Strict Dietary Sodium Reduction Worsens Insulin Sensitivity by Increasing Sympathetic Nervous Activity in Patients With Primary Hypertension

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To assess the effects of sodium reduction on insulin sensitivity in hypertension, we examined the change of insulin sensitivity after two degrees of dietary sodium restriction by the euglycemic hyperinsulinemic glucose clamp method in 12 subjects with primary hypertension. A controlled period of 1 week, when the subjects were taking a normal sodium diet, was followed by a randomized crossover study in which the subjects were placed on either moderate or strict reduced sodium diets for 1 week. The result of the 1-week moderate dietary sodium reduction from 200 to 100 mmol/day showed significant decreases in systolic and diastolic blood pressure by 6.5 and 5.0 mm Hg, respectively. Strict dietary sodium reduction to 30 mmol/day for 1 week resulted in no further decrease in blood pressure, but it increased plasma insulin by 40.6% without changing plasma glucose. There were no changes in glucose infusion rate (GIR) or insulin sensitivity index (ISI), which is a measure of GIR divided by plasma insulin, after moderate dietary sodium reduction. However, strict dietary sodium reduction induced decreases in GIR by 19.8% (from 1318 ± 189 to 1057 ± 173 μmol/m^2/min; $P < .01$), and ISI by 20.5% (from 16.6 ± 2.1 to 13.2 ± 1.9 μmol/m^2/min/μU/mL; $P < .01$) with a paralleled increase of plasma norepinephrine by 90.0% (from 150.5 ± 61.6 to 287.3 ± 114.9 pg/mL; $P < .01$). These results indicate that dietary sodium restriction leads to a deterioration of insulin sensitivity when plasma norepinephrine levels increase, and suggest that moderate dietary sodium reduction may lower blood pressure without a distinct adverse effect on glucose metabolism in subjects with primary hypertension. Am J Hypertens 1998;11:1048–1055 © 1998 American Journal of Hypertension, Ltd.

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Dietary sodium reduction is considered to be an important component of standard therapy for hypertension, because dietary sodium reduction can lower blood pressure at least in some hypertensive individuals, and may reduce subsequent cardiovascular disease complicated by hypertension.[1,2] However, some investigators have challenged the efficacy of dietary sodium

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reduction for routine treatment of hypertensive patients.[3–7] Indeed, reduction of dietary sodium intake has been reported to have some adverse effects on glucose metabolism,[8–12] probably mediated by an activation of the renin-angiotensin-aldosterone system and sympathetic nervous system. A low sodium diet raises plasma insulin levels, but not blood glucose levels, suggesting an induction of insulin resistance by reduction of dietary sodium intake.[10–12] A short-term reduction of sodium intake has been reported to have no effect on insulin sensitivity measured by the euglycemic glucose clamp method in normotensive volunteers.[13,14] On the other hand, Donovan et al[15] observed that low sodium intake increased the insulin sensitivity index in normotensive nondiabetic white men. In the study by Gaboury et al,[16] dietary sodium reduction improved insulin sensitivity in normotensive control subjects, whereas the same regimen had no effect on insulin sensitivity in hypertensive patients. Thus, there seems to be some discrepancy among the results from earlier reports that investigated the change of insulin sensitivity after dietary sodium reduction.

The goals of this study were to clarify the effect of different degrees of reduction in dietary sodium on blood pressure and insulin sensitivity in hypertensive patients, and to try to estimate an adequate degree of dietary sodium reduction in routine antihypertensive therapy.

