Angiotensin Receptor Blockade Blunts Hyperinsulinemia-Induced Hypertension in Rats

Te-Chao Fang, Wann-Chu Huang

Abstract—The study was conducted to examine the effects of the angiotensin subtype 1 and 2 receptor antagonists (losartan and PD123319, respectively) on blood pressure (BP) and renal excretory function in chronic hyperinsulinemia–induced hypertension in rats. Hyperinsulinemia was achieved by insulin infusion (21.5 pmol/kg per minute) via osmotic minipump for 6 weeks. Losartan or PD123319 was coinfused either at the beginning or after 4 weeks of insulin infusion. The results showed that insulin infusion significantly increased the plasma insulin concentration from 259.0±22.2 to 646.5±33.0 and 713.9±26.5 pmol/L (P<0.05) by the end of the fourth and sixth weeks, respectively, after insulin infusion. There were no significant changes in plasma glucose and triglyceride concentrations. Systolic BP increased from 139±3 to 156±1 and 157±2 mm Hg (P<0.05) at the corresponding time points. Combined losartan (3.5 µg/kg per minute) and insulin infusion prevented the rise in BP and improved insulin resistance. When hypertension had been established after 4 weeks of insulin infusion, superimposed infusion of losartan on insulin reversed the elevated BP to control levels within 1 week. In contrast, administration of PD123319 (0.5 and 10 µg/kg per minute) failed to alter insulin-induced hypertension. Combined PD123319 with losartan did not alter the losartan-induced hypotensive effect in insulin-infused rats. There were no significant differences in water intake, urine flow, body weight gain, and sodium gain before and after antagonist administration among groups. These results indicate that angiotensin type 1 receptors play a determinant role in the pathogenesis of insulin-induced hypertension in rats. (Hypertension. 1998;32:235-242.)

Key Words: hyperinsulinemia ■ insulin resistance ■ losartan ■ PD123319 ■ angiotensin receptor antagonist

Numerous clinical and epidemiological studies have demonstrated that essential hypertension is correlated with insulin resistance and hyperinsulinemia.1–3 The close association between hypertension and insulin resistance–hyperinsulinemia has been noted to occur in some genetically hypertensive rat models, such as spontaneously hypertensive rats,4,5 Milan hypertensive rats, 6 and Dahl salt-sensitive rats.7 Rodents fed sucrose-, fructose-, or glucose-enriched diets can develop hypertension that is also related to insulin resistance and hyperinsulinemia.8–10 Moreover, exogenous insulin or fructose-feeding can accelerate and aggravate the development of hypertension in spontaneously hypertensive and Dahl salt-sensitive rats.11–14 These observations strongly suggest an etiologic link between insulin resistance–hyperinsulinemia and hypertension. This notion is further supported by the direct evidence that euglycemic hyperinsulinemia achieved by long-term insulin administration produces hypertension in the rat.15–17 However, the underlying mechanism responsible for the coupling of hyperinsulinemia–insulin resistance with the pathogenesis of hypertension is not fully understood, although hyperinsulinemia-induced changes in renal, neural, vascular, and hormonal functions have been documented to be involved in the pressor effect.8,9,18–21

It is well recognized that the RAS plays an important physiological role in body fluid and sodium homeostasis and BP regulation, whereas activation of the RAS causes hypertension and other cardiovascular diseases.22 Experimental and clinical studies have demonstrated the benefits of blockade of the RAS in the treatment of such cardiovascular diseases.22 It has also been shown that ACE inhibition and Ang II antagonism can improve insulin sensitivity and reduce BP in essential hypertension and fructose-induced hyperinsulinemic, hypertensive rats,23–27 suggesting a significant role for Ang II blockade in this mechanism. In addition, an increase in plasma insulin level has been demonstrated to stimulate the sympathetic nervous system.19,28 It is possible that hyperinsulinemia stimulates the sympathetic nervous system that in turn activates the RAS and thereby leads to the development of hyperinsulinemia-associated hypertension. Thus, the aim of the present study was to characterize the role of Ang II and its subtype receptors in the pathogenesis of chronic hyperinsulinemia–induced hypertension in rats.

