Insulin Sensitivity and the Effects of Insulin on Renal Sodium Handling and Pressor Systems in Essential Hypertensive Patients

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Abstract Insulin resistance and hyperinsulinemia are linked with essential hypertension. To clarify insulin sensitivity in Japanese essential hypertensive patients and the role of insulin resistance in these patients, a euglycemic hyperinsulinemic glucose clamp was applied in 17 essential hypertensive patients and 12 normotensive subjects. The mean glucose infusion rate was used as an indicator of insulin sensitivity (M value). This study revealed a significantly lower M value in essential hypertensive patients than in normotensive subjects. Increased plasma norepinephrine, renin activity, and aldosterone levels were observed after hyperinsulinemia for 120 minutes after glucose clamp in normotensive subjects and essential hypertensive patients. Uri-

Hypertension and insulin resistance have been linked to obesity and hypertension. Evidence supporting this concept has been derived mainly from epidemiologic studies showing a correlation between insulin resistance, hyperinsulinemia, and blood pressure.1,2 Recently, from studies in young nonobese normotensive subjects or obese insulin-resistant individuals, it was suggested that insulin increases renal tubular sodium reabsorption,5-11 and stimulates the renin-aldosterone system,1,5-14 which might contribute to the development or maintenance of hypertension.

In essential hypertensive patients, Ferrannini et al12 reported that insulin sensitivity measured by the euglycemic hyperinsulinemic glucose clamp technique was markedly suppressed compared with that in age- and weight-matched control subjects. Recently, Ferrari et al12 reported that young normotensive humans in apparently excellent health but with one essential hypertensive parent tend to have hyperinsulinemia and an insulin resistance, suggesting that insulin resistance occurs at the prehypertensive state. However, it is still unknown whether the pressor actions and renal sodium handling of insulin remain in hypertensive insulin-resistant individuals or not. Therefore, in this study we measured insulin sensitivity and investigated the effects of insulin on pressor systems and renal sodium handling using the euglycemic hyperinsulinemic glucose clamp technique in untreated essential hypertensive patients. Urinary sodium excretion and fractional excretion of sodium were decreased in essential hypertensive patients as well as normotensive subjects during glucose clamp compared with the period before glucose clamp. No difference in the percent change was observed between essential hypertensive patients and normotensive subjects. These results indicate that selective insulin resistance with respect to glucose metabolism exists in essential hypertensive patients and that insulin action on renal sodium handling and pressor systems was maintained in these patients. (Hypertension. 1994;23[suppl I]:I-29-I-33.)

Key Words • insulin resistance • glucose clamp technique • hypertension, essential

Methods

Seventeen essential hypertensive (EHT) patients (8 men, 9 women) who had no complication due to hypertension were studied. Blood pressure measurements were taken with the patient in a supine position using a mercury sphygmomanometer after 10 minutes of rest. Their age, body mass index, and mean blood pressure were 47.6±3.2 years, 23.7±0.5 kg/m², and 112±2 mm Hg, respectively. They were withdrawn from all antihypertensive drugs for more than 2 weeks. A control group, 12 normotensive (NT) subjects (6 men, 6 women) were used in this study. Their age, body mass index, and mean blood pressure were 45.4±3.2 years, 22.7±0.7 kg/m², and 87±3 mm Hg, respectively. All subjects were hospitalized for more than 1 week and received a regular diet containing 120 mol/L (mEq) per day of sodium and 75 mmol (mEq) per day of potassium. Before the studies, the aim of the study was explained to subjects and their informed consent was obtained.

Insulin Sensitivity Studies

The 2-hour euglycemic hyperinsulinemic glucose clamp technique according to DeFronzo et al23 was used to estimate in vivo sensitivity for insulin in the EHT and NT groups. At 8 AM on the morning of the study, these subjects drank 150 mL/m² body surface area of water. After a 1-hour equilibration period, they were asked to empty their bladder, and urine collection was begun. The urine collection period lasted for 1 hour before the clamp technique. Urine samples were collected for 2 hours during the clamp technique. Blood samples were obtained at 30 minutes before the clamp study and just before termination of the clamp study. During the entire study, all subjects were in a supine position, except when voiding.

In the glucose clamp study, blood was continuously withdrawn at 2.0 mL/h through a double-lumen catheter for glucose analysis of arterialized blood. In addition, a contralateral antecubital vein was cannulated with a No. 18 plastic cannula for infusion of insulin and glucose. Continuous insulin infusion, monitoring of glucose concentration, and infusion of
variable amounts of glucose for clamping glucose levels at the basal state were performed with a model STG-22 artificial endocrine pancreas (Nikkiso Corp, Tokyo, Japan). The infusion rate of insulin (Actrapid Human, Novo Industries, Copenhagen, Denmark) was 40 mU/m² of body surface area. During insulin infusion, euglycemia was maintained by a variable infusion of a 20% glucose solution. The mean rate of glucose infusion for the last 30 minutes of the clamp was used as an indicator of insulin sensitivity (M value): milligrams of glucose per square meter of body surface area or kilogram of body weight per minute.²³ Before and after the clamp, mean blood pressure, heart rate, creatinine clearance, urinary sodium excretion, fractional excretion of sodium, blood sugar level, plasma insulin levels, plasma renin activity, plasma aldosterone levels, and plasma norepinephrine levels were measured in each subject.

