

Insulin Resistance in Young Salt-Sensitive Normotensive Subjects

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Insulin resistance has been demonstrated in patients with essential hypertension, and insulin-mediated sodium retention is believed to contribute to hypertension in these individuals. Recently, a hyperinsulinemic response to an oral glucose load has been found in salt-sensitive normotensive subjects, suggesting that insulin resistance may be present in these hypertension-prone individuals before the development of hypertension. In the present study, we examined the relation between insulin sensitivity and blood pressure response to salt intake in young, lean normotensive subjects on a high and a low salt diet. Insulin sensitivity was estimated by the "insulin suppression test," i.e., by measuring the plasma glucose and insulin concentrations achieved during a 180-minute infusion of somatostatin, insulin, and glucose in 18 healthy male volunteers (age, 21–28 years) given a standardized low salt diet (20 mmol/day) for 2 weeks, supplemented by either 220 mmol of NaCl per day or placebo in a single-blind randomized order for 1 week each. We defined salt sensitivity as a significant decrease in mean arterial blood pressure (>3 mm Hg [$p < 0.05$]) measured for 60 minutes at 1-minute intervals on the low salt diet. By this definition, seven of the 18 subjects were salt sensitive. Although insulin infusion resulted in similar plasma insulin levels (approximately 50 milliunits/L) in both groups, concomitant glucose infusion resulted in plasma glucose levels that were more than 50% higher in the salt-sensitive than in the salt-resistant group ($p < 0.005$ by two-way analysis of variance). The steady-state glucose-to-insulin ratio was almost twice as high in the salt-sensitive than in the salt-resistant subjects ($p < 0.005$). Thus, insulin-mediated glucose disposal is reduced in otherwise healthy, lean normotensive salt-sensitive subjects, indicating that insulin resistance is present in these hypertension-prone individuals before the development of hypertension. (*Hypertension* 1993;21:273–279)

KEY WORDS • hypertension, sodium sensitive • insulin resistance • family characteristics • diet, sodium-restricted • metabolism

Recently, insulin resistance characterized by a hyperinsulinemic response to glucose administration^{1–7} and a decreased insulin-mediated glucose disposal^{3,5–8} has been found in patients with essential hypertension. Furthermore, based on evidence from epidemiological studies, hyperinsulinemia is now recognized as an independent risk factor for cardiovascular disease.^{9–11} Because insulin can increase renal tubular sodium reabsorption,^{12–15} hyperinsulinemia could contribute to a rise in blood pressure by causing sodium retention and therefore has been suggested to contribute to the pathogenesis of salt-sensitive hypertension.^{15–18} In a previous study, we found that salt sensitivity in young, lean normotensive adults is associated with a hyperinsulinemic response to oral glucose.¹⁹ This latter finding could imply that insulin resistance is present in salt-sensitive normotensive individuals be-

lieved to be genetically predisposed to the development of hypertension.^{20–24} However, the insulin response to an oral glucose load provides only a crude measure of insulin sensitivity.²⁵ In the present study, we therefore examined the relation between insulin sensitivity as measured by the "insulin suppression test"^{26,27} and blood pressure sensitivity to salt intake in young, lean normotensive subjects. The insulin suppression test uses the intravenous infusion of a fixed combination of insulin and glucose during which endogenous insulin release is suppressed by the concomitant administration of somatostatin. Under steady-state conditions, plasma glucose levels are inversely proportional to insulin-mediated glucose disposal and thus insulin sensitivity.²⁵ This technique has been repeatedly used to demonstrate insulin resistance in patients with essential hypertension.^{6,7}

Methods

The protocol of the study was approved by the ethics committee of our hospital. All participants gave their informed consent. The study was performed in an ambulatory setting. All diets were prepared in the hospital kitchen.

