Blockade of the Renin-Angiotensin System Increases Adiponectin Concentrations in Patients With Essential Hypertension

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Abstract—Adiponectin, an adipocyte-derived protein, has been suggested to play an important role in insulin sensitivity. We examined the association between insulin sensitivity (M value) evaluated by the euglycemic-hyperinsulinemic glucose clamp and adiponectin concentrations in 30 essential hypertensives (EHT) and 20 normotensives (NT) and investigated the effect of blockade of the renin-angiotensin system (RAS) on adiponectin concentrations. EHT were divided into 12 insulin-resistant EHT (EHT-R) and 18 non–insulin-resistant EHT (EHT-N) using mean−1 SD of the M value in NT. There were no intergroup differences in age, gender, and body mass index (BMI). EHT-R had significantly higher levels of insulin and triglyceride and lower levels of adiponectin than did NT and EHT-N. EHT-R had higher levels of free fatty acid and lower levels of high-density lipoprotein (HDL) cholesterol than did EHT-N. Adiponectin concentrations were positively correlated with M value and HDL cholesterol and negatively correlated with BMI, insulin, free fatty acid, and triglyceride but not with blood pressure. M value, BMI, and HDL cholesterol were independent determinants of adiponectin concentrations in multiple and stepwise regression analyses. Sixteen EHT were treated with an angiotensin-converting enzyme inhibitor (temocapril, 4 mg/d; n=9) or an angiotensin II receptor blocker (candesartan, 8 mg/d; n=7) for 2 weeks. Treatment with temocapril or candesartan significantly decreased blood pressure and increased M value and adiponectin concentrations but did not affect BMI and HDL cholesterol. These results suggest that hypoadiponectinemia is related to insulin resistance in essential hypertension and that RAS blockade increases adiponectin concentrations with improvement in insulin sensitivity. (Hypertension. 2003;42:76-81.)

Key Words: adiponectin • hypertension, essential • insulin resistance • renin-angiotensin system

Adipose tissue was once thought to be simply a depot for fuel storage in the form of triglyceride. However, it is now known that adipocytes secrete a variety of proteins, such as tumor necrosis factor (TNF)-α, plasminogen activator inhibitor-1, leptin, resistin, and adiponectin. These proteins are implicated in a wide range of biological effects. Adiponectin, an adipocyte-derived protein referred to as Acrp30, apM1, AdipoQ, and GBP28, has been independently identified and characterized. In contrast to other adipocyte-derived proteins, the circulating levels of adiponectin are reduced in patients with coronary artery disease and in states of insulin resistance such as obesity and type 2 diabetes. Adiponectin has been suggested to enhance insulin sensitivity and prevent atherosclerosis. Furthermore, thiazolidinediones, currently being used as insulin sensitizers in the treatment of type 2 diabetes, have been shown to enhance the mRNA levels and plasma levels of adiponectin in human subjects and animal models of insulin resistance and type 2 diabetes.

Insulin resistance and accompanying hyperinsulinemia have been linked to the onset and progression of hypertension and atherosclerosis. It has been shown that approximately 40% of essential hypertensives are insulin-resistant. Although there have been 2 recent studies on the concentrations of adiponectin in patients with essential hypertension, the results are inconsistent. In those studies, some subjects had been taking antihypertensive drugs, which might influence insulin sensitivity, and a method for reliable and direct assessment of insulin sensitivity such as the euglycemic-hyperinsulinemic glucose clamp method was not used. In addition, antihypertensive drugs such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been reported to improve insulin sensitivity, but there are no reports on the relationship between adiponectin concentrations and blockade of the renin-angiotensin system (RAS).

We therefore examined the association between insulin sensitivity assessed by the euglycemic-hyperinsulinemic glucose clamp technique and adiponectin concentrations in patients with essential hypertension as well as the effect of RAS blockade on adiponectin concentrations in patients with essential hypertension.
Methods

