Acute Suppression of Muscle Sympathetic Nerve Activity by Hydrocortisone in Humans

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Abstract—In the present study, we examined the acute influence of hydrocortisone on human sympathetic nerve activity and cardiovascular parameters. Muscle sympathetic nerve activity (MSA), heart rate, and blood pressure were monitored in 8 healthy subjects (20 to 37 years old) before and after a bolus injection of 50 mg hydrocortisone followed by a continuous infusion at 50 mg/h during a period of 3 hours in a placebo-controlled, double-blind, crossover protocol. Recordings were performed at rest and during repeated transient sympathoexcitation induced by voluntary apneas. Resting MSA and endogenous serum cortisol concentrations were also measured in a larger study group (49 experiments, 25 subjects). During the experimental period, MSA burst number increased by 56% from the control level in the placebo group. In contrast, MSA was suppressed by 25% at the end of the hydrocortisone infusion, resulting in a significant treatment effect ($P<0.05$). In addition, sympathoexcitation during apnea was significantly reduced with hydrocortisone after 180 minutes. In parallel with the sympathetic outflow, blood pressure decreased in the hydrocortisone-treated group, whereas it rose in the placebo group ($P<0.05$ between groups). No correlation was found between basal MSA and basal cortisol levels. Our results indicate that pharmacological doses of hydrocortisone acutely influence MSA responses to short- and long-lasting environmental stimuli, whereas basal native cortisol levels do not appear to be tonically involved in the regulation of resting MSA. The suppressive hydrocortisone effect is most likely induced via supraspinal autonomic centers and cannot be explained by peripheral steroid mechanisms. The effect of elevated corticosteroid levels on sympathetic nerve discharge may be an important mechanism in cardiovascular adaptations to stress. *(Hypertension. 2000;35:758-763.)*

Key Words: hormones ■ glucocorticoids ■ sympathetic nervous system

Glucocorticoids play an important role in human hemodynamic regulation, as clearly demonstrated in diseases with hyposecretion or hypersecretion of the steroid. A defect in cortisol production may elicit life-threatening hypotension, especially under conditions of stress. Corticosteroid excess, on the other hand, can cause pronounced hypertension. The hemodynamic effects of cortisol can be explained by multiple mechanisms, including the regulation of total body water and sodium content, an increased vascular contractility in response to catecholamines and angiotensin II, and influences on catecholamine synthesis.

In addition to these peripheral effects, corticosteroids could affect the regulation of the sympathetic nervous system (SNS) via central autonomic nuclei. Binding sites for endogenous corticosteroids, both the glucocorticoid (GR) and the mineralocorticoid (MR) receptor, are expressed in hypothalamic and brain stem regions involved in hemodynamic regulation (ie, the paraventricular nuclei and the nucleus tractus solitarii). Studies in animals have demonstrated clear hemodynamic effects of intracerebroventricularly administered corticosteroid agonists and antagonists, with GR and MR mediating different effects. While pure glucocorticoids such as dexamethasone have resulted in a reduction in blood pressure, mineralocorticoids have caused it to increase. The native steroid (ie, corticosterone in rats, cortisol in dogs and humans) binds to both receptors in most brain areas, but in some areas (eg, the nucleus tractus solitarii), 11β-hydroxysteroid dehydrogenase type 2 is expressed, which inactivates cortisol and guarantees specific mineralocorticoid binding to MR. Given the differential distribution and specificity of the GR and MR in the brain, the net effect of cortisol on central blood pressure regulation is difficult to predict. Furthermore, the mechanisms that mediate central glucocorticoid effects on hemodynamic target organs have not been established, but the SNS is likely to be involved.

High doses of dexamethasone suppress basal and stimulated norepinephrine levels in humans. More recent studies with microneurography to specifically determine sympathetic outflow to the muscle vascular bed reported that dexamethasone inhibited the sympathoexcitation induced by insulin or alcohol. A single administration of hydrocortisone to a plasma level that resembles the hypoglycemia-induced en-
dogenous cortisol surge has also been shown to suppress the muscle sympathetic nerve activity (MSA) increase during hypoglycemia on the next day. This glucocorticoid blunting of sympathoexcitatory responses to quite different stimuli may suggest a crucial role for this hormone in the regulation of the SNS, although the exact mechanism remains to be determined. A recent study reported a reduction in MSA at rest after the administration of hydrocortisone for 5 days, suggesting that glucocorticoids may exert a tonic influence on sympathetic outflow.

