

Kinins Contribute to the Improvement of Insulin Sensitivity During Treatment With Angiotensin Converting Enzyme Inhibitor

Hirofumi Tomiyama, Toshio Kushiro, Hiromi Abeta, Toshiaki Ishii, Atsuhiko Takahashi, Luzia Furukawa, Tomoko Asagami, Toru Hino, Fumio Saito, Yuji Otsuka, Hitoshi Kurumatani, Fumiyuki Kobayashi, Katsuo Kanmatsuse, Nagao Kajiwara

Abstract Although angiotensin converting enzyme inhibitors and α_1 -blockers have been reported to improve insulin sensitivity, their mechanisms of action have not been elucidated. To investigate the role of kinins in insulin sensitivity, we treated 4-week-old spontaneously hypertensive rats with either an angiotensin converting enzyme inhibitor (enalapril), an α_1 -blocker (doxazosin), or an angiotensin II antagonist (losartan) for 3 weeks. A control group received no drugs. In addition, 18 rats treated with enalapril or doxazosin received a simultaneous administration of a kinin antagonist (Hoe 140). Glucose clamp testing was performed in each group. Enalapril (128 ± 1 mm Hg) and doxazosin (132 ± 2 mm Hg) decreased mean blood pressure compared with control levels (148 ± 1 mm Hg) ($P < .01$). The glucose requirement for the clamp test during the administration of enalapril (25.8 ± 0.5 mg/kg per

minute) or doxazosin (28.6 ± 0.7 mg/kg per minute) was higher than that of the control group (19.8 ± 0.5 mg/kg per minute) ($P < .05$). Although Hoe 140 did not alter the glucose requirement of doxazosin (27.8 ± 0.5 mg/kg per minute), it decreased that of enalapril (22.6 ± 0.9 mg/kg per minute) ($P < .05$) without affecting the changes in mean blood pressure induced by enalapril. In addition, losartan decreased mean blood pressure but did not affect the glucose requirement. Thus, the improvement in insulin sensitivity produced by an angiotensin converting enzyme inhibitor is mostly dependent on kinins but not on angiotensin II antagonism, and an α_1 -blocker improves insulin sensitivity irrespective of kinins. (*Hypertension*. 1994;23:450-455.)

Key Words • angiotensin-converting enzyme inhibitors • insulin • kallikrein-kinin system

Although recent antihypertensive medications control blood pressure (BP) as expected, it has not been entirely determined that they prevent cardiovascular events.¹ The management of concomitant conditions such as obesity, diabetes mellitus, and hyperlipidemia is advocated as one of the keys to improving the prevention of cardiovascular events. Insulin resistance is common in the above-mentioned conditions, and hypertension itself is believed to be an insulin-resistant state.² It has been proposed that the management of insulin resistance may contribute to the prevention of cardiovascular events.¹ Thus, in the management of hypertension, consideration should be given to the influence of antihypertensive medication on insulin sensitivity. It has been demonstrated that angiotensin converting enzyme (ACE) inhibitors and α_1 -blockers have a beneficial effect on insulin sensitivity.³ With regard to the effect of ACE inhibitors, the renin-angiotensin system, kallikrein-kinin system, or both have been suggested to participate, but the precise mechanisms of action of ACE inhibitors have not been determined. ACE is also known as kininase II and acts to degrade several kinins. Thus, ACE inhibitors de-

crease angiotensin II (Ang II) levels and increase kinin levels. This activity makes elucidating the precise mechanisms of ACE inhibitors difficult.

Recently, specific antagonists of kinins and Ang II have become available and may be useful tools for clarifying the precise mechanisms of ACE inhibitors. We conducted the present study to examine the roles of the renin-angiotensin and kallikrein-kinin systems in the influence of antihypertensive medication on insulin sensitivity.