Study Protocol 1

Two groups of subjects were enrolled in this study: 30 mild-to-moderate essential hypertensive patients (EHT; mean age: 46.4 ± 10.6 years) and 20 body mass index (BMI)-matched normotensive subjects (NT; mean age: 45.6 ± 13.9 years). The subjects had been taking no medication or had stopped taking all drugs that may affect insulin sensitivity at least 2 weeks before the start of the study. None of the subjects had any evidence of complications such as endocrine or metabolic disturbances, cerebrovascular or cardiovascular disease, or renal disease. All of the subjects were hospitalized and were put on a regular diet (2000 kcal/d) that included 310 g of carbohydrate, 50 g of fat, 80 g of protein, 120 mmol of sodium, and 75 mmol of potassium for more than 1 week. Insulin sensitivity was evaluated as the M value (metabolic clearance rate of glucose, mg·m⁻²·min⁻¹) by the euglycemic-hyperinsulinemic glucose clamp technique. Mean ± 1 SD of the M value in the NT was chosen as the cutoff point for insulin resistance. On the basis of this value, the EHT were divided into two groups: one group of insulin-resistant EHT (EHT-R) and one of non-insulin-resistant EHT (EHT-N). Before the clamp study, blood pressure was measured and blood samples were obtained from all of the subjects. The concentrations of adiponectin, glucose, insulin, and lipid variables were measured. This study was performed with the approval of the ethics committee of our institution, and informed consent was obtained from all of the subjects.

Study Protocol 2

We also examined the effect of RAS blockade on insulin resistance and serum adiponectin concentrations in patients with essential hypertension. Sixteen patients with essential hypertension were recruited from the EHT in study protocol 1 and treated with an angiotensin-converting enzyme inhibitor, temocapril (4 mg/d, n = 12) or an angiotensin II receptor blocker, candesartan (8 mg/d, n = 4) for 2 weeks in hospital. Insulin sensitivity was evaluated by glucose clamp study before and after treatment. Blood samples were obtained before the clamp study.

Euglycemic-Hyperinsulinemic Glucose Clamp Technique

A 2-hour euglycemic-hyperinsulinemic glucose clamp was performed according to the method described by DeFronzo et al.²⁰ A vein in a forearm was cannulated for blood glucose monitoring. During the glucose clamp, blood was continuously withdrawn at 2.0 mL/h through a catheter. In addition, a contralateral antecubital vein was cannulated with a plastic cannula for the infusion of insulin and glucose. Continuous insulin infusion, monitoring of glucose concentration, and infusion of various amounts of glucose in order to clamp glucose levels in the basal state were performed with a model STG-22 artificial endocrine pancreas (Nikkiso Corp). The infusion rate of insulin (human R U-40, Shionogi Pharmaceutical Co) was 40 mU · m⁻² · min⁻¹. During insulin infusion, euglycemia was maintained by infusion of a 20% glucose solution. The mean rate of glucose infusion for the last 30 minutes of the clamp was used as an index of insulin sensitivity (M value). The M value was expressed as milligrams of glucose per square meter of body surface area.

Laboratory Investigations

Serum adiponectin level was measured using a commercially available sandwich enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals Co, Ltd) as previously reported.¹³ Fasting plasma glucose was determined by the glucose oxidase method. Fasting plasma insulin was measured by a radioimmunoassay method (Insulin RIA bead, Dianabot). Serum lipid profiles, including total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and free fatty acid (FFA), were estimated by enzymatic methods.

Statistical Analysis

Numeric variables are expressed as mean ± SD in protocol 1 and as median (range) in protocol 2. Group statistical comparisons were assessed by one-way analysis of variance and the χ² test. Linear regression analysis was used to determine the correlation between 2 variables. Multiple linear regression analysis was performed by using serum adiponectin level as a dependent variable and age, gender, BMI, mean blood pressure, M value, HDL cholesterol, triglycerides, and FFA as independent variables. Stepwise regression analysis was also performed in a forward direction with F for the entry set to 4, showing the percentage of variance in the adiponectin concentration that significant independent variables explained (r²). The difference between 2 paired variables in protocol 2 was analyzed by Wilcoxon signed rank test. A probability value of < 0.05 was considered statistically significant.

Results

Study Protocol 1

The EHT showed a significantly higher mean blood pressure and a lower M value than did the NT. Using a cutoff point of mean ± 1 SD of the M value in the NT, the EHT were divided into two groups: one group of 12 EHT-R and one group of 18 EHT-N. As shown in Table 1, there were no intergroup differences in age, gender, and BMI. Mean blood pressures in the EHT-R and EHT-N were comparable. The EHT-R had significantly higher levels of fasting insulin and triglyceride than did the NT and EHT-N. The EHT-R had higher levels of FFA and lower levels of HDL cholesterol than did the EHT-N. The levels of fasting plasma glucose and total cholesterol in the three groups were similar. No significant differences were found between lipid variables in the NT and EHT-N. In all of the subjects, the M value was negatively correlated with the levels of fasting insulin (r = -0.57, P < 0.01) and FFA (r = -0.44, P < 0.01).