Subjects

Eighteen healthy men (age range, 21–28 years) volunteered for the study. Before entering the study, all

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subjects underwent an examination of routine physical and basal laboratory parameters to ensure that none had hypertension, hyperlipidemia, diabetes mellitus, or hepatic or renal disease. Only subjects with a diastolic pressure <85 mm Hg and a systolic pressure <140 mm Hg were included in the study. Parental histories regarding hypertension and non-insulin-dependent diabetes mellitus (NIDDM) were obtained by direct personal communication with the family physicians. Subjects with at least one parent undergoing treatment for hypertension or NIDDM were regarded as having positive familial histories of hypertension or NIDDM, respectively. Seven subjects had a positive familial history of hypertension, and only one had a positive familial history of NIDDM.

To avoid the confounding effect of varying levels of physical activity on insulin sensitivity, we requested that subjects maintain an accustomed level of activity throughout the study. Repeat measurements were performed in each subject on the same day of the week.

Dietary Regimen

Subjects were given a standardized diet containing 80 g protein, 250 g carbohydrates, 80 g fat, 20 mmol sodium chloride, 60 mmol potassium, and 20 mmol calcium per day for 14 days. Caloric intake ranged between 2,000 and 2,400 kcal/day according to body weight and physical activity. The subjects were advised to drink approximately 2 L of water per day. In a randomized single-blind crossover fashion, a daily supplement of 22 tablets of slow sodium (10 mmol NaCl per tablet; gift of CIBA-GEIGY, Horsham, UK) or placebo was administered for 7 days each. The resulting daily salt intake of 240 mmol during the high salt period exceeds the average sodium intake in Western European societies by roughly 30%²⁸ but is still within the normal range.

Procedures

Blood pressure and insulin sensitivity were assessed in each subject on both the high and the low salt diet. On the morning of the seventh day of each period, an antecubital vein and a contralateral hand vein were cannulated in the fasting subject. After a 30-minute resting period, blood pressure was measured for assessment of salt sensitivity in the recumbent subject over 1 hour at 1-minute intervals with an automatic oscillometric device (DINAMAP 1846 SX, Critikon, Tampa, Fla.). Then the hand with the cannula was placed in a thermostated box and gradually warmed to 65°C to obtain "arterialized" blood samples during the insulin suppression test.²⁹ After two baseline samples were drawn for the measurement of plasma glucose, insulin, C-peptide, sodium, chloride, and potassium levels at a 15-minute interval, a constant intravenous infusion of insulin (24 milliunits/m² per minute, Hoechst, Frankfurt, FRG), glucose (150 mg/m² per minute, Braun-Melsungen, Melsungen, FRG), and somatostatin (350 µg/hr, Ribopharm, Haan, FRG) was started on the contralateral arm. The infusion was given for 180 minutes, during which further blood samples were obtained at 30-minute intervals for 90 minutes and thereafter every 15 minutes. A final blood sample was drawn 15 minutes after the end of the infusion.

Throughout the study, dietary compliance was assessed by measuring the daily 24-hour urinary sodium,

chloride, potassium, and creatinine excretion by standard laboratory methods. Subjects were considered compliant when sodium and chloride excretion was <35 mmol per 24 hours during the last 3 days of the low salt period and >200 mmol per 24 hours during the last 3 days of the high salt period.

Laboratory Procedures

Plasma and urinary sodium and potassium were measured by an Ionometer EF (Fresenius, Bad Homburg, FRG), chloride by a Chloride Analyzer 925 (Ciba-Corning, Fernwald, FRG), and plasma glucose by a Glucose Analyzer 2 (Beckman Instruments, Munich, FRG). A radioimmunoassay was used for measuring insulin (Biermann, Bad Nauheim, FRG) and C-peptide (Serono, Freiburg, FRG).

Data Analysis

Statistical analysis was performed using the SPSS/PC+ software package (SPSS Inc., Chicago). Data are reported as mean ± SD. Differences were considered significant at a value of $p < 0.05$.