Methods

General Protocol
Male Sprague-Dawley rats initially weighing 200 to 230 g were used for the experiments. All experimental procedures were carried out in accordance with prior approval of the Institutional Animal Care and Use Committee of this school. Rats were housed in individual metabolism cages in a room with the temperature controlled at

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22±0.5°C, were fed a controlled-sodium diet containing 0.31% sodium (TD 93065, Teklad Premier), and had access to tap water ad libitum throughout the experiments. Food intake, water intake, and urine flow were measured daily and body weight was measured twice a week. The systolic BP was measured twice a week by the tail-cuff method. Blood samples were taken before (day 0) and during insulin infusion (days 28 and 42) from the femoral artery under sodium pentobarbital anesthesia (40 mg/kg IP). Plasma was separated, divided into aliquots, and frozen until analysis.

Animal Groups

**Experiment 1: Effects of AT1 Receptor Blockade on BP and Renal Function in Chronic Insulin-Infused Rats**

Rats were divided into 4 groups of 8 animals each. Group 1 (CON, control) received injection of vehicle only; group 2 (INLa) received porcine insulin administration (21.5 pmol/kg per minute) via an osmotic minipump implanted subcutaneously for 6 weeks; group 3 (INLa) and were coinfused with porcine insulin (21.5 pmol/kg per minute) and losartan (3.5 μg/kg per minute) via a subcutaneous osmotic minipump for 6 weeks; and group 4 (INLb) received insulin infusion as did group 2, but losartan (3.5 μg/kg per minute) was administered 4 weeks later.

**Experiment 2: Effects of AT2 Receptor Blockade on BP and Renal Function in Sustained Insulin-Infused Rats**

Rats were divided into 3 groups of 8 animals each. Group 1 (CON, control) received vehicle alone; group 2 (INPD) received insulin infusion (21.5 pmol/kg per minute) via an osmotic minipump, and PD123319 (0.5 μg/kg per minute) was administered 4 weeks later; and group 3 (INPD) was treated in the same manner as group 2 except that a higher dose of PD123319 (10 μg/kg per minute) was administered.

**Experiment 3: Effects of Combined AT1 and AT2 Receptor Blockade on BP and Renal Function in Sustained Insulin-Infused Rats**

Two groups of rats with 8 rats in each group were used. One group was given insulin infusion alone for 6 weeks as described above. The other group of rats (group INLd) was coinfused with losartan and insulin for the first 2 weeks, and then PD123319 (10 μg/kg per minute) was added for an additional 2 weeks. Subsequently, losartan and PD123319 infusions were terminated while the insulin infusion was continued. The BP and renal excretory responses were followed up for 2 weeks.

**Miniosmotic Pump Installation**

After a control period of 1 week, an osmotic minipump (No. 2002, 14 days of active life, Alza Corp) filled with either porcine insulin (21.5 pmol/kg per minute) in a glycerin-ethanol (1:1, vol/vol) mixture or vehicle was implanted subcutaneously in rats under brief anesthesia with ketamine (60 mg/kg IP) and xylazine (7.5 mg/kg IP). When it was necessary to administer losartan or PD123319, a separate osmotic minipump was filled with the agent, which had been dissolved in normal saline, and implanted subcutaneously. Aqueous penicillin (5000 U/kg SC) was administered immediately after minipump implantation. At the end of the life of minipump, a new minipump was implanted and the used one removed. The residual volume in each minipump removed was carefully examined to ensure that the minipump release function was normal.

**BP Measurement**

Rats were removed from the animal room and taken to the laboratory at 8 AM; they were allowed free access to water and were kept in a quiet area before BP was measured at 9 AM. The tail-cuff method was used to measure systolic BP with the use of a programmed electrosphygmomanometer (model UR-5000, Ueda) as described previously. The mean of 6 consecutive readings was used as the measurement of systolic BP of each rat for that day, and systolic BP was determined twice a week during the control (1 week) and experimental (6 weeks) periods.

**Drinking Test**

To ascertain the extent of blockade of angiotensin receptors in the hyperinsulinemic rats, the dipogenic response of rats to Ang II was determined at the fifth week of the experimental period. The basal water intake of rats was measured by the volume difference of water in the water bottle 1 hour before Ang II was administered. The dipogenic response of rats to Ang II (150 μg/kg SC) was then determined 1 hour after Ang II was administered. Water intake was measured over a period of 1 hour and expressed as mL/kg of body weight.

