Progesterone Increases Blood Pressure in Spontaneous Gestational Hypertension in Rats

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**Background:** Gestational hypertensive disorders are a leading cause of maternal mortality in the US, accounting for up to 10% of these deaths. During pregnancy, a new rat model (SHHF rat) has been shown to develop spontaneous hypertension with increases of more than 40 mm Hg systolic blood pressure (BP), which resolves after delivery, and which lead us to ask whether the hypertension may be triggered by increased levels of progesterone in these rats.

**Methods:** To test this hypothesis, groups of SHHF rats were treated with progesterone (PROG), estrogen (EST), or progesterone and estrogen (PROG+EST) that correspond to levels that occur during pregnancy. Control (CON) rats received saline-filled implants and pseudopregnancy was induced in another group. Wistar-Kyoto rats served as controls for SHHF rats.

**Results:** By experimental day 3, progesterone caused a significantly higher systolic BP, similar to pseudopregnancy and to previously reported values during pregnancy in this strain. Blood pressure in SHHF rats given estrogen was not significantly different. RU486 reversibly prevented the increase in BP induced by progesterone.

**Conclusions:** These results indicate that an anomalous response to progesterone causes dramatic increases in BP in SHHF rats during a short period of time, in contrast to the decrease in BP in response to progesterone, which has been reported in other rat models of hypertension. An abnormal pressor response to progesterone should be considered a potential mechanism contributing to the development of hypertension during pregnancy. Am J Hypertens 2005;18:36–43 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** SHHF rat, preeclampsia, pregnancy-induced hypertension, intrauterine growth restriction, kidney and pseudopregnancy, RU486.
blood flow, and glomerular filtration rate (GFR).5–10 Despite these changes, BP during gestation is normally maintained at normal to below normal values due to simultaneous and marked vasodilation, presumably mediated by mechanisms involving estrogen and progesterone. Because SHHF rats develop spontaneous hypertension during pregnancy,3 it seems reasonable to ask whether there is evidence of renal dysfunction during pregnancy and to determine whether estrogen and progesterone may have an anomalous effect on BP in these animals. Here we report significant alterations in creatinine clearance and renal fractional excretion of electrolytes during pregnancy. Furthermore, progesterone and not estrogen can induce a profound hypertension in these gestational hypertension-prone rats at a magnitude similar to that induced by pseudopregnancy and by a mechanism reversibly inhibited by RU486.

**Methods**

**BP Measurements, Serum Biochemical and Progesterone Analysis, Urinary Protein and Electrolyte Excretion, and Endogenous Creatinine Clearance**

Lean male and female spontaneously hypertensive heart failure (SHHF/Mcc-fadP or SHHF) rats were obtained from Genetic Models, Inc. (Indianapolis, IN). This unique model of cardiovascular disease does not require surgical, dietary, or pharmacologic intervention to express hypertension and heart failure.11 Wistar-Kyoto (WKY) rats were obtained from Charles River Laboratories (Wilmington, MA). Sixteen 4-month-old lean virgin female SHHF rats and 12 4-month-old virgin WKY rats were accommodated to conscious resting systolic BP measurement and baseline BP data were recorded as the average of three acceptable readings. All rats were weighed and placed in stainless steel metabolic cages with access to food and water for 24-h urine collection during the estrous phase of their cycle as determined by vaginal cytology. Water consumption was recorded and 2 mL of blood was collected by the tail clip method for baseline serum biochemical and hormone analysis. SHHF and WKY rats were matched by body weight (in kilograms). Urinary fractional excretions of electrolytes were calculated using the following formula: urine concentration of electrolyte [(mEq/L)/serum concentration of electrolyte (mEq/L)] divided by urine creatinine concentration (in milligrams per deciliter)/serum creatinine concentration (in milligrams per deciliter)] × 100.

Serum progesterone measurements by radioimmunoassays were performed on serum samples using a Coat-A-Count kit produced by Diagnostic Products Corporation (Los Angeles, CA). Each sample was performed in duplicate and the reported value is the mean of the repeated measure.