As in previous studies, salt sensitivity was defined as a significant drop in mean arterial pressure >3 mm Hg during the low salt diet^{19,20,22,30} calculated as the difference between the average of the 60 readings under the high and low salt periods ($p < 0.05$, two-tailed t test for independent samples). The SEM for a single 60-minute period ranged between 0.36 and 0.65 mm Hg. Subjects whose blood pressure did not change or increased on the low salt diet were considered salt resistant. We have previously shown salt sensitivity defined thus to be a well-reproducible phenomenon in normotensive individuals.²²

During the insulin suppression test, between-group and within-group differences over time on both diets were assessed by two-way repeated-measures analysis of variance (ANOVA) for time-related changes. Steady-state plasma glucose (SSPG) and insulin (SSPI) levels were calculated as the means of the measurements made at 150, 165, and 180 minutes during the insulin suppression test, as previous studies have indicated that steady-state conditions are reached within 150 minutes.^{26,27} The two-tailed Student's t test for independent and paired samples was used to analyze the between- and within-group effects of the dietary regimens on plasma variables and blood pressure at baseline and on the SSPG and SSPI levels during the insulin suppression test. Because the steady-state plasma glucose-to-insulin ratio (SSPG/SSPI) was not normally distributed in the salt-sensitive group, this variable was compared between the groups by the nonparametric Mann-Whitney U test. The relation between selected variables was tested by calculating Pearson's correlation coefficient.

Results

Five of the seven subjects considered salt sensitive according to the above definition had a positive familial history of hypertension, whereas only two of the 11 salt-resistant subjects had positive familial histories. One salt-resistant subject had a positive familial history of diabetes but not of hypertension. There was no difference in either age (25.6 ± 3.1 versus 24.4 ± 1.7 years) or body mass index (22.1 ± 1.4 versus 22.2 ± 2.0 kg/m²) between the salt-resistant and salt-sensitive groups. Because of mild thrombophlebitis after glucose

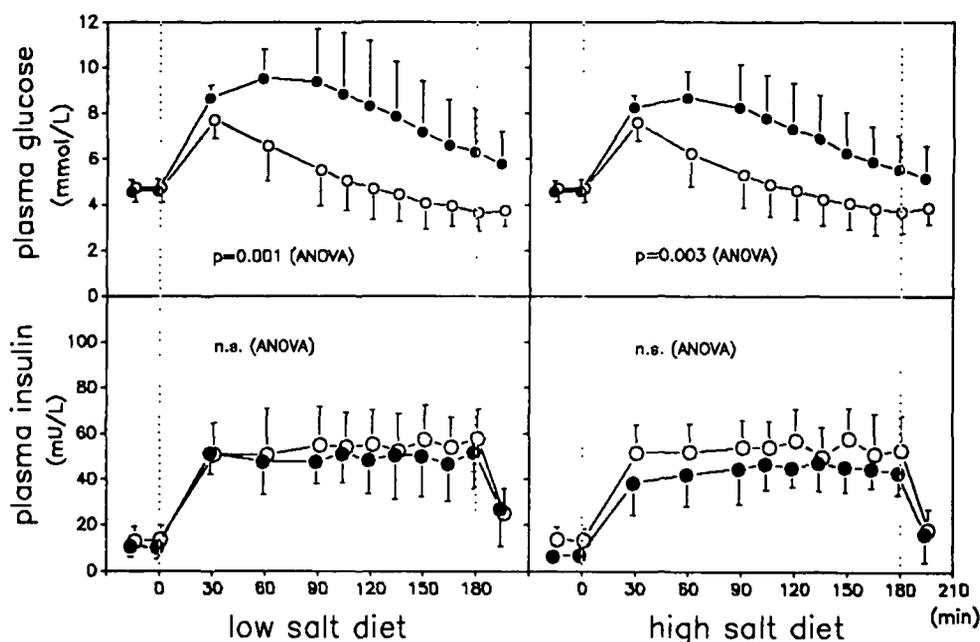


FIGURE 1. Plots show time course of plasma glucose and insulin during insulin suppression test in salt-resistant (\circ , $n=11$) and salt-sensitive (\bullet , $n=7$) normotensive men on a low and high salt diet (mean \pm SD).

infusion on the high salt regimen, the insulin suppression test was not repeated in one salt-sensitive subject on the subsequent low salt diet.

