Impaired Insulin Action on Skeletal Muscle Metabolism in Essential Hypertension

Andrea Natali, Donatella Santoro, Carlo Palombo, Maurizio Cerri, Sergio Ghione, and Eleuterio Ferrannini

Previous studies have shown that essential hypertension is frequently associated with insulin resistance. The tissues responsible for this metabolic alteration have not been defined. We tested the hypothesis that skeletal muscle is the site of insulin resistance of essential hypertension with the use of the perfused forearm technique. Eight hypertensive (age 42±3 years, body mass index 27±1 kg/m², intra-arterial mean blood pressure 126±4 mm Hg) and seven normotensive (age 48±3 years, body mass index 26±1 kg/m², mean blood pressure 95±4 mm Hg) male volunteers were studied. After glucose ingestion (40 g/m²), normal glucose tolerance in the patients was maintained at the expense of a heightened plasma insulin response, suggesting the presence of insulin resistance. During graded, local (intra-arterial) hyperinsulinemia encompassing the physiological range (12-120 milliunits/l), glucose uptake by forearm tissues was significantly (>0.03) reduced in the hypertensive subjects as compared with the controls at each of five insulin steps, by 43% on the average. In addition, forearm lactate and pyruvate release were significantly less stimulated in the hypertensive than in the normotensive group (p<0.01 for both), presumably as a consequence of the decreased glucose influx. Forearm exchange of oxygen, carbon dioxide, lipid substrates (free fatty acids, glycerol, and β-hydroxybutyrate), and potassium were similar in the hypertensive and normotensive groups in the basal state. Insulin had no effect on oxygen consumption, carbon dioxide production, and respiratory quotient in either study group, whereas it stimulated free fatty acids, glycerol, and potassium uptake to the same extent in the hypertensive and normotensive groups. We conclude that the insulin resistance of untreated essential hypertension is present in skeletal muscle, is not secondary to increased fatty substrate use (normal respiratory quotient), and is selective for glucose metabolism. Because forearm substrate oxidation is unaltered, the defect in glucose disposal must predominantly involve glucose conversion into glycogen. (Hypertension 1991;17:170–178)
TABLE 1. Clinical Characteristics of Patients With Hypertension and of Normal Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=8)</th>
<th>Controls (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>42±3</td>
<td>48±3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>80±3</td>
<td>82±2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27±1</td>
<td>26±1</td>
</tr>
<tr>
<td>Ponderal index (%)</td>
<td>103±3</td>
<td>101±3</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>55.9±0.8</td>
<td>55.2±1.8</td>
</tr>
<tr>
<td>Resting energy expenditure (kJ/min)</td>
<td>5.32±0.15</td>
<td>5.05±0.20</td>
</tr>
<tr>
<td>Intra-arterial blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>165±7</td>
<td>126±6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>102±4</td>
<td>72±3</td>
</tr>
<tr>
<td>Mean</td>
<td>126±4</td>
<td>95±4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64±4</td>
<td>63±3</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>1.32±0.26</td>
<td>0.98±0.07</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/l)</td>
<td>4.06±0.16</td>
<td>5.07±0.29</td>
</tr>
</tbody>
</table>

Body mass index was calculated as the ratio of weight (kg) to the square of the height (m); Ponderal index was calculated as the ratio of actual weight to the body weight specified as desirable in life insurance tables; lean body mass was calculated according to Hume; resting energy expenditure was estimated by indirect calorimetry; values for intra-arterial blood pressure and heart rate are the mean of a 30-minute basal period with the patient in a supine position.

