Insulin Receptor Number in Arterial Hypertension
Response to Treatment With Fosinopril or Atenolol
Thomas Makris, Panagiota Krespi, Filippos Triposkiadis, Vasilios Votteas, Antonios Hatzizaharias, and Michael Kyriakidis

Human insulin receptor (hINR) number and its response to medical treatment was evaluated in 14 male controls and 40 male hypertensive patients. Twenty patients treated with fosinopril (10 to 20 mg daily orally) comprised Group A and 20 treated with atenolol (25 to 50 mg daily orally) Group B. The hINR number (receptors $\times 10^3$/red cell) was greater in controls compared to untreated patients ($8.22 \pm 2.4 v 5.53 \pm 1.27, P < .001$). After 6 months of treatment the hINR number increased in Group A ($5.73 \pm 1.47 v 7.5 \pm 2.06, P < .001$) and remained unchanged ($5.35 \pm 1.09 v 5.5 \pm 1.31, P = NS$) in Group B. Thus, hINR number is decreased in hypertension and, in contrast to atenolol, fosinopril treatment is associated with an increase in hINR number, suggesting a favorable effect on glucose metabolism.

R esistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia are common in arterial hypertension, occurring in approximately 50% of patients. $^{1,2}$ The underlying mechanism, which has not yet been delineated, may include disturbances of insulin transport from plasma into the interstitial fluid, binding of insulin to its receptor (human insulin receptor, hINR), and the activity of a range of postreceptor signaling pathways. $^3$ The purpose of the present study was two-fold: 1) to determine the hINR number in normotensive subjects and hypertensive patients, and 2) to evaluate the effect of arterial pressure reduction with an angiotensin converting enzyme inhibitor (fosinopril) or a $\beta_1$-selective blocker (atenolol) on hINR number.

PATIENTS AND METHODS

Study Population Fourteen male normotensive subjects and 40 male patients with newly detected essential hypertension were studied. Twenty of the hypertensive patients, who were subsequently treated with fosinopril (10 to 20 mg orally) comprised Group A and the rest, who were treated with atenolol (25 to 50 mg orally) Group B. Patients with clinical or laboratory evidence of hepatic, renal, thyroid, obstructive pulmonary, or coronary artery disease, or diabetes mellitus were excluded.

Blood Pressure Systolic and diastolic blood pressures were measured at the time of the first and fifth Korotkoff sound, respectively. Measurements were made on the right arm to the nearest millimeter of mercury using a mercury sphygmomanometer. All
measurements were made in the supine position after the patients had rested for 10 min. The means of these measurements were used in the analyses. Arterial hypertension was diagnosed according to the 1993 criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.

**Insulin Receptor Number** The hINR number was determined in all study patients. In hypertensives the hINR number was measured before and after 6 months of medical treatment. For hINR number determination, 10 mL of blood was obtained between 8 and 9 AM after an overnight fast. The number of insulin receptors was determined by a radioimmunoassay method, through the application of a technique that is a slight modification of the method proposed by Gambhir et al. Each blood sample was centrifuged for 5 min at room temperature and a rate of 1500 revolutions/min. After absorption of the overlying plasma, the layer of blood cells remained in the tube. The blood cells were mixed with 4 mL Tris buffer (pH = 7.4) and after three successive centrifugations at 1500 revolutions/min, the red blood cells were separated from the other blood elements. Subsequently, 200 pg (125I)-TyrA14 human insulin (Amersham Radiochemical, Amersham, Buckinghamshire, England) were added to 1 mL of the mixture of red blood cells/Tris buffer followed by unlabeled insulin. The endproduct was incubated at a temperature of 25°C for 60 min. The receptors were determined by the amount of the measured radiation (number of strikes) in the overlying (free insulin) and underlying (bound insulin) layer of the mixture after centrifugation (Hewlett Packard, Andover, MA; RIA Star A5405).

**Statistical Analysis** Values are expressed as mean ± 1 standard deviation. The Student paired and unpaired t tests were used for intra- and intergroup comparisons of continuous variables, respectively, as appropriate. A P < .05 was considered statistically significant.

