Hyperinsulinemia in Normotensive Offspring of Hypertensive Parents

Beatriz Grunfeld, Marta Balzareti, Myriam Romo, Marisa Gimenez, Raul Gutman

Abstract

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 pathogenetic 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

Hyperinsulinemia and insulin resistance have been extensively reported in adult hypertensive patients, thus raising the hypothesis that insulin may be involved in the pathogenesis of essential hypertension. Furthermore, it has been suggested that hyperinsulinemia could lead to hypertension via its known effects on sodium ion transport, among others.

We have previously shown that Na⁺-Li⁺ countertransport and intracellular sodium in red blood cells are both elevated in normotensive offspring of essential hypertensive parents (N-EH), confirming and enlarging similar observations by other authors. Based on its similarities with Na⁺-H⁺ ion exchange of the renal proximal tubule, a high Na⁺-Li⁺ countertransport, presumably indicating its association with an increase in proximal sodium reabsorption and overall Na⁺ retention, has also been linked previously to the pathophysiology of hypertension.

Insulin has recently been reported to be involved in the modulation of Na⁺-Li⁺ countertransport. Thus, if insulin were involved in the pathogenesis of essential hypertension, it could be assumed that hyperinsulinemia would precede the onset of clinical hypertension and therefore already be present in a normotensive population at high risk of developing essential hypertension, such as our N-EH children. Moreover, if the above-mentioned high Na⁺-Li⁺ countertransport and intracellular Na⁺ shown by N-EH were a direct consequence of hyperinsulinemia, then a relation between those parameters may be demonstrable in this population.

The purpose of this study was to examine serum glucose and insulin levels both after an overnight fast and after 0.25 g/kg IV glucose and to relate these findings to the status of Na⁺-Li⁺ countertransport and intracellular sodium in a population of normotensive offspring of at least one essential hypertensive parent.

Methods

Twenty-one offspring of essential hypertensive parents (both parents hypertensive in 12 offspring and just 1 in the remaining 9) with no family history of diabetes mellitus attending the Hypertension Clinic at our Medical Center and 13 healthy control children with no family history of hypertension or diabetes matched for age, body mass index (weight/height²), and pubertal stage (Tanner stages III and IV) were included in this study.

Blood pressure was consistently below the 95th percentile for age and body mass according to the Report of the Second Task Force on Blood Pressure Control in Children. We chose to present blood pressures as z scores (number of standard deviations from the mean), because our population included children and adolescents over an age span (12 to 18 years of age) in which normal mean blood pressure values vary widely. The z score is defined as (x—y′)/s, where y′ and s are the sample mean and standard deviation, respectively, of blood pressure for children of the same age group and y is the child's blood pressure. Blood pressure of parents was assessed by one of the authors. Procedures were carefully explained to both parents and children, and informed consent was obtained from parents.

At approximately 9 AM and after an overnight fast, an indwelling needle catheter was placed in an antecubital vein 30 minutes before blood sampling for a basic chemistry profile, lipoproteins, red blood cell intracellular Na⁺, and Na⁺-Li⁺ transport (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 pathogenetic 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.)
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</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>(170±5.5 mg%)</td>
<td>(177±6.1 mg%)</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.20±0.06</td>
<td>1.21±0.04</td>
</tr>
<tr>
<td>(46±2.3 mg%)</td>
<td>(47±1.4 mg%)</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.77±0.19</td>
<td>2.79±0.14</td>
</tr>
<tr>
<td>(107±7.5 mg%)</td>
<td>(108±5.6 mg%)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.93±0.13</td>
<td>0.87±0.05</td>
</tr>
<tr>
<td>(93±13 mg%)</td>
<td>(87±5.0 mg%)</td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index; zSBP, systolic blood pressure z score; zDBP, diastolic blood pressure z score; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. Values are mean±SEM.

The disappearance rate of the glucose fractional coefficient (glucose disposal rate) after glucose injection was expressed as a k value calculated from the formula $k = \frac{100\log(2t_{1/2})}{t_{1/2}}$, where $t_{1/2}$ is the time in minutes required to halve the glucose concentration.

Statistical analysis was performed with the statistical software package NWA STATPAC. Insulin and area under the curve values were natural log transformed to improve normality. Student's nonpaired t test was applied for comparison between two related samples. Pearson correlation analysis was used for assessment of relations between variables. Multiple regression analysis was performed with a procedure that fit least-squares estimates to linear-regression models. Values are given as mean±SEM.

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-
Fig 2. Bar graphs show red blood cell Na+–Li+ countertransport and intracellular sodium ([INa+]i) in children of hypertensive parents (N-EH) and children of normotensive parents (C). Closed square indicates P<.002; *P<.01.

Fig 3. Plot shows insulin-secreted area under the curve values (β IU/mL per hour × 1000) vs Na+–Li+ countertransport in red blood cells of children of hypertensive parents. P=NS.

Discussion

Our findings indicate that hyperinsulinemia precedes the onset of clinical hypertension in a population of genetically hyperinsulinemia-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 isofrom 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 (and thus the lack of relation in a cross-sectional study) of a third so far undetermined pathogenetic factor underlying essential hypertension.

In summary, we have shown that hyperinsulinemia (and possibly insulin resistance) precedes the appearance 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 pathogenic role in the etiology of hypertension.

Acknowledgments

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References

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