Against this background, we studied the acute effects of cortisol on intraneurally recorded MSA (the hemodynamically most important sympathetic subdivision accessible in humans), heart rate, and blood pressure in healthy volunteers. We hypothesized that putative central effects of the steroid should have a fast onset and could be expected to precede peripheral effects. To reveal a putative central effect, a 3-hour infusion of hydrocortisone was monitored. In addition, we tested whether basal MSA is correlated to resting endogenous cortisol levels.

**Methods**

Experiments were performed on 25 healthy subjects (12 women and 13 men, age range 18 to 38, body mass index 22.5±1.5 kg/m²). Thirteen subjects participated in the hydrocortisone protocol, but 5 subjects were excluded due to insufficient recording quality or evidence of electrode dislocation during the first or second experimental session. Eight subjects completed both sessions (4 women and 4 men, age range 24 to 38 years, body mass index 23.3±0.76 kg/m²). In the entire study group (n=25), resting MSA and serum cortisol levels were measured in a total of 49 experimental sessions (1 experiment for 1 subject, 2 experiments for each of 24 subjects, resting periods from the hydrocortisone protocol included).

Subjects were nonsmokers and were not taking any medications. They were asked to maintain their usual diet and were examined in the postabsorptive state, 6 hours before the start of the experiment. Sudden alterations in electrode position are easy to detect, whereas it may be difficult or impossible to recognize minor successive changes. Such subtle changes of the recording conditions will not usually affect the detection of bursts, but the mean voltage amplification amplitude or surface area of the bursts may change. Therefore, the risk that the electrode position will change during the course of the experiment. In microneurographic protocols of a long duration, there always is a possibility that the electrode position will change during the course of the experiment. Sudden alterations in electrode position are easy to detect, whereas it may be difficult or impossible to recognize minor successive changes. Such subtle changes of the recording conditions will not usually affect the detection of bursts, but the mean voltage amplification amplitude or surface area of the bursts may change. Therefore, the number of bursts/100 heartbeats or bursts/min is a much more robust measure of the strength of activity than are measures that include mean peak amplitude or surface area of the bursts. As such, it may be possible to detect bursts more easily in the presence of some movement artifact. In microneurographic protocols of a long duration, it may be possible to detect bursts more easily in the presence of some movement artifact. In microneurographic protocols of a long duration, it may be possible to detect bursts more easily in the presence of some movement artifact. In microneurographic protocols of a long duration, it may be possible to detect bursts more easily in the presence of some movement artifact.

**Data Analysis**

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15 minutes throughout the next 3 hours. Furthermore, the MSA activity of the final 15 seconds of the apneas was analyzed to monitor the effects of hydrocortisone on a transient sympathoexcitatory pair of recordings, in which 1 showed baseline shifts during the experiment, which could indicate a changed electrode position, were excluded from the crossover protocol (n=5).

For the correlation of basal MSA with basal cortisol levels, the final 5 minutes of the recorded resting period were used for analysis.

**Statistical Analysis**

The effects of cortisol were assessed by ANCOVA with the baseline period as covariant and treatment and time as repeated measures factors. A Greenhouse-Geisser corrected P value of <0.05 was considered statistically significant. The relationship between basal MSA and cortisol levels was assessed with regression analysis.

**Results**

**Biochemistry and Hormonal Data**

Serum concentrations of Na\(^+\) and K\(^+\) and serum osmolality did not differ between the 2 treatment conditions before the administration of the substances or after their infusion during a period of 180 minutes (Table). Baseline ACTH levels were similar for the 2 treatment groups. The infusion of hydrocortisone significantly suppressed ACTH secretion. This effect was observed after 40 minutes and remained stable until the end of the experiment (Table).

