The Effects of an Angiotensin-Converting Enzyme Inhibitor and an Angiotensin II Receptor Antagonist on Insulin Resistance in Fructose-Fed Rats

Katsuhiro Higashiura, Nobuyuki Ura, Tamaki Takada, Yi Li, Takaaki Torii, Nobuhiko Togashi, Mikio Takada, Hideki Takizawa, and Kazuaki Shimamoto

The aim of this study was to compare the effects of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin II receptor (AT) antagonist on insulin resistance, especially on muscle fiber composition in fructose-induced insulin-resistant and hypertensive rats. Six-week-old male Sprague-Dawley rats were fed either normal rat chow (control) or a fructose-rich diet (FFR). For the last two weeks of a six-week period of either diet, the rats were treated with gum arabic solution as a vehicle (control or FFR), angiotensin-converting enzyme inhibitor (FFR + ACE), temocapril (1 mg/kg/day) or an angiotensin II receptor antagonist (FFR + AT), CS-866 (0.3 mg/kg/day), by gavage, and then the euglycemic hyperinsulinemic glucose clamp technique was performed to evaluate insulin sensitivity. At the end of the glucose clamp, the soleus muscle was dissected for determination of the muscle fiber composition by ATPase methods. Blood pressure at the glucose clamp in the FFR group was significantly higher than that of the control group, and both temocapril and CS-866 significantly lowered the blood pressure of the FFR group. The average rate of glucose infusion during the glucose clamp, as a measure of insulin sensitivity (M value), was significantly lower in the FFR rats compared to the controls (15.4 ± 0.4, 10.9 ± 0.6 mg/kg/min, for control and FFR, respectively, P < .01). Both temocapril and CS-866 partially improved the M values compared to FFR (13.2 ± 0.7, 12.8 ± 0.5 mg/kg/min, for FFR + ACE, FFR + AT, respectively, P < .01 compared with FFR, P < .05 compared with control). The composite ratio of type I fibers of the soleus muscle was decreased significantly in the FFR rats compared with the controls (82% ± 2%, 75% ± 2%, for control and FFR, respectively, P < .01), and both temocapril and CS-866 restored a composite ratio of type I fibers to the same level as that of the controls (81% ± 1%, 80% ± 1% for FFR + ACE and FFR + AT, respectively). The M value was significantly correlated with the composition of type I and type II fibers. These results suggest that the fiber composition of skeletal muscle is correlated to insulin resistance, and that both ACE inhibitors and AT antagonists may modulate the muscle fiber composition in a hypertensive and insulin-resistant animal model, fructose-fed rats, to the same extent. Am J Hypertens 2000;13:290–297 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Insulin resistance, hypertension, muscle fiber composition, ACE inhibitor, angiotensin II receptor antagonist, fructose-fed rats.
Insulin resistance and hyperinsulinemia are common findings in patients with essential hypertension. These impairments in glucose metabolism are associated with a high risk of cardiovascular diseases, and recent evidence indicates that they may play a role in the development of hypertension, dyslipidemia, and atherosclerosis. Insulin resistance has also been reported in several animal models for hypertension, including the spontaneously hypertensive rat and the fructose-fed hypertensive rat. It has been indicated that a diet of fructose has induced diminishing glucose tolerance and elevated blood pressure in rats. Fructose-fed rats show an acquired form of hypertension, in which the rise in blood pressure (BP) is not genetically determined but is diet induced. Although it has been speculated that the rise in BP is secondary to the development of insulin resistance and hyperinsulinemia, the precise mechanism of insulin resistance in fructose-fed rats remains unclear.

The importance of skeletal muscle in insulin-mediated glucose metabolism has been established by a number of investigators. Euglycemic hyperinsulinemic glucose clamp studies have demonstrated that skeletal muscle accounts for more than 80% of glucose disposal under hyperinsulinemic conditions in humans. Several animal studies have demonstrated that substantial differences exist between muscle groups in insulin-mediated glucose uptake, which may relate to muscle fiber composition. Moreover, insulin action is greater in the red type I (slow twitch, oxidative) and type IIa (fast twitch, oxidative/glycolytic) fibers compared with the white type IIb (fast twitch, glycolytic) fibers. We have previously reported that the composite ratio of type I fibers of the soleus muscle was decreased in fructose-fed rats. Thus, changes of muscle fiber composition may be one of the important mechanisms of insulin resistance in fructose-fed rats.

