Hypertension and Abnormalities of Carbohydrate Metabolism Possible Role of the Sympathetic Nervous System

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To investigate the relationships between the sympathetic nervous system (SNS) and parameters of glucose metabolism in arterial hypertension, daily urinary excretion of catecholamines and plasma glucose, insulin, and C-peptide response to an oral glucose load (OGL) have been evaluated in 77 untreated patients with mild-to-moderate essential hypertension and in 31 normotensive controls. Urinary excretion of norepinephrine (UNE) was positively correlated with body mass index and with plasma glucose levels both at fast and after OGL. No correlations were found between urinary excretion of catecholamines and plasma insulin and C-peptide levels both at fast and in response to OGL. Because the frequency distribution of UNE was bimodal, hypertensive subjects were separated into two subgroups using an arbitrary cutoff, and the parameters of glucose metabolism were compared. Subjects with UNE > 205 ng/day had greater levels of fasting glucose and greater glycemic response to OGL than subjects with UNE < 205 ng/day, whereas no significant differences between the groups were found in fasting and stimulated plasma insulin and C-peptide. Thus, activation of SNS is related to glucose tolerance but not hyperinsulinemia and insulin hypersecretion in essential hypertension. Plasma glucose levels, independent of insulin, may contribute to the relationship between SNS activity and blood pressure in essential hypertension. Am J Hypertens 1997;10:678–682

KEY WORDS: Catecholamines, C-peptide, glucose tolerance, insulin, sodium excretion.

Many studies have demonstrated that hyperinsulinemia and insulin resistance occur in patients with essential hypertension and normal body mass1–5 and in animal models of hypertension.4 The relationship between insulin and hypertension does not seem to occur in humans3 and animals5 with secondary hypertension, indicating that these metabolic abnormalities are not just a consequence of high blood pressure. These observations have led to the hypothesis that insulin might be involved in the pathophysiology of genetic hypertension.6

Several mechanisms have been proposed as mediators of the prohypertensive action of insulin, including activation of renal sodium reabsorption, proliferation of vascular smooth muscle cells, modulation of transmembrane cation transport, and stimulation of the sympathetic nervous system (SNS).6 With regard
to the latter mechanism, it has been demonstrated that acute insulin infusion increases plasma norepinephrine (NE) levels even when plasma glucose concentration is maintained constant and that overfeeding-induced hyperinsulinemia increases NE turnover. However, there have been only a few studies that have examined the relationships between insulin, blood pressure, and adrenergic activity. The aim of this study was to evaluate these relationships in nonobese essential hypertensive patients.

METHODS

Seventy-seven untreated patients (age: 51 ± 3; 38 men, 39 women) with mild-to-moderate essential hypertension (Stage I–II World Health Organization) were included in an observational, cross-sectional study. Exclusion criteria were age <30 years or >70 years, body-mass index >30, diabetes mellitus or impaired glucose tolerance as defined by the National Diabetes Data Group criteria, renal failure with creatinine clearance <70 mL/min/1.73 m² body surface area, presence of other diseases or treatments that might interfere with glucose metabolism or catecholamine secretion. No woman was taking oral contraceptives. Secondary causes of hypertension were excluded on the basis of the history, physical examination, and exhaustive laboratory testing. Subjects were kept on a standard diet for the 7 days before the study and were instructed to collect their 24-h urine to measure electrolyte and catecholamines excretion, which was performed on the seventh day. After overnight fasting, blood pressure was measured by sphygmomanometry after each subject had been supine for 15 min. The average of three readings obtained in 5 min was recorded. Then an intravenous catheter was placed in the antecubital vein of one arm to obtain venous blood samples for measurement of glucose, insulin, and C-peptide. These parameters were measured at baseline and after (30, 60, 90, 120, 180 min) a standard oral glucose load (OGL; 75 g) and the area under the response curve was calculated by the trapezoidal rule.

Thirty-one normotensive subjects (age 51 ± 3; 15 men, 16 women) served as controls. These subjects were selected from the general population of the same geographic area as the hypertensive patients to match the age, sex, and body-mass index distribution.