sion. All had diastolic blood pressure values equaling or exceeding 100 mm Hg on at least three measurements that were taken by the same physician and after the patient had been resting in the supine position for 30 minutes. A complete medical workup was carried out to exclude secondary forms of hypertension. Renal, liver, and endocrine function was normal; none of the patients had experienced recent changes in body weight or dietary habits or an intercurrent illness. Additional criteria for inclusion in the study were normal body weight (less than 20% above or below desirable body weight, according to life insurance tables) and normal tolerance to oral glucose (according to criteria set by the National Diabetes Data Group). Known duration of hypertension was 6±1 years. Treatment of hypertension (in four patients with a known duration of 8±1 years) consisted of angiotensin converting enzyme inhibitors in two subjects, β-blockers in one, and diuretics in one; in all, treatment was discontinued 1–3 weeks before the study. In newly diagnosed patients (n=4, with a known duration of 5±0.2 years of high blood pressure), antihypertensive therapy was not begun until after the study was completed. Seven healthy normotensive men, carefully matched to the hypertensive patients for age, body weight, and composition, served as the control group (Table 1). Both patients and controls had negative family histories for diabetes mellitus, were taking no other medication, and were following a diet of standard composition (the Italian diet typically contains 45% carbohydrate, 40% fat, and 15% protein) that would maintain weight; no restrictions were placed on salt intake. None of the subjects were engaged in competitive sports, and all were asked to avoid heavy physical exercise on the day before the study.

The research protocol was approved by the Institutional Review Board. All subjects gave informed consent before participating in the study.

Procedures

The studies were begun at 8:00 AM after an overnight fast (10–14 hours), with the subjects lying supine in a quiet room with a constant temperature of 21–24°C. Each subject was studied on two separate occasions, a few days apart. On one day, subjects received an oral glucose tolerance test (OGTT) in which venous plasma glucose, insulin, and free fatty acid (FFA) levels were measured basally and then at 30-minute intervals for 3 hours after the ingestion of a drink containing 40 g glucose/m² body surface area. Urine was collected before and again at the end of the OGTT for measurement of nonprotein nitrogen excretion. This study was combined with indirect calorimetry to assess whole body rates of substrate oxidation and energy expenditure. Continuous, open-circuit computerized calorimetry was performed with the use of a Metabolic Measurement Cart Horizon apparatus (SensorMedics Corp., Anaheim, Calif.) with a canopy system, as previously described in detail. On another day, subjects underwent a forearm perfusion study. For this, a polyethylene catheter (18-G Abbott, Sliigo, Ireland) was inserted percutaneously into the brachial artery under local anesthesia (2% xylocaine, Byk Gulden Italia S.p.A, Milano, Italy). Another polyethylene cannula was threaded into a deep vein of the forearm retrogradely; this cannula was judged to be correctly positioned if its tip could not be palpated superficially and if the blood it sampled had an oxygen saturation of less than 70%. Both catheters were kept patent by slow saline infusions. The arterial line was connected to a pressure transducer (Statham P-23 dB, Transamerica Delval Inc., Pasadena, Calif.) interfaced with a monitor (12-Channel Recorder, OTE Biomedica, Florence, Italy); heart rate was also monitored by continuous electrocardiographic recording (lead DII). Systolic, diastolic, and mean blood pressure readings were recorded continuously and were averaged over 20-minute time intervals. Two minutes before sampling, circulation to the hand was excluded by inflating a pediatric cuff at suprasystolic pressure around the wrist.

Three sets of arterial and deep venous blood samples were obtained over 30 minutes in the basal period for determination of metabolites and hormones. One additional blood sample pair was drawn at time zero for gas analysis. At time zero, an intra-arterial infusion of regular insulin (Eli Lilly, Indianapolis, Ind., made up in a saline solution containing 1% human serum albumin) was started at a rate of 0.3 milliunits/min; this rate was maintained for 40 minutes and then doubled every 40 minutes until 200 minutes, thereby creating five steps of regional hyperinsulinemia. Arterial and deep venous
blood were sampled at 20-minute intervals for hormone and metabolite determinations and at 40-minute intervals for gas analysis.

