Differences in Insulin and Sympathetic Responses to Glucose Ingestion Due to Family History of Hypertension

Kazuko Masuo, Hiroshi Mikami, Toshio Oghara, and Michael L. Tuck

To evaluate the relationship of metabolic and neural factors in familial hypertension, we examined blood pressure (BP), blood glucose, and plasma insulin and norepinephrine (NE) levels before and every 30 min for 120 min after glucose ingestion in six groups with 20 subjects each: normotensive subjects (NT) with and without a family history of hypertension; borderline hypertensive patients (BHT) with and without a family history of hypertension; and established hypertensive patients (EH) with and without a family history of hypertension. The changes in blood glucose were similar in the six groups. In the subjects with a positive family history of hypertension regardless of BP levels, the basal levels and changes in insulin levels after glucose ingestion were significantly greater than those in the subjects without a family history of hypertension (F = 13.32, P = .0001). In BHT and EH subjects, regardless of family history, changes in insulin were greater than in NT (F = 16.00, P = .0001). Basal levels and changes in plasma NE were higher in BHT and EH (F = 26.55, P = .0001) than NT and changes in plasma NE were greater in subjects with a family history than those in subjects without a family history (F = 13.32, P = .0001). Thus, abnormal insulin and NE responses to glucose appear to aggregate in subjects with a history of familial hypertension, regardless of the level of BP. Furthermore, the ratio of ΔNE/Δinsulin (changes from basal to peak) in NT and BHT, and in subjects with a family history were significantly greater than in EH and in subjects without a family history. Thus, we demonstrated that concomitant abnormalities in the glucose-insulin regulatory system and the sympathetic nervous system characterize the early phase in the development of hypertension and these abnormalities have an apparent genetic basis. Am J Hypertens 1996;9:739-745

KEY WORDS: Hypertension, hyperinsulinemia, sympathetic nervous system, family history, glucose, insulin, plasma norepinephrine.

Essential hypertension is accompanied by insulin resistance and high levels of circulating insulin. Several factors including hereditary background may influence the relationship between insulin and blood pressure. Conditions characterized by insulin resistance such as obesity, type 2 diabetes mellitus, and hypertension are polygenic in inheritance. One method for studying genetic influence for a trait is to study unaffected individuals with a family history of the trait. In this way, the role...
of insulin has been studied in normotensive individuals with a family history of hypertension. Ferrari et al\(^9\) described altered insulin sensitivity, hyperinsulinemia, and dyslipidemia in normotensive subjects from hypertensive parents. Ishibashi\(^10\) noted in 21 junior high school girls who had at least one hypertensive parent that insulin levels were higher and related to body fat mass. In 30 normotensive subjects with at least one hypertensive parent, euglycemic glucose clamp and intravenous glucose tolerance tests showed reduced insulin sensitivity in all subjects.\(^11\) Thus, young normotensives who are at increased risk of developing hypertension appear to have early abnormalities in insulin.

Insulin may influence blood pressure through activation of the sympathetic nervous system. It has been proposed that insulin may mediate the increased sympathetic nerve activity in essential hypertension.\(^12\) Rowe et al\(^1\) first reported in normotensive sympathetic nerve activity (measured by microneurography) in both normotensive and borderline hypertensive patients. In this study despite sympathetic activation, forearm vascular resistance fell and blood pressure did not change. However, these results regarding the relation between insulin and sympathetic nerve activity have been reported in only acute insulin infusion protocols and not in chronic studies. Sympathetic nervous system activity is elevated in essential hypertension\(^12\) and there is evidence that this abnormality is partly influenced by heredity. For example, abnormal neurogenic control of blood pressure, such as reduced venous compliance, has been found in normotensive men with a positive family history of hypertension.\(^12\)

The goal of the present study was to examine, in individuals with three levels of BP, ie, normotensive, borderline, and established hypertensive subjects, the effect of family history of hypertension on basal levels of glucose, insulin, and NE and on their responses to glucose ingestion.

**SUBJECTS AND METHODS**

**Subjects** Six groups with 20 subjects each were studied. These groups consisted of normotensive subjects (NT) with and without a family history of hypertension; borderline hypertensive patients (BHT) with and without a family history of hypertension; and established hypertensive patients (EH) with and without a family history of hypertension. These groups were strictly matched in age and body mass index. All subjects were male volunteers and healthy, except for hypertension. A positive family history of hypertension was defined as both parents having hypertension as documented by previous medical records or by direct blood pressure measurements in the parents, where possible. A negative family history was defined as both parents being normotensive. No participant had diabetes mellitus, obesity, or a past history of myocardial infarction or cerebrovascular accident.