**Implantation for Progesterone Delivery**

Thirty 4-month-old SHHF rats were accommodated to conscious resting systolic tail cuff BP measurements. Baseline data were obtained, and rats were matched by baseline systolic BP and randomly assigned to one of five groups. One group (PROG1) received progesterone implants (n = 8); a second group (EST) received estrogen implants (n = 8); a third group received PROG and EST; a control group (CON1) received saline implants (n = 6); and a final group (PSEUDOPREG) was bred with sterile vasectomized males to induce pseudopregnancy (n = 8). Blood pressure, body weight, and estrous cycle data were collected every 3 days for 23 days, approximately the length of gestation in the rat. Hormone-treated and control animals were sacrificed at the end of the study for necropsy and organ weight measurements. Pseudopregnant females were monitored until the resumption of normal estrous cycles; once the body weights and cycling patterns returned to baseline, final BP measurements were recorded.

**Inhibition of Progesterone with RU486 (mifepristone)**

To test our hypothesis that progesterone plays an important role in the development of pregnancy-induced hypertension in SHHF rats, we performed a second experiment pharmacologically to block the action of progesterone treatment. For this experiment, 16 lean virgin female 4- to 5-month-old SHHF rats were accommodated to the measurement of conscious tail cuff systolic BP as described for the previous experiments. Animals were randomly assigned to either control (CON2) (n = 4), progesterone implant (PROG) (n = 7), or progesterone implant + RU486 treatment (RU) (n = 5). Control rats received saline-filled implants. Progesterone implants were performed as described previously. The RU486-treated rats received 200 µL of a 5 mg/mL solution of the drug suspended in olive oil daily for 11 days by subcutaneous injection in addition to the progesterone implants. These
injections were begun the day before the placement of the progesterone implants to maximize the ability of the drug to block the action of progesterone. Control and progesterone-treated rats received injections of vehicle (olive oil) without the drug. The injections were stopped on day 10 of the experiment. Body weight and BP measurements were taken every other day and estrous cycling was followed using vaginal cytology for 19 days, corresponding to 8 days after discontinuation of RU486 treatment.

**Hormone Implants**

Hormone implants were fashioned according to the method described by Bridges.12 Progesterone (4-pregnene-3,20-dione; Steraloids, Inc., Newport, RI) and estrogen (1,3,5(10)-estratrien-3,17β-diol; Steraloids, Inc.) in powder form were packed into silastic tubing (0.078 in ID × 0.125 in OD; Dow Corning, Midland, MI) and sealed with medical grade elastomer/catalyst (Factor II, Lakeside, AZ). The hormone implants were inserted subcutaneously to rats under general anesthesia (60 mg/kg ketamine [ketamine HCl; Abbott Laboratories, N. Chicago, IL] and 6 mg/kg xylazine [Rompun, Bayer Corporation, Shawnee Mission, KS] delivered intraperitoneally). Rats receiving progesterone had three 30-mm length progesterone implants inserted on day 0, and on day 9 an additional three implants were placed, for a total of 180-mm. For the EST group, 5-mm length estrogen implants were inserted on day 0. For the CON1 and CON2 groups, 10-mm saline filled implants were inserted on day 0. The PSEUDO-PREG group received no implants. For the RU486 experiments, the rats in the PROG and RU486 groups received three 30-mm progesterone implants. The length of the implants was calculated based on data from Bridges showing that implants of these lengths should result in circulating hormone levels approximating those measured during pregnancy in the rat.12 The physiologic efficacy of the hormone implants was verified by measurement of body weight, uterine weights, and vaginal smears.

**Vasectomy Procedure and Pseudopregnancy in SHHF Rats**

Five male rats were anesthetized using 90 mg/kg ketamine (ketamine HCl, Abbott Laboratories) and 9 mg/kg xylazine (Rompun, Bayer Corporation) intraperitoneally. These rats were vasectomized according to the procedure described by Laber-Laird et al.13 After a recovery period of 7 days, the males were paired with normally cycling female WKY rats (not assigned to this experiment) for a period of 5 days to confirm that the males were sterile. Daily microscopic examination of vaginal smears from these females was negative for sperm. Each male was then caged with one or two SHHF females assigned to the pseudopregnancy group. Eight of these females subsequently became pseudopregnant, as determined by measurement of weight and estrous cycle cessation. Females were considered pseudopregnant when steady weight gain and mixed vaginal cytology occurred.

