Adrenal splanchnic innervation contributes to the diurnal rhythm of plasma corticosterone in rats by modulating adrenal sensitivity to ACTH

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Submitted 24 January 2003; accepted in final form 5 December 2005

Ulrich-Lai, Yvonne M., Michelle M. Arnhold, and William C. Engeland. Adrenal splanchnic innervation contributes to the diurnal rhythm of plasma corticosterone in rats by modulating adrenal sensitivity to ACTH. Am J Physiol Regul Integr Comp Physiol 290: R1128–R1135, 2006. First published December 15, 2005; doi:10.1152/ajpregu.00042.2003.—Activity of the hypothalamic-pituitary-adrenal axis is characterized by a diurnal rhythm with an AM nadir and PM peak. Splanchnic nerve transection disrupts the diurnal rhythm in plasma corticosterone; however, there is a controversy as to whether the nerve-mediated effect is 1) via inhibition in the AM vs. excitation in the PM, or 2) involves changes in adrenal sensitivity to ACTH. The present studies were designed to address these issues. Adult male rats were anesthetized and underwent bilateral transection of the thoracic splanchnic nerve or sham transection. One week after surgery, rats were killed in the AM or PM with collection of nonstress plasma for measurement of corticosterone and ACTH. Plasma corticosterone was increased in the PM relative to the AM; however, plasma corticosterone in the PM was attenuated by splanchnic nerve transection, without affecting plasma ACTH. This decrease in PM plasma corticosterone after nerve transection was 1) associated with decreased adrenal responsivity to ACTH, 2) associated with decreased adrenal cAMP content, 3) prevented by adrenal demedullation, and 4) not affected by removal of adrenal capsaicin-sensitive afferent fibers. Repeated serial blood sampling from individual rats confirmed the excitatory effect of splanchnic innervation in the PM. These results support the hypothesis that the adrenal splanchnic innervation modulates the diurnal rhythm in plasma corticosterone by increasing adrenal responsivity to ACTH and augmenting steroidogenesis in the PM and suggest that alterations in adrenal corticosterone secretion obscured by pulsatile secretion are more clearly revealed with repeated serial blood sampling.

splanchnic nerve; cyclic 3’5’-adenosine monophosphate; steroidogenic acute regulatory protein; capsaicin; medullectomy

Most systems in the body exhibit a diurnal rhythm entrained to the light cycle. This includes activity in the hypothalamic-pituitary-adrenal (HPA) axis, a stress responsive system, in which activation of hypophysiotrophic neurons in the paraventricular nucleus of the hypothalamus results in the release of corticotropin-releasing hormone (CRH) into the portal blood supply of the median eminence. CRH activates pituitary corticotrophs to release ACTH into the systemic circulation. ACTH acts in the adrenal cortex to stimulate the production of glucocorticoids (e.g., cortisol in humans and corticosterone in rats) by increasing intracellular cAMP (5). Elevations in cAMP increase the amount of free cholesterol and its transfer to the mitochondria, which is considered the rate-limiting step in steroidogenesis. Steroidogenic acute regulatory protein (StAR) and peripheral benzodiazepine receptor (PBR) are two molecules implicated in the cholesterol transport process (reviewed in Ref. 13).

In rats, there is a diurnal rhythm in nonstress plasma ACTH and corticosterone, with a nadir at the onset of the inactive period (i.e., in the morning for these nocturnal animals) and a peak at the onset of the active period (i.e., in the late afternoon). The diurnal rhythm in nonstress plasma corticosterone is of high amplitude, typically of 5- to 10-fold from the trough (AM) to peak (PM) levels, whereas the rhythm in plasma ACTH is of low amplitude (up to twofold), which is frequently not significant throughout the day (2, 9, 20, 21, 34). The robust rhythm in plasma corticosterone despite a modest rhythm in plasma ACTH is largely due to coincident rhythm in adrenal sensitivity to ACTH (9, 21, 22). This diurnal rhythm in HPA activity is largely controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus, the primary pacemaker of the brain. Lesions of SCN eliminate the diurnal rhythm of adrenal and plasma corticosterone (1, 27) and plasma ACTH (30). The SCN has been implicated in inhibiting the HPA axis at the nadir of the diurnal rhythm, as well as stimulating the HPA axis at the peak (6, 20).