SUBJECTS AND METHODS

Subjects This study was conducted on 12 Japanese subjects (8 men and 4 women; mean age, 51.8 years; range, 38 to 65 years) with moderate, established primary hypertension. Four women included in this study were menopausal with an age range from 51 to 65 years. Hypertension was diagnosed when subjects were taking an antihypertensive medication or when blood pressure measured at the outpatient clinic had been higher than 160 mm Hg systolic and 95 mm Hg diastolic on three consecutive visits at least 1 week apart without antihypertensive medication. Subjects with a secondary form of hypertension or with diabetes mellitus, as diagnosed according to the glucose criteria of the World Health Organization (WHO) Study Group (fasting plasma glucose levels, $\geq$7.8 mmol/L; 2 h after glucose load, $\geq$11.1 mmol/L),[17] were excluded from the study. Physical and laboratory examinations, chest radiographs, electrocardiograms, and fundoscopy were performed for determination of hypertensive organ damage. Our subjects included 3 at stage I and 9 at stage II of the WHO classification of hypertension by extent of organ damage.[18] Clinical information about the subjects was obtained from their medical records, which included the duration of hypertension, a family history of hypertension and diabetes mellitus, daily alcohol intake, and tobacco consumption. Estimated duration of hypertension was 12.5 $\pm$ 7.8 years (range, 3 to 22 years). Seven subjects had never received any antihypertensive medication. For 5 subjects who were taking antihypertensive medication, all drugs were withdrawn for at least 2 weeks before the study. Eight subjects (67%) had a family history of hypertension, but only 1 subject exhibited a family history of diabetes mellitus. Seven subjects drank alcohol every day and 5 subjects were smokers.

The nature of the study and potential risk associated with it were explained to all subjects, who gave their written informed consent before participating in the study. The study protocol was approved by the Institutional Review Board on Human Investigations of NTT Kanto Teishin Hospital.

Study Protocol All subjects were admitted to the Clinical Research Ward at NTT Kanto Teishin Hospital and placed on a normocaloric and normal sodium diet to stabilize blood pressure and sodium balance. The normal sodium diet contained 7955 kJ (1900 kcal) and consisted of 305 g of carbohydrates, 50 g of proteins, and 60 g of fats. The sodium and potassium contents were 200 mmol/day and 35 mmol/day, respectively. Seven days after hospitalization, insulin sensitivity in the control period was examined by the euglycemic hyperinsulinemic glucose clamp method. The study started at 8:00 AM with the subjects fasting over 12 h in a temperature-controlled (25°C) and humidity-controlled (55%) quiet experimental room. Subjects rested in the supine position for 30 min after voiding of urine and measurement of body weight. Blood pressure and pulse rate used for analysis were averaged from five values at intervals of 3 min measured by an automatic blood pressure monitor (PC-203, Nihon Koden, Tokyo, Japan). A double-lumen catheter for glucose analysis was introduced into the antecubital vein. The contralateral antecubital vein was cannulated with a No.18 plastic cannula for infusion of an insulin and glucose solution. Thirty minutes after implantation of the catheter, blood samples were taken for determinations of serum creatinine, sodium, potassium, plasma glucose, insulin, plasma renin activity (PRA), and plasma levels of aldosterone and norepinephrine. Twenty-four-hour urine samples taken during 2 days before the clamp study were used for determination of creatinine, sodium, and potassium excretion. Fractional excretion of sodium was calculated from the ratio of sodium clearance to creatinine clearance.

The day after the clamp study in the control period, subjects were randomly allocated to either group A or group B. Group A patients were placed on a moderate sodium reduced diet for 1 week, and then switched to a strict sodium-reduced diet and maintained for 1 week. Group B patients were given the sodium-re-

TABLE 1. ANTHROPOMETRIC MEASUREMENTS, BLOOD PRESSURE, AND PULSE RATE IN SUBJECTS ON NORMAL (200 mmol/day), MODERATE (100 mmol/day), AND STRICT (30 mmol/day) SODIUM RESTRICTED DIETS

Variable	200 mmol Sodium	100 mmol Sodium	30 mmol Sodium
Body weight (kg)	59.3 ± 8.9	59.3 ± 8.9	58.1 ± 9.2
Body mass index (kg/m^2)	23.0 ± 3.0	23.0 ± 2.9	22.5 ± 3.0
Body surface area (m^2)	1.62 ± 0.16	1.62 ± 0.16	1.60 ± 0.16
Systolic blood pressure (mm Hg)	145.7 ± 9.1	139.2 ± 8.1*	138.1 ± 7.2*
Diastolic blood pressure (mm Hg)	93.3 ± 3.7	88.4 ± 3.7*	88.7 ± 4.3*
Mean blood pressure (mm Hg)	110.8 ± 4.5	94.4 ± 4.5*	105.2 ± 4.2*
Pulse rate (beats/min)	62.9 ± 3.8	63.0 ± 2.6	68.4 ± 4.2*†

Values are mean ± SD.