**Sympathetic Activity**

The MSA burst frequency before the administration of the substance was similar during the placebo and hydrocortisone sessions (16.6±2.2 versus 17.7±3.1 bursts/min). During 3 hours of placebo administration, MSA burst frequency increased successively, reaching a mean of 25.0±5.3 bursts/min at 180 minutes (56% increase; P<0.05 compared with baseline). In contrast, MSA burst frequency was reduced to a mean value of 13.1±3.2 bursts/min (25% decrease) at the end of the 3-hour hydrocortisone infusion. In relation to the baseline value before the administration of hydrocortisone, this decrease was not significant. However, compared with the placebo condition, there was a significant treatment effect (P<0.05; Figures 1 and 2). This suppressive hydrocortisone effect was significant at 100 minutes after the start of the infusion. The MSA changes during placebo and hydrocortisone infusions were similar regardless of whether nerve activity was expressed as burst frequency (burst/min) or burst incidence (burst/100 heartbeats) (Figure 2).

The mean duration of apneas was similar during both treatment conditions (placebo 74.9±1.6 seconds, hydrocortisone 75.6±1.6 seconds) and did not change during the course of the experiment. Apneas regularly caused a highly significant increase in the MSA burst frequency, regardless of the treatment condition. However, the sympathoexcitatory capacity of the apnea was blunted by hydrocortisone, with the increase in MSA burst frequency during the final 15 seconds of the apnea being lower (P<0.05) than that under the placebo condition at 180 minutes after infusion (Figure 3).

In 49 recordings, no relation was found between the basal MSA activity and the basal cortisol levels.

**Hemodynamic Data**

Oscillometrically measured blood pressure was not significantly different before the administration of hydrocortisone or placebo (133±4.8/82±3.8 versus 127±7.7/81±4.1 mm Hg, NS). Both systolic and diastolic blood pressures increased slightly during the placebo treatment, whereas they decreased during hydrocortisone administration. After 140 minutes, the hydrocortisone effect on blood pressure was significant for the systolic pressure, and there also was a trend toward a lowered diastolic pressure. At 160 and 180 minutes after the administration of hydrocortisone, both the diastolic and systolic pressures were significantly lower in the hydrocortisone-treated group (Figure 4). The heart rate was not significantly affected by the treatment.

**Discussion**

The present study demonstrates that the acute effects of an intravenous hydrocortisone injection in healthy humans are (1) a reduction in MSA, (2) a reduction in transient sympathoexcitatory responses to voluntary apneas, and (3) a reduction in blood pressure compared with a time-vehicle control group.

Corticosteroids bind to cytoplasmic receptors, which subsequently enter the nucleus and bind to a hormone response element of the DNA, which then initiates steroid-specific changes in protein synthesis. This classic GR-mediated pro-
cess starts ≈30 minutes after the administration of the hormone and reaches its maximum after 60 to 90 minutes,18 which is in good agreement with the onset of effects on MSA and blood pressure seen in our study. However, it cannot be excluded that a rapid membrane receptor–mediated effect of the steroid, which starts within minutes,19 contributed to our results.

The early MSA and blood pressure reductions demonstrated in the present study reveal a glucocorticoid effect that differs from its well characterized peripheral effects after long-term administration. A chronic elevation of corticosteroids increases blood pressure as a consequence of peripheral effects, which include sodium and volume retention together with an enhanced vascular contractility in response to vasoconstrictor substances.2–4 In our experiments with acute steroid administration, no significant effects were observed on serum electrolytes and osmolality, and the blood pressure was lower in the hydrocortisone condition. These changes could be explained by centrally elicited effects, which are likely to be hidden under circumstances of persistently elevated peripheral steroid levels. This interpretation is supported by studies with continuous intracerebroventricular glucocorticoid administration to avoid peripheral steroid effects, which have demonstrated blood pressure–lowering effects that persisted for long periods.20,21 The parallel decrease in MSA and blood pressure also supports a centrally mediated effect, decreasing blood pressure as result of a reduced sympathetic outflow.

Evidence that the central nervous system is an important site for the cardiovascular effects of adrenocortical hormones emanates from experiments in rats and dogs.8,22 The central administration of a pure glucocorticoid agonist decreases blood pressure, whereas the intracerebroventricular injection of corticosterone (the native steroid of the rat) affects blood pressure only in high doses.22 The intracerebroventricular administration of dexamethasone decreases blood pressure, cardiac output, and heart rate, whereas a systemic administration of the same substance enhances blood pressure.8 Mineralocorticoids, on the other hand, enhance blood pressure after both central and peripheral administration.22,23 Thus, the hemodynamic effects of adrenocortical steroids depend both on the region of action (ie, central versus peripheral) and the binding receptor (ie, GR versus MR). Whether the receptor is protected by 11β-hydroxysteroid-dehydrogenase type 2 is also of importance, because this enzyme inactivates cortisol and protects the MR from the corticosteroid, which would otherwise bind to the MR.24 An inhibition of this enzyme in the central nervous system has been shown to increase the blood pressure in animals.25 The corticosteroid receptor responsible for the observed sympathoinhibitory effect of hydrocortisone in our experiments remains to be elucidated. However, given the blood pressure decrease after that central administration of dexamethasone8,22 mentioned earlier, one could speculate that the high cortisol concentration in our experiment favored a vasodepressor GR effect.

