SUMMARY The early phase of hypertension induced in rats by a glucocorticoid agonist RU 26988 was studied. Systolic blood pressure increased by 35 mm Hg. Water and sodium urinary excretion increased transiently, and plasma volume decreased. Total and ouabain-sensitive sodium efflux, as well as rubidium efflux, were enhanced by glucocorticoid administration. Low salt intake did not prevent hypertension. Pretreatment with RU 38486, a steroid with antiglucocorticoid properties, largely prevented the rise in blood pressure (+10 mm Hg) and suppressed transient natriuresis and the decrease in plasma volume. Changes in total and ouabain-sensitive sodium efflux were completely prevented, whereas changes in rubidium efflux were only partly reversed. Similarly, administration of progesterone, a steroid with antiglucocorticoid effects, prevented glucocorticoid hypertension (+11 mm Hg) and vascular ionic changes. In contrast administration of RU 28318, an antimineralocorticoid agent, was without effect on glucocorticoid hypertension (+38 mm Hg). Progesterone or RU 38486 administered after glucocorticoid also decreased blood pressure. Present data indicate that glucocorticoid hypertension may be prevented or reversed in its early phase by steroid drugs with antiglucocorticoid properties. These drugs also appeared to prevent the sodium and rubidium flux abnormalities induced by glucocorticoid. We suggest that activation of the vascular glucocorticoid receptors may be involved in the pathophysiology of glucocorticoid hypertension. (Hypertension 7: 292-299, 1985)

KEY WORDS  • hypertension  • glucocorticoid  • antiglucocorticoid  • progesterone  • Na⁺-K⁺-ATPase

GLUCOCORTICOID excess in the rat induces a rapid increase in blood pressure. Such hypertension has been observed with glucocorticoids almost completely devoid of mineralocorticoid activity.1-3 Glucocorticoid-induced hypertension has been attributed to changes in the various systems — renin-angiotensin,1 catecholamines,2 and plasma volume3 — involved in blood pressure control. Receptor sites for steroids recently have been demonstrated in vascular tissues.4 It has been hypothesized that the vascular ionic changes induced by mineralocorticoids may contribute to mineralocorticoid hypertension.5-8 Vascular binding sites for glucocorticoid have been demonstrated,9,10 but the ionic changes induced by glucocorticoid have not been analyzed in detail.

We therefore initiated a study of the in vivo effects of RU 26988 in the rat. RU 26988 is a specific glucocorticoid receptor agonist that exhibits high affinity for glucocorticoid receptor sites and does not compete with aldosterone for the mineralocorticoid receptor.11,12 We attempted to antagonize glucocorticoid-induced hypertension by administration of an antimineralocorticoid (RU 28318) and steroid derivatives known to bind competitively at the glucocorticoid receptor — progesterone and RU 38486. The latter steroid has mainly antiprogestrone properties; in vitro studies have also shown antiglucocorticoid activity.13,14 Lastly, we investigated the ionic changes induced by glucocorticoid and antiglucocorticoids on the rat tail artery after in vivo administration of the steroid drugs.

Material and Methods

Studies were performed in Wistar rats that were approximately 8 weeks old with initial body weights ranging from 150 to 250 g. The animals were housed in individual metabolic cages. They received water ad
dimethylaminophenyl)-17a-(prop-1-ynyl)-estra-4,9-dien-3-one] is a steroid with mainly antiprogesterone properties; in addition, it exerts antiglucocorticoid activity. It was administered at a dose of 100 mg/kg/day by stomach tube. Progesterone in oil was administered in two intramuscular injections at a dose of 50 mg/kg/day. RU 28318 [17β-hydroxy-3-oxo-7α-propyl-(17α)-pregn 4-ene, 21 potassium carboxylate], a mineralocorticoid antagonist, was administered at a dose of 5 mg/kg/day.

The following experimental groups were studied:

**Group I.** RU 26988 was administered for 3 days to 17 rats with normal salt intake (Group Ia). The drug was also administered to six rats on a low-sodium diet (Group Ib). The animals were studied before, during, and after RU 26988 administration.

**Group II.** RU 38486 alone was administered for 2 days and then was given with RU 26988 for 3 days (8 rats on a normal-sodium diet). In five rats only RU 38486 was administered for 5 days.

**Group III.** Progesterone was first administered for 2 days, then was given with RU 26988 for 3 days (14 rats with normal salt intake). In five additional rats only progesterone was administered for 5 days.

**Group IV.** RU 28318 was administered for 2 days, then was given with RU 26988 for 3 days in 10 rats on a normal-sodium diet.