The EHT-R had significantly lower levels of serum adiponectin concentrations than did the NT and EHT-N (Table 1). Although adiponectin concentrations were significantly higher in women than in men (6.3 ± 2.0 versus 4.8 ± 2.0 μg/mL, P < 0.01), serum adiponectin concentrations in the

<table>
<thead>
<tr>
<th>Variables</th>
<th>NT (n = 20)</th>
<th>EHT-N (n = 18)</th>
<th>EHT-R (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.6 ± 13.9</td>
<td>46.3 ± 9.7</td>
<td>46.3 ± 12.1</td>
</tr>
<tr>
<td>Men/Women, n</td>
<td>10/10</td>
<td>9/9</td>
<td>5/7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5 ± 2.7</td>
<td>24.7 ± 2.9</td>
<td>25.3 ± 2.5</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>93.4 ± 10.7</td>
<td>111.5 ± 13.9*</td>
<td>106.3 ± 21.0*</td>
</tr>
<tr>
<td>M value, mg · m⁻² · min⁻¹</td>
<td>184.6 ± 46.5</td>
<td>197.0 ± 41.2</td>
<td>120.3 ± 13.9*</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>4.9 ± 0.5</td>
<td>4.8 ± 0.4</td>
<td>4.9 ± 0.6</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>29.2 ± 13.9</td>
<td>23.7 ± 8.7</td>
<td>48.5 ± 28.7†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.9 ± 0.9</td>
<td>4.7 ± 1.0</td>
<td>4.6 ± 1.0</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.1†</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.4</td>
<td>1.3 ± 1.0†</td>
</tr>
<tr>
<td>Free fatty acid, mmol/L</td>
<td>0.51 ± 0.26</td>
<td>0.34 ± 0.17</td>
<td>0.62 ± 0.39†</td>
</tr>
<tr>
<td>Adiponectin, μg/mL</td>
<td>5.7 ± 2.3</td>
<td>6.0 ± 2.1</td>
<td>4.2 ± 1.4†</td>
</tr>
</tbody>
</table>

Values are expressed as number (n) or mean ± SD. NT indicates normotensive subjects; EHT-N, essential hypertensive patients with no insulin resistance; EHT-R, essential hypertensive patients with insulin resistance; and M value, metabolic clearance rate of glucose as an index of insulin sensitivity. Group comparisons were assessed by one-way analysis of variance and the χ² test. *P < 0.01 vs NT; †P < 0.01 vs EHT-N.
EHT-R were lower than those in the NT and EHT-N regardless of gender. In all of the subjects, serum adiponectin levels were positively correlated with the M value \((r=0.44, P<0.01)\) and HDL cholesterol levels \((r=0.51, P<0.01)\) and negatively with BMI \((r=-0.62, P<0.01)\) and levels of fasting insulin \((r=-0.39, P<0.01)\), FFA \((r=-0.29, P<0.05)\), and triglyceride \((r=-0.33, P<0.05)\) but not correlated with mean blood pressure. Multiple regression analysis showed that gender, the M value, BMI, and HDL cholesterol levels were independently correlated with the serum adiponectin concentrations. Stepwise regression analysis also revealed that gender, the M value, BMI, and HDL cholesterol levels were independent determinants of adiponectin concentrations, explaining a total of 67\% of the variance in this measure \((r^2=0.67)\).

**Study Protocol 2**

Treatment with temocapril or candesartan significantly decreased mean blood pressure and FFA levels and increased the M value (Table 2). Fasting insulin levels were decreased, but not significantly, by treatment with temocapril \((P=0.06)\) or candesartan \((P=0.08)\). There were no significant changes in BMI and levels of fasting plasma glucose, total cholesterol, HDL cholesterol, and triglyceride. Both temocapril and candesartan significantly increased adiponectin concentrations (Figure). There were mean 15\% and 30\% increases in adiponectin levels after treatment with temocapril and candesartan, respectively. Adiponectin concentrations were increased in 15 of the 16 patients. The change in M value was significantly correlated with that in adiponectin concentrations \((r=0.59, P<0.05)\). There was no significant difference between the changes in adiponectin levels by treatment in men and women.

