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Glucocorticoid-induced sympathoinhibition in humans

Objective: To test whether glucocorticoids inhibit sympathetic nerve activity or norepinephrine release in humans, as has been suggested by results in laboratory animals.

Methods: This was a double-blind, placebo-controlled, randomized crossover study performed at the Clinical Center of the National Institutes of Health. Thirteen normal volunteers received 20 mg prednisone or placebo orally each morning for 1 week, followed by a washout period of 1 week and then by treatment with the other drug for 1 week. On the last day of each treatment week, blood samples were drawn for measurements of plasma levels of catecholamines and their metabolites, of cortisol, and of corticotropin at baseline and during reflexive sympathetic stimulation elicited by lower body negative pressure (-15 mm Hg). A 24-hour urine collection was obtained at the end of each week of treatment for measurement of urinary excretion of catechols. In eight subjects, directly recorded peroneal skeletal muscle sympathetic nerve activity was also measured after both treatments.

Results: Prednisone significantly decreased sympathetic nerve activity by $23\% \pm 6\%$, plasma norepinephrine levels by $27\% \pm 6\%$, and plasma corticotropin levels by 77%. Blood pressure, heart rate, body weight, and urinary excretion of catechols and electrolytes were unaffected. Prednisone did not alter proportionate increments in sympathetic nerve activity or plasma norepinephrine levels during lower body negative pressure. Relationships between sympathetic nerve activity and plasma norepinephrine levels were unchanged.

Conclusions: Glucocorticoids decrease sympathoneural outflows in humans without affecting acute sympathoneural responses to decreased cardiac filling and probably without affecting presynaptic modulation of norepinephrine release. (CLIN PHARMACOL THER 1995;58:90-8.)

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The hypothalamo-pituitary-adrenocortical (HPA), sympathoneural, and adrenomedullary systems interact complexly to maintain homeostasis. Exogenously administered glucocorticoids are well known to inhibit HPA activity. This study focused on effects of exogenously administered glucocorticoids on sympathoneural function.

Whether glucocorticoids inhibit sympathoneural outflows at baseline or during exposure to stimuli that increase sympathoneural outflows reflexively has been unclear. In rats, hypercortisolemia decreases plasma levels of catecholamines and inhibits catecholamine synthesis, and endogenous glucocorticoids restrain nor-

adrenergic responses to immobilization.^{1,2} These effects are associated with decreased catecholamine synthesis and decreased norepinephrine release in the brain.³ In humans, Stene et al.⁴ found that oral dexamethasone decreased plasma norepinephrine levels at baseline and during orthostasis, whereas Rupprecht et al.⁵ and Scherrer et al.⁶ did not. Scherrer et al.⁶ also reported that dexamethasone did not affect directly recorded skeletal muscle sympathetic nerve activity at baseline or during the cold pressor test. Sudhir et al.⁷ reported that oral hydrocortisone treatment for 1 week at a dose of 200 mg/day increased systolic blood pressure and enhanced forearm vascular responses to intraarterial norepinephrine but did not significantly alter estimated rates of norepinephrine spillover into arterial or forearm venous plasma.

We examined the effects of 1 week of oral treatment with prednisone on plasma levels of catechols and on sympathetic nerve activity, during resting conditions and in response to lower body negative pres-

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sure, in a double-blind, placebo-controlled, randomized crossover study of healthy adult volunteers. The study was designed to determine whether 1 week of glucocorticoid administration to humans would affect sympathetic nerve activity, plasma norepinephrine levels, or urinary norepinephrine excretion and whether the extents of these effects would be proportionately similar. The study also addressed whether prednisone treatment alters sympathetic nerve activity or norepinephrine responses to lower body negative pressure, a laboratory model of orthostasis that decreases cardiac filling and reflexively increases sympathetic outflow.⁸

METHODS

Subjects. Thirteen healthy volunteers (10 men and three women; mean age, 33 years; age range, 21 to 54 years) participated in the study after each gave written informed consent. Each subject had a normal medical history, physical examination, screening laboratory tests of blood and urine, and electrocardiogram (ECG). The participants refrained from smoking and from drinking alcohol or caffeinated beverages for 24 hours before each testing session. 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 each morning for 7 days and after placebo for 7 days. The sequence of the double-blind treatments was randomized. Between the treatments there was a washout period of 7 days. A testing session occurred on the last day of each treatment. The subjects were advised to take the last dose 1 to 2 hours before the testing session. The chosen dose of prednisone is known to suppress HPA activity.⁹

On the morning of each testing session, each subject delivered a 24-hour collection of spontaneously voided urine in a container to which 30 ml of 6 mol/L hydrochloric acid had been added. The urine volume was recorded and an aliquot frozen for assays of levels of catechols, creatinine, sodium, and potassium.

Setup. The experiments were conducted in a quiet room with constant temperature (about 24° C) and with the subjects in the supine position. Blood pressure was measured with an automated cuff device (Critikon, Inc., Tampa, Fla.). Heart rate was recorded continuously by ECG. An intravenous catheter was inserted for sampling blood.