**Insulin Suppression Test**

To examine the capability of the tissues of hyperinsulinemic rats to dispose of a glucose load, the insulin suppression test was conducted as described previously. The aim of this method is to reach a comparable steady-state level of insulin in vivo by a constant intravenous infusion of a fixed insulin-glucose dose. Under this condition, glucose liberation from the liver is presumably suppressed by the combination of high concentrations of glucose and insulin, and the rate of glucose uptake in the whole body approximates the exogenous glucose infusion rate. Therefore, a higher glucose level implies resistance to insulin-stimulated glucose uptake.

At the end of the experiments, rats were fasted for 12 hours, anesthetized with sodium pentobarbital (40 mg/kg IP), and intubated after tracheostomy to keep the airway patent. The right common carotid artery was exposed and cannulated with PE-50 for collecting blood samples. The right external jugular vein was catheterized with PE-10 for continuous infusion of porcine insulin (17.9 pmol/kg per minute) and glucose (0.044 mmol/kg per minute) simultaneously for 180 minutes. Steady-state plasma glucose (SSPG) and steady-state plasma insulin (SSIPI) levels were calculated from the mean glucose and insulin levels of blood samples taken at 15-minute intervals during the last 60 minutes of the infusion.

**Chemical Measurements**

The blood samples were centrifuged at 4000g at 4°C for 10 minutes immediately after they were drawn. The plasma samples were separated and kept at −70°C for later determination of glucose, triglyceride, and insulin levels as described previously. Urinary sodium concentration was determined by flame photometry (model 943, Instrumentation Laboratory). The sodium gain was computed as the difference between sodium intake and urinary sodium excretion.

**Drugs**

Porcine insulin was purchased from Sigma Chemical Co. Losartan was kindly provided by Du Pont-Merck Pharmaceutical Co. PD123319 was purchased from RBI.

**Statistical Analysis**

Experimental data were compared with control data with the use of the Newman-Keuls test at specific time points. Dunnett’s test for testing within-group effects was also performed. Statistical significance was considered at P<0.05. All results are expressed as mean±SEM.
The Table summarizes the effects of administration of insulin alone and in combination with losartan on plasma insulin, triglyceride, and glucose concentrations. There were no significant differences in the basal insulin levels among the 4 groups of rats. Insulin administration significantly increased the plasma insulin concentration from 259.0 ± 22.2 pmol/L during the control period to 646.5 ± 33.0 and 713.9 ± 26.5 pmol/L by the fourth and sixth weeks, respectively, of insulin administration (group IN). However, the plasma insulin level in rats with concurrent administration of insulin and losartan (group INLa) did not differ significantly from that of the control (CON) group. The plasma insulin concentration in group INLb increased from 310.0 ± 29.4 pmol/L during the control period to 620.6 ± 17.7 pmol/L (P < 0.01) after 4 weeks of insulin infusion and then declined to 388.9 ± 23.0 pmol/L (P < 0.01) after losartan treatment for 2 weeks. There were no significant differences in plasma triglyceride and glucose levels among the 4 groups during the corresponding time periods throughout the experiments.

SSPG and SSPI in control rats and insulin-infused rats with or without losartan treatment are presented in Figure 3. No significant difference in SSPG was noted between control and insulin-infused groups. However, the SSPG level of insulin-infused rats (group IN, 8.88 ± 0.29 mmol/L) was significantly higher than that of control rats (5.44 ± 0.24 mmol/L, P < 0.01). On the contrary, the SSPG levels in losartan-treated groups (6.11 ± 0.26 mmol/L for group INLa and 5.90 ± 0.21 mmol/L for group INLb) were significantly lower than that of group IN but were not different from that of the control group. Furthermore, there was no significant difference in SSPG between groups INLa and INLb. Thus, resistance to insulin-stimulated glucose uptake apparently occurred in rats with chronic insulin administration, and losartan treatment could prevent and improve insulin resistance in these rats.

