Glucocorticoids Modulate Vascular Reactivity in the Rat

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SUMMARY To clarify the role of endogenous glucocorticoids in the regulation of blood pressure, the cardiovascular effects of RU 486, a steroid derivative with antiglucocorticoid properties, were investigated in Wistar rats. Pressor responses to angiotensin II (Ang II), norepinephrine, and vasopressin were studied in normal conscious rats before and after administration of RU 486. At 20 mg/kg/day, RU 486 significantly blunted pressor responses to Ang II and norepinephrine, whereas those to vasopressin were not greatly affected. At a lower dose, RU 486 did not alter pressor responses; at a higher dose, it augmented them, probably through its agonistic glucocorticoid effect. At 20 mg/kg/day, RU 486 antagonized the enhancing effect of a glucocorticoid agonist on pressor responses to Ang II, norepinephrine, and vasopressin. Cardiac output and renal blood flow were measured in anesthetized rats by the microsphere method. RU 486 at 20 mg/kg/day did not alter basal cardiac output and renal blood flow. RU 486 pretreatment attenuated pressor responses to Ang II and norepinephrine but did not alter cardiac output. It significantly blunted the decrease in renal blood flow and the increase in renal vascular resistance induced by Ang II. In rats fed a low sodium diet (where the pressor systems are stimulated), administration of RU 486 (20 mg/kg/day for 5 days) decreased total peripheral vascular resistance by 29% and mean blood pressure by 20 mm Hg. This effect was unrelated to any antimineralocorticoid activity of the compound, as shown by unchanged urinary sodium excretion, sodium balance, and plasma renin concentration. In contrast, it was due to the antiglucocorticoid activity, as shown by restoration of mean blood pressure by corticosterone, the major glucocorticoid in rats. Renal vascular resistance decreased during RU 486 administration in anesthetized (— 25%) and unanesthetized (— 19%) rats. Glomerular filtration rate, estimated from inulin clearance in conscious rats, did not change significantly. In conclusion, the present results suggest that endogenous glucocorticoids increase vascular reactivity and therefore contribute to blood pressure regulation. They also participate in the control of renal hemodynamics. This effect is most apparent in salt-restricted rats. The vascular action of glucocorticoids was unmasked by the administration of the antiglucocorticoid compound RU 486. (Hypertension 10: 608-618, 1987)

KEY WORDS • antiglucocorticoid • norepinephrine • angiotensin II • vasopressin • low sodium intake • renal hemodynamics • cardiac output • microspheres

The regulation of blood pressure depends on the interplay of multiple control systems. Analysis of these interactions has been facilitated by the synthesis and development of inhibitors of the hormones or mediators involved. In this regard, the use of inhibitors or antagonists of the adrenergic or renin-angiotensin system, prostaglandin and arginine vasopressin (AVP), has provided a large body of information about the physiologic roles of catecholamines, angiotensin II (Ang II), prostaglandins, and AVP in blood pressure regulation. Investigation into glucocorticoids was long precluded by the lack of an antiglucocorticoid compound with in vivo activity.1

Many data, however, point to an important role for glucocorticoids in the control of blood pressure. Glucocorticoid excess induces hypertension in humans and in rats.2,3 Glucocorticoid deficiency is accompanied by low blood pressure and reduced vascular reactivity. In the 1960s the question of how corticosteroids affected the cardiovascular system generated a large number of investigations (see the review in Reference 4). The results were collected from experiments performed either in acutely or chronically adrenalectomized animals or after administration of massive doses

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of corticosteroids in animals with various forms of circulatory shock. In more recent years, the specific role of glucocorticoids in blood pressure control has been progressively delineated in chronically adrenalectomized animals maintained on high salt intake for at least 3 days after operation. Basal MBP was taken as the mean of at least 3 measurements in prewarmed rats under light ether anesthesia.

Measurements

In unanesthetized and anesthetized rats pretreated with either RU 486 or vehicle, the systemic and renal hemodynamic effects of RU 486 were also studied in rats on chronic low sodium intake, a condition in which the pressor systems are activated. Our observations support the view that the antiglucocorticoid blunts vascular reactivity and therefore unmasks the enhancing effect that endogenous glucocorticoids normally exert on vascular responsiveness in the rat.