Microneurography. In eight subjects, multifiber recordings of sympathetic nerve activity were obtained successfully after both drug treatments from a muscle

fascicle of the peroneal nerve at the head of the fibula. The right and left peroneal nerves were used alternatively for the two study sessions. The course of the nerve was mapped with transcutaneous electrical stimulation (40 to 60 V, 0.2 msec, 1 Hz) with use of a pencil-shaped electrode. A sterile tungsten-wire microelectrode was inserted in the region of the nerve. A similar reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. Weak electrical stimuli (2 to 4 V, 0.2 msec, 1 Hz) were delivered to the recording electrode with a stimulator connected to an isolation unit. The elicitation of involuntary twitches in the lower leg indicated that the electrode tip was located within or close to the muscle nerve fascicle. The electrode was then moved until there was acceptable recording from sympathetic nerve fibers. Recording of sympathetic nerve activity was accepted if (1) tapping or stretching the muscles or tendons supplied by the impaled nerve produced afferent mechanoreceptor discharges, while rubbing the skin in the sensory field of the nerve evoked no afferent response, and (2) spontaneous, pulse-synchronous bursts of muscle sympathetic nerve activity were observed, with the frequency and amplitude of the bursts increasing 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 with the MacLab/8 data recording system (ADInstruments, Castle Hill, Australia) and a Macintosh computer. The number and the amplitude of sympathetic bursts were measured during 5-minute periods and expressed in bursts per minute and microvolts per minute. The measurements were performed with use of Chart and Peaks software from ADInstruments.

Lower body negative pressure. The legs and lower abdomen of the subject were enclosed in a specially designed lower body negative pressure chamber, with a hinged door permitting access to the leg for nerve recordings (Medical Instruments, University of Iowa, Iowa City, Iowa). The chamber was sealed around the upper abdomen of the subject with plastic sheeting and was attached to a vacuum motor.

Experimental protocol. After the subject had been at supine rest for at least 15 minutes, blood pressure was recorded each minute and heart rate and sympathetic nerve activity were recorded continuously for 5 minutes. Baseline blood samples (about 10 ml) were drawn. Lower body negative pressure was then applied at -15 mm Hg for 15 minutes. Blood pressure

Table I. Effects of prednisone treatment (20 mg orally each morning) on blood pressure, heart rate, skeletal muscle sympathetic nerve activity, and plasma levels of catechols, at baseline and in response to lower body negative pressure (-15 mm Hg) in healthy volunteers

	Placebo		Prednisone	
	Baseline	LBNP	Baseline	LBNP
Body weight (kg)	75.7 ± 4.0		76.0 ± 4.1	
Systolic BP (mm Hg)	123 ± 5**	119 ± 5	116 ± 3	117 ± 4
Diastolic BP (mm Hg)	69 ± 3	70 ± 2	67 ± 1	67 ± 1
MAP (mm Hg)	87 ± 3	86 ± 3	84 ± 2	84 ± 2
Heart rate (beats/min)	63 ± 3	64 ± 3	61 ± 3**	64 ± 3
Sympathetic nerve activity (bursts/min)	42 ± 3*	48 ± 4	33 ± 4†††**	37 ± 5††
Sympathetic nerve activity (μV/min)	98.6 ± 12.8*	157.1 ± 25.7	52.9 ± 5.7††	74.3 ± 14.3†
Norepinephrine (nmol/L)	1.46 ± 0.14**	1.88 ± 0.22	1.02 ± 0.10††***	1.32 ± 0.12††
Epinephrine (nmol/L)	0.15 ± 0.03	0.14 ± 0.03	0.11 ± 0.02	0.11 ± 0.02
Dihydroxyphenylglycol (nmol/L)	6.00 ± 0.36	6.41 ± 0.47	4.75 ± 0.21††**	5.26 ± 0.32††
Dihydroxyphenylalanine (nmol/L)	8.87 ± 0.66	9.47 ± 0.90	7.40 ± 0.46††*	7.83 ± 0.53
Dihydroxyphenylacetic acid (nmol/L)	9.95 ± 1.69	9.06 ± 1.14	9.14 ± 1.41	9.31 ± 1.29

LBNP, Lower body negative pressure; BP, blood pressure; MAP, mean arterial blood pressure.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, lower body negative pressure versus baseline.† $p < 0.05$; †† $p < 0.01$; ††† $p < 0.001$, prednisone versus placebo.

was recorded each minute, and heart rate and sympathetic nerve activity were recorded continuously for the last 5 minutes of lower body negative pressure. In the last minute of lower body negative pressure, another blood sample was drawn.

Assays. Blood samples were collected into chilled heparinized glass tubes and centrifuged at 4° C and 3500g for 15 minutes before storage of the plasma at -75° C until assayed. Plasma and urine levels of catechols were assayed by liquid chromatography with electrochemical detection after adsorption on aluminum oxide.^{10,11} The limits of detection were about 0.04 nmol/L for norepinephrine and about 0.06 nmol/L for epinephrine. Intraassay and interassay coefficients of variation for catechol assays in this laboratory have been published previously.¹⁰ Urine concentrations of creatinine, sodium, and potassium were assayed according to standard clinical laboratory methods. Serum cortisol levels were measured by radioimmunoassay (Quanticat, Kallestad Diagnostics, Chaska, Minn.). The antibody crossreacts minimally with prednisone at 0.39% and has a sensitivity of 0.5 μg/dl. The intraassay coefficient of variation (CV) was less than 10%. Plasma corticotropin levels were measured by a highly specific two-site radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, Calif.) with a sensitivity of 1 pg/ml and intra-assay coefficient of variation of less than 5%.

