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Research Article

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Homologous Upregulation of Human Arterial α -Adrenergic Responses by Guanadrel

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Abstract

The purpose of this study was to test the hypothesis that there is homologous upregulation of arterial α -adrenergic responsiveness during suppression of sympathetic nervous system (SNS) activity in humans. 10 subjects (19–28 yr) were studied during placebo and when SNS activity was suppressed by guanadrel. Changes in forearm blood flow (FABF) mediated by the intraarterial infusion of norepinephrine (NE), angiotensin II (AII), and phentolamine were measured by plethysmography. During guanadrel compared with placebo, plasma NE levels (1.28 ± 0.09 – 0.85 ± 0.06 nM; $P = 0.0001$) and the extra vascular NE release rate derived from [^3H]NE kinetics were lower (7.1 ± 0.7 – 4.0 ± 0.2 nmol/min per m^2 ; $P = 0.0004$), suggesting suppression of SNS activity. During guanadrel, there was increased sensitivity in the FABF response to NE (analysis of variance $P = 0.03$). In contrast, there was no difference in the FABF response to AII (analysis of variance $P = 0.81$), suggesting that the upregulation observed to NE was homologous. The increase in FABF during phentolamine was similar during guanadrel compared with placebo (guanadrel: 141 ± 37 vs. placebo: $187 \pm 27\%$ increase; $P = 0.33$), suggesting that there was at least partial compensation to maintain constant endogenous arterial α -adrenergic tone. We conclude that there is homologous upregulation of arterial α -adrenergic responsiveness in humans when SNS activity is suppressed by guanadrel. (*J. Clin. Invest.* 1993. 91:1429–1435.) Key words: sympathetic nervous system • norepinephrine • guanadrel • angiotensin II • phentolamine • plethysmography • kinetics

Introduction

The sympathetic nervous system (SNS)¹ plays an important role in the control of vascular smooth muscle adrenergic tone, which may be of significant pathophysiological importance in disease states such as hypertension. Vascular smooth muscle adrenergic tone is regulated by SNS activity (the release of norepinephrine [NE] into the neuroeffector junction) and postsynaptic adrenergic receptor responses to NE.

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1. *Abbreviations used in this paper:* AII, angiotensin II; FABF, forearm blood flow; FAVR, forearm vascular resistance; MAP, mean arterial pressure; PRA, plasma renin activity; SNS, sympathetic nervous system.

Alterations in SNS activity may result in corresponding up- or downregulation of adrenergic receptor responses. We have previously reported downregulation of the platelet α_2 -adrenergic receptor-adenylate cyclase complex in response to an increase in plasma NE levels resulting from 7 d of low sodium diet (1). We have also studied upregulation of α -adrenergic responsiveness in dorsal hand veins (2, 3). These studies have used guanadrel, a postganglionic sympatholytic antihypertensive medication to suppress SNS activity. We demonstrated upregulation of both venous α_1 - and α_2 -adrenergic responses during decreased SNS activity in healthy young subjects (2) and upregulation of venous α_2 - but not α_1 -adrenergic responses in healthy elderly subjects (3).

Adrenergic control of arterial vasoconstriction is important in blood pressure homeostasis. Although arterial α -adrenergic regulation resulting from pharmacological manipulation of SNS activity has been studied in animal models (4–6), similar studies have not been performed in humans. The objectives of this study were to determine whether there would be upregulation of arterial α -adrenergic responsiveness during suppression of SNS activity by guanadrel in humans and to determine if the upregulation were homologous or heterologous. We measured forearm blood flow (FABF) by plethysmography during intraarterial infusions of NE to determine arterial α -adrenergic responsiveness and angiotensin II (AII) to determine the vasoconstriction response to a nonadrenergic agonist, both during a placebo phase and when SNS activity was suppressed by guanadrel. We also infused the α -adrenergic antagonist phentolamine to assess endogenous arterial α -adrenergic tone (the summation of endogenous basal NE release and α -adrenergic receptor response) during both phases. In addition to measures of SNS activity, we also measured plasma renin activity (as a surrogate for AII levels) and plasma arginine vasopressin (AVP) levels to determine whether guanadrel treatment might activate either the renin-angiotensin or AVP system while the level of SNS activity is suppressed. Our results indicate that there is homologous upregulation of arterial α -adrenergic responsiveness during suppression of SNS activity by guanadrel in humans.