Established hypertension was defined as a supine reading of 160/95 mm Hg or more on three separate visits. Borderline hypertension was defined as a supine reading of 140 to 159/90 to 94 mm Hg. Normotension was defined as a supine reading of < 140/90 mm Hg on three separate visits. None of the subjects had received antihypertensive medications for at least 4 weeks preceding the study.

Studies were approved by the Ethics Committee of Osaka University Medical School and informed consent was obtained from each subject. After overnight fasting, blood pressure (BP), pulse rate (PR), and venous blood sampling for measurements of blood glucose, plasma insulin, and plasma norepinephrine (NE) levels were obtained in each subject.

**Measurements** Blood pressure and pulse rate were measured with an automated sphygmomanometer (A&D, TM-2713, Tokyo, Japan) which was standardized against a mercury sphygmomanometer. Plasma immunoreactive insulin was measured by a standard radioimmunoassay method (insulin Ribabeed II, DinaBott, Tokyo, Japan) using anti-insulin antibody mixture (intrassay coefficient of variation [CV] = 1.9%; interassay CV = 2.2%; sensitivity = 0.75 to 300 \(\mu\)U/mL) and plasma NE was measured after separation by high performance liquid chromatography by the fluorometric method\(^20\) (intrassay CV = 2.1%; interassay CV = 3.6%; sensitivity = 0.010 to 20 ng/mL). Blood glucose and lipid fractions were measured by an autoanalyzer (Hitachi-7050, Tokyo, Japan).

**Statistical Analyses** Values are shown as mean ± SD. Changes in variables within each group and differences among groups were examined by two-way analysis of variance (ANOVA) and when significant, Dunnett's test was used to determine the significance of the differences of the mean at each time point from the baseline and those among groups. Values of \(P < .05\) were considered significant.

**RESULTS**

Table 1 shows the baseline values for the six subgroups studied. The study groups did not differ significantly in age or body mass index. Mean baseline blood pressure levels in normotensive, borderline, and established hypertensive subjects (110 ± 4/67 ± 4, 156 ± 3/92 ± 2, 165 ± 3/100 ± 3 mm Hg, \(P < .01\) in normotensives) did not differ within each group between those with and without a positive family his-
Table 1. Baseline Demographic, Hemodynamic, and Metabolic Values for the Six Study Groups

<table>
<thead>
<tr>
<th>Normotensive Subjects</th>
<th>Established Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Number</td>
<td>20</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>37 ± 8</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>52.0 ± 4.6</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>223 ± 4.1</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>100 ± 6.4</td>
</tr>
<tr>
<td>Supine plasma insulin (µU/mL)</td>
<td>52 ± 3.5</td>
</tr>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>100 ± 6.4</td>
</tr>
<tr>
<td>VLDL cholesterol (mg/dL)</td>
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<td>HDL cholesterol (mg/dL)</td>
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<td>LDL cholesterol (mg/dL)</td>
<td>140 ± 7.1</td>
</tr>
<tr>
<td>HDL/total cholesterol</td>
<td>0.28 ± 0.12</td>
</tr>
</tbody>
</table>

*P < .05 compared with the values in subjects without a positive family history.

Mean glucose, insulin, and norepinephrine levels were greater in established hypertensive patients compared to normotensive subjects. Changes in systolic, diastolic, and mean BP after glucose ingestion were also similar in subjects with and without a family history of hypertension in three study groups (data not shown). Fasting plasma insulin were significantly greater in the subjects with a positive family history than in subjects without a family history, regardless of BP levels. Plasma insulin levels were also greater in established hypertensive subjects than in normotensive subjects (P < .05) or in borderline hypertensive subjects (P = NS). Supine basal plasma NE levels were greater in subjects with a positive family history than in subjects without a family history. Mean values were also significantly greater in borderline hypertensive patients than in normotensive (P < .01) or established hypertensive subjects (P < .05).

Mean total cholesterol levels were significantly higher in established hypertensive patients with a positive family history compared to other study groups. Levels of triglyceride, HDL cholesterol, and VLDL cholesterol and the ratio of VLDL/HDL + LDL cholesterol did not differ among the six study groups.