The robust rhythm in nonstress plasma corticosterone despite a modest rhythm in nonstress plasma ACTH suggests that non-ACTH factors may contribute to the diurnal rhythm in plasma corticosterone. In support of this, the rhythm of plasma corticosterone persists in hypophysectomized rats that have been implanted with ACTH pellets, suggesting that the corticosterone rhythm does not depend on the rhythmic release of ACTH (26). Importantly, the adrenal is extensively innervated by several nerve fibers of both intrinsic and extrinsic origin. The extrinsic innervation of the rat adrenal gland includes calcitonin gene-related peptide (CGRP)-positive primary afferent fibers (25), neuronal nitric oxide synthase (nNOS)-positive cholinergic preganglionic sympathetic fibers (14), and tyrosine hydroxylase (TH)- and neuropeptide Y (NPY)-positive postganglionic sympathetic fibers (15, 24). The intrinsic innervation originates from two types of medullary ganglion cells: type I cells are noradrenergic and NPY-positive, whereas type II cells produce nNOS and vasoactive intestinal peptide (15). The thoracic splanchnic nerve constitutes a primary conduit for the extrinsic innervation to the adrenal (15), in addition to the innervation that enters the gland along the blood vessels (23). Using intra-adrenal microdialysis in rats, Jasper and Engeland (17) showed that transection of the splanchnic nerve increased the frequency of intra-adrenal corticosterone pulses in the AM and had no effect in the PM, suggesting that the splanchnic...
nerve normally exerts inhibitory control of corticosterone secretion in the AM. Moreover, additional studies demonstrated a splanchnic nerve-mediated decrease in adrenal sensitivity to ACTH in nonstressed rats (18). In contrast, Dijkstra et al. (10) showed that splanchnic denervation reduced resting plasma corticosterone levels in the PM and had no effect in the AM, suggesting that the splanchnic nerve normally exerts excitatory control of corticosterone secretion in the PM. Moreover, this effect did not involve a change in adrenal sensitivity to ACTH (10). Given these apparent discrepancies, the present studies were designed to clarify the role of the splanchnic innervation in controlling the diurnal variation in plasma corticosterone and to determine whether neural control of the cortex involves capsaicin-sensitive afferent fibers or requires an intact adrenal medulla.

MATERIALS AND METHODS

Animals. Male, Sprague-Dawley rats (175–225 g; Harlan, Indianapolis, IN) were used in all experiments. The rats were housed on a 12:12-h light-dark cycle with free access to food and water. In addition, rats were allowed to adjust to the facilities for several days before the initiation of experiments. All procedures were approved by the University of Minnesota Animal Care and Use Committee and performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experiment 1. Rats (n = 8/group) were anesthetized with pentobarbital sodium (60 mg/kg ip) and given atropine (40 μg/rat sc). Rats then received bilateral splanchicectomy, as described previously (16), or sham surgery in which the nerve was visualized but not manipulated. Immediately after surgery, rats were administered antibiotic (Naxcel, 2 mg/kg im). After 7 days of recovery, nonstressed rats were decapitated at the nadir (AM; 1.5 h after lights on) or peak (PM; 1.5 h before lights off) of the diurnal rhythm. Trunk blood was collected, centrifuged (2,000 g, 20 min, 4°C), and the plasma was stored at −80°C until measurement of plasma corticosterone, ACTH, aldosterone, and renin activity. Adrenals from each group (n = 4/group) were randomly selected, cleaned, and frozen for Western blot analysis of adrenal StAR and PBR. An equal number of left and right adrenals were included in the analysis, as we have found no systematic left-right differences in adrenal StAR or PBR (unpublished observations).