**Laboratory Investigations**

Blood sugar was measured by the glucose oxidase technique. Serum or urinary sodium level was determined by the ion-electrode method. Plasma insulin, plasma renin activity, and plasma aldosterone were measured by various radioimmunoassay techniques (Insulin RIA bead, Dainabot, Tokyo, Japan; Gamma Cord, Baxter Healthcare, Tokyo, Japan; and Aldosterone RIA kit II, Dainabot, respectively). Plasma norepinephrine was measured by the high-performance liquid chromatography-trihydroxyindol method.

**Statistical Analysis**

All data are expressed as mean±SEM. Student’s t test was used to assess differences between the EHT and NT groups for mean blood pressure and M value or between urinary sodium excretion, fractional excretion of sodium, plasma renin activity, and plasma aldosterone and norepinephrine levels before and after the clamp technique.

**Results**

**Insulin Sensitivity**

Fasting blood sugar in the EHT group (87.7±1.9 mg/dL) was similar to the NT group (89.7±2.4 mg/dL). There was no significant difference in fasting plasma insulin levels between the EHT (6.9±0.8 mU/L) and NT (6.0±1.0 mU/L) groups. During the clamp period, blood sugar level stayed at the basal level (approximately 80 mg/dL), and plasma insulin levels elevated remarkably in the EHT (92.7±8.5 mU/L) and NT (90.7±9.4 mU/L) groups. The M value, which was corrected by body surface area to attenuate the effect of obesity on insulin sensitivity and body weight, was significantly (P<.05) lower in the EHT group (232±25 mg/m² per minute and 4.17±0.43 mg/kg per minute) than in the NT group (232±25 mg/m² per minute and 6.31±0.58 mg/kg per minute) (Fig 1).

**Mean Blood Pressure, Heart Rate, Plasma Norepinephrine and Aldosterone Levels, and Plasma Renin Activity**

No significant change was found in mean blood pressure and heart rate during the clamp technique in the NT and EHT groups. There was no difference in plasma renin activity and plasma norepinephrine or aldosterone levels before clamping between the two groups. During the clamp technique, significant increases (P<.05) in plasma norepinephrine (from 166±16 to 208±24 pg/mL in the NT group and 135±18 to 168±7 pg/mL in the EHT group), plasma renin activity (from 1.41±0.56 to 2.31±0.63 ng/mL per hour in the NT group and 1.13±0.44 to 1.67±0.65 ng/mL per hour in the EHT group), and plasma aldosterone levels (from 49.6±6.8 to 65.2±10.0 pg/mL in the NT group and 63.7±6.9 to 78.5±9.4 pg/mL in the EHT group) were observed. Percent changes of plasma norepinephrine (26.5±8.8% in the NT group and 36.1±11.4% in the EHT group), plasma renin activity (131.1±25.5% in the NT group and 73.3±20.9% in the EHT group), and plasma aldosterone (35.6±13.9% in the NT group and 33.8±11.5% in the EHT group) showed no significant difference between the two groups (Fig 2).

**Renal Sodium Handling**

Twenty-four-hour urinary sodium excretions were 118±13 and 109±17 mmol (mEq)/d in the NT and EHT groups, respectively. Creatinine clearance did not change during the clamp technique in the NT group (from 112.7±15.1 to 81.9±9.6 mL/min) and EHT group (from 87.6±3.8 to 83.9±5.4 mL/min). On the other hand, urinary sodium excretion was decreased signifi-
cantly \((P<.05)\) during the insulin infusion by the clamp technique in the NT group (from 157±28 to 85±17 \(\mu\)mol [\(\mu\)Eq]/min) and EHT group (from 94±9 to 66±8 \(\mu\)mol [\(\mu\)Eq]/min). Fractional excretion of sodium was also decreased significantly in the NT group (from 0.87±0.17\% to 0.67±0.10\%) and EHT group (from 0.69±0.07\% to 0.56±0.06\%). Percent changes of urinary sodium excretion and fractional excretion of sodium did not show any significant difference between the EHT group (-29.8±5.9\% and -20.6±5.4\%, respectively) and NT group (-39.4±8.7\% and -14.2±7.3\%, respectively) (Fig 3).