**Discussion**

Four notable findings were obtained in the present study. First, adiponectin concentrations in insulin-resistant essential hypertensives were lower than those in normotensives and non–insulin-resistant hypertensives, suggesting that hypoadiponecetinemia in essential hypertensives is attributable to insulin resistance. This finding is in accordance with previous findings that adiponectin levels are reduced in states of insulin resistance such as obesity and type 2 diabetes. Second, adiponectin levels were significantly correlated with the degree of insulin sensitivity in the whole body (M value) estimated by glucose clamp study, and the M value was an independent predictor of adiponectin concentration. Third, our findings are generally consistent with previous findings in Japanese women of a positive association between adiponectin concentrations and HDL cholesterol levels. This relationship was independent of obesity and insulin sensitivity in the present study. Finally, RAS blocking agents such as temocapril and candesartan increased adiponectin levels with accompanying improvement in insulin sensitivity but did not affect the degree of adiposity. To the best of our knowledge,
this is the first report on the effect of RAS blockade on circulating adiponectin concentrations.

Both temocapril and candesartan, which were used in the present study, have been reported to improve insulin sensitivity. Several possible mechanisms of improvement in insulin sensitivity by RAS blockade have been suggested. Angiotensin II has been shown to increase serine phosphorylation of the insulin receptor, insulin receptor substrate 1, and phosphatidylinositol-3-kinase (PI3K), which result in an impairment of insulin signaling. A possible mechanism of improvement in insulin sensitivity is that RAS blockade causes inhibition of the impairment of insulin signaling by angiotensin II, resulting in activation of the glucose transporter and its translocation from an intracellular membrane compartment to a plasma membrane fraction. Other mechanisms may include the following: vasodilation, which increases the blood flow in skeletal muscle; an increase in the ratio of insulin-sensitive type 1 fiber in muscle fiber composition; and a decrease in TNF-α in skeletal muscle. An increase in adiponectin levels caused by RAS blockade may also be a novel mechanism for RAS blockade-mediated enhancement of whole-body insulin sensitivity.

However, the precise mechanisms by which RAS blockade leads to an increase in circulating adiponectin levels are unclear. It has been suggested that adiponectin levels can be increased after weight reduction. RAS blockade, however, does not affect BMI in the present study. We speculate that the mechanisms of an increase in adiponectin concentrations may include the following processes.

First, the increase in serum adiponectin levels could be the result of enhanced insulin sensitivity. It has been reported that insulin infusion during a glucose clamp study leads to a decrease in adiponectin concentrations, suggesting that chronic hyperinsulinemia associated with an insulin-resistant state leads to a decrease in adiponectin concentrations. This raises the idea that the effect of RAS blockade on adiponectin levels is, at least partly, mediated by the decrease in insulin levels, which is secondary to the effect of RAS blockade on enhancing insulin sensitivity. Although administration of thiazolidinediones, peroxisome proliferator-activated receptor (PPAR) agonists, has been shown to increase adiponectin concentrations, treatment with metformin, a non-PPAR-α-associated antihyperglycemic agent, or fenofibrate, a PPAR agonist that has recently been shown to improve insulin sensitivity, has been reported to have no effect on adiponectin concentrations in mice. This indicates that the change in adiponectin concentrations is not simply a consequence of an improved metabolic phenotype and that the change in adiponectin levels is indeed (directly or indirectly) RAS blockade-mediated.

Second, based on results of recent in vitro studies showing that angiotensin II markedly inhibits adipogenic differentiation of human adipocytes via the angiotensin type 1 receptor and that expression of angiotensin II–forming enzymes in adipose tissue is inversely correlated with insulin sensitivity, Sharma et al have hypothesized that RAS blockade promotes the recruitment and differentiation of preadipocytes and that increased formation of small insulin-sensitive adipocytes counteracts the ectopic deposition of lipids in muscle and liver, thereby improving insulin sensitivity. With regard to thiazolidinediones, it has been shown in a previous study that 15-day treatment with troglitazone did not change the total weight of white adipose tissues but increased the number of small adipocytes and decreased the number of large adipocytes. Adiponectin secretion may be directly affected by adipocyte differentiation. RAS blockade is likely to promote an increase in adipogenesis that may result in a greater net capacity for adiponectin production. However, because the hypothesis by Sharma et al has not been proved yet in vivo, further investigations of adipogenesis during a relatively short period of RAS blockade seem to be needed.

