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Glucocorticoids, Sympathetic Activity, and Presynaptic α_2-Adrenoceptor Function in Humans

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ABSTRACT

The sympathetic nervous system and the pituitary-adrenocortical system are two of the body's main stress effector systems. Animal studies have indicated that exogenously administered glucocorticoids inhibit sympathetic outflows and interfere with the function of presynaptic α_2-adrenoceptors modulating neuronal norepinephrine (NE) release. The present study tested whether glucocorticoids produce similar effects in humans. In a randomized, double-blind, placebo-controlled cross-over experiment, 15 healthy subjects took 20 mg prednisone or placebo orally daily each morning for 1 week, followed by the other drug after a 1-week washout. On the last day of each treatment week, blood samples were drawn for assays of plasma levels of catechols and ACTH before and after iv infusion of the α_2-adrenoceptor antagonist yohimbine (YOH) (0.125 mg/kg bolus, 0.001 $mg \cdot kg^{-1} \cdot min^{-1}$ infusion). In 7 subjects, directly recorded peroneal skeletal muscle sympathetic nerve activity (MSNA) was also measured at baseline and after YOH infusion at the end of both treatment weeks. Prednisone decreased plasma NE levels and MSNA compared with levels after placebo (1.09 ± 0.11 nmol/L *vs.* 1.40 ± 0.13 nmol/L, $P < 0.01$; 30 ± 4 bursts/min *vs.* 36 ± 3 bursts/min, $P < 0.05$) without affecting blood pressure or pulse rate. YOH increased mean arterial blood pressure by 12% ($P < 0.001$) and heart rate by 7% ($P < 0.05$); prednisone did not alter these effects of YOH. YOH-induced proportionate increments in plasma NE levels averaged about 10 times those in MSNA. Prednisone did not affect the YOH-induced proportionate increments in plasma NE levels (placebo, 243%; prednisone, 237%) or MSNA (placebo, 22%; prednisone, 23%). The decrements in MSNA and plasma NE levels after prednisone treatment indicate that glucocorticoids inhibit sympathoneural outflows in humans. The 10-fold larger NE than MSNA response to YOH confirms substantial inhibitory modulation of NE release by α_2-adrenoceptors on noradrenergic terminals, and the similarity of responses to YOH after prednisone or placebo suggests that glucocorticoid-induced sympathoinhibition occurs independently of altered modulatory function of α_2-adrenoceptors on noradrenergic terminals. (*J Clin Endocrinol Metab* **80:** 1804–1808, 1995)

THE HYPOTHALAMO-PITUITARY-ADRENOCORTICAL and sympathoneural systems interact in complex ways to maintain homeostasis: 1) exposure to stressors often increases hypothalamo-pituitary-adrenocortical and sympathoneural outflows concurrently; 2) central administration of corticotropin-releasing hormone evokes large increases in plasma levels of ACTH and catecholamines; 3) ACTH (probably via adrenal corticosteroids) increases activities of dopamine-β-hydroxylase and phenylethanolamine-N-methyltransferase, enhancing the capacity to synthesize norepinephrine (NE) and convert NE to epinephrine; 4) steroids generally inhibit extraneuronal uptake of catecholamines; and 5) steroids augment β-adrenoceptor-mediated processes (5, 6). Conversely, catecholaminergic pathways in the brain contribute to ACTH release (7), and β-adrenoceptor agonists increase (8) or decrease (9) pituitary ACTH secretion.

In laboratory animals, administration of glucocorticoids decreases plasma levels of catecholamines, inhibits catecholamine synthesis (10), and can attenuate plasma catecholamine responses to at least some stressors (11), suggesting that glucocorticoids inhibit sympathoneural outflows under resting conditions and during stress. Endogenous glucocorticoids restrain catecholaminergic responses to immobilization in conscious rats (12). The occurrence of glucocorticoid-induced attenuation of catecholaminergic stress responses seems to depend on the type of stressor (11, 13, 14).

Exogenously administered glucocorticoids may also interfere with the function of α_2-adrenoceptors on noradrenergic terminals in the brain and periphery. Thus, hypercortisolemic animals have blunted responses of levels of NE and its intraneuronal metabolite dihydroxyphenylglycol (DHPG) in brain microdialysate (10) and in plasma (15) after administration of the α_2-adrenoceptor blocker yohimbine (YOH).

