Norepinephrine Kinetics in Essential Hypertension
Defective Neuronal Uptake of Norepinephrine in Some Patients

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SUMMARY To assess sympathetic nervous system function in essential hypertension, we measured the rates of release to and removal from plasma of the sympathetic neurotransmitter, norepinephrine. In normal subjects, disappearance of tritiated norepinephrine from plasma, after infusion to steady state, was biexponential, with $t_{1/2} = 2.0 \pm 0.4$ minutes (mean ± standard deviation) and $t_{1/2} = 33 \pm 15$ minutes. The rapid component of removal seemed to represent neuronal uptake of norepinephrine: the $t_{1/2}$ was lengthened by the selective inhibitor of neuronal norepinephrine uptake, desipramine; it was not changed by the extraneuronal uptake blocker, cortisol; and it was prolonged in patients with peripheral sympathetic nerve dysfunction (idiopathic autonomic insufficiency). In eight of 37 hypertensive patients, the $t_{1/2}$ was $> 2.8$ minutes (range, 3.3-6.0 min), longer than in any normal subject; this appears to be presumptive evidence of the existence of defective neuronal norepinephrine uptake. In these patients the rate of spillover of norepinephrine to plasma, of transmitter escaping uptake after release, was $0.73 \pm 0.39$ ng/m$^2$/min (43 ± 23 nmoles/m$^2$/min), higher than in normal subjects, $0.36 \pm 0.14$ ng/m$^2$/min (2.1 ± 0.8 nmoles/m$^2$/min) ($p < 0.01$). A defect in neuronal uptake of norepinephrine, by exposing adrenergic receptors to high local norepinephrine concentration, may be important in the pathogenesis of blood pressure elevation in some patients with essential hypertension.

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KEY WORDS • norepinephrine • arterial hypertension • sympathetic nervous system • tricyclic antidepressant • cortisol • idiopathic autonomic insufficiency

The finding of increased levels of the sympathetic neurotransmitter, norepinephrine, in the plasma of some patients with essential hypertension, although disputed, suggests that sympathetic nervous overactivity is involved in the pathogenesis of the blood pressure (BP) elevation. But the plasma concentration of norepinephrine provides a very indirect measure of sympathetic nerve discharge rate. Only a small proportion of the norepinephrine released escapes to plasma; most is subject to local reuptake by the sympathetic nerves. Furthermore, the plasma concentration of norepinephrine is determined not only by the rate of spillover to plasma after release, but also by the subsequent rate of removal of norepinephrine from the circulation.

We have developed methods for studying the kinetics of norepinephrine in humans. The rates of spillover of norepinephrine to plasma and clearance of norepinephrine from plasma are determined using radiotracer techniques. With these methods, the rate of norepinephrine spillover to plasma in patients with peripheral autonomic insufficiency has been found to be significantly decreased, indicating that the norepinephrine spillover rate provides at least qualitative information about net sympathetic nerve activity. In the evaluation of possibly increased norepinephrine spillover in patients with essential hypertension, it seemed important to differentiate between a true increase in norepinephrine release (with increased sympathetic nerve firing rates) and increased spillover from defective local inactivation of transmitter (neuronal reuptake). To this end, a method based on the analysis of tritiated norepinephrine postinfusion decay curves has been developed for assessing neuronal uptake of norepinephrine in humans.

We have applied these measures of norepinephrine kinetics to the study of sympathetic nervous system...
function in essential hypertension. The results presented here suggest that in a proportion of patients with essential hypertension, neuronal uptake of norepinephrine is defective, leading to greater spillover of norepinephrine to plasma, and higher plasma norepinephrine concentrations.

