Glucocorticoids potentiate central actions of angiotensin to increase arterial pressure

DEBORAH A. SCHEUER AND ANDREA G. BECHTOLD
Department of Pharmacology, The University of Missouri-Kansas City, Kansas City, Missouri 64108
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Scheuer, Deborah A., and Andrea G. Bechtold. Glucocorticoids potentiate central actions of angiotensin to increase arterial pressure. Am J Physiol Regulatory Integrative Comp Physiol 280: R1719–R1726, 2001.—Experiments were performed to determine if glucocorticoids potentiate central hypertensive actions of ANG II. Male Sprague-Dawley rats were treated for 3 days to 3 wk with corticosterone (Cort). Experiments were performed in conscious rats that had previously been instrumented with arterial and venous catheters and an intracerebroventricular guide cannula in a lateral ventricle. Baseline arterial pressure (AP) was greater in Cort-treated rats than in control rats (119 ± 2 vs. 107 ± 1 mmHg, P < 0.01). Microinjection of ANG II intracerebroventricularly produced a significantly larger increase in AP in Cort-treated rats than in control rats. For example, at 30 ng ANG II, AP increased by 23 ± 1 and 16 ± 2 mmHg in Cort-treated and control rats, respectively (P < 0.01). Microinjection of an angiotensin type 1 receptor antagonist significantly decreased AP (−6 ± 2 mmHg) and heart rate (−26 ± 7 beats/min) in Cort-treated but not control rats. Increases in AP produced by intravenous administration of ANG II were not different between control and Cort-treated rats. Intravenous injections of ANG II antagonist had no significant effects on mean AP or heart rate in control or Cort-treated rats. Therefore, a sustained increase in plasma Cort augments the central pressor effects of ANG II without altering the pressor response to peripheral administration of the hormone.

corticosterone; hypertension; sympathetic nervous system; central nervous system; intracerebroventricular

IT IS WELL ESTABLISHED THAT glucocorticoids are essential for normal control of arterial pressure (15), and there is growing recognition that they participate in the pathogenesis of essential hypertension (5, 27, 38, 43–45). It is known that glucocorticoids influence arterial pressure regulation through multiple peripheral mechanisms, including upregulation of both the sympathetic nervous system and the renin-angiotensin system (31). Both the renin-angiotensin system and the sympathetic nervous system are thought to contribute to the development and maintenance of human hypertension through interrelated peripheral and central mechanisms (30, 39, 41). However, there is no consensus regarding the effects of glucocorticoids on central neural control of the circulation, and the effects of glucocorticoids on central nervous system angiotensin-mediated mechanisms of hypertension are not known. Evidence that glucocorticoids functionally upregulate the sympathetic nervous system includes results from previous studies showing that exogenous administration or endogenous overproduction of glucocorticoids in rats or humans results in exaggerated blood pressure and vascular responses to adrenergic agonists (7, 16, 28, 31, 45). It has also been reported that glucocorticoid treatment increased the magnitude of pressure reduction following ganglionic blockade (22). However, the effect of glucocorticoids on central regulation of sympathetic activity in response to glucocorticoids has been reported (8, 10, 14, 20, 24, 32, 35, 40). The relative importance of changes in sympathetic nerve activity vs. vascular reactivity in the development of glucocorticoid hypertension has not been established.

A role for the renin-angiotensin system in the mechanism of glucocorticoid hypertension has also been demonstrated. Several investigators have reported that intravenous administration of an ANG II antagonist attenuated glucocorticoid-induced hypertension in humans and rats (6, 22, 42). Glucocorticoids have been shown to augment the increase in arterial pressure in response to peripheral (intravenous) administration of ANG II in both rats and humans (22, 31, 47). Glucocorticoids also increase the expression of angiotensin type 1 (AT1) receptors both in the peripheral vasculature and in the central nervous system (1, 4, 31, 36), and they elevate ANG II-converting enzyme (30). In addition, elevated peripheral angiotensinogen has been reported in patients with endogenous overproduction of cortisol and in experimental animals treated with glucocorticoids (21, 22), and elevated central angiotensinogen has been observed in rats (4). Functionally, it has been demonstrated that glucocorticoids potentiate ANG II-induced drinking (13).