Data analysis. Results are presented as mean values ±SE. Responses were expressed both as absolute and

as percentage changes from the resting values. Paired *t* tests were used to compare the effects of prednisone on basal values and to assess the effects of lower body negative pressure during each treatment. Two-way ANOVA was used to test for interactions between prednisone treatment and responses to lower body negative pressure. The average coefficient of correlation between sympathetic nerve activity and plasma norepinephrine levels was calculated using the Fisher *z* transformation. A *p* value less than 0.05 defined statistical significance.

RESULTS

Effects of prednisone. Prednisone administration at a dose of 20 mg each morning for 1 week did not affect systolic, diastolic, or mean blood pressures, heart rate, or body weight (Table I). Plasma cortisol levels averaged 9.9 ± 1.3 μg/dl during placebo and 8.6 ± 1.4 μg/dl during prednisone (difference not significant). Plasma corticotropin levels decreased by a mean of 77%, from 25.2 ± 5.6 to 5.1 ± 1.3 pg/ml ($p < 0.01$).

For all eight subjects in whom microneurographic recordings were obtained successfully after both treatments, prednisone suppressed sympathetic nerve activity (Table I). The proportionate decrease averaged 23% ± 6% when sympathetic nerve activity was expressed as bursts per minute and 42% ± 7% when sympathetic nerve activity was expressed as microvolts per minute. Individual values for sympathetic

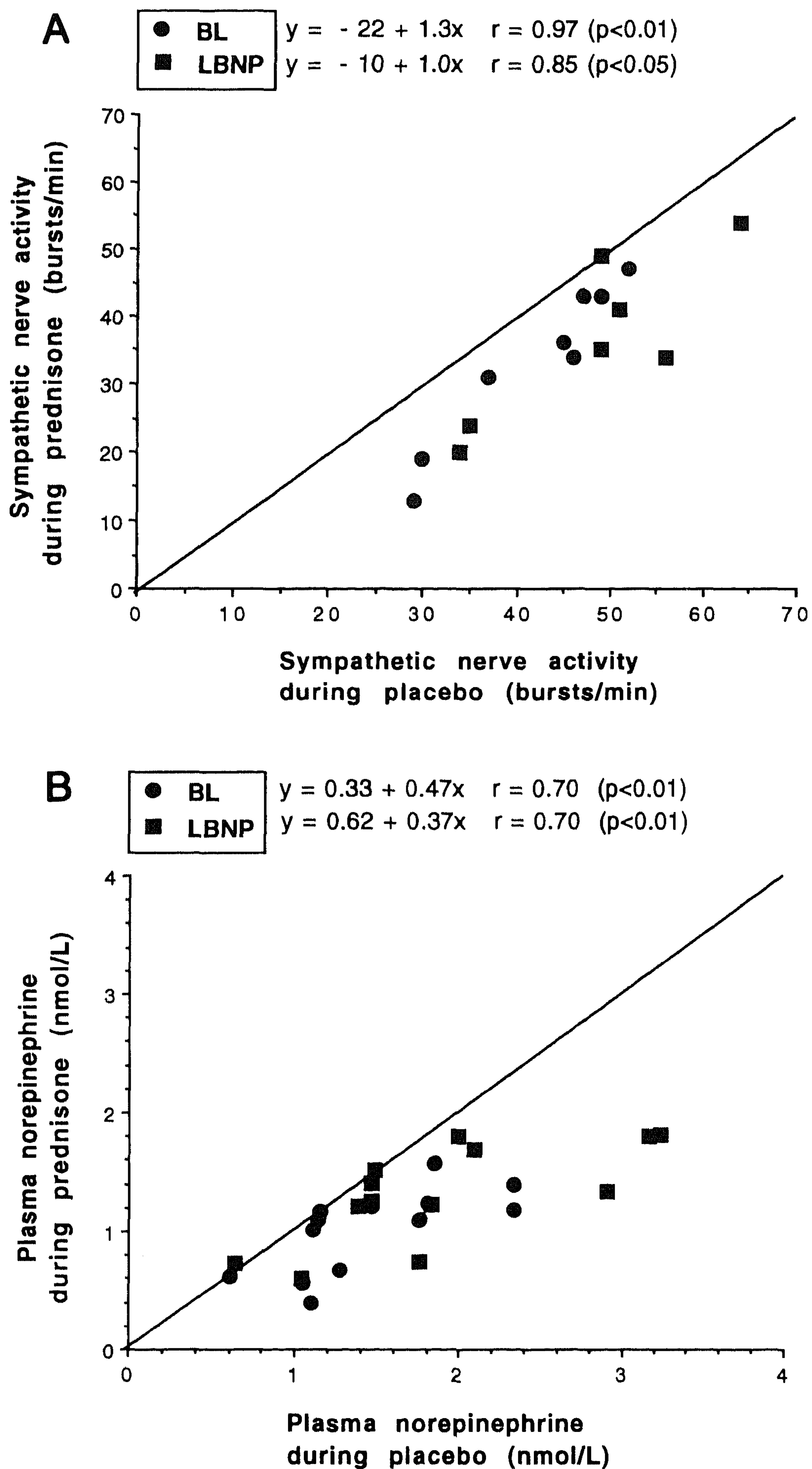


Fig. 1. Correlations between indexes of sympathetic nervous system activity after placebo and prednisone treatment, at baseline (BL) and during lower body negative pressure (LBNP). **A**, Muscle sympathetic nerve activity. **B**, Antecubital venous plasma levels of norepinephrine.