Methods

Subjects. 10 young normotensive subjects (mean age 23 yr, range 19–28; 6 male and 4 female) in good general health were recruited through newspaper advertisement. Subjects were screened before study with a history and physical examination and laboratory tests, including a complete blood count and routine chemistries. Subjects were excluded from participation if they exceeded 120% of ideal body weight (Metropolitan Life Insurance tables, 1983), had a resting seated blood pressure > 140 mmHg systolic or > 90 mmHg diastolic, were taking any medication, or had evidence from either history, physical exam, or laboratory results of significant underlying illness. Each gave written

informed consent that was approved by the University of Michigan Human Use Committee.

Study protocol. The study was designed as a double-blind randomized cross-over protocol, comparing placebo with the antihypertensive medication guanadrel. Guanadrel acts through blockade of peripheral sympathetic efferent pathways and has been shown to decrease the release of NE from SNS terminals and deplete neuronal stores of NE (2, 7). By random assignment, subjects began taking capsules containing either 5 mg of guanadrel or an equivalent amount of sucrose. They were instructed to take one capsule twice daily for 3 d (10 mg guanadrel/d), two capsules twice daily for 3 d (20 mg guanadrel/d), and then three capsules twice daily (30 mg guanadrel/d) for the remainder of a 3-wk period. There was a 1-wk wash out period between phases, during which time no capsules were taken, following which the second 3-wk placebo/guanadrel phase began. Each of the 10 subjects completed the double-blind protocol without incident. Specifically, there were no symptoms of postural hypotension or other adverse effects related to guanadrel administration.

Subjects reported to the Clinical Research Center of the University of Michigan Hospitals at 0730 on day 21 of each phase to control for any diurnal variation in NE metabolism (8) or arterial α -adrenergic tone (9). They were instructed to fast from 2200 the night before each of the study days and to abstain from cigarettes, caffeine, and other known modulators of catecholamines for 12 h before each study began. They were allowed a small amount of water to take with their capsules the morning of each study day. Subjects were studied in the supine position in a quiet room maintained at a constant temperature of 23–25°C to facilitate achieving an adequate baseline FABF.

Forearm volume was measured using water displacement. A 20-gauge 1.25-inch Insyte catheter was placed into the brachial artery of the left arm and was connected to a pressure transducer (model 1290A quartz transducer; Hewlett-Packard Co., Andover, MA). One of the three basic electrocardiogram (ECG) limb leads was monitored.

[³H]NE kinetics protocol. This protocol was carried out as previously described (10), except that sampling was from the brachial arterial catheter in the current study.

FABF protocol. FABF was measured using venous occlusion plethysmography (11). The left forearm (the side with the brachial arterial catheter) was supported at the wrist and elbow above heart level by a brace. A mercury-in-silastic strain gauge encircled the forearm at its

largest diameter ~ 7-cm distal from the olecranon process and was connected to a plethysmograph (model EC-4; D. E. Hokanson, Bellevue, WA). A blood pressure cuff was placed just proximal to the elbow and was inflated to 45 mmHg during FABF measurements using a rapid cuff inflator (model E-10; D. E. Hokanson). A pediatric cuff was placed at the wrist and inflated to 200 mmHg to exclude hand blood flow beginning 30 s before taking a FABF reading. FABF (ml/100 ml FAV per min) was determined from the average of three readings, with each reading representing the mean vertical deflection per minute divided by a 1% calibration signal height (12).

An example of the study protocol for FABF illustrating mean arterial pressure (MAP) and FABF data for one subject is shown in Fig. 1. This protocol began after the tracer [³H]NE infusion protocol (i.e., ≥ 110 min after arterial catheter placement). To establish a stable baseline, FABF readings were taken until three consecutive readings representing similar FABF were obtained. To determine the effect of intraarterial infusions of NE on FABF, NE (Levophed bitartrate; Sterling Drug Inc., New York, NY) was diluted in 5% dextrose to achieve stepwise increasing infusion doses of 7.4, 30, 118, 473, and 1,420 pmol/100 ml FAV per min. A sample of the infusates was obtained for subsequent measurement of NE concentration by HPLC. The coefficient of variation of the infusate concentrations was 8%. Each NE dose was administered by an infusion pump (model 970T; Harvard Apparatus, South Natick, MA) for 4 min before recording FABF. After the FABF measurement at the 1,420-pmol dose, the NE infusion was stopped.

