Norepinephrine: hormone and neurotransmitter in man

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Silverberg, Alan B., Suresh D. Shah, Morey W. Haymond, and Philip E. Cryer. Norepinephrine: hormone and neurotransmitter in man. Am. J. Physiol. 234(3): E252-E256, 1978 or Am. J. Physiol.: Endocrinol. Metah. Gastrointest. Physiol 3(3): E252-E256, 1978. To determine whether norepinephrine could subserve a hormonal as well as a neurotransmitter function, norepinephrine was infused for 60 min into each of five normal young men in doses of 0.1, 0.5, 1.0, 2.5, and 5.0 µg/min. After infusion, the plasma norepinephrine concentration fell with a mean (±SD) half-time of 2.4 ± 0.7 min. The mean (±SD) norepinephrine metabolic clearance rate was 3,070 ± 200 ml/min. The calculated basal plasma norepinephrine production rate was 0.7 µg/min. The blood pressure and circulating glycerol, acetocetate, β-hydroxybutyrate, and glucose (increased) and the heart rate and circulating insulin, lactate, pyruvate, and alanine (decreased) exhibited highly significant parabolic relationships with the steady-state plasma norepinephrine concentrations. However, norepinephrine levels in excess of 1,800 pg/ml were required to produce hemodynamic and/or metabolic effects. Thus, under usual conditions, the biologic actions of norepinephrine can be attributed only to its sympathetic neurotransmitter function. Plasma norepinephrine concentrations do at times exceed 1,800 pg/ml during exercise and during major acute illness. Thus, under conditions of stress, norepinephrine may subserve a hormonal, as well as a neurotransmitter, function.

catecholamines; catecholamine effects; adrenergic physiology; norepinephrine plasma half-time; norepinephrine metabolic clearance rate; norepinephrine production rate

A HORMONE is a biologically active substance transported via the blood from its site of origin to its target cells. Insofar as is presently known, outside of the central nervous system, epinephrine arises only from the adrenal medullas (8). Thus, the systemic metabolic and hemodynamic effects of epinephrine require transport of epinephrine via the circulation, and epinephrine can be viewed as a hormone of the adrenal medullas. Norepinephrine, on the other hand, is the neurotransmitter released from axon terminals of sympathetic postganglionic neurons in direct relation to its effector cells; transport via the circulation is not required to explain its metabolic and hemodynamic effects. Norepinephrine does, however, escape into the circulation. Is norepinephrine in plasma merely spilled neurotransmitter in route to metabolic degradation and excretion or is it a biologically active hormone in route to its target cells? This question is relevant not only to an understanding of adrenergic physiology but also, at a very pragmatic level, to the interpretation of measurements of plasma norepinephrine in the study of adrenergic physiology and pathophysiology.

Norepinephrine introduced directly into the circulation, whether infused intravenously into normal subjects or released from a norepinephrine-secreting pheochromocytoma, clearly produces biologic effects. It is quite conceivable, however, that the plasma levels of norepinephrine so produced far exceeded those ever achieved under physiologic conditions. Because the principal routes of dissipation of norepinephrine released from sympathetic axon terminals are believed to be axonal reuptake and local metabolism rather than escape into the plasma (2), a steep norepinephrine concentration gradient between the synaptic clefts and the plasma probably occurs at times when there are biologically effective concentrations of norepinephrine within the synaptic clefts. Thus, one would expect that very high plasma norepinephrine concentrations would be required to produce measurable effects when the norepinephrine is introduced directly into the circulation. This expectation is supported by the markedly elevated plasma norepinephrine concentrations found in patients with pheochromocytomas (9, 12, 20, 21).

In order to determine whether supraphysiologic plasma norepinephrine concentrations are required to produce biologic effects, plasma norepinephrine concentrations, hemodynamic changes, and a variety of metabolic variables were measured during the intravenous infusion of five different doses of norepinephrine into each of five normal young men.

METHODS

Five normal men (Table 1) were studied after an overnight fast in the Washington University School of Medicine Clinical Research Center, each on five separate occasions. All gave informed consent prior to study.

Subjects were supine throughout. An intravenous catheter was inserted in an antecubital vein in one arm (for infusions) and an intravenous needle was inserted into a vein in the opposite arm (for sampling) at ~30 min. The blood pressure (sphygmomanometer)
and heart rate were recorded at 5-min intervals. Blood samples were drawn at -15, 0, 5, 10, 20, 30, 40, 50, 60, 75, and 90 min. With the 5.0 μg/min norepinephrine infusions, additional samples were drawn at 62.5, 65, 67.5, 70, and 72.5 min.

Norepinephrine (levaterenol bitartrate, Levophed) was infused with a Harvard infusion pump in a total volume of 60 ml from 0 to 60 min. Ascorbic acid (0.5 mg/ml) was added to each infusate. Each subject received norepinephrine doses of 0.1, 0.5, 1.0, 2.5, and 5.0 μg/min. The dose sequence was varied and was not known to the subject. All doses were well tolerated. After the fifth study, the subjects were asked to identify the largest dose. They were unable to do so.