Materials and Methods

Experimental Subjects

Thirty-seven white patients (29 men, 8 women) with essential hypertension (mean age 38 years, range 18–55) and 17 healthy volunteers (12 men, 5 women, mean age 34 years, range 18–54) were studied. The study protocol was approved by the Alfred Hospital medical research ethics committee, and was fully explained to all subjects, who gave their informed consent. No women with childbearing potential participated in the study. Patients were recruited consecutively from the hypertension outpatient clinic of the Alfred Hospital and from the Risk Evaluation Clinic of the Baker Medical Research Institute. Normal volunteers were recruited by advertisement from the general community. The average clinic BP of patients (minimum of three visits) was above 155 mm Hg systolic, or 90 mm Hg diastolic, or both. Five had isolated systolic hypertension. None had a serum creatinine concentration greater than 2.0 mg/dl (18 μmoles/dl), Grade 3 or 4 hypertensive retinopathy, or were in heart failure. Most patients had never received treatment for hypertension, and none had been treated in the preceding 6 weeks. Secondary hypertension was excluded by clinical testing.

Investigation of Norepinephrine Kinetics

We studied the kinetics of norepinephrine using methods we have previously described, measuring the apparent rate of release of norepinephrine (rate of entry of norepinephrine to plasma), clearance of norepinephrine from plasma, the time course of disappearance of norepinephrine from plasma, and plasma norepinephrine concentration. When tritiated norepinephrine (NE) is infused intravenously at a constant rate to reach plateau concentration (steady state conditions), the rate of release of endogenous norepinephrine into plasma and norepinephrine clearance from plasma may be determined, using the following equations:

\[
\text{apparent NE release rate} = \frac{\text{NE-}^3\text{H infusion rate}}{\text{specific activity of plasma NE}} \quad (1)
\]

\[
\text{NE clearance} = \frac{\text{NE-}^3\text{H infusion rate}}{\text{steady state plasma NE-}^3\text{H concentration}}. \quad (2)
\]

The calculated rate of norepinephrine release is "apparent" rather than "real" as it gives, rather than the rate of release of norepinephrine from sympathetic nerve varicosities, the rate at which released norepinephrine spills over into plasma.

Norepinephrine Apparent Release Rate and Clearance

In 25 hypertensive patients and all normal subjects, we determined the apparent release rate of norepinephrine and clearance of norepinephrine from plasma. In principle, this involved the intravenous infusion of tritiated norepinephrine to reach plateau concentration, and measurement of plasma tritiated-norepinephrine concentration and norepinephrine specific activity at steady state, from which norepinephrine release rate and clearance values are derived. Studies were performed with subjects resting supine in a single-bed ward. Tests were conducted always in the morning, after subjects had eaten a light breakfast. Tea, coffee, alcohol, and tobacco were forbidden during the preceding 12 hours. No patients were hospitalized, all attending as outpatients on the morning of the test. One hour prior to the commencement of the infusion, intravenous needles were inserted in antecubital veins for subsequent infusion of norepinephrine and withdrawal of blood samples. In a preliminary study on 10 patients and 10 normal subjects, tritiated norepinephrine was infused into an antecubital vein of one arm at a constant rate of 0.35 μCi/m²/min for 90 minutes, and 10 ml of blood was sampled sequentially from the other arm for assay of tritiated norepinephrine. The concentration of tritiated norepinephrine had reached plateau in plasma in normal subjects and was at, or close to, plateau in hypertensive patients by 60 minutes (not quite to plateau in two patients) (fig. 1) in agreement with previous reports. For the present study, which did not include the 20 subjects participating in the preliminary testing, the halftime of the slowest component of norepinephrine removal, which influences the time to reach plateau concentration, was known, and the 90-minute infusion was immediately preceded by a bolus injection of 15 μCi/m² of radiolabelled norepinephrine in all subjects, to hasten the approach to plateau concentration and to ensure that steady-state conditions were in fact reached in every case. At 70, 80, and 90 minutes, 10 ml of blood was withdrawn for determination of mean plasma norepinephrine specific activity at steady state, and a further 10 ml at 80 minutes for assay of plasma norepinephrine concentration.

Time Course of Disappearance of Tritiated Norepinephrine from Plasma

At the end of the infusion of tritiated norepinephrine, venous blood was sampled sequentially over 40 minutes, to follow the time course of disappearance of norepinephrine from plasma. This was done in all subjects, including 12 hypertensive patients in whom norepinephrine release rate and clearance measurements were not performed. The components of the norepinephrine disappearance curve were resolved by graphical analysis.

