Angiotensin II–Induced Insulin Resistance Is Associated With Enhanced Insulin Signaling

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Abstract—Angiotensin II (AII) is involved in the pathogenesis of both hypertension and insulin resistance, though few studies have examined the relationship between the two. We therefore investigated the effects of chronic AII infusion on blood pressure and insulin sensitivity in rats fed a normal (0.3% NaCl) or high-salt (8% NaCl) diet. AII infusion for 12 days significantly elevated blood pressure and significant insulin resistance, assessed by a hyperinsulinemic-euglycemic clamp study and glucose uptake into isolated muscle and adipocytes. High-salt loading exacerbated the effects of AII infusion significantly. Despite the insulin resistance, insulin-induced tyrosine phosphorylation of the insulin receptor and insulin receptor substrates, activation of phosphatidylinositol (PI) 3-kinase, and phosphorylation of Akt were all enhanced by AII infusion. Subsequently, to investigate whether oxidative stress induced by AII contributes to insulin resistance, the membrane-permeable superoxide dismutase mimetic, tempol, was administered to AII-infused rats. Chronic AII infusion induced an accumulated plasma cholesteryl ester hydroperoxide levels, indicating the increased oxidative stress, whereas the treatment with tempol normalized plasma cholesteryl ester hydroperoxide levels in AII-infused rats. In addition, the treatment with tempol normalized insulin resistance in AII-infused rats, shown as a decreased glucose infusion rate in the hyperinsulinemic euglycemic clamp study and a decreased insulin-induced glucose uptake into isolated skeletal muscle, as well as enhanced insulin-induced PI 3-kinase activation to those in the control rats. These results strongly suggest that AII-induced insulin resistance cannot be attributed to impairment of early insulin-signaling steps and that increased oxidative stress, possibly through impaired insulin signaling located downstream from PI 3-kinase activation, is involved in AII-induced insulin resistance. (Hypertension. 2002;40:872-879.)

Key Words: angiotensin II ■ insulin resistance ■ oxidative stress ■ glucose clamp technique ■ sodium ■ kinase

Several lines of evidence point to an association between hypertension and insulin resistance,1,2 eg, hypertensive individuals are more likely to become diabetic than normotensive ones.3 It is therefore notable that angiotensin II (AII) is reportedly involved in the development of both hypertension and insulin resistance,4–7 and agents that inhibit the action of AII, ie, angiotensin-converting enzyme inhibitors and type 1 AII (AT1) receptor antagonists, not only reduce blood pressure but also restore insulin sensitivity.8–14 It has been suggested that crosstalk between AII- and insulin-signaling pathways underlies AII-induced insulin resistance. According to that model, AII induces tyrosine phosphorylation of insulin receptor substrate (IRS)-1 by Janus kinase 2 (JAK2) associated with the AT1 receptor, thereby attenuating insulin-induced activation of phosphatidylinositol (PI) 3-kinase associated with IRS-1, which in turn diminishes insulin sensitivity.15,16 However, these findings are based solely on the acute effects of a single stimulation of heart tissue15 or cultured aortic smooth muscle cells.16 We felt that a more accurate picture of the signaling pathway mediating AII-induced insulin resistance would be obtained by examining the chronic in vivo effects of AII on insulin-sensitive tissues. We hypothesized that AII would induce insulin resistance in vivo, whether administered acutely or chronically, but that the molecular mechanism underlying the insulin resistance induced by chronic AII infusion might differ somewhat from that induced by a single acute infusion.

Recently, considerable attention has been given to the role of increased oxidative stress in the development of AII-induced hypertension and vascular injury.17,18 We, therefore,
considered the possibility that oxidative stress is involved in the molecular mechanism underlying AII-induced insulin resistance and examined the effects of tempol, a membrane-permeable superoxide dismutase mimetic that should eliminate oxidative stress. Given the results obtained, we discuss the potential importance of oxidative stress in the pathogenesis of AII-induced insulin resistance.

**Methods**

**Materials**

Affinity-purified antibodies against IRS-1, IRS-2, IRS-3, and glucose transporter 4 (GLUT4) were prepared as previously described. Antibodies against Akt and phosho-Scr473 Akt were purchased from Upstate Biotech Inc. Human AII was from Sigma-Aldrich Japan and human insulin (Novolin™ R) was from Novo Nordisk. Tempol (4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) was from Wako Pure Chemical Industries, Ltd.

