Hyperinsulinemia and insulin resistance have been extensively reported in adult patients with essential hypertension. The aim of this study was to examine serum glucose and insulin levels both in the fasting state and after 0.25 g/kg IV glucose and to relate those findings to the status of intracellular Na+ and red blood cell Na+-Li+ countertransport in a population of 21 normolipemic normotensive offspring of hypertensive parents (N-EH) and 13 control children without a history of parental essential hypertension or diabetes mellitus matched for age, body mass index, and pubertal stage. Offspring of hypertensive parents presented significantly higher serum insulin levels both after an overnight fast (17.4±1.6 versus 11.6±1.6 μU/mL in control [mean±SEM], P<.01) and after intravenous glucose than control subjects (insulin area under the curve, 3015±310 and 2057±234 μU/mL per hour, respectively, P<.01). No relation could be established between the high red blood cell Na+-Li+ countertransport (343±22 versus 215±15 μmol/L per hour, N-EH versus control; P<.002) or high intracellular Na+ (9.8±0.28 versus 8.7±0.36 mEq/L, N-EH versus control) and hyperinsulinemia found in children of hypertensive parents. We conclude that the time precedence of hyperinsulinemia (and possibly insulin resistance) over the appearance of clinical hypertension in a high-risk population further supports the contention that an abnormal insulin action may play a pathogenic role in essential hypertension. The lack of relation between hyperinsulinemia and red blood cell Na+-Li+ countertransport or intracellular Na+ suggests that either they are not linked in the causal pathway of hypertension or they are both an untimely product of a third yet undetermined pathogenetic factor. (Hypertension. 1994;23[suppl I]:I-12-I-15.)

Key Words • hyperinsulinism • hypertension, genetic • sodium • lithium

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Characteristics of Normotensive Children of Normotensive and Hypertensive Parents

<table>
<thead>
<tr>
<th></th>
<th>Normotensive Parents (n=13)</th>
<th>Hypertensive Parents (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>14±2.1</td>
<td>13.2±1.1</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6/13</td>
<td>9/21</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.3±0.9</td>
<td>24.7±0.9</td>
</tr>
<tr>
<td>zSBP</td>
<td>0.66±0.2</td>
<td>1.1±0.15</td>
</tr>
<tr>
<td>zDBP</td>
<td>1.06±0.2</td>
<td>1.3±0.12</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.39±0.14</td>
<td>4.57±0.15</td>
</tr>
<tr>
<td></td>
<td>(170±5.5 mg%)</td>
<td>(177±6.1 mg%)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.20±0.06</td>
<td>1.21±0.04</td>
</tr>
<tr>
<td></td>
<td>(46±2.3 mg%)</td>
<td>(47±1.4 mg%)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.77±0.19</td>
<td>2.79±0.14</td>
</tr>
<tr>
<td></td>
<td>(107±7.5 mg%)</td>
<td>(108±5.6 mg%)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.93±0.13</td>
<td>0.87±0.05</td>
</tr>
<tr>
<td></td>
<td>(93±13 mg%)</td>
<td>(87±5.0 mg%)</td>
</tr>
</tbody>
</table>

Results

The Table shows that both groups of children under study did not differ significantly in regard to age, body mass index, lipoproteins, or z scores for systolic or diastolic blood pressures. Mean fasting plasma glucose and mean glucose disposal rates after intravenous glucose did not differ in the two groups. In contrast, both mean fasting plasma insulin and the mean insulin response to glucose challenge (indicated by the insulin area under the curve at 0 to 60 minutes) were significantly higher in the N-EH than control group (Fig 1). Moreover, N-EH children whose parents were both hypertensive (n=12) presented significantly higher mean insulin under the curve values (3682±413 μU/mL per hour) than N-EH children with just one hypertensive parent (n=9, 2346±281 μU/mL per hour, P<.05). The latter value was not significantly different from that recorded in control children (2057±234, P=NS). Finally, a significant correlation was found between fast-

![Graphs showing overnight fasting serum insulin and glucose levels and intravenous glucose test results for children of hypertensive parents (N-EH) and children of normotensive parents (C).](http://hyper.ahajournals.org/)

Fig 1. Bar graphs show overnight fasting serum insulin and glucose levels (top) and intravenous glucose test (bottom) in children of hypertensive parents (N-EH) and children of normotensive parents (C). Serum insulin area under the curve (AUC) and glucose disappearance rate (Kg) are shown. Closed circle indicates P<.01.
Discussion

Our findings indicate that hyperinsulinemia precedes the onset of clinical hypertension in a population of genetically hypertension-prone individuals such as children of at least one essential hypertensive parent. Although insulin sensitivity was not directly assessed in this work, the fact that hyperinsulinemia coexisted with a normal glucose tolerance suggests that insulin resistance was also present in this patient population. That our normotensive offspring of two hypertensive parents were significantly more hyperinsulinemic than offspring of one hypertensive parent reinforces the proposal that the development of hyperinsulinemia, similar to that of hypertension, is also genetically determined. Although our children were nonobese and showed body mass index values comparable to those of control children, we cannot rule out the possibility that a relative increase in central body fat distribution could have contributed to our findings.

Falkner et al and Ferrari et al also reported recently that hyperinsulinemia and insulin resistance were present in nonclinically hypertensive offspring of parents with essential hypertension. However, their population was of adult age and presented already overt dyslipidemia and/or borderline hypertension. Our findings in a much younger population with normal blood pressure and in the absence of significant lipid or carbohydrate abnormalities point to a very early beginning for some pathophysiological traits associated with hypertensive disease. Despite the limited information available at present, it may be tempting to speculate that the natural history of essential hypertension may proceed from hyperinsulinemia or insulin resistance (whichever comes first) on to dyslipidemia and then to borderline hypertension.

The present findings are a mirror image of those reported by the San Antonio Heart Study, in which nondiabetic, hyperinsulinemic offspring of diabetic parents showed a high prevalence of hypertension, enlarging former epidemiologic and clinical evidence that impaired glucose tolerance or non-insulin-dependent diabetes mellitus, dyslipidemia, and essential hypertension are pathophysiologically closely linked entities. Our data also argue strongly against the proposal that hyperinsulinemia may be secondary to the presence of hypertension, in agreement with recent data in experimental animals.

Although both insulin levels and red blood cell Na⁺-Li⁺ countertransport were found elevated in offspring of hypertensive parents, no correlation could be established between these two parameters, suggesting that
hyperinsulinemia and a derangement in sodium handling may not be linearly linked in the causal pathway leading to hypertension. This latter statement should be cautiously considered because Na⁺-Li⁺ countertransport may not be truly representative of the status of the Na⁺-H⁺ exchange isomere present in the renal proximal tubule and/or overall sodium handling. Finally, the possibility remains that hyperinsulinemia and an abnormal Na⁺ transport both may be an untimely product of clinical hypertension in a population of genetically hypertension-prone, nonobese, normolipemic children, further supporting the contention that an abnormal insulin action may play some pathogenetic role in the etiology of hypertension.

Acknowledgments

This work was supported by a grant of the CONICET (PID #3-147700/88). We acknowledge Lucia Paez for her skilful secretarial help.

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Hypertension. 1994;23:I12
doi: 10.1161/01.HYP.23.1_Suppl.I12

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