Experiment 2. Rats (n = 4–6/group) were surgically treated the same as in experiment 1, except only the PM time point was examined. After 7 days of recovery, rats received dexamethasone phosphate pretreatment (400 μg sc; American Pharmaceutical Partners, Los Angeles, CA) to block endogenous ACTH. After 2 h, rats were given exogenous rat ACTH subcutaneously (pH 7.4; Peninsula Laboratories, Belmont, CA) at a dose of 0, 60, 100, 200, or 3,000 ng. Fifteen minutes after ACTH injection, rats were decapitated with collection of trunk blood for measurement of plasma corticosterone, aldosterone, and ACTH.

Experiment 3. Rats (n = 9/group) were surgically treated the same as in experiment 1, except only the PM time point was examined. After 7 days of recovery, nonstressed rats were decapitated in the PM and trunk blood was collected for measurement of plasma corticosterone. The left adrenal from each rat was quickly collected, cleaned, and frozen for measurement of cAMP content.

Experiment 4. Rats (n = 8–11/group) received bilateral adrenal enucleation or sham enucleation, as described previously (30); rats were allowed to recovery for 5 wk to allow adequate time for adrenal cortical regeneration. Rats then received bilateral splanchic nerve transection or sham transection, as described for experiment 1, and were allowed to recover for an additional 7 days. Nonstressed rats were decapitated in the PM with collection of trunk blood for assay of plasma corticosterone, ACTH, and aldosterone.

Experiment 5. Rats (n = 8–10/group) were anesthetized and received bilateral periaxial application of capsaicin (33 mM; 15 min) or vehicle (5% ethanol, 5% Tween-80, 90% saline) to the splanchnic nerve, as described previously (31). After 7 days of recovery, nonstressed rats were decapitated in the AM or PM with collection of trunk blood for measurement of plasma corticosterone, ACTH, and aldosterone. Adrenals from each drug treatment (n = 4/group) were randomly collected, separated into capsules (including the outer cortex) and cores (containing the medulla and inner cortex), and frozen for measurement of adrenal CGRP content (to verify the effectiveness of the capsaicin treatment); an equal number of left and right adrenals were included in the analysis, as left-right differences in adrenal CGRP have not been observed (unpublished observations).

Experiment 6. Rats (n = 7/group) were surgically treated the same as in experiment 1, followed by placement of chronic indwelling catheters in the abdominal aorta and vena cava via the femoral vessels, as described previously (36). The distal ends of the catheters were tunneled subcutaneously to the dorsal surface of the neck. The ends of the catheters were then passed through a flexible stainless steel spring. The rats were placed in a loosely fitted cloth jacket; one end of the spring was fastened to the jacket with the other end attached to a hydraulic swivel. Animals were housed individually in plastic cages and received acetaminophen (children’s Tylenol; 3.2 mg/ml in the drinking water) for 48 h and antibiotics (1 mg tobramycin, 15 mg ampicillin iv) for 3 days. After a 5-day recovery, six blood samples (300 μl each) were taken at 10-min intervals from the arterial catheter for measurement of plasma corticosterone and ACTH; after each sample, isotonic saline was given to replace lost volume. Blood sampling was initiated at 1.5 h before lights off (PM) on day 5 and again at 1.5 h after lights on (AM) on day 6.

Plasma hormone measurements. Plasma levels of corticosterone, ACTH, and aldosterone were determined by RIA, as described previously (32). Plasma renin activity was determined using a commercially available kit (NEN LifeScience Products, Boston, MA). Briefly, ANG I was generated in plasma samples in the presence of EDTA, dimercaprol and 8-hydroxyquinoline to inhibit converting enzyme and angiotensinase activity. The amount of generated ANG I was then measured via RIA.

