Insulin and Renal Sodium Retention in Obese Adolescents

Albert P. Rocchini, Victor Katch, Daniel Kveselis, Catherine Moorehead, Monica Martin, Richard Lampman, and Melissa Gregory

The effect of insulin on the renal handling of sodium was studied in obese and nonobese subjects by using euglycemic hyperinsulinemia. Seven water-loaded obese (14–19 years old) and five nonobese young adults (18–21 years old) had insulin given intravenously at a rate of 40 munits/m²/min. Blood glucose and creatinine clearance were not altered by euglycemic hyperinsulinemia in either the obese or the nonobese group. Hyperinsulinemia resulted in a significant decrease in urinary sodium excretion in both groups of subjects (by 54.2±3% [mean±SEM] in the obese and by 50.9±3.1% in the nonobese group). However, the amount of glucose required to maintain euglycemia was significantly less in the obese versus nonobese group, 89.5±6.2 versus 329.2±16 mg glucose/m²/min (p<0.001). There was no relation in either group between the amount of glucose required to maintain euglycemia and the change in urinary sodium excretion. On a separate day, all of the obese subjects underwent 3 hours of water diuresis but without insulin. There was no change in urinary sodium excretion with sustained water diuresis alone. However, when compared with the nonobese group, the obese group of subjects had a significantly higher resting mean arterial pressure, heart rate, and plasma norepinephrine concentration; during the insulin clamp, neither group experienced a significant change in mean arterial pressure or heart rate, and only the nonobese group experienced an increase in plasma norepinephrine. In obese subjects, we have found, despite the presence of insulin resistance to carbohydrate metabolism, that euglycemic hyperinsulinemia was associated with a normal decrease in urinary sodium excretion. Therefore, the data support the hypothesis that insulin resistance with respect to glucose metabolism leads to hyperinsulinemia, which in turn could lead to chronic sodium retention. (Hypertension 1989;14:367–374)

Studies conducted on subjects with essential hypertension,1,2 obesity,3–5 or non-insulin-dependent diabetes mellitus6 have demonstrated an association between hyperinsulinemia and hypertension. Numerous in vitro and in vivo studies have been published documenting that physiological changes in plasma insulin concentration are capable of altering electrolyte transport by the kidney.7–12 Since obesity is associated with hyperinsulinemia and insulin resistance, it has been suggested that obesity hypertension may in part be due to a direct effect of insulin on the kidney to cause enhanced sodium retention.13–15 However, to date it has not been demonstrated in obese subjects that, despite the presence of insulin resistance to glucose uptake, the kidney still remains sensitive to the sodium-retaining actions of insulin. In fact, Kolanowski et al16 observed no reduction in sodium excretion when insulin, without glucose, was infused into fasting obese subjects. Thus, the present study was undertaken to determine if young obese subjects were insulin resistant to glucose uptake yet still sensitive to the renal sodium-retaining effects of insulin.

Subjects and Methods

Subjects

The study group consisted of seven white obese males, 14–19 years old, and five white nonobese males, 18–21 years old. All but the 14-year-old were sexually mature (Tanner stage V17). Family history of all of the subjects was negative for diabetes, and only one of the obese subjects had a positive family history for hypertension. To be able to administer a
comparable amount of insulin to the two groups of subjects, the nonobese and obese subjects were matched for body surface area. Obesity was defined as height for weight greater than the 75th percentile and triceps and subscapular skin fold thickness greater than the 80th percentile for age and sex.18,19 The triceps and subscapular skin folds of the obese subjects were 24±0.5 (mean±SEM) and 22±0.7 mm, respectively, and for the nonobese subjects were 6.2±1 and 6.8±0.9 mm, respectively. All obese subjects had been obese for at least 4 years and were felt to have exogenous obesity, as documented by a normal physical examination, normal thyroid function, and normal cortisol levels. None of the subjects were receiving medications, and all were free of any medical illness including renal, liver, endocrine, or cardiovascular disease. The subjects were placed on a diet containing more than 250 meq/day sodium by supplementation with five 1-g sodium chloride tablets per day for 2 weeks. Twenty-four-hour urinary sodium excretion, collected on the day before the euglycemic clamp study, was not significantly different between the two groups (nonobese, 214±35 vs. obese, 258±42 meq/day). The anthropometric, blood pressure, and heart rate data from the two groups of subjects are summarized in Table 1. None of the subjects were engaged in either a regular exercise program or competitive sports, and all were asked to avoid strenuous exercise on the day before the study. The research protocol was approved by the Clinical Research Center and the Human Subjects Research Review Committee of the University of Michigan Medical Center. All subjects or parents gave informed consent before participating in the study.