Forearm blood flow was measured (by venous occlusion plethysmography,\textsuperscript{19} Vasculab Strain-Gauge Plethysmograph SPG 16, Meda Sonics, Mountain View, Calif.) in four hypertensive and three normotensive subjects and was found to be similar between the two subgroups and not to change in response to local insulin infusion. In previous forearm studies from our laboratory, local physiological hyperinsulinemia likewise elicited no detectable effect on forearm blood flow.\textsuperscript{20} In larger series of hypertensive patients, resting forearm blood flow has consistently been found to be within the normal limits.\textsuperscript{21,22}

**Analytical Procedures**

For metabolite determination, blood was drawn into chilled tubes containing IN perchloric acid (1:1 wt/wt) and was immediately centrifuged. The deproteinized supernatants were stored at -20°C until analysis, which was always carried out within a few days. Glucose, lactate, pyruvate, glycerol, 3-hydroxybutyrate, alanine, and citrate were all assayed by enzymatic methods by continuous flow fluorimetry.\textsuperscript{23} Arterial and venous sample pairs were always assayed in the same run. FFA were measured on the plasma of simultaneously drawn samples by an enzymatic method (Wako Chemical GmbH, Neuss 1, FRG). Serum triglycerides, total cholesterol, and urea were assayed by standard enzymatic methods. Plasma potassium was assayed in duplicate by flame photometry and nonprotein urinary nitrogen by the Kjeldhal method.\textsuperscript{24} Insulin was measured in plasma by radioimmunoassay. Complete gas analysis (O\textsubscript{2}, CO\textsubscript{2}, and pH) was carried out by using an Instrumentation Laboratory (I.L.) System 1302 and an I.L. 282 CO-Oxymeter (Instrumentation Laboratory S.p.A., Milano, Italy).

**Data Analysis**

Protein oxidation was estimated from the urinary nonprotein nitrogen excretion rate after correcting for changes in the body urea pool.\textsuperscript{25} Whole body net rates of carbohydrate and lipid oxidation and energy expenditure were estimated from gaseous exchange measurements (and protein oxidation rates) according to standard calorimetric equations, as described in detail elsewhere.\textsuperscript{10} Because the resting rate of energy expenditure is a faithful reflection of the entire body mass of metabolically active cells, rates of substrate oxidation were normalized by the resting energy expenditure to allow a fair comparison between the hypertensive and the normotensive group.\textsuperscript{16}

Heart rate and blood pressure values were averaged over 20-minute intervals. Total arterial and deep venous whole blood CO\textsubscript{2} content were calculated from the measured partial CO\textsubscript{2} pressure and pH values according to Henderson-Hasselbalch equation,\textsuperscript{26} after correcting for Haldane effect and the influence of pH on CO\textsubscript{2} binding to hemoglobin.\textsuperscript{27} The respiratory quotient was calculated as the ratio between the arteriovenous difference of CO\textsubscript{2} and that of O\textsubscript{2}. The net forearm balance (uptake or release) of any metabolite was expressed as the ratio of the arteriovenous concentration gradient to the arterial concentration [i.e., (A - V)/A]). Such an index corrects for any changes in arterial levels and is flow independent.

All data are expressed as mean±SEM. For data presentation, values measured at 20-minute intervals were averaged over the 40-minute intervals corresponding to each of the five insulin infusion rates. Between-group differences in mean values over time were assessed with the use of two-way analysis of variance (ANOVA) with a repeated-measure design for time-related changes. Multiple linear regression was carried out by standard methods.

**Results**

**Oral Glucose Tolerance**

The plasma glucose, insulin, and FFA profiles after oral glucose administration are shown in Figure 1 for the hypertensive and normotensive group. It can be seen that both glucose and insulin levels were higher in the hypertensive than in the normotensive subjects throughout the test. When the product of plasma insulin times plasma glucose (a commonly used index of insulin sensitivity) was calculated, the hypertensive group had significantly (p = 0.04 by two-way ANOVA) higher products than the control group (by 27% on the average). In response to hyperinsulinemia, on the other hand, FFA concentrations were suppressed to a similar extent in the two groups. Basal rates of substrate oxidation and energy expenditure were superimposable in the two groups (Table 2). In the control subjects, glucose ingestion induced a marked increase in carbohydrate oxidation (averaging + 100% over the 3 hours of the test, p<0.001), a consistent 50% decrease in lipid oxidation (p<0.001), and a 20% decline in protein oxidation (p<0.01). These metabolic responses to oral glucose were at all similar in the hypertensive patients (Table 2). Energy expenditure was significantly stimulated (+8% on the average over 3 hours) by oral glucose (i.e., diet-induced thermogenesis), in a parallel fashion in the two groups of study subjects (Table 2).