**Animals**

Seven-week-old male Sprague-Dawley rats (Tokyo Experimental Animals, Tokyo, Japan) were intravenously infused with normal saline (control group) or AII for 12 days at a rate of ~100 ng/kg per minute using Alzet osmotic minipumps (model 2002). All-infused rats were fed a standard rodent diet containing 0.3% NaCl (AII salt group) or high-salt diet containing 8% NaCl (AII salt group) during the infusion period. In some experiments, tempol was administered in the drinking water (1 mMol/l) for 12 days. The animal care and use was in strict accordance with the policies of the University of Tokyo, and the study protocol was approved by the Institutional Review Board of the Institute for Adult Diseases, Asahi Life Foundation.

**Hyperinsulinemic-Euglycemic Clamp Study**

Rats were anesthetized by intraperitoneal injection of pentobarbital sodium (60 mg/kg body weight), after which the jugular and femoral veins were catheterized for blood sampling and infusion, respectively. Hyperinsulinemic-euglycemic clamp analysis was performed as described previously.

**Glucose Uptake Into Isolated Soleus Muscle**

Rats were anesthetized and the soleus muscles were dissected out and rapidly cut into 20- to 40-mg strips. The rats were then euthanized by intracardiac injection of pentobarbital. Isolated strips of soleus muscle were incubated for 20 minutes, with or without 1.44 x 10^-9 mol/L human insulin (equivalent to 2 mL/mL), as described previously. 2-DG uptake into the strips was measured as described previously.

**Preparation of Rat Adipocytes and Measurement of Glucose Uptake**

Isolated rat adipocytes were prepared from epididymal adipose tissue harvested from fasted rats using the collagenase method, and then 2-DG uptake was assayed as previously described.

**Insulin-Induced GLUT4 Translocation in Isolated Soleus Muscle and Adipocytes**

Isolated soleus muscle was incubated for 20 minutes, with or without 1.44 x 10^-9 mol/L human insulin, as described above. In addition, isolated adipocytes were suspended in Krebs-Ringer bicarbonate (KRB) buffer containing 1% BSA and incubated with or without 10^-6 mol/L insulin for 15 minutes at 37°C. Insulin-induced GLUT4 translocation was then measured essentially as described previously. Briefly, subcellular membrane fractions were prepared by sequential differential centrifugation. Homogenates of isolated soleus muscle and adipocytes were centrifuged at 3000g for 15 minutes to sediment the crude membrane fraction. The supernatant was then centrifuged at 12 000g for 15 minutes to sediment the plasma membrane (PM) fraction. This supernatant was in turn centrifuged at 28 000g for 15 minutes, after which the resultant supernatant was centrifuged at 146 000g for 75 minutes, yielding a particulate fraction termed the low-density microsomes (LDM). Proteins (0.05 mg) in the PM and LDM fractions were separated by SDS-PAGE, transferred to a polyvinylidene fluoride membrane, immunoblotted with anti-GLUT4 antibody, and reacted with enhanced chemiluminescence (ECL) reagent (Amersham Life Science). Levels of chemiluminescence were quantified using a molecular imager GS-525 with a Screen-HC.

**Preparation of Rat Primary Hepatocytes and Measurement of Glycogen Synthase Activity**

Hepatocytes were isolated from fasted rats by collagenase perfusion, as described previously. The cells were serum-starved for 3 hours and then incubated with 10^-6 mol/L insulin for 15 minutes at 37°C. Insulin-induced glycogen synthase activation was evaluated as described previously.

**Protein Levels and Tyrosine Phosphorylation of the Insulin Receptor (IR) and IRSs**

Rats fasted overnight were anesthetized, and within 10 to 15 minutes the abdominal cavity was opened, the portal vein exposed, and 16 mL/kg body weight of normal saline (0.9% NaCl), with or without 10^-7 mol/L human insulin, were injected. Livers, hindlimb muscles, and epididymal adipose tissue were then removed and immediately homogenized as described previously. After the centrifugation, the resultant supernatants were used for immunonephelometry or immunoblotting as described previously.