Moreover, the increase in adiponectin levels caused by RAS blockade may be regulated at a level of posttranscription, including translation and/or secretion, because the magnitude of increase in adiponectin levels caused by RAS blockade for 2 weeks in the present study was low compared with the previously reported 130% increase in circulating adiponectin concentrations in normal glucose-tolerant subjects after 14-day treatment with rosiglitazone, a PPAR-γ agonist. It has also been shown that angiotensin II does not influence the gene expression of adiponectin in 3T3-L1 adipocytes. The fact that insulin-stimulated adiponectin exocytosis in 3T3-L1 adipocytes is mediated in a PI3K-dependent fashion may be relevant to a posttranslational mechanism, because angiotensin II has been shown to inhibit insulin-mediated PI3K activity.

Lastly, since it has been shown that TNF-α suppresses expression and secretion of adiponectin in 3T3-L1 adipocytes and that RAS blockade decreases TNF-α levels in skeletal muscle and mononuclear cells but not yet confirmed in adipose tissue, the increase in adiponectin secretion could be caused by a decrease in TNF-α levels or actions in adipocytes.

The influence of candesartan on serum adiponectin concentrations seems to be greater than that of temocapril in the present study. However, the mean change in the M value caused by candesartan was higher, but not significantly, than that caused by temocapril. Because change in the M value was correlated with change in adiponectin concentrations, the difference between changes in adiponectin levels caused by candesartan and temocapril may be related to the change in the M value.

There have been 2 recent reports on the concentrations of adiponectin in patients with essential hypertension. Adamczak et al reported that plasma adiponectin concentrations were decreased in patients with essential hypertension. In contrast, Mallamaci et al showed that adiponectin levels were higher in hypertensive patients than in normotensive subjects and were inversely related to creatinine clearance in hypertensive patients and that creatinine clearance was the only independent predictor of adiponectin concentrations. It is possible that latent renal dysfunction had complicated essential hypertension in the latter study. Thus, results of recent studies on adiponectin in essential hypertension have been inconsistent. Our results showed that adiponectin concentrations were reduced in insulin-resistant essential hypertensives but not normotensives or non-insulin-resistant
hypertensives, suggesting that hypoadiponectinemia in essential hypertensives is associated with insulin resistance.

Adiponectin concentrations were not related to mean blood pressure in the present study. Contrary to this result, significant negative correlations were found between plasma adiponectin concentration and mean, systolic, and diastolic blood pressures in 33 essential hypertensives and 33 normotensives. Other studies, however, demonstrated that adiponectin levels were not related to blood pressure in 180 overweight/obese Asian subjects or in 36 hypertensive patients. Moreover, another study showed that serum adiponectin levels were negatively correlated with systolic blood pressure and diastolic blood pressure in a large number of Japanese subjects (705 men and 262 women), but these correlations were not significant after adjustment for age, gender, and BMI. In animal studies, effects of recombinant adiponectin on body weight, glucose, and lipid metabolism have been clearly demonstrated. However, its effect on blood pressure regulation has not been reported. The delineation of the relation between adiponectin and blood pressure requires more study.

One limitation of this study is the small number of subjects enrolled. We demonstrated that serum adiponectin concentrations were gender-related, being higher in women than in men as previously reported. Although there was no intergroup difference in gender in the present study, it is important to confirm our findings by studies with more patients. Furthermore, studies with larger populations of subjects in whom various kinds of RAS blocking agents are used seem to be needed.

In conclusion, our results suggest that hypoadiponectinemia and disturbance of lipid metabolism are associated with insulin resistance in patients with essential hypertension and that RAS blockade increases serum adiponectin concentrations with improvement in insulin sensitivity.

Perspectives

It has been suggested that adiponectin modulates endothelial function and has an inhibitory effect on vascular smooth muscle cell proliferation. Moreover, adiponectin has been shown to be accumulated in an injured artery from the plasma and to suppress macrophage-to-foam cell transformation in vitro and in vivo. On the basis of these observations, it is possible that reduction in adiponectin concentrations may account, at least in part, for the higher incidence of atherosclerotic diseases in essential hypertension and that RAS blockade increases serum adiponectin concentrations with improvement in insulin sensitivity.

Recent clinical trials, such as the Captopril Primary Prevention Project (CAPP), the Heart Outcomes Prevention Evaluation (HOPE), and the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), suggest that RAS blockade may substantially lower the risk for type 2 diabetes. One of the mechanisms underlying this effect may be an increase in adiponectin concentrations by RAS blockade. The demonstration that RAS blockade increases adiponectin concentrations with improvement in insulin sensitivity might provide a scientific rationale for the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers for the prevention of diabetes in high-risk hypertensive patients.

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