Mechanism of Norepinephrine Removal from Plasma

Because removal of norepinephrine from plasma was found to be slowed in some patients with essential
hypertension, the mechanism of removal of norepinephrine from the circulation was investigated. The principal means of removal of norepinephrine from plasma is thought to involve a specific uptake mechanism, the "norepinephrine pump," in sympathetic nerve varicosities (neuronal uptake) and some other tissues (extraneuronal uptake), so we tested the effect of interference with neuronal and extraneuronal uptake of norepinephrine. The time course of disappearance of norepinephrine from plasma was studied in seven normal subjects, both before and 3 hours after selective inhibition of neuronal uptake by the tricyclic antidepressant, desipramine, administered orally in a dose of 125 mg (470 μmoles). The tests were performed 1 week apart, in randomized order. Five additional normal subjects were similarly studied, before and immediately after intravenous administration of the selective extraneuronal uptake inhibitor, cortisol, 500 mg (1.38 mmoles). This dose of cortisol is adequate to achieve extraneuronal uptake blockade in vivo.

In addition, norepinephrine disappearance was studied in six patients with idiopathic peripheral autonomic insufficiency, who had peripheral sympathetic neuronal dysfunction including defective neuronal uptake of norepinephrine. They were tested to provide a further experimental group in whom neuronal uptake of norepinephrine was subnormal. These patients had incapacitating orthostatic hypotension, and no evidence of central nervous system disease on clinical neurological examination. For comparison, we tested four patients with an intact peripheral sympathetic nervous system, but autonomic insufficiency and orthostatic hypotension from central nervous system disease.

Biochemical Methods

Methods were needed to measure tritiated norepinephrine in plasma, endogenous plasma norepinephrine concentration, and, independently, specific activity of norepinephrine in plasma. The specific activity assay utilized an initial adsorption of norepinephrine on to alumina, with direct measurement of tritiated norepinephrine in an aliquot of acid eluate by liquid scintillation counting, and enzymatic assay of unlabelled norepinephrine in the remainder. The possibility that the eluate contained tritiated dihydroxy metabolites which, if present, would be extracted on alumina, was rigorously excluded. Plasma samples at 70, 80, and 90 minutes of infusion were assayed, mean plasma norepinephrine specific activity at steady state calculated, and apparent release rate of norepinephrine derived from this value.

Plasma norepinephrine concentration at steady state was measured independently of the method used for specific activity determination, using a different assay for establishing agreement or otherwise between plasma norepinephrine values and norepinephrine release rate measurements. Plasma tritiated norepinephrine was assayed, also independently of specific activity measurements, to follow the time course of accumulation of norepinephrine in plasma during the infusion, to calculate norepinephrine clearance at steady state and to study the disappearance of norepinephrine from plasma at the end of the infusion.

Preparation and Storage of Tritiated Norepinephrine

Levo norepinephrine 7,8-3H (N), of specific activity 24–28 Ci/m mole (New England Nuclear Corporation) was pharmaceutically prepared for human administration, and stored under nitrogen in glass vials at −20°C until needed (maximum storage, 2 months). Thin layer chromatography was used to estimate radiochemical purity prior to each experiment, with 98% purity being taken as the minimum acceptable.

**Figure 1.** Time course of accumulation of tritiated norepinephrine in plasma of normal subjects and hypertensive patients during constant rate infusion (0.35 μCi/m2/min) in the preliminary experiment, and of disappearance of norepinephrine from plasma on terminating the infusion.
Statistical Methods

Much of the data from hypertensive patients did not follow a Gaussian distribution, necessitating the use of nonparametric statistical methods. When applicable, the Mann-Whitney U test and Spearman's rank correlation test, both distribution-free methods of statistical analysis, were used. Normally distributed data was analyzed using independent and paired sample t tests and linear regression analysis.