Materials and Methods

Studies were performed in male Wistar rats whose weights ranged from 175 to 340 g (age, 0-12 weeks; Iffa-Credo, L’Arbesle, France). They received water ad libitum and were fed either a normal sodium diet containing 143 mmol Na/kg, or a low sodium diet containing 43 mmol Na/kg (Extralabo, Longueville, France), for at least 3 weeks before the experimental procedures. RU 486 (Roussel-UCLAF, Paris, France) was administered by stomach tube once daily. In all protocols, it was administered 2 hours before the experimental procedures.

Chronic Vascular Catheterization and Blood Pressure Measurements

Catheters were placed into the abdominal aorta and vena cava through the femoral artery and vein in the rats under general anesthesia (ketamine, 60 mg/kg body weight intramuscularly, and pentobarbital, 20 mg/kg body weight intraperitoneally). Medical grade Tygon tubing (S-54-HL, Norton, Akron, OH, USA) was used. The catheters (internal diameter, 0.015 in.; outer diameter, 0.030 in.) were passed under the skin and exteriorized at the back of the neck, then filled with heparinized solution and sealed through insertion of stainless steel rods. Mean blood pressure (MBP) was measured in conscious rats through a P23ID transducer (Gould, Ballainvilliers, France) at least 3 days after operation. Basal MBP was taken as the mean of at least two measurements. In other rats, systolic blood pressure (SBP) was measured by the tail-cuff method in prewarmed rats under light ether anesthesia.

Radionabeled Microsphere Method

Cardiac output and its distribution were measured in anesthetized rats (pentobarbital, 60 mg/kg i.p.). Following tracheostomy, the left jugular vein and both femoral arteries were catheterized with PE-50 tubes (Clay Adams, Parsippany, NJ, USA). Blood pressure was recorded continuously through the right femoral artery, and the heart rate was calculated from blood pressure recordings. The left ventricle was catheterized through the right carotid artery with a PE-50 tube. At least 30 minutes elapsed after surgical preparation.

We used 15 ± 3 μm microspheres labeled with cobalt-57 (New England Nuclear, Dreieich, West Germany); 60 to 80,000 spheres suspended in 20% dextran solution + 0.01% polysorbate 80 (Twee 80) were injected into the left ventricle within 10 to 15 seconds. The catheter was then flushed with isotonic saline solution. Reference blood samples were collected through the left femoral artery for 90 seconds at 0.6 ml/min with a Sage pump (Cambridge, MA, USA) just before and after microsphere injection. At the end of the experiments, rats were killed by i.v. injection of pentobarbital. The position of the catheter within the left ventricle was checked. Kidneys and heart were removed, weighed, and counted. An LKB-Wallac 1282 gamma counter (LKB, Orsay, France) was used to determine the radioactivity injected into the rat, collected in the reference sample, and present in the various organs. Cardiac index (in ml/min/kg body weight) was calculated from the amount of radioactivity injected and the radioactivity found in the reference sample. Regional blood flows (in ml/min/g) were calculated from radioactivity measured in organs and that found in the femoral reference sample. For calculations, blood density was considered 1.06. The fraction of cardiac output distributed to the kidneys was calculated from the radioactivity injected and that found in both kidneys. Adequate mixing of spheres was assessed from symmetry in radioactivity in the two kidneys. Experiments in which the difference between the kidneys exceeded 20% were not taken into account.

Experiments in Rats Fed a Normal Sodium Diet

Pressor responsiveness was studied in unanesthetized, chronically catheterized rats. It was tested after bolus i.v. injections of Ang II (Hypertensin, CIBA), 25, 50, 100, and 200 ng/kg; NE (levaterenol bitartrate, Sigma), 200, 400, and 800 ng/kg; and AVP (Calbiochem), 10, 40, and 80 ng/kg body weight. In three groups of Wistar rats (8, 8, and 9 rats), pressor responses were measured before and 2 hours after administration of RU 486 at a dosage of 10, 20, or 100 mg/kg/day for 5 days. Pressor responsiveness was also studied in eight Wistar rats before and after administration of a glucocorticoid agonist, RU 26988,11β,17β-dihydroxy-17α(1-propynyl)androsta-1,4,6-trien-3-one, by stomach tube, at 10 mg/kg/day for 3 days. In another group of eight rats, RU 486, at 20 mg/kg/day, was administered first alone for 2 days, then in combination with RU 26988 (10 mg/kg/day) for 3 days.