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Adrenal cAMP content. Adrenal glands were homogenized in trichloroacetic acid (6%, 300 μl, 4°C) and centrifuged (2,500 g, 15 min, 4°C). Supernatants were washed 4 times with 5 volumes of water-saturated diethyl ether and lyophilized. Dried extracts were dissolved in assay buffer, and cAMP was measured with a commercially available kit (NEN LifeScience Products, Boston, MA). Briefly, ANG I was generated in plasma samples in the presence of EDTA, dimercaprol and 8-hydroxyquinoline to inhibit converting enzyme and angiotensinase activity. The amount of generated ANG I was then measured via RIA.

Adrenal CGRP content. Adrenal content of CGRP was determined by RIA, as previously described (32).

Western blot analysis. Adrenal content of StAR and PBR proteins was determined using Western blot analysis. Adrenal glands were homogenized in boiling buffer (5% SDS, 10% glycerol, 50 mM Tris; pH 6.8), boiled (90°C, 10 min), and centrifuged (16,000 g, 10 min); the supernatant protein concentration was determined using the BCA protein assay (Pierce, Rockford, IL). Samples were separated by SDS-polyacrylamide gel electrophoresis using Tris-glycine gels (4–20% gradient), and Multimark molecular weight standard (Novex, San Diego, CA), with subsequent electrophoretic blot onto Immobilon-P membranes (Millipore, Bedford, MA). Samples were separated, proteins were measured, and gels were loaded in random order by an individual blinded to treatment groups. StAR was detected using a rabbit polyclonal antibody [kindly provided by W. Miller, UCSF, San Francisco, CA; (41)] at 1:20,000 dilution. PBR was detected using a rabbit polyclonal antibody [kindly provided by V. Papadopoulos, Georgetown University; (3)] at 1:2,000 dilution. Incubation with primary antibody was followed by chemiluminescent detection (SuperSignal, Pierce, Rockford, IL) using donkey F(ab′)2 fragments of anti-rabbit IgG conjugated to horseradish peroxidase (1:10,000; Jackson Immu-
no Research Laboratories, West Grove, PA). The primary bands were located at the appropriate molecular weight of ~30 kDa for StAR (4) and 18 kDa for PBR (3). These bands were not observed when the primary antibodies were omitted. The integrated optical density of the band of interest was measured by a blinded observer and expressed in arbitrary units.

**Statistical analysis.** Data are presented as means ± SE. When experiments required comparison of two groups, statistical differences were determined by Student’s t-test. When multiple groups were compared, statistical differences were determined by two-way or three-way ANOVA (as appropriate), with repeated measures when applicable. When necessary, homogeneity of variance was obtained by performing analysis on the values after square-root transformation. Specific differences were determined by Fisher’s post hoc analysis.

For experiment 2, plasma corticosterone responses to ACTH (doses 60–200 ng) were analyzed by linear regression and analysis of covariance. For experiment 6, differences between treatment groups in plasma ACTH and corticosterone in serial blood samples were assessed by three-way ANOVA corrected for repeated measures on two variables (sample number and time of day). Statistical significance was taken as $P < 0.05$.

**RESULTS**

**Experiment 1.** Nonstress plasma corticosterone was greater in the PM than in the AM (Fig. 1A). Splanchnic nerve transection did not affect AM plasma corticosterone levels but decreased PM plasma corticosterone levels (Fig. 1A). Plasma ACTH (Fig. 1B) did not differ with time of day ($P = 0.984$) or with nerve transection ($P = 0.367$; interaction $P = 0.778$). Similarly, plasma aldosterone (Fig. 1C) did not differ with time of day ($P = 0.179$) or with nerve transection ($P = 0.154$; interaction $P = 0.220$). Plasma renin activity (Fig. 1D) and adrenal StAR content (Fig. 1E) were greater in the PM than in the AM but were not affected by nerve transection. Lastly, adrenal PBR content (Fig. 1F) did not differ with time of day ($P = 0.805$) or with nerve transection ($P = 0.732$; interaction $P = 0.687$).