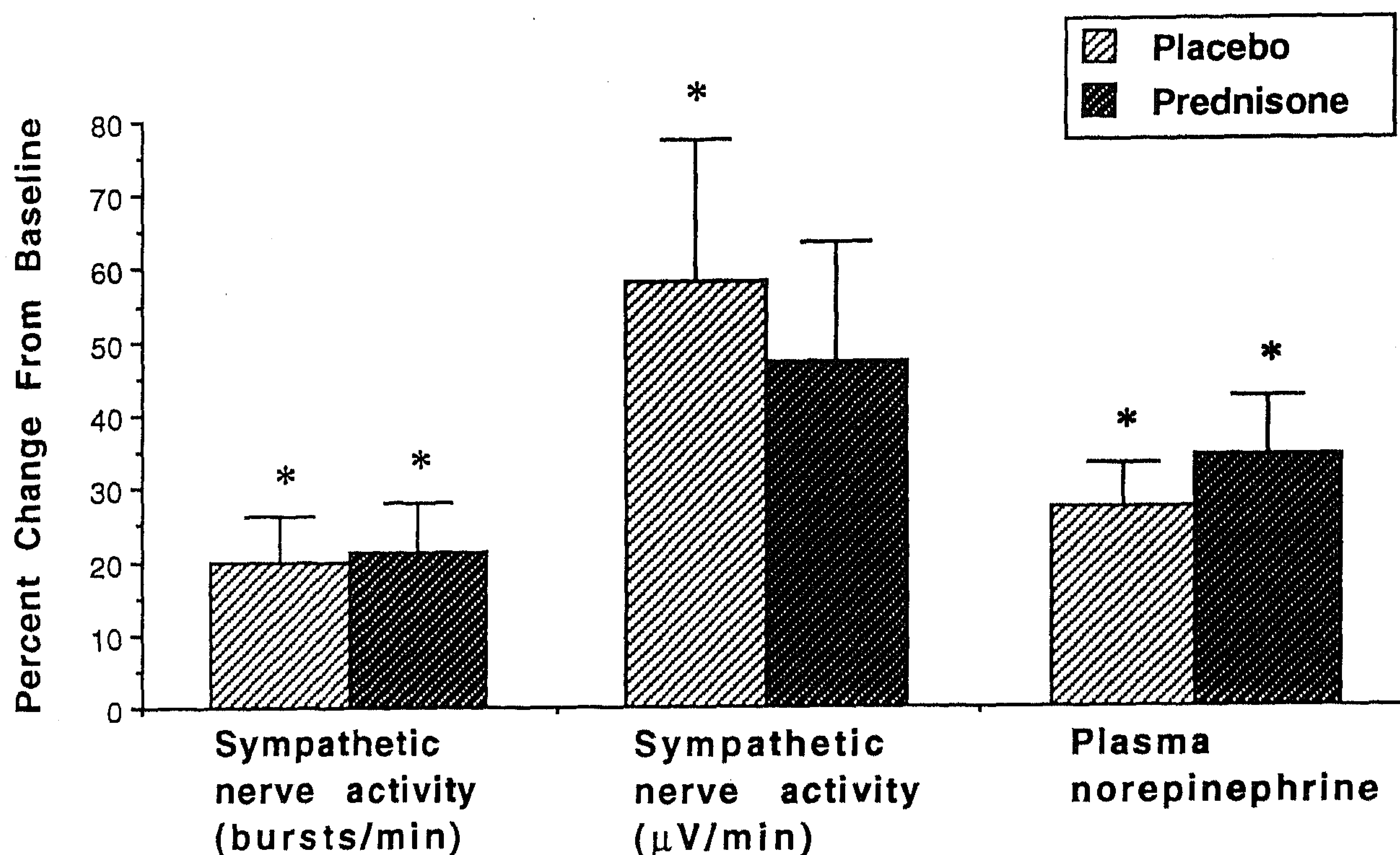


Fig. 2. Percentage changes in sympathetic nervous system activity produced by lower body negative pressure (-15 mmHg) after placebo or prednisone treatment. Muscle sympathetic nerve activity is expressed in bursts per minute (bursts/min) or in total amplitude per minute (μ V/min). *Denotes significant increase from baseline, $p < 0.05$.

Table II. Effects of prednisone (20 mg orally each morning) on 24-hour urinary excretion of electrolytes, creatinine, and catechols in normal volunteers

	Placebo	Prednisone
Creatinine (gm)	1.70 ± 0.24	1.62 ± 0.19
Sodium (mmol)	128 ± 25	132 ± 26
Potassium (mmol)	62 ± 9	56 ± 13
Norepinephrine (nmol)	1.61 ± 0.31	1.61 ± 0.27
Epinephrine (nmol)	0.21 ± 0.05	0.14 ± 0.02
Dopamine (nmol)	10.43 ± 1.30	10.39 ± 0.98
Dihydroxyphenylglycol (nmol)	2.74 ± 0.39	2.87 ± 0.38
Dihydroxyphenylalanine (nmol)	0.74 ± 0.13	0.76 ± 0.15
Dihydroxyphenylacetic acid (nmol)	49.7 ± 8.9	55.5 ± 9.6
Volume (ml)	1173 ± 109	1280 ± 253

There were no statistically significant differences in values for the above indexes between the placebo and prednisone treatments.

nerve activity in the two study sessions were closely related, and the slopes of the regression lines were close to 1 (Fig. 1, A).