ANG II elevates arterial pressure by several mechanisms, as reviewed by Saavedra (30). Peripheral administration of ANG II produces direct and immediate vasoconstriction of arterioles and increases release of
catecholamines by acting presynaptically on sympathetic nerve terminals. In addition, ANG II acts in the central nervous system as a neurotransmitter, elevating sympathetic nerve activity, stimulating vasopressin release, and attenuating the arterial baroreceptor reflex.

The present experiments were performed to test the hypothesis that glucocorticoids potentiate central actions of ANG II to increase arterial pressure. In these experiments, elevations in plasma glucocorticoid concentrations were achieved by implantation of a subcutaneous pellet of corticosterone (Cort) that approximately doubled plasma Cort concentration. After 3–21 days of glucocorticoid treatment, ANG II or an AT1-receptor antagonist was administered into the cerebral ventricles of control and glucocorticoid-treated conscious rats, and changes in arterial pressure and heart rate were recorded. For comparison, the effects of the glucocorticoid treatment on peripheral actions of ANG II and phenylephrine to increase arterial pressure were also determined.

METHODS

These experiments were performed using 58 male Sprague-Dawley rats purchased from either Harlan or Charles River Laboratories. The experiments were performed either at the University of Texas Health Science Center, San Antonio (13 rats) or at The University of Missouri, Kansas City (45 rats). All animals were housed in U. S. Department of Agriculture and American Association for Accreditation of Laboratory Animal Care accredited animal care facilities and were provided food and water ad libitum. The rats were on a normal sodium diet (0.12 mmol/g in San Antonio and 0.17 mmol/g in Kansas City).

Surgical Procedures

General. All surgical procedures were performed using aseptic technique, and the depth of anesthesia was always maintained to eliminate the withdrawal reflex to pinch of the hind paw. After all surgeries, rats were placed in clean recovery cages.

Intracerebroventricular guide cannula. Intracerebroventricular guide cannulas extending 2.5 mm below the surface of the skull were either manufactured in the laboratory using 23-gauge steel tubing or purchased from Plastics One (Roanoke, VA). Surgery to implant the guide cannula was done under Dormitor (0.5 mg/kg ip metomididine hydrochloride; Pfizer Animal Health, Exton, PA) and Vetame (75 mg/kg ip ketamine hydrochloride; Solvay Animal Health, Mendota Hts., MN) anesthesia (12). The rat was positioned in a stereotaxic instrument, and the skull was exposed through a midline incision. A hole was drilled in the skull at 1.5 mm lateral (left or right) and 1.0 to 1.1 mm caudal to bregma for insertion of the guide cannula. Two to four anchoring screws were placed in the skull, the guide cannula was inserted, and dental cement was used to keep the cannula in place. After completion of the surgery, the guide cannula was plugged using a “dummy” internal cannula, and the anesthetic antagonist Antisedan (1 mg/kg ip atipamezole hydrochloride) was administered to hasten recovery of the animal from anesthesia (12). Rats were allowed 1–2 wk to recover before implantation of arterial and venous catheters for measuring arterial pressure, obtaining blood samples for the measurement of plasma Cort, and administration of drugs.

Arterial and venous catheters. Surgery to implant catheters into the femoral artery and vein was performed under isoflurane or methoxyflurane anesthesia. The femoral artery and vein were isolated through a small skin incision and catheterized with Teflon-tipped Tygon tubing in the artery and PE-50 tubing, pulled out to a finer tip, in the vein. The catheters were tunneled under the skin and exteriorized at the back of the neck. The incision was sutured closed, and the catheters were anchored to the skin. The arterial catheter was filled with sterile heparin (1,000 U/ml), and the venous catheter was filled with sterile heparinized saline (20 U/ml).