Procedures

All subjects were in a fasting condition from 8:00 PM of the day preceding the clamp. On the day of the euglycemic clamp, all subjects were asked to awaken at 7:00 AM and drink 500–1,000 ml water before reporting to the Clinical Research Center at 7:30 AM. With the subjects in a semisupine position, polyethylene cannulas were inserted into an antecubital vein in one arm and into a dorsal hand vein in the other arm. The subjects remained semisupine (45° elevation) throughout the study. The subjects replaced the volume of each voiding by taking water orally to achieve steady-state water diuresis. After a 30-minute equilibration period of sustained water diuresis, three consecutive 30-minute urine collections were obtained. The urine was analyzed for glucose, sodium, potassium, and creatinine. Arterialized blood samples were obtained at the midpoint of each clearance period for sodium, potassium, creatinine, norepinephrine, plasma renin activity, and aldosterone. Blood pressure and heart rate were determined every 15 minutes with an Air- Shields (Healthdyne Co., Hartboro, Pennsylvania) automated blood pressure recorder and an appropriately sized blood pressure cuff.20 The blood pressure cuff was placed on the arm that was not receiving the glucose and insulin infusion.

After the third 30-minute control period, a primed, constant infusion of insulin was administered that started at a dose of 800 munits/m², exponentially decreased over 10 minutes, and was followed by a constant dose of 40 munits/m²/min.21 Concomitantly with the insulin, an intravenous infusion of 20% glucose was administered by a variable infusion syringe pump (Harvard Apparatus, Millis, Massachusetts). Blood samples were obtained at 5-minute intervals for determination of blood glucose concentration. The glucose infusion rate was varied every 5 minutes to hold the plasma glucose concentration constant at baseline. The amount of glucose required to maintain euglycemia equals whole-body disposal of glucose, provided that endogenous glucose production is negligible. Although endogenous glucose production was not measured in this study, it seems likely, based on the report of Kolterman et al,22 that endogenous glucose production was suppressed by 50–70% in our obese patients. Blood insulin values were obtained every 15 minutes. Blood and urine samples were collected every 30 minutes for 90 minutes as in the preinsulin control period.

Control Water Diuresis Studies

To confirm that water diuresis did not affect urinary electrolyte excretion, all obese subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Insulin</th>
<th>Nonobese</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt (kg)</td>
<td>82.2±7</td>
<td>. . .</td>
<td>70.3±3</td>
<td>. . .</td>
</tr>
<tr>
<td>Wt/Ht² (kg/m²)</td>
<td>34.2±2</td>
<td>. . .</td>
<td>21.9±1</td>
<td>. . .</td>
</tr>
<tr>
<td>Surface area (m²)</td>
<td>1.86±0.07</td>
<td>. . .</td>
<td>1.87±0.04</td>
<td>. . .</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>132.0±2*</td>
<td>135.0±2*</td>
<td>118.0±2</td>
<td>123±4</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80.0±1*</td>
<td>82.0±2*</td>
<td>78.0±1</td>
<td>75±1</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>98.0±1*</td>
<td>99.0±2*</td>
<td>86.0±1</td>
<td>88±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79.0±3*</td>
<td>79.0±6*</td>
<td>65.0±5</td>
<td>66±3</td>
</tr>
</tbody>
</table>

Values are mean±SEM for the 90 and 180 min values. Wt, weight; Ht, height; SBP, systolic blood pressure; DBP, diastolic blood pressure; Mean BP, mean blood pressure.

*p<0.01 obese vs. nonobese.
were studied on alternate days and in a random sequence, under similar conditions of sustained water diuresis and semisupine recumbency, but without insulin administration. The obese subjects were all admitted overnight to the Clinical Research Center and maintained on the high sodium diet. The insulin clamp studies and water diuresis alone were performed on two separate days. The total duration of the control water diuresis was also 210 minutes. During the period of water diuresis without insulin administration, two intravenous cannulas were inserted, and blood and urine were collected in the exact fashion as in the insulin clamp study.