Results

Plasma norepinephrine specific activity was constant from 70 through 90 minutes of infusion, indicating that steady-state conditions prevailed. Norepinephrine specific activity in normal subjects at 70 and 80 minutes was 97% ± 4% (mean ± standard error) and 101% ± 6%, respectively, of the 90-minute value. In hypertensive patients, the corresponding figures were 96% ± 4% and 99% ± 5%. The time course of disappearance of tritiated norepinephrine from plasma, after termination of the infusion, is shown in normal subjects and hypertensive patients in fig. 1. The disappearance curve for norepinephrine was biexponential, and could be resolved into a rapid removal phase with a halftime (t1/2) of 2.0 ± 0.4 minutes (mean ± standard deviation) in normal subjects, and a slow component with a halftime (t2/2) of 33 ± 15 minutes.

The major mechanism by which norepinephrine is removed from the circulation is thought to be uptake by the norepinephrine pump. The fast component of removal observed here almost certainly represented neuronal uptake of norepinephrine by sympathetic nerves, since the halftime of the first (but not the second) exponential was prolonged in normal subjects by the selective inhibitor of neuronal uptake, desipramine (p < 0.01, paired t test), while cortisol, which selectively inhibits extraneuronal uptake of norepinephrine, did not significantly affect the rapid removal phase (fig. 2). Furthermore, the t1/2, but not the t2/2, was prolonged in patients with idiopathic peripheral autonomic insufficiency (p < 0.01, fig. 2), who have a generalized defect in peripheral sympathetic nerve function, including a defect in norepinephrine uptake. The t1/2 was normal, however, in patients whose autonomic insufficiency resulting from central nervous system disease (fig. 2) was accompanied by normal peripheral sympathetic function.

The distribution of t1/2 values in hypertensive patients was non-Gaussian (fig. 2), and differed significantly from that of normal subjects (p = 0.05, Mann Whitney U test). The t2/2 was prolonged in eight of 37 hypertensive patients, giving presumptive evidence of slowed neuronal uptake of norepinephrine. In these patients, the t1/2 was 3.3 to 6.0 minutes, well above the range of values found in normal subjects (1.5 to 2.8 min). With duplicate measurement of norepinephrine disappearance rates in five normal subjects and 14 hypertensive patients after intervals of 3 weeks to 2 years (mean, 7 months), t1/2 measurements were highly reproducible (r = 0.87). In patients with prolonged t1/2, halftime values were consistently reproduced on replicate testing.

The apparent release rate, clearance, and plasma concentration of norepinephrine in normal subjects and hypertensive patients are shown in figure 3. The plasma concentration of norepinephrine in hypertensive patients was 266 ± 120 pg/ml (1.57 ± 0.71 pmoles/ml), 25% higher than in normal subjects.
Norepinephrine apparent release rate, clearance from plasma, and plasma concentration in normal subjects and patients with essential hypertension.

whose concentration was 212 ± 78 pg/ml (1.25 ± 0.46 pmoles/ml, 0.05 < p < 0.1; Mann Whitney U test). Total clearance of norepinephrine from plasma, which is dependent on extraneuronal uptake and metabolism of norepinephrine in addition to neuronal uptake, was similar in hypertensive patients (1.34 ± 0.26 l/min/m²) to that in normal subjects (1.32 ± 0.27 l/min/m²). Norepinephrine clearance was approximately 10% lower in hypertensive patients with a prolonged t₁/₂ value (1.19 ± 0.29 l/min/m²); this difference was not statistically significant. The apparent rate of release of norepinephrine (rate of spillover to plasma after release from sympathetic nerves) was 0.44 ± 0.27 μg/min/m² (2.6 ± 1.6 nmoles/min/m²) in hypertensive patients and 0.36 ± 0.14 μg/min/m² (2.1 ± 0.8 nmoles/min/m²) in normal subjects (difference not significant).

The distribution of norepinephrine release rate and plasma concentration values in patients were similar, with skewness toward higher values (fig. 3). Plasma norepinephrine concentration and norepinephrine apparent release rate correlated significantly overall in both hypertensive patients, rₛ (Spearman's rank correlation) = 0.79, p < 0.01, and normal subjects, r = 0.58, p < 0.02 (fig. 4).