Cort treatment. Increases in plasma Cort concentration were produced (n = 31) by subcutaneous implantation of Cort pellets weighing 127 ± 5 mg. Pellets were made using an established technique (3, 33). Briefly, Cort was liquefied and pipetted into a mold designed specifically for manufacturing the pellets (Ted Pella, Redding, CA). Surgery for implantation of the pellets was performed either at the time of intracerebroventricular cannulation, at the time of the femoral catheterization, or in a separate surgery under isoflurane or methoxyflurane anesthesia. A small skin incision was made in the dorsal lumbar region, and a pellet was inserted subcutaneously. The incision was sutured closed. Experiments were performed 3 to 22 days following implantation of the pellets.

During many experiments, plasma samples (200 µl) for the measurement of plasma Cort were obtained before the initiation of any experimental protocol. The blood samples were centrifuged at 4°C, and the plasma was stored at −20°C until being assayed. Plasma Cort was determined as previously described (33) using a commercially available kit (ImmuChem double antibody Cort 125 I RIA kit; ICN Biomedicals, Costa Mesa, CA). Exogenous Cort decreases thymus and adrenal weight (3). Therefore, at the conclusion of each experiment, the animals were euthanized with an overdose of isoflurane, then the thymus and adrenal glands were removed, patted dry, and weighed. For data analysis, thymus and adrenal weights were normalized to body weight.

Experimental Protocols

General. The experiments were performed in conscious rats at least 2 days, but usually 3 or more days, after implantation of the catheters. The rats were brought to the laboratory in their home cages between 7 and 8 AM, and their arterial catheters were connected to pressure transducers (Maxxim Medical, Athens, TX). The rats were allowed a minimum of 1 h to acclimatize to the laboratory setting before the baseline blood sample was obtained. Blood samples were collected between 9 and 11 AM. After the collection of the blood sample, at least 15 min elapsed before initiation of the experimental protocol. There was a total of five experimental protocols involving the intracerebroventricular or intravenous administration of drugs: 1) intracerebroventricular ANG II, 2) intracerebroventricular ANG II antagonist, 3) intravenous ANG II, 4) intravenous ANG II antagonist, and 5) intravenous phenylephrine. Some rats were used in more than one protocol.

Intracerebroventricular microinjections. Microinjections were made by inserting an internal cannula into the guide cannula at least 15 min before the injection. The internal cannula projected either 1.0 or (usually) 1.4 mm past the end of the guide cannula. All drugs administered into the cerebral ventricles were dissolved in 5 µl of sterile artificial cerebral spinal fluid of the following composition (in mM): 128 NaCl, 2.6 KCl, 1.3 CaCl2, 0.9 MgCl2, 20 NaHCO3, and 1.3 Na2HPO4 at a pH of 7.4. ANG II (Sigma, St. Louis, MO)
was administered at doses of 0 (vehicle), 10, 30, 100, and 300 ng. The ANG II injections were separated by a minimum of 90 min. Not all doses were administered on the same day or to every animal. Two ANG II antagonists were administered in separate experiments: Losartan (10 μg, n = 6) and L-158809 (10 μg, n = 9) (37). Similar results were obtained using the two antagonists, so the results were combined. Arterial pressure and heart rate were recorded for a 30-min baseline period, then the ANG II antagonist was administered and arterial pressure and heart rate were recorded for the next 60 min. In some rats, the effectiveness of the ANG II antagonist was tested by administration of intracerebroventricular ANG II (30 ng, n = 7) and/or intravenous ANG II (30 ng/kg, n = 6).

*Intravenous injections.* All drugs administered intravenously were dissolved in sterile 0.9% sodium chloride in volumes of 400 μl or less. ANG II was administered at doses of 0 (vehicle), 1, 3, 10, 30, and 100 ng/kg. Each animal included in this protocol received all doses of ANG II. The angiotensin-receptor antagonist L-158809 (0.1 mg/kg) was administered following a 30-min baseline period. Arterial pressure and heart rate were recorded continuously throughout the baseline period and for 60 min following administration of ANG II antagonist. In some rats, the effectiveness of the ANG II antagonist was tested by administration of intracerebroventricular ANG II (30 ng, n = 7) and/or intravenous ANG II (30 ng/kg, n = 12).

