SHORT COMMUNICATION

Erythrocyte catechol-\(O\)-methyltransferase activity and indices of sympathetic activity in man

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Summary

1. Erythrocyte catechol-\(O\)-methyltransferase was studied in a population sample of 147 subjects.
2. There was a wide interindividual variability of catechol-\(O\)-methyltransferase activity, which was not unimodally distributed. Catechol-\(O\)-methyltransferase activity was not influenced by blood pressure, age or sex, nor was it related to plasma noradrenaline or urinary catecholamines or metanephrines.
3. It is not likely that inactivation of noradrenaline by \(O\)-methylation at least by erythrocytes is an important mechanism determining plasma noradrenaline, let alone arterial pressure.

Key words: catechol-\(O\)-methyltransferase, population, sympathetic nervous system.

Introduction

Increased concentrations of plasma noradrenaline have been noted in essential hypertensive patients by some workers (Louis, Doyle & Anavekar, 1973; de Champlain, Fairley, Cousineau & Van Amerigan, 1976) and have been assumed to reflect increased sympathetic nervous activity. We have recently found that a reduction of noradrenaline clearance may be as relevant to the development of hypertension as an increased rate of neuronal release (FitzGerald, Hossmann & Dollery, 1979). Catechol-\(O\)-methyltransferase is one of the principal pathways of metabolism of noradrenaline and the activity of this enzyme is readily measured in erythrocytes (Raymond & Weinsilboum, 1975). Erythrocyte catechol-\(O\)-methyltransferase activity correlates well with activity in the liver and kidney in rat strains (Weinsilboum & Raymond, 1977) and has similar substrate specificity and Michaelis-Menten kinetic parameters to those of hepatic catechol-\(O\)-methyltransferase (Axelrod & Cohn, 1971). We therefore decided to study the relationship of erythrocyte catechol-\(O\)-methyltransferase activity with indices of sympathetic activity and the implication for its role in the regulation of blood pressure.

Materials and methods

The subjects examined took part in a health screen of non-medical workers at Hammersmith Hospital. The methodology and population studied have been extensively reported elsewhere (Jones, Hamilton & Reid, 1978). One hundred and forty-seven subjects took part in this study.

Blood pressure was measured indirectly by Arteriosonde 1217 (Roche) after 10 min supine rest. Heart rate was measured by a minute count of the radial pulse. Blood was then drawn for...
measurement of plasma noradrenaline (Henry, Starman, Johnson & Williams, 1975) and erythrocyte catechol-O-methyltransferase activity by venepuncture of an antecubital vein and kept on ice until centrifugation at 4°C and storage at -20°C. Free catecholamines (von Euler & Lishajko, 1961) and total metanephrines (Pisano, 1960) were measured in aliquots of an acidified 24 h urine collection made within 10 days of blood collection. Plasma noradrenaline assays were performed within 4 weeks of collection and erythrocyte catechol-O-methyltransferase assays within 5 days.

Erythrocyte catechol-O-methyltransferase activity was measured with dihydroxybenzoic acid used as a substrate (Raymond & Weinsilboum, 1975) rather than noradrenaline, as this increases both the sensitivity and reproducibility of the assay. A back extraction was included to remove some products of non-specific methylation and thus further increase the sensitivity and reproducibility of the assay. The reaction was terminated with HCl (1 mol/l) solution; the methoxyhydroxybenzoic acid was extracted into toluene and back extracted into 1 ml of borate buffer (1 mol/l), pH 10. Finally, 1 ml of HCl (1 mol/l) was added and the [14C]methoxybenzoic acid returned to toluene for radioactivity counting. Recovery was calculated by taking a known amount of vanillic acid through the extraction procedure in parallel to the 14C-labelled compounds. The between-assay coefficient of variation was 13%.

All results are expressed as mean ± SEM and groups were compared by analysis of variance. Erythrocyte catechol-O-methyltransferase activity, blood pressure and other variables were examined by stepwise regression analysis.