Cardiac output and distribution were measured in...
rats pretreated by vehicle or RU 486 (20 mg/kg/day for 5 days). Measurements were performed in the basal state in 25 rats and after a 20-minute i.v. perfusion of NE (10 μg/min/kg; n = 21 rats), Ang II (5 μg/min/kg; n = 24 rats), or AVP (100 ng/min/kg; n = 29 rats). Microspheres were injected at the end of the infusion periods.

**Experiments in Rats Fed a Low Sodium Diet**

In all rats fed a low sodium diet, RU 486 was administered at a dosage of 20 mg/kg/day for 5 days unless otherwise specified. Five groups were studied.

**Group 1**

Basal studies were conducted in Group 1. Sixteen chronically catheterized rats were treated with either vehicle (n = 8) or RU 486 (n = 8). MBP and body weight were measured daily. In 16 rats maintained in metabolic cages, daily urinary sodium excretion, sodium intake, and sodium balance were determined before, during, and after RU 486 administration. Urinary sodium was measured by flame photometry. SBP was measured. Eight additional rats received RU 486 at 10 mg/kg/day.

**Group 2**

In 24 unanesthetized and chronically catheterized rats, RU 486 was administered for 5 days and corticosterone, the major glucocorticoid in rats, was superimposed during the 2 final days to overcome the antiglucocorticoid effect of RU 486. Corticosterone (Sigma) in 0.1% carboxymethylcellulose + 0.1% polysorbate 80, was injected subcutaneously at doses of 0.5 (n = 8 rats), 1 (n = 8 rats), and 2 mg/kg/day (n = 8 rats). MBP and body weight were measured. The results of corticosterone experiments were compared with those of RU 486 interruption after a 3-day administration (n = 8 rats).

**Group 3**

Plasma renin concentration and plasma angiotensinogen level were measured by radioimmunoassays in rats receiving either vehicle (n = 10 rats) or RU 486 (n = 10 rats). Blood was collected by decapitation. Twenty rats fed a normal sodium diet were submitted to similar experimental procedures.

**Group 4**

Thirteen Wistar rats were prepared with chronic vascular and urinary bladder catheterization as described by Gellai and Valtin. Inulin (Inutest; Laevosan, Linz, Austria) and p-aminophippurate (PAH; BDH Chemicals, Poole, England) in 5% dextrose solution (to avoid sodium administration) were infused at a rate of 8 μl/min/100 g. Renal clearances were measured by standard procedures; each value represents the mean of four consecutive 20-minute urine collection periods. Conscious rats were studied before and after a 5-day administration of vehicle (n = 5) or RU 486 (n = 8). Glomerular filtration rate (GFR), effective renal blood flow (ERBF), and renal vascular resistance were calculated from inulin clearance, PAH clearance/1 - hematocrit, and MBP/ERBF, respectively.

**Group 5**

Twenty-seven rats received either vehicle (n = 13) or RU 486 (n = 14) and were anesthetized and prepared for microsphere measurements as already described.

**Statistical Analysis**

Student's t tests were used for comparison between groups. For comparison between repeated measures, variance analysis and Dunnett's method were used. Means ± SEM are presented.

**Results**

**Rats Fed a Normal Sodium Diet**

Basal MBP in the various groups of rats is shown in Table 1. RU 486 alone did not significantly alter basal blood pressure. In contrast, the glucocorticoid agonist RU 26988 induced an increase in blood pressure that was inhibited by RU 486 administration (see Table 1). Pressor responsiveness to NE in normal unanesthetized rats is depicted in Figure 1A. It was not significantly altered by treatment with RU 486, at 10 mg/kg/day for 1, 3, or 5 days. There was a slight decrease in pressor response on Days 3 and 5 for the highest dose. At 20 mg/kg/day, RU 486 depressed pressor responsiveness on Day 5 for all NE doses tested. The dose-response curve was shifted to the right (see Figure 1A). At 100 mg/kg/day, RU 486 induced a slight increase in pressor responsiveness on Day 5.