Laboratory Procedures

Plasma glucose was assayed by the glucose oxidase method (Beckman Glucose Analyzer, Beckman Instr., Fullerton, California). Plasma insulin, plasma renin activity, and plasma aldosterone were measured by radioimmunoassay. Plasma and urine sodium and potassium were measured by flame photometry. Plasma norepinephrine was measured by high-performance liquid chromatography with electrochemical detection.23

Statistical Analysis

All data are expressed as mean±SEM. Student's t test was used to assess differences between the obese and nonobese groups for blood pressure, heart rate, weight, and body mass index before the clamp study. Within each group, a repeated-measures analysis of variance was performed for each variable to determine whether a significant change in that variable occurred as a result of the insulin infusion. A two-factor analysis of variance for repeated measures was then performed for each variable to assess differences between the obese and nonobese groups and between water diuresis with and without insulin. For the two-way analysis of variance, all values were normalized to the preclamp values.

Results

Insulin and Glucose

In the fasting state, plasma glucose levels were similar in the obese and nonobese groups (90.5±1.9 vs. 86.5±1.7 mg/dl), whereas fasting insulin levels were significantly elevated in the obese group (30.1±3.4 vs. 7.5±2.1 μunits/ml, p<0.01). During the euglycemic insulin clamp period (Figure 1), insulin levels increased by the same amount in both obese and nonobese groups, but because fasting insulin levels were higher in the obese group, the plateau insulin values obtained during the 40 munit/m2/min infusion were higher in the obese group (mean value over the last 30 minutes in obese vs. nonobese group, 144±11 vs. 119±11 μunits/ml) (Table 2). Glucose levels remained unchanged from preclamp fasting values in both the obese and nonobese groups (mean value over last 30-minute period in obese vs. nonobese group, 86±1.1 vs. 87.9±3.1 mg/dl). However, in comparison with the nonobese group, the amount of glucose required to maintain euglycemia was significantly less in the obese group (Figure 1) (mean glucose infused during the insulin clamp in the obese vs. nonobese group, 2.18±0.45 vs. 8.9±0.51 mg glucose/kg/min or 89.5±6.2 vs. 329.2±16 mg glucose/m2/min, p<0.001). None of the subjects experienced any glucosuria either before, during, or after the insulin clamp.

Urine and Serum Sodium

Serum sodium concentrations were similar in the obese and nonobese groups both before and after the euglycemic insulin clamp (137±1 vs. 138±0.8 meq/l preinsulin and 138±0.2 vs. 138±0.8 meq/l after 90 minutes of the insulin clamp). Figure 2 demonstrates that, in both the obese and the nonobese groups, sodium excretion was significantly reduced during the euglycemic insulin clamp (p<0.01). We observed no difference between the two groups in the percent change in urinary sodium excretion (Table 2) (obese 54.2±2.8 vs. nonobese 50.2±3%). As can also be seen in Table 2, there was not a significant relation between plateau insulin
TABLE 2. Plasma Insulin Concentrations and Percent Change in Urinary Sodium Excretion During a Euglycemic Insulin Clamp in Obese and Nonobese Subjects

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Peak insulin (μunits/ml)</th>
<th>Percent change in UNaV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>140</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>109</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>184</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>160</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>152</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>149</td>
<td>56</td>
</tr>
<tr>
<td>Nonobese subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>142</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>122</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>85</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>138</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>109</td>
<td>52</td>
</tr>
</tbody>
</table>

Percent change in urinary sodium excretion (UNaV) was calculated as follows: [(Control UNaV (average preinsulin) - UNaV during the last 30-minute urine collection) / (Control UNaV)] *100

values attained during euglycemic insulin clamp and the percent change in urinary sodium excretion that also occurred. Both the obese and nonobese groups of subjects experienced a significant decrease in sodium clearance and fractional sodium excretion during euglycemic hyperinsulinemia (Table 3).

Urine and Serum Potassium

Baseline serum potassium concentrations were significantly lower in the obese group (3.9±0.08 vs. 4.4±0.08 meq/l, p<0.05), and after 90 minutes of the euglycemic insulin clamp, serum potassium decreased in both groups (3.51±0.03 vs. 3.57±0.11 meq/l, obese vs. nonobese). Since baseline serum potassium was significantly higher in the nonobese group before the insulin clamp, the percent decrease in serum potassium that occurred during the insulin infusion was significantly greater in the nonobese group (p<0.05, Table 2). Therefore, it appears that an increased potassium uptake may have occurred in the nonobese versus the obese group of subjects. Figure 3 demonstrates that, during the insulin clamp, urinary potassium excretion was decreased to the same extent in the obese and nonobese groups.