**PI 3-Kinase Activity**

After preparing tissue samples as described above, IRS-1, IRS-2, and IRS-3 (liver and adipose tissue lysates only) were immunoprecipitated and PI 3-kinase activity in the immunoprecipitates was assayed as previously described.

**Analysis of Lipid Hydroperoxide in Plasma**

Cholesteryl ester hydroperoxides (CEOOH) were analyzed by high-performance liquid chromatography (HPLC) using 234 nm UV detection and post-column chemiluminescence detection on an LC-8 column (Supelco, 4×250 mm, 5 μm particles) and methanol/tert-butyl alcohol (95/5 vol) as an eluent as described previously, with slight modifications. Briefly, plasma was extracted with 10 volumes of methanol and 50 volumes of hexane. After removing the hexane phase, the samples were dried under N2 gas and redissolved in an eluent for HPLC injection.

**Statistical Analysis**

Data are expressed as means±SE. Comparisons were made using unpaired t tests. Values of P<0.05 were considered significant.

**Results**

Characterization of the Rats Studied

The AII-infused rats had significantly lower body weights than control rats; food intake by AII-infused rats was lower and water intake was higher than for controls (Table 1). Although food intake was similar among all AII-infused animals, body weights were lower in the AII-salt group than in the AII group. Both the AII and AII-salt groups showed significantly higher systolic and diastolic blood pressures than controls, and the systolic pressures in the AII-salt group were also significantly higher than in the AII group. Although fasting blood glucose and plasma insulin levels in the AII-infused rats were slightly, but not significantly, higher than for controls, when randomly fed, plasma insulin levels were significantly higher in AII-infused rats. Plasma renin...
activity in AII-infused rats was significantly lower than in controls, and again the effect was significantly more pronounced in the AII+salt group than in the AII group. Plasma aldosterone levels in AII-infused rats were significantly higher than in controls.

**Hyperinsulinemic-Euglycemic Clamp Analysis**
Whole-body insulin sensitivity was evaluated using the hyperinsulinemic-euglycemic clamp technique (Table 1). During submaximal insulin infusion into AII-infused rats, the glucose infusion rate (GIR) was 55.1% lower and the glucose use rate, mg/kg per minute was 261% higher than in controls, suggesting impairment of insulin's ability to suppress HGP. Finally, glucose uptake into muscle during the clamp (Rg) was reduced to 58.5% of control in AII-infused rats. The effects of AII infusion on GIR, GUR, HGP, and Rg were all significantly enhanced in the AII+salt group, suggesting that chronic infusion of AII induces insulin resistance and that the effects are exacerbated by salt loading.

**Insulin-Induced Glucose Uptake and GLUT4 Translocation in Isolated Adipocytes**
Insulin-induced glucose uptake by isolated adipocytes was reduced to 79.3% and 50.0% of control in the AII and AII+salt groups, respectively (Figure 1C). Although the total GLUT4 content was similar among all 3 groups, insulin-stimulated GLUT4 translocation was significantly lower in the AII and AII+salt groups (Figure 1D).

**Insulin-Induced Glycogen Synthase Activation in Primary Cultured Hepatocytes**
In liver, insulin stimulates glycogen synthesis through activation of glycogen synthase, the rate-limiting synthetic enzyme. We found that insulin-stimulated glycogen synthase activation was reduced to 75.4% and 63.9% of that in controls, respectively, in primary cultured hepatocytes from AII and AII+salt groups (Figure 1E).

Taken together, the findings presented thus far indicate that chronic infusion of AII induces insulin resistance in skeletal muscle, adipose tissue, and liver and that high-salt loading exacerbates this AII-induced insulin resistance.