Methods

Evaluation of Insulin Sensitivity

Animals and Protocol for the ACE Inhibitor, α_1 -Blocker, and Kinin Antagonist

Four-week-old male spontaneously hypertensive rats (SHR) (Charles River Co Ltd) were housed singly at a constant room temperature (24°C) with a 12-hour light/dark cycle; food and control water (distilled water) were available ad libitum. At the beginning of the experiment, rats were divided into six groups, and an ACE inhibitor (enalapril, Merck-Banyu Corp) or α_1 -blocker (doxazosin, Pfizer Japan Corp) was added to the control water. The concentration of all of drugs in the water was 100 mg/L. The rats drank either treated or control water. During the first 3 days of the experiment, the amount of water drunk in the treated groups was less than that in the control group, but after that the same amount of water was drunk in the treated and control groups (approximately 20 mL/d). One week after the beginning of the experiment, an osmotic minipump (2002 minipump, Alza Corp) filled with normal saline or the kinin antagonist Hoe 140 (kindly provided by

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From the Department of Cardiology, Surugadai Nihon University Hospital, Tokyo, Japan.

Reprint requests to Hirofumi Tomiyama, MD, PhD, Department of Cardiology, Surugadai Nihon University Hospital, 1-8-13, Kandasurugadai, Chiyoda-ku, Tokyo, Japan, 101.

Hoechst Japan Co Ltd) was subcutaneously implanted in the abdominal wall with rats under ether anesthesia, and subcutaneous infusion of saline or Hoe 140 (150 $\mu\text{g}/\text{kg}$ body wt per day) was performed.

The six groups were treated as follows: (1) the drinking water was control water, and the content of the minipump was saline (control group, $n=18$); (2) the drinking water included ACE inhibitor, and the content of the minipump was saline (ACE inhibitor group, $n=18$); (3) the drinking water included α_1 -blocker, and the content of the minipump was saline (α_1 -blocker group, $n=18$); (4) the drinking water was control water, and the content of the minipump was Hoe 140 (Hoe 140 group, $n=18$); (5) the drinking water included ACE inhibitor, and the content of the minipump was Hoe 140 (ACE inhibitor plus Hoe 140 group, $n=18$); and (6) the drinking water included α_1 -blocker, and the content of the minipump was Hoe 140 (α_1 -blocker plus Hoe 140 group, $n=18$).

Animals and Protocol for the Ang II Antagonist

Four-week-old male SHR were housed as above. At the beginning of the experiment, rats were divided into two groups, and an Ang II antagonist (losartan [MK954], kindly provided by Merck-Banyu Corp) was added to the control water (100 mg/L water). Rats drank either treated ($n=18$) or control ($n=12$) water. One week after the beginning of the experiment, an osmotic minipump filled with normal saline was subcutaneously implanted in the abdominal wall with rats under ether anesthesia, and subcutaneous infusion of saline (0.5 $\mu\text{L}/\text{h}$) was performed.

Blood Pressure Measurements and Euglycemic Clamp Test

Body weight and systolic BP were measured using tail plethysmography (KN210 series, Natsume Corp) at the beginning of the experiment. Twenty days after the beginning of the experiment (13 days after the implantation of the minipump), rats were anesthetized with ether, and a polyethylene catheter (PE-50, Clay Adams) was inserted into the descending aorta via the left carotid artery. Two other catheters were inserted into the inferior vena cava via the left internal jugular vein, and these catheters were subcutaneously tunneled to the back of the neck. The next day, mean arterial pressure was recorded on a polygraph (RM-6100, Nihon-Koden Corp) with the rats in a conscious state. BP was allowed to stabilize for 20 minutes, and then the mean determined over a 10-minute period was calculated.

After this measurement, body weight was measured. Then euglycemic hyperinsulinemic clamping was performed to assess whole-body insulin sensitivity. Rats were in a fasting condition for 12 to 18 hours before receiving two sequential 75-minute infusions of crystalline human insulin (Humulin-R, 40 IU/mL, Shionogi Corp). Insulin was infused through one of the catheters inserted into the inferior vena cava, and glucose (25% wt/vol water) was infused through another catheter by means of infusion pumps (ATICOM model 202). First, an insulin load of 18 mU/kg was given, and then insulin was continuously infused for 75 minutes at 3 mU/kg per minute. After this insulin infusion, an insulin load of 50 mU/kg was given, and then insulin was infused for 75 minutes at 8 mU/kg per minute. Before the first insulin infusion, 30- μL samples of carotid artery blood were drawn two times, and the mean glucose level of these two measurements was used as the basal blood glucose level. During insulin infusion, 30 μL of blood was drawn at 7-minute, 30-second intervals for the determination of blood glucose levels. Based on this determination, glucose was infused at a rate sufficient to maintain it at the basal level. At the end of glucose clamp testing, 2 mL of blood was drawn to determine plasma insulin, sodium, and potassium levels.