In an insulin-resistant state, the plasma magnesium concentration has been found to be decreased and inversely correlated to the glucose level. Balon et al. reported that magnesium deficiency leads to insulin sensitivity in skeletal muscle and an elevation in blood pressure in rats. It has also been reported that magnesium in blood is only about 1% of total body magnesium, and therefore a magnesium deficiency in blood may not reflect a magnesium deficiency in the whole body. We recently reported that there was a reduction in the plasma magnesium level but no correlation between the plasma magnesium level and insulin sensitivity in fructose-fed rats. Thus, it is still unclear whether the reduction in the plasma magnesium level has a significant effect on insulin sensitivity.

Hypotensive drugs such as ACE inhibitors, α1-blockers and long-acting dihydropyridine Ca channel antagonists improve insulin sensitivity in essential hypertensives, although the precise mechanisms are still unknown. ACE inhibitors with or without a sulfhydryl improve insulin sensitivity, suggesting an important role for the suppression of angiotensin II generation. ACE inhibitors also increase kinin activity, which may contribute to the effect of ACE inhibitors in insulin sensitivity. It has been proposed that ACE inhibitors improve insulin sensitivity in the following ways: vasodilation increases the delivery of glucose and insulin, kinin has a direct effect on the glucose metabolism similar to insulin, or sympathetic nerve activity may be suppressed through the inhibition of angiotensin II production. If the ACE inhibitor increases insulin sensitivity through enhanced endogenous kinin, it would appear to be more effective to use an ACE inhibitor than an angiotensin II receptor antagonist. Therefore, an evaluation of the blocking effects on the angiotensin II receptor can help to explain the mechanism of ACE inhibitors in insulin sensitivity. However, it is unclear whether angiotensin II receptor antagonists improve insulin sensitivity. Angiotensin II receptor antagonism has recently been shown to affect insulin resistance; some reports on insulin sensitivity are of an improvement, and others are of no change. The present study was designed to examine the muscle fiber composition and clarify the effect of an angiotensin II receptor antagonist on insulin resistance and the mechanism by which an ACE inhibitor increases insulin sensitivity in an animal model of insulin-resistant hypertensive fructose-fed rats.

METHODS

General Protocol Six-week-old male Sprague-Dawley rats (Charles River Japan, Yokohama, Japan) were used for the experiments. The care of animals was in strict accordance with the guiding principles of the Physiological Society of Japan. Prior to any manipulation, all rats were fed standard rat chow containing 60% vegetable starch, 5% fat, 24% protein and 0.24% magnesium (Oriental Yeast Co., Tokyo, Japan). They were maintained on a 12-h light/dark cycle and water and chow ad libitum. The rats were acclimated to handling prior to randomization, then divided into two groups at the start of the study: those maintaining a standard chow diet (control; n = 20) and those given fructose-rich chow (FFR) containing 60% fructose, 5% fat, 20% protein and 0.06% magnesium (Teklad, Madison, WI) for 6 weeks. The FFR group was treated with 1 mg/kg/day of temocapril, an angiotensin-converting enzyme inhibitor (Sankyo Co., Tokyo; FFR + ACE, n = 12) or 0.3 mg/kg/day of CS-866, an angiotensin II receptor antagonist (Sankyo Co.; FFR + AT, n = 18) or vehicle (2.5% gum arabic solution; FFR, n = 18). The control group was also treated with the vehicle by gavage for the last 2 weeks of a 6-week period of either diet. Systolic BP was measured...
each week by the tail-cuff method in the FFR, FFR+ACE, and FFR+AT groups and at the beginning, fourth and sixth week in all four groups. At termination, insulin sensitivity was assessed in all conscious rats by the euglycemic hyperinsulinemic glucose clamp technique. To evaluate the effect of a dietary deficiency of magnesium, fructose-rich chow containing 0.24% magnesium, which is the same as fructose-rich chow with the exception of the magnesium content (Teklad; FFR-Mg, n = 10) was also studied.

**Blood Pressure Measurement** Systolic BP was measured in all conscious rats using the indirect tail-cuff method on a 37°C preheated plate for approximately 20 min. The rats were preconditioned to the experimental procedure before actual measurements were conducted. The equipment included a BP sensor/cuff, a BP amplifier, and digital recorder (Natsume Seisakusho Co., Tokyo). An average of six such recordings were taken as the individual systolic BP. This method correlates highly with direct cannulation measurements. The heart rate was measured at the same time as the BP measurement, using the same device.