**Group V.** Hypertension was first induced by glucocorticoid administration (RU 26988), then on Day 3 when hypertension was documented RU 38486 (Group Va; 7 rats) or progesterone (Group Vb; 8 rats) was administered concomitantly with RU 26988 for 3 days. These experiments were made in rats with normal sodium intake. The results were compared with those obtained in rats on normal-sodium diets treated by RU 26988 alone for 5 days (Group Vc; 10 rats).

Ex vivo studies were performed in the following animals: (1) Twenty rats received RU 26988 as for Group Ia rats. (2) Twenty-one rats received both RU 26988 and RU 38486 for 3 days. (3) Twenty-one rats received both RU 26988 and progesterone for 3 days. In the latter two groups, it was verified that blood pressure results were identical to those obtained in rats of Groups II and III (data not shown). (4) Twenty-one rats received only RU 38486, and eighteen rats received progesterone only.

Student’s *t* tests were used in statistical analysis for comparison between different groups. For comparison between repeated measures, analysis of variance and Dunnnett’s method were used.

**Results**

**In Vivo Studies**

**Group I**

The administration of RU 26988, a glucocorticoid agonist, resulted in a prompt rise in SBP (approximately 35 mm Hg) (Figure 1). Body weight decreased slightly (—10 g). On Day 1, urine water and sodium excretion increased transiently. Cumulative sodium balance was negative (—850 μmol on Day 3). Plasma volume (expressed in milliliters per 100 grams of body...
weight, BW) was decreased on the third day of glucocorticoid administration (from 4.42 ± 0.09 to 4.28 ± 0.08 ml/100 g BW). After RU 26988 administration was stopped, blood pressure returned rapidly to a normal level, and growth rate was restored to normal. Urine sodium excretion was depressed transiently, then positive sodium balance was reattained. Plasma volume returned to basal values (Figure 1).

In rats on a low-sodium diet, glucocorticoid administration induced a similar rise in SBP (from 109 ± 4.3 to 142 ± 2.5 mm Hg). Urinary sodium excretion increased dramatically, from 5.8 to 500 μmol/24 hours (on Day 3). Cumulative sodium balance was —1000 μmol on Day 3. Plasma volume did not change appreciably (from 4.3 ± 0.06 to 4.26 ± 0.08 ml/100 g BW). These changes reverted to baseline levels after stopping the glucocorticoid administration.

Group II

Administration of antiglucocorticoid (RU 38486) alone for 5 days did not consistently modify body weight or urine water and sodium excretion (Figure 2). The SBP increased slightly from the basal mean value of 106 ± 1.7 to 118 ± 2.5 mm Hg (Day 5), whereas the other parameters measured (including plasma volume) did not change appreciably.

The antiglucocorticoid drug prevented the increase in SBP induced by the glucocorticoid agonist RU 26988 (Figure 3). A slight rise in blood pressure was observed, which averaged 10 mm Hg on Day 5. Weight loss was not prevented by the antiglucocorticoid. In contrast, the increase in urine sodium excretion was completely prevented, and even natriuresis dropped on Days 4 and 5. This decrease probably was due to low food and sodium intake as sodium balance remained positive in these rats throughout the experimental period. Mean cumulative sodium balance on Day 5 (calculated from Day 3 to Day 5) was +550 μmol. Plasma volume did not decrease substantially. After drug administration was stopped, blood pressure returned to basal values, growth rate resumed, urine sodium excretion and sodium intake remained low, and plasma volume was unchanged (Figure 3).

Group III

Progesterone administration alone had no appreciable effect on blood pressure, weight, plasma volume, or urinary sodium excretion. When glucocorticoid was added (Figure 4) progesterone blunted the rise in SBP: SBP rose slightly, from 109 ± 1.8 to 115 ± 2.4 mm Hg (Day 5). The protective effect was similar to that afforded by the antiglucocorticoid compound. In con-

Figure 1. Changes in SBP, weight, diuresis, natriuresis, and plasma volume in Group Ia rats (n = 17; normal sodium intake) before, during, and after administration of the glucocorticoid RU 26988. Values are means ± SEM. * = p < 0.05 versus controls (Dunnett's method).