Evaluation of the Inhibitory Effect of Hoe 140

Five-week-old SHR ($n=10$) were divided into two groups. In one group ($n=5$), an osmotic minipump filled with Hoe 140 (infusion rate, 150 $\mu\text{g}/\text{kg}$ body wt per day) was subcutaneously implanted, and in another group ($n=5$), an osmotic minipump filled with normal saline was implanted. Two weeks after implantation, experiments were performed. One day before the experiments, rats were cannulated under ether anesthesia with catheters in the right femoral artery (PE-10) for mean BP recordings and in the right carotid artery (PE-50) for intra-arterial drug applications. The next day, mean arterial pressure was recorded on a polygraph with rats in a conscious state. BP was allowed to stabilize for 20 minutes, then bradykinin (100 ng, 0.1 mL) was injected via a carotid arterial catheter.

Evaluations of the Inhibitory Effects of the ACE Inhibitor and Ang II Antagonist

Four-week-old SHR ($n=15$) were divided into three groups: rats that drank control water, water with enalapril (100 mg/L) added, or water with losartan (100 mg/L) added for 3 weeks. Three weeks later the experiments were performed. One day before the experiments, rats were cannulated under ether anesthesia with PE-50 catheters in the left carotid artery for mean BP recordings and in the left carotid vein for intravenous drug applications. The next day, mean arterial pressure was recorded on a polygraph with rats in a conscious state. BP was allowed to stabilize for 20 minutes, then Ang I (250 ng, 0.1 mL) was injected via the carotid venous catheter.

Evaluation of the Effect of Chronic Infusion of Bradykinin on Insulin Sensitivity

Five-week-old male SHR drank water with enalapril (100 mg/L water) added throughout the experiment. One week later rats were divided into two groups. Osmotic minipumps (connected with a PE-10 catheter) were prepared. In one group ($n=6$), the osmotic minipump filled with bradykinin (infusion rate, 80 ng/min) was subcutaneously implanted, and the catheter was cannulated into the inferior vena cava via a branch of the left femoral vein. In another group ($n=6$), the osmotic minipump filled with normal saline was implanted, and the catheter was cannulated similarly. Four days after implantation of the minipump, rats were anesthetized with ether, and a PE-50 catheter was inserted into the descending aorta via the left carotid artery. Two other catheters were inserted into the inferior vena cava via the left internal jugular vein, and these catheters were subcutaneously tunneled to the back of the neck. The next day euglycemic hyperinsulinemic glucose clamping was performed to assess whole-body insulin sensitivity.

Analysis

Blood glucose levels were determined by the glucose oxidase H_2O_2 electrode method (ANTOSENSE, Miles-Sankyo Corp). Plasma insulin and plasma bradykinin levels were determined by radioimmunoassay. In the radioimmunoassay of insulin, a monoclonal antibody to human insulin was used; in the radioimmunoassay of bradykinin, a polyclonal antibody to bradykinin was used (both from Special Reference Laboratory, Tokyo, Japan). Plasma sodium and potassium levels were determined by flame photometry.

Steady-state blood glucose levels and glucose infusion rates during glucose clamping were calculated using data obtained from the last three measurements during each 75-minute insulin infusion. The values of these three measurements for an individual animal were averaged to give a single value for that animal. The individual averages were used to calculate group means for the steady-state blood glucose level and glucose infusion rate.