** P < .01 compared with value of normal sodium diet; † P < .01 compared with value of moderate sodium-restricted diet.*

duced diets but in the opposite order. Sodium contents in the moderate and strict sodium-reduced diets were 100 and 30 mmol/day, respectively. Both diets contained the same number of calories and components of carbohydrates, proteins, fats, and potassium as the normal sodium diet. On the eighth day of each sodium-reduced diet when sodium equilibrium had been established, the same recordings were carried out under the same conditions as during the control periods. Subjects were instructed to keep their daily activity constant throughout the study protocol.

Insulin Sensitivity Studies Insulin sensitivity was examined by the euglycemic hyperinsulinemic glucose clamp method according to DeFronzo et al,[19] with an artificial endocrine pancreas (model STG-22, Nikkiso, Tokyo, Japan) as previously described.[20] Glucose concentration monitoring was done in blood samples that were continuously withdrawn at 2 mL/h through a double-lumen catheter. The hand with the catheter was gradually warmed with heating mats to obtain arterialized blood samples during the glucose clamp study.[21] A priming dose of short-acting human insulin (Humulin R, Shionogi, Tokyo, Japan) with a total dose of 700 mU/m^2 was administered during the initial 10 min in a logarithmically decreasing manner to quickly increase plasma insulin to the desired level, and was followed by continuous insulin infusion at a rate of 40 mU/m^2/min for 110 min to achieve steady-state hyperinsulinemia. The glucose clamp level was set at 4.9 mmol/L during the 2-h clamp study and was maintained by measurement of plasma glucose every 5 min and adjustment of the infusion rate of a 20% glucose solution. These procedures were done automatically by the insulin and glucose algorithms controlled by a computer system built into the artificial endocrine pancreas. The glucose infusion rate (GIR, μmol/m^2/min) was estimated by the mean glucose infusion rate during the last 30 min of the clamp study. The insulin sensitivity index (ISI) was calculated by dividing GIR by plasma insulin concentration (μU/mL) estimated at the 90th and 120th minute of the clamp study.

Analytical Methods Plasma glucose was measured by the glucokinase method on an automatic analyzer (model H 736, Hitachi, Tokyo, Japan). The plasma insulin level was determined by competitive enzyme immunoassay with a double antibody procedure with EIA Test Insulin II (Boehringer, Mannheim, Germany). The sensitivity of the insulin assay was 2 μU/mL. Creatinine, sodium, and potassium in both serum and urine were measured by an automatic analyzer. PRA was determined by radioimmunoassay of generated angiotensin I with a Gamma Coat (^{125}I) PRA Radioimmunoassay Kit (Baxter Healthcare, Cambridge, MA). Plasma aldosterone was measured by a nonchromatographic, nonextraction radioimmunoassay method with Aldosterone RIA Kit (Dinabot, Tokyo, Japan). Plasma norepinephrine was determined according to the modified trihydroxyindole method with high-performance liquid chromatography.

Statistical Analysis All data in the text, tables, and figures are mean ± standard deviations of the mean (SD). Cross-over analysis of variance was used to test changes between groups, period, and each dietary sodium-reduced diet.[22] One-way analysis of variance and Fisher's protected least significance difference were used for analyzing the difference of data during usual sodium diet and each sodium-reduced diet when no carryover effect was observed. The Pearson product moment formula was used for calculation of coefficients of correlation between the changes of various parameters after the diet was changed from the moderate to strict sodium-reduced diet.

RESULTS

Anthropometric Measurements, Blood Pressure, and Pulse Rate Table 1 presents anthropometric, blood

TABLE 2. PLASMA LEVELS OF METABOLITES, HORMONES, AND RENAL SODIUM HANDLING IN SUBJECTS ON NORMAL (200 mmol/day), MODERATE (100 mmol/day), AND STRICT (30 mmol/day) SODIUM RESTRICTED DIETS

