Determination of noradrenaline uptake, spillover to plasma and plasma concentration in patients with essential hypertension

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Summary
1. The rates of entry of noradrenaline to plasma and of removal of noradrenaline from plasma, and plasma noradrenaline concentration, were determined in normal subjects and in patients with essential hypertension. Neuronal uptake of noradrenaline was assessed from the plasma tritiated noradrenaline disappearance curve, after infusion to steady state.

2. Noradrenaline disappearance was biexponential. Rapid removal was dependent on neuronal uptake, being slowed if neuronal noradrenaline uptake was reduced, either by desipramine in normal subjects, or in patients with sympathetic nerve dysfunction (autonomic insufficiency).

3. In 10 of 41 hypertensive patients the t½ similarly was prolonged, presumptive evidence of a defect in neuronal noradrenaline uptake. Endogenous noradrenaline escaping uptake after release, and spilling over into plasma, and plasma noradrenaline concentration, were increased in these patients.

4. Defective neuronal uptake of noradrenaline, by exposing adrenoreceptors to high local transmitter concentration, may be important in the pathogenesis of essential hypertension in some patients.

Key words: arterial hypertension, autonomic insufficiency, cortisol, noradrenaline, sympathetic nervous system, tricyclic antidepressant.

Introduction
It has proved very difficult to measure sympathetic nervous system activity in man.

Biochemical methods have been extensively used, in particular assays to determine the plasma concentration of the sympathetic neurotransmitter, noradrenaline. However, the rate of spillover of noradrenaline to the circulation, and plasma concentration, are low because a very efficient active transport system, the ‘noradrenaline pump’, returns the majority of the transmitter back into the sympathetic nerve immediately after its release (Bevan, 1979). To avoid reliance on plasma noradrenaline measurements, we have developed alternative kinetic measures of sympathetic nervous function (Esler, Jackman, Bobik, Kelleher, Jennings, Leonard, Skews & Korner, 1979). These may be more closely linked to noradrenaline’s function as a transmitter than is the plasma noradrenaline concentration, and should allow better assessment of sympathetic nervous function in essential hypertension.

Methods
In 41 white patients with untreated, uncomplicated essential hypertension (32 men, nine women, mean age 37 years) and 24 healthy, paid volunteers recruited by advertisement (16 men, eight women, mean age 34 years), tritiated L-noradrenaline of specific radioactivity 24–28 Ci/mmol (New England Nuclear Corporation) and purity greater than 98% was infused intravenously, under resting conditions, at a rate of 0.35 μCi min⁻¹ m⁻² for 90 min. This was equivalent to an infusion rate of unlabelled noradrenaline of 0.002 μg/min, insufficient to elevate plasma noradrenaline concentration or blood pressure (Esler et al., 1979). The infusion was immediately preceded by an intravenous bolus injection of 15 μCi/m² to shorten the time to plateau concentration (Gibaldi & Perrier, 1975), which was reached by 60 min in each
case. Blood samples, for assay of plasma tritiated noradrenaline, and plasma noradrenaline concentration and specific radioactivity, by methods previously described (Esler et al., 1979), were withdrawn sequentially through an indwelling needle in an antecubital vein of the non-infused arm.

Assessment of neuronal uptake of noradrenaline

At the end of the infusion, the disappearance of tritiated noradrenaline from plasma was followed in all subjects. Further tests were performed to investigate the mechanism by which noradrenaline is removed from the circulation, specifically to study what effect interference with neuronal uptake of noradrenaline had on the plasma tritiated noradrenaline decay curve. Tests were done on seven normal subjects before and 3 h after administration of the selective inhibitor of neuronal uptake, desipramine (Paton, 1976), 125 mg orally, and in seven patients with sympathetic nerve dysfunction (idiopathic peripheral autonomic insufficiency) (Ziegler, Lake & Kopin, 1977). For comparison, four patients with autonomic insufficiency and postural hypotension from central nervous system disease, in whom sympathetic nerve endings are intact, were also studied. In addition, the effect of the selective extraneuronal uptake blocker, cortisol (Paton, 1976), 500 mg intravenously, was also investigated.

Noradrenaline spillover rate

In 29 of the hypertensive patients, and in all 24 normal subjects, the rate of spillover of endogenous noradrenaline to plasma and the plasma noradrenaline concentration were determined. Venous blood was sampled at the 70, 80 and 90 min points of the infusion, and plasma noradrenaline specific radioactivity measured. Noradrenaline (NA) spillover rate at steady state (plateau plasma concentration of tracer) was derived (Shipley & Clark, 1972; Esler et al., 1979) from the following relationship:

\[
\text{NA spillover rate} = \frac{[^3H]\text{NA infusion rate}}{\text{specific radioactivity of plasma NA}}
\]

The bulk of noradrenaline entering plasma appears to come from sympathetic nerves, with a small proportion only, under resting conditions, coming from the adrenal medulla (Esler et al., 1979).