Blood Pressure, Heart Rate, and Plasma Norepinephrine, Aldosterone, and Renin Activity

Compared with the nonobese group, the obese group had a significantly elevated mean arterial pressure and heart rate (p<0.01, Table 1). However, neither group experienced a significant change in either mean arterial pressure or heart rate during the euglycemic insulin clamp.

Before the insulin clamp, the obese group had a significantly increased plasma norepinephrine concentration (374±57 vs. 288±36 pg/ml, p<0.05). During the clamp study, only the nonobese group experienced a change in norepinephrine concentration (increasing from 288±36 to 373±28 pg/ml, p=0.052) (Figure 4).

Plasma renin activity and aldosterone concentration did not change in either the obese or nonobese group during euglycemic hyperinsulinemia.

Control Water Diuresis Studies

Two hundred and ten minutes of water diuresis alone did not cause any significant change in urine or serum electrolyte concentrations, plasma norepinephrine, blood pressure, or heart rate (Figures 2 and 4). Similar results have been reported by DeFronzo et al10 in nonobese adults.

Discussion

In the present study, we demonstrated for the first time that young obese subjects, despite being insulin resistant with respect to glucose metabolism, were still as sensitive as nonobese subjects to the effect of insulin on the renal handling of sodium and potassium. Glucose uptake in our obese subjects and glucose uptake and the insulin-induced reduction in urinary sodium and potassium excretion in our nonobese subjects were similar to those previously reported by Kolterman et al22 and DeFronzo et al,10 respectively, although the insulin clamp in the present study was only 90 minutes in duration.

However, a limitation of the present study is that hepatic glucose output was not measured. Kolterman et al22 have demonstrated that, in nonobese subjects, 100% suppression of hepatic glucose output occurred at insulin levels of 100–150 μunits/ml...
Table 3. Effect of Insulin on Serum and Urine Electrolytes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Insulin</th>
<th>Control</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{Na}}/C_{\text{o}} \times 100 )</td>
<td>2.18±0.39</td>
<td>1.07±0.19*</td>
<td>1.94±0.51</td>
<td>1.02±0.41*</td>
</tr>
<tr>
<td>( C_{o}/C_{\text{Cr}} \times 100 )</td>
<td>18.50±2.3</td>
<td>9.6±1.20*</td>
<td>16.9±2.8</td>
<td>8.74±1.6*</td>
</tr>
<tr>
<td>( C_{\text{K}} ) (mg/ml)</td>
<td>122.00±8.6†</td>
<td>124.00±7.5†</td>
<td>107.00±8.5</td>
<td>111.00±10</td>
</tr>
<tr>
<td>%Change ( U_{\text{Na}}V )</td>
<td>...</td>
<td>53.90±1.1</td>
<td>...</td>
<td>50.00±3.1</td>
</tr>
<tr>
<td>%Change ( U_{\text{K}}V )</td>
<td>...</td>
<td>46.00±6</td>
<td>...</td>
<td>45.12±5.0</td>
</tr>
<tr>
<td>%Change ( K )</td>
<td>...</td>
<td>11.20±0.02</td>
<td>...</td>
<td>18.86±0.02†</td>
</tr>
</tbody>
</table>

Mean ± SEM for 90- and 180-minute values. \( C_{\text{Na}}/C_{\text{o}} \times 100 \), fractional sodium excretion; \( C_{o}/C_{\text{Cr}} \times 100 \), fractional potassium excretion; \( C_{\text{Cr}}\), creatinine clearance; \( U_{\text{Na}}V \), urinary sodium excretion; \( U_{\text{K}}V \), urinary potassium excretion; \( K \), serum potassium.

*\( p<0.01 \) insulin vs. control; †\( p<0.05 \) obese vs. nonobese.

(values reached in our subjects), but only 50-70% suppression of hepatic glucose production was observed in their obese subjects. Therefore, it is possible that part of the explanation for the difference in the amounts of glucose required to maintain euglycemia in our obese and nonobese subjects could be the result of different degrees of suppression of hepatic glucose output. However, since basal hepatic glucose production is 66 mg/m²/min or 1.8 mg/kg/min, the possible differences in degree of suppression of hepatic glucose output between the obese and nonobese subjects can explain only a small portion of the observed differences between the obese and nonobese subjects in the amount of glucose required to maintain euglycemia. Thus, our data suggest that, compared with the nonobese subjects, our obese subjects were insulin resistant with respect to glucose uptake.