Whether glucocorticoids decrease sympathoneural activity or plasma NE levels in humans, at baseline or in response to α_2-adrenoceptor blockade, has not been established. Such effects could be relevant clinically; α_2-adrenoceptor blockers are currently undergoing clinical trials as antidepressants, and many depressed patients have high circulating cortisol levels. More generally, such effects would implicate the α_2-adrenoceptor as a potentially important site of interaction between two of the main stress effector systems of the body.

We previously reported that YOH infusion in humans increases both MSNA and the rate of spillover of NE for a given amount of directly recorded skeletal muscle sympathetic nerve activity (MSNA), *i.e.* that α_2-adrenoceptors in the brain and on noradrenergic terminals in the periphery restrain NE release into the bloodstream (16). In this study, we examined the effects of 1 week of oral prednisone treatment on plasma levels of catechols and on MSNA, under resting conditions and in response to iv infused YOH, in a double-

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blind, placebo-controlled, randomized cross-over study of healthy adult volunteers. The study was designed to address whether glucocorticoid administration affects plasma NE and MSNA levels at baseline and in response to α_2-adrenoceptor blockade and if so whether the extent of attenuation of the MSNA and plasma NE responses are proportionately similar. If the extent of attenuation of the plasma NE response to YOH were the same as the extent of attenuation of the MSNA response to YOH, this would suggest that glucocorticoids interfere with YOH-induced increases in sympathetic nerve traffic, whereas if the extent of attenuation of the plasma NE response to YOH were larger than the extent of attenuation of the MSNA response to YOH, this would suggest that glucocorticoids interfere with YOH-induced NE release from sympathetic terminals for a given amount of nerve traffic. Thus, the study design enabled separate examination of effects of glucocorticoids on α_2-adrenoceptor restraint of central sympathetic outflow and on NE release from sympathetic terminals in the periphery.

Subjects and Methods

Subjects

Fifteen healthy volunteers (12 men and 3 women; mean age 33 yr, range 21–54 yr) participated in the study after giving written informed consent. All subjects had a normal medical history, physical examination, screening laboratory tests of blood and urine, and electrocardiogram. The participants refrained from smoking and from drinking alcohol or caffeinated beverages for 24 h before each YOH challenge test. The study protocol was approved by the Intramural Research Board of the National Institute of Neurological Disorders and Stroke.

Study design

All subjects were studied twice, after 20 mg prednisone per day for 7 days and after placebo for 7 days. The sequence of the double-blind treatments was randomized. Between the two treatments there was a washout period of 7 days. On the last day of each treatment, a YOH challenge test was performed. The subjects were advised to take the last dose 1 to 2 h before the YOH infusion. The chosen dose of prednisone is known to suppress hypothalamo-pituitary-adrenocortical activity (17).

Setup

The experiments were conducted in a quiet room with constant temperature (~ 24°C) and with the subjects in the supine position. Blood pressure was measured by an automated cuff device (Critikon, Tampa, FL). Heart rate was recorded continuously by electrocardiogram. An iv catheter was inserted in each arm, one iv for infusing YOH and one for sampling blood.

Microneurography

In seven subjects, multifiber recordings of MSNA were obtained successfully from a muscle fascicle of the peroneal nerve at the head of the fibula after each drug treatment. The course of the nerve was mapped by transcutaneous electrical stimulation (40–60 volts, 0.2 millisec, 1 hertz) with a pencil-shaped electrode. A sterile, tungsten wire microelectrode was then inserted in the region of the nerve. A similar reference electrode was inserted sc 1–3 cm from the recording electrode. Weak electrical stimuli (2–4 volts, 0.2 millisec, 1 hertz) were delivered to the recording electrode by a stimulator connected to an isolation unit. The elicitation of involuntary twitches in the foot indicated that the electrode tip was located within or was close to the muscle nerve fascicle. The electrode was then moved until there was acceptable recording from sympathetic nerve fibers. Recordings of MSNA were accepted if tapping or stretching the muscles or tendons supplied by the impaled nerve produced afferent mechanoreceptor discharges and rubbing the skin in the sensory field of the nerve evoked no afferent response and if spontaneous, pulse synchronous bursts of muscle sympathetic nerve activity were observed, with the frequency and amplitude of the bursts increaseing during held expiration but not during arousal stimuli. Electrodes remained in place throughout the study. The electrodes were connected to a preamplifier (gain 1000) and an amplifier (gain 70). The nerve signals were played through a loudspeaker, displayed on a monitor, and recorded using a MacLab/8 data recording system (MacLab, ADInstruments Pty, Ltd, Castle Hill, Australia) controlled by a Macintosh computer. The number and the amplitude of sympathetic bursts were measured during 5-min periods and expressed as bursts per min and μvolts per min. The measurements were performed by Peaks software from MacLab.