**Experiment 2.** Plasma corticosterone responses in the PM in dexamethasone-blocked rats were low in the absence of exogenous ACTH, establishing the effectiveness of the dexameth-

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**Fig. 1.** Splanchnic nerve transection reduced PM plasma corticosterone levels, but not plasma ACTH, plasma aldosterone, plasma renin activity, adrenal StAR, or adrenal PBR. Plasma hormones and adrenal proteins assessed at the nadir (AM) and peak (PM) of the diurnal rhythm after splanchnic nerve transection (open bars) or sham nerve transection (solid bars). A: plasma corticosterone. B: plasma ACTH. C: plasma aldosterone. D: plasma renin activity. E: adrenal StAR. F: adrenal PBR. Data are shown as means ± SE; $n = 8$ group for A–D and $4$ group for E and F. **$P < 0.01$ vs. AM; **$P < 0.01$ vs. sham nerve transection.
as one blockade of endogenous ACTH (Fig. 2). Moreover, in the absence of exogenous ACTH, plasma corticosterone responses were not affected by splanchnic nerve transection (Fig. 2). In the presence of submaximal doses of exogenous ACTH (60–200 ng), splanchnic nerve transection decreased the slope of the corticosterone response in sham-transected rats was 1.78 ± 0.26, whereas that in transected rats was 0.97 ± 0.15 (P = 0.011). Data are shown as means ± SE; n = 4–6/group, ##P < 0.01 vs. 200 ng dose.

Plasma aldosterone responses to exogenous ACTH showed a significant dose effect that was not affected by splanchnic nerve transection (data not shown). Similarly, plasma ACTH levels after exogenous ACTH injection showed a significant dose effect that was not affected by splanchnic nerve transection (data not shown).

**Experiment 3.** The PM adrenal cAMP content was reduced by splanchnic nerve transection (Fig. 3). In this experiment, PM plasma corticosterone was not significantly decreased by splanchnic nerve transection (sham 216.4 ± 36.2 ng/ml vs. cut 169.3 ± 23.3 ng/ml, P = 0.289).

**Experiment 4.** Plasma corticosterone in the PM was decreased by splanchnic nerve transection in rats with intact adrenals, but not rats with demedullated adrenals (Fig. 4A). Plasma ACTH in the PM (Fig. 4B) was not affected by demedullation (P = 0.148) or splanchnic nerve transection (P = 0.344; interaction P = 0.829). Similarly, plasma aldosterone in the PM (Fig. 4C) was not affected by demedullation (P = 0.853) or splanchnic nerve transection (P = 0.547; interaction P = 0.931).

**Experiment 5.** Plasma corticosterone levels were low in the AM and increased in the PM; neither the AM nor the PM plasma corticosterone levels were affected by splanchnic capsaicin pretreatment (Fig. 5A). Similarly, plasma ACTH (Fig. 5B) and aldosterone (Fig. 5C) were greater in the PM than the AM, and neither were affected by splanchnic capsaicin pretreatment. Importantly, adrenal capsule CGRP content was...
periaxonal pretreatment with capsaicin effectively reduced adrenal CGRP content in the capsule but not in the core (Fig. 5D). Data are shown as means ± SE. **P < 0.01 vs. AM; ***P < 0.01 vs. vehicle; *P < 0.05, **P < 0.01 vs. capsule.

increased by splanchnic capsaicin pretreatment (Fig. 5D), confirming the effectiveness of the capsaicin treatment.