Variable	200 mmol Sodium	100 mmol Sodium	30 mmol Sodium
Plasma glucose (mmol/L)	4.64 ± 0.24	4.67 ± 0.23	4.66 ± 0.39
Plasma insulin (μU/mL)	7.61 ± 2.22	7.75 ± 2.55	10.90 ± 3.50*†
Plasma renin activity (ng/mL/h)	0.52 ± 0.30	0.81 ± 0.54*	1.87 ± 1.01*†
Plasma aldosterone (pg/mL)	62.7 ± 21.5	68.2 ± 27.1	130.0 ± 55.3*†
Plasma norepinephrine (pg/mL)	144.7 ± 69.6	150.5 ± 61.6	287.3 ± 114.9*†
Serum creatinine (μmol/L)	75.5 ± 8.3	75.5 ± 10.7	76.4 ± 12.0
Serum sodium (mmol/L)	140.9 ± 2.5	141.2 ± 2.8	139.9 ± 1.8
Serum potassium (mmol/L)	4.05 ± 0.32	4.04 ± 0.35	4.05 ± 0.30
Urine creatinine excretion (mmol/day)	10.5 ± 2.2	10.5 ± 2.1	10.3 ± 2.1
Urine sodium excretion (mmol/day)	198.0 ± 18.4	94.4 ± 12.5*	24.6 ± 8.0*†
Urine potassium excretion (mmol/day)	34.7 ± 8.8	34.1 ± 7.5	32.8 ± 7.2
Creatinine clearance (L/day/1.73 m^2)	147.4 ± 14.6	148.6 ± 20.9	147.4 ± 22.5
Fractional sodium excretion (%)	1.047 ± 0.236	0.561 ± 0.107*	0.130 ± 0.042*†

Values are mean ± SD.

** P < .01 compared with value of normal sodium diet; † P < .01 compared with value of moderate sodium-restricted diet.*

pressure, and pulse rate data. One week of dietary sodium reduction from 200 to 100 mmol/day decreases in systolic, diastolic, and mean blood pressure were by 6.5 ± 4.4, 5.0 ± 3.1, and 5.5 ± 2.8 mm Hg, respectively, which represented average decreases of 4.5%, 5.4%, and 5.0% from baseline values. However, strict dietary sodium reduction to 30 mmol/day for 1 week resulted in no further decreases in blood pressure. Pulse rate increased significantly by 5.3 ± 2.8 beats/min, which corresponded to an 8.4% increase of the initial pulse rate only after low sodium diet of 30 mmol/day. No significant change in body weight, body mass index, or body surface area was observed after reduction of sodium intake.

Metabolites, Hormone Levels, and Renal Sodium Handling Table 2 shows plasma levels of metabolites, hormones, and renal sodium handling. Reduction of sodium intake to 100 mmol/day resulted in no change of metabolites or hormone levels, except for an increase in PRA. However, when the dietary sodium intake was decreased from 100 to 30 mmol/day, fasting plasma levels of insulin increased by 40.6% without any change in plasma glucose. An increase in plasma norepinephrine was associated with increases in PRA and aldosterone levels. Serum creatinine, urinary excretion of creatinine, or creatinine clearance was not changed by either the 100 or 30 mmol/day sodium diet.

Insulin Sensitivity Studies Steady-state plasma glucose concentration during the last 30 min of the glucose clamp study was 4.80 ± 0.07 mmol/L on 200 mmol/day sodium diet, 4.81 ± 0.09 mmol/L after 100 mmol/day sodium diet, and 4.81 ± 0.26 mmol/L after 30 mmol/day sodium diet. The coefficient of variance of plasma glucose during the glucose clamp study was <3% during each sodium diet. The mean values of plasma insulin determined at the 90th and 120th min of the glucose clamp study were 78.1 ± 8.1, 79.6 ± 8.4, and 80.1 ± 5.8 μU/mL on 200, 100, and 30 mmol/day sodium diets, respectively. Insulin sensitivity, as measured by GIR during the last 30 min of the glucose clamp study after 100 mmol/day sodium diet, did not differ from that under 200 mmol/day the normal sodium diet. However, GIR decreased significantly by 19.8% from 1318 ± 189 to 1057 ± 173 μmol/m^2/min after 30 mmol/day sodium diet. The ISI, which is a measurement of GIR per unit of plasma insulin, decreased significantly by 20.5% from 16.6 ± 2.1 to 13.2 ± 1.9 μmol/m^2/min/μU/mL after 30 mmol/day sodium diet (Figure 1).