Similar results were obtained with Ang II. At the low dose, RU 486 did not significantly modify pressor responsiveness. At 20 mg/kg/day, it depressed pressor responsiveness, mainly after 5 days of treatment. At 100 mg/kg/day, RU 486 induced a tendency toward increased pressor responsiveness that was significant only for the high doses of Ang II (Figure 1B).

In contrast with results obtained with NE and Ang II, pressor responses to AVP were not greatly affected by RU 486 (Figure 1C). No effect was seen at 10 mg/kg/day. At 20 mg/kg/day, a slight decrease was observed, but only after 5 days of administration and only for the highest AVP dose. At 100 mg/kg/day, pressor responses were slightly increased after 5 days.

Administration of the glucocorticoid agonist RU 26988 increased pressor responses to NE, Ang II, and AVP. This effect appeared rapidly after 1 day of administration and was further augmented after 3 days (Figure 2). In contrast, preceding and concomitant treatment by RU 486 abolished or even slightly reversed glucocorticoid-induced pressor hyperresponsiveness to the three vasoactive substances (see Figure 2).

The results of microsphere experiments performed in anesthetized rats are summarized in Table 2. Pre-treatment with RU 486 at 20 mg/kg/day did not alter basal blood pressure, heart rate, cardiac index, or heart and kidney blood flows. NE infusion increased MBP significantly less in RU 486-pretreated anesthetized rats than in controls, confirming data obtained in conscious rats. Cardiac index measured during NE infusion was not significantly different in the two groups.
Total peripheral vascular resistance was slightly lower in RU 486-treated rats, but the difference was not significant when compared with controls. Renal blood flow was not different in the two groups. Heart blood flow increased similarly in both groups.

Ang II infusion induced an increase in MBP that was clearly higher in controls than in RU 486-treated rats (see Table 2). Cardiac index was not different in the two groups. Total peripheral vascular resistance was slightly lower in RU 486-treated rats, but the difference did not achieve statistical significance. Renal blood flow was decreased by Ang II infusion. The decrease was significantly attenuated by RU 486 pretreatment. Renal vascular resistance increased significantly less in RU 486-treated rats than in controls (see Table 2). Ang II decreased the fraction of cardiac output delivered to the kidneys. This fraction was better preserved in RU 486–treated rats than in controls (9.8 ± 0.7 vs 7.0 ± 0.2%, p<0.001). Heart blood flow was increased similarly in vehicle-treated and RU 486–treated rats.

AVP infusion led to identical increases in MBP in vehicle-treated and RU 486–treated rats (see Table 2). This result was similar to that obtained in unanesthetized rats. AVP administration depressed heart rate and cardiac output, but these effects were not significantly different in the two groups of rats. Cardiac index was slightly lower and total peripheral vascular resistance slightly higher in RU 486–treated rats. Renal blood flow was not altered. Intestinal vascular resistance was significantly increased in AVP-treated rats compared with controls (99.1 ± 5.4 mm Hg·min⁻¹·mm⁻²; n = 7), but the increase did not differ in vehicle-treated and RU 486–treated rats (169.2 ± 19.0 and 194.8 ± 29.5 mm Hg·min⁻¹·mm⁻², respectively).

### Rats Fed a Low Sodium Diet

#### Group 1

Administration of RU 486 for 5 days induced a progressive fall in MBP of approximately 20 mm Hg (from 112.9 ± 1.3 to 92.3 ± 1.7 mm Hg; see Table 1). In the rats maintained in metabolic cages (Figure 3), SBP decreased similarly, whereas growth rate and urinary sodium excretion were not different from those found in vehicle-treated rats. In addition, sodium and potassium balance (data not shown) was not significantly affected by RU 486 treatment. After treatment was stopped, SBP returned to basal values within 2 days without any change in the other measured parameters (see Figure 3). At 10 mg/kg/day, RU 486 did not decrease SBP, except for a slight and transient effect on Day 1 (see Table 1).