Figure 1 (upper panel) shows the mean basal blood glucose and the responses to glucose ingestion in the three blood pressure groups divided by the presence or absence of a positive family history of hypertension. There were no differences in baseline glucose or blood glucose responses to glucose ingestion in normotensive, borderline hypertension, and established hypertensive subjects with and without a family history of hypertension (NT: F = 0.56, P = .7580; BHT: F = 0.57, P = .7554; EH: F = 0.53, P = .7992).

Figure 1 (middle panel) shows basal insulin and changes with glucose ingestion. Mean values were greater in established hypertensive (F = 7.02, P = .0001) than in the normotensive and borderline hypertensive subjects. Basal insulin levels and changes in insulin levels were also greater in borderline hypertensive subjects compared to normotensive subjects (F = 6.97, P = .0001). In addition, basal and glucose-stimulated insulin levels were greater in all three BP groups in those with a positive family history of hypertension (F = 13.32, P = .0001). Figure 1 (lower panel) shows the basal NE values and changes after glucose. Mean NE values were greater in established and borderline hypertensive subjects (F = 26.55, P < .0001) than in normotensive subjects. In addition, all three BP groups (normotensive, borderline hypertensive, and established hypertensive subjects) with a positive family history of hypertension had significantly greater NE responses to glucose than subjects without a family history (P = 18.32, P = .0001). Changes in plasma NE levels after glucose in the borderline hypertensive subjects differed significantly between those with and without a family history (F = 10.18, P = .0001), and these NE re-
responses were greater compared to the responses in normotensives ($F = 7.04, P = .0003$) and in the established hypertensive subjects ($F = 4.74, P = .0005$).

Figure 2 shows the sum of mean blood glucose, plasma insulin and NE responses to glucose in the six study groups. There were no significant differences in the sum of glucose response in the six groups. The sum of plasma insulin responses was greater in borderline and established hypertensives compared to normotensives ($P < .05$ and $P < .01$, respectively). Additionally, in all three study groups, the sum of insulin responses was greater in family history positive individuals versus family history negative individuals. The sum of plasma NE after glucose was significantly greater in borderline and established hypertensives versus normotensives ($P < .01$ and $P < .05$, respectively). For all BP groups, the sum of plasma NE values was greater in those with a positive family history (Figure 2).

The ratio of $\Delta$NE/Δinsulin (Δ: changes in the absolute values from baseline to peak), as an index of the relation between sympathetic nerve activity and insulin responses to glucose ingestion, was significantly greater in normotensive and borderline hypertensive subjects than in established hypertensive patients (NT: $4.74 \pm 0.41, P < .01$ v EH; BHT: $3.72 \pm 0.29, P < .05$ v EH; EH: $3.15 \pm 0.28$). In addition, the ratio was also significantly greater in normotensive and borderline hypertensive subjects with a family history of hypertension than in subjects without a family history of hypertension (NT: $5.14 \pm 0.23$ v $4.16 \pm 0.36, P < .05$; BHT: $4.55 \pm 0.39$ v $2.65 \pm 0.37, P < .01$; EH: $3.46 \pm 0.34$ v $2.70 \pm 0.22, P = NS$, respectively).

DISCUSSION

The main finding from the present study is that basal and glucose stimulated insulin levels and plasma NE
levels are greater in normotensive, borderline, and established hypertensive subjects with a family history of hypertension compared to those without a family history of hypertension. Abnormal insulin responses in normotensive individuals with a positive family history of hypertension indicate that the metabolic abnormalities in hypertension may precede the onset of blood pressure changes. However, even with the onset of hypertension, those with a positive family history seem to retain a greater degree of abnormal metabolic function than individuals without familial hypertension. This study also demonstrates that insulin responses to glucose ingestion are greater in borderline and established hypertensives than normotensive subjects, regardless of family history. Numerous studies have now reported the presence of insulin resistance and hyperinsulinemia in both lean and obese subjects with essential hypertension.\(^1\) \(^6\) These findings are best explained by reduced insulin mediated glucose disposal mainly localized to skeletal muscle and differing from other insulin resistant states in its mediation only through the nonoxidative pathway (glucose synthesis) for glucose disposal.\(^3\) \(^7\) Most studies describing insulin resistance and hyperinsulinemia in hypertension have been in white subjects. There appears to be significant racial differences in the relationship of insulin to blood pressure.\(^2\) \(^1\) Therefore, the present study showing higher fasting and glucose stimulated insulin levels in hypertensive subjects in Japan suggests that a relationship between insulin and blood pressure exists in the Japanese hypertensive population.\(^2\)