**Discussion**

Ferrannini et al\(^2\) studied insulin sensitivity in normal-weight young EHT patients with a more quantitatively precise euglycemic hyperinsulinemic glucose clamp technique. Compared with NT control subjects, insulin sensitivity was reduced by 30\% to 40\%, and the fasting insulin level was elevated by 59\% in nonobese
EHT patients. Saad et al\textsuperscript{24} reported on racial differences in the relation between blood pressure and insulin resistance in whites but not in the Pima Indians or blacks of the United States. Little is known about this condition in the Japanese population. Recent Japanese epidemiologic studies suggested that hyperinsulinemia can be related to hypertension in the general population of Japan.\textsuperscript{25,26} In our study using the euglycemic hyperinsulinemic glucose clamp technique, we observed that Japanese EHT patients also had insulin resistance in relation to glucose metabolism. Body mass index was slightly greater in the EHT compared with the NT group, but a significant difference was not found between the two groups. Therefore, it seems unlikely that the difference in body mass index is a major factor in the suppression of insulin sensitivity in essential hypertension. Suzuki et al\textsuperscript{27} also reported on the insulin insensitivity in Japanese essential hypertension using the steady-state plasma glucose method. These studies indicated that insulin resistance was closely associated with hypertension in the Japanese population.

In our study, plasma glucose and insulin levels showed normal levels at the basal conditions in essential hypertension. Singer et al\textsuperscript{28} Manicardi et al.\textsuperscript{2} and Ferrannini et al\textsuperscript{2} reported that, in EHT patients whose basal plasma insulin and glucose levels were similar compared with NT subjects, a significantly greater increase of plasma insulin and plasma glucose levels was observed after a 75-g oral glucose tolerance test\textsuperscript{4,21} and after each meal\textsuperscript{28} than in NT subjects. Therefore, we cannot exclude the possibility that plasma glucose and insulin levels are significantly higher after meals or after the glucose tolerance test in EHT patients than in NT subjects. If hyperinsulinemia exists in EHT patients, as indicated by several reports,\textsuperscript{4,21,28} the insulin resistance per se and/or resultant hyperinsulinemia may be concerned with the etiology of essential hypertension.

Previous studies\textsuperscript{4-11} using the euglycemic hyperinsulinemic glucose clamp technique have been carried out in healthy young subjects with a sodium and/or water load and showed that hyperinsulinemia increases renal sodium reabsorption. Rocchini et al\textsuperscript{9} reported that obesity was associated with insulin resistance and hyperinsulinemia but that the renal sodium-retaining effects of insulin still remained in obese subjects and NT control subjects. It has not been clarified whether insulin action on the renal sodium handling and pressor systems is maintained in EHT patients as well as NT subjects. In this study, we demonstrated that infused insulin markedly reduced renal sodium excretion in middle-aged NT subjects and EHT patients. Moreover, percent change of renal sodium excretion during the clamp technique in EHT patients was not different from NT subjects. These data suggest that the effect of insulin on renal sodium handling was maintained in EHT as well as NT individuals.

In this study, plasma norepinephrine and aldosterone levels and plasma renin activity were significantly increased in the NT and EHT groups during the clamp technique, and no significant difference was observed in the percent changes of these variables during the clamp technique between the two groups. Landsberg et al\textsuperscript{10} reported that the effect of insulin to increase sympathetic nervous system activity was initiated in the central nervous system, which may be related to the ventromedial portion of the hypothalamus.\textsuperscript{30} In fact, Rowe et al\textsuperscript{12} and Anderson et al\textsuperscript{13} demonstrated a significant increase in plasma norepinephrine by euglycemic hyperinsulinemia in NT subjects. Our results in NT subjects and EHT patients were consistent with theirs. Falkner et al\textsuperscript{14} in young NT subjects and borderline hypertensive patients, Gans et al\textsuperscript{14} in young NT subjects, and Rocchini et al\textsuperscript{10} in nonobese and obese adolescents reported that there was no increase in plasma norepinephrine levels in response to euglycemic hyperinsulinemia. This discrepancy may be caused by the difference in the ages of subjects\textsuperscript{9,11,14} and/or the state of sodium and water loading.\textsuperscript{11,14} The stimulating effects of hyperinsulinemia on the renin-angiotensin-aldosterone system have also been controversial. Some studies reported that plasma renin activity and/or plasma aldosterone level did not increase during euglycemic hyperinsulinemia.\textsuperscript{5,8-10} In those reports, subjects received a high intake of sodium and water before the clamp study. Therefore, the altered sodium and/or water loading may be related to the discrepant results regarding the effects of insulin on the renin-aldosterone system. The stimulating effects of insulin on the renin-aldosterone system may be caused in part by the increased sympathetic nerve activity due to insulin.\textsuperscript{19,20,32}

We demonstrated that essential hypertension accompanied insulin resistance with respect to glucose metabolism, but insulin action on renal sodium handling and pressor systems in essential hypertension was maintained. If insulin resistance exists not only in glucose metabolism but also in renal sodium handling and the sympathetic nervous system, the resultant hyperinsulinemia does not induce sodium retention or augmentation of sympathetic nervous system activity. Therefore, the existence of selective insulin resistance in essential hypertension seems to be important. This differential tissue sensitivity with respect to glucose metabolism might lead to chronic sodium retention and pressor system stimulation in essential hypertension.

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