#### Group 2

Corticosterone, at 0.5 mg/kg/day, did not antagonize the hypotensive effect of RU 486; in this group, MBP decreased from 121.9 ± 3.3 to 100.5 ± 2.9 mm Hg from Day 0 to Day 5 (Figure 4). In contrast, corticosterone, at 2 mg/kg/day, restored MBP to basal levels within 2 days but impaired growth rate, which is indicative of glucocorticoid excess. At 1 mg/kg/day, corticosterone restored MBP toward basal values, but less completely than did the higher dose. Growth rate was altered slightly (see Figure 4). The effect of corticosterone mimicked that resulting from RU 486 interruption after 3 days of treatment: MBP was decreased to 107.7 ± 2.5 mm Hg on Day 3 and then returned to 120.3 ± 1.7 mm Hg on Day 4 and to 124.1 ± 1.5 mm Hg on Day 5 (p<0.01 vs Day 3, by Dunnett’s method). Restoration of blood pressure was, however, more rapid than that observed after corticosterone administration.

#### Group 3

Plasma renin concentration and plasma angiotensinogen levels were not significantly modified by RU 486 treatment. As expected, plasma renin concentration was increased by low sodium intake (Table 3).

#### Group 4

Administration of RU 486 decreased MBP without altering heart rate (Table 4), as in the other series of
FIGURE 1. Pressor responses to norepinephrine (A), Ang II (B), and arginine vasopressin (AVP; C) in unanesthetized male Wistar rats. Rats received 10, 20, or 100 mg/kg/day of RU 486. They were studied first in the basal state (control), then after 1, 3, and 5 days of RU 486 administration. The increase in mean blood pressure is given in ordinates. The dose administered is given in abscissa (log scale).

experiments. During the clearance periods, urine flow rate and sodium excretion did not differ before and after RU 486 treatment. GFR measured from inulin clearance was unchanged, whereas PAH clearance increased slightly but not significantly. Renal vascular resistance decreased during RU 486 administration \( (p<0.01, \text{ by paired } \text{t} \text{ test}) \), and filtration fraction fell slightly but not significantly (see Table 4). In control rats, renal function was unchanged after 5 days of vehicle administration (see Table 4).

Group 5

The microsphere experiments produced the following results. MBP was significantly lower in RU 486-treated rats: 102.1 ± 1.7 vs 127.7 ± 3.2 mm Hg in vehicle-treated rats \( (p<0.001, \text{ by } \text{t} \text{ test}) \). Cardiac index increased significantly \( (236.3 ± 12.1 \text{ vs } 204.6 ± 5.7 \text{ ml/min/kg}; p<0.05) \). Renal blood flow increased slightly but not significantly in RU 486-treated rats \( (4.16 ± 0.48 \text{ vs } 3.62 ± 0.53 \text{ ml/min/g kidney weight}) \). Total peripheral and renal vascular resistance decreased significantly by 29% \( (p<0.001) \) and 25% \( (p<0.01) \), respectively, during RU 486 administration.

Discussion

Pressor responsiveness to NE and Ang II was blunted in conscious and in anesthetized rats by an anti-glucoorticoid steroid compound, RU 486 (20 mg/kg/day). This effect was independent of a change in cardiac output and was related to the dose of RU 486 used. At a lower dose (10 mg/kg/day), RU 486 did not affect vascular responsiveness. These results suggest that endogenous glucocorticoids increase vascular reactivity to NE and Ang II and that this action is inhibited by RU 486.

In addition, chronic low sodium intake stimulates the renin-angiotensin system and sympathetic activity, which contributes to the maintenance of blood pres-
Glucocorticoids participate in this mechanism in rats by maintaining adequate vascular sensitivity to NE and Ang II. Indeed, the AG RU 486 decreased total peripheral vascular resistance and blood pressure in sodium-restricted rats, whereas it did not affect blood pressure levels in rats fed a normal sodium diet.

The effect of RU 486 in sodium-restricted rats was dose-dependent and unrelated to any antimineralocorticoid properties. In vitro, RU 486 is devoid of mineralocorticoid activity. In vivo, urinary sodium excretion, sodium balance, plasma renin concentration, and body weight were not altered by RU 486 administration. In addition, administration of corticosterone, the major glucocorticoid in rats, superimposed on RU 486, restored blood pressure approximately to basal levels (although it was difficult to determine the dose of corticosterone necessary to overcome antiglucocorticoid activity without inducing glucocorticoid excess). Corticosterone induced slight mineralocorticoid activity, but it appears to be 1000 times less active than aldosterone, and correction of blood pressure by corticosterone was not accompanied by a positive sodium balance, as estimated from changes in body weight.