During the insulin suppression test, plasma glucose levels were significantly higher in the salt-sensitive than in the salt-resistant group by two-way ANOVA on both the low ($p=0.001$) and the high ($p=0.003$) salt diet (Figure 1), whereas plasma insulin levels were similar in the two groups under both regimens. SSPG after 150–180 minutes of glucose infusion was $>50\%$ higher in the salt-sensitive than in the salt-resistant group on both the low (3.9 ± 0.9 [SD] versus 6.7 ± 2.0 mmol/L, $p=0.001$) and the high (3.8 ± 1.1 versus 5.9 ± 1.6 mmol/L, $p=0.005$) salt diet. Likewise, SSPG/SSPI was almost twice as high in the salt-sensitive than in the salt-resistant group on both diets ($p \leq 0.005$) (Figure 2). Dietary salt intake had no significant effect on SSPG or SSPG/SSPI in either group. Transient hyperglycemia was observed in two salt-sensitive subjects during the early part of the insulin

suppression test (11.5 and 12.25 mmol/L), and hypoglycemia (2.45 mmol/L) was observed in one salt-resistant subject under steady-state conditions. Insulin infusion in both groups consistently resulted in a similarly small but significant ($p < 0.001$, ANOVA) reduction in plasma potassium levels of approximately 0.15 mmol/L at 180 minutes. Plasma levels of sodium and chloride did not change significantly during the insulin suppression test. During the infusion, C-peptide levels decreased to <0.05 $\mu\text{g/L}$ in all subjects and remained at that level throughout the insulin suppression test, indicating effective inhibition of endogenous insulin release by somatostatin.

Although there was no significant difference in blood pressure between the salt-sensitive and the salt-resistant subjects on the low salt diet (Table 1), blood pressure on the high salt diet was by definition higher in the salt-sensitive than in the salt-resistant group. Mean arterial blood pressure in the salt-sensitive group was 6.6 ± 4.4 mm Hg lower with salt restriction than on the high salt diet ($p < 0.005$). When both groups were analyzed together, there were significant correlations between SSPG/SSPI and systolic ($r=0.58$, $p=0.01$), diastolic ($r=0.48$, $p=0.04$), and mean ($r=0.56$, $p=0.01$) arterial pressures under this regimen, indicating a positive relation between blood pressure and insulin sensitivity on the high salt diet.

Urinary and plasma electrolytes changed as expected under the dietary regimens and were not significantly different between the two groups (Table 1).

Discussion

Our data demonstrate the presence of insulin resistance in young, lean salt-sensitive normotensive subjects as evidenced by consistently higher plasma glucose levels during the insulin suppression test, reflecting reduced insulin-mediated glucose disposal. This finding is well in line with our previous demonstration of a

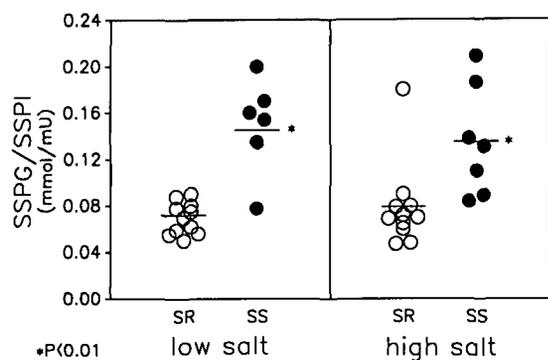


FIGURE 2. Plots show steady-state plasma glucose (SSPG)/insulin (SSPI) quotients during insulin suppression test in salt-resistant (SR, \circ) and salt-sensitive (SS, \bullet) normotensive men on a low and high salt diet.