Vaginal smears were typically examined microscopically for the presence of sperm when determining the date at which a female rat had been bred by a male. Because the male rats were vasectomized and released no sperm, it was difficult to determine prospectively the precise date at which each rat in group 5 (pseudopregnancy group) was bred and subsequently induced to become pseudopregnant. Blood pressure, vaginal cytology, and weight data from this group were therefore examined at the end of the experiment, and breeding dates for each rat were assigned retrospectively, based on the data patterns determined from previous experiments. A postbreeding date at which body weight reached a plateau was used for comparison with the other groups. The plateau date was approximately day 15 after the determined breeding date for all pseudopregnant rats, therefore a postimplant day 15 was used for comparison between the pseudopregnant and implant groups.

**Tissue Collection**

Heart, kidneys, uterus, and brain were removed and weighed. Terminal blood samples were collected by cardiac puncture. Whole heart weight was measured; subsequently the atria were separated by a single cut with a razor blade and weighed together. The right ventricle was removed by cutting along its attachment to the left ventricle and septum and weighed separately. The left ventricle and septum were weighed as a unit. All tissues were examined for gross pathology. The same investigator performed all prosections (LCS).

**Statistical Analysis**

Data are expressed as the mean ± standard error of the mean for each group. Comparisons between two groups of the spontaneous experiment were done using Student *t* test for parametric data and the Mann-Whitney *U* test for nonparametric data using the Instat statistical program. Differences are reported as significant if *P* < .05. Comparisons for the implantation experiments were done using ANOVA and post-tests (Tukey-Kramer multiple comparisons test) using the Instat statistical program. Differences were reported as significant if the value of *P* < .05.

**Results**

**BP and Renal Function During Pregnancy**

Figure 1A summarizes the BP measurements in pregnant SHHF and WKY rats. At baseline, SHHF conscious systolic BP is significantly higher than WKY, and remains higher, peaking at midgestation (*P* < .05). WKY have minimal decreases in systolic BP by midgestation, demonstrating a normal, slightly hypotensive response to pregnancy. Body weight changes were almost identical for both strains of rats (Fig. 1B). Despite the significant dif-
ferences in BP between SHHF and WKY rats, daily water intake was similar for most of gestation, although SHHF tended to have slightly greater water consumption in the first trimester of pregnancy, corresponding to the period of increasing systolic BP in SHHF (Fig. 1C). However, these differences were only statistically significant by days 3 and 4. At midgestation, the trend reversed, and SHHF had slightly lower daily water consumption than WKY, which became significant only on days 19 and 20. Differences in water consumption were not reflected in total body weights, which were similar for SHHF and WKY rats throughout pregnancy (Fig. 1B).

Endogenous creatinine clearance was used to estimate GFR early in pregnancy during the period of increasing systolic BP in SHHF (Fig. 2A). Creatinine clearance was significantly higher in WKY compared to SHHF at all times measured. In addition, creatinine clearance increased appropriately in response to pregnancy by day 5 in WKY, whereas SHHF rats failed to increase GFR in response to pregnancy until day 10. Urinary fractional excretion of potassium was not different between SHHF and WKY at baseline or days 5 and 10 of pregnancy (Table 1), whereas urinary fractional excretion of sodium was significantly greater in WKY than SHHF at day 5, corresponding to decreased GFR and increasing systolic BP in SHHF. Urinary fractional excretion of calcium was lower in SHHF before pregnancy, whereas magnesium excretion was not affected by pregnancy or strain.