The five smokers had a small ISI compared with the 7 nonsmokers on 200 mmol/day sodium diet (15.7 ± 1.6 *v* 18.1 ± 2.3 μmol/m^2/min/μU/mL; $P = .0890$), on 100 mmol/day sodium diet (15.6 ± 1.5 *v* 17.4 ± 2.3 μmol/m^2/min/μU/mL; $P = .1698$), and on 30 mmol/day sodium diet (12.2 ± 1.6 *v* 14.0 ± 1.7 μmol/m^2/min/μU/mL; $P = .095$).

Relation Between Change of Insulin Sensitivity and Parameters There was no significant correlation among the changes of parameters after moderate reduction of sodium intake. A significant correlation was found between the change of ISI and the change of plasma levels of norepinephrine when the diet was changed from 100 to 30 mmol/day sodium diet ($r = -0.804$; $P < .01$; Figure 2).

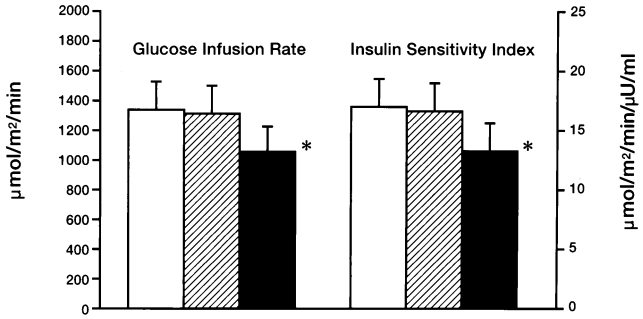

FIGURE 1. *Glucose infusion rate and insulin sensitivity index of normal sodium (200 mmol/day, open bars), moderate sodium restricted (100 mmol/day, hatched bars), and strict sodium restricted (30 mmol/day, solid bars) diets. *indicates* $P < .01$ *compared with value of normal sodium diet and moderate sodium restricted diet.*

DISCUSSION

We found that moderate dietary sodium reduction resulted in a decrease in urinary sodium excretion from 198 to 94 mmol/day and a decrease in mean blood pressure by 5.0%, without changes of GIR and ISI, which were good indicators of insulin sensitivity. However, strict reduction of sodium intake induced a significant reduction of GIR and ISI, without a further decrease in mean blood pressure. The decreases in GIR and ISI are associated with an increase in fasting plasma insulin levels without change of plasma glucose concentration. These findings indicate that insulin resistance is introduced by strict reduction of dietary sodium intake. The infusion of short-acting insulin during the glucose clamp study increased the plasma insulin level to approximately 80 μU/mL, which is well within the physiologic range and sufficiently high enough to suppress hepatic glucose production to a negligible rate even in the presence of insulin resistance.[23–25] Thus, the GIR is equal to the glucose disposal in peripheral tissues, mainly in the muscle, which reflects the insulin sensitivity of each individual. The decrease in GIR after the strict sodium-reduced diet was estimated to be 20% to 22% of those of the normal and moderate sodium-reduced diets. Mean values of plasma insulin during the insulin clamp studies under the three sodium diet regimens were identical, but some difference was observed in individual patients. The ISI calculated by dividing the GIR by plasma insulin level may be a more precise index for insulin sensitivity when the plasma insulin levels are different during the glucose clamp study. In this study, the ISI was the same for the normal sodium diet and moderate reduced-sodium diet, but it decreased by 21% to 23% after strict reduction of dietary sodium intake.