**Euglycemic Hyperinsulinemic Glucose Clamp Technique** At the end of the treatment period, rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneal; ip). The left common carotid artery and the left jugular vein were exposed, then cannulated with polyethylene tubing (PE50, Becton Dickinson and Co., Sparks, MD) for collecting blood samples and for the administration of the infusate. After overnight fasting (approximately 12 h), each rat was placed in a plastic foam jacket that allowed movement of all four limbs and forward vision. At the start of the glucose clamp, fasting blood glucose measurements were obtained and the initial load of insulin (25 mU/kg of humalin R, U-40, Shionogi Pharmaceutical Co., Osaka, Japan) was infused by bolus, followed by an infusion of insulin at a rate of 4 mU/kg/min for 150 min. During the glucose clamp, a 12.5% glucose solution was infused as needed to maintain blood glucose at the preinfusion level. Ten ml of arterial blood was sampled at 7-min intervals for the determination of blood glucose. At the end of the glucose clamp, 1.5 ml of blood was withdrawn for measurements of plasma insulin and the plasma magnesium level. The average of the rate of glucose infusion for the last 35 min was taken as the index of insulin sensitivity (M value) of each rat.

**Determination of Muscle Fiber Composition** At the end of the glucose clamp study, with the rat under anesthesia with sodium pentobarbital (50 mg/kg, ip), the bilateral soleus muscles were dissected and immediately frozen in liquid nitrogen. Ten-millimeter sections sliced by microtome were stained with 4 mmol/L adenosine triphosphatase and 18 mmol/L CaCl₂ at pH 9.5 for 45 min at room temperature after preincubation at pH 10.4, 4.6, and 4.3, after which the muscle fiber composition was determined under a low-power microscope. Only type I fibers are characterized by dark staining following preincubation at pH 4.3. Type I and type IIb fibers are characterized by dark staining with preincubation at pH 4.6, and type IIa and IIb fibers are sensitive to preincubation at pH 10.4. The composite ratio of type IIb fibers was calculated as the subtraction from type I + type IIb fibers of type I fibers, and the composite ratio of type IIa fibers was characterized by an inhibition of staining preincubation at both pH 4.3 and pH 4.6. A minimum of 400 fibers were counted by two investigators individually after coding preparations to minimize individual bias.

**Biochemical Measurements** Blood glucose levels were measured by the glucose oxidase method in an Exacta 2A glucose analyzer (MediSense, Waltham, MA). Plasma insulin levels were assayed by a double antibody radioimmunoassay technique using human insulin standards (Ohtsuka Assay Lab, Tokushima, Japan). The plasma magnesium concentration was ascertained by the atomic absorption method (Atomic Absorption Spectrophotometer 208, Hitachi Seisakusyo, Tokyo).

**Statistical Analyses** All data are expressed as mean ± SEM. Changes within each group over time were assessed by two-way ANOVA, and a comparison of the four groups was done by one-way ANOVA. Regression analyses were used to compare the relationship between M values and muscle fiber composition. Values of P < .05 were considered statistically significant.

**RESULTS**

**Body Weight, Blood Pressure, Heart Rate, and Fasting Blood Glucose** The body weights of the control group were significantly higher than those of the other groups. Systolic BP was elevated significantly at 2 weeks after the start of the fructose-rich chow, and persisted throughout the study in the FFR group. As shown in Table 1, the BP values in the FFR group were significantly higher than those of the other groups. Both the ACE inhibitor and the AT antagonist significantly lowered the BP of the FFR. The heart rate was significantly higher in the FFR, FFR+ACE, and FFR+AT groups compared with that of the control group. Both the FFR+ACE and FFR+AT groups had slightly lower heart rates compared with those of the FFR, but there was no significant difference. There was no significant difference in fasting blood glucose levels among the four groups. There were also no significant differences between the fasting blood glucose and steady state blood glucose values in each group.
TABLE 1. CHARACTERISTICS OF CONTROL AND TREATED RATS AT 12 WEEKS OF AGE