After a 10-min wash out period, repeat measurement of baseline FABF was carried out as described above. To determine the effect of infusion of a nonadrenergic vasoconstrictor on FABF, AII (Hypertensin; Ciba-Geigy Corp., Summit, NJ) was diluted in 0.9% normal saline to achieve stepwise increasing infusion doses of 0.12, 0.48, 1.9, 7.8, and 23.3 pmol/100 ml FAV per min. After completion of the AII infusion protocol and another 10-min wash out period, the α -antagonist phentolamine was infused to determine the increase in FABF above baseline as a measure of endogenous arterial α -adrenergic tone (12). Phentolamine (Regitine mesylate; Ciba-Geigy Corp.) was diluted in 0.9% normal saline and infused at a single dose of 0.043 μ mol/100 ml FAV per min and FABF was measured at 10 min.

Analytical methods. MAP was determined from the electronically integrated area under the blood pressure curve from the Marquette telemetry system (series 7700; Marquette Electronics Inc., Milwaukee,

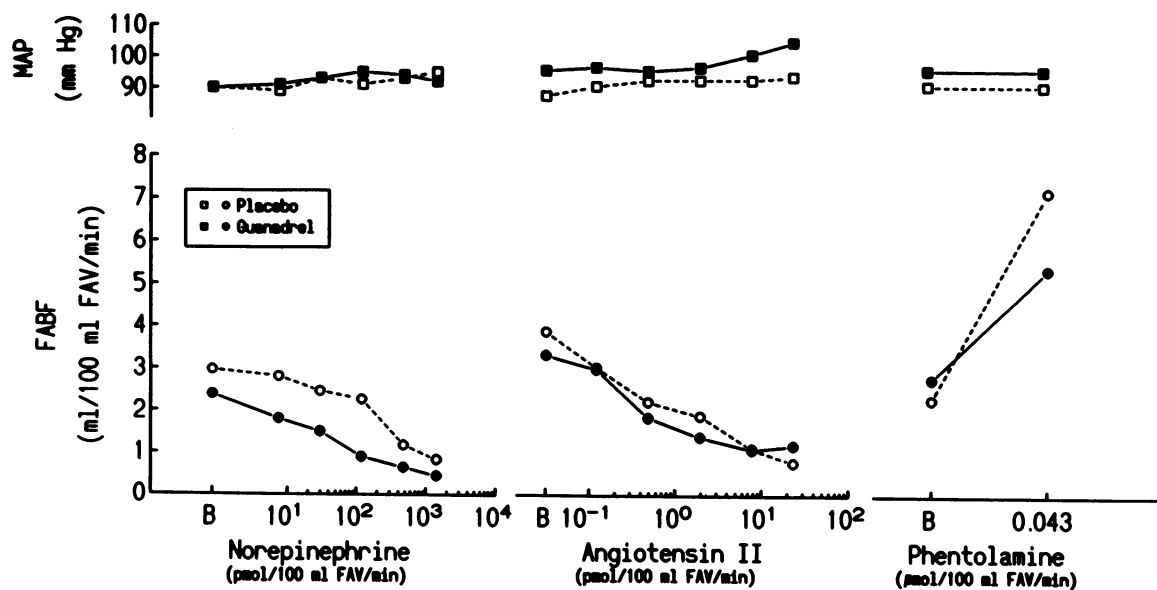


Figure 1. Mean arterial pressure (MAP) and forearm blood flow (FABF) measurements in one subject during each of the three intraarterial infusions to illustrate the study protocol. The MAP readings are represented by square symbols and the FABF measurements are represented by the circles. B, baseline pre-infusion values; FAV, forearm volume.

WI) just before each FABF measurement. Forearm vascular resistance (FAVR, arbitrary units) was calculated by dividing MAP by FABF.