Despite the fact that all subjects, both obese and nonobese, received a comparable amount of insulin (40 munits/m²/min) the average insulin value of the obese group during the last 60 minutes of the euglycemic insulin clamp was higher. Although we are not certain exactly why plasma insulin was higher in the obese group, we believe that it may have been due to the higher fasting insulin concentration that was present in the obese subjects or due to a diminished hepatic insulin extraction that has been reported to occur in some obese subjects. It is possible, because the plateau insulin concentrations during the insulin clamp were higher in the obese versus the nonobese subjects, that had the insulin been the same in both groups of subjects, a difference in the decrease in urinary electrolyte excretion may have been observed between the obese and nonobese subjects. However, this does not appear to be the case. Although the obese subjects as a group achieved a higher plasma insulin concentration during the insulin clamp, there was considerable overlap in insulin concentrations between the obese and nonobese groups, and there was no relation observed between plasma insulin level reached during the insulin clamp and the percent decrease in urinary electrolyte excretion (Table 2). In addition, the six nonobese subjects reported by DeFronzo et al achieved plasma insulin values during the insulin clamp that were higher.
than those observed in our seven obese subjects, yet DeFronzo's subjects experienced a decrease in urinary electrolyte excretion similar to that which was observed in our subjects. Further studies using multiple doses of insulin will need to be performed before it can be definitively concluded that no differences in the renal actions of insulin exist between obese and nonobese subjects.

Another limitation of the present study is that the obese subjects were younger than the nonobese subjects. Although the obese subjects were sexually mature, as assessed by Tanner staging, it is likely that they had not yet achieved their ultimate height. Since Amiel et al.25 have previously demonstrated that insulin-stimulated glucose metabolism was reduced in pubertal children, it is possible that part of the insulin resistance observed in the obese group was due to their pubertal status. However, the insulin-stimulated glycol metabolism observed in our obese adolescents was still significantly lower than that reported by Amiel et al.25 for pubertal boys (89.5 ± 6.2 vs. 199 ± 16 mg/m²/min, p < 0.01). In addition, pubertal status cannot explain the differences in insulin sensitivity between tissues that were observed in our obese adolescents.

Whether insulin acts directly on the renal tubules to enhance sodium retention or through some other indirect mechanism was not independently tested in the present study. However, based on observations from our study and the previous reports of others, it seems likely that the reduction in urinary sodium excretion that occurred during euglycemic hyperinsulinemia was due to the direct action of insulin on the renal tubules. More specifically, in vitro and in vivo studies have suggested that insulin exerts a direct effect on the renal tubule to promote sodium and potassium retention.7–12 DeFronzo et al.10 in 1975, demonstrated in nonobese men that insulin administration causes a reduction in urinary sodium and potassium excretion, independent of changes in the filtered load of glucose, glomerular filtration rate, and plasma aldosterone. Since insulin also caused an increase in water clearance without an increase in urine volume, DeFronzo concluded that insulin acted on the distal nephron (either the thick ascending limb of Henle or the distal convoluted tubule) to promote sodium reabsorption. More recently Baum7 has demonstrated (using in vitro microperfusion studies in the rabbit) that insulin also directly stimulates volume absorption in the proximal convoluted tubule. In the present study, we also demonstrated that insulin promoted renal sodium retention in obese as well as nonobese subjects and that the sodium retention appeared not to be due to water diuresis alone, changes in endogenous creatinine clearance, plasma aldosterone, or plasma norepinephrine.