Plasma norepinephrine levels decreased significantly by $27\% \pm 6\%$ during prednisone treatment. Plasma norepinephrine levels were positively corre-

lated between the two treatments (Fig. 1, B); the slopes of the regression lines for plasma norepinephrine levels were significantly smaller than 1. Prednisone also significantly decreased plasma levels of dihydroxyphenylglycol (DHPG) by $18\% \pm 5\%$ and dihydroxyphenylalanine (DOPA) by $15\% \pm 4\%$. Prednisone did not significantly alter plasma levels of epinephrine or dihydroxyphenylacetic acid (DOPAC, Table I).

Prednisone treatment did not affect 24-hour urinary excretion rates of norepinephrine or of other catechols (Table II). The 24-hour urinary excretion rates of sodium, potassium, and creatinine did not differ between the two treatment phases.

Effects of lower body negative pressure. After placebo treatment, lower body negative pressure produced slight but consistent decreases ($p < 0.01$) in systolic blood pressure, without affecting diastolic or mean blood pressure or heart rate (Table I).

Lower body negative pressure increased sympathetic nerve activity and plasma norepinephrine levels in all subjects. Sympathetic nerve activity increased by $20\% \pm 6\%$ when expressed as bursts per minute and by $58\% \pm 19\%$ when expressed as microvolts per minute (Fig. 2). Plasma norepinephrine levels increased by $27\% \pm 6\%$. Plasma dihydroxyphenylglycol levels increased slightly and nonsignificantly by

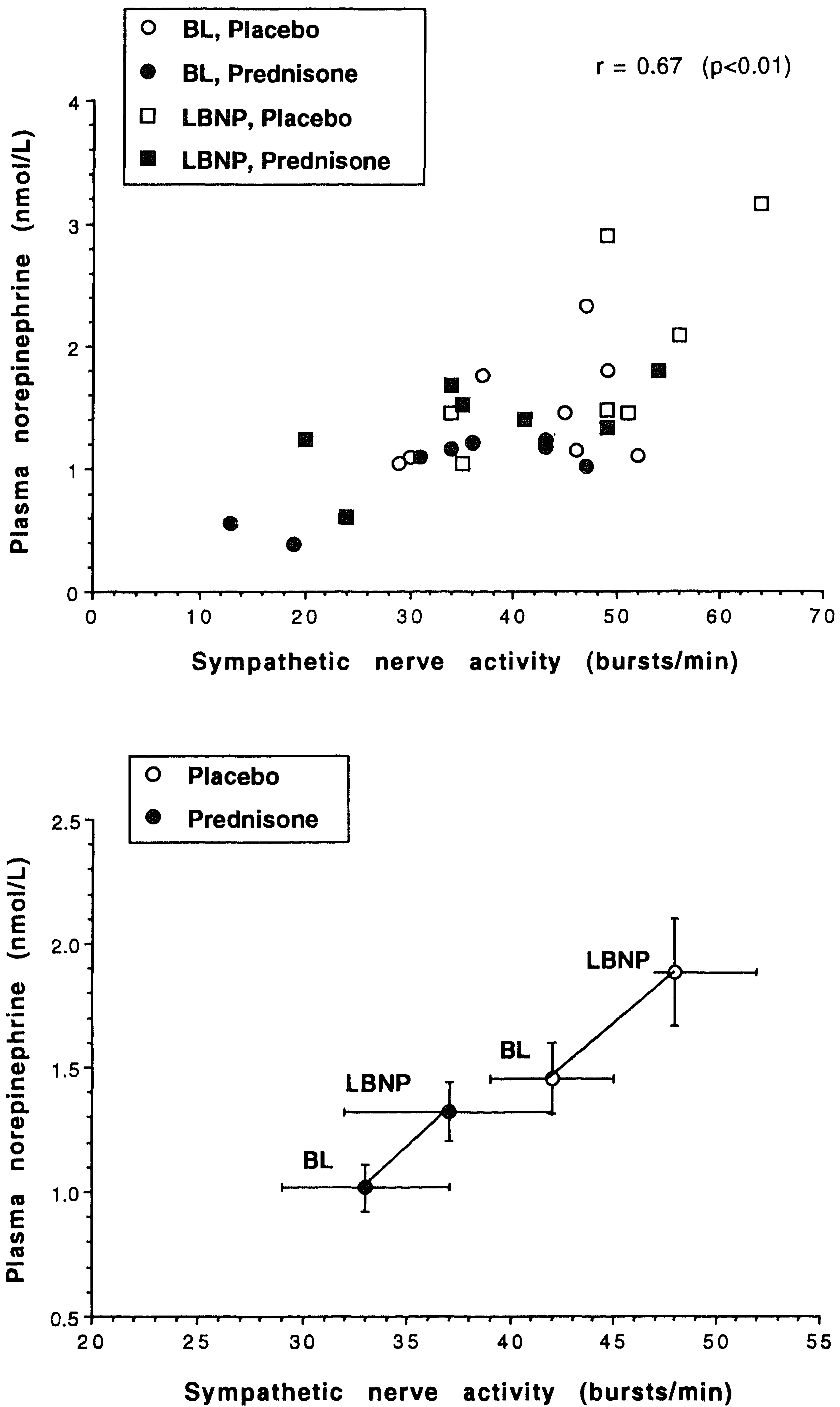


Fig. 3. Relationships between muscle sympathetic nerve activity and plasma levels of norepinephrine after placebo and prednisone treatment. BL, Baseline; LBNP, lower body negative pressure (−15 mmHg). **Top panel,** Individual values. **Bottom,** Mean values ± SEM.

