
SHORT COMMUNICATION

Age-dependence of noradrenaline kinetics in normal subjects

M. ESLER, H. SKEWS, P. LEONARD, G. JACKMAN, A. BOBIK AND P. KORNER
Baker Medical Research Institute, Melbourne, Australia

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Summary

1. The influence of age on the rate of spillover of noradrenaline into plasma, clearance of noradrenaline from plasma, and plasma noradrenaline concentration at rest was studied in 34 healthy subjects aged 20–69 years.

2. The plasma concentration of noradrenaline was dependent on age, values being higher in older subjects.

3. This age-dependence of plasma noradrenaline concentration was due principally to a reduced clearance of noradrenaline from the circulation in older subjects.

4. The rate of spillover of noradrenaline into plasma was little influenced by age. The higher plasma noradrenaline values found in older subjects do not seem to be due to an increase in sympathetic nervous system tone with aging.

Key words: age, noradrenaline, sympathetic nervous system.

Introduction

The plasma concentration of the sympathetic neurotransmitter, noradrenaline, can be used as an index of overall sympathetic nervous system activity (Yamaguchi, DeChamplain & Nardeau, 1975; Esler, Zweifler, Randall, Julius & DeQuattro, 1977). Measurement of plasma noradrenaline concentration to this end in healthy subjects (who served as a reference population in clinical studies of essential hypertension) led to the observation that plasma noradrenaline values rise with age (Ziegler, Lake & Kopin, 1976).

Correspondence: Dr M. Esler, Baker Medical Research Institute, Commercial Road, Prahran, 3181, Victoria, Australia.

These higher plasma noradrenaline values have been taken by some to indicate that sympathetic nervous system tone increases with aging. But, as the plasma concentration of noradrenaline is determined by the simultaneous rates of noradrenaline release into and removal from plasma, higher plasma noradrenaline concentrations in older subjects could be due to reduced clearance of noradrenaline from the circulation. We have tried to establish which mechanism is operating by measuring concurrently the rate of spillover of noradrenaline into plasma, clearance of noradrenaline from plasma, and the plasma concentration of noradrenaline in 34 healthy subjects with ages spanning the range of 20–69 years.

Methods

The plasma kinetics of noradrenaline were studied in 34 healthy, Caucasian subjects (24 males, 10 females) aged 20–69 years. Participants were paid volunteers recruited from the general community by advertisement. No woman with child-bearing potential was included. The methods used were based on those of Esler, Jackman, Bobik, Kelleher, Jennings, Leonard, Skews & Korner (1979). The procedure involved the intravenous infusion of tritiated (−)-noradrenaline until a plateau concentration was reached in plasma, and determination of plasma tritiated noradrenaline concentration and plasma noradrenaline specific radioactivity at steady state. The test was performed at the same time of day, between 09.00 and 11.00 hours, with subjects lying flat in a single-bed ward. All had eaten a light breakfast before attending, but coffee, tea, tobacco and alcohol were forbidden during the preceding 12 h.
Tritiated (-) noradrenaline of specific radioactivity 24–28 Ci/mmol (New England Nuclear Corp.), and purity greater than 98%, was pharmaceutically prepared for administration to man and infused into an antecubital vein at a rate of 0.35 μCi min⁻¹ m⁻² for 90 min. This was equivalent to an infusion rate of 0.012 nmol/min, and was insufficient to elevate either the 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 (Shipley & Clark, 1972), which was reached by 60 min in each case. Venous blood for assay of plasma tritiated noradrenaline and plasma noradrenaline concentration and specific radioactivity, by methods described previously (Esler et al., 1979), was withdrawn sequentially during the course of the infusion through an indwelling needle in an antecubital vein of the non-infused arm. The rate of spillover of noradrenaline (NA) into plasma and of clearance of noradrenaline from plasma at steady state (plateau plasma concentration of tracer) were derived (Shipley & Clark, 1972; Esler et al., 1979) from the following two relationships.

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

\[
\text{Plasma clearance of } NA = \frac{[3H]NA \text{ infusion rate}}{\text{Plasma } [3H]NA \text{ concentration}}
\]

The bulk of noradrenaline entering plasma under resting conditions appears to come from sympathetic nerves, with a small proportion only 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.

**Results**

The relation of noradrenaline spillover rate, plasma noradrenaline clearance and concentration to age is shown in Fig. 1. A significant curvilinear relation of plasma noradrenaline concentration (NA) to age existed, expressed by the relationship: \( NA = 0.86e^{-0.0058ge} \) (\( F = 5.55; \) d.f. 1,32; \( P < 0.03, \) Snedecor & Cochran, 1967). Plasma noradrenaline values were approxi-}

mately 45% higher in subjects over 50 years than in those under 30 years. Noradrenaline clearance (CL) fell with age: \( CL = 1.66e^{-0.00578ge} \) (\( F = 6.87; \) d.f. 1,32; \( P < 0.02 \)).

Noradrenaline clearance was approximately 30% lower in subjects over 50 years than in those under 30 years. Age and noradrenaline spillover rate were not significantly related overall. Spill-over rate was 14% higher in the over-50 years subset than in subjects under 30 years, but this difference was not statistically significant.

**Discussion**

The age-dependence of the plasma concentration of noradrenaline previously reported by others (Ziegler et al., 1976; Saar & Gordon, 1979), which we observe here, seems to result largely from a reduction in the plasma clearance of noradrenaline with aging. It is unlikely that
sympathetic nervous system tone is increased in older healthy subjects, since the rate of spillover of noradrenaline into plasma, which is a better index of overall sympathetic activity than the plasma concentration of noradrenaline (Esler et al., 1979), was little influenced by age.

Removal of noradrenaline from plasma is achieved by neuronal uptake into sympathetic nerve endings, extraneuronal uptake by other tissues, such as vascular endothelium, and metabolic conversion by O-methylation, oxidative deamination, and conjugation (Kopin, 1979). The relative contribution to total clearance by each mechanism is uncertain, and which of these processes, if any, is diminished by aging is not known. It is possible, in fact, that an effect of age on a specific removal mechanism is not involved, rather that the reduction in noradrenaline clearance is due to lower organ blood flow rates in older subjects.

Our results illustrate that fallacies may arise if the plasma noradrenaline concentration is used uncritically as a measure of overall sympathetic nervous system activity. The plasma concentration is determined by the rates of noradrenaline entry into and removal from plasma. If plasma clearance is lowered, the plasma concentration will be disproportionately high. We have found the plasma clearance of noradrenaline to be reduced in a variety of situations, including in patients with peripheral idiopathic autonomic insufficiency who seem to have deficient neuronal uptake of noradrenaline (Esler et al., 1979), in normal subjects given the neuronal noradrenaline uptake blocker, desipramine (Esler et al., 1979), and in patients with essential hypertension treated with propranolol (M. Esler, unpublished work). In each case the clearance defect invalidates plasma noradrenaline measurements as an index of overall sympathetic tone. In untreated patients with essential hypertension, however, noradrenaline clearance is similar to that of age-matched normal subjects, and noradrenaline spillover rate and plasma noradrenaline concentration are in harmony (Esler, Jackman, Bobik, Leonard, Kelleher, Skews, Jennings & Korner, 1981). This, together with the observed agreement between plasma values and independent haemodynamic indices of sympathetic tone (Esler et al., 1977), indicate that plasma noradrenaline levels do provide some guide to sympathetic nervous system activity in essential hypertension.

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References