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 20)</th>
<th>FFR (n = 18)</th>
<th>FFR+ACE (n = 12)</th>
<th>FFR+AT (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>362 ± 6</td>
<td>335 ± 6*</td>
<td>326 ± 4*</td>
<td>343 ± 4*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>142 ± 2</td>
<td>155 ± 2†</td>
<td>143 ± 3</td>
<td>147 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>342 ± 6</td>
<td>380 ± 8</td>
<td>374 ± 9†</td>
<td>370 ± 7†</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>5.4 ± 0.2</td>
<td>5.3 ± 0.1</td>
<td>5.0 ± 0.2</td>
<td>5.3 ± 0.1</td>
</tr>
</tbody>
</table>

FFR: fructose-fed rats, FFR+ACE: fructose-fed rats treated with ACE inhibitor, FFR+AT: fructose-fed rats treated with AT receptor antagonist.

Values are mean ± SEM. *P < .01 v control, †P < .01 v control, FFR+ACE and P < .05 v FFR+AT, ‡P < .05 v control.

Glucose Clamp and Muscle Fiber Composition

The steady state blood glucose levels during the glucose clamp were similar to those of the fasting blood glucose in the four experimental groups. The average rate of the glucose infusion during the last 35 min of the glucose clamp, as an index of insulin sensitivity (M value) was significantly lower in the FFR compared with the controls (15.4 ± 0.4, 10.9 ± 0.6 mg/kg/min, for control and FFR, respectively, P < .01) (Table 2). Both the ACE inhibitor and the AT antagonist significantly improved the M values compared with FFR, but not completely (13.2 ± 0.7, 12.8 ± 0.5 mg/kg/min, for FFR+ACE, FFR+AT, respectively, P < .01 compared with FFR, P<.05 compared with control) (Table 2).

The composite ratio of type I fibers of the soleus muscle were significantly decreased in the FFR compared with that of the controls (82% ± 2%, 75% ± 2%, for control and FFR, respectively, P < .01), and the ACE inhibitor and the AT antagonist recovered the composite ratio of type I fibers to the same level as that of the controls (81 ± 1, 80 ± 1% for FFR+ACE and FFR+AT, respectively)(Table 3). The composite ratio of type IIa fibers of the soleus muscle was significantly increased in the FFR compared with that of the controls, and both the ACE inhibitor and AT antagonist recovered the composite ratio of type IIa fibers to the same level as that of the controls. The M values were significantly correlated with the composite ratio of type I and type II fibers (for type I fibers, r = 0.68, P < .01, Fig.1A; for type II fibers, r = −0.68, P < .01, Fig.1B). There were no correlations between M values and body weights, fasting blood glucose, plasma insulin levels, or plasma magnesium levels (data not shown).

The Effect of Dietary Magnesium on Hypertension and Insulin Sensitivity

Although the plasma magnesium level was significantly lower in the FFR (0.06% magnesium diet), there was no significant difference in the plasma magnesium level between the controls and the FFR-Mg group (0.24% magnesium diet), and no significant differences in systolic blood pressure, steady state plasma insulin, or M value between the FFR and FFR-Mg groups (Table 4).

DISCUSSION

Our results confirm previous reports that feeding healthy rats a fructose-rich chow results in insulin resistance and hypertension.5,28 The fructose diet used here (60% fructose, 20% protein, and 5% fat) was specially prepared so that it had a protein and fat content comparable to the standard chow. Balon et al.14 reported that magnesium deficiency leads to insulin insensitivity in skeletal muscle and elevated blood pressure in rats. We used a fructose rich diet including 0.06% magnesium according to the original report of Hwang et al.,5 which was less than that of the control diet (0.24% magnesium), and the plasma magnesium level was significantly lower in the FFR compared with the controls. It has also been reported that magnesium in blood is only about 1% of total body magnesium,15 and that low magnesium intake (as in

TABLE 2. RESULTS OF GLUCOSE CLAMP STUDIES

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 20)</th>
<th>FFR (n = 18)</th>
<th>FFR+ACE (n = 12)</th>
<th>FFR+AT (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state plasma insulin (pmol/L)</td>
<td>669 ± 21</td>
<td>668 ± 17</td>
<td>632 ± 29</td>
<td>667 ± 40</td>
</tr>
<tr>
<td>M value (mg/kg/min)</td>
<td>15.4 ± 0.4</td>
<td>10.9 ± 0.6*</td>
<td>13.2 ± 0.7†</td>
<td>12.8 ± 0.5†</td>
</tr>
</tbody>
</table>

FFR: fructose-fed rats, FFR+ACE: fructose-fed rats treated with ACE inhibitor, FFR+AT: fructose-fed rats treated with AT receptor antagonist.