TABLE 1. Physical, Plasma, and Urinary Variables in Young Normotensive Salt-Resistant and Salt-Sensitive Men on Low and High Salt Diet

| Parameter | Salt resistant (n=11) | | Salt sensitive (n=7) | |
|-------------------------|-----------------------|------------|----------------------|------------|
| | Low salt | High salt | Low salt | High salt |
| Systolic BP (mm Hg) | 110.5±8.1 | 107.6±6.7 | 106.7±5.8 | 115.9±4.6* |
| Diastolic BP (mm Hg) | 57.2±5.7 | 54.3±6.1 | 56.0±4.8 | 61.6±4.7* |
| Mean BP (mm Hg) | 79.4±3.8 | 76.7±4.1 | 77.2±5.5 | 83.8±4.7* |
| Weight (kg) | 71.2±6.4 | 72.4±6.2 | 67.1±6.1 | 68.4±6.2 |
| Plasma variables | | | | |
| Glucose (mmol/L) | 4.7±0.2 | 4.7±0.2 | 4.6±0.2 | 4.6±0.3 |
| Insulin (milliunits/L) | 13.8±5.9 | 13.4±5.2 | 10.4±5.2 | 7.7±3.2 |
| Sodium (mmol/L) | 135.0±1.0 | 137.8±1.6† | 135.0±0.6 | 137.6±0.6† |
| Chloride (mmol/L) | 101.8±1.9 | 105.4±1.2† | 101.4±1.9 | 104.9±0.8† |
| Potassium (mmol/L) | 4.2±0.2 | 4.1±0.2 | 4.1±0.2 | 4.0±0.1 |
| Urine variables | | | | |
| Volume (mL/24 hrs) | 1,334±169 | 1,977±301† | 1,420±182 | 1,731±153† |
| Sodium (mmol/24 hrs) | 12±3 | 230±16† | 25±3 | 242±14† |
| Chloride (mmol/24 hrs) | 16±2 | 240±16† | 30±3 | 265±14† |
| Potassium (mmol/24 hrs) | 43±5 | 46±4 | 45±3 | 55±3 |

BP, blood pressure. Values are mean±SD.

* $p \leq 0.01$ vs. salt resistant and $p \leq 0.01$ vs. low salt.

† $p < 0.01$ vs. low salt.

hyperinsulinemic response to oral glucose in normotensive salt-sensitive subjects.¹⁹ Together with earlier reports on abnormal glucose tolerance in patients with mild hypertension,^{4,31} on mildly elevated blood pressure levels in subjects with impaired glucose tolerance,³² on the positive correlation of blood pressure with basal insulin levels in normotensive subjects,^{11,33,34} and on a hyperinsulinemic response to an intravenous glucose load in normotensive individuals with a positive familial history of hypertension,³⁵ our findings support the hypothesis that an abnormality of carbohydrate metabolism exists before the development of overt hypertension in genetically hypertension-prone individuals.

In this study, insulin resistance was assessed by the insulin suppression test.^{26,27} The measure of insulin resistance obtained by this test has been shown to be well reproducible and to closely correlate to insulin resistance as assessed by the euglycemic insulin-clamp technique over a wide range of insulin sensitivity.²⁷ However, some limitations of this test must be considered. As with the insulin-clamp technique, steady-state plasma glucose levels during the insulin suppression test represent the sum of insulin-mediated and non-insulin-mediated glucose disposal minus endogenous glucose production. Transient hyperglycemia (>10 mmol/L) during the insulin suppression test as observed in some of our salt-sensitive individuals may increase the proportion of non-insulin-mediated glucose disposal.²⁵ On the other hand, hypoglycemia (<2.5 mmol/L), as observed in one of our salt-resistant subjects, may lead to a counter-regulatory rise in plasma glucose.²⁵ These factors could have resulted either in an underestimation of insulin resistance in the former or in an underestimation of insulin sensitivity in the latter case.²⁵ Thus, the difference in insulin sensitivity between the salt-sensitive and the salt-resistant subjects in our study may have been even somewhat greater than indicated by our data.