Arterial blood samples were collected into chilled plastic tubes containing EGTA and reduced glutathione. The tubes were kept on ice until centrifugation at 4°C. Plasma samples were stored at -70°C until assayed. Plasma NE and epinephrine were quantified by a single-isotope radioenzymatic assay, with all samples from a given subject analyzed in the same assay (13). The intraassay coefficient of variation for NE in this assay is 5%. Alumina extraction of plasma samples and measurement of [³H]NE levels were carried out as previously described (10, 14). Plasma renin activity (PRA) was quantified by radioimmunoassay quantitation of enzymatically generated angiotensin I (15). After an extraction step, plasma AVP levels were measured by radioimmunoassay (16).

Data and statistical analysis. Compartmental analysis of NE kinetics was performed using the previously described minimal two-compartment model (10). A single set of values for the fractional transfer rate coefficients of the model were found to satisfy all the data from each subject during both the placebo and guanadrel studies. In applying Berman's minimal change postulate (17), no changes in the independent model parameters were required to explain the changes seen in NE kinetics comparing the placebo with the guanadrel phase. The quantity of NE in each compartment (NE mass in the intravascular compartment Q_1 and in the extravascular compartment, Q_2), the rate of NE appearance into each compartment (R_{12} into compartment 1 and NE_2 into compartment 2), the NE metabolic clearance rate from compartment 1 (MCR_1), and the volume of distribution of NE in compartment 1 (V_1) were calculated from the two-compartment model as functions of the estimated transfer rate coefficients as previously described (10). Data are presented for only nine subjects as plasma was not available from one subject's placebo study to perform the catecholamine, PRA, and AVP assays.

MAP, FABF, and FAVR determined during baseline periods before the infusion of each of the three medications (NE, AII, and phentolamine) were analyzed by two-way repeated measures analysis of variance (ANOVA) for a time effect during each individual's study and for a phase (i.e., placebo vs. guanadrel) effect. MAP, FABF, and FAVR at each of the five NE and AII doses infused were analyzed by two-way repeated measures ANOVA for a dose effect and a phase (i.e., placebo vs. guanadrel) effect.

To control for potential differences in baseline FABF between placebo and guanadrel phases of the study, dose-response data for NE and AII were analyzed as the percent change in FABF from the baseline value obtained before the infusion of each drug. The NE data were analyzed by two-way repeated measures ANOVA after also taking the crossover study design into account.

Values are presented as mean±SE. Statistical analysis was performed using Statview II (Abacus Concepts, Berkeley, CA) and SAS (SAS Institute Inc., Cary, NC). Student's pairwise *t* tests were used to compare differences between placebo and guanadrel phases (for the variables of MAP; heart rate; plasma catecholamine, PRA, and AVP

levels; parameters derived from NE kinetics; and the percent increase above baseline FABF during phentolamine infusion). A value of *P* < 0.05 was selected to indicate statistical significance.

Results

Blood pressure and heart rate

Baseline (pre-NE infusion) supine intraarterial MAP tended to be less during guanadrel (G) compared with placebo (P) (P, 89±2 vs. G, 86±2 mmHg; *P* = 0.06), but there was no phase effect (P vs. G) noted when MAP measurements before each of the three drug infusions were analyzed (ANOVA *P* = 0.85) (Table I). There was also no phase effect (P vs. G) for MAP recorded during the infusion of each dose of NE and AII (NE, *P* = 0.60 and AII, *P* = 0.62). However, there was a dose effect on MAP during infusions of both NE and AII (NE, *P* = 0.0001 and AII, *P* = 0.0001). The mean increase in MAP from baseline to the highest infused dose of NE was 10 mmHg, and the mean increase for AII was 13 mmHg. Phentolamine had no detectable effect on MAP (*P* = 0.82). Consistent with a reduction in sympathetic input to the heart, there was a significant decrease in baseline heart rate during guanadrel compared with placebo (P, 66±3 vs. G, 54±2 beats/min; *P* < 0.05).

NE kinetics, plasma catecholamine and AVP levels, and plasma renin activity

The effect of guanadrel treatment on NE kinetics is summarized in Table II. As illustrated in Fig. 2, *a* and *b*, both the arterial plasma NE level (Fig. 2 *a*) and the extravascular NE release rate (NE_2) (Fig. 2 *b*) were lower in each subject during guanadrel; the mean plasma NE level during guanadrel was ~ 35% less than the placebo level and the mean NE_2 value was ~ 44% less than the placebo level. The rate of NE spillover, or NE mass flux rate from compartment 2 to 1 (R_{12}), was also significantly lower during guanadrel.