Plasma glucose was assayed by the glucose oxidase method. Plasma insulin and C-peptide levels were measured by radioimmunoassay (Behring, Marburg, Germany). Urine norepinephrine (NE), epinephrine, and dopamine concentrations were measured after high-performance liquid chromatography separation and corrected by 24-h urinary volume. All measurements were done in duplicate.

Data are presented as mean ± SEM. Student’s t-test for unpaired data was used for comparisons between two groups. Correlations are expressed by the correlation coefficient. Multivariate analysis was performed in the evaluation of independent relationships between blood pressure, body mass index, and biochemical parameters.

RESULTS

Data are summarized in Table 1. Both at fast and after OGL plasma insulin and C-peptide levels were significantly greater in hypertensive subjects, as compared with controls. Body mass index, waist/hip ratio, plasma glucose, urinary steroids excretion, and plasma renin activity were comparable in hypertensive and normotensive subjects. Urinary NE excretion was significantly greater in hypertensive than normotensive subjects. In hypertensive subjects, body mass index (r = 0.393, P < .001), fasting plasma insulin (r = 0.327; P < .01), and 24-h urinary NE (r = 0.344, P < .01) were significantly and independently correlated with mean blood pressure. Urinary NE excretion was correlated with body mass index (r = 0.330, P < .01) and plasma glucose levels both at fast (r = 0.468, P < .001; Figure 1) and after OGL (r = 0.358, P < .01; Figure 1), whereas no correlation was found with either fasting or post-OGL plasma insulin and C-peptide levels. No correlations were found between urinary excretion of epinephrine and dopamine and parameters of glucose metabolism.

Because the frequency distribution of urinary NE excretion was bimodal, hypertensive subjects were separated into two subgroups using an arbitrary cutoff of 205 µg/day, and the parameters of glucose metabolism were compared. Hypertensive subjects with “high” urinary NE excretion (>205 µg/day) had greater levels of fasting glucose and greater glycemic response to OGL than subjects with “low” urinary NE excretion (<205 µg/day). No significant differences were found in both fasting and stimulated plasma insulin and C-peptide levels and in blood pressure, urinary excretion of sodium and steroids, and plasma renin activity.

DISCUSSION

Our findings demonstrate that in nonobese essential hypertensive subjects an association exists between SNS activity, as assessed by measuring 24-h urinary excretion of NE, and plasma glucose levels measured both at fast and after an OGL. Conversely, no relationships of urinary NE with plasma insulin and C-peptide levels have been observed. Both urinary NE excretion and fasting plasma insulin levels were positively correlated with blood pressure and the correlation persisted after adjustment for...
pathetic nerve activity 9 have been shown to increase in SNS activity. 13 Sympathetic overactivity may lead,

other variables, such as body mass index and body fat distribution.

The epidemiological evidence of an association between arterial hypertension and abnormalities of carbohydrate metabolism is clearly established and following the demonstration of insulin resistance and hyperinsulinemia in hypertensive patients, 1±3 insulin has been proposed as the key factor in this association. Increased activity of the SNS is one of the mechanisms that might explain the prohypertensive action of insulin, and the results of many studies have supported this possibility. Plasma NE levels 7,8 and muscle sympathetic nerve activity 9 have been shown to increase in a dose-dependent manner during a hyperinsulinemic-euglycemic clamp. However, because the increase in plasma NE levels occurs together with a fall in arterial pressure, and a decrease in forearm vascular resistance, 9 the increase in plasma NE levels may be secondary to a reflex activation of SNS. We have not observed a relationship between SNS activity, as evaluated by measurement of urinary catecholamine excretion, and fasting and stimulated plasma insulin and C-peptide levels. Using a similar approach, in a population survey conducted in Denmark 10 no significant association was found between plasma NE and insulin sensitivity. The relationships between insulin, blood pressure, and adrenergic activity were investigated in a large cohort followed as part of the Normative Aging Study11,12 that included also obese subjects. Similar to the present study, an association between body mass index, 24-h NE excretion, plasma glucose, and blood pressure was found, but significant association was observed also between urinary NE and plasma insulin, suggesting that the SNS is the link between glucose metabolism abnormalities and blood pressure.