7% \pm 3% (Table I); plasma epinephrine, dihydroxyphenylalanine, and dihydroxyphenylacetic acid levels were unchanged.

Effects of prednisone on responses to lower body negative pressure. After prednisone treatment, lower body negative pressure did not affect systolic, diastolic or mean blood pressures and slightly but consistently increased heart rate ($p < 0.01$; Table I). ANOVA indicated a significant effect of prednisone treatment on responses of systolic blood pressure to lower body negative pressure.

Neither absolute nor proportionate responses of sympathetic nerve activity during lower body negative pressure differed between placebo (8 ± 2 bursts/min; 20% \pm 6%) and prednisone (5 ± 1 bursts/min; 21% \pm 7%) treatments (Table I; Fig. 2). The mean absolute and proportionate increments in plasma norepinephrine levels during lower body negative pressure were not significantly changed by prednisone treatment (0.30 ± 0.06 versus 0.42 ± 0.11 nmol/L and 34% \pm 8% versus 27% \pm 6%; Table I; Fig. 2). After prednisone, plasma dihydroxyphenylglycol levels during lower body negative pressure increased by 10% \pm 3% ($p < 0.01$; Table I), an amount that did not differ from that after placebo. Responses of plasma epinephrine, dihydroxyphenylalanine, and dihydroxyphenylacetic acid levels during lower body negative pressure also did not differ between the two treatments. ANOVA revealed no significant interaction effects between prednisone treatment and responses of any of the dependent neuronal or neurochemical measures during lower body negative pressure.

Antecubital plasma norepinephrine levels correlated positively with sympathetic nerve activity levels (average correlation coefficient, 0.67; $p < 0.01$; Fig. 3). Prednisone treatment did not change the relationship between sympathetic nerve activity and plasma norepinephrine levels at baseline or during lower body negative pressure (Fig. 3).

DISCUSSION

The main findings in this double-blind, placebo-controlled, randomized crossover study were that oral prednisone administration at a dose of 20 mg/day decreased directly recorded skeletal muscle sympathetic nerve traffic and concurrently decreased antecubital venous plasma levels of the sympathetic neurotransmitter norepinephrine and of its intraneuronal metabolite dihydroxyphenylglycol.

The results extend to humans previous observations from studies of laboratory animals in which 1 week of

cortisol administration by means of a subcutaneous minipump reservoir reduced baseline norepinephrine concentrations in arterial plasma by about 50% in conscious rats.^{2,12} The results of this study about prednisone effects agree with those about dexamethasone effects in the study of Stene et al.⁴ but disagree with those about dexamethasone effects in the studies of Rupprecht et al.⁵ and Scherrer et al.⁶ None of these studies involved a double-blind, placebo-controlled, crossover design.

Mineralocorticoids can inhibit sympathoneural outflows, as indicated by decreased plasma norepinephrine levels¹³ and decreased sympathetic nerve activity,¹⁴ in normal volunteers treated with 9 α -fludrocortisone acetate and in patients with primary aldosteronism.¹⁵ Mineralocorticoid-induced sympathoinhibition may result from activation of low- and high-pressure baroreceptors caused by extracellular volume expansion and arterial hypertension. Because prednisone did not affect body weight, electrolyte excretion, pulse rate, or blood pressure in this study, baroreceptor activation seems to be an unlikely explanation for prednisone-induced sympathoinhibition.

The reductions in directly recorded sympathoneural activity raise the possibility that glucocorticoids inhibit sympathetic outflows by actions in the central nervous system. Endogenous and synthetic glucocorticoids cross the blood-brain barrier relatively easily, and the cerebral cortex and most noradrenergic and adrenergic cells in the rat brain possess nuclear glucocorticoid receptors.¹⁶ Removal of endogenous corticosteroids by bilateral adrenalectomy increases norepinephrine turnover in the whole brain and in specific areas such as the hypothalamus.^{3,17} Conversely, hypercortisolemic rats have neurochemical changes that indicate decreased release of norepinephrine and decreased catecholamine biosynthesis in the paraventricular nucleus of the hypothalamus.¹²

The possibility of ganglionic blockade by glucocorticoids has received insufficient study to exclude this as an explanation for prednisone-induced sympathoinhibition. Whether or not sympathetic ganglia possess cytoplasmic glucocorticoid receptors has been unclear.^{18,19} Cortisol and corticosterone hyperpolarize celiac ganglion cells, with a short latency that suggests that membrane-bound glucocorticoid receptors may decrease ganglion cell activity by a nongenomic mechanism.²⁰ Sympathetic ganglia also possess functional receptors for corticotropin-releasing hormone,²¹ and exogenously administered glucocorticoids, by decreasing release of corticotropin-releasing hormone, theoretically could affect ganglionic transmission.