Experiment 6. Using repeated sampling to assess diurnal changes, the ANOVA revealed a time × treatment interaction for plasma corticosterone. Plasma corticosterone in the AM was modestly increased by splanchnic nerve transection with differences observed in only 1 of 6 sample points (Fig. 6A). In contrast, plasma corticosterone in the PM was markedly reduced after splanchnic nerve transection with differences found in 4 of 6 sample points (Fig. 6B). Splanchnic nerve transection had no effect on plasma ACTH in the AM or PM (Fig. 6C and D). When the average corticosterone across samples was calculated for individual rats, both plasma corticosterone and ACTH showed increases in the PM (Fig. 7A and B). Plasma corticosterone was reduced in the PM by nerve transection, but the transection-induced increase was not observed in the AM (Fig. 7A); these data parallel those obtained using trunk blood sampling in experiments 1 and 4. The diurnal variation in plasma ACTH was not affected by nerve transection (Fig. 7B).

DISCUSSION

The diurnal rhythm of the HPA axis showed a consistent, robust (tenfold) increase in plasma corticosterone, as reported previously (2, 9, 21, 34). Increases in plasma corticosterone were accompanied by inconsistent, modest (1–2.5 fold) increases in plasma ACTH. Other groups have previously shown either no change, or modest increases in plasma ACTH in the
PM, similar to the range of responses presently described (2, 9, 20, 21, 34). Collectively, this work demonstrating robust increases in plasma corticosterone in the PM with no or modest increases in plasma ACTH suggest that an additional factor(s), such as the adrenal splanchnic innervation, may be involved in controlling adrenal steroidogenesis in the PM.

The current studies demonstrate that splanchnic nerve transection reduces plasma corticosterone levels in the PM without affecting plasma ACTH, supporting the contention initially proposed by others (10, 28) that increases in adrenal neural activity represent a non-ACTH mechanism that contributes to the diurnal peak in plasma corticosterone. To assess whether splanchnic nerve-mediated effects on steroidogenesis resulted from changes in adrenal sensitivity to ACTH, dexamethasone-blocked rats were given exogenous ACTH in the PM. Plasma corticosterone responses to submaximal doses of ACTH (60–200 ng) were reduced by splanchnic nerve transection, suggesting a decreased adrenal sensitivity to ACTH. Plasma corticosterone responses to 3,000 ng ACTH, a supraphysiological dose given to drive maximal adrenal responses, were not affected by splanchnic nerve transection, indicating that maximal responses in the PM are not affected splanchnic neural input. Moreover, plasma corticosterone in the absence of exogenous ACTH was not affected by splanchnic nerve transection, suggesting that the splanchnic nerve-mediated effects require the presence of ACTH. Lastly, plasma aldosterone was not affected by splanchnic nerve transection, suggesting that the splanchnic nerve does not mediate the diurnal rhythm of plasma aldosterone. Collectively, these results suggest that the splanchnic nerve normally acts in the PM to increase plasma corticosterone, but not aldosterone, by increasing adrenal responsiveness to ACTH. These results contradict those by Dijkstra et al. (10), who showed that splanchnic nerve transection does not affect adrenal responsivity to a single intravenous dose of ACTH (7.5 ng ACTH 1–24) in the PM. The present studies used a wide range of ACTH doses and clearly demonstrate that splanchnic nerve transection reduced adrenal responsivity to submaximal doses of ACTH in the PM.

It has previously been shown that there is a diurnal rhythm in adrenal cAMP levels that persists in hypophysectomized rats (11, 12); cAMP (via activation of protein kinase A) increases the amount of free cholesterol and its transfer into the mitochondria, which is considered the rate-limiting step in steroidogenesis (reviewed in Ref. 13). The present studies demonstrate that there is also a diurnal rhythm in adrenal StAR, but not adrenal PBR; StAR and PBR are two additional molecules implicated in the transport of cholesterol into the mitochondria. Thus cAMP and StAR are potential factors regulating the PM rise in plasma corticosterone. Splanchnic nerve transection decreased PM levels of adrenal cAMP, establishing that increases in adrenal cAMP are associated with the splanchnic-mediated component of the PM rise in plasma corticosterone. It is not clear whether the splanchnic innervation can account completely for the increases in adrenal cAMP in the PM, as comparisons between rats in the AM and PM with splanchnic nerve transections were not made. However, this result suggests that the splanchnic nerve acts, at least in part, proximal to the generation of cAMP, perhaps regulating adrenal blood flow or ACTH receptor activity. In contrast, splanchnic nerve transection did not affect adrenal content of StAR or PBR in the PM. Although upregulation of adrenal StAR may be involved in the PM rise in plasma corticosterone, it appears to be a splanchnic nerve-independent component.