YOH infusion

After the subject had been at supine rest for 20 min, blood pressure and heart rate were recorded every 2 min for 10 min, and baseline blood samples (~ 10 cm^3) were drawn.

YOH hydrochloride was obtained from Sigma F and D Division (St. Louis, MO) and administered under Investigation New Drug number 21,220. YOH was injected as a bolus (0.125 $mg \cdot kg^{-1}$ for 3 min) followed by a continuous infusion at 0.001 $mg \cdot kg^{-1} \cdot min^{-1}$ for 12 min. Blood pressure and heart rate were recorded every 2 min during the infusion; the last three values were used for data analysis. In the last min of the infusion, another blood sample was drawn.

Assays

Blood samples were collected into chilled heparinized glass tubes and centrifuged at 4C and 3,500 × *g* for 15 min before storage of the plasma at −75C until assayed. Plasma levels of catechols were measured by liquid chromatography with electrochemical detection after adsorption on alumina (18). The limits of detection were about 0.04 nmol/L for NE and about 60 pmol/L for epinephrine.

ACTH assays were conducted using a dual antibody immunoradiometric assay (Allegro HS-ACTH; Nichols Institute, Los Angeles, CA), as previously described (19). The intraassay coefficients of variation were 20% and 6.5% at concentrations of 1.5 and 9.0 pmol/L, and the minimum detectable concentration was 0.44 pmol/L (range 0.22–1.1 pmol/L).

Data analysis

Results are presented as means ± SE. Responses were expressed both as absolute and as percentage changes from the resting value. The Wilcoxon signed rank test was used to compare the effects of prednisone and placebo on basal values and to assess the effects of YOH during placebo treatment. Two-way analyses of variance were used to test for interactions between prednisone and YOH. A P value less than 0.05 defined statistical significance.

Results

Effects of prednisone on basal values

Prednisone administration for 1 week did not affect systolic, diastolic, or mean blood pressure, heart rate, or body weight (Table 1). Plasma ACTH levels decreased significantly from 21.7 ± 5.6 pmol/L to 10.6 ± 3.7 pmol/L ($P < 0.05$). Plasma levels of NE decreased by 20% ($P < 0.01$), and DHPG levels decreased by 15% ($P < 0.01$). MSNA (bursts per min) decreased by 21% ($P < 0.05$, Table 1); the proportionate decrease in MSNA was larger (51%) when MSNA was expressed as μvolts per min ($P < 0.05$). Prednisone did not affect plasma levels of epinephrine, 3,4-dihydroxyphenylalanine, or dihydroxyphenylacetic acid. Urinary sodium excretion was not significantly affected by

TABLE 1. Effects of 1 week of treatment with placebo or prednisone (20 mg orally each morning) on responses of blood pressure, heart rate, plasma levels of catechols, and skeletal muscle sympathetic nerve activity (MSNA) responses to yohimbine (YOH) in healthy volunteers[a]

	Placebo		Prednisone	
	Baseline	YOH	Baseline	YOH
Systolic BP (mm Hg)	121 ± 4[b]	136 ± 5	119 ± 3[b]	133 ± 4
Diastolic BP (mm Hg)	70 ± 2[b]	77 ± 2	70 ± 1[b]	76 ± 2
MAP (mm Hg)	87 ± 2[b]	97 ± 3	86 ± 2[b]	95 ± 2
Heart rate (beats/min)	63 ± 2[b]	67 ± 3	64 ± 3[c]	67 ± 3
Plasma NE (nmol/L)	1.40 ± 0.13[b]	4.83 ± 0.56	1.09 ± 0.11[b,d]	3.47 ± 0.38
Plasma E (pmol/L)	150 ± 30	220 ± 40	110 ± 20[c]	150 ± 30
Plasma DHPG (nmol/L)	6.10 ± 0.37[e]	7.59 ± 0.49	5.02 ± 0.24[b,d]	6.37 ± 0.29
Plasma DOPA (nmol/L)	9.08 ± 0.71	9.16 ± 0.82	7.68 ± 0.39	8.24 ± 0.38
Plasma DOPAC (nmol/L)	8.05 ± 1.09	8.70 ± 1.24	8.90 ± 1.48	9.06 ± 1.56
MSNA (bursts/min)	36 ± 3[c]	44 ± 4	30 ± 4[e,f]	35 ± 4
MSNA (μvolts/min)	6.56 ± 0.93[c]	9.45 ± 1.72	3.26 ± 0.31[c,f]	4.69 ± 0.65