In addition, NE mass in the vascular compartment, Q_1 , was lower during guanadrel. Mass in the extravascular compartment Q_2 , the estimated NE clearance rate from compartment 1 (MCR_1), and the NE volume of distribution (V_1) also tended to be lower during guanadrel, but these decreases were not statistically significant. There was no significant difference in arterial plasma epinephrine levels between the two phases of this study (P, 0.41±0.05 vs. G, 0.38±0.06 nM; *P* = 0.33).

There was no significant difference in the level of PRA between the two study phases (P, 0.672±0.189 vs. G, 0.568±0.117 ng/ml per h; *P* = 0.67). Similarly, there was no

Table I. MAP, FABF, and FAVR Values during Placebo and Guanadrel Phases Obtained Before Each of the Three Drug Infusions

	Pre-NE		Pre-AII		Prephentolamine		ANOVA <i>P</i> values	
	P	G	P	G	P	G	Phase effect	Time effect
MAP (mmHg)	89±2	86±2	91±2	92±2	90±2	90±2	0.85	0.0005
FABF (ml/100 ml FAV per min)	3.72±.65	3.09±.32	4.44±.60	3.58±.32	3.38±.53	2.80±.21	0.29	0.0005
FAVR (U)	29.5±4.0	30.6±3.2	23.9±3.4	27.6±3.2	30.1±4.0	34.1±3.0	0.47	0.001

Values are means±SE; *n* = 10 except for phentolamine where *n* = 9 subjects. MAP, mean arterial blood pressure; FABF, forearm blood flow; FAV, forearm volume; FAVR, forearm vascular resistance; NE, norepinephrine; AII, angiotensin II; Phase effect, the comparison of placebo and guanadrel phases inclusive of all three preinfusion points; Time effect, the comparison of values before each infusion across the time required to complete the study protocol.

significant difference in AVP levels between phases (P, 2.656 ± 1.108 vs. G, 1.178 ± 0.046 pg/ml; $P = 0.21$).

FABF during vasoactive intraarterial infusions

Baseline FABF measured over the course of the study protocol during each phase is shown in Table I. There was no phase effect for either baseline FABF or FAVR measured before each of the three drug infusions (FABF, $P = 0.29$ and FAVR, $P = 0.47$). However, there was a time effect identified for both; FABF was greater and, consequently, FAVR was less before the infusion of AII relative to the other two baseline values (FABF, $P = 0.0005$; FAVR, $P = 0.0013$).

Norepinephrine. Dose-response curves representing the percent decrease in FABF from baseline during intraarterial infusions of NE for placebo and guanadrel phases are shown in Fig. 3. The dose-response curve during guanadrel was significantly shifted to the left, indicating increased sensitivity to NE-mediated vasoconstriction during guanadrel (ANOVA $P = 0.03$). In addition, analysis of the NE percent change in FABF at the 1,420 pmol (maximal) dose indicated that there was greater response during guanadrel (P, -72.9 ± 4.1 vs. G, $-84.1 \pm 2.0\%$; $P = 0.01$). Analysis of the absolute FABF and FAVR (Fig. 4) dose-response data also demonstrated an increase in sensitivity to NE during guanadrel (ANOVA: FABF, $P = 0.05$; FAVR, $P = 0.005$).

Angiotensin II. The dose-response curves representing the percent decrease in FABF from baseline during the intraarterial infusion of AII for placebo and guanadrel phases are shown in Fig. 5. There was no significant difference between phases (P vs. G) in the percent change in FABF from baseline to the local intraarterial infusion of AII (ANOVA $P = 0.81$). Similarly, analysis of absolute FABF and FAVR data demonstrated no significant difference in the vasoconstrictor response to AII during guanadrel (ANOVA: FABF, $P = 0.21$; FAVR, $P = 0.34$).

Phentolamine. There was no statistically significant difference in mean percent increase from baseline FABF in response to phentolamine between phases (Fig. 6) (P, 187 ± 27 vs. G, $141 \pm 37\%$ increase; $P = 0.33$). There was heterogeneity in the effect of guanadrel on the FABF response to phentolamine.