Prednisone treatment did not affect increments in sympathetic nerve activity or plasma norepinephrine levels during lower body negative pressure, suggesting that although prednisone inhibited sympathoneural outflows at baseline, it did not attenuate reflexive sympathoneural responses to decreased cardiac filling. Analogously, hypercortisolemia does not affect plasma norepinephrine responses to nitroprusside-induced hypotension in rats.^{2,22} Inhibitory effects of other glucocorticoids on sympathoneural responses seem to vary with the type of stressor.^{6,23}

Prednisone treatment also did not alter relationships between sympathetic nerve activity and plasma levels of norepinephrine at baseline or during lower body negative pressure. These findings suggest that, in humans, glucocorticoids do not affect presynaptic modulation of norepinephrine release from sympathetic nerves. Analogously, in pithed rats, glucocorticoid treatment does not alter plasma norepinephrine responses to electrical stimulation of the entire sympathetic outflow.²⁴

The 24-hour urinary excretion of catecholamines remained unchanged after prednisone treatment, despite decreased levels of sympathetic nerve activity and of antecubital plasma norepinephrine. The sympathoinhibitory effect of prednisone may be too brief and too small to affect daily urinary norepinephrine excretion. In addition, local release of norepinephrine in the kidneys contributes importantly to urinary norepinephrine excretion.²⁵ Because sympathetic neural outflows to various organs are differentiated,²⁶ it is possible that prednisone did not suppress sympathoneural traffic to the kidneys and therefore did not decrease urinary norepinephrine excretion.

Lower body negative pressure produced small but significant decreases in systolic blood pressure during the placebo phase, whereas lower body negative pressure increased heart rate without affecting systolic blood pressure during the prednisone phase. Because sympathoneural responses to lower body negative pressure did not differ between the placebo and prednisone treatment phases, the results suggest that altered postsynaptic responsiveness could have produced these small but statistically significant hemodynamic differences. Patients with Cushing's disease²⁷ and subjects treated for 1 week with oral hydrocortisone⁷ have been reported to have enhanced pressor and vasoconstrictor responses to exogenous norepinephrine. Patients with Cushing's disease also have increased cardiac sensitivity to isoproterenol.²⁸ Analogously, arterial walls and cardiac tissue from rats treated with dexamethasone have increased

postsynaptic sensitivity to catecholamines.²⁹ This could be explained by an ability of dexamethasone to increase gene expression for α_1 -adrenergic receptors in smooth muscle cells.³⁰

With use of a highly sensitive radioimmunoassay for corticotropin, and consistent timing of blood sampling, this study revealed decreased corticotropin plasma levels during prednisone treatment comparing with placebo treatment in every subject tested, verifying that the dose of 20 mg/day prednisone was adequate to attenuate HPA activity, as reported in other studies.⁹ Nevertheless, simultaneously obtained plasma cortisol levels remained unchanged. Other clinical studies have reported analogous dissociation between cortisol and corticotropin changes in normal subjects.^{31,32} Thus, factors other than corticotropin appear to contribute to regulation of adrenocortical secretion.

In summary, the results of this study indicate that prednisone decreases sympathoneural outflows in healthy humans without affecting reflexive sympathoneural responses during lower body negative pressure, a laboratory model of orthostasis, and without affecting modulation of norepinephrine release from sympathetic nerves.

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References

1. Kvetnansky R, Fukuhara K, Pacak K, Cizza G, Goldstein DS, Kopin IJ. Endogenous glucocorticoids restrain catecholamine synthesis and release at rest and during immobilization stress in rats. *Endocrinology* 1993;133:1411-9.
2. Szemerédi K, Bagdy G, Stull R, Calogero AE, Kopin IJ, Goldstein DS. Sympathoadrenomedullary inhibition by chronic glucocorticoid treatment in conscious rats. *Endocrinology* 1988;123:2585-90.
3. Pacak K, Kvetnansky R, Palkovits M, et al. Adrenalectomy augments in vivo release of norepinephrine in the paraventricular nucleus during immobilization stress. *Endocrinology* 1993;133:1404-10.
4. Stene M, Panagiotis N, Tuck ML, Sowers JR, Mayes D, Berg G. Plasma norepinephrine levels are influenced by sodium intake, glucocorticoid administration, and circadian changes in normal man. *J Clin Endocrinol Metab* 1980;51:1340-5.
5. Rupprecht R, Rupprecht M, Rupprecht C, et al. Effects of glucocorticoids on plasma catecholamines in depression. *Psychiatry Res* 1989;29:187-98.
6. Scherrer U, Vollenweider P, Randin D, Jequier E, Nicod P, Tappy L. Suppression of insulin-induced sym-

