An inherited sodium ion—potassium ion cotransport defect in essential hypertension

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Summary

1. In erythrocytes, the extrusion of a cell sodium load is accomplished by the ouabain-sensitive sodium–potassium pump and by the frusemide-sensitive sodium–potassium cotransport, which operate against the passive sodium permeability. All these three components of the cell sodium balance were studied in essential hypertension (410 subjects were investigated).

2. An abnormally low rate of net sodium extrusion by the sodium–potassium cotransport system was observed in essential hypertensive patients and in a high proportion of their young normotensive offspring. A normal cotransport system found in secondary hypertensive subjects devoid of familial history of hypertension confirmed that the abnormal cotransport system is not the consequence of high blood pressure per se.

3. A 20–40% increase in the rate of net sodium extrusion by the sodium–potassium pump seems to compensate for the abnormal cotransport in erythrocytes from some young normotensive subjects born of essential hypertensive parents and from some benign essential hypertensive subjects.

4. No difference could be detected between the passive sodium permeability of erythrocytes from hypertensive subjects and in those from normotensive controls.

5. In conclusion, essential hypertension seems to be associated with an inherited defect in the sodium–potassium cotransport system. We propose therefore the laboratory study of this system for: (i) the distinction between essential and secondary hypertension and (ii) the preventive investigation of young normotensive subjects in hypertensive families.

Key words: erythrocytes, frusemide, ouabain, sodium–potassium cotransport, potassium.

Introduction

Na+-loaded/K+-depleted erythrocytes incubated in physiological conditions tend to recover their original low Na+/high K+ content. Surprisingly, in erythrocytes from essential hypertensive patients and some of their descendants the Na+ extrusion/K+ influx ratio is abnormally low as compared with that for normotensive controls and secondary hypertensive subjects (Garay & Meyer, 1979; Garay, Elghozi, Dagher & Meyer, 1980).

We present here a study of the effect of ouabain and frusemide on the erythrocyte Na+ and K+ net fluxes. We report that an inherited defect in a Na+-K+ cotransport system is responsible for the abnormally low ratio of Na+/K+ net fluxes in essential hypertension.

Thus the laboratory detection of a defective cotransport in a young normotensive born of hypertensive parents may predict the ‘genetic risk’ of essential hypertension.

Methods and patients

The different transmembrane pathways involved in net Na+ and K+ transport in Na+-loaded/K+-depleted erythrocytes were analysed in the following groups: normotensive and secondary hypertensive subjects devoid of familial hypertension, benign and accelerated essential hypertensive patients and those offspring of hypertensive patients with an abnormal low ratio of Na+/K+ net fluxes. Ouabain was used to block the Na+-K+ pump and frusemide to inhibit the
Na+-K+ cotransport (details on methods and patients are given by Garay, Dagher, Pernollet, Devynck & Meyer, 1980).

Results

The addition of ouabain (0.1 mmol/l) to Na+-loaded/K+-depleted erythrocytes incubated in a physiological Na+ and K+-containing Ringer solution inhibits to a great extent the net cation movements in both hypertensive and normotensive subjects. As the internal sites of the Na+-K+ pump are saturated with internal Na+ (Garay & Garrahan, 1973), these inhibited fluxes correspond to the maximal pump rate in a physiological Na+-K+-Ringer medium.

In erythrocytes from six out of eight benign essential hypertensive subjects and from all of six young normotensive subjects with abnormal erythrocytes fluxes, born of hypertensive parents, we observed pump fluxes 20-40% higher than in normal erythrocytes. This observation agrees with the increase in Na++,K+-dependent ATPase recently reported for benign essential hypertensive subjects (Wambach, Helber, Bonner & Hummerich, 1979). Surprisingly, normal erythrocytes in the presence of ouabain (0.1 mmol/l) showed a residual net Na+ extrusion against the electrochemical Na+ gradient. This ouabain-resistant net Na+ extrusion could be completely inhibited by raising the external K+ concentration, or by adding frusemide (1 mmol/l) or by ATP depletion, thus showing properties similar to the Na+-K+ cotransport system described in rat (Beauge & Ortiz, 1973), avian (McManus & Schmidt, 1978) and human erythrocytes (Beauge & Adragna, 1971; Wiley & Cooper, 1974; Garay, Adragna, Canessa & Tosteson, 1980).

No ouabain-resistant net Na+ extrusion was observed in erythrocytes from young normotensive offspring of essential hypertensive patients with abnormal erythrocyte fluxes and from essential hypertensive patients. This finding led us to investigate the Na+-K+ cotransport system in erythrocytes from these subjects.