**Forearm Studies**

The arterial concentrations of oxygen, carbon dioxide, and protons were stable throughout the study period and were no different between hypertensive and normotensive subjects. The basal fractional extraction of oxygen across the deep forearm tissues was 29±3% and 33±3% in the control and hypertensive groups, respectively (p=NS), whereas the fractional release of carbon dioxide averaged 10±1% and 10±1%, respectively (p=NS), and that of protons averaged 6.6±1.0% and 7.2±1.0% (p=NS). Insulin infusion failed to alter the forearm exchange of either respiratory gases or protons in normoten-
Insensitive as well as hypertensive individuals. In both groups, intra-arterial blood pressure and heart rate remained stable during local insulinization.

In the basal state, deep venous endogenous plasma insulin concentrations were similar in hypertensive and normotensive individuals (Table 3). During graded intra-arterial infusion of exogenous insulin, equivalent plateaus of -17, 27, 40, 70, and 120 milliunits/l were achieved in the two groups. Basally, the arterial levels of all measured metabolites were within the normal range and were similar in the two groups. During the 200 minutes of local insulin infusion, the systemic concentrations of the insulin-sensitive substrates (glucose, lactate, pyruvate, FFA, glycerol, and potassium) all showed a gradual, statistically significant decline, ranging from -36% (pyruvate) to -4% (FFA) (Table 3).

However, the arterial levels of β-hydroxybutyrate, alanine, and citrate remained stable throughout (data not shown).

In control subjects, basal forearm glucose extraction averaged 4.7%, and insulin stimulated glucose extraction in a dose-dependent fashion (Figure 2). In the hypertensive group, forearm glucose extraction was less than in the control group at each insulin concentration (p<0.03 by ANOVA), such that the whole dose–response curve was shifted downward (Figure 2). When sigmoidal functions were fitted to the individual dose–response curves, the calculated maximal response (Vmax) was found to be significantly lower in the hypertensive than in the normotensive group (21±4% versus 9±1%, p<0.01), whereas the apparent Km, although higher in the patients than in the control group, did not differ statistically between the two groups (56±10 versus 33±6 milliunits/l, p=NS).

In the basal state, lactate was released and pyruvate was extracted by forearm tissues in the control group; in response to insulin, lactate release increased and pyruvate uptake switched to a net release (p<0.01 for both). For both metabolites, the effect of insulin was significantly blunted in the hypertensive group in comparison with the control group (p<0.03 for lactate and p<0.05 for pyruvate) (Figure 3). In contrast, the ability of hyperinsulinemia to stimulate net FFA uptake was equivalent in patients and the control group (Figure 4). Likewise, insulin promoted net potassium uptake into forearm tissues in a dose-related, parallel manner in the two groups (Figure 4). As for the other measured metabolites, the net forearm balance was neutral for glycerol, triglycerides, and total cholesterol, whereas there was a significant net fractional release of alanine (17%) and citrate (43%), and a fractional uptake of β-hydroxybutyrate (24%). Insulin only caused a switch in glycerol balance to a net fractional uptake (22%, p<0.005) without af-
TABLE 2. Net Whole Body Rates of Carbohydrate, Lipid, and Protein Oxidation, and of Energy Expenditure During Oral Glucose Loading in Patients With Hypertension and in Normal Subjects

