Insulin infusion induces endothelin-1-dependent hypertension in rats

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Am J Physiol Endocrinol Metab 287: E948–E954, 2004. First published June 29, 2004; doi: 10.1152/ajpendo.00536.2003.—We previously showed that chronic insulin infusion induces insulin resistance, hyperendothelinemia, and hypertension in rats (C. C. Juan, V. S. Fang, C. F. Kwok, J. C. Perrng, Y. C. Chou, and L. T. Ho. Metabolism 48: 465–471, 1999). Endothelin-1 (ET-1), a potent vasoconstrictor, is suggested to play an important role in maintaining vascular tone and regulating blood pressure, and insulin increases ET-1 production in vivo and in vitro. In the present study, BQ-610, a selective endothelin A receptor antagonist, was used to examine the role of ET-1 in insulin-induced hypertension in rats. BQ-610 (0.7 mg/ml; 0.5 ml/kg body wt) or saline was given intraperitoneally twice daily for 25 days to groups of rats infused with either saline or insulin (2 U/day via sc-implanted osmotic pumps), and changes in plasma levels of insulin, glucose, and ET-1 and the systolic blood pressure were measured over the experimental period, whereas changes in insulin sensitivity were examined at the end of the experimental period. Plasma insulin and ET-1 levels were measured by RIA, plasma glucose levels using a glucose analyzer, systolic blood pressure by the tail-cuff method, and insulin sensitivity by an oral glucose tolerance test. Our studies showed that insulin infusion caused sustained hyperinsulinemia in both saline- and BQ-610-injected rats over the infusion period. After pump implantation (2 wk), the systolic blood pressure was significantly higher in insulin-infused rats than in saline-infused rats in the saline-injected group (133 ± 3.1 vs. 113 ± 1.1 mmHg, P < 0.05) but not in the BQ-610-injected group (117 ± 1.2 vs. 117 ± 1.8 mmHg). Plasma ET-1 levels in both sets of insulin-infused rats were higher than in saline-infused controls (2.5 ± 0.6 and 2.5 ± 0.8 vs. 1.8 ± 0.4 and 1.7 ± 0.3 pmol/l, P < 0.05). Oral glucose tolerance tests showed that BQ-610 treatment did not prevent the insulin resistance caused by chronic insulin infusion. No significant changes were found in insulin sensitivity and blood pressure in saline-infused rats treated with BQ-610. In a separate experiment, insulin infusion induced the increase in arterial ET-1 content, hypertension, and subsequent plasma ET-1 elevation in rats. These results suggest that, in the insulin infusion rat model, ET-1 plays a mediating role in the development of hypertension, but not of insulin resistance.

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between 1400 and 1600, with the pumps; Alza, Palo Alto, CA) rats. The pumps were implanted at saline-infused or insulin-infused (2 U/day via sc-implanted osmotic pumps) given intraperitoneally two times daily for 25 days to groups of saline-injected saline-infused group.

In a separate experiment, the time profile measurements were performed on alternate days. In 1800 the same day and were then given daily at 0800 and 1800. Blood samples were collected by tail bleeding in a 1.5-ml heparin-coated polyethylene microfuge tube on ice. For ET-1 determinations, a minimum of 5 ml blood was collected from each rat after decapitation. Plasma was separated by centrifugation and stored at −20°C until assayed.

**Blood pressure measurement.** Narco Bio-Systems Physiograph equipment was used to measure blood pressure by the tail-cuff method, as described previously (16). The small animal study unit of the system has a rat holder base with a built-in warming element to raise the ambient temperature to 37°C and maintain an adequate circulation in the tail for indirect systolic blood pressure measurement. The animal was positioned in the Lucite housing with its tail firmly held outside. The oculding metal tubular cuff (11.1 mm, ID) and the pneumatic pulse sensor-transducer were then placed on the tail and connected to the electrophysmograph (PE-300). The oculding cuff pressure was controlled at a preadjusted inflation-deflation rate until the first pulse was recorded, this representing the systolic blood pressure. Because normal blood pressure shows intrinsic diurnal variation and may be disturbed by environmental conditions, all measurements were carried out in a quiet room starting at 1000 on sets of saline-infused insulin-infused rats, with the order of testing of the different sets being changed on subsequent days of testing. Because an experienced technician can make three to five measurements per rat in 20–30 min, the measurements were finished before 1900. Before the start of the infusion experimental protocol, all rats had been trained for the blood pressure recording procedure.