**Insulin-Induced Tyrosine Phosphorylation of the IR and IRS Proteins**
We next investigated insulin-induced tyrosine phosphorylation of the IR and IRSs in skeletal muscle, liver, and adipose tissue.
tissue in vivo. In muscle from AII-infused rats, insulin-induced tyrosine phosphorylation of IR, indicated by a band at ~90 kDa immunoprecipitated by α-PY, was increased 2.4-fold over control (Figure 2A). Expression of muscle IRS-1 and IRS-2 in AII-infused rats was similar to that in controls (Figures 2B and 2C, upper panels), though insulin-induced tyrosine phosphorylation of those proteins was increased 3.6- and 4.3-fold, respectively (Figures 2B and 2C, lower panels). Among AII-infused rats, levels of insulin-induced tyrosine phosphorylation of IR, IRS-1, and IRS-2 were slightly higher in muscle from the AII+salt group than that from the AII group. Similar patterns of enhanced insulin-induced tyrosine phosphorylation of IR, IRS-1, IRS-2, and IRS-3 were observed in liver and adipose tissue, whereas expression of these proteins in AII-infused rats was not different from that in control rats (Figures 2D to 2K). Thus, chronic infusion of AII enhanced insulin-induced tyrosine phosphorylation of IR and IRSs and, as with induction of insulin resistance, salt loading exacerbated the effect.

**Insulin-Induced PI 3-Kinase Activation and Akt Phosphorylation**

Insulin-stimulated PI 3-kinase activity associated with IRS-1 and IRS-2 was increased 2.5- and 2.1-fold, respectively, in muscle from the AII-infused rats (Figures 3A and 3B); the activity associated with IRS-1 was increased still further in...
the AII+salt group. In liver and adipose tissue from AII-infused rats, insulin-stimulated PI 3-kinase activities associated with IRS-1, IRS-2, and IRS-3 were significantly increased 1.9- to 4.0-fold (Figures 3C to 3H), and further increased in the AII+salt group.

The kinase activity of Akt is regulated by PI 3-kinase products and by serine/threonine phosphorylation, in part, on Ser-473. Although the amounts of Akt protein in the control, AII, and AII+salt groups were comparable, insulin-stimulated phosphorylation of Ser-473 of Akt in skeletal muscle, liver, and adipose tissue from AII-infused rats was increased 2.3-, 2.2-, and 2.5-fold, respectively, over controls (Figures 3I to 3K). Among the AII-infused rats, high-salt loading enhanced Akt phosphorylation in all 3 tissues, with significant effects being observed in liver and adipose tissue. Apparently, the early insulin-signaling steps leading to PI 3-kinase activation and Akt phosphorylation are not impaired in AII-infused rats, despite the presence of insulin resistance.

**Effects of Tempol Administration on AII-Infused Rats**

To investigate the role of oxidative stress in AII-induced insulin resistance, AII-infused rats were administered tempol, a stable spin trap for superoxide. The average body weight of the tempol-treated, AII-infused rats was slightly higher than that of nontreated AII-infused rats (Table 2). Furthermore, tempol treatment significantly decreased blood pressure in AII-infused rats, but not in control rats. We then measured plasma levels of CEOOH as an indicator of oxidative stress and found them to be 2.0-fold higher than controls in AII-infused rats. Tempol administration reversed the elevated CEOOH levels seen in AII-infused rats (Figure 4A).

### Table 2. Effects of Tempol Administration on All-Infused Rats

<table>
<thead>
<tr>
<th>Characterization of rats</th>
<th>Control</th>
<th>All</th>
<th>Control+Tempol</th>
<th>All+Tempol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>313.4±4.3</td>
<td>250.2±6.8</td>
<td>292.7±8.1</td>
<td>262.2±6.2</td>
</tr>
<tr>
<td>Food intake, g/day</td>
<td>29.4±2.5</td>
<td>21.4±1.3*</td>
<td>28.4±0.6</td>
<td>21.6±0.2</td>
</tr>
<tr>
<td>Water intake, ml/day</td>
<td>37.1±1.8</td>
<td>60.3±1.1†</td>
<td>41.3±1.4</td>
<td>38.8±3.3§</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>126.6±5.2</td>
<td>183.5±5.0</td>
<td>126.1±4.7</td>
<td>149.8±5.8§</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74.3±5.4</td>
<td>107.4±9.5</td>
<td>66.7±2.6</td>
<td>91.2±10.4</td>
</tr>
<tr>
<td>Hyperinsulinemic euglycemic clamp study</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Glucose infusion rate, mg/kg per minute</td>
<td>22.8±0.7</td>
<td>14.3±0.6†</td>
<td>23.6±0.4</td>
<td>20.8±0.6§</td>
</tr>
<tr>
<td>Glucose use rate, mg/kg per minute</td>
<td>23.7±1.1</td>
<td>16.8±1.4*</td>
<td>24.0±0.5</td>
<td>20.9±0.4‡</td>
</tr>
<tr>
<td>Hepatic glucose production, mg/kg per minute</td>
<td>0.78±0.40</td>
<td>2.93±0.76*</td>
<td>0.45±0.44</td>
<td>0.38±0.56‡</td>
</tr>
<tr>
<td>Rg' in muscle, mmol/100 g per minute</td>
<td>5.93±0.49</td>
<td>2.66±0.07*</td>
<td>5.44±0.71</td>
<td>5.26±0.69§</td>
</tr>
</tbody>
</table>