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Basal</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
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<tbody>
<tr>
<td>Carbohydrate oxidation (μmol/kJ of REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>98±17</td>
<td>84±17</td>
<td>166±11</td>
<td>216±18</td>
<td>275±55</td>
<td>226±18</td>
<td>242±21</td>
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<tr>
<td>Controls</td>
<td>117±26</td>
<td>119±27</td>
<td>180±29</td>
<td>236±31</td>
<td>252±32</td>
<td>253±26</td>
<td>248±28</td>
</tr>
<tr>
<td>Lipid oxidation (μmol/kJ of REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Patients</td>
<td>57±5</td>
<td>67±5</td>
<td>48±4</td>
<td>35±6</td>
<td>20±5</td>
<td>29±6</td>
<td>26±7</td>
</tr>
<tr>
<td>Controls</td>
<td>51±8</td>
<td>56±8</td>
<td>44±8</td>
<td>29±8</td>
<td>26±9</td>
<td>26±8</td>
<td>25±8</td>
</tr>
<tr>
<td>Protein oxidation (μmol/kJ of REE)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>76±20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Controls</td>
<td>74±17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Energy expenditure (kJ/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>5.3±0.2</td>
<td>5.6±0.2</td>
<td>5.8±0.2</td>
<td>5.9±0.1</td>
<td>5.9±0.2</td>
<td>5.7±0.2</td>
<td>5.8±0.2</td>
</tr>
<tr>
<td>Controls</td>
<td>5.1±0.2</td>
<td>5.2±0.2</td>
<td>5.4±0.2</td>
<td>5.4±0.2</td>
<td>5.5±0.2</td>
<td>5.5±0.2</td>
<td>5.4±0.2</td>
</tr>
</tbody>
</table>

Values given are mean±SEM. REE, resting energy expenditure.

...effecting the exchange of the other substrates. For each metabolite, the observed values were superimposable in the hypertensive and normotensive group, basally as well as during insulin infusion.

In a multiple regression model, forearm glucose extraction was significantly (p<0.001) related both to deep venous plasma insulin concentrations (positively) and to blood pressure values (negatively). When forearm glucose extraction was divided by the concurrent insulin level (thereby deriving a crude index of insulin-mediated glucose uptake by forearm tissues), a significant (p<0.02) inverse relation with intra-arterial diastolic blood pressure was found (Figure 5). As can be seen, the data in the normotensive subjects are somewhat more scattered than those of the hypertensive subjects but reasonably continuous with them, suggesting a quantitative impact of higher blood pressure levels on insulin-mediated glucose extraction across the two study groups. From the regression in Figure 5, it can be estimated that an increase in diastolic blood pressure of 30 mm Hg is associated with a 43% decrement in insulin-mediated glucose uptake.

TABLE 3. Deep Venous Plasma Insulin Levels and Arterial Substrate Concentrations in the Normotensive and Hypertensive Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Basal</th>
<th>40</th>
<th>80</th>
<th>120</th>
<th>160</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (millimolars)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>10±1</td>
<td>21±3</td>
<td>29±4</td>
<td>41±3</td>
<td>83±7</td>
<td>125±12 *</td>
</tr>
<tr>
<td>HT</td>
<td>12±1</td>
<td>14±1</td>
<td>26±4</td>
<td>40±6</td>
<td>61±8</td>
<td>123±18 *</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>6.61±0.12</td>
<td>6.47±0.13</td>
<td>6.28±0.10</td>
<td>6.24±0.08</td>
<td>6.08±0.10</td>
<td>5.93±0.12 *</td>
</tr>
<tr>
<td>HT</td>
<td>6.03±0.07</td>
<td>5.97±0.08</td>
<td>5.92±0.06</td>
<td>5.89±0.07</td>
<td>5.82±0.06</td>
<td>5.78±0.07 *</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>0.654±0.027</td>
<td>0.614±0.027</td>
<td>0.583±0.024</td>
<td>0.596±0.030</td>
<td>0.594±0.028</td>
<td>0.575±0.029 *</td>
</tr>
<tr>
<td>HT</td>
<td>0.814±0.058</td>
<td>0.800±0.070</td>
<td>0.751±0.063</td>
<td>0.722±0.057</td>
<td>0.710±0.051</td>
<td>0.679±0.053 *</td>
</tr>
<tr>
<td>Pyruvate (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>0.059±0.003</td>
<td>0.053±0.003</td>
<td>0.050±0.002</td>
<td>0.051±0.003</td>
<td>0.044±0.004</td>
<td>0.041±0.032 *</td>
</tr>
<tr>
<td>HT</td>
<td>0.084±0.007</td>
<td>0.081±0.009</td>
<td>0.073±0.007</td>
<td>0.066±0.007</td>
<td>0.055±0.005</td>
<td>0.049±0.006 *</td>
</tr>
<tr>
<td>FFA (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>0.537±0.035</td>
<td>0.572±0.035</td>
<td>0.638±0.035</td>
<td>0.654±0.044</td>
<td>0.611±0.046</td>
<td>0.506±0.045 *</td>
</tr>
<tr>
<td>HT</td>
<td>0.519±0.050</td>
<td>0.600±0.051</td>
<td>0.547±0.046</td>
<td>0.602±0.076</td>
<td>0.565±0.052</td>
<td>0.510±0.037</td>
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<tr>
<td>Glycerol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>0.062±0.005</td>
<td>0.067±0.006</td>
<td>0.072±0.007</td>
<td>0.079±0.007</td>
<td>0.067±0.008</td>
<td>0.052±0.004 *</td>
</tr>
<tr>
<td>HT</td>
<td>0.058±0.005</td>
<td>0.059±0.005</td>
<td>0.057±0.004</td>
<td>0.069±0.009</td>
<td>0.060±0.004</td>
<td>0.054±0.004 *</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>5.0±0.2</td>
<td>4.6±0.2</td>
<td>4.5±0.2</td>
<td>4.3±0.2</td>
<td>4.2±0.2</td>
<td>4.0±0.2 *</td>
</tr>
<tr>
<td>HT</td>
<td>5.4±0.3</td>
<td>5.3±0.4</td>
<td>5.0±0.4</td>
<td>4.8±0.4</td>
<td>4.3±0.3</td>
<td>4.1±0.1 *</td>
</tr>
</tbody>
</table>