**Blood sample collection.** Blood sampling was carried out in a quiet room starting at 1000 on sets of saline-infused insulin-infused rats, with the order of testing of the different sets being changed on subsequent days of testing. Blood samples for glucose and insulin measurements (~300 μl) were collected by tail bleeding in a 1.5-ml heparin-coated polyethylene microfuge tube on ice. For ET-1 determinations, a minimum of 5 ml blood was collected from each rat after decapitation. Plasma was separated by centrifugation and stored at −20°C until assayed.

**Oral glucose tolerance test.** On the 22nd day of the experiment, the rats were subjected to an oral glucose test, which was performed on the unanesthetized animal after 24 h of fasting, as described by Whittington et al. (42). Immediately after the collection of a tail vein blood sample, glucose solution (1 g/ml; 1 ml/kg body wt) was given by gavage and then four more blood samples were collected at 30, 60, 90, and 120 min.

**Measurement of plasma glucose, insulin, and ET-1 and arterial ET-1.** The plasma insulin concentration was determined with an RIA developed in our laboratory (14), using a guinea pig anti-porcine insulin antiserum, which cross-reacts 100% with human and rat insulin. Each plasma sample (100 μl) was assayed in duplicate with a welfare committees of the Veterans General Hospital-Taipei and National Yang-Ming University.

**METHODS**

**Animal and experimental design.** Male Sprague-Dawley rats, weighing 250–300 g, were purchased from a local breeder and housed four to a cage in a temperature (20–22°C)- and light-controlled room on an alternating 12:12-h light-dark cycle (lights on, 0700). Except when scheduled for an oral glucose tolerance test or death, all animals had free access to food and water. After 1 wk of acclimatization, BQ-610 (0.35 mg·0.5 ml−1·kg body wt−1) or normal saline was given intraperitoneally two times daily for 25 days to groups of saline-infused or insulin-infused (2 U/day via sc-implanted osmotic pumps; Alza, Palo Alto, CA) rats. The pumps were implanted at about 1400 and 1600, with the first insulin expected to be released about 6 h later, whereas the intraperitoneal injections were started at 1800 the same day and were then given daily at 0800 and 1800. Blood pressure measurements or blood sample collection (for plasma glucose and insulin measurements) was performed on alternate days. In a separate experiment, the time profile measurements of mesenteric and plasma ET-1 and blood pressure were monitored in insulin- and saline-infused rats. All procedures were carried out in accordance with the guidelines of the Taiwan Government Guide for the Care and Use of Laboratory Animals, and the protocol was approved by the animal welfare committees of the Veterans General Hospital-Taipei and National Yang-Ming University.

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**Fig. 1.** Changes in plasma insulin and glucose levels in saline- or insulin-infused rats with or without BQ-610 treatment. ○, saline-infused saline-injected group (n = 6); ●, saline-infused BQ-610-injected group (n = 6); ▲, insulin-infused saline-injected group (n = 7); ▼, insulin-infused BQ-610-injected group (n = 7). Values are means ± SD. *P < 0.05 compared with the saline-injected saline-infused group.

**Fig. 2.** Systolic blood pressure in the four experimental groups. Details as in Fig. 1. ○, saline-infused saline-injected group (n = 6); ●, saline-infused BQ-610-injected group (n = 6); ▲, insulin-infused saline-injected group (n = 7); ▼, insulin-infused BQ-610-injected group (n = 7). Values are means ± SD. *P < 0.05 compared with the saline-injected saline-infused group.
mean variation of 4% (1–8%). Plasma glucose in a 25-μl sample was measured using a glucose analyzer (model 23A; Yellow Springs Instrument, Yellow Springs, OH). ET-1 in 2 ml of plasma was extracted using