**Results**

Effects of AT₁ Receptor Blockade on BP and Renal Function in Chronic Insulin-Infused Rats

The changes in BP of control rats and insulin-infused rats with or without losartan treatment are illustrated in Figure 1. Chronic administration of insulin alone significantly increased the systolic BP from 139 ± 3 mm Hg during the control period to 156 ± 1 and 157 ± 2 mm Hg (P < 0.05) by the end of the fourth and sixth weeks, respectively, of insulin infusion (group IN). The insulin-induced increases in BP failed to occur when losartan was superimposed on insulin administration (group INLa). When insulin-induced hypertension had been established in group INLb (systolic BP increase from 129 ± 3 to 161 ± 2 mm Hg by the end of the fourth week, P < 0.05), administration of losartan for the subsequent 2 weeks markedly reduced the elevated systolic BP to 139 ± 2 mm Hg (P < 0.05). These results indicate that losartan administration can prevent and reverse insulin-induced hypertension in rats.

Figure 2 demonstrates the changes in food and water intake, urine flow, sodium excretion, sodium gain, and body weight gain in control rats, rats with insulin infusion alone, rats with concomitant administration of insulin and losartan, and rats with insulin infusion with losartan 4 weeks later. There were no significant differences in food and water intake and renal excretion rates of sodium and water among all groups throughout the experiments. In addition, neither the daily sodium gain nor the weekly body weight gain exhibited a significant difference among groups at the corresponding time points.

**Effects of AT₂ Receptor Blockade on BP and Renal Function in Chronic Insulin-Infused Rats**

Figure 4 demonstrates the BP changes in control rats and insulin-infused rats with PD123319 treatment. The BP of control rats was not altered significantly over the entire period of the experiments. In contrast, insulin administration for 4 weeks significantly increased the systolic BP from 131 ± 2 to 155 ± 3 mm Hg (P < 0.05), and this elevated BP was still maintained after PD123319 administration (0.5 μg/kg per minute, group INPD₂) for 2 weeks. Similarly, a much higher dose of PD123319 (10 μg/kg per minute, group INPD₃) did not change the insulin-induced pressor response.

The effects of insulin infusion alone and combined with PD123319 on food and water intake, urine flow, sodium excretion, sodium gain, and body weight gain are shown in Figure 5. There were no significant differences in food and water intake and urinary excretion of water and sodium among groups of rats at each time-matched period. Also, the daily sodium gains were similar among groups at specific time-matched periods, and body weight gain per week also showed a similar pattern throughout the experiments.
Effects of Combined AT<sub>1</sub> and AT<sub>2</sub> Receptor Blockade on BP and Renal Function in Sustained Insulin-Infused Rats

Figure 6 depicts the BP responses to insulin infusion alone and combined with both AT<sub>1</sub> and AT<sub>2</sub> receptor antagonists. Insulin administration alone (group IN) increased the systolic BP from 133±2 mm Hg during the control period to 157±2 and 159±2 mm Hg (P<0.05) by the end of the fourth and sixth weeks, respectively, of insulin infusion. Addition of losartan to the insulin infusion for 2 weeks (group INLPD) prevented the insulin-induced rise in BP. Subsequently, superimposed PD123319 on losartan and insulin infusion did not significantly alter BP. When coinfusion of both AT<sub>1</sub> and AT<sub>2</sub> receptor antagonists was terminated while insulin infusion was maintained, the systolic BP progressively increased. There were no significant differences in food and water intake, urinary output of sodium and water, and sodium and body weight gains throughout the experiments between groups as shown in Figure 7.

The dipsogenic responses to Ang II in control rats, rats with insulin infusion alone, and rats with combined insulin and either losartan or PD123319 administration are illustrated in Figure 8. No significant differences in basal water intake were noted among groups. After subcutaneous administration of Ang II, the water intakes in rats that received insulin and losartan (6.0±1.0 mL/kg for group INLa and 6.7±1.2 mL/kg for group INLb) were significantly lower than those of the other groups (25.0±1.1 mL/kg for the control group, 21.3±1.3 mL/kg for group IN, and 22.4±1.5 mL/kg for group INPDb, all P values <0.05). The inhibitory effect of losartan on the Ang II–induced dipsogenic response reflects the fact that the effectiveness of AT<sub>1</sub> receptor antagonism persisted throughout the experiments.