Table II. Comparison of Norepinephrine (NE) Kinetics Derived from Compartmental Analysis of the [3 H]NE Infusion Protocol during Placebo and Guanadrel

	Placebo	Guanadrel	P
Plasma NE (nM)	1.28 ± 0.09	0.85 ± 0.06	0.0001
NE ₂ (nmol/min per m ²)	7.1 ± 0.7	4.0 ± 0.2	0.0004
Q ₁ (nmol/m ²)	2.1 ± 0.3	1.2 ± 0.1	0.002
Q ₂ (nmol/m ²)	450 ± 213	229 ± 102	0.08
R ₁₂ (nmol/min per m ²)	1.74 ± 0.20	0.98 ± 0.09	0.0008
MCR ₁ (liter/min per m ²)	1.07 ± 0.07	0.97 ± 0.06	0.17
V ₁ (liter)	3.0 ± 0.2	2.7 ± 0.2	0.20

Values are means \pm SE; $n = 9$ subjects. NE₂, extravascular NE release rate; Q₁ and Q₂, mass of NE in compartments 1 and 2; R₁₂, rate of NE appearance into compartment 1; MCR₁, rate of NE clearance from compartment 1; V₁, NE volume of distribution in compartment 1.

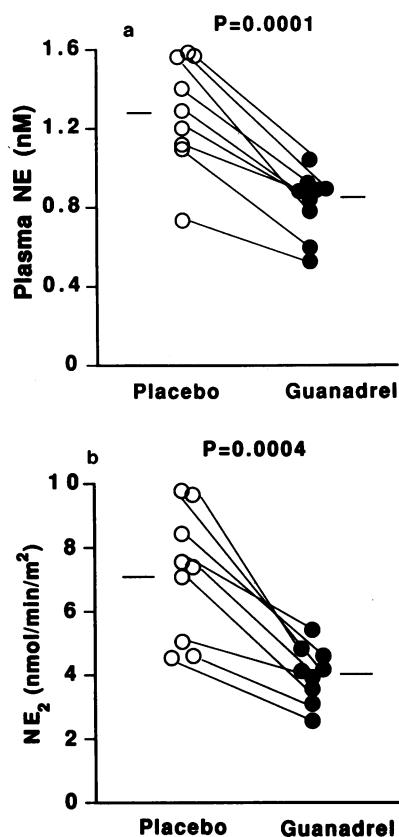


Figure 2. Individual data for plasma norepinephrine (NE) (a) and extravascular NE release rate (NE₂) (b) during placebo and guanadrel phases. Group mean values are represented by horizontal lines.

Examination of the results from the individual subjects, depicted in Fig. 6, reveals that the response to phentolamine either increased or did not change in four subjects and that it decreased in five subjects during the guanadrel phase. Given this variability in the individual results, the single dose of phentolamine that was used, and the relatively small number of subjects, the power with which a 50% decrease in the mean response to phentolamine during guanadrel can be excluded was only 24%.

Discussion

In this study, we used intraarterial infusions of NE and AII to estimate the effect of suppression of SNS activity by guanadrel on sensitivity to these vasoconstrictors. Because intraarterial NE and AII caused dose-dependent decreases in FABF, we were able to quantitate vasoconstriction sensitivity. Our results

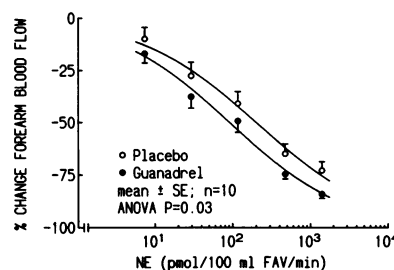


Figure 3. Group mean data for percent change in forearm blood flow from baseline in response to intraarterial infusion of norepinephrine (NE) during placebo and guanadrel phases.

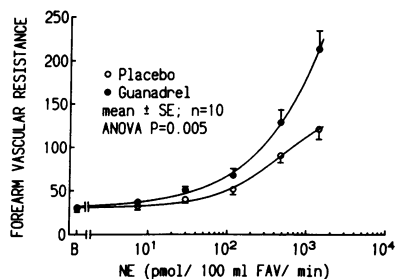


Figure 4. Group mean data for absolute forearm vascular resistance in response to intraarterial infusion of norepinephrine (NE) during placebo and guanadrel phases.

indicate that there is homologous upregulation of the vasoconstrictor response to intraarterial NE during suppression of SNS activity by guanadrel.

