hypertensive action of ketanserin is thus characterised by a favourable haemodynamic profile. The observation that ketanserin lowered not only systemic arterial pressure but also cardiac filling pressures suggests that this balanced vasodilatation may be of particular interest for the treatment of congestive heart failure. Indeed, a favourable response to ketanserin in this condition has been reported recently.11

5-HT not only acts as a direct vasoconstrictor, but it also amplifies the vasoconstrictor responses to agents such as noradrenaline and angiotensin II.4 5-HT is released by aggregating platelets in atherosclerotic arteries, which are abnormally responsive to this amine.12 Ketanserin antagonises not only the direct vasoconstrictor effect of 5-HT but also its amplifying effects on other vasoactive substances.5 These mechanisms may all be implicated in the haemodynamic effects of 5-HT2 receptor blockade by ketanserin. This compound is thus a new therapeutic tool for investigating the role of 5-HT in the pathogenesis of various forms of hypertension. Experience so far warrants further assessment of its place in the management of hypertension.

We thank Dr J Symoens of Janssen Pharmaceutica for generous supplies of ketanserin.

References

Sodium-potassium cotransport activity as genetic marker in essential hypertension

J S DAVIDSON, L H OPIE, BRITTA KEDING

Abstract
Sodium-potassium cotransport activity is thought to be defective in essential hypertension and could be a useful genetic marker for susceptibility to essential hypertension. In this study cotransport activity in subjects with hypertension was compared with that in normotensive controls. The effects of ethnic differences, environment, and antihypertensive drugs were also studied. Mean cotransport activity was lower in hypertensive subjects than in controls of the same ethnic groups. There was, however, a large overlap between controls and hypertensive subjects. No ethnic or environmental influences were found.

The large overlap found suggests that sodium-potassium cotransport activity is not a useful genetic marker in essential hypertension.

Introduction
The sodium-potassium cotransport system in human erythrocytes was characterised by Wile and Cooper in 1974.1 This cotransport system is distinct from the sodium-potassium adenosine triphosphatase pump; it is specifically inhibited by the diuretic frusemide; and transports sodium and potassium ions in the same direction, in a 1:1 ratio, either into or out of the cell depending on the prevailing concentration gradients of sodium and potassium.1 Several reports have suggested that the sodium-potassium cotransport system is defective in essential hypertension1-4 and that this is a useful genetic marker for susceptibility to essential hypertension, low cotransport activity being inherited as a single autosomal dominant gene.5

We compared cotransport activity in patients with essential hypertension and in normotensive controls, and assessed the effect of antihypertensive drug treatment on cotransport activity in different ethnic groups and in identical twins.

Subjects and methods
Sodium-potassium cotransport was assayed in sodium-loaded red cells by measuring frusemide-sensitive sodium and potassium efflux in the presence of ouabain, according to the method of Dagher and Garay.6 The only modification we made to this method was in the sodium-loading medium, which contained 50 mmol (mEq/l) sodium, 150 or 170 mmol/l (0.12 or 0.14 mg/100 ml) choline, and 0.015 mmol/l p-chloromercuribenzenesulphonate. This was necessary to achieve intracellular sodium concentrations as close as possible to 25 mmol

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BRITTA KEDING, medical technologist
TABLE II—Effect of antihypertensive drug treatment on cotransport activity

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Ethnic group</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Cotransport activity (mmol/l cells/h)</th>
<th>Period of no treatment</th>
<th>During treatment</th>
<th>Drugs</th>
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</table>

Results

**Assay reproducibility**—In samples taken from 24 subjects and assayed in duplicate the mean variation was 13.3%, for potassium and 18.1%, for sodium frusemide-sensitive efflux.

**Definition of cotransport activity**—In both controls and hypertensive subjects frusemide-sensitive effluxes of sodium and potassium were highly correlated, confirming that sodium and potassium ions are cotransported in a 1:1 ratio under these conditions. A plot of frusemide-sensitive sodium efflux against frusemide-sensitive potassium efflux for all controls and hypertensives had a slope of 0.95 when the best straight line was fitted by linear regression analysis, with a correlation coefficient of 0.91. Thus the mean of the frusemide-sensitive effuxes of sodium and potassium is taken as the cotransport activity in each subject. When the data were analysed in terms of sodium and potassium fluxes separately the results were essentially the same.