Data are mean±SE (n=4–6 rats in each group). Control+tempol indicates normal saline-infused rats given tempol (1 mol/L in drinking water for 12 days); All+Tempol, All-infused rats given tempol; Rg', glucose metabolic index.
*P<0.05 and †P<0.01 compared with the control; §P<0.05 and ‡P<0.01 compared with the All.
Effects of Tempol Administration on AII-Induced Insulin Resistance and Insulin Signaling

When analyzed in a hyperinsulinemic-euglycemic clamp study, tempol administration reversed the diminished GIR, GUR, and RG, and elevated HGP seen in AII-infused rats (Table 2). In addition, tempol improved insulin-induced 2-DG uptake in isolated soleus skeletal muscle (B), and reduced PI 3-kinase activation to control levels without affecting PI 3-kinase activation in control rats (Figures 5A and 5B, muscle; 5C to 5E, liver; and 5F to 5H, fat).

Taken together, the results of the tempol experiments suggest that AII-infusion induces oxidative stress that leads to insulin resistance and altered insulin signaling, and that both insulin sensitivity and signaling can be restored to normal by removing the oxidative stress.

Discussion

In the present study, we demonstrated that chronic infusion of AII into normal rats induces hypertension and insulin resistance. Euglycemic-hyperinsulinemic clamp analysis showed that peripheral glucose use was impaired in AII-infused rats, as was insulin-induced glucose uptake and GLUT4 translocation in isolated muscle and adipocytes and glycogen synthase activation in primary hepatocytes. It is unclear why the body weights of AII-infused rats were slightly lower than those of control rats, though it is notable that AII-infused rats were more insulin-resistant than controls despite the lower body weight. High-salt loading exacerbated the effects of AII on both blood pressure and insulin sensitivity in AII-infused rats.

Earlier reports have suggested that insulin resistance is associated with impaired insulin-induced PI 3-kinase activation in skeletal muscle and liver from ob/ob mice, Zucker fatty rats, and dexamethasone-treated rats, and in skeletal muscle from type 2 diabetes patients and free fatty acid–infused subjects. Because PI 3-kinase activation is critical for insulin’s metabolic actions, including translocation of GLUT4 to the cell surface, glycogen synthesis, and suppression of gluconeogenesis, the explanation that insufficient PI 3-kinase activity results in a deficiency of insulin-induced glucose metabolism would seem reasonable. In addition, acute stimulation with AII induces tyrosine phosphorylation of IRS-1 by JAK2 kinase associated with the AT1 receptor in heart tissue and cultured aortic smooth muscle cells, leading to reduction of insulin-induced activation of PI 3-kinase associated with IRS-1. For that reason, attenuation of PI 3-kinase activity has been thought to occur via crosstalk between AII- and insulin-signaling pathways.

In our experiment, however, chronic AII stimulation did not, by itself, induce IRS-1 phosphorylation or reduce PI 3-kinase activation in skeletal muscle, liver, or adipose tissue (Figures 2 and 3). In fact, insulin-induced tyrosine phosphorylation of IRS, activation of PI 3-kinase, and phosphorylation of Akt were all enhanced in AII-infused rats in vivo. The discrepancy between earlier findings and those of the present study with respect to PI 3-kinase activation may be attributable to differences in the experimental conditions, eg, differences in the effects of chronically and acutely administered AII or difference in the tissues. Furthermore, we believe our analysis of the chronic effects of AII on insulin-sensitive tissues provides a more accurate picture of the impaired insulin-signaling that mediates AII-induced insulin resistance. It is likely that the step in the insulin-signaling pathway impaired by AII infusion is located downstream of PI 3-kinase and Akt, which suggests an alternative mechanism for obesity- and fatty acid–induced insulin resistance.