The blood vessels of the normal kidney are remarkably sensitive to Ang II. Present results show that RU 486 strikingly blunts the vasoconstrictive effects of infused Ang II on renal circulation. Renal blood flow, renal vascular resistance, and renal fraction of cardiac output were clearly higher in RU 486-treated than in control rats. However, in the basal state (i.e., in the absence of Ang II infusion, in a condition where only endogenous Ang II was involved), RU 486 administration had no effect on renal circulation (see Table 2).

In contrast, during chronic low sodium intake, where Ang II formation is enhanced, RU 486 led to a striking fall in renal vascular resistance in both unanesthetized and anesthetized rats. Experiments in conscious rats showed that RU 486 does not alter GFR and tends to increase renal blood flow and therefore to decrease filtration fraction. Endogenous Ang II during dietary NaCl restriction is thought to decrease glomerular plasma flow rate and ultrafiltration coefficient (both mechanisms tend to depress GFR) and preferentially increase efferent, postglomerular vascular resistance (thus augmenting glomerular capillary pressure and preserving GFR). The resulting effect on GFR depends on the balance between these various mechanisms, which were not analyzed in detail in the present study. Endogenous glucocorticoids may magnify intrarenal actions of Ang II, whereas an antiglucocorticoid such as RU 486 inhibits them. The renal hemodynamic changes observed in the present experiments may result from blunting of the intrarenal effects of Ang II. Blunting of the renal adrenergic activity may also be involved, but there is no good evidence that acute renal denervation directly influences glomerular hemodynamics in normal rats. The physiological modulation exerted by endogenous glucocorticoids cannot be compared with the augmentation in renal blood flow and GFR produced by massive doses of corticosteroids.

Angiotensinogen synthesis by the liver is stimulated by glucocorticoids and depressed by adrenalectomy. In vitro experiments have shown that RU 486 inhibits the production of angiotensinogen from rat liver cells stimulated by hydrocortisone but does not change the basal rate of angiotensinogen synthesis. Our data are in accordance with the latter results: No significant change in plasma angiotensinogen concentration was induced by RU 486. The lack of effect may be ascribed to the large pool of circulating angiotensinogen, to the short period of administration of RU 486, or to a glucocorticoid-independent mechanism that may control the basal rate of angiotensinogen production.

Pressor responses to AVP were not altered by pretreatment with RU 486. This finding may indicate that endogenous glucocorticoids are not involved in modulating pressor responsiveness to AVP. However, as has long been demonstrated, AVP decreases heart rate and cardiac output. The fall in cardiac output leads to circulatory adjustments, and no definitive conclusion can be drawn regarding the vascular interactions of AVP and glucocorticoids.

Exogenous glucocorticoid at high doses potentiated...
FIGURE 2. Pressor responses to norepinephrine (A), Ang II (B), and arginine vasopressin (AVP; C) in unanesthetized Wistar rats. Rats were studied in the basal state (control). A first group of rats (upper panel) received a glucocorticoid (G), RU 26988; rats were studied after 1 and 3 days of RU 26988 treatment. A second group of rats (lower panel) received both an antiglucocorticoid (AG), RU 486, and G and were tested after 1 and 3 days of G administration.

pressor responses to NE, Ang II, and AVP; this potentiation was prevented by antiglucocorticoid pretreatment. Increased vascular responsiveness was also elicited by a high dose (100 mg/kg/day) of RU 486 alone, which most probably exerted an agonistic glucocorticoid action. The effects of exogenous glucocorticoids administered at high pressor doses can hardly be compared with those of endogenous glucocorticoids, which are released in small amounts and probably have no detectable effect on basal blood pressure. This is probably relevant in explaining the discrepancy in pressor responsiveness to AVP, which was unaltered by antiglucocorticoid but enhanced by exogenous glucocorticoid.