Results

Erythrocyte catechol-O-methyltransferase activity was measured in 147 individuals aged 18-65 (mean 41.4 ± 6.3) years. Forty-five of the subjects were Caucasian males, 70 were Caucasian females, seven were black males, 20 were black females and five were Asian males. Supine blood pressure ranged from 91 to 168 mmHg systolic and from 58 to 113 mmHg diastolic and was log-normally distributed. No subjects were on antihypertensive medication or other drugs known to influence catecholamine metabolism.

Plasma noradrenaline ranged from 0.11 to 9.85 nmol/l (mean 4.01 ± 0.05 nmol/l). Erythrocyte catechol-O-methyltransferase activity ranged from 0 to 24 units with a mean activity of 10.87 ± 0.45 units. The frequency distribution is not unimodal (Fig. 1). The probable distribution is bimodal with population peaks at 8 and 14 units of activity. There appears to be a further peak at 17 units, but this may be a result of the small numbers with high activity. The same pattern is present in the frequency distributions for males and females. Age, sex and race did not significantly affect erythrocyte catechol-O-methyltransferase activity. The small numbers studied did not permit extensive analysis of racial groups separately. Erythrocyte catechol-O-methyltransferase activity did not correlate with plasma noradrenaline, urinary catecholamines or metanephrines. Eight women taking oral contraceptives did not have significantly (P > 0.1) different erythrocyte catechol-O-methyltransferase activity (5.6 ± 1.1 units) from eight age-matched control subjects (10.7 ± 2.0 units).

Discussion

These results demonstrate a non-unimodal distribution of erythrocyte catechol-O-methyltransferase activity similar to that previously described. Both the range and the peaks of distribution are similar to those found by Raymond & Weinsilboum (1975). However, we were unable to attribute any biological significance to the variation in the activity of this enzyme between individuals.

A prolonged clearance of noradrenaline from the circulation of hypertensive patients was first suggested by studies with [3H]noradrenaline (Gillow, Mendelowitz, Wilk & Naftchi, 1964) and more recently confirmed with L-noradrenaline (FitzGerald et al., 1979). Family studies have suggested that inheritance of
low enzyme activity of catechol-O-methyltransferase occurs by an autosomal recessive mechanism (Grunhaus, Erbstein, Belemaker, Sandler & Jones, 1976; Weinshilboum & Raymond, 1977) and a reduction of catechol-O-methyltransferase activity has been postulated as a possible metabolic expression of heritability in hypertension (Mendlowitz, Gitlow & Naftchi, 1959). However, our studies do not support this hypothesis. No correlation was found with systolic or diastolic blood pressure, plasma noradrenaline, urinary catecholamines or metanephrines. Other workers have reported changes in catechol-O-methyltransferase activity in hypertension. Atuk, Bailey, Turner, Peach & Westervelt (1976) found an inverse correlation of erythrocyte catechol-O-methyltransferase with plasma catecholamines measured by a fluorimetric method in patients with renal failure. Although the individual lysed erythrocyte catechol-O-methyltransferase activity was decreased, there was a reduction in erythrocyte volume in these patients and individual erythrocyte enzyme activity was actually increased. Catecholamines are cleared from the circulation by a variety of mechanisms apart from metabolism to metanephrines. These include uptake, monoamine oxidation, conjugation and excretion of unchanged catechols. Any of these mechanisms might compensate when a low activity of enzyme is inherited. It is, of course, possible that erythrocyte catechol-O-methyltransferase may not be an accurate reflection of the enzyme activity at the synaptic cleft site or other peripheral sites of catecholamine metabolism.

Low erythrocyte catechol-O-methyltransferase activity has previously been reported in women taking both oral oestrogens and progestogenes (Briggs & Briggs, 1973). We failed to confirm this finding in eight women taking low-dose (30 μg) oestrogen anovulants. The discrepancy between our findings and those of Briggs & Briggs (1973) could be due to the lower dose of oestrogen being taken by women in our study or to the small sample size.

In conclusion, our data suggest that catechol-O-methyltransferase activity is not a major determinant in the rate of removal of noradrenaline from the circulation in man. Furthermore, erythrocyte activities of this enzyme do not appear to influence blood pressure so the inheritance of a low activity is unlikely to be linked to the hereditary component of hypertension.

References