BP, blood pressure; MAP, mean arterial blood pressure; DHPG, dihydroxyphenylglycol; DOPAC, dihydroxyphenylacetic acid.
[a] MSNA recording was carried out in 7 out of the 15 subjects.
[b] $P < 0.001$ (YOH *vs.* baseline).
[c] $P < 0.05$ (YOH *vs.* baseline).
[d] $P < 0.01$ (baseline value, prednisone *vs.* placebo).
[e] $P < 0.01$ (YOH *vs.* baseline).
[f] $P < 0.05$ (baseline value, prednisone *vs.* placebo).

prednisone (after placebo, 9.6 ± 1.9 mmol sodium per mmol creatine excretion; after prednisone, 9.8 ± 1.6 mmol sodium per mmol creatinine excretion).

Effects of YOH infusion during placebo phase

During placebo treatment, YOH increased systolic, diastolic, and mean arterial blood pressure significantly by 13%, 11%, and 12% (all $P < 0.001$), respectively, and heart rate by 7% ($P < 0.05$; Table 1). YOH also increased plasma NE levels and MSNA (bursts per min) in all subjects. The mean increment in plasma NE levels was 243% (Fig. 1), about 10-fold larger than the 22% increase in MSNA (Fig. 2). Plasma DHPG levels increased by 25% (Table 1). MSNA (μvolts per min) increased by about 40%. Plasma epinephrine levels did not increase significantly, and plasma 3,4-dihydroxyphenylalanine and dihydroxyphenylacetic acid levels were unchanged.

Effects of YOH during prednisone treatment phase

Prednisone did not affect absolute or percentage responses of blood pressure or heart rate to YOH (Table 1). The absolute increment in plasma NE levels during YOH infusion was not significantly smaller after prednisone than after placebo (2.38 ± 0.34 nmol/L and 3.44 ± 0.46 nmol/L, $0.05 < P < 0.10$); the proportionate increments did not differ (237 ± 41% and 243 ± 24%, Fig. 1). Prednisone also did not influence the YOH-induced proportionate increments in plasma DHPG levels (Table 1).

Analogously, neither absolute nor proportionate responses of MSNA to YOH differed between placebo (7 ± 3 bursts/min, 22 ± 7%) and prednisone (6 ± 1 bursts/min, 23 ± 7%) treatments (Fig. 2). The proportionate plasma NE response to YOH remained about 10 times the MSNA response. Analyses of variance revealed no interaction between the effects of prednisone and of YOH for any of the dependent neuronal or neurochemical measures. The relative responses of NE levels and MSNA (Δ%NE/Δ%MSNA) also did not differ between the prednisone and placebo treatments.

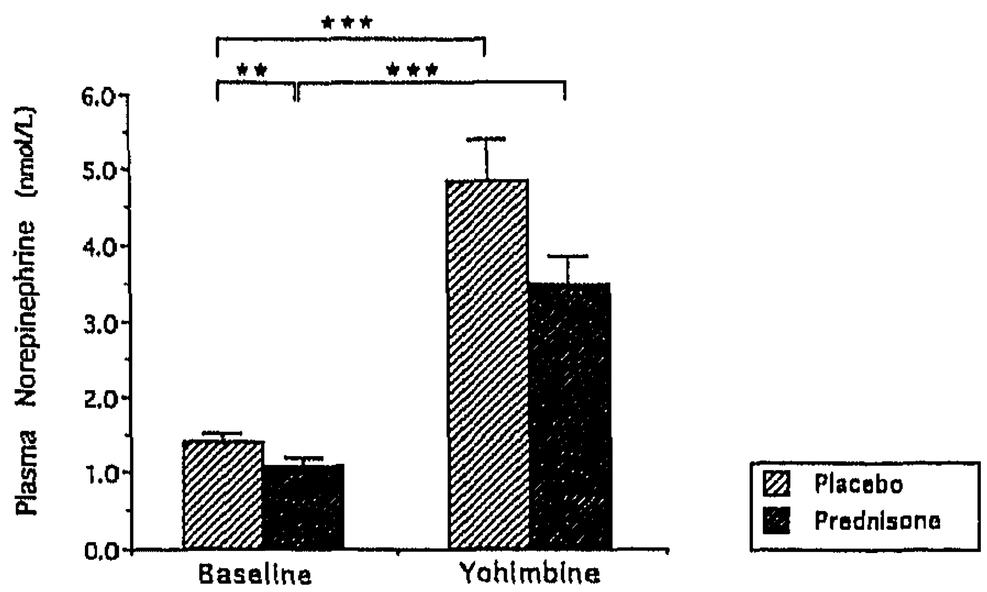

FIG. 1. Mean (± SEM) plasma NE levels at baseline and during infusion of YOH after 1 week of placebo and after 1 week of prednisone *(upper panel)* and absolute and percentage responses of NE levels during YOH infusion *(lower panel)* (**$P < 0.01$; ***$P < 0.001$).