Experimental results have suggested that glucocorticoids, by their permissive effect on other hormones such as the catecholamines, maintain cardiac contractility and vascular tone. 23-26 In adrenalectomized rats 5-7

TABLE 2. Hemodynamic Data in Anesthetized Wistar Rats Given Norepinephrine, Ang II, or Vasopressin and Pretreated with Either Vehicle or RU 486 (20 mg/kg/day for 3 days)

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>Body weight (g)</th>
<th>Basal MBP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>ΔMBP (mm Hg)</th>
<th>ΔHR (beats/min)</th>
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<tr>
<td>Vehicle (n=13)</td>
<td>259±6.3</td>
<td>117±2.0</td>
<td>421±7.8</td>
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<td>—</td>
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<tr>
<td>RU 486 (n=12)</td>
<td>249±4.8</td>
<td>118±1.9</td>
<td>417±10.8</td>
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<td>—</td>
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<tr>
<td>NE, 10 μg/kg/min</td>
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<tr>
<td>Vehicle (n=10)</td>
<td>240±10</td>
<td>130±4.3</td>
<td>425±13.6</td>
<td>25.6±3.0</td>
<td>115±14.6</td>
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<tr>
<td>RU 486 (n=11)</td>
<td>238±13.7</td>
<td>130±4.1</td>
<td>414±10.4</td>
<td>14.2±1.7*</td>
<td>111±6.7</td>
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<td>Ang II, 5 μg/kg/min</td>
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<td>Vehicle (n=12)</td>
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<td>120±3.8</td>
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<td>34±7.4</td>
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<td>RU 486 (n=12)</td>
<td>250±3.2</td>
<td>127±3.8</td>
<td>445±7.3</td>
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<td>AVP, 100 ng/kg/min</td>
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<tr>
<td>Vehicle (n=15)</td>
<td>267±4.8</td>
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<td>425±9.1</td>
<td>29.1±2.4</td>
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<tr>
<td>RU 486 (n=14)</td>
<td>268±4.3</td>
<td>121±3.6</td>
<td>431±12.1</td>
<td>30.9±1.9</td>
<td>−21±10</td>
</tr>
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</table>

Values are means ± SEM. MBP = mean blood pressure; HR = heart rate; Δ = variation from basal state to NE or Ang II infusion; CI = cardiac index; TPVR = total peripheral vascular resistance; RBF = renal blood flow; RVR = renal vascular resistance; CO = cardiac output; NE = norepinephrine.

*p<0.01, †p<0.001, compared with control values (by Student's t test).
treated successfully with RU 486 at high doses. With therapy, all biochemical glucocorticoid-sensitive parameters normalized, the somatic features of hypercortisolism were ameliorated, and mean arterial blood pressure returned to normal. 28

The present data provide no further insight into the mechanism through which glucocorticoids (and the antiglucocorticoids) modulate vascular reactivity. Two hypotheses may be considered. First, glucocorticoids are known to inhibit the synthesis of prostaglandins, including prostacyclin, by inducing lipocortin, a phospholipase A2 inhibitory protein. 29 RU 486 administration is expected to abolish inhibition due to endogenous glucocorticoids. It has recently been demonstrated that glucocorticoids inhibit spontaneous or stimulated prostacyclin synthesis by rat aorta. 30, 31 In in vitro experiments, RU 486 blocks the inhibitory action of hydrocortisone. 32 In ex vivo experiments, pretreatment of rats by RU 486 magnifies the A23187 calcium ionophore and Ang II stimulation of vascular prostacyclin production. 33 There is also good evidence from in vitro and in vivo experiments that Ang II 33-35 and NE 35-36 (as well as AVP 37-38) stimulate vascular release of prostacyclin, which in turn blunts their vasoconstrictive activity. It may therefore be expected that glucocorticoids, by inhibiting production of vasodilator prostacyclin, 34, 39 and antiglucocorticoids, by potentiating this production, respectively enhance and attenuate the pressor and vasoconstrictive effects of Ang II and NE. Additional information is needed, however, to prove or disprove such a hypothesis. Indeed, RU 486 at a high dose (100 mg/kg/day) increased pressor responses to Ang II and NE and magnified A23187 stimulation of prostacyclin vascular synthesis, 31 as did RU 486 at a lower dose (20 mg/kg/day). In contrast, this dose blunted pressor responsiveness. High doses of RU 486 possibly exert additional, nonspecific effects that counterbalance the action on prostacyclin synthesis.