Values given are mean±SEM. NT, normotensive; HT, hypertensive; FFA, free fatty acids.

*Indicates a statistically significant change over time (by analysis of variance for repeated measures).
Discussion

The present results confirm the notion\textsuperscript{28,29} that patients with essential hypertension frequently have a hyperinsulinemic response to oral glucose, for which mild hyperglycemia (still within the boundary of normal glucose tolerance) is the stimulatory signal (Figure 1). The association of higher insulin concentrations with higher glucose levels constitutes indirect evidence for the presence of insulin resistance. The new finding is that, despite such insulin resistance, the pattern of oxidative fuel use during the OGTT with higher glucose levels constitutes indirect evidence for the presence of insulin resistance. The new finding is that, despite such insulin resistance, the pattern of oxidative fuel use during the OGTT was similar in normotensive and hypertensive individuals, in that glucose-induced hyperinsulinemia caused the same shift in whole body net substrate oxidation (i.e., stimulation of carbohydrate oxidation at the expense of lipid and protein oxidation) regardless of blood pressure (Table 2). Furthermore, neither resting energy metabolism nor glucose-induced thermogenesis was affected by the presence of hypertension (Table 2). Thus, at least in response to glucose ingestion, the insulin resistance of the hypertensive state appears to be perfectly compensated by virtue of the attendant increase in insulin and glucose levels. In another state of insulin resistance, namely simple obesity, the hyperinsulinemic response to oral glucose is capable of maintaining glucose tolerance, but unlike the present case of hypertension, substrate use is not normal, with a decrease in carbohydrate

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Scatterplots showing dose-response curves for net lactate release (top panel) and net pyruvate exchange (bottom panel) as a function of plasma insulin concentration in hypertensive and normotensive subjects. Note logarithmic scale for abscissas.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Scatterplot showing dose-response curves for net forearm extraction of free fatty acids (FFA) (top panel) and net potassium exchange (bottom panel) as a function of plasma insulin concentration in hypertensive (•) and normotensive (□) subjects. Results for two groups are essentially superimposable.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Scatterplot showing relation between intra-arterial diastolic blood pressure and average insulin-mediated forearm glucose extraction (=fractional glucose extraction divided by the natural logarithm of plasma insulin concentration) in normotensive (□) and hypertensive (●) subjects. B.P., blood pressure.}
\end{figure}
oxidation and an increase in lipid oxidation in comparison with nonobese individuals. Thus, simply on these grounds it is clear that the metabolic basis of the insulin resistance of hypertension versus obesity is different even in the face of the same compensatory response (hyperinsulinemia).