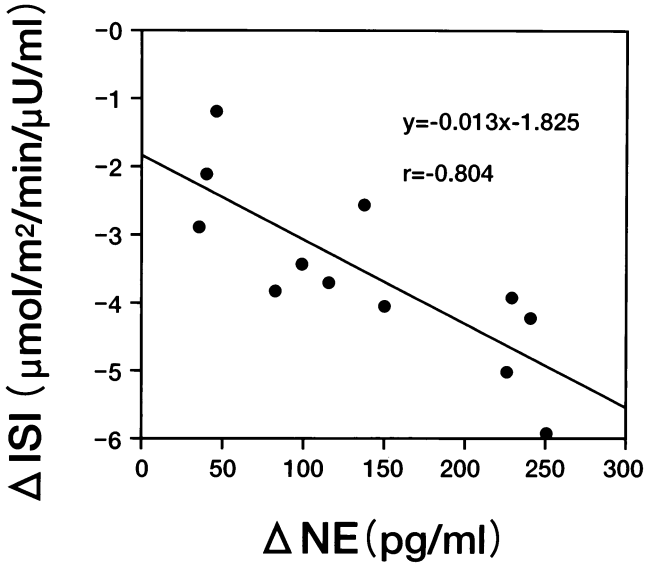

FIGURE 2. *Correlation between change of insulin sensitivity index (ΔISI) and plasma norepinephrine (ΔNE) when the diet was changed from moderate sodium-restricted (100 mmol/day) to strict sodium-restricted (30 mmol/day) diet.*

Because there was no relation between the magnitude of blood pressure reduction and the deterioration of insulin sensitivity after sodium reduction, it appears that dietary sodium intake affects blood pressure and insulin sensitivity by independent mechanisms. Strict reduction of dietary sodium intake induced increases in pulse rate and plasma norepinephrine, which were considered a good indication of enhanced sympathetic discharge. Furthermore, increase in plasma norepinephrine was well correlated with the deterioration of insulin sensitivity when the dietary sodium intake was changed from moderately to strictly reduced levels. Sympathetic hyperactivity itself can cause hemodynamic and structural changes in the peripheral vessels and may promote insulin resistance by reducing skeletal muscle blood flow.[26,27] Baron et al[26] reported that insulin-mediated glucose uptake, as well as insulin-mediated increase in skeletal muscle blood flow, was inversely proportional to basal blood pressure in humans. They suggested that attenuated insulin-mediated skeletal muscle blood flow was a major cause of insulin resistance. Moan et al[27] observed that ISI estimated by the euglycemic glucose clamp technique was correlated with supine and stressed diastolic blood pressure values and maximum plasma norepinephrine during stress in healthy young men. In this study, we found a significant negative correlation between changes of ISI and plasma norepinephrine when the subjects were placed on strict reduction of dietary sodium intake. These lines of evidence seem to support the argument that an activated sympathetic nervous system after strict re-

duction of dietary sodium intake may be a dominant regulator of insulin sensitivity.

Several reports have indicated that moderate to severe reduction of dietary sodium intake may have some adverse effects on glucose metabolism in normotensive volunteers and hypertensive patients.[8–12] A short-term dietary reduction of sodium intake induced an increase in plasma insulin levels without a change of plasma glucose levels,[10–12] and the increase in plasma insulin levels after glucose load were greater for a low sodium diet.[8] This evidence indicates that the reduction of dietary sodium intake causes a deterioration in insulin sensitivity. However, the reports in which the insulin sensitivity was directly examined by euglycemic hyperinsulinemic glucose clamp method have failed to draw a definitive conclusion. Fliser et al[13] reported that dietary sodium restriction from 200 to 20 mmol/day for 3 days caused a decrease in GIR, but it returned to basal values after 7 days of sodium reduction in 14 healthy white men. Grey et al[14] proved that dietary reduction of sodium intake to 52 mmol/day for 1 week had no effect on insulin sensitivity estimated by continuous infusion of glucose with model assessment in 34 normotensive young white men. On the other hand, Donovan et al[15] showed that reduction of sodium intake from 200 to 10 mmol/day resulted in an increase in GIR in 8 healthy white male subjects, and indicated that the salt reduction had a beneficial effect on insulin sensitivity. These reports investigated the change of insulin sensitivity induced by reduction of sodium intake in normotensive subjects. However, we have only one report in which the change of insulin sensitivity after reduction of dietary sodium intake was evaluated in subjects with primary hypertension. The study by Gaboury et al[16] from the same laboratory as Donovan et al,[15] compared the change of insulin sensitivity after dietary sodium reduction by the euglycemic hyperinsulinemic insulin clamp method in 21 hypertensive patients (12 men and 9 women) and 8 normotensive male subjects. They demonstrated that dietary reduction of sodium intake to 10 mmol/day for 5 days had no effect on insulin sensitivity in hypertensive patients, whereas the same regimen caused an improvement of insulin sensitivity in normotensive control subjects. The explanation for the discrepancy between our data and those of Gaboury et al[18] is unclear. It may be a result from the difference in ethnicity of the study populations (Japanese and American). Another potential explanation is the difference of the sympathetic nerve activation. In this study, we observed a marked increase in plasma norepinephrine associated with increases in PRA and pulse rate, which are considered good indicators of sympathetic discharge, after strict reduction of dietary sodium intake. But plasma norepinephrine did not change in the study by Gaboury et al,[16] although the dietary sodium intake was reduced to a more strict level (mean sodium intake 10 mmol/day). The reason why 30 mmol/day sodium diet resulted in an increase of plasma norepinephrine in this study whereas a more strict diet sodium restriction did not lead to an increase in plasma norepinephrine in the study of Gaboury et al[16] is not clear. Thus, the results from previous studies concerning dietary sodium intake and insulin sensitivity are a topic of controversy. In this study, we observed a significant depressor effect after moderate reduction of sodium intake without a change of insulin sensitivity. However, a strict reduction of dietary sodium intake to 30 mmol/day induced a significant reduction both in GIR and ISI, without further depressor effects. Because this study was designed to evaluate the effect of short-term dietary sodium reduction on insulin sensitivity, we cannot provide any evidence concerning the effect of long-term dietary sodium reduction on insulin sensitivity. Further long-term prospective control studies are needed to estimate the adequate reduction of sodium intake in routine antihypertensive therapy in the general population with hypertension. However, this study provided some additional evidence related to the philosophy that it is enough to reduce sodium intake to moderate levels at about 100 mmol/day for routine antihypertensive therapy. One must be aware that more strict reduction of sodium intake may induce an adverse effect on glucose metabolism due to the deterioration of insulin sensitivity when plasma norepinephrine levels increase.