There was a significant reduction in arterial plasma NE and NE₂ during guanadrel, indicating suppression of SNS activity. These values represent estimates of systemic SNS activity, and it is assumed that a similar decrease of regional SNS activity occurs in the forearm during guanadrel. Also consistent with a reduction in systemic SNS activity were decreases in the NE kinetic parameters of compartmental mass sizes (Q₁ and Q₂) and the NE spillover rate into compartment 1 (R₁₂) during guanadrel. These findings are similar to NE kinetics results from our previous studies using guanadrel (2, 3).

Accompanying the reduction in SNS activity in these subjects during guanadrel, there was greater sensitivity of arterial vasoconstriction to intraarterial NE infusions. This upregulation of arterial α -adrenergic responsiveness was identified by a difference in dose-response for NE between placebo and guanadrel phases with respect to FABF, FAVR, and percent change FABF from baseline. Regulation of α -adrenergic responses has been studied in vivo in a variety of systems in both animals and man. Bevan and Tsuru (6) used denervation to decrease SNS activity and studied vasoconstriction in isolated central ear arteries of white New Zealand rabbits. An increase in sensitivity to the vasoconstriction effects of NE was identified in the denervated central ear artery. Nasser et al. (5) used chronic reserpine treatment to decrease SNS activity in rats. A significant 1.8-fold increased potency of phenylephrine to cause vasoconstriction was noted in the reserpine-treated rat caudal artery. Using denervation to decrease SNS activity, Flavahan et al. (4) demonstrated augmentation in the vasoconstriction response of canine saphenous veins to the specific α_2 agonist UK-14,304, but not to the α_1 agonist phenylephrine. In younger humans we have previously demonstrated upregulation of venous α_1 - and α_2 -adrenergic responses during suppression of SNS activity by guanadrel (2). The present study extends these findings by uniquely demonstrating pharmacological upregula-

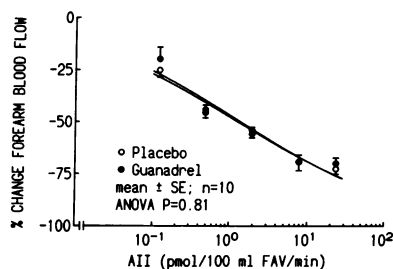


Figure 5. Group mean data for percent change in forearm blood flow from baseline in response to intraarterial infusion of angiotensin II (AII) during placebo and guanadrel phases.

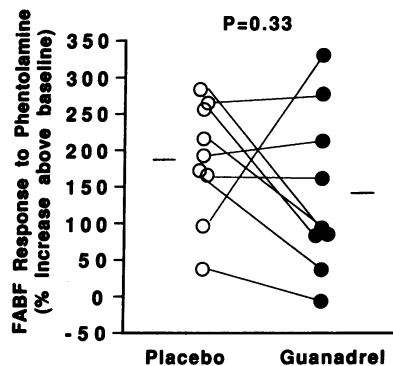


Figure 6. Individual data for percent increase above baseline forearm blood flow (FABF) in response to intraarterial infusion of phentolamine during placebo and guanadrel phases. The group mean values are represented by horizontal lines.

tion of arterial α -adrenergic responsiveness in humans. Taken together with our previous demonstration of downregulation of platelet α_2 -adrenergic responsiveness (1), these results suggest that there is qualitatively appropriate regulation of α -adrenergic responsiveness during short-term (1–3 wk) perturbations of SNS activity in humans.

In contrast to the shift in NE dose-response during guanadrel, there was no significant difference in AII dose-response between placebo and guanadrel phases. The upregulation demonstrated to NE-mediated vasoconstriction appears to be specific for the adrenergic system since the upregulation did not generalize to the nonadrenergic agonist AII. This represents a unique demonstration of homologous in vivo arterial α -adrenergic upregulation.

The interpretation of our results as homologous upregulation is on the basis of the assumption that guanadrel therapy leads to SNS suppression without activation of other neurohumoral systems involved in blood pressure homeostasis that would interact with vascular responses to NE. In particular, since it is known that AII can augment vascular vasoconstrictor responses to NE (18) and since we used AII infusions as a nonadrenergic control in this study, it is important to know whether AII levels increased during guanadrel. Technical limitations prevented the direct measurement of plasma AII levels. The level of PRA parallels AII except when there is angiotensin-converting enzyme inhibition (19).