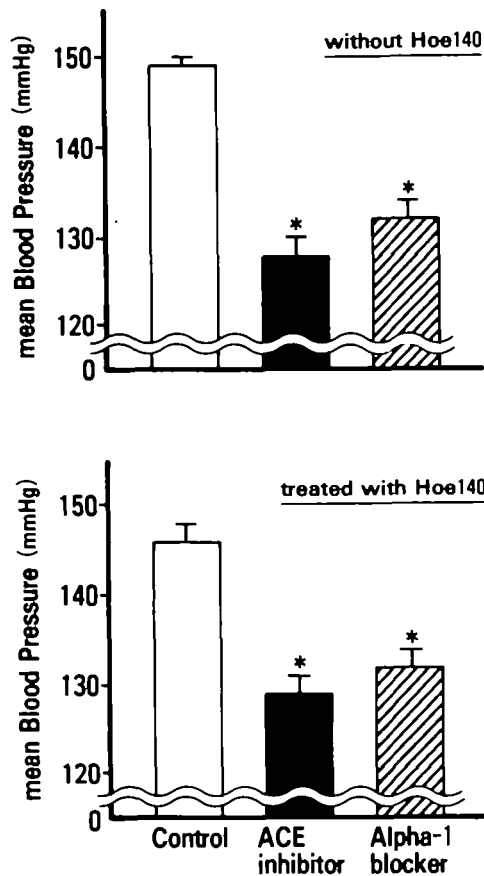


FIG 1. Bar graphs show mean blood pressure at the third experimental week in the six rat groups (see "Methods" for group descriptions). Mean arterial blood pressures of ACE inhibitor and α_1 -blocker groups were lower than control group (top); those of ACE inhibitor plus Hoe 140 and α_1 -blocker plus Hoe 140 groups were also lower than Hoe 140 group (bottom). * $P < .05$ vs control or Hoe 140 group.

Statistics

Data are expressed as mean \pm SEM. In the assessments of glucose infusion rate and mean BP for the ACE inhibitor, α_1 -blocker, and kinin antagonist, two-way ANOVA was performed in the evaluation of six group comparisons (the groups were as follows: control drinking water or water that included ACE inhibitor or α_1 -blocker) and the effect of the kinin antagonist. Then, one-way ANOVA followed by Scheffé's test was used for group comparisons in control, ACE inhibitor, and α_1 -blocker groups and in Hoe 140, ACE inhibitor plus Hoe 140, and α_1 -blocker plus Hoe 140 groups. In addition, one-way ANOVA followed by Wilcoxon's unpaired *t* test was used for the evaluation of the effect of the kinin antagonist in each group (between control group and Hoe 140 group, ACE inhibitor group and ACE inhibitor plus Hoe 140 group, and α_1 -blocker group and α_1 -blocker plus Hoe 140 group). In other experiments, one-way ANOVA was used followed by Scheffé's test or Wilcoxon's unpaired *t* test. A value of $P < .05$ was considered statistically significant.

All procedures were in accordance with the guidelines of the Nihon University School of Medicine for research animal use.

Results

Mean BPs at the third experimental week of the six groups are shown in Fig 1. Two-way ANOVA demonstrated a significant difference in the group comparison but not in the effect of the kinin antagonist. The mean

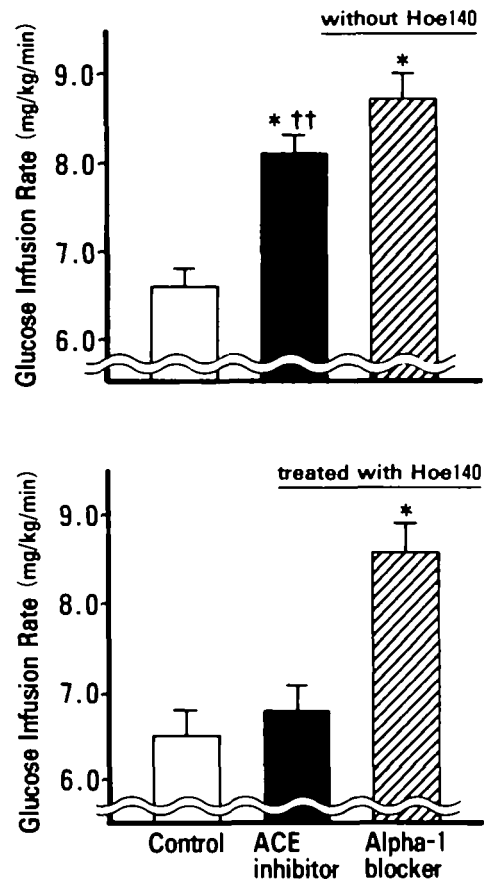


FIG 2. Bar graphs show glucose infusion rates at 3 mU/kg per minute insulin infusion in the six rat groups (see "Methods" for group descriptions). Glucose infusion rates of ACE inhibitor and α_1 -blocker groups were significantly higher than control group (top); that of α_1 -blocker plus Hoe 140 group was significantly higher than Hoe 140 group (bottom). Glucose infusion rate of ACE inhibitor group was significantly higher than ACE inhibitor plus Hoe 140 group. * $P < .05$ vs control or Hoe 140 group; ^{††} $P < .01$ between groups without and with Hoe 140 treatment.