Figure 2. Changes in SBP, weight, diuresis, natriuresis, and plasma volume in Group II rats (n = 5) before, during, and after administration of the antiglucocorticoid RU 38486. * = p < 0.05 versus controls (Dunnett's method).
Contrast, progesterone administration did not prevent and even magnified the transient natriuretic effect of RU 26988 (3662 ± 165, Group III, versus 2992 ± 106 μmol/24 hr, Group I; p < 0.01, Student's t test). In Group III rats urinary sodium excretion increased slightly (p < 0.05, Dunnett's method) on Day 2 when progesterone alone was administered. On Days 4 and 5 (Figure 4) urine sodium excretion dropped, which contrasts with the data obtained in Group I (Figure 1). On Day 5 the mean cumulative sodium balance was −800 μmol. Plasma volume did not change significantly on Day 5, but the basal value (Day 2) was lower than in Group I (4.05 ± 0.08 versus 4.42 ± 0.09 ml/100 g BW). This decrease was possibly related to the natriuretic effect of progesterone.

Group IV

Administration of the antimineralocorticoid alone did not change SBP (Figure 5). Urine water and sodium excretion increased slightly but not significantly in the rats on a normal-sodium diet. Glucocorticoid administration resulted in a rapid and more pronounced rise in SBP, from 113.4 ± 2.9 to 151 ± 3.5 mm Hg, and a weight loss. A transient increase in urine water and sodium excretion persisted and was followed by an abrupt drop in urine sodium excretion, as in Group III. On Day 5, cumulative sodium balance was close to 0. Surprisingly, plasma volume increased on Day 5 (Figure 5). It returned to basal value on Day 11, as did blood pressure.

Group V

Glucocorticoid administration for 5 consecutive days induced an increase in SBP that was maximal on Day 2 and subsequently remained stable (Figure 6). In Groups Va and Vb, after hypertension was induced the antagonist, either RU 38486 or progesterone, was administered for 3 days (Figure 6). This resulted in a fall in blood pressure that was slightly more pronounced with RU 38486. Urine sodium excretion was not modified (except on Day 1 when the transient rise in urine sodium excretion occurred). On Day 5 cumulative sodium balance was 1250 μmol and 250 μmol in Groups Va and Vb respectively.

Ex Vivo Studies

Results of ex vivo studies are summarized in Table 1. The glucocorticoid agonist RU 26988 increased to-
FIGURE 5. Changes in SBP, weight, diuresis, natriuresis, and plasma volume in Group IV rats (n = 10) before, during, and after administration of the antimineralocorticoid RU 28318 and then RU 26988. * = p < 0.05 versus controls (Dunnett's method); * = p < 0.05 versus Group I (Student's t test).

The antiglucocorticoid drug RU 38486 decreased total sodium efflux and passive sodium permeability, but did not alter sodium pump activity and rubidium efflux. The concomitant administration of RU 26988 and RU 38486 reversed some changes induced by RU 26988 and restored total sodium efflux and sodium pump activity to control values. Passive sodium permeability was, however, significantly depressed when compared with controls (p < 0.05). This finding might be related to the effect of RU 38486. The rubidium efflux was depressed when compared with the results of administration of RU 26988 alone, but was slightly higher than in controls. Progesterone administration decreased total sodium efflux by depressing both passive permeability and sodium pump activity. The rubidium efflux was slightly enhanced. The concomitant administration of RU 26988 and progesterone strikingly depressed total sodium efflux, passive permeability, and sodium pump activity below control values. The rubidium efflux in this group was decreased when compared with that of RU 26988-treated rats.

Discussion

The present results indicate that in the rat the early phase of glucocorticoid hypertension can be prevented or reversed by steroids with antiglucocorticoid activ-

Table 1. $^{22}$Na and $^{86}$Rb Efflux from Tail Arteries of Control Rats and Rats Treated with Glucocorticoid Agonists, Antagonists, or Both