The interrelationship between the slowed neuronal uptake of norepinephrine noted in some hypertensive patients, norepinephrine apparent release rate, and plasma norepinephrine concentration is shown in figure 5. Spillover of norepinephrine to plasma correlated inversely with neuronal uptake, gauged from the halftime of norepinephrine rapid removal, in hypertensive patients (rₛ = 0.63, p < 0.01, fig. 5) and also in normal subjects; r = 0.63, p < 0.01. In patients with presumptive evidence of slowed neuronal uptake, norepinephrine escaping uptake and spilling over into plasma was increased, 0.73 ± 0.39 μg/min/m² (4.3 ± 2.3 nmoles/min/m²) compared with 0.36 ± 0.14 μg/min/m² (2.1 ± 0.8 nmoles/min/m²) in normal subjects (p < 0.01, Mann Whitney U test) and 0.37 ± 0.17 μg/min/m² (2.2 ± 1.0 nmoles/min/m²) in the other hypertensive patients (p < 0.01). Plasma norepinephrine concentration, 364 ± 178 pg/ml (2.15 ± 1.05 pmoles/ml), was also higher than in normal subjects, 212 ± 78 pg/ml (1.25 ± 0.46 pmoles/ml, p < 0.05; Mann Whitney U test, fig. 5).

Discussion

Plasma concentration of the sympathetic nervous system transmitter, norepinephrine, has been used as a biochemical index of sympathetic activity in essential hypertension. But since only a small fraction of norepinephrine released by sympathetic nerves enters the circulation, how well plasma norepinephrine concentration reflects sympathetic nerve firing rates is open to question. Several workers have attempted to
avoid the problems of interpretation encountered when measurements of plasma norepinephrine concentration are relied upon to estimate sympathetic nervous tone in essential hypertension, by instead studying the kinetics of radiolabelled norepinephrine and its metabolites in plasma and urine.34-36

Our technique differs in several ways from those published previously. The principal difference is that we studied norepinephrine kinetics in the central compartment, thus enabling measurement of the rates of norepinephrine release to and removal from plasma.4 This was made possible by our development of an assay that allowed the concentration of both radiolabelled and endogenous norepinephrine in plasma to be followed simultaneously during an infusion of tritiated norepinephrine. The levo form of radiolabelled norepinephrine was infused, unlike in earlier studies in which d,l-norepinephrine was used,4,41 enabling steady-state conditions to be reached in the central (plasma) compartment. Attainment of steady state is a prerequisite for adoption of this model-independent form of kinetic analysis. With d,l-norepinephrine, the time to steady state is much prolonged,4,41 presumably because norepinephrine uptake is in part stereospecific.4 Use of high specific activity radiolabelled norepinephrine ensured that the infusion was strictly a tracer one, insufficient unlabelled norepinephrine being administered to alter BP, sympathetic activity, or norepinephrine clearance. The infusion rate of 0.35 μCi/m2/min was equivalent to 0.002 μg/min (0.012 nmoles/min), raising plasma norepinephrine concentration at the end of the infusion by no more than 3 pg/ml (0.018 pmoles/ml), far below the threshold for cardiovascular and metabolic effects.12

The principal abnormality of norepinephrine kinetics noted in hypertensive patients, present in approximately 20% (8 of 37), was prolongation of the halftime of the rapid component of norepinephrine disappearance from plasma. This halftime is not a simple index of a single removal mechanism,11 and because disposition of norepinephrine in man is complex, defying precise compartmental analysis,11 the rate constant of neuronal uptake of norepinephrine cannot be calculated. But as the t1/2 was lengthened by desipramine, a selective neuronal uptake blocker,47 not changed by cortisol, a selective inhibitor of extraneuronal uptake,4 and prolonged in patients with peripheral sympathetic nerve dysfunction, it appears highly likely that neuronal uptake of norepinephrine is its major determinant.