The forearm studies showed that in hypertensive individuals, the ability of insulin to promote glucose uptake by the deep tissues of the forearm (mostly, skeletal muscle) is impaired throughout the range of local insulin concentrations explored (Figure 2). The shape of the dose–response curve suggests that the maximal response (i.e., responsiveness) rather than the half-maximal response (i.e., sensitivity) was reduced in the hypertensive group. However, this interpretation must be carefully applied. By design, only the physiological range of plasma insulin levels was explored in the present study, thereby precluding the determination of the true “maximal” response. This choice is justified by the fact that, as the rate of local insulin infusion is progressively increased, the spillover of insulin into the systemic circulation also increases. In the current data, for example, the arterial concentration of the insulin-sensitive substrates had already declined significantly by the end of the study, at average rates ranging from 0.02% to 0.18% per minute for different metabolites (Table 3). If the above changes are too small and too slow to challenge the validity of the forearm technique (which demands constancy of arterial substrate input), larger decrements would certainly have induced a shift in whole body metabolism, possibly biasing the assessment of regional metabolism. Therefore, the conclusion that the forearm tissues of hypertensive individuals show a marked reduction in responsiveness, with a lesser impairment of sensitivity, to insulin per se must be circumscribed to the physiological interval of insulin concentrations. With this specification, the result suggests the presence of a postreceptor defect in insulin action, according to the commonly accepted schematization that ascribes changes in responsiveness to post-binding defects. Of note is that systemic glucose concentrations fell by 10% in the normotensive group and by only 4% in the hypertensive group (p<0.05 by two-way ANOVA), indicating that the insulin spilling from the intrarterial infusion over into the systemic circulation was less effective in lowering blood glucose in the patients than in the control subjects. In other words, there was concordance between forearm and whole body insulin resistance.

An important issue is the quantitative relevance of the observed defect in forearm glucose uptake to whole body glucose homeostasis. With regard to this, it is possible to calculate from our data that at local insulin levels of ~70 milliunits/l (i.e., a typical post-prandial value), the average percent reduction in forearm glucose extraction in the hypertensive group was 43% (Figure 2). If, as commonly assumed, muscle blood flow is three fourths of total forearm flow, and muscle occupies 70% of forearm volume, then the percent reduction in forearm muscle glucose extraction was 50%. Because total skeletal muscle mass has been shown to contribute approximately 70% of whole body glucose use (during euglycemia with systemic insulin concentrations of ~70 milliunits/l), it follows that in hypertensive patients, the observed 50% reduction in forearm muscle glucose disposal would translate into a 35% decrease in whole body glucose disposal. This figure is quite close to that previously reported in another group of patients with essential hypertension during a euglycemic insulin clamp (with an insulin plateau of 70 milliunits/l). This broad correspondence between forearm and whole body data obtained in different groups of study subjects again emphasizes the quantitative significance of a regional defect for whole body glucose homeostasis. Obviously, it does not exclude impairment of insulin-stimulated glucose uptake in other tissues as well.

The regression in Figure 5 predicts that a 40% decline after normalizing for insulin concentration in insulin-mediated forearm glucose uptake is expected for each 30 mm Hg increment in diastolic blood pressure. Although blood pressure explained only less than 10% of the overall variance of forearm glucose extraction, there nevertheless is the suggestion that blood pressure bears a quantitative relation to insulin-mediated glucose metabolism in the human forearm, such that progressively higher pressure values are associated with progressively smaller responses to insulin.