<table>
<thead>
<tr>
<th>Efflux rate</th>
<th>Controls</th>
<th>RU 26988</th>
<th>RU 38486</th>
<th>RU 26988 + RU 3846</th>
<th>Progesterone</th>
<th>RU 26988 + progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total $^{22}$Na efflux (min$^{-1}$)</td>
<td>0.135 ± 0.003*</td>
<td>0.155 ± 0.004*</td>
<td>0.124 ± 0.003*</td>
<td>0.127 ± 0.003</td>
<td>0.107 ± 0.005*</td>
<td>0.110 ± 0.004*</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 11)</td>
<td>(n = 8)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>Ouabain insensitive</td>
<td>0.100 ± 0.003</td>
<td>0.096 ± 0.002</td>
<td>0.086 ± 0.003*</td>
<td>0.089 ± 0.003*†</td>
<td>0.084 ± 0.003*</td>
<td>0.083 ± 0.003†</td>
</tr>
<tr>
<td>Ouabain sensitive</td>
<td>0.035 ± 0.003</td>
<td>0.059* ± 0.003</td>
<td>0.038 ± 0.002</td>
<td>0.038 ± 0.002</td>
<td>0.023 ± 0.003*</td>
<td>0.027 ± 0.004†</td>
</tr>
<tr>
<td>$^{86}$Rb efflux (min$^{-1}$)</td>
<td>0.0103 ± 0.0001</td>
<td>0.0128 ± 0.0004*</td>
<td>0.0099 ± 0.0002</td>
<td>0.0111* ± 0.0002</td>
<td>0.0110 ± 0.0002*</td>
<td>0.0105 ± 0.0002†</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 13)</td>
<td>(n = 11)</td>
<td>(n = 8)</td>
<td>(n = 11)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 versus controls.
†p < 0.05 versus RU 26988.
All values are means ± SEM.
The rise in blood pressure was of rapid onset and by the glucocorticoid agonist, which demonstrates that administration did not prevent the weight loss induced antiglucocorticoid compound suppressed glucocorticoid activity. A slight glucocorticoid agonistic activity of this steroid derivative alone for 5 days produced a reverse in blood pressure. This increase may be explained by a slight glucocorticoid agonistic activity (not found at lower doses) or by the stimulatory effect of the drug on adenocorticotropic hormone and endogenous corticosterone secretion or by both. As previously shown by Philibert and colleagues, the antiglucocorticoid compound suppressed glucocorticoid-induced diuresis as well as natriuresis. RU 38486 administration did not prevent the weight loss induced by the glucocorticoid agonist, which demonstrates that weight loss is not dependent on the transient increase in natriuresis. Similarly, the decrease in plasma volume was not suppressed by RU 38486 administration. This finding is surprising because cumulative sodium balance was positive during concomitant glucocorticoid and antiglucocorticoid administration (Group II).

During recent years, various antiglucocorticoid derivatives have been synthesized and tested in vitro. Few compounds, however, have been shown to exert antiglucocorticoid activity in vivo in intact animals. In addition, they have not been used so far to antagonize the vascular and pressor effect of a glucocorticoid.

Several lines of evidence indicate that RU 38486 exerts a protective effect against glucocorticoid hypertension through its antiglucocorticoid action. The preventive effect was evident despite a similar fall in plasma volume and despite a positive sodium balance. This finding clearly indicates that volume changes are not involved in this hypertension model. A mineralocorticoid antagonist, RU 28318, at a dose that decreased blood pressure in mineralocorticoid hypertension, did not prevent glucocorticoid hypertension. (3) Administration of progesterone, which has antiglucocorticoid activity, prevented glucocorticoid hypertension, as did administration of RU 38486. The kidney, however, was not affected in a similar manner by the two antiglucocorticoid drugs. RU 38486 administration prevented the transient diuresis and natriuresis induced by the glucocorticoid, whereas progesterone, probably through its antimineralocorticoid action, tended to magnify them. Neither drug prevented the weight loss caused by the glucocorticoid.

The antiglucocorticoid drugs RU 38486 and progesterone exerted not only a preventive effect but also a curative effect on glucocorticoid hypertension in its early phase. This effect could not be ascribed to changes in sodium balance. Progesterone has been shown to decrease blood pressure in some hypertensive patients and animals, and it has been suggested that its blood pressure lowering effect may not depend on its antimineralocorticoid properties.

Arterial hypertension induced by the glucocorticoid RU 26988 was accompanied by an increase in total 22Na efflux from vascular smooth muscle that appears to be caused exclusively by a stimulation of the sodium pump. Simultaneously, RU 26988-induced hypertension was characterized by an increase in 86Rb efflux. This latter effect could result from an enhancement of transmembrane permeability to potassium or be secondary to the activation of the sodium pump. Indeed, glucocorticoids have been shown to increase the Na+ - K+-stimulated ATPase activity in various tissues, including the rat kidney and liver and human erythrocytes. Furthermore, Pandini and co-workers found increased activity of the sodium pump in vessels excised from dexamethasone-treated rats. The changes in ionic fluxes from smooth muscle observed during the hypertension induced by RU 26988 may result from the long-term effects of the glucocorticoid. In fact, short-term administration of RU 26988 to adrenalecto-
Hypertension induced by a glucocorticoid is accompanied by an activation of the vascular smooth muscle. It is not presently possible to ascertain whether these changes are a causal factor of hypertension in this animal model.

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