As described in the introduction (30), the rapid increase in pressure in response to the intracerebroventricular injection of ANG II is due, in part, to activation of the sympathetic nervous system. Under some conditions, glucocorticoids can increase vascular responsiveness to adrenergic stimulation (7, 22, 31). Therefore, any enhancement of the pressure response to intracerebroventricular ANG II in glucocorticoid-treated animals could be due to an increased vasoconstrictor response to sympathetic activation, rather than an increase in sympathetic nerve activity. To eliminate this as a possible explanation for the results, the increase in pressure in response to intravenous administration of the α-adrenergic receptor agonist phenylephrine was compared in control and Cort-treated rats. Phenylephrine was administered at doses of 0 (vehicle), 0.1, 0.3, and 1 μg/kg. Each animal included in this protocol received all doses of phenylephrine.

**Data Analysis**

**Cardiovascular data.** Pulsatile arterial pressure was measured from the arterial catheter using a pressure transducer (Maxxim Medical) connected to a bridge amplifier (World Precision Instruments, Sarasota, FL). The output from the bridge amplifier was fed into a MacLab (ADInstruments) analog-to-digital processor connected to a Macintosh computer. Mean arterial pressure (MAP) and heart rate were determined online from the pulsatile pressure using the MacLab software. Baseline values for MAP and heart rate were determined before administration of the antagonist or the “0” dose of agonist. With the intracerebroventricular administration of ANG II, not all rats received the “0” dose. For this protocol, average baseline MAP and heart rate were determined for each animal. To quantify the responses to administration of ANG II or phenylephrine, average values for MAP and heart rate were determined just before and during the peak of the rapid response to administration of each dose of each agonist, and the changes in MAP and heart rate were calculated. To quantify the responses to administration of ANG II antagonist, values for MAP and heart rate were determined during a 30-min baseline period and for 60 min following administration of ANG II antagonist or vehicle. Changes in MAP and heart rate in response to the antagonist were then calculated.

**Statistics.** There was no observed relationship between any measured values or responses and the duration of Cort treatment, so all the data for Cort-treated rats were combined for presentation and analysis. Values for MAP, heart rate, plasma Cort, and thymus and adrenal weights were analyzed by one- or two-way ANOVA as appropriate. Effects of ANG II antagonist were analyzed over time using the absolute values for MAP and heart rate. Responses to agonists were analyzed using calculated changes from baseline. Repeated-measures analysis was used for all within-subject variables. For post hoc analysis, Tukey’s test was used for between-subject variables, and least-square means were used for within-subject variables. Significance was accepted at P < 0.05. Values are expressed as means ± SE.

**RESULTS**

The Cort treatment used in these experiments approximately doubled plasma Cort from 3.13 ± 0.56 μg/dl in control rats (n = 19) to 7.11 ± 0.89 μg/dl in Cort-treated rats (n = 25, P < 0.01). Cort treatment reduces both thymus and adrenal weights, so these weights were used to assess the physiological effectiveness of the Cort treatment. Cort treatment significantly reduced thymus weight (in mg/kg of body wt) from 872 ± 92 mg/kg in control rats to 626 ± 29 mg/kg in the Cort-treated rats (P < 0.01). Adrenal weight was also reduced in Cort-treated rats, going from 182 ± 12 mg/kg in control rats to 126 ± 11 mg/kg in Cort-treated rats (P < 0.01). Body weight at the time of the experiments did not differ significantly between control (395 ± 23 g) and Cort-treated rats (382 ± 5 g).

Overall, average MAP measured during the baseline period of the experiments was higher in the Cort-treated rats (119 ± 2 mmHg, n = 31) than in the control rats (107 ± 1 mmHg, n = 27, P < 0.01). Cort treatment had no significant effect on baseline heart rate, which was 341 ± 4 vs. 353 ± 7 beats/min in control vs. Cort rats, respectively. Intracerebroventricular administration of ANG II (10, 30, 100, and 300 ng) produced dose-dependent increases in arterial pressure in both control and Cort-treated rats (P < 0.01; Fig. 1, top). Pretreatment of rats with Cort significantly enhanced the pressure response to ANG II at all doses of ANG II (P < 0.02 for all doses except vehicle). The increase in arterial pressure produced a reflex reduction in heart rate (P < 0.01) that was not significantly greater in Cort-treated rats, despite the larger increase in arterial pressure (Fig. 1, bottom).