arterial BPs of the ACE inhibitor group and α_1 -blocker group were significantly lower than those of the control group. Between these two groups, mean BP was not significantly different. Hoe 140 did not affect these depressor effects of the ACE inhibitor and α_1 -blocker.

Fig 2 shows the glucose infusion rates of the 3 mU/kg per minute insulin infusion, and Fig 3 shows those of the 8 mU/kg per minute insulin infusion in the six groups. Two-way ANOVA demonstrated a significant difference in the group comparison and also in the effect of the kinin antagonist. At both insulin infusion rates, the glucose infusion rates of the ACE inhibitor group and α_1 -blocker group were significantly higher than those of the control group. The increase in the glucose infusion rate of the ACE inhibitor group was inhibited by Hoe 140, but Hoe 140 did not affect the glucose infusion rates of the control or α_1 -blocker groups.

Although the Ang II antagonist decreased mean BP significantly (129 ± 2 mm Hg, $P < .01$) compared with the control group (148 ± 3 mm Hg), there were no significant differences in the glucose infusion rates of both groups at both insulin infusion rates (Table 1).

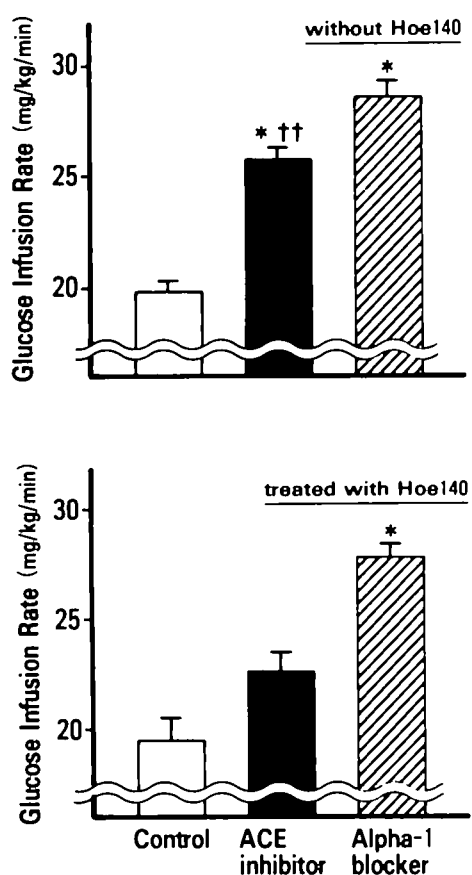


FIG 3. Bar graphs show glucose infusion rates at 8 mU/kg per minute insulin infusion in the six rat groups (see "Methods" for group descriptions). Glucose infusion rates of ACE inhibitor and α_1 -blocker groups were significantly higher than control group (top); that of α_1 -blocker plus Hoe 140 group was significantly higher than Hoe 140 group (bottom). Glucose infusion rate of ACE inhibitor group was significantly higher than ACE inhibitor plus Hoe 140 group. * $P < .05$ vs control or Hoe 140 group; †† $P < .01$ between groups without and with Hoe 140 treatment.

Basal glucose level and plasma insulin, sodium, and potassium levels at the end of glucose clamp testing as well as body weight at clamp testing are shown in Table 2. These parameters were not significantly different among the groups. In addition, body weight and systolic BP at the beginning of the experiment did not show any significant differences among groups.

The injection of 100 ng bradykinin decreased BP (Δ BP, -20 ± 3 mm Hg) in nontreated SHR, but Hoe 140 prevented this depressor effect of bradykinin significantly (Δ BP, -9 ± 2 mm Hg, $P < .05$).