An alternative explanation of the prolonged halftime, namely, the presence of increased central pool size11 in the patients affected, we tentatively excluded by compartmental analysis adopting the model that best fits the available data, a two-pool open system,17,37 which showed the volume of the central pool to be unremarkable in hypertensive patients with prolonged halftime. Gitlow et al.48 have suggested that neuronal uptake of norepinephrine is defective in some
patients with essential hypertension. Since uptake by sympathetic nerve varicosities is believed to be the principal method of terminating the effect of norepinephrine after its release, particularly at sites within the cardiovascular system where the sympathetic synaptic cleft is narrow, a peripheral mechanism for sympathtic nervous overactivity, based on defective inactivation of the neurotransmitter, appears to be present in a subset of patients with essential hypertension.

A defect of neuronal uptake of norepinephrine of this type would be expected to lead, with even normal rates of sympathetic nerve firing, to higher concentration of the transmitter at receptor sites, greater stimulation of the cardiovascular system, and increased spillover of norepinephrine into plasma. This certainly is the case in animals in which nerve firing rates are kept constant and neuronal uptake of norepinephrine by sympathetic nerves is blocked acutely with drugs.

In the present study, although the apparent release rate and plasma concentration of norepinephrine were not significantly elevated in hypertensive patients overall, patients with defective neuronal uptake of norepinephrine did have a higher rate of norepinephrine spillover to plasma and higher plasma concentration. Our results further suggest that the rate at which norepinephrine leaks to plasma, after release from sympathetic nerves, is determined, under resting conditions, by the efficiency of the local mechanism for norepinephrine inactivation at the synaptic cleft. Although the higher plasma concentrations of norepinephrine reported in essential hypertension have most commonly been explained in terms of increased rates of sympathetic nerve firing, originating from central nervous system dysfunction, the defect in neuronal uptake of norepinephrine we describe could be responsible.

It should be emphasized that desipramine did not elevate the BP of normal subjects in this study. Desipramine, in fact, lowers the rate of spillover of norepinephrine to plasma, which, in the presence of uptake inhibition, must be due to a substantial diminution in release of norepinephrine by the sympathetic nerves. The mechanism of this effect is not clear; an anticholinergic action of the drug within the central nervous system is one possibility.

Steady-state clearance of norepinephrine from plasma was normal in hypertensive patients overall. Norepinephrine clearance was 10% lower in patients with a prolonged \( t_\text{1/2} \) value than in normal subjects, but this difference was not statistically significant. Clearance is lowered 20%–25% by desipramine in normal subjects, and similarly reduced in patients with peripheral autonomic insufficiency. Total clearance of norepinephrine from plasma was influenced to a considerable degree by the slow component of removal, perhaps reflecting extraneuronal uptake and metabolism, which was normal in hypertensive patients. Experimental studies in animals indicate that, if norepinephrine is diverted from neuronal to extraneuronal uptake by a block of neuronal uptake, metabolism is enhanced and removal of norepinephrine from the body overall is retarded less than might be expected. Our results differ from a recent report, based on a different method, that clearance of norepinephrine from plasma is slowed in patients with essential hypertension.

The finding of a defect in neuronal uptake of norepinephrine, present in some patients, could be reproduced consistently with repeat testing over 2 years in patients affected. The abnormality appears not to be a secondary consequence of severe or long-standing hypertension: four of eight patients affected were young men with mild high-renin hypertension. In all eight patients, a clearcut family history of hypertension was obtained. Whether the patients with defective neuronal uptake belong to a distinct subpopulation, distinct from the majority of hypertensive patients, is uncertain. With the relatively small number of patients studied, it is not clear whether the \( t_\text{1/2} \) values in hypertensive patients followed a skewed or a bimodal distribution. The pathophysiological significance of the norepinephrine uptake defect remains to be elucidated. But such an abnormality, by potentiating at the adrenergic receptor level any increase in sympathetic nerve traffic that occurs with mental stress, head-up tilting, and exercise, could be the cause of the greater BP and plasma norepinephrine responses to these stimuli that have been repeatedly reported in a proportion, but certainly not all, of patients with essential hypertension.

It is our viewpoint that essential hypertension is a syndrome with multiple primary causes, differing from case to case, and that these discrete initiating causes of the BP elevation may be identifiable in individual patients. We propose that a defect in neuronal uptake of norepinephrine is one such initiating cause, present in a minority, perhaps 20%, of all patients with essential hypertension.

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