Ten-milliliter blood samples were distributed into iced tubes containing heparin alone, heparin plus 5 mM reduced glutathione, and aprotinin (Trasyrol, 500 U/ml). Heparinized blood (500 μl) was immediately pipetted into tubes containing 500 μl of 3 M perchloric acid. All tubes were promptly centrifuged at 4°C and the supernatants frozen until the time of analyses. Norepinephrine and epinephrine were measured in 250 μl of plasma with a single isotope method (11) based on that of Passon and Peuler (26). Between-assay coefficients of variation are consistently less than 10% for both norepinephrine and epinephrine. Blood lactate and pyruvate (22), glyceral (27), and acetoacetate and beta-hydroxybutyrate (4), and plasma alanine (18), glucose (22), glucagon (19), insulin (24), cortisol (3), and growth hormone (29) were measured with micro- or semimicrotechniques. Growth hormone and insulin concentrations below the lower limit of assay sensitivity were assigned that value for calculation of mean values.

Standard statistical methods, including a t test for paired data and parabolic regression analysis (31), were used.

**RESULTS**

Plasma norepinephrine concentrations rose rapidly during infusions reaching maximal levels by 5 min. Mean (±SE) steady-state plasma norepinephrine concentrations were 275 ± 14, 672 ± 38, 807 ± 67, 1,440 ± 120, and 2,150 ± 66 pg/ml at the five infusion doses. The corresponding epinephrine values were 49 ± 9, 50 ± 7, 72 ± 14, 79 ± 11, and 83 ± 20 pg/ml.

After completion of the 5.0 μg/min infusions, the plasma norepinephrine concentration fell with a mean (±SD) half-time of 2.4 ± 0.7 min (range 1.5–3.1 min), a value similar to that found by Cohen and co-workers (7). The mean (±SD) plasma norepinephrine metabolic clearance rate, calculated as the infusion rate divided by the difference between the basal and the steady-state plasma norepinephrine concentration during infusion (30), was 3,070 ± 200 ml/min (range 2,730–3,220 ml/min) from the 5.0 μg/min infusion data. This calculation assumes that endogenous norepinephrine release continued during the infusions. If one assumes that endogenous norepinephrine release ceased during the infusions, the calculated mean plasma metabolic clearance rate would be 7% lower. The mean plasma norepinephrine metabolic clearance rates calculated from the 2.5 and 1.0 μg/min infusion data were similar (3,340 ± 610 and 3,310 ± 910 ml/min, respectively) to that calculated from the 5.0 μg/min infusion data, indicating that the plasma metabolic clearance rate did not change over a broad range of plasma norepinephrine concentrations.

The hemodynamic effects of the norepinephrine infusions are illustrated in Fig. 1. For simplicity, only the data from the 0.1 and 5.0 μg/min infusions, the smallest and largest doses used, are shown. During the 5.0 μg/min norepinephrine infusions the mean (±SE) systolic blood pressure rose from 107 ± 5 to 131 ± 5 mmHg (P < 0.01), the diastolic blood pressure rose from 61 ± 4 to 80 ± 3 mmHg (P < 0.001) and the heart rate fell from 64 ± 4 to 55 ± 2 per min (P < 0.01). No significant changes in these variables occurred during the 0.1 μg/min norepinephrine infusions. These findings are similar to those of Goldenberg and co-workers (16), who found the average minimum pressor dose of intravenous norepinephrine to be 0.05 μg/kg per min (3.5 μg/min in a 70-kg subject).

The metabolic effects of the infusions of norepinephrine are summarized in Table 2. The plasma glucose and blood glycerol, β-hydroxybutyrate, and acetoacetate concentrations rose during the 5.0 μg/min norepinephrine infusions, whereas blood lactate and pyruvate and plasma alanine concentrations declined. Although the latter changes were small, they were effects of the high dose of norepinephrine because significant changes in the means of these (and other) metabolic variables did not occur during the 0.1, 0.5, 1.0, or 2.5 μg/min

<table>
<thead>
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<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
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<tbody>
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<td>20</td>
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</table>

**TABLE 1. Subjects**

**FIG. 1.** Mean (±SE) systolic blood pressures, diastolic blood pressures, heart rates, and plasma norepinephrine concentrations in 5 normal men during intravenous infusion of norepinephrine in doses of 5.0 (closed symbols) and 0.1 μg/min (open symbols).
TABLE 2. Metabolic effects of norepinephrine infusions

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.1 µg/min</th>
<th>0.5 µg/min</th>
<th>1.0 µg/min</th>
<th>2.5 µg/min</th>
<th>5.0 µg/min</th>
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<td>Glucose, mg/dl</td>
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<td>100 ± 5</td>
<td>100 ± 5</td>
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<td>Lactate, µM</td>
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<td>30 ± 2</td>
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<tr>
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<td>5 ± 1</td>
<td>5 ± 1</td>
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<tr>
<td>Alamine, µM</td>
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<td>15 ± 2</td>
<td>15 ± 2</td>
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</tr>
<tr>
<td>Glycerol, µM</td>
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<td>2 ± 1</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
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<td>3 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Growth hormone, ng/ml</td>
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<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. B, baseline; I, infusion. *P < 0.05. **P < 0.02. ***P < 0.001. ****P < 0.0001.