In addition to a rhythm in plasma corticosterone, plasma aldosterone also is characterized by diurnal rhythmicity (e.g., Fig. 5; Ref. 29). Because ACTH is a potent secretagogue for aldosterone secretion in rats that is mediated in part by the cAMP-PKA pathway (8), one might expect to find parallel decreases in plasma corticosterone and aldosterone in the PM after splanchnic transection. Although there was some indication in our initial experiment that the plasma aldosterone rhythm may have been affected (experiment 1), this did not reach statistical significance and subsequent experiments showed no effect of splanchnic transection either on plasma aldosterone in the PM (experiment 4) or on aldosterone responses to ACTH in the PM (experiment 2). Because the diurnal rhythm in plasma renin activity was not affected by splanchnic transection, it is possible that an inhibitory effect of the splanchnic nerve on aldosterone secretion exists but that stimulation by ANG II offsets the effect. Additional work is required to define the contribution of ACTH, splanchnic innervation, and the renin-angiotensin system in mediating the diurnal rhythm in plasma aldosterone.

Given that the splanchnic nerve consists of a mixed population of fibers, experiments were done to assess which splanchnic neural elements are responsible for the excitatory effects of splanchnic innervation in the PM. It has been shown previously that transection of the thoracic splanchnic nerve removes the vesicular acetylcholine transporter (VAChT)-positive preganglionic sympathetic and CGRP-positive primary afferent innervation from the rat adrenal gland; the TH- and NPY-positive postganglionic sympathetic innervation is not...
were designed to compare the effect of splanchnic nerve transection. Serial sampling after points (with some rats near the trough and others near the peak) is possible that single trunk blood sampling adds inter-rat variability because samples are taken at random intrapulse time points (compare sham vs. nerve transection in experiments 1, 3, and 4). Again, the episodic nature of corticosterone most likely underlies this variability.

The current work demonstrates that splanchnic nerve transaction decreases the PM rise in nonstress plasma corticosterone and is associated with decreased adrenal sensitivity to ACTH and decreased adrenal cAMP content. We have previously shown that the plasma corticosterone response to 48 h of dehydration stress is similarly attenuated by splanchnic nerve transection and that this decrease in postdehydration plasma corticosterone is also associated with decreased adrenal responsivity to ACTH and decreased adrenal cAMP content (31). The parallel findings for splanchnic neural mediation of plasma corticosterone at the peak of the diurnal rhythm and after dehydration stress suggest a common mechanism for splanchnic neural activation of steroidogenesis. Additional investigations will be required to reveal the full extent of neural control of adrenal steroidogenesis in the AM and PM. However, the collective results suggest that the brain can control glucocorticoid production through at least two mechanisms, by activation of the neuroendocrine HPA axis and by direct activation of adrenal neural substrates to modulate responses to ACTH.

ACKNOWLEDGMENTS

The authors thank Cheryl Wotus, Carolyn Morris, and Erica Melief for their technical assistance. The antibodies used in the Western blot analysis were generously provided by Dr. W. Miller (University of California, San Francisco, CA) and Dr. V. Papadopoulos (Georgetown University, Washington, DC).

GRANTS

This work was support by National Science Foundation Grant IBN-0112543, a Howard Hughes Medical Institute Predoctoral Fellowship (to Y. M. Ulrich-Lai), and a University of Minnesota Graduate School Doctoral Dissertation Fellowship (to Y. M. Ulrich-Lai).

REFERENCES


ADRENAL SPLANCHNIC INNERVATION