Although our findings do not conclusively pinpoint the molecular mechanism underlying AII-induced insulin resis-
tance, one possibility is that insulin resistance is related to oxidative stress caused by AII, which is a key feature of AII-induced hypertension.\(^{44}\) To confirm the contribution of oxidative stress to AII-induced insulin resistance, we investigated the level of plasma lipid hydroperoxide (CEOOH) and the effect of administering tempol, a stable spin trap for superoxide,\(^{45}\) on insulin resistance in AII-infused rats. This agent, which acts as a membrane-permeable superoxide dismutase mimetic and is assumed to decrease the level of superoxide in vivo, has been widely used to prove the involvement of superoxide-related molecular events in the occurrence of brain injury,\(^{46}\) mucosal damage in experimental colitis,\(^{47}\) and radiation-induced alopecia.\(^{48}\) Recently, tempol was shown to reduce vascular superoxide production\(^{49}\) and LOX-1 expression in aortic endothelium\(^{50}\) in AII-infused rats. Taking these previous reports into consideration, our data showing that tempol administration reverses the elevated CEOOH levels and insulin resistance in AII-infused rats strongly support the involvement of oxidative stress in the mechanism leading to insulin resistance. We did not measure levels of oxidative stress in muscle, liver, and adipose in this study because the low levels of cholesteryl ester in those tissues make it difficult to detect lipid hydroperoxide; moreover, data from tissues are highly prone to artifacts. Nevertheless, our blood sample data are very clear, which means that even if we cannot say that the level of oxidative stress in tissues is precisely the same as in blood, certainly the levels in blood would be expected to reflect those in the tissues.

Given the mechanism by which tempol improves insulin resistance, we must consider the possibility that tempol induces vasodilation because reduced insulin delivery into muscle and liver, secondary to diminished blood flow, might be involved in the insulin resistance of hypertensive humans and animals.\(^{51,52}\) Indeed, it should be noted that tempol administration reduced blood pressure slightly in AII-infused rats, though we did not measure regional blood flow in the present study. However, the fact that tempol administration reversed the diminished GIR in AII-infused rats to nearly normal levels suggests that the effects of tempol are attributable to decreased oxidative stress rather than to vasodilation.

In the case of 3T3-L1 adipocytes, exposure to \(\text{H}_2\text{O}_2\) resulted in impaired insulin-stimulated glucose transport and GLUT4 translocation without affecting insulin-induced PI 3-kinase activation.\(^{53,54}\) In addition, the subcellular distribution of IRS-1 and PI 3-kinase in 3T3-L1 adipocytes is reportedly affected by treatment with \(\text{H}_2\text{O}_2.\)\(^{55}\) We therefore speculate that the altered subcellular distribution of these molecules could be one of the causes of insulin resistance in AII-infused rat tissues, if oxidative stress also impairs insulin-induced GLUT4 translocation at stages distal to the activation of PI 3-kinase. In light of our findings and those of earlier investigations, it is reasonable to suggest that the enhanced PI 3-kinase activation in AII-infused rats is a compensatory reaction mediated by the impaired downstream pathway and is restored by the removal of oxidative stress.

**Perspective**

In the present study, we demonstrated that chronic infusion of AII into normal rats induces hypertension and insulin resistance; moreover, high-salt loading exacerbated most effects of AII-infusion significantly. Despite the insulin resistance, insulin-induced PI 3-kinase activation and Akt phosphorylation were actually enhanced by AII infusion. However, the fact that tempol administration normalized the level of oxidative stress in AII-infused rats, as well as the insulin resistance and PI 3-kinase activity, suggests that the mechanism underlying AII-induced insulin resistance differs from that previously associated with obesity and fatty acid-infusion. Instead, the mechanism appears to involve increased oxidative stress, possibly via impaired insulin signaling to a point downstream of PI 3-kinase activation. Although further study will be necessary to fully understand the mechanism underlying AII-induced insulin resistance, the findings of this study strongly suggest oxidative stress causes insulin resistance with hypertension.

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**References**


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