Insulin resistance associated with hyperinsulinemia may be related to salt sensitivity.¹⁵⁻¹⁸ This hypothesis was suggested by the following observations: 1) hyperinsulinemia can stimulate renal sodium reabsorption, resulting in sodium retention¹²; 2) plasma levels of insulin correlate to salt-induced changes in blood pressure in obese subjects, and improvement of insulin sensitivity by weight reduction is associated with decreased salt sensitivity in these individuals¹⁶; 3) a hyperinsulinemic response to oral glucose has been demonstrated in normotensive salt-sensitive men¹⁹; and 4) essential hypertension sensitive to salt intake is commonly found in obesity,^{16,36} NIDDM,^{36,37} and nonobese hypertensive subjects.^{24,30} All of these conditions are now known to be associated with insulin resistance.^{5,16,17} Our data, providing conclusive evidence that insulin resistance is also present in lean salt-sensitive normotensive subjects, are compatible with the hypothesis that insulin resistance associated with sustained or intermittent (postprandial) hyperinsulinemia may be the underlying common denominator accounting for salt sensitivity in all these states.

Several lines of evidence indicate that salt-sensitive normotensive individuals are genetically prone to the development of hypertension. Genetic determination of salt sensitivity is indicated by evidence from twin studies²¹ and by its strong relation to a positive family history of hypertension,^{20,22} to the haptoglobin 1-1 phenotype,³⁸ and to certain human leukocyte antigens.²⁰ Furthermore, recent data showing that salt-sensitive individuals experience a greater rise in blood pressure with time than salt-resistant controls suggest that salt-sensitive individuals are prone to the later development of hypertension.^{23,24} Salt-sensitive normotensive subjects display several characteristics frequently found in patients with salt-sensitive essential hypertension, including increased pressor responsiveness to norepinephrine^{20,39} and angiotensin,³⁹ increased forearm vas-

cular resistance,⁴⁰ decreased venous compliance,²⁴ suppressed plasma renin activity,^{24,30} lower plasma aldosterone concentrations,^{20,24,30} upregulation of the α_2/β_2 -adrenergic receptor ratio,⁴¹ and mild metabolic acidosis.⁴² Our finding of insulin resistance now adds to this list of abnormalities common to both salt-sensitive normotensive and hypertensive individuals, indicating that increased blood pressure is the rather late clinical manifestation of a syndrome that begins long before the individual becomes overtly hypertensive.

The mechanisms underlying insulin resistance were not examined in this study. However, findings in patients with essential hypertension indicate that impaired glucose disposal predominantly involves nonoxidative glucose disposal in skeletal muscle and therefore may involve an abnormality of glycogen synthesis.⁸ A similar defect in nonoxidative glucose disposal could be operative in our salt-sensitive normotensive subjects. However, other possible mechanisms must also be considered. It has been suggested that insulin resistance in patients with hypertension may be secondary to abnormal intracellular concentrations of calcium,⁴³ magnesium,⁴⁴ or sodium⁴⁵ and that similar abnormalities may be present in normotensive hypertension-prone individuals.^{46,47} On the other hand, insulin is known to have a significant effect on several transmembrane ion-exchange systems, including Na^+, K^+ -ATPase,⁴⁸ $\text{Ca}^{2+}, \text{Mg}^{2+}$ -ATPase,⁴³ and Na^+/H^+ -exchanger,⁴⁹ and therefore hyperinsulinemia may in itself be partly responsible for the intracellular cation imbalance rather than vice versa. Whatever the mechanisms involved, it is evident that the abnormality in insulin sensitivity found in our salt-sensitive subjects is not secondary to hypertension but rather precedes the development of high blood pressure in these genetically hypertension-prone men.

