Cardiovascular Hormonal Effects of Circulating Norepinephrine

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SUMMARY The hormonal effects of circulating norepinephrine (NE) were evaluated with two-step NE infusion studies in normal volunteers. At an infusion rate that increased plasma NE 2.5-fold (approximately equivalent to the change from supine to upright posture), there were small but consistent increases in diastolic pressure (+5 mm Hg) and plasma renin activity (+13%). At the high extreme of the physiologic range (a 9-fold increase over supine basal), circulating NE caused major changes in blood pressure (+22/15 mm Hg), heart rate (−7 bpm), and plasma renin activity (+67%). Thus, at physiologic concentrations, circulating NE should be considered to be a cardiovascular hormone as well as an index of sympathetic nervous activity. (Hypertension 5: 787-789, 1983)

KEY WORDS • norepinephrine • hormone • blood pressure • renin • epinephrine

NOREPINEPHRINE (NE) has been said to have trivial importance as a hormone except at very high concentrations. In early experiments, Celander1 found sympathetic nerve stimulation to be much more potent than infused NE. Fokkow et al.2 estimated intrasynaptic NE to be up to 1000-fold more concentrated than plasma NE. More recently, Silverberg et al.3 infused NE into humans and reported a threshold of activity eight to nine times the supine basal concentration, which is at the extreme of the physiologic range.

Nevertheless, other evidence points to a discrete role for circulating NE in cardiovascular homeostasis. Mellander and Johansson5 observed that the media of arterioles only sparsely innervated by sympathetic fibers. It is also known6 that intimal cells have adrenergic receptors and that vasoconstriction is easily effected by intimal but not adventitial application of NE. These observations have taken on added significance since the discovery of extrasynaptic alpha-adrenergic receptors (probably of the alpha2 subtype)7 anatomically located to respond to circulating NE. The present study suggests that NE indeed has discrete hormonal effects within the physiologic range and implicates circulating NE in cardiovascular homeostasis.

Methods

Five normal volunteers (aged 22 to 34 years, weighing 59 to 82 kg) who consumed no food, caffeine, or nicotine for 10 hours prior to the study, gave informed consent and reported to the General Clinical Research Center at 8:00 a.m. After they voided and were weighed, a flexible plastic catheter was inserted into one forearm vein and attached to a keep-open saline drip. A heparin lock was placed in the contralateral forearm for blood sampling. Subjects remained supine for 60 minutes (30 minutes after needle insertions) before baseline blood samples were taken. Blood pressures and heart rates were determined at 2- to 3-minute intervals for the final 15 minutes of the control period. An NE solution (Levofed, 0.1 mg/kg/liter with ascorbic acid 0.1% in normal saline) was then infused via a Sage infusion pump starting at a rate of 0.02 μg/kg/min. Blood pressure (mercury sphygmomanometer) and heart rate were measured every 2 minutes by an independent observer for the next 24 minutes followed by a second (duplicate) blood sampling. The infusion rate was then increased to 0.08 μg/kg/min for 24 minutes, with clinical monitoring and blood sampling performed as during the control and low infusion periods. Twenty minutes after the infusion was discontinued, a supine blood sample was obtained. A final blood sample was taken after 5 minutes of upright posture and the study was then terminated. In each case, the total amount of blood withdrawn (100 ml) was replaced with normal saline over the course of the experiment. Blood pressures and heart rates for each subject were means of the last three observations for each period. No adverse effects occurred.

Standard laboratory methods were used to measure the variables reported. Microhematocrit was estimated...
from the mean of duplicate samples, plasma renin activity (PRA) was determined by radioimmunoassay of generated angiotensin I (Rianen kit, New England Nuclear, Boston, Massachusetts), and plasma catecholamines were quantitated against internal standards with a modified radioenzymatic assay.\(^8,9\) The normal range (95% confidence limits) for morning supine plasma NE (95–370 ng/liter) and epinephrine (20–110 ng/liter) in our laboratory is similar to other observers. Sensitivity of the assay (twice blank) is 30 ng/liter for NE and 20 ng/liter for epinephrine; intra- and inter-assay coefficients of variation (sd/mean) are <6% and <13% respectively for both catecholamines in the range of 100 pg/ml.

Data were expressed as means ± se. At the low infusion rate, data were both directly compared to supine basal by paired Student \(t\) test and separately analyzed as % change: (observed - basal)/basal \(\times 100\). Changes at the low and high infusion rates over supine basal control were compared by two-way analysis of variance and by paired Student \(t\) test with Bonferroni modification, necessary for adjustment of probabilities during multiple comparisons.\(^10\) Low infusion rate data were also compared to supine basal by paired one-tailed Student \(t\) test. Statistical significance was accepted at the 5% level.