The above data demonstrate that Cort enhanced the pressure response to central administration of exogenous ANG II. To determine if Cort enhanced the contribution of endogenous central ANG II to the maintenance of arterial pressure and heart rate, an ANG II antagonist was administered intracerebroventricularly. Either L-158809 (n = 9) or losartan (n = 6) was administered intracerebroventricularly to control and Cort-treated rats. In Cort-treated rats, ANG II antagonist produced a small but significant reduction in arterial pressure that reached a maximum of −5.9 ±
1.5 mmHg at 30–40 min following administration of ANG II antagonist (Fig. 2, top; $P < 0.01$). ANG II antagonist also reduced heart rate in Cort-treated rats by a maximum of $-26 \pm 7$ beats/min at 30–40 min following administration of ANG II antagonist (Fig. 2, bottom; $P < 0.01$). ANG II antagonist had no significant effect on arterial pressure or heart rate in control rats. The effectiveness of the ANG II antagonist was tested in seven rats that received 30 ng of ANG II intracerebroventricularly before and at least 60 min after administration of ANG II antagonist. The average increase in arterial pressure before the ANG II antagonist was $24 \pm 3$ mmHg ($P < 0.01$), whereas after ANG II antagonist arterial pressure did not change significantly in response to intracerebroventricular ANG II ($1 \pm 1$ mmHg). To determine if the intracerebroventricular administration of ANG II antagonist was blocking peripheral receptors, intravenous ANG II (30 ng/kg) was administered after intracerebroventricular administration of ANG II antagonist in six rats. The average increase in arterial pressure in response to intravenous ANG II was $54 \pm 1$ mmHg ($P < 0.01$). In another experimental protocol (Fig. 3), intravenous ANG II (30 ng/kg) increased MAP by $41 \pm 3$ mmHg in control rats in the absence of intracerebroventricular ANG II antagonist. Therefore, intracerebroventricular ANG II antagonist did not block peripheral actions of ANG II in these experiments.

Several investigators have reported that glucocorticoids increase the peripheral vasoconstrictor effects of ANG II (22, 31, 47). To determine if the dose of Cort used in this study was sufficient to increase vascular responsiveness to ANG II, ANG II was administered intravenously to control and Cort-treated rats. Intravenous administration of ANG II caused a dose-dependent increase in arterial pressure (Fig. 3, top; $P < 0.01$), the magnitude of which was not significantly affected by Cort treatment. The magnitude of the reflex reduction in heart rate was also unaffected by Cort.
treatment (Fig. 3, bottom). To confirm that the Cort treatment did not alter the contribution of peripheral ANG II to the maintenance of arterial pressure, the ANG II antagonist L-158809 was administered intravenously. Arterial pressure and heart rate were monitored for 60 min following administration of the ANG II antagonist, and the data were averaged into 10-min periods. The ANG II antagonist had no effect on either arterial pressure or heart rate in either control or Cort-treated rats (Fig. 4). To test the effectiveness of the intravenous ANG II antagonist, the arterial pressure response to 30 ng/kg of intravenous ANG II was determined before and after intravenous ANG II antagonist (n = 5). There was no effect of Cort on the increase in MAP or the reflex decrease in heart rate in response to intravenous administration of ANG II.

Fig. 3. Average changes in MAP (top) and heart rate (bottom) in response to intravenous injections of ANG II in control or Cort-treated rats. Baseline MAP was significantly higher in Cort-treated (116 ± 3 mmHg, n = 9) than in control rats (105 ± 2 mmHg, n = 10, P < 0.01). Baseline heart rate tended to be higher in Cort-treated rats, but the difference was not significant (329 ± 7 vs. 351 ± 13 beats/min in control vs. Cort rats, respectively). There was no effect of Cort on the increase in MAP or the reflex decrease in heart rate in response to intravenous administration of ANG II.