Other studies have noted abnormal glucose and insulin metabolism in normotensive subjects with a family history of hypertension. Ferrari et al\(^5\) reported that normotensive subjects with one hypertensive parent had reduced insulin sensitivity, hyperinsulinemia, and dyslipidemia when compared to subjects without a family history of hypertension. In this study, in vivo insulin sensitivity was determined only in men. Ishibashi\(^6\) noted higher serum insulin levels in 21 junior high school girls who were offspring of patients with essential hypertension compared to 131 girls who had normotensive parents. In this study the higher insulin was related to greater total body fat mass. Beaty et al\(^11\) performed euglycemic glucose clamps and intravenous glucose tolerance tests in normotensive offspring of hypertensive parents finding reduced insulin mediated glucose disposal.

The present study supports the above findings, but differs in that only men were studied. Normotensive, borderline, and established hypertensive subjects were included and the subjects were carefully matched for age and body mass index. This study is also one of the first to link familial abnormalities in blood pressure and insulin to the activity of the sympathetic nervous system. Plasma NE levels were measured as an index of sympathetic nervous system activity to evaluate the relationship between NE and insulin responses to glucose. Several studies have found that insulin infusion in normal subjects leads to increased NE release\(^15\) \(^16\) and regional sympathetic nerve activity as assessed by microneurography.\(^14\) \(^15\) In addition, Lembo et al\(^24\) found that insulin infusion in patients with essential hypertension produces exaggerated NE responses compared to normotensive controls.
Esler et al.23-27 and Anderson et al.28 reported that NE spillover or muscle sympathetic nerve activity is better than plasma NE concentration as an index of sympathetic nerve activity. However, they also reported that the spillover of NE, muscle sympathetic nerve activity, and blood flow were different in each organ, and thus, that plasma NE concentration reflects only partially whole body sympathetic activity. Radaelli et al.29 have also reported, by the method of power spectrum analysis, differences in autonomic nervous system activity in the heart compared to the peripheral vessels. Therefore, we used plasma NE concentration as a general index of sympathetic nerve activity, realizing that it may only partially reflect real sympathetic nervous system activity.

Our results using glucose-mediated insulin release indicate that in normotensive subjects both insulin and NE levels increase significantly and responses parallel each other in a temporal fashion. In established hypertensive subjects, especially in patients without a family history of hypertension, plasma NE levels were high at baseline but the NE response to glucose appeared blunted compared to normotensive subjects. In contrast, in borderline hypertensive patients, especially those with a positive family history, basal NE levels and responses to glucose were significantly greater in BHT than in normotensive subjects. Also, a positive family history of hypertension appeared to lead to markedly accentuated NE responses to glucose in all three BP groups (normotensive, borderline hypertensive, established hypertensive subjects). Thus, there appears to be good tracking of the insulin and NE responses to glucose in normotensive and borderline hypertensive subjects, especially in those subjects with a positive family history. In contrast, the relationship of insulin and NE during glucose is less consistent in borderline hypertensive subjects and in subjects without a positive family history. Our results show that there is a considerable familial influence on insulin and sympathetic nervous system responsiveness to glucose ingestion. Our results are in accordance with the previous reports that family history could be an important determinant of neurogenic activity, as shown by venous compliance in normotensive and borderline hypertensive subjects with a positive family history of hypertension.30,31

We used Δplasma NE/Δplasma insulin responses to glucose as an index of the relation between insulin and sympathetic nerve activity: the greater the ratio, the higher the sympathetic nerve activity in a given change in insulin level. The ratio was significantly greater in normotensive and borderline hypertensive subjects with a positive family history compared to those without a family history or to those with established hypertension. These results, especially in the BHT patients, indicate that sympathetic nerve hyperactivity is closely connected to the emergence of insulin resistance perhaps occurring in the early stages of hypertension. One could speculate that increased sympathetic nerve activity may chronically lead to structural vascular changes that would reduce the glucose delivery to skeletal muscle, thereby inducing insulin resistance, however, the cross-sectional design of this study cannot definitely answer this question.

In summary, the present study presents data to show that in early hypertension (BHT) the reduced insulin sensitivity is determined, in part, by a hereditary background that is accompanied by evidence for hyperactivity of the sympathetic nervous system in the setting of a glucose challenge.

REFERENCES
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