**RESULTS**

Age (57.2 ± 5.8 v 56.9 ± 7.6 years, P = NS) and body mass index (26.6 ± 1.2 v 24.1 ± 2.36 kg/m², P = NS) were similar between normotensive subjects and hypertensive patients as well as between Group A and Group B patients (age: 56.7 ± 8.3 v 57.2 ± 6.7 years, P = NS; body mass index 23.7 ± 2.4 v 24.3 ± 2.3 kg/m², P = NS). As expected, systolic (130 ± 6 v 147 ± 7 mm Hg, P < .001) and diastolic blood pressure (78 ± 5 v 100 ± 5 mm Hg, P < .001) in normotensive subjects was lower compared to untreated hypertensive patients. In contrast, the hINR number (receptors × 10³/red cell) was greater in normotensive subjects compared to untreated hypertensive patients (8.22 ± 2.4 v 5.53 ± 1.27, P < .001).

<table>
<thead>
<tr>
<th>Group</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (fosinopril)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>146 ± 8</td>
<td>129 ± 9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>99 ± 4</td>
<td>83 ± 5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>hINR number (receptors × 10³/red cell)</td>
<td>5.73 ± 1.47</td>
<td>7.5 ± 2.06*</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>B (atenolol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>148 ± 10</td>
<td>130 ± 12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>100 ± 6</td>
<td>85 ± 4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>hINR number (receptors × 10³/red cell)</td>
<td>5.35 ± 1.09</td>
<td>5.5 ± 1.31</td>
<td>NS</td>
</tr>
</tbody>
</table>

hINR, human insulin receptor.

*P < .01 v Group B.

Table 1 shows that systolic and diastolic blood pressures were not significantly different between Group A and Group B patients, both before or after medical treatment. Likewise, the hINR number was not significantly different between the two groups before medical treatment. However, following 6 months of antihypertensive therapy, the hINR number significantly increased in Group A and remained unchanged in Group B. As a result, the hINR number was higher in Group A compared to Group B after 6 months of medical treatment.

**DISCUSSION**

The findings of the present study indicate that: a) the hINR number was decreased in patients with hypertension compared to normal controls; and b) at similar diastolic and systolic blood pressure reduction, treatment with the angiotensin converting enzyme inhibitor fosinopril was associated with an increase in hINR number while treatment with the β₁-selective blocker atenolol was associated with no changes in hINR number.

The hINR, a heterotetramer composed of two α-subunits and two β-subunits, is an integral membrane protein present on the surface of all cells mediating the diverse tissue or cell-specific cellular responses to insulin.6,7 The cell surface hINR number is inversely regulated by insulin.8,9 Amelioration of hyperinsulinemia leads to reversal of receptor loss.10 However, previous studies in hypertensive patients have demonstrated that patients with essential hypertension can show decreased erythrocyte insulin receptors without
detectable hyperinsulinemia. Moreover, blood pressure lowering with β1-selective blockers is associated with no change or an increase in insulin resistance, the latter reflected in an increase in insulin and glucose plasma concentrations. In contrast, treatment with angiotensin converting enzyme inhibitors results in decreased insulin resistance, as indicated by the low fasting and post–glucose-load insulin plasma concentrations. Thus, the changes in the hINR number observed in the present study are in accordance with the previous reports on the effects of β1-selective blockers and angiotensin converting enzyme inhibitors on carbohydrate metabolism and insulin resistance.

The adverse effects of β1-selective adrenergic blockade on glucose disposal mediated by insulin have been attributed to a reduction in cardiac output with β1-blockade, interference with the capacity for glucose oxidation in insulin sensitive type-1 fibers, and to an increased release of growth hormone. The increase in the rate of insulin disposal mediated by angiotensin converting enzyme inhibition is believed to be due to local accumulation of bradykinin and vasodilation. The latter may increase the access of insulin and glucose to skeletal muscle tissue, the major site of insulin-mediated glucose removal.

Glucose and insulin plasma concentrations were not measured in this study. The association, therefore, between the changes in the hINR number and insulin resistance could not be assessed. Based on the findings of previous reports, it is reasonable to assume that the observed hINR number changes following antihypertensive treatment were secondary and inversely related to changes in plasma insulin concentration and insulin resistance. The possibility, however, of a primary effect of antihypertensive agents on hINR number cannot be excluded.

In conclusion, the low hINR number in hypertensive patients increases following medical treatment with angiotensin converting enzyme inhibitors and remains unchanged after treatment with β1-selective blockers. Although these findings are in accordance with the favorable effects of angiotensin converting enzyme inhibitors on carbohydrate metabolism, further studies are necessary to clarify the relationship between insulin resistance and hINR number in essential hypertension.

REFERENCES