In 2 previous studies, dexamethasone has been reported to blunt sympathoexcitatory responses in human subjects. Dexamethasone was administered for 2 days at a dose of 2 mg/d in

Figure 2. Hydrocortisone infusion (●) abolished slow increase in MSA seen in placebo session (○), with treatment effect being significant from 100 minutes on. Values are mean±SEM for muscle sympathetic burst frequency (bursts/min, left) and muscle sympathetic burst incidence (bursts/100 heartbeats, right) from 8 subjects (●P<0.08, *P<0.05, **P<0.01, ***P<0.005).

Figure 3. Hydrocortisone (cross-hatched columns) reduced sympathoexcitatory response to an inspiratory apnea, whereas responses remained unaffected throughout placebo session (filled columns). Histograms represent mean burst frequency (bursts/min, ±SEM) during final 15 seconds of an inspiratory apnea of maximal length in 8 normal subjects (*P<0.05).
Presently, it is not known which central sympathoexcitatory systems are affected by glucocorticoids. Corticosteroids suppress central nervous corticotropin-releasing hormone and increase hypothalamic neuropeptide. Both of these effects could cause a decrease in sympathetic outflow. Furthermore, a suppression of ACTH could contribute to the reduced MSA because this peptide has been shown to induce sympathoexcitation in humans. The diversity of the sympathoexcitatory responses found to be blunted argues against the notion that only 1 specific peptidergic system, like corticotropin-releasing hormone–containing neurons, is affected by the steroid. One could also consider a corticosteroid effect that directly affects autonomic centers. High densities of GR receptors have been demonstrated on neurons of different autonomic centers such as the locus ceruleus, the paraventricular nuclei, and nucleus tractus solitarii in rats.

Given the repeatedly demonstrated glucocorticoid effects on stimulated MSA and the effect on resting MSA of 5 days of hydrocortisone treatment, we also examined whether the prevailing activity of the hypophyseal/adrenocortical axis could be one predictor of MSA. However, the lack of correlation between cortisol levels and resting MSA in our study suggests that endogenous glucocorticoid levels are not tonically involved in the control of sympathetic outflow.

The results of our experiment, with a pharmacological cortisone dose commonly used in the clinical setting, may also apply to hydrocortisone levels in the high physiological range. Davis et al demonstrated that an infusion of hydrocortisone in a dose imitating the massive cortisol surge after hypoglycemia suppressed a hypoglycemia-induced activation of MSA the next day. This inhibition of the SNS could be one important factor that causes hypoglycemia unawareness in insulin-treated diabetics. In healthy subjects, a general cortisol-mediated inhibition of sympathoexcitation could be one important adaptive mechanism to repeated stress. This would not constitute an immediate cortisol-mediated feedback inhibition of an acute stress response, but the stress-induced cortisol surge would result in a feed-forward reduction in central sympathetic excitability in response to subsequent stressful events, while at the same time the peripheral steroid effects (eg, an enhanced responsiveness to catecholamines) would guarantee an appropriate reactivity of sympathetic effector organs. A disturbance in the central sympathoinhibitory corticosteroid effects could be one contributing factor to the well known sympathetic hyperreactivity in stressful situations in subjects who are likely to develop primary hypertension.

In conclusion, our study demonstrates an inhibitory effect of acutely administered hydrocortisone on stimulated MSA in healthy humans. The MSA inhibition was associated with a reduced blood pressure level and was most likely mediated directly via GRs within supraspinal autonomic centers. Basal cortisol levels did not correlate with basal MSA, suggesting a glucocorticoid role in the regulation of responsiveness rather than in tonic control of sympathetic outflow. The observed corticosteroid effects could represent an important mechanism for adaptation to repeated stress.
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References
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