Discussion

In the present study we have demonstrated that sustained administration of insulin to approximately double the normal plasma insulin level significantly increased BP but did not change plasma glucose and triglyceride concentrations in rats. Insulin treatment for 6 weeks did not alter the normal growth of the rats, since the weekly body weight gain did not differ significantly between insulin-infused and vehicle-treated rats, suggesting that euglycemic hyperinsulinemia–associated hypertension is unrelated to obesity. These results are consistent with those reported previously by this and other laboratories<sup>15–17</sup> and support the notion that sustained hyperinsulinemia causes species-specific hypertension in rats.<sup>30</sup> In addition, we found that administration of losartan, an AT<sub>1</sub>
Effects of Administration of Insulin Alone and in Combination With Losartan on Plasma Concentrations of Insulin, Triglycerides, and Glucose in Rats

<table>
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<th>Group</th>
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<th>Day 42</th>
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<td>620.6 ± 17.7†</td>
<td>388.9 ± 23.0</td>
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Triglycerides, mmol/L

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Glucose, mmol/L

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<th>Day 42</th>
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<td>7.28 ± 1.28</td>
<td>6.46 ± 1.34</td>
<td>5.13 ± 1.00</td>
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</table>

CON indicates control, with vehicle infusion only; IN, insulin infusion alone; INLa, insulin combined with losartan; INLb, insulin infusion and further losartan treatment after 4 weeks of insulin administration. Plasma insulin, triglyceride, and glucose concentrations on day 28 were measured before losartan treatment. *P<0.05 vs preinsulin; †P<0.05 vs control group.

receptor antagonist, prevented the development of hypertension due to chronic insulin infusion. When insulin-induced hypertension had become established, superimposed administration of losartan on insulin reversed the elevated BP to normal levels within 1 week. In contrast, PD123319, an AT2 receptor antagonist, failed to alter the insulin-induced rise in BP or the losartan-induced hypotensive effect in insulin-infused rats. These observations suggest a determinative role for an Ang II–associated mechanism or Ang II per se via its AT1 receptors in the initiation and maintenance of insulin infusion–induced hypertension.

Similar Ang II dependency has been shown in hypertensive rats that received subchronic insulin administration or a fructose-enriched diet. Brands et al21 reported that ACE inhibition attenuated the insulin-induced increase in BP in rats. It is unclear from the present study whether or not and to what extent chronic insulin activated the RAS, since we did not measure systemic or local plasma renin activities or Ang II levels. It has been shown that insulin administration for 1 week either decreased or did not affect plasma renin activity. However, tissue renin activity or Ang II production could be dissociated from their systemic levels in some hypertensive models.32,33 The hypotensive effect of chronic losartan treatment has also been seen in normotensive rats with sodium- replete and normal plasma renin activity.34 Furthermore, there are some studies showing that Ang II receptor blockade reduces or abolishes BP elevation and hyperinsulinemia in fructose-fed rats. A recent study demonstrated that maintenance of baseline Ang II levels potentiated insulin-induced hypertension in rats. Taken together, these observations rather support the contention that the RAS predominantly determines the development of hyperinsulinemia-induced hypertension due to either sustained insulin administration or high fructose feeding in the rat.

Chronic administration of losartan was associated with selective blockade of AT1 receptors. The effectiveness of angiotensin receptor antagonism was assessed by determining the dipsogenic response to exogenous Ang II in losartan-treated rats before the end of the present experiments. As shown in Figure 8, the dipsogenic response to subcutaneous injection of Ang II was
substantially inhibited in losartan-treated rats compared with control rats and rats that received insulin alone, suggesting effective blockade of AT1 receptors during losartan treatment. In contrast, chronic treatment of insulin-infused rats with PD123319 failed to blunt the drinking response to exogenous Ang II. These findings are not unexpected, since the dipsogenic response to peripheral Ang II is mediated by AT1 and not AT2 receptors. 36 In the vasculature, AT2 receptors have been reported to mediate vasodilation and suppression of vascular growth and tend to “buffer” the vasoconstricting and angiogenic actions of the more dominant AT1 receptors. 37–39 Thus, it could be argued that the hypotensive effect of losartan might be attributed partly to AT2 receptor activation or that the ineffectiveness of PD123319 used in the present study should have produced an effective AT2 blockade without affecting the AT1 receptors. We found that administration of PD123319 alone did not change BP in insulin-infused rats (Figure 4). Combined administration of PD123319 and losartan in insulin-infused rats also failed to alter BP or attenuate the hypotensive effect of losartan (Figure 6). Thus, the lack of an effect of PD123319 on BP in rats treated with insulin suggests the involvement of Ang II via its AT1 but not its AT2 receptors in the initiation and maintenance of hypertension produced by chronic insulin infusion.