Fig. 4. Average changes in MAP (top) and heart rate (bottom) following intravenous administration of an AT1-receptor antagonist to control (n = 6) or Cort-treated rats (n = 6). Cort treatment significantly increased baseline MAP from an average of 109 ± 3 mmHg in control rats to 119 ± 2 mmHg in Cort-treated rats (P = 0.01). Baseline heart rate tended to be higher Cort-treated (377 ± 11 beats/min) than in control rats (350 ± 6 beats/min), but the difference was not significant. ANG II antagonist had no significant effect on MAP or heart rate in either group of rats.

Glucocorticoids have also been shown to increase vascular responsiveness to adrenergic agonists (7, 16, 28, 31, 45). Because central ANG II increases arterial pressure in part by activation of the sympathetic nervous system, it is possible that the enhanced effect of ANG II in the Cort-treated rats was due to an increase in vascular responsiveness to adrenergic stimulation, rather than to an increase in nerve activity. To investigate the effects of Cort treatment on vascular sensitivity to α-adrenergic agonists in this study, intravenous phenylephrine was administered to control and Cort-treated rats. Figure 5 shows that phenylephrine produced equivalent increases in arterial pressure in control and Cort-treated rats, indicating that increased end-organ responsiveness could not account for enhanced effects of intracerebroventricular ANG II on arterial pressure in Cort-treated rats.
Doses for ANG II were chosen based on ranges used in the literature and were estimated to provide a range of dose-dependent increases in arterial pressure. In retrospect, one or two lower intracerebroventricular doses could have been tested. Doses for intracerebroventricular ANG II were not normalized to body weight, as seems to be the convention in the literature (e.g., Ref. 46). However, because there was no significant difference in body weight between control and Cort-treated rats at the time of the experiments, the lack of normalization does not affect the interpretation of the data. The rats weighed ~400 g, making the doses of intracerebroventricular ANG II range from 25 to 750 ng/kg. The two lower doses of intracerebroventricular ANG II were thus in the range of the two highest doses of intravenous ANG II. At these comparable mass doses of ANG II, there was a significant augmentation of the pressor response to intracerebroventricular, but not intravenous, ANG II. Thus the difference in dose range also does not alter interpretation of the results.

Intracerebroventricular administration of ANG II increases arterial pressure both by activating the sympathetic nervous system and by stimulating vasopressin release, with the sympathetic nervous system accounting for most of the immediate rapid increase in pressure (11). In these experiments, the peak of the rapid arterial pressure increase following intracerebroventricular ANG II was measured. Moreover, glucocorticoids inhibit the release of vasopressin (29). Although additional experiments are needed to unequivocally determine the mechanism, it is very likely that the effects of Cort to enhance central actions of ANG II are due to augmented activation of the sympathetic nervous system rather than to enhanced vasopressin release.

On the basis of the results from previous studies, glucocorticoids could augment ANG II-mediated activation of the sympathetic nervous system by more than one mechanism. First, glucocorticoids could increase peripheral vascular responsiveness to α-adrenergic stimulation, as has been shown by some investigators (7, 16, 28, 31, 45). However, in these experiments, Cort treatment had no effect on the magnitude of arterial pressure increases produced by phenylephrine. A more likely explanation for the results presented here is that glucocorticoids can increase efferent sympathetic nerve activity through an ANG II-dependent mechanism. Previous studies have reported both inhibitory and stimulatory effects of glucocorticoids on sympathetic nerve activity (8, 10, 14, 20, 24, 32, 35, 40). The lack of agreement in these data suggests a complex effect of glucocorticoids on sympathetic outflow. One study has reported that acute intracerebroventricular administration of hydrocortisone increased renal sympathetic nerve activity by a mechanism that was blocked by central administration of an ANG II antagonist (40). Further experiments are needed to determine if chronic administration of Cort also stimulates sympathetic nerve activity through an ANG II-dependent mechanism.