**Stability of cotransport activity over time**—In seven subjects cotransport activity was measured repeatedly at intervals ranging from...
one to five months. The mean variation in each subject was 15%, indicating that it is a stable value over time.

Comparison of controls and hypertensive subjects—Figure 2 shows the distribution of cotransport activity in the controls and hypertensive subjects. Mean cotransport activity was lower in treated and untreated hypertensive subjects than in controls of the same ethnic groups, but these differences were significant only when the ethnic groups were combined (table I). A large overlap was apparent between controls and hypertensives. The passive permeabilities to sodium and potassium—that is, the rate constants for frusemide-resistant efflux—were similar to those previously reported and were not significantly different in any of the groups studied (data not shown).

Ethnic comparison—In the subjects selected at random mean cotransport activity in blacks (19 subjects) was 0.309 ± SEM 0.033, in subjects of mixed ancestry (14) 0.278 ± 0.027, and in whites (16) 0.332 ± 0.029. The differences were not significant.

Identical twins—In the three pairs of monozygotic twins there was a wide variation in cotransport activity between the pairs, while within each pair the values were closely concordant (fig 1).

![Figure 1](image1.png)

**Figure 1**—Cotransport activity in three pairs of monozygotic twins compared with means ± SEM for controls and hypertensive subjects.

![Figure 2](image2.png)

**Figure 2**—Distribution of cotransport activity in normotensive controls and hypertensive subjects from three ethnic groups.

Discussion

These results support the finding by Garay and Meyer that sodium-potassium cotransport activity tends to be reduced in essential hypertension.

A genetic marker for essential hypertension would be of great value (a) in distinguishing between essential and secondary hypertension, (b) in identifying “pre-hypertensive” subjects, and (c) as a research tool in identifying the environmental factors that cause hypertension in susceptible individuals. To be useful as such a marker any measurement must have at most a small overlap between proved normotensive and hypertensive groups. The large overlap found in this study suggests that sodium-potassium cotransport activity does not satisfy this condition and will not prove useful in hypertension, either as a marker in genetic studies or as a clinical test in individual patients. Moreover, the large overlap does not support the suggestion that low cotransport activity can identify the presence of a single autosomal dominant gene.

Black races are well known to be particularly susceptible to essential hypertension and South African blacks are no exception. These results suggest that this susceptibility is not due to an ethnic difference in sodium-potassium cotransport activity.

The similarity within pairs of monozygotic twins suggests that the variations in sodium-potassium cotransport activity between individuals are due mainly to genetic factors and are not influenced appreciably by environmental factors.

We thank Dr E du Toit of the Provincial Blood Grouping Laboratory for establishing monozygosity in the twins, Hoechst (South Africa) for the gift of frusemide, and the physicians in the Hypertension Clinic, Groote Schuur Hospital, for allowing us to study patients under their care.

References


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ONE HUNDRED YEARS AGO

At a recent discussion at one of the American medical societies, there was a statement made that, for delicate women, horseback-exercise was not a good practice as a rule. Another statement was quoted by one of the speakers to the effect that no woman ought to ride on horseback. American physicians may take heart of grace from the larger experience in this respect of English practitioners. In this country, happily, equestrian exercise is the splendid privilege and daily practice of thousands of all ages, and of delicate as well as robust constitutions. It is impossible for anyone who has seen the healthy glow spread over the cheeks, pale just before, of some lady after half an hour’s exercise on horseback, to agree with the above assertions. Ladies take far too little exercise in the fresh air. It is rather the duty of the medical man to seek to encourage athletic exercise of all kinds, than to deprecate it from fanciful fear. Americans will gain health, and lose nothing in grace or refinements, by emulating the accomplishments of their English sisters as horsewomen. (British Medical Journal, 1982.)