- pathetic activation and vasodilation by dexamethasone in humans. *Circulation* 1993;88:388-94.
7. Sudhir K, Jennings GL, Esler MD, et al. Hydrocortisone-induced hypertension in humans: pressor responsiveness and sympathetic function. *Hypertension* 1989;13:416-21.
 8. Rea RF, Wallin BG. Sympathetic nerve activity in arm and leg muscles during lower body negative pressure in humans. *J Appl Physiol* 1989;66:2778-81.
 9. Axelrod L. Corticosteroid therapy. In: Becker KL, Bilezikian JP, Bremner WJ, et al., eds. Principles and practice of endocrinology and metabolism. Philadelphia: Lippincott, 1990:613-23.
 10. Eisenhofer G, Goldstein DS, Stull R, et al. Simultaneous liquid chromatographic determination of 3,4-dihydroxyphenylglycol, catecholamines, and 3,4-dihydroxyphenyl alanine in plasma and their responses to inhibition of monoamine oxidase. *Clin Chem* 1986;32:2030-3.
 11. Goldstein DS, Grossman E, Armando I, et al. Correlates of urinary excretion of catechols in humans. *Biogenic Amines* 1993;10:3-17.
 12. Pacak K, Armando I, Komoly S, et al. Hypercortisolism inhibits yohimbine-induced release of norepinephrine in the posterolateral hypothalamus of conscious rats. *Endocrinology* 1992;131:1369-76.
 13. Weidman P, Matter DR, Matter EE, et al. Glucocorticoid and mineralocorticoid stimulation of atrial natriuretic peptide release in man. *J Clin Endocrinol Metab* 1988;66:1233-9.
 14. Mion D Jr, Rea RF, Anderson EA, Kahn D, Sinkey CA, Mark AL. Effects of fludrocortisone on sympathetic nerve activity in humans. *Hypertension* 1994;23:123-30.
 15. Miyajima E, Yamada Y, Yoshida Y, et al. Muscle sympathetic nerve activity in renovascular hypertension and primary aldosteronism. *Hypertension* 1991;17:1057-62.
 16. Harfstrand A, Fuxe K, Cintra A, et al. Glucocorticoid receptor immunoreactivity in monoaminergic neurons of rat brain. *Proc Natl Acad Sci USA* 1986;83:9779-83.
 17. Meyer JS. Biochemical effects of corticosteroids on neural tissues. *Physiol Rev* 1985;65:946-1020.
 18. Bohn MC, McEwen B, Luine VN, Black IB. Development and characterization of glucocorticoid receptors in rat superior cervical ganglion. *Brain Res* 1984;316:211-8.
 19. Towle AC, Sze PY. [³H]Corticosterone binding in rat superior cervical ganglion. *Brain Res* 1982;253:221-9.
 20. Chen YZ, Hua SY, Wang CA, Wu LG, Gu Q, Xing BR. An electrophysiological study on the membrane receptor-mediated action of glucocorticoids in mammalian neurons. *Neuroendocrinology* 1991;53(suppl 1):25-30.
 21. Udelsman R, Harwood JP, Millan MA, et al. Functional corticotropin releasing factor receptors in the primate peripheral sympathetic nervous system. *Nature* 1986;319:147-50.
 22. Szemerédi K, Bagdy G, Kopin IJ, Goldstein DS. Neurocirculatory regulation in cortisol-induced hypertension. *Clin Exp Hypertens* 1989;A11:1425-39.
 23. Komersaroff PA, Funder JW. Differential glucocorticoid effects on catecholamine responses to stress. *Am J Physiol* 1994;266(1 pt 1):E118-28.
 24. Szemerédi K, Zukowska-Grojec Z, Bagdy G, Fekete MI, Kopin IJ. Opposite effects of chronic cortisol treatment on pre- and postsynaptic actions of clonidine in pithed rats. *J Auton Pharmacol* 1989;9:35-43.
 25. Link L, Weidmann P, Probst P, Futterlieb A. Renal handling of norepinephrine and epinephrine in the pig. *Pflugers Arch* 1985;405:66-9.
 26. Hjerdahl P, Freyschuss U, Juhlin-Dannfelt A, Linde B. Differentiated sympathetic activation during mental stress evoked by the Stroop test. *Acta Physiol Scand Suppl* 1984;527:25-9.
 27. Saruta T, Suzuki H, Handa M, Igarashi Y, Kondo K, Senba S. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. *J Clin Endocrinol Metab* 1986;62:275-9.
 28. Ritchie CM, Sheridan B, Fraser R, et al. Studies on the pathogenesis of hypertension in Cushing's disease and acromegaly. *Q J Med* 1990;76:855-67.
 29. Chan MY, Dai S, He JH, Ogle CW. In-vivo and in-vitro studies on the effects of chronic dexamethasone treatment on cardiovascular responses to sympathetic stimulation. *Arch Int Physiol Biochim Biophys* 1991;99:323-9.
 30. Sakaue M, Hoffman BB. Glucocorticoids induce transcription and expression of the α_1 B-adrenergic receptor gene in DTT1 MF-2 smooth muscle cells. *J Clin Invest* 1991;88:385-9.
 31. Krishnan KRR, Ritchie JC, Manepalli AN, et al. What is the relationship between plasma ACTH and plasma cortisol in normal humans and depressed patients? In: Schatzberg AF, Nemeroff CB, eds. The hypothalamic-pituitary-adrenal axis: physiology, pathophysiology and psychiatric implications. New York: Raven Press, 1988:115-31.
 32. Fehm HL, Holl R, Steiner K, Klein E, Voigt KH. Evidence for ACTH-unrelated mechanisms in the regulation of cortisol secretion in man. *Klin Wochenschr* 1984;62:19-24.