Since both the administration of catecholamines and the acute stimulation of the renal sympathetic nerves cause increased reabsorption of sodium independent of changes in renal hemodynamics or adrenal steroid secretion, it is possible that the changes in urinary sodium excretion observed during euglycemic hyperinsulinemia were in part due to activation of the sympathetic nervous system.26 The data presented in this study do not support this hypothesis. We did not observe a significant increase in plasma norepinephrine, blood pressure, or heart rate during the insulin clamp in the obese group. In the present study, we have shown that euglycemic hyperinsulinemia is associated with an acute increase in sympathetic tone in our nonobese subjects but not in the obese subjects. Other investigators have also shown that euglycemic hyperinsulinemia is associated with an acute increase in sympathetic tone.27–29 Rowe et al.27 studied the effect of insulin and glucose infusions on sympathetic system activity in 12 nonobese men. They observed that 2 munits/kg/min of insulin infused for 150 minutes did not change mean arterial pressure or heart rate, but did increase plasma norepinephrine (from 240 ± 34 to 360 ± 41 pg/ml). Danforth et al.29 have demonstrated in eight nonobese subjects that euglycemic hyperinsulinemia results in not only an increase in serum norepinephrine concentration but also in norepinephrine appearance rates and clearance. These investigators have also shown that plasma norepinephrine appearance rates and clearance, but not plasma norepinephrine concentration, correlate with resting and insulin/glucose-stimulated energy expenditure. O'Hare et al.28 reported that 200 munits/m²/min insulin (over five times the amount of insulin that was administered in the present study) caused an increase in plasma norepinephrine in eight lean and eight obese subjects. Our results in the obese subjects are in conflict with the report of O'Hare et al.28 The dose of insulin used in our study is smaller than that used in O'Hare's study, and it is possible that, had we used a larger dose of insulin, we also might have seen an increase in plasma norepinephrine in our obese group. Other differences between our study and O'Hare's were that all multiple doses of insulin will need to be performed before it can be definitively concluded that no differences in the renal actions of insulin exist between obese and nonobese subjects.

The mechanism whereby obese subjects are insulin resistant to carbohydrate metabolism, yet still sensitive to the renal effects of insulin is unknown. Other studies in patients with essential hypertension,1 obesity,22,34,35 or non–insulin-dependent diabetes mellitus26 have demonstrated that insulin resistance to glucose uptake may be present despite the fact that some of the other biological effects of insulin are still preserved (i.e., suppression of hepatic
glucose output, lipid oxidation, or promotion of potassium uptake). Considerable evidence exists indicating that resistance to the metabolic effects of insulin in obese subjects resides at the level of the target tissues.22,36-40 Howard et al40 have demonstrated sensitivity to the antilipolytic effects of insulin in obese, maturity-onset diabetes considered to be resistant to the glucose-lowering action of insulin. Kolterman et al,22 using a modification of the euglycemic insulin clamp technique, have documented evidence for receptor and postreceptor defects in obese subjects. Kolterman’s study also suggested that, within an individual, different target tissues can manifest variable degrees of sensitivity or responsiveness to insulin. In the present study, we have also demonstrated, in obese adolescents, that differential tissue sensitivity to insulin appears to be present. Based on the data presented in this study, along with the reports of others, we speculate that in obese subjects insulin sensitivity or responsiveness is decreased to the greatest extent in its ability to affect whole-body glucose uptake, followed to a lesser degree by its ability to promote potassium uptake by body tissues and to stimulate the sympathetic nervous system, and that the ability of insulin to alter the renal handling of electrolytes is the least affected. To accurately assess, in an individual patient, the degree of resistance for each of the biological actions of insulin, dose-response curves would need to be performed.

Recent clinical and epidemiological studies have documented an association between hypertension and hyperinsulinemia in obese and nonobese subjects.1-6,41,42 We,3 as have others, have shown that in obese subjects there is a relation between the degree of insulin resistance to glucose metabolism and the degree of blood pressure elevation.4,5,43 In addition, we have demonstrated in the obese adolescent that the amount of blood pressure reduction that occurred during weight loss produced by the combination of caloric restriction and physical exercise directly related to the degree of improvement in both the fasting insulin concentration and the insulin response to an oral glucose tolerance test. It is well known that obesity is characterized by fasting hyperinsulinemia and excessive insulin secretion to a glucose load.43,44 In obese adolescents, it is not uncommon to find plasma insulin levels exceeding 100 µunits/ml even 2 hours after an oral glucose tolerance test.3 Since we have demonstrated in the present study that young obese subjects are insulin resistant with respect to glucose metabolism, yet still sensitive to the renal sodium-retaining effects of insulin, we believe it is possible that this differential tissue sensitivity to insulin could lead to chronic sodium retention.

References

lin metabolism and peripheral glucose utilization in premenopausal women. J Clin Endocrinol Metab 1987;64:162-169

Key Words • euglycemic clamp • sodium excretion • hyperinsulinemia • insulin
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