<table>
<thead>
<tr>
<th>CI (ml/min/kg)</th>
<th>TPVR (mm Hg·ml⁻¹·min⁻¹·kg⁻¹)</th>
<th>RBF (ml/min/g)</th>
<th>Renal fraction of CO (%)</th>
<th>RVR (mm Hg·ml⁻¹·min⁻¹·g⁻¹)</th>
<th>Heart blood flow (ml/min/g)</th>
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<tr>
<td>229.7±13.2</td>
<td>0.53±0.03</td>
<td>3.65±0.24</td>
<td>14.3±0.7</td>
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<td>240.4±13.2</td>
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<td>12.7±0.9</td>
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<td>283.9±7.2</td>
<td>0.55±0.02</td>
<td>3.94±0.28</td>
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<td>42.0±3.9</td>
<td>9.30±0.90</td>
</tr>
<tr>
<td>282.8±14.3</td>
<td>0.52±0.03</td>
<td>3.95±0.26</td>
<td>11.7±0.5</td>
<td>38.5±3.2</td>
<td>7.23±0.54</td>
</tr>
<tr>
<td>266.7±10.6</td>
<td>0.59±0.03</td>
<td>2.14±0.07</td>
<td>7.0±0.2</td>
<td>71.5±2.6</td>
<td>7.38±0.76</td>
</tr>
<tr>
<td>259.7±12.3</td>
<td>0.56±0.03</td>
<td>2.93±0.10†</td>
<td>9.8±0.7†</td>
<td>49.1±1.9†</td>
<td>7.03±0.52</td>
</tr>
<tr>
<td>192.5±14.1</td>
<td>0.84±0.07</td>
<td>3.30±0.35</td>
<td>14.2±1.8</td>
<td>54.9±7.5</td>
<td>5.07±0.88</td>
</tr>
<tr>
<td>173.1±12.4</td>
<td>0.93±0.07</td>
<td>3.45±0.21</td>
<td>17.2±1.3</td>
<td>46.5±4.0</td>
<td>3.48±0.66</td>
</tr>
</tbody>
</table>
Second, glucocorticoids may induce changes in receptor affinity or number, in the contractile machinery, or in the stimulus-contraction coupling in the smooth muscle cells. Other steroids, such as estrogens, have been shown to modulate the number of Ang II and AVP receptors. Glucocorticoids are also known to induce changes in catecholamine metabolism, which could in turn interfere with vascular reactivity. Schönig et al. have shown, however, that neither changes in neuronal uptake nor extraneuronal metabolism of NE was responsible for the enhanced sensitivity of vascular smooth muscle after corticosterone.

Finally, glucocorticoids stimulate renal Na\(^+\)-H\(^+\) exchange activity. A similar system is present in vascular smooth muscle cells. It has not been reported whether glucocorticoids contribute to the regulation of this system or whether the resulting changes in Na\(^+\) and H\(^+\) content in vascular smooth muscle induce changes in vascular reactivity.

In conclusion, administration of the antiglucocorticoid compound RU 486 to the normal rat revealed that endogenous glucocorticoids increase vascular reactivity and therefore contribute to blood pressure regulation.

### Table 3. Plasma Renin Concentration and Angiotensinogen Level in Rats Fed a Low or Normal Sodium Diet and Treated with Either Vehicle or RU 486

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low sodium</th>
<th>Normal sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>RU 486</td>
</tr>
<tr>
<td></td>
<td>((n = 10))</td>
<td>((n = 10))</td>
</tr>
<tr>
<td>Plasma renin concentration</td>
<td>118.7 ± 9.0(\ast)</td>
<td>134.1 ± 14.1(\ast)</td>
</tr>
<tr>
<td>Plasma angiotensinogen</td>
<td>1210 ± 40</td>
<td>1095 ± 24</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Plasma renin concentration and plasma angiotensinogen are expressed in nanograms of angiotensin I (Ang I) formed per milliliter of plasma per hour of incubation.

\(\ast p < 0.001\), compared with normal sodium diet values (by Student's \(t\) test).
tion in the rat. This effect was most apparent in conditions where the renin-angiotensin system and sympathetic activity were stimulated, such as in chronic low sodium intake. Glucocorticoids also participated in the control of renal hemodynamics, in part by modulating Ang II effects.

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