As shown in Table 1, the frusemide-sensitive net Na+ and K+ extrusion is markedly reduced in erythrocytes from essential hypertensive patients, thus explaining why the ratio of total Na+/K+ net fluxes is abnormally low in these erythrocytes (Garay & Meyer, 1979). On the other hand, 53.6% of 97 young normotensive offspring of one hypertensive parent and 73.7% of 19 normotensive offspring of both hypertensive parents had an abnormal cotransport. A normal cotransport was found in secondary hypertensive subjects devoid of familial hypertension.

No difference could be detected between the Na+ and K+ passive permeabilities of erythrocytes from 60 hypertensive patients and those from 45 normotensive controls. Thus the increase in the ouabain-resistant unidirectional Na+ influx (Wessels, Junge-Hülsing & Losse, 1967) and efflux (Postnov, Orlov, Shevchenko & Adler, 1977), previously reported in erythrocytes from essential hypertensive patients, rather than being due to an increased Na+ permeability could reflect a disorder in a specific transport system such as the ouabain-resistant 1:1 Na+-Na+ exchange, which is increased in these erythrocytes (Canessa, Adragna, Solomon, Connolly & Tosteson, 1980).

Table 1. Maximum rate of outward Na+-K+ cotransport in hypertension

Values represent means ± SD; n denotes the number of subjects in each group. * P < 0.001. Abnormal cotransport was considered to be when the reduction of the Na+/K+ net flux ratio was higher than 25% or when the frusemide-sensitive net Na+ extrusion was lower than 70% of the mean value for normotensive controls.

<table>
<thead>
<tr>
<th>Studied group</th>
<th>Frusemide-sensitive net Na+ extrusion (µmol h⁻¹ l⁻¹ of cells)</th>
<th>Frusemide-sensitive net K+ extrusion (µmol h⁻¹ l⁻¹ of cells)</th>
<th>Subjects with abnormal cotransport (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive controls</td>
<td>498 ± 118 (n = 35)</td>
<td>578 ± 163 (n = 35)</td>
<td>3.5 (n = 86)</td>
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<tr>
<td>Essential hypertensive</td>
<td>191 ± 119* (n = 50)</td>
<td>254 ± 124* (n = 50)</td>
<td>96.9 (n = 129)</td>
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<tr>
<td>Secondary hypertensive†</td>
<td>396 ± 79 (n = 5)</td>
<td>458 ± 131 (n = 5)</td>
<td>7.1 (n = 28)</td>
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<tr>
<td>Young normotensive offspring of one hypertensive parent</td>
<td>53.6 (n = 97)</td>
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<tr>
<td>Young normotensive offspring of both hypertensive parents</td>
<td>73.7 (n = 19)</td>
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† Devoid of family history of hypertension.
Discussion

The results presented here indicate that the net extrusion of an erythrocyte's Na⁺ load is accomplished by two different mechanisms: the Na⁺–K⁺ pump and Na⁺–K⁺ cotransport, which operate against the passive Na⁺ permeability. Furthermore, they suggest that an inherited defect in the Na⁺–K⁺ cotransport system may be genetically associated with essential hypertension. In avian erythrocytes this transport system participates in the regulation of cell volume and is under hormonal control. These observations have led us to formulate the hypothesis that essential hypertension may result from an inefficient hormonal regulation of the extrusion of a cell Na⁺ load after an excess Na⁺ intake, due to a functional disorder of the Na⁺–K⁺ cotransport system. Such a process in excitable cells of high surface/volume ratio, such as smooth muscle cells or catecholaminergic neurons, may lead to a temporary or permanent increase in intracellular Na⁺, producing critical changes capable of raising blood pressure (De Champlain, Krakoff & Axelrod, 1968; Blaustein, 1977). The high Na⁺–K⁺ pump activity seen in some young normotensive offspring of hypertensive parents and benign essential hypertensive subjects may therefore represent a compensatory mechanism for extruding a cell Na⁺ load and thus preventing severe hypertension in subjects with this genetic abnormality.

The fact that a normal cotransport was found in authentic secondary hypertensive offspring of normotensive parents, confirms that this abnormality is not the consequence of high blood pressure per se. Moreover, the familial pattern of the defective cotransport suggests a monogenic, dominant and autosomal mode of genetic transmission.

In conclusion, the finding of an abnormal cotransport in a young normotensive with a family history of hypertension may indicate an inherited tendency to develop high blood pressure and may thus elicit appropriate preventive measures such as regular medical examination, appropriate Na⁺ diet, prevention of excessive weight gain, clinical follow-up during contraception by oestrogens and during pregnancy.

References