Although the injection of 250 ng Ang I increased BP (Δ BP, 45 ± 3 mm Hg), the treatments with ACE inhibi-

tor and Ang II antagonist prevented this pressor effect of Ang I significantly (Δ BP [ACE inhibitor], 7 ± 2 mm Hg, $P < .05$; Δ BP [Ang II antagonist], 8 ± 2 mm Hg, $P < .05$).

The glucose infusion rates of the chronic bradykinin-infused group (10.3 ± 1.2 mg/kg per minute at 3 mU/kg per minute insulin infusion, $P < .05$; 32.1 ± 3.8 mg/kg per minute at 8 mU/kg per minute insulin infusion, $P < .05$) were significantly higher than those of the control group (7.6 ± 1.1 mg/kg per minute at 3 mU/kg per minute insulin infusion; 23.8 ± 2.9 mg/kg per minute at 8 mU/kg per minute insulin infusion). Mean BP was lower in the chronic bradykinin-infused group (122 ± 4 mm Hg, $P < .05$) than in the control group (134 ± 3 mm Hg), and the plasma bradykinin level was higher in the chronic bradykinin-infused group (102.0 ± 31.3 pg/mL, $P < .05$) than in the control group (42.4 ± 11.1 pg/mL).

Discussion

The glucose infusion rates in the ACE inhibitor-treated group and α_1 -blocker-treated group were significantly higher than in the control group. The Ang II antagonist lowered BP but did not affect glucose infusion rate. The kinin antagonist attenuated the increase of the glucose requirement in the ACE inhibitor-treated group but did not affect the glucose requirement in the control group or α_1 -blocker-treated group. In addition, the chronic administration of exogenous bradykinin improved insulin sensitivity. These results suggest that kinins may contribute to the improvement of insulin sensitivity during treatment with an ACE inhibitor.

DeFronzo et al⁴ used euglycemic glucose clamp testing to quantify insulin sensitivity. Glucose uptake by body tissue or endogenous glucose production contributes to insulin sensitivity. Smith et al⁵ demonstrated that in rats the half-maximal inhibition of endogenous glucose production occurs at an insulin concentration between 30 and 40 μ U/mL, and endogenous glucose production is completely suppressed at insulin concentrations greater than 70 μ U/mL during euglycemic glucose clamping. Although we did not measure endogenous hepatic glucose production in the present study, our finding of an increase in glucose infusion rate induced by an ACE inhibitor and α_1 -blocker at both low (plasma insulin level of 41 ± 3 μ U/mL at 3 mU/kg per minute insulin infusion [$n=5$], unpublished observation) and high (greater than 100 μ U/mL) insulin concentrations suggests that these improvements in insulin sensitivity originate from improvements in tissue glucose uptake.

Tissue glucose uptake is determined by (1) glucose and insulin delivery to tissue, (2) transmembrane glucose transport by glucose transporters, (3) insulin receptors and mediators, or (4) enzymatic steps of intracellular glucose metabolism.⁶ Kinins induce vasodilation, increase vascular permeability, and prevent vascular rarefaction.^{7,8} These changes may increase glucose and insulin delivery to tissue. Rett et al⁷ demonstrated the beneficial effect of kinins on glucose metabolism, and our results support their report. However, the beneficial effect was small (approximately 20%), and the precise mechanisms whereby kinins have

TABLE 1. Glucose Infusion Rates of Angiotensin II Antagonist and Control Groups

Insulin Infusion Rate	Ang II Antagonist (n=18)	Control (n=12)
3 mU/kg per minute	6.9 ± 0.3	6.5 ± 0.4
8 mU/kg per minute	21.2 ± 1.4	20.2 ± 1.0

Ang II indicates angiotensin II. Values are mean \pm SEM and expressed in milligrams per kilogram per minute.