Therefore, on the basis of measures of the level of PRA in our subjects, we infer that there is no increase in AII levels during guanadrel therapy and the enhanced vasoconstrictor response to NE during guanadrel is unlikely to be secondary to an AII-mediated augmentation. We also determined if release of AVP was stimulated during guanadrel in light of the interaction between the SNS and AVP (20). There was no significant difference in plasma AVP between placebo and guanadrel. Thus, the enhanced vasoconstrictor response to NE during guanadrel appears not to be confounded by AVP-mediated augmentation. The lack of an increase in either AII or AVP despite the significant suppression of SNS activity during guanadrel is perhaps related to the fact that there was only a small decrease in supine blood pressure in these subjects. In addition, although we have data concerning only the renin-angiotensin and AVP systems, it seems unlikely that there was activation of other neurohumoral systems during guanadrel.

The interpretation of our results also assumes that there is no confounding effect of concurrent β -adrenergic receptor regulation since we did not block β -adrenergic receptors during the

measurement of FABF. Downregulation of β -adrenergic receptor responses have been demonstrated when SNS activity is increased (21, 22). Therefore, the predicted change in β -adrenergic receptor response during SNS suppression during guanadrel would be upregulation. Since β -adrenergic receptor stimulation by NE mediates vasodilation, upregulation of β -adrenergic response would be reflected by less vasoconstriction during NE infusion. Thus, if there were β -adrenergic receptor upregulation we may have underestimated the extent of enhanced α -adrenergic vasoconstriction sensitivity to NE during guanadrel.

In this study NE and AII were infused directly into the brachial artery to produce changes in FABF without producing major systemic effects that could confound interpretation of the results. A statistically significant effect of dose on MAP was observed for both NE and AII. However, the magnitude of the increase in MAP in each case was relatively modest and unlikely to have had a major influence on FABF. Moreover, there was no interaction observed between study phase and the dose effect on MAP.

These results do not allow us to determine whether the upregulation of NE-mediated vasoconstriction we observed involved α_1 or α_2 postsynaptic adrenergic receptors or both. Several studies have demonstrated the presence of postsynaptic α_1 and α_2 receptors on arterial smooth muscle (23–26). It has been suggested that the location of postsynaptic α_2 -adrenergic receptors is predominantly extrasynaptic (24). Thus, exogenously infused NE may exert a relatively greater α_2 effect compared with endogenous NE released into the synapse where the α_1 component may predominate. Therefore, it is possible that the exogenously administered NE in this study resulted predominantly in α_2 -adrenergic receptor stimulation. Additional studies will be needed to help clarify which receptor subtype is involved in the vasoconstriction response to intraarterial NE and the upregulation of the response identified in this study.

We observed an increase in FABF during the intraarterial infusion of the nonspecific α -adrenergic antagonist phentolamine. The FABF response to phentolamine has been used as an estimate of endogenous arterial vascular α -adrenergic tone (12). The mean increase in FABF during phentolamine infusion during the guanadrel phase was similar when compared with the placebo phase. This suggests that endogenous arterial α -adrenergic tone was maintained despite the effect of guanadrel to decrease SNS activity. The apparent maintenance of arterial α -adrenergic tone suggests that the upregulation of α -adrenergic responsiveness during guanadrel compensates at least in part for the decrease in SNS activity. Such compensation may provide a mechanism to explain why there was a minimal overall effect of guanadrel on resting supine blood pressure in these subjects despite substantial suppression of systemic SNS activity. It is not possible to conclude that there was complete compensation, particularly in light of the heterogeneity observed in the FABF response to phentolamine (i.e., the response to phentolamine was less during the guanadrel phase in five of nine subjects) and the relatively poor power that the study had to exclude a significant decrease in the phentolamine response.

There are multiple systems contributing to the maintenance of blood pressure homeostasis in humans. Since vascular arterial adrenergic tone is an important component, regulation of arterial tone is key in maintaining blood pressure homeosta-

sis. On the basis of these results, we hypothesize that homologous upregulation of α -adrenergic receptor function is important in the maintenance of blood pressure during suppression of SNS activity in humans.

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