**Results**

Figure 1 shows the response of blood pressure, heart rate, hematocrit, and PRA to NE infused at low (0.02 \(\mu\)g/kg/min) and high (0.08 \(\mu\)g/kg/min) rates. Basal steady state plasma NE (209 ± 16 ng/liter) rose to 513 ± 27 ng/liter at the low NE infusion rate and to 1850 ± 230 ng/liter at the high infusion rate. These two-step NE infusions increased systolic pressure from 112 ± 2 mm Hg basal to 115 ± 2 and 134 ± 1 mm Hg (\(F = 49, p < 0.001\)), increased diastolic pressures from 72 ± 2 mm Hg basal to 77 ± 3 and 87 ± 3 mm Hg (\(F = 93, p < 0.001\)), increased hematocrit from 43% ± 0.4% basal to 43.6% ± 0.5% and 44.8% ± 0.5% (\(F = 5.7, p < 0.05\)), increased basal PRA from 0.36 ± 0.05 ng/ml/hr to 0.41 ± 0.06 and 0.60 ± 0.14 ng/ml/hr (\(F = 5.2, p < 0.05\)), decreased heart rate from 64 ± 2 bpm basal to 62 ± 4 and 57 ± 4 bpm (\(F = 6.1, p < 0.025\)), and did not affect plasma epinephrine (F = 1.0). Blood pressure and heart rate returned to basal within a few minutes after the infusion was stopped; plasma NE was 213 ± 15 ng/liter, and PRA and hematocrit had also returned to basal by 20 minutes after the infusion. Five minutes after assumption of the upright position, plasma NE rose to 497 ± 38 ng/liter.

Expressed in another way, physiologic changes at the low infusion rate included significant increases in PRA 13% ± 4%, (\(p < 0.05\)), and diastolic pressure 6.2% ± 1.5%, (\(p < 0.01\)) and lesser changes in systolic blood pressure and hematocrit. The relative magnitude of degrees of change in measured variables at the low NE infusion rate is shown in figure 2. Changes at the higher NE infusion rate (compared to basal by paired Student's \(t\) test with Bonferroni modification) included systolic and diastolic pressure increases of 19% ± 2.8% and 21% ± 1.7% (\(p < 0.001\)), heart rate decrease of 11% ± 3.5% (\(p < 0.01\)), PRA increase of 65% ± 20% (\(p < 0.05\)), and hematocrit increase of 4% ± 1.6% (\(p 0.05\)). Plasma epinephrine again did not change.

**Discussion**

These results demonstrate small but measurable effects of circulating norepinephrine (NE) on blood pressure and plasma renin activity (PRA) during plasma NE increases comparable to the change induced by upright posture. At the extremes of the physiologic range, infused NE caused major increases in blood pressure (22/15 mm Hg) and PRA (+67%), lesser increases in hematocrit, and decreases in heart rate. It can be concluded from these observations that circulating NE should not be considered to be simply an index of sympathetic neurotransmission. Rather, a continu-
Many well-conducted studies corroborate the hormonal effects of circulating NE, although these studies were not originally designed for this purpose. FitzGerald et al. demonstrated a 6/5 mm Hg blood pressure increase in five normal volunteers at a NE infusion rate of 0.03 μg/kg/min, which in their studies caused the same 300 pg/ml increase in plasma NE as we observed at 0.02 μg/kg/min. Grimm et al. employed graded NE infusions in 28 normotensive and 35 hypertensive subjects. Interpolation on their graphs reveals that an increase in plasma NE from 200 to 500 pg/ml results in the same 300 pg/ml increase in plasma NE as we observed.

In opposition are the widely quoted conclusions of Silverberg et al. and Cryer that NE concentrations in excess of 1800 pg/ml are required to produce measurable hemodynamic or metabolic changes. Careful scrutiny of their methods and data, however, reveals certain discrepancies that may require modification of their conclusions. These investigators estimated activity thresholds by linear regression intercepts, a less accurate and sensitive method than the intradividual comparisons used here and in other studies. Perhaps most important, their subjects may not have been truly under unstimulated basal conditions prior to the NE infusions. They did not report their preinfusion plasma NE values, but back-calculation from available data reveals basal plasma NE levels of 691, 504, and 521 pg/ml prior to the 1.0, 2.5 and 5.0 μg/min NE infusions, respectively. These values are more than twice their reported normal basal plasma NE (228 pg/ml), and are actually higher than the plasma NE (275 pg/ml) reported at steady state during the 0.1 μg/min NE infusion. These high basal NE values preclude adequate interpretation of their data, which were presented as change from basal. As an example, if basal blood pressures were artifically low or temporarily elevated by stress-related increased sympathetic activity during the preinfusion periods, the small changes induced by low-level NE infusions would have been missed, especially if basal sympathetic activity returned toward normal during the subsequent NE infusion period.

Recognition of the hormonal role of NE may be important in improving our understanding of various cardiovascular regulatory interactions such as renin release. The release of renin by circulating NE is probably not artifactual because PRA rapidly returned to normal after the NE infusion was stopped. In addition, we found no effect of phenylephrine (an alpha agonist) on PRA during a similar (equivpressor) two-step phenylephrine infusion protocol in these same subjects (Izzo, unpublished observations, n = 5). Because circulating NE may also affect other neurohumoral systems, further investigation of the hormonal role of NE is needed.

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