Values are mean ± SEM. *P < .01 v other three groups, †P < .05 v control and P < .05 v FFR.
the present study) leads to a 75% reduction in magnesium excretion in urine.14

When dietary magnesium is restricted, it is likely that homeostasis will be maintained by reducing magnesium excretion in urine and increasing the absorption of magnesium in the small intestine. In the present study, although insulin sensitivity was decreased in fructose-fed rats, the decrease in plasma magnesium was less than 10%, and there was no correlation between the plasma magnesium level and M values. In the present study, the diet of fructose-rich chow, containing 0.24% magnesium, showed no effect on the systolic BP or M values compared with those of the FFR (0.06% magnesium diet). This would indicate that a low magnesium diet is not involved in the insulin resistance in FFR.

The reason for the lower body weights of the fructose-fed rats compared with the controls was unclear. Although we did not evaluate the amount of food intake in each group, the FFR might have had a lower food intake compared with the controls. One reason for this might be that the fructose-rich chow is slightly hygroscopic and causes the FFR to consume a lower food amount. Insulin sensitivity was negatively correlated to body weights; however, it did not play an important role in the insulin resistance in the fructose-fed rats.

Hyperinsulinemia can stimulate an activation of the sympathetic nervous systems, renin–angiotensin systems, increases in renal sodium reabsorption, and a proliferation of vascular smooth muscle tissue, and it may be involved in the hypertensive mechanism.1 Although we did not determine fasting insulin levels, there was insulin resistance and hyperinsulinemia in the fructose-fed rats.5 There was also a negative correlation between the systolic BP and M values. These results suggest that fructose feeding leads to insulin resistance and a compensatory hyperinsulinemia that may result in hypertension.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>FFR</th>
<th>FFR+ACE</th>
<th>FFR+ATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (%)</td>
<td>82 ± 2</td>
<td>75 ± 2*</td>
<td>81 ± 1</td>
<td>80 ± 1</td>
</tr>
<tr>
<td>Type II (%)</td>
<td>18 ± 2</td>
<td>25 ± 2†</td>
<td>19 ± 1</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Type IIa (%)</td>
<td>18 ± 1</td>
<td>24 ± 2†</td>
<td>19 ± 1</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Type IIb (%)</td>
<td>0 ± 1</td>
<td>1 ± 2</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>

FFR: fructose-fed rats, FFR+ACE: fructose-fed rats treated with ACE inhibitor, FFR+AT: indicates fructose-fed rats treated with AT receptor antagonist.

Values are mean ± SEM. * P < .01 v other three groups, † P < .01 v control, P < .05 v FFR+ACE and AT, respectively.

FIGURE 1. The correlations between M values and the composition ratios of type I fibers (A) and type II fibers (B).
In vivo insulin action is significantly correlated with the histologically determined proportions of muscle fiber types.\(^{29}\) In addition, alterations in insulin action may occur because of specific biochemical changes occurring in association with variations in cellular oxidative capacity, and biochemical changes are induced in parallel with the specific twitch characteristics (fiber type) of muscle fibers.\(^{11,30}\) On the other hand, testosterone produced a dramatic insulin resistance and changes in muscle morphology toward less red, insulin-sensitive type I fiber and more white, insulin-insensitive type II fibers in rats.\(^{31}\) These results indicated that an interchange may occur between the type I and type II muscle fibers. We have previously reported\(^{12}\) that insulin resistance in fructose-fed rats is accompanied by changes of muscle fiber composition, and there is a correlation between insulin sensitivity and the composition of type I or type II fibers in the soleus muscle. In addition, the long-acting dihydropyridine Ca channel antagonist used in our previous study\(^{12}\) and the ACE inhibitor and AT antagonist used in the present study not only improved the insulin sensitivity but also restored the muscle fiber composition. However, details of the mechanisms by which the composition of type I fibers is lower in fructose-fed rats are still unknown. An impairment of insulin signal transduction,\(^{32}\) a change in plasma membrane fatty acid composition,\(^{33}\) or an increase in sympathetic nerve activity because of fructose-rich chow\(^{34}\) might induce a decrease in insulin sensitivity and compensatory hyperinsulinemia. Insulin resistance and hyperinsulinemia exist in fructose-fed rats,\(^{5}\) and hyperinsulinemia can change the muscle fiber composition, i.e., type I fiber toward type II fiber in soleus muscle.\(^{35}\)