DISCUSSION

The intravenous infusion of norepinephrine at 5.0 µg/min into normal human subjects produced typical hemodynamic and metabolic responses. The former included vasoconstriction with hypertension and reflex bradycardia and the latter lipolysis with elevated blood glycerol concentrations, ketogenesis with elevated blood concentrations of acetooacetate and β-hydroxybutyrate, and glycosgenesis with hyperglycemia. It is possible that gluconeogenesis also contributed to the elevated plasma glucose concentrations because 1) adrenergic stimulation has been shown to accelerate gluconeogenesis, most recently in isolated hepatocytes (17); 2) the resumption of gluconeogenesis during insulin-induced hypoglycemia coincides with norepinephrine release and precedes release of glucagon, cortisol, and growth hormone (14), and 3) a decline in blood lactate and pyruvate occurred during the development of hyperglycemia. The observed decline in plasma alanine could be attributed to its increased utilization as a gluconeogenic precursor; however, inhibition of alanine release from muscle by norepinephrine has been demonstrated (15).

The intravenous infusion of graded doses of norepinephrine, in doses ranging from 0.1 to 5.0 µg/min, produced stable plasma norepinephrine concentrations that spanned the physiologic range. Steady-state plasma norepinephrine concentrations in excess of 1,800 pg/ml were required to produce measurable hemodynamic or metabolic changes. Assuming unimpeded movement of norepinephrine from the plasma into the sympathetic synaptic clefts, the steady-state plasma and synaptic cleft norepinephrine concentrations would be similar. Thus, one can estimate from these data that the minimum biologically effective synaptic cleft norepinephrine concentration is approximately 1,800 pg/ml (roughly eight-fold over basal levels); and that, in order to subserve its physiologic neurotransmitter function, sufficient norepinephrine must be released from stimulated sympathetic axon terminals to produce at least an eight-fold increment in the synaptic cleft.
The present data is approximately 25% of the norepinephrine production rate calculated from 0.7 pg/min. On the other hand, the basal endogenous production rate (0.018/0.025) would be approximately 3% of the norepinephrine released into the circulation if the urinary excretion rate of norepinephrine by sedentary adults could be made from previously available data. The use of a fluorometric, rather than an isotope derivative, method for the measurement of plasma norepinephrine is a fundamental difference between the latter study and the present one.

Endogenous norepinephrine release sufficient to produce adrenergic hemodynamic and metabolic effects has been associated with an increase in the mean plasma norepinephrine concentration of as little as 100 pg/ml (10), an increment in the calculated plasma norepinephrine production rate to approximately 1.0 μg/min. On the assumption that the synaptic cleft production rate must increase by at least eight fold to produce biologic effects, as discussed above, this 1.4-fold increment in the plasma norepinephrine production rate represents less than 20% of the estimated minimum rate of axonal norepinephrine release required for biologic activity, suggesting that more than 80% of released norepinephrine is dissipated by mechanisms other than escape into the plasma, i.e., axonal reuptake and/or local metabolism. Clearly, norepinephrine release into the synaptic clefts may well have exceeded the minimum required for biologic action so that the fraction of released norepinephrine dissipated by the latter mechanisms may have been much higher than 80%.

Normal individuals seldom, if ever, achieve plasma norepinephrine concentrations in excess of 1,800 pg/ml under conditions of sedentary activity. In 60 normal subjects studied in our laboratory the mean (+SD) supine resting plasma norepinephrine concentration was 228 ± 81 pg/ml with a maximum individual value of 406 pg/ml. In 40 normal subjects, the mean level rose to 526 ± 198 pg/ml in the upright position with a maximum individual value of 956 pg/ml. Even in response to the metabolic stress of insulin-induced hypoglycemia, with a mean plasma glucose nadir of 39 mg/100 ml, the maximum mean norepinephrine concentration was 770 ± 241 pg/ml (14) with a maximum individual value of 1,180 pg/ml. Plasma norepinephrine concentrations do, however, exceed 1,800 pg/ml in some persons during short-term exercise and in many persons during prolonged or maximal exercise (13, 25), as well as in many patients with major acute illnesses such as diabetic ketoacidosis (5) and myocardial infarction (6). Thus, under usual conditions, the biologic actions of norepinephrine can be attributed only to its sympathetic neurotransmitter function. However, under conditions of stress, including that of vigorous physical exercise, norepinephrine may also subserve a hormonal function.

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REFERENCES


