesterone for 14 days had no effect on blood pressures of these renal hypertensive rats. Also shown in Fig. 2, blood pressures of NZGH rats were not altered during a 2-week course of daily progesterone treatment.

Discussion. First noted in renal hypertensive rats (1), reduction of blood pressure during late pregnancy has also been reported to occur in renal hypertensive rabbits and dogs (2). In other rat models of experimental hypertension the phenomenon appears to be less consistently demonstrable. For example, in rats made hypertensive by mineralocorticoid treatment and excess sodium chloride intake, blood pressure was reported to fall during late pregnancy by some investigators (3, 5), while others reported no such effect (11, 12). In the present study, we found that blood pressure of NZGH hypertensive rats fell during the last days of pregnancy to approximately normotensive levels; the timecourse and extent of the blood pressure reduction closely resembled those reported by other investigators to occur in another model of genetic hypertension, the Okamoto SH rat (3, 4). Despite extensive investigation, the mechanism underlying this rapid reduction of blood pressure, and the subsequent and even more rapid rise back to hypertensive levels, has not been defined. The possibility that the changes in blood pressure might be related to changes in progesterone levels has not, to our knowledge, been previously tested. Several pieces of information suggested that progesterone could be responsible. First, Armstrong reported that progesterone treatment reduced the blood pressure of 1-kidney, 1-clip hypertensive rats, renal hypertensive dogs, and human essential hypertensive patients to nearly normotensive levels, and that pressure returned rapidly to hypertensive levels when progesterone treatment was stopped (7). Second, in pregnant rats plasma progesterone rises to a maximum on Days 15–20, then falls back to prepregnancy values by Day 1 postparturition (6); blood pressure in pregnant hypertensive rats changes in a mirror-image fashion with respect to progesterone, falling from about Day 15 of pregnancy to a minimum level on Days 20–21, then rising rapidly back to prepregnancy values by the first or second day postparturition (4, 5). And, third, the dose of progesterone reported to reduce blood pressure of hypertensive rats was 15 mg/kg/day (7); this amount is quite similar to the calculated rate at which progesterone is produced, 4.55 mg/day, in Day 15 pregnant rats (8).

The findings of the present study, however, do not support the hypothesis that progesterone is responsible for blood pressure changes in late-pregnant hypertensive rats and, in addition, are in clear conflict with one of the published findings (7) that was basic to the formulation of that hypothesis. From our finding that blood pressure fell during the last days of pregnancy in ovariectomized rats as it did in intact rats, it is clear that the high levels of progesterone characteristic of this phase of pregnancy are not requisite for the blood pressure reduction. In addition, administration of progesterone to NZGH rats, at doses equal to or in excess of the rate of progesterone production in late pregnancy, had no effect on blood pressure. Finally, we were unable to confirm the previously reported (7) hypotensive effect of progesterone in hypertensive rats, although the model of hypertension (1-kidney, 1-clip), the progesterone formulation (Injection Progesterone USP; Eli Lilly and Co.), and the dosage schedule and experimental protocol were identical to those of the earlier study; we have no explanation

for the disparity between the results of the two studies. In any case, the results of this study indicate that progesterone is not a factor in the blood pressure reduction of late pregnancy in NZGH rats, since the pressure reduction occurred even when the late rise in progesterone was prevented, and administration of progesterone did not affect blood pressure of nonpregnant NZGH.

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