An alternative hypothesis postulates that the association of hypertension with abnormalities of carbohydrate metabolism could result from a primary increase in SNS activity. 13 Sympathetic overactivity may lead, in fact, both to insulin resistance and hypertension. 14 High blood pressure causes vascular hypertrophy, which is further enhanced by the growth promoting effects of sympathetics, leading to increased α-adrenergic responsiveness of the vasculature 15 with a vicious circle that maintains hypertension. Consequently, the same process may lead to vascular rarefaction in the skeletal muscle and insulin resistance. 14

Several studies have addressed the metabolic and hormonal influences of NE using different experimental approaches. Marangou et al 16 reported a significant decrease in insulin sensitivity, as evaluated by the glucose disposal rate, in healthy subjects infused with NE. These findings were not confirmed by Silverberg

TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normotensive (N = 31)</th>
<th>All (N = 77)</th>
<th>UNE &lt; 205 µg/day (N = 37)</th>
<th>UNE &gt; 205 µg/day (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134 ± 3</td>
<td>168 ± 4*</td>
<td>166 ± 4</td>
<td>169 ± 5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74 ± 2</td>
<td>102 ± 2*</td>
<td>100 ± 3</td>
<td>103 ± 3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.1 ± 0.9</td>
<td>26.7 ± 1.7</td>
<td>25.7 ± 2.3</td>
<td>27.3 ± 2.2*</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.92 ± 0.03</td>
<td>0.92 ± 0.03</td>
<td>0.92 ± 0.02</td>
<td>0.93 ± 0.04</td>
</tr>
<tr>
<td>Subscapular fold (cm)</td>
<td>2.3 ± 0.3</td>
<td>2.5 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>0.94 ± 0.03</td>
<td>0.99 ± 0.04</td>
<td>1.00 ± 0.04</td>
<td>0.98 ± 0.05</td>
</tr>
<tr>
<td>Urinary dopamine (µg/day)</td>
<td>174 ± 2013</td>
<td>31*</td>
<td>18*</td>
<td>22*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>91 ± 3</td>
<td>90 ± 4</td>
<td>88 ± 4</td>
<td>96 ± 5*</td>
</tr>
<tr>
<td>Fasting plasma insulin (µU/mL)</td>
<td>7.9 ± 0.8</td>
<td>10.4 ± 1.5*</td>
<td>10.7 ± 1.4</td>
<td>10.1 ± 1.3</td>
</tr>
<tr>
<td>Plasma glucose (area, mg/dL·min)</td>
<td>1.83 ± 0.16</td>
<td>2.37 ± 0.24*</td>
<td>2.31 ± 0.25</td>
<td>2.42 ± 0.36</td>
</tr>
<tr>
<td>Plasma insulin (area, µU/mL·min)</td>
<td>478 ± 22</td>
<td>492 ± 22</td>
<td>460 ± 29</td>
<td>521 ± 35*</td>
</tr>
<tr>
<td>Plasma C-peptide (area, ng/mL·min)</td>
<td>114 ± 7</td>
<td>143 ± 18*</td>
<td>140 ± 19</td>
<td>146 ± 17</td>
</tr>
<tr>
<td>Urinary norepinephrine (µg/day)</td>
<td>154 ± 18</td>
<td>210 ± 32*</td>
<td>149 ± 23</td>
<td>291 ± 17*</td>
</tr>
<tr>
<td>Urinary epinephrine (µg/day)</td>
<td>25 ± 5</td>
<td>28 ± 4</td>
<td>26 ± 4</td>
<td>30 ± 5*</td>
</tr>
<tr>
<td>Urinary dopamine (µg/day)</td>
<td>2102 ± 174</td>
<td>2193 ± 193</td>
<td>2013 ± 206</td>
<td>2305 ± 202‡</td>
</tr>
</tbody>
</table>

Values are means ± SE.
* P < .01 v normotensive subjects; ‡ P < .01; ‡ P < .05 v hypertensive subjects with UNE < 205 µg/day.
In summary, our results confirm the close relationship between blood pressure, glucose tolerance, and SNS activity in nonobese essential hypertensive subjects. In these subjects, lack of association between urinary NE and hyperinsulinemia suggests that activation of the SNS is not involved in the prohypertensive action of insulin. The correlation between the plasma glucose levels, measured both at fasting and post-OGL, and urinary NE indicates that the plasma glucose concentration, independent of insulin, may contribute to the relationship between SNS activity and blood pressure in essential hypertension.

REFERENCES