Differences in liver enzyme elevations (ALP, ALT, AST) were not apparent at days 5 and 10 of pregnancy in either strain (Table 1). The AST levels were higher in SHHF than WKY at all time points, but remained within the calculated reference interval for the strain (62 to 377 U/L, as determined by the mean ± 2 standard deviations of serum AST mea-
serum liver enzyme and urinary excretion data in early pregnancy for SHHF/Mcc-fa<sup>op</sup> (SHHF) and Wistar-Kyoto (WKY) rats.

| Day 0     | Day 5     | Day 10    |
|-----------|-----------|-----------|
| **WKY**   | **SHHF**  | **WKY**   | **SHHF**  | **WKY**   | **SHHF**  |
| ALP U/L   | 171.5 ± 10| 190 ± 15  | 178 ± 7   | 185 ± 25  | 165 ± 10  | 192 ± 21  |
| ALT U/L   | 78 ± 10   | 99 ± 6    | 75 ± 5    | 102 ± 20  | 73 ± 3    | 90 ± 10   |
| AST U/L   | 100 ± 10  | 230 ± 15* | 125 ± 7   | 325 ± 60* | 125 ± 5   | 175 ± 15* |
| UFE<sub>Na</sub> | 0.34 ± 0.02 | 0.31 ± 0.02 | 0.52 ± 0.04 | 0.31 ± 0.07* | 0.39 ± 0.06 | 0.31 ± 0.03 |
| UFE<sub>K</sub> | 14.82 ± 2.03 | 14.50 ± 0.69 | 20.20 ± 2.62 | 14.27 ± 1.63 | 14.47 ± 3.46 | 12.81 ± 2.80 |
| UFE<sub>Ca</sub> | 1.06 ± 0.07 | 0.83 ± 0.05* | 1.67 ± 0.25 | 0.96 ± 0.13* | 1.54 ± 0.10 | 0.87 ± 0.14* |
| UFE<sub>Mg</sub> | 8.81 ± 0.98 | 7.4 ± 0.80 | 5.79 ± 0.96 | 4.51 ± 0.81 | 8.53 ± 0.60 | 7.11 ± 1.45 |
| UPC       | 0.64 ± 0.06 | 0.73 ± 0.05 | 0.65 ± 0.04 | 0.66 ± 0.11 | 0.64 ± 0.05 | 0.68 ± 0.09 |

All urine and serum analysis was performed using a Hitachi 911 automated chemistry analyzer (Indianapolis, IN). Urine samples were 24-h samples collected in stainless steel metabolic cages.

**BP Response to Hormone Treatment**

Fig. 3A summarizes the BP measurements after hormone treatment. Initial systolic tail cuff BPs were similar for all the 40 4- to 5-month-old virgin SHHF rats. These differences were statistically significant, but are not considered biologically significant given the large reference intervals that are typical for these enzymes in most domestic animal species. There were no significant differences in urinary protein creatinine (UPC) ratio between strains or after conception (Table 1).

Although baseline progesterone concentration during estrus (determined by vaginal cytology) was slightly higher in SHHF compared with WKY rats, WKY had significantly higher progesterone levels at days 5 and 10 of pregnancy compared to SHHF (Fig. 2B). At day 5, SHHF rats had progesterone levels 3-fold higher than baseline, whereas WKY rats were 13-fold baseline; day 10 progesterone levels increased further to 4-fold baseline in SHHF rats, whereas WKY were relatively stable at 12-fold above baseline estrous values.

**BP Response to Progesterone Blockade with RU486**

Fig. 3B shows reversible blockade of progesterone-induced hypertension in SHHF rats by RU486. The PROG2-treated rats had significantly higher systolic BP compared to CON2 and RU486-treated rats from day 2 through day 10 of the study. However, 9 days after discontinuation of the RU486 treatment, BP of the rats in this group increased to that of the progesterone-treated group and was significantly greater than the BP of the control group (P < .05). Efficacy of progesterone treatment was verified by the significantly increased weight gain compared to controls and RU486 + progesterone-treated rats (data not shown).
and persistent diestrus/proestrus vaginal cytology (data not shown). Rats treated with RU486 had minimal weight gain that was comparable to controls during the first 10 days of the treatment. In addition, vaginal cytology of RU486 indicated a state of continuous estrus. By 9 days after discontinuation of RU486 treatment, all rats in this group had converted from continuous estrus to continuous diestrus and gained significant weight between days 11 and 19.