TABLE 2. Levels of Basal Blood Glucose, Plasma Insulin, Plasma Sodium, Plasma Potassium, and Body Weight at the End of Clamp Testing in Rats

	Control (n=18)	Hoe 140 (n=18)	ACE (n=18)	ACE+Hoe 140 (n=18)	α_1 (n=18)	α_1 +Hoe 140 (n=18)	Ang II (n=18)	Control for Ang II (n=12)
Blood glucose, mg/dL	124±3	128±2	119±3	123±2	118±3	124±2	122±3	120±3
Insulin, μ U/mL	101±5	100±5	104±4	108±6	99±5	110±5	104±4	103±5
Sodium, mmol/L	141±2	139±2	142±3	142±2	142±2	140±3	141±2	141±3
Potassium, mmol/L	3.8±0.2	3.6±0.2	3.5±0.2	3.7±0.1	3.5±0.2	3.6±0.1	3.6±0.2	3.7±0.2
Body weight, g	228±4	222±6	223±6	216±8	220±8	223±5	226±4	218±9

ACE indicates angiotensin converting enzyme; Ang II, angiotensin II. Values are mean±SEM. See "Methods" for description of experimental groups.

a beneficial effect on glucose metabolism remain unclear.

Vasoconstriction, vascular hypertrophy, and activation of the sympathetic nervous system induced by Ang II may worsen insulin sensitivity. In the present study, the Ang II antagonist decreased BP significantly. Both the ACE inhibitor and Ang II antagonist prevented the pressor effect of Ang I similarly. However, the Ang II antagonist did not influence insulin sensitivity. These results suggest that the decrease in endogenous Ang II induced by ACE inhibition does not contribute to the improvement in insulin sensitivity produced by ACE inhibition. Actually, in two-kidney, one clip (2K1C) hypertensive rats, which demonstrate activation of the renin-angiotensin system, it has been reported that insulin sensitivity is not worsened compared with normotensive control rats.⁹ However, it is difficult to conclude that the renin-angiotensin system and Ang II antagonists do not affect insulin sensitivity because of the following: (1) The renin-angiotensin system always links with other hormonal systems, and the suppression or activation of the renin-angiotensin system may affect other hormonal factors. The suppression or activation of other hormonal factors may affect insulin sensitivity. (2) A local renin-angiotensin system has been demonstrated,¹⁰ and we could not evaluate whether the doses of ACE inhibitor and Ang II antagonist used in the present study were enough to suppress this local system. Further studies are proposed to elucidate the effect of the renin-angiotensin system (including Ang II antagonists) on insulin sensitivity.

Hoe 140 did not affect the depressor effect of the ACE inhibitor in the present study, but Bao et al¹¹ demonstrated that endogenous kinins may contribute to the chronic depressor effect of ramipril (an ACE inhibitor) in 2K1C hypertensive rats using Hoe 140. The dose of Hoe 140 that we used might be sufficient to inhibit the effects of endogenous kinins, because this dose produced 50% inhibition of the depressor effect of a 100-ng injection of exogenous bradykinin. The Ang II antagonist decreased BP to the same extent as the ACE inhibitor in the present study. In addition, Bao et al reported that the depressor effect of kinins during treatment with an ACE inhibitor in a normal-renin hypertensive model (SHR) was less than that in a high-renin hypertensive model (2K1C rat). These findings support our speculation that a great part of the chronic depressor effect of ACE inhibition in SHR

contributes to the inhibition of the production of Ang II by ACE inhibitors.

Although our findings of the beneficial effects of ACE inhibitors on insulin sensitivity are supported by the data of some investigators,³ Santoro et al¹² reported that ACE inhibitors did not affect insulin sensitivity. The discrepancy between these studies may be partially due to protocol differences, including the drugs used (enalapril, captopril, and cirazapril), their dosages, and the duration of treatment. In addition, the study subjects may be important. We used young SHR, which are at an early stage of hypertension. Santoro et al used human subjects that had established hypertension. It is proposed that the progression of hypertension may be associated with changes in the activity of the kallikrein-kinin system.¹³ These changes may contribute to the degree of the increase of endogenous kinins induced by ACE inhibitors.

The α_1 -blocker also improved insulin sensitivity. This improvement was not attenuated by the simultaneous administration of Hoe 140, suggesting that endogenous kinins may not contribute to this improvement. The activation of sympathetic activity may be the basic pathophysiological underpinning of the frequent association between insulin resistance and hypertension.¹⁴ However, the present study cannot go into the precise mechanism of the improvement of insulin sensitivity induced by α_1 -blockers.

In conclusion, this study demonstrated that an ACE inhibitor and α_1 -blocker improve insulin sensitivity. The increase in endogenous kinins induced by ACE inhibitors may contribute to the improvement produced by ACE inhibitors.

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