Besides the RAS, a number of additional mechanisms have been proposed to contribute to insulin-induced hypertension in rats, but none are conclusive. For example, acute administration of insulin can enhance renal reabsorption of sodium and fluid and stimulate sympathetic nerve activity.18,19 If the acute antinatriuretic and antidiuretic effects of insulin can persist over the long term and are of sufficient magnitude, the resultant sodium retention may contribute to the development of hypertension. However, we found no significant differences in sodium and water excretion, sodium gain, and body weight gain between control and insulin-infused rats despite progressive increases in BP in hyperinsulinemic rats. These observations confirm the previous studies16,31 and support the hypothesis that chronic hyperinsulinemia in rats produces a rightward shift of the renal arterial pressure–natriuretic function relationship, which enables the hyperinsulinemic rats to maintain sodium balance at an elevated BP.16,31 Chronically superimposed infusion of losartan on insulin blunted the insulin-induced increase in BP but did not alter the renal excretion rates of sodium and water or the sodium gain as shown in Figure 2. Thus, the rise in BP noted in insulin-infused rats was not associated with sodium or volume retention. This notion is further fostered by the observation that changes in sodium intake did not significantly alter chronic hyperinsulinemia–induced hypertension in rats.35 It has been reported that acute insulin administration in the absence of
hypoglycemia stimulates the sympathetic nervous system.\textsuperscript{19,28} Thus, increased sympathetic nerve activity per se or the resultant activation of the RAS may be another potential mechanism for hypertension accompanying insulin infusion. However, observations on the necessity of increased sympathetic nerve activity for the development of hypertension associated with chronic insulin infusion are inconsistent.\textsuperscript{14,16,17,42} On the one hand, some studies showed that the pressor response to chronic insulin infusion was attenuated by administrations of an \( \alpha_1 \)-receptor antagonist or an \( \alpha_2 \)-agonist.\textsuperscript{14,17} On the other hand, Keen et al.\textsuperscript{42} showed that chronic blockade of adrenergic activity with a combined \( \alpha_1 \)- and \( \beta \)-receptor antagonist did not prevent hyperinsulinemia-induced hypertension when euglycemia was maintained in rats. The reason for these discrepancies is unknown, and the neural mechanism of hypertension associated with hyperinsulinemia or insulin resistance awaits further investigation.

In addition to an increase in BP, sustained insulin administration caused the rats to develop insulin resistance, as reflected by an increased SSPG level estimated by the insulin suppression test in the present study. The causal relationship between insulin resistance and high BP is unclear from the present study, since we did not determine the time sequence of their occurrence. However, it has been shown that secondary hypertension is not associated with insulin resistance,\textsuperscript{7,43,44} suggesting that hypertension per se does not lead to insulin resistance. Medications that improve insulin sensitivity can decrease BP, but a reduction in BP may not be the cause of improvement in insulin sensitivity.\textsuperscript{45,46} Nevertheless, losartan treatment not only blunted and reversed high BP but also improved insulin sensitivity in insulin-treated rats as shown in Figure 3. It has been demonstrated that inhibition of Ang II formation by an ACE inhibitor ameliorates the insulin sensitivity mainly via the inhibition of Ang II formation rather than the accumulation of kinins.\textsuperscript{24,26} The results of the present study support this notion and further suggest that Ang II plays an important role in the mechanism of insulin resistance, whereas blockade of AT\(_1\) receptors contributes to the amelioration of insulin sensitivity. This may be of clinical significance for the treatment of hypertension with glucose intolerance, because losartan can exert beneficial effects by reducing BP and improving insulin sensitivity via AT\(_1\) receptor antagonism.

In summary, the present study demonstrates that sustained insulin infusion increases BP without significant changes in food and water intake, urine flow, sodium excretion, sodium gain, and body weight gain in insulin-infused rats. A indicates insulin alone, \( n=8 \); \( \square \), combined losartan, PD123319, and insulin infusion, \( n=8 \); and PD, PD123319 (10 \( \mu \)g/kg per minute).
AT1 receptors plays a determinant role in the initiation and maintenance of hyperinsulinemia-induced high BP in rats.

Acknowledgments

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