Discussion

The pronounced hypertension experienced by SHHF rats during gestation may be associated with a delayed and inadequate increase in GFR in response to pregnancy when compared with WKY rats. During the first 10 days of pregnancy, when systolic BPs are increasing, SHHF rats consume significantly more water than WKY and have significantly lower urinary fractional excretion of sodium. These factors could contribute to increasing BP through volume loading, although this was not measured and may be not sufficient to result in significantly increased total body weights compared to WKY rats. Urinary fractional excretion of calcium was significantly lower in SHHF than WKY rats at all measure time points. Interestingly, urinary calcium excretion is also abnormally low in some women with hypertensive disorders of pregnancy, suggesting intrinsic renal tubular dysfunction. Dietary deficiency of calcium has also been implicated in the development of these disorders in women. However, the controlled diet fed to rats in this study excludes dietary content as a factor influencing calcium status. Proteinuria also characterizes some hypertensive disorders of pregnancy in women; however, urinary protein creatinine ratios were not significantly different between SHHF and WKY rats. Nor were liver enzymes significantly affected by pregnancy in either strain, although SHHF rats had higher AST than WKY rats at all evaluated time points, but the significance of this is unclear.

Despite higher baseline values, serum progesterone levels failed to increase appropriately in response to pregnancy at days 5 and 10 in SHHF rats compared with WKY rats. Although strain differences should be considered, serum progesterone values in WKY rats were almost identical to values reported for Sprague-Dawley rats on those gestational days, suggesting that the progesterone values in SHHF rats may be abnormally low. The potential relationship between low progesterone levels and other abnormalities of pregnancy in SHHF rats was not evaluated in these experiments. We have observed that SHHF rats have difficulty maintaining their pregnancies when invasive procedures or instrumentation are attempted during pregnancy.

The results of implantations demonstrate that exogenous progesterone can cause marked increases in BP within 2 to 3 days in female SHHF rats and that this effect can be blocked by treatment with a type II progesterone antagonist, RU486. The degree of hypertension induced by exogenous progesterone supplementation is almost identical to that associated with pseudopregnancy, and comparable to previously reported levels in pregnant SHHF rat. This appears to be an anomalous response to progesterone, as previous work has shown that progesterone decreases BP in ewes and normotensive and hypertensive Sprague Dawley rats. Even in the spontaneously hypertensive (SHR) rat, BPs decrease to almost normotensive levels during the third trimester of gestation, suggesting a hypotensive effect of progesterone. Progesterone treatment lowered the BP of normotensive Sprague Dawley rats and male and female Sprague Dawley rats that had been made hypertensive using the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME). Treatment with the pure progesterone agonist R5020 was shown to decreased BP in L-NAME-treated Sprague Dawley rats and male SHR rats in the same series of
Nerve responses,25 and causing nonendothelium-dependent vasodilation by stimulating the activity of the large conductance, calcium and voltage-activated potassium channel.26

Antagonists may also promote association of the progesterone receptor with corepressors that are normally irrelevant due to distinct conformation changes induced by antagonist binding.28 RU486 has been shown to act as an agonist in some systems, depending on cAMP levels29 or the ratio of coactivators and corepressors.30 On the basis of the data observed in these studies, it seems likely that progesterone is having an anomalous, yet undefined, effect on BP regulation in women.

In summary, SHHF rats demonstrate dramatic exacerbation of hypertension associated with pregnancy and have renal dysfunction and altered progesterone levels. However, they do not have significant proteinuria or liver enzyme elevations that may characterize human disorders such as preeclampsia. In addition, although exacerbation of hypertension occurs during pregnancy, the presence of a fetal placental unit does not appear to be required. Further investigations into the hormonal mechanisms for altered BP regulation could prove valuable in understanding BP regulation in women.

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