In resting skeletal muscle, the intracellular disposition of glucose can follow three main routes: 1) complete oxidation in the Krebs cycle, 2) anaerobic glycolysis with net lactate production, and 3) glycogen synthesis. As recently demonstrated with the use of nuclear magnetic resonance in humans, the vast majority of insulin-stimulated forearm muscle glucose uptake is routed directly to glycogen. In the present studies, local hyperinsulinemia enhanced glucose uptake but failed to stimulate oxygen consumption or carbon dioxide production by the forearm in normotensive as well as hypertensive subjects. This result (within the precision limits of regional gas exchange measurements) indicates that local insulin administration does not change the pattern of substrate oxidation (i.e., the local respiratory quotient). Therefore, the insulin-induced increase in inward glucose flux must be directed away from oxidation and into muscle glycogen for the most part. It follows that the defect in forearm glucose extraction shown by the hypertensive patients essentially implies a reduced ability of insulin to stimulate muscle glycogen synthesis.

In the hypertensive group, the observed reduction in lactate and pyruvate net release (Figure 3) can be interpreted as dependent on the decreased glucose extraction by the forearm. In both study groups, net lactate output accounted for 20% of concurrent basal glucose uptake; with insulin infusion, this fraction declined to similar extents in control subjects and in patients (to 14% versus 17%, respectively, by the end
of the study). Similar calculations obtained with pyruvate, consistent with the idea that changes in the forearm balance of either metabolite reflect opposite changes in their common precursor, glucose.17

In contrast to glucose and its metabolites, all the other substrates were handled by the forearm in similar fashion in hypertensive and normotensive subjects, both basally and in response to graded insulin infusion (Figure 4). Thus, insulin promptly stimulated a net extraction of FFA and potassium, with apparent plateaus of effect being reached at local insulin levels of 20–40 milliunits/L. This finding confirms Zierler’s original observation (Zierler and Rabinowitz26) that in the forearm, suppression of lipolysis and promotion of potassium influx are more sensitive to insulin than enhancement of glucose uptake and demonstrates that the presence of high blood pressure does not interfere with the effects of insulin on FFA and potassium metabolism. Incidentally, in the forearm stimulation of net FFA uptake results from suppression by insulin of the concurrent FFA release (from hydrolysis of endogenous triglycerides), as indicated by the switch in glycerol balance from a net release to a net uptake.37 In the hypertensive subjects, the normal response of FFA and glycerol exchange to insulin infusion is in keeping with the observed normal fall in systemic FFA levels seen after oral glucose (Figure 1) as well as with the normal shift in substrate oxidation that followed glucose ingestion (Table 2). In other words, in this group of hypertensive patients no differences in lipid metabolism in response to insulin were present whether analyzed regionally in the forearm or at the whole body level. The fact that citrate (a Krebs cycle intermediate that accumulates in the presence of excessive lipid oxidation38) was released in both study groups at similar net rates (basally as well as during insulin infusion) is in accordance with the idea that overall, the partition of energy production between lipid and carbohydrate in forearm muscle is not influenced by either local insulin or the blood pressure status. A corollary to this conclusion is that substrate competition (such as that between FFA and glucose oxidation, or Randle’s cycle38) is unlikely to explain the observed resistance of muscle glucose uptake to insulin stimulation.

In summary, in our patients with untreated essential hypertension as the sole abnormality there was present an insulin resistance in skeletal muscle that is apparently primary (i.e., not secondary to obesity or glucose intolerance), mostly involves glycogen synthesis, and probably results from a postreceptor defect in insulin action. The basis of such a defect is presently unknown.39 In general, a change in membrane glucose transport or in the activity/concentration of glycogen synthase (the rate-limiting enzyme for glycogen synthesis40), or both, could account for the kind of insulin insensitivity here described. In addition, the possibility that the composition of skeletal muscle fibers may differ in normotensive and hypertensive subjects must be considered. In Pima Indians, insulin sensitivity at the whole body level is inversely related to the percentage of type IIb (fast-twitch, glycolytic) muscle fibers and directly related to the percentage of type I (slow-twitch, oxidative) fibers in quadriceps muscle.41

In the only report that we are aware of,42 the hypertensive group had a lower percentage of type I quadriceps muscle fibers than did the normotensive group. Because these fibers are more vascularized and more sensitive to insulin,43 it is possible that either a mal-distribution of muscle blood flow44,45 or, at equal perfusion rates, a qualitative difference in fiber insulin sensitivity may produce the observed defect in insulin action in muscle.

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