It has been suggested that hyperinsulinemia secondary to insulin resistance could directly contribute to hypertension by activation of the sympathetic nervous system or enhancement of sodium reabsorption.^{17,18} Yet, a causal relation between hyperinsulinemia resulting from insulin resistance and high blood pressure in humans still remains to be proved. It is important in this context to note that hyperinsulinemia per se, as encountered in patients with insulinoma, is not associated with hypertension.⁵⁰ However, in this condition, insulin could fail to raise blood pressure because of several factors, including counter-regulatory mechanisms secondary to hypoglycemia, lack of genetic susceptibility to hypertension, or the vasodilator effects of excessively high insulin levels.⁵¹ Furthermore, the insulin resistance associated with hypertension and obesity appears to be selective for the effect of insulin on glucose disposal, because the effects of insulin on renal sodium reabsorption⁵² and sympathetic nervous activity⁵³ remain normal. In contrast, the hyperinsulinemia associated with insulinoma or the administration of exogenous insulin could lead to a nonselective downregulation of insulin receptors,⁵⁴ thus resulting in a form of insulin resistance that may decrease both the insulin effects on glucose uptake and those on sodium homeostasis and sympathetic nervous activity. "Selective" insulin resistance thus could be the prerequisite for the development of insulin-induced hypertension. Nevertheless, because both insulin resistance^{55,56} and salt-sensitive hypertension^{21,30} are well known to be genetically determined, one must also

consider the possibility that insulin resistance and salt sensitivity in genetically hypertension-prone individuals could represent parallel, independent phenotypes in predisposed individuals.

In our previous study, dietary salt restriction appeared to ameliorate the hyperinsulinemic response to oral glucose in salt-sensitive individuals.¹⁹ In contrast, in this study, salt restriction had no significant effect on insulin sensitivity in either group. The most likely explanation for this discrepancy is that in our previous study, preceding salt intake may have significantly affected intestinal glucose reabsorption, at least in the salt-sensitive group. In fact, salt is well known to increase glucose absorption from the gut.^{57,58} Thus, accelerated glucose absorption on the high salt diet may have exacerbated the insulin response in the salt-sensitive group in the presence of insulin resistance, whereas in the salt-resistant group, glucose tolerance remained normal. On the other hand, delayed glucose absorption in the absence of a high salt intake may have ameliorated glucose intolerance in the salt-sensitive individuals without, however, directly affecting insulin sensitivity.

Our demonstration of insulin resistance in young, normotensive hypertension-prone individuals could have important implications both for understanding the pathogenesis of hypertension and for the development of preventive strategies in these individuals. First, hyperinsulinemia associated with insulin resistance per se may increase the risk for cardiovascular disease⁹⁻¹¹ in these normotensive salt-sensitive individuals even before they become overtly hypertensive. Second, the intermittent increase in blood pressure, mediated by a high salt intake in the presence of insulin resistance in combination with a proliferative effect of insulin on vascular smooth muscle cells,⁵⁹ may, in the course of time, contribute to the development of structural changes in the systemic and renal vascular beds, thus eventually contributing to the development of sustained hypertension. Finally, our data provide a rationale for implementing preventive measures such as exercise and weight control, primarily aimed at improving insulin sensitivity⁶⁰ in these salt-sensitive individuals, as has recently been recommended for the prevention of NIDDM.⁶¹ If, as suggested by our data, insulin resistance by itself contributes to salt sensitivity, increasing insulin sensitivity could abolish the effect of salt intake on blood pressure, thus neutralizing one of the primary environmental factors contributing to the development of hypertension in these individuals.

In summary, we have shown that salt sensitivity in young, lean normotensive individuals is associated with decreased insulin-mediated glucose disposal and thus insulin resistance. This finding implies that insulin resistance is present in otherwise healthy, hypertension-prone individuals before overt hypertension develops. Early recognition of insulin resistance and the implementation of measures aimed at improving insulin sensitivity could be important for the prevention of cardiovascular disease in these individuals.

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