In these experiments, ANG II and ANG II antagonist were administered into the cerebral ventricles rather
than into a specific area of the central nervous system. Intracerebroventricular administration of ANG II through the lateral ventricle produces an increase in sympathetic nerve activity primarily by activating receptors in the anterior region of the third ventricle (30). These receptors are close to the site of administration of ANG II and mediate potent effects of ANG II on arterial pressure. However, ANG II also activates receptors in other areas of the brain (30). For example, activation of ANG II receptors in the nucleus of the solitary tract attenuates the arterial baroreceptor reflex (19, 26, 30), and in the rostral ventral lateral medulla it increases sympathetic outflow (18). In addition, glucocorticoid type II receptors are found in the nucleus of the solitary tract and the rostral ventral lateral medulla (2). With intracerebroventricular administration of nonpeptide ANG II antagonists in this study, the maximum reductions in arterial pressure and heart rate in Cort-treated rats were not observed until 30–40 min after administration of the antagonist. This suggests the possibility that cumulative blockade of ANG II receptors at multiple central nervous system loci, or a cascade of effects following blockade of forebrain receptors, may have contributed to the decrease in arterial pressure and heart rate in the Cort-treated rats.

The maximum decrease in arterial pressure following intracerebroventricular administration of ANG II antagonist to Cort-treated rats was only $-5.9 \pm 1.5$ mmHg, whereas the difference in average baseline arterial pressure in control vs. Cort-treated rats was $10.8$ mmHg. Therefore, the intracerebroventricular administration of ANG II antagonist reversed just 55% of the increase in arterial pressure caused by Cort treatment. Several mechanisms could account for this. First, the antagonist may not have blocked all central nervous system sites at which Cort acts through ANG II receptors to increase arterial pressure. Second, the effect of the ANG II antagonist to decrease arterial pressure was only followed for 1 h. Because ANG II has the capability of activating early immediate genes (17), some actions of ANG II on neuronal function may take longer than 1 h to reverse. Furthermore, events leading to gene transcription triggered by ANG II may not be reversible by an ANG II antagonist once the increase in gene transcription has been triggered. In any case, there is general agreement that the mechanism of glucocorticoid-induced hypertension is multifactorial, and it would not be expected that blockade of a single receptor type would completely reverse a glucocorticoid-induced increase in arterial pressure.

Intracerebroventricular administration of an ANG II antagonist to Cort-treated rats decreased heart rate by a maximum of $-26$ beats/min, despite the fact that the reduction in arterial pressure should have caused a baroreflex-mediated increase in heart rate. The antagonist had no effect on heart rate in control rats. However, there was no significant difference in baseline heart rate between control and Cort-treated rats. These results suggest that Cort may have an effect to elevate heart rate through an ANG II-dependent mechanism. However, the increase in arterial pressure caused by Cort may activate reflex or other mechanisms that return heart rate back toward control values, even in the presence of baroreceptor reflex resetting.

**Perspectives**

There is increasing evidence that abnormalities in glucocorticoid receptors, metabolism, and responsiveness contribute to the mechanisms of human hypertension (5, 27, 38, 43–45). Glucocorticoids are also elevated by stress, an accepted risk factor for hypertension. Peripheral mechanisms of glucocorticoid-induced hypertension have been extensively investigated, whereas much less is known regarding central effects of glucocorticoids on arterial pressure regulation. In contrast, ANG II is an established mediator of hypertension, and ANG II inhibitors and antagonists comprise a major class of antihypertensive pharmaceuticals (30). The data reported here demonstrate for the first time that glucocorticoids enhance central actions of ANG II to increase arterial pressure at a dose that does not affect peripheral vasoconstriction mediated by ANG II or $\alpha$-adrenergic receptors. Thus even slightly elevated levels of glucocorticoids could act in concert with other mechanisms to produce central nervous system-mediated hypertension.

Understanding the mechanisms of glucocorticoid-induced hypertension has additional relevance in light of reports that in humans and experimental animals, exposure to elevated glucocorticoids during critical prenatal periods increases plasma glucocorticoid levels in the adult offspring (25). These offspring are also at an increased risk for hypertension in adulthood (9, 34). Increased activation of the renin-angiotensin system has been suggested as a mechanism for the adult hypertension (23). Glucocorticoids are administered to pregnant women, and maternal stress, poor diet, and other conditions can increase endogenous glucocorticoids in pregnancy. Thus the clinical relevance of understanding the effects of glucocorticoids on central regulation of arterial pressure by ANG II and other hormones and neurotransmitters is significant.

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