Discussion

The results show that oral prednisone treatment for 1 week at a dose of 20 mg each morning produces sympathoinhibition, because directly recorded MSNA and plasma levels

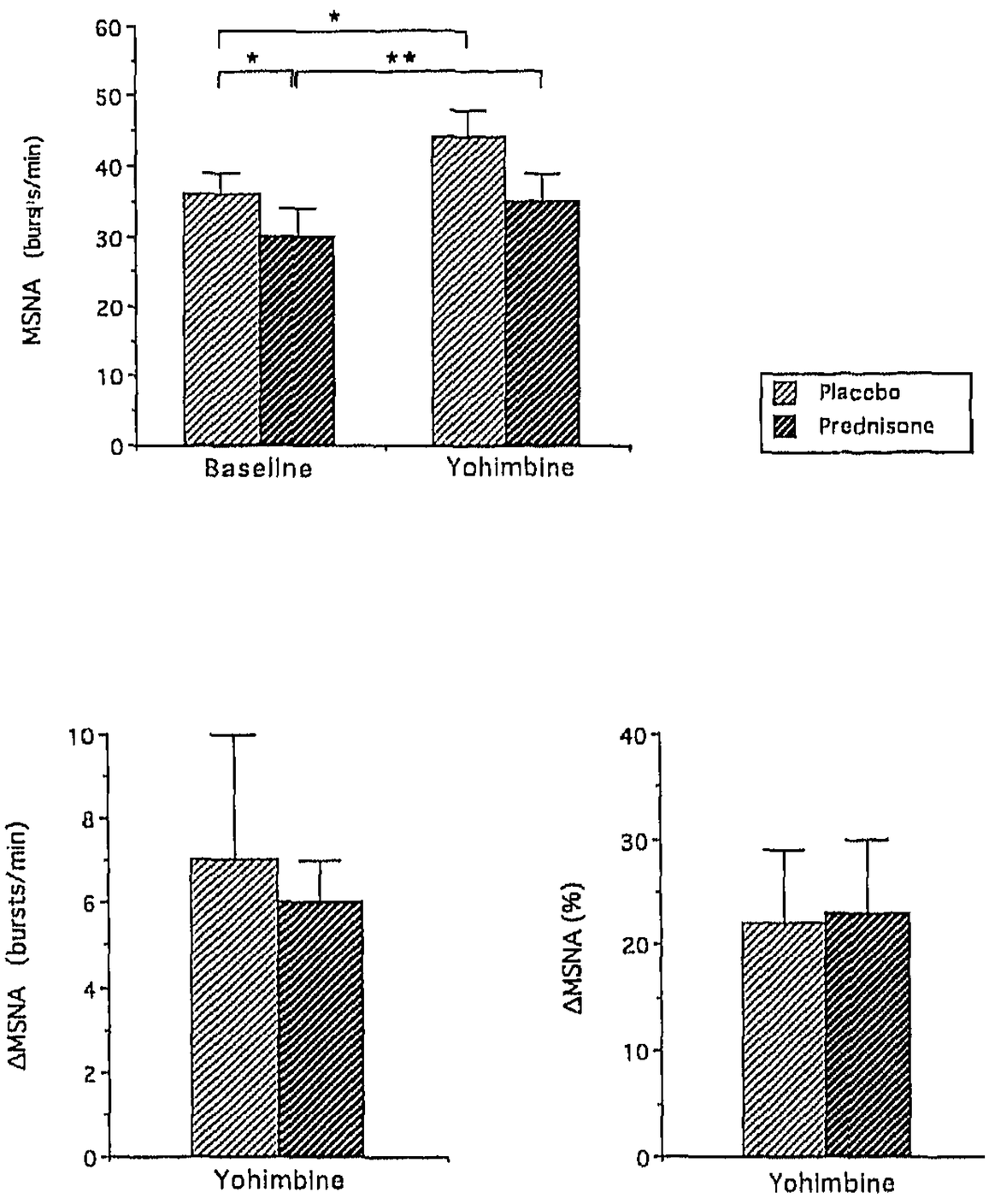

FIG. 2. MSNA expressed as bursts per min (mean ± SEM) at baseline and during infusion of YOH after 1 week of placebo and after 1 week of prednisone *(upper panel)* and absolute and percentage responses of MSNA to YOH infusion *(lower panel)* (**$P < 0.01$; ***$P < 0.001$).