The research was approved by the Alfred Hospital Clinical Research Ethics Committee, and was fully explained to all subjects, who gave their informed consent.

![Graph showing the disappearance of tritiated noradrenaline from plasma](image-url)

**Fig. 1.** Disappearance of tritiated noradrenaline ([^3H]NA) from plasma, after infusion to plateau concentration, in normal subjects (top panel). The half-time (t_{1/2}) of the rapid removal component was lengthened by desipramine (D), P < 0.01, but not cortisol (C) (middle panel). The t_{1/2} was prolonged in patients with essential hypertension, P < 0.05 (bottom panel).

**Results**

In normal subjects, the noradrenaline disappearance curve was biexponential, with t_{1/2} = 2.0 ± 0.4 min and t_{1/2} = 34 ± 17 min (Fig. 1). Neuronal uptake of noradrenaline by sympathetic nerves seemed to be the major determinant of the half-time of the rapid removal phase. The t_{1/2} was lengthened by the selective
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inhibitor of neuronal uptake, desipramine ($P < 0.01$, paired $t$-test), which had no effect on the $t_{1/2}$, and the selective extraneuronal uptake blocker, cortisol, left the rapid removal component unaffected (Fig. 1). Similarly, the half-time of the first exponential was prolonged in patients with peripheral ($P < 0.01$, $t$-test), but not central autonomic insufficiency (Fig. 1).

The $t_{1/2}$ was prolonged in patients with essential hypertension ($P < 0.05$, Mann-Whitney $U$-test). In 10 of 41 hypertensive patients the $t_{1/2}$ value was greater than that of any normal subject (Fig. 1). In patients with prolonged $t_{1/2}$, noradrenaline escaping reuptake and spilling over into plasma was increased, $4.1 \pm 1.9$ nmol min$^{-1}$ m$^{-2}$, compared with $2.1 \pm 1.0$ nmol min$^{-1}$ m$^{-2}$ in the remaining hypertensive patients ($P < 0.01$, $t$-test) and $1.9 \pm 0.7$ nmol min$^{-1}$ m$^{-2}$ in normal subjects ($P < 0.01$). The plasma noradrenaline concentration, $1.91 \pm 0.70$ pmol/ml, was also higher than in normal subjects ($1.16 \pm 0.42$ pmol/ml) ($P < 0.05$).

Discussion

A defect in neuronal uptake of noradrenaline seems to exist in a portion of patients with essential hypertension. In approximately 25% of patients (10 of 41) the half-time of the rapid component of noradrenaline disappearance from plasma was prolonged. Although this half-time is not a simple index of a single removal mechanism (Shipley & Clark, 1972), the studies with desipramine and in patients with peripheral autonomic insufficiency indicate that neuronal uptake is its major determinant. An alternative explanation of the prolonged half-time, the presence of increased central pool size (Shipley & Clark, 1972) in the patients affected, was excluded by compartmental analysis adopting a two-pool open model (Bufano, Vaona & Starcich, 1973; Gibaldi & Perrier, 1975), which showed the central pool size to be unremarkable in hypertensive patients with prolonged half-time.

Ghione, Palombo, Pellegrini, Formeii, Pil6 & Donato (1978) have reported that removal of noradrenaline from the circulation is slowed in essential hypertension, and Gitlow, Mendlowitz, Kruk-Wilk, Wilk, Wolf & Naftchi (1964) have suggested previously that noradrenaline uptake might be abnormal in essential hypertension. This slowed neuronal uptake does not seem to be a secondary consequence of severe or long-standing hypertension: five of 10 patients affected were young men with mild, high-renin essential hypertension (Esler, Julius, Zweifler, Randall, Harburg, Gardiner & DeQuattro, 1977). Such a defect in noradrenaline uptake would be expected to lead, with even normal rates of sympathetic nerve firing, to high concentration of the transmitter at receptor sites, greater stimulation of the cardiovascular system, increased spillover of noradrenaline to plasma and higher plasma noradrenaline concentration (Yamaguchi, De Champlain & Nardeau, 1977). In the present study, the rate of spillover of noradrenaline to plasma was in fact higher in patients with evidence of defective neuronal noradrenaline uptake than in normal subjects or the other hypertensive patients.

A peripheral mechanism for sympathetic nervous overactivity, based on defective inactivation of the neurotransmitter, appears to be present in a subset of patients with essential hypertension. This abnormality, by exposing adrenergic receptors to high local noradrenaline concentrations, may be of importance in the pathogenesis of the blood pressure elevation.

Acknowledgment

This work was supported by a grant from the National Health and Medical Research Council of Australia.

References