Taking the results of previous studies into consideration, it is possible that compensatory hyperinsulinemia may also change type I fiber toward type II fiber, and Ca channel antagonists, ACE inhibitors, and AT antagonists may improve insulin sensitivity and cancel hyperinsulinemia in FFR, resulting in a muscle fiber composition recovery to that of the control level. In the present study, the ACE inhibitor and the AT antagonist partially improved insulin sensitivity in fructose-fed rats, although the rats’ muscle fiber composition was almost completely recovered. This indicates that insulin resistance in fructose-fed rats is regulated not only by muscle fiber composition, but also by another mechanism which remains unclear. Further studies are required to clarify the mechanism of insulin resistance in fructose-fed rats.

Hyperinsulinemia increases sympathetic nervous activity and the renin–angiotensin system and may be involved in the hypertensive mechanism in essential hypertensives.\(^{1}\) ACE inhibitors improve insulin sensitivity in essential hypertensives\(^{19,20}\), however, there have been few reports on the effect of angiotensin receptor antagonists on insulin sensitivity. Paolisso et al.\(^{22}\) reported that losartan, an AT antagonist, improves insulin-mediated glucose uptake through an increase in nonoxidative glucose metabolism and blood flow in hypertensive patients. Moan et al.\(^{24}\) found that losartan improves insulin sensitivity in patients with severe essential hypertension, but has little effect on insulin sensitivity in those with mild essential hypertension. In the present study, the AT antagonist improved insulin sensitivity to the same extent that the ACE inhibitor did. This indicates that the mechanism of ACE inhibitors’ improvement of insulin sensitivity might be mainly through a blocking of the generation of angiotensin II as opposed to increased kinin activity in FFR. Several possible mechanisms of improved insulin sensitivity by inhibition of angiotensin II have been suggested. These include vasodilation, which increases the blood flow in skeletal muscles, activation of the glucose transporter and its translocation from an intracellular membrane compartment to a plasma membrane fraction, and suppression of norepinephrine release induced by angiotensin II antagonism. The dose–response curve between insulin action and increased leg blood flow is shifted to the right in insulin-resistant patients,\(^{36}\) which suggests that the vasodilative action of insulin is reduced and the blood flow in feeding capillaries is decreased in an insulin-resistant state. In addition,
capillary density and the diffusion distance from capillaries to the muscle cells play a significant role in determining in vivo insulin action. Thus, vasodilation by an inhibition of angiotensin II may lead to increased blood flow in the capillaries of skeletal muscles, resulting in improved insulin sensitivity. Translocation of glucose transporter 4 (GLUT 4) from an intracellular membrane compartment to a plasma membrane fraction is a key pathway of insulin-mediated glucose uptake in insulin-sensitive tissues. It has been proposed that there is an impairment of the translocation of GLUT 4 by insulin, and that this impairment is one of the mechanisms of insulin resistance in diabetic model rats. Recent data have provided evidence that inhibition of the angiotensin II improves the translocation of GLUT 4 from an intracellular membrane compartment to a plasma membrane fraction. Although we did not assess sympathetic nervous activity in the present study, it is possible that there was an acceleration of sympathetic nervous activity in the fructose-fed rats due to hyperinsulinemia or fructose-rich chow, and the ACE inhibitor and AT antagonist might have attenuated the sympathetic nervous activity, resulting in improved insulin sensitivity.

In conclusion, insulin resistance and hypertension in fructose-fed rats were accompanied by a decrease of the composition ratio of type I fibers in the rat soleus muscle. An ACE inhibitor and an AT antagonist improved the insulin resistance and restored the composition ratio of type I fibers toward control levels. These results suggest that the fiber composition of skeletal muscles plays an important role in insulin resistance, and that the mechanism by which ACE inhibitors increase insulin sensitivity may be a suppression of angiotensin II generation in a hypertensive and insulin-resistant model, fructose-fed rats.

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