of the sympathetic neurotransmitter NE and of the intraneuronal NE metabolite DHPG were significantly lower after prednisone treatment than after placebo treatment in the same subjects. The double-blind, placebo-controlled, randomized cross-over design excluded important sequence effects or observer biases. The sympathoinhibition probably resulted at least partly from effects of prednisone in the central nervous system or sympathetic ganglia, because prednisone decreased the rate of directly recorded sympathetic nerve traffic in the peroneal nerve, and because peroneal sympathetic fibers are postganglionic (16).

Studies of laboratory animals have indicated that α_2-adrenoceptors in the brain tonically inhibit sympathoneural outflows (20). The same may hold true for humans, because patients with spinal cord transections with disruption of descending pathways from the brain to the intermediolateral columns of the thoracolumbar spinal cord do not demonstrate a decrease in blood pressure in response to clonidine (21), and iv infusion of the α_2-adrenoceptor blocker YOH in healthy volunteers increases MSNA (16). An increase in the number or affinity of central α_2-adrenoceptors during prednisone treatment could therefore inhibit sympathoneural outflows. Consistent with this view, elevated plasma cortisol levels in anorexic patients are associated with an increased number of platelet α_2-adrenoceptors (22); however, such an effect of prednisone would be expected to augment sympathoneural responses to α_2-adrenoceptor blockade, and the present results failed to confirm this hypothesis.

Other animal studies have suggested that glucocorticoids interfere with the modulatory function of α_2-adrenoceptors in the brain and periphery (5, 10). The failure in the present study to detect attenuation of responses of either MSNA or of plasma NE levels after prednisone treatment casts doubt on the generalization of these findings in rats to healthy adult humans.

In the present study, the proportionate increases in antecubital venous plasma NE levels during YOH infusion averaged about 10 times those in MSNA, confirming previous clinical reports that the human forearm possesses abundant, functional α_2-adrenoceptors on sympathetic nerves (23).

Prednisone treatment failed to attenuate the marked effects of YOH on plasma NE or MSNA levels. The fact that there was no significant difference in the relative plasma NE response for a given neural response (Δ%NE/Δ%MSNA) to YOH between the prednisone and placebo treatments suggests the absence of an effect of prednisone on the modulatory function of presynaptic α_2-adrenoceptors in the periphery. Therefore the findings are consistent with the view that the sympathoinhibition produced by prednisone occurs independently of effects of prednisone on the function of peripheral and central neural α_2-adrenoceptors.

Plasma DHPG levels reflect NE turnover in sympathetic nerves (24, 25). The fall in plasma DHPG levels after prednisone treatment therefore confirms glucocorticoid-induced sympathoinhibition. YOH increases plasma DHPG levels in humans because of reuptake and intraneuronal oxidative deamination of endogenously released NE (24). The finding that increments in plasma DHPG levels during YOH infusion did not differ after placebo or prednisone treatment suggests that prednisone does not interfere with neuronal uptake of NE (Uptake-1) or with monoamine oxidase. Because of the relatively small proportion of endogenously released NE that is removed by nonneuronal uptake (Uptake-2, reference 26), prednisone treatment would not be expected to alter plasma NE responses to YOH, even though exogenously administered steroids inhibit Uptake-2 (4).

Several reports noted glucocorticoid-induced augmentation of pressor or vasoconstrictor responses to exogenously administered NE and augmentation of tachycardic responses to β-adrenoceptor agonists (5, 27). In the present study, YOH-induced pressor and tachycardic responses were similar after placebo and after prednisone. These results suggest that glucocorticoids may not accentuate responses for a given amount of endogenously released NE in humans, but a simultaneous effect of prednisone on other vasopressor or depressor hormone systems could have obscured an augmented pressor response to YOH.

In conclusion, administration of prednisone to humans causes sympathoinhibition. In contrast to previous findings in laboratory animals, this inhibition seems to occur independently of inhibitory modulation of sympathoneural outflows by α_2-adrenoceptors in the central nervous system and of inhibitory modulation of NE release by α_2-adrenoceptors on noradrenergic terminals in the periphery.

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