It has been shown that smoking influences insulin sensitivity. Facchini et al[28] reported that chronic cigarette smokers were insulin resistant in response to the oral glucose load compared with a matched group of nonsmokers. They suggest that insulin resistance in cigarette smokers may contributes to their increased risk of coronary heart disease. However, Godsland et al[29] reported that there was no evidence of any effect of cigarette smoking on glucose, insulin, or C-peptide concentrations after intravenous glucose tolerance test. In this study, smokers had smaller ISI levels compared with nonsmokers in the three sodium regimens, but the difference did not reach statistical significance.

Another topic of relationship between sodium intake and insulin sensitivity is whether the insulin resistance and salt sensitivity are associated in hypertension. Sharma et al observed that insulin resistance was present in young, lean normotensive subjects with salt sensitivity for hypertension by oral glucose tolerance test[30] and insulin suppression test.[31] They postulate the hypothesis that an abnormality of glucose metabolism exists before the development of overt hypertension in genetically hypertension-prone individuals. Bigazzi et al[32] compared the blood insulin

and glucose response to an oral glucose load between salt-sensitive and salt-resistant primary hypertensive patients. After an oral glucose load, both the area-under-the curve of glucose and insulin were significantly greater in salt-sensitive than salt-resistant patients. However, a correlation between insulin area-under-the curve and salt sensitivity was very weak and at the limit of statistical significance. They suggest that hyperinsulinemia induced by insulin resistance may be one of the contributing factor for cardiovascular risk factors in salt-sensitive hypertensive patients as well as urinary albumin excretion and atherogenic lipoproteinemia. Unfortunately, our study was not designed to evaluate the relationship between insulin sensitivity and salt dependency of hypertension. The averaged decease in mean blood pressure of our subjects was only 5.6 mm Hg, with range of 1.8 to 10.7 mm Hg, which was the mean decrease of 5.1% with a range of 0.7% to 9.3% of initial value when the dietary sodium intake was decreased from 200 to 30 mmol/day. Because only one patient in this study had a decrease in mean blood pressure more than 10 mm Hg, who met the criteria for salt sensitivity used by Bigazzi et al,[32] we cannot provide any evidence concerning the role of insulin resistance on salt sensitivity for hypertension. The effect, if any, of insulin resistance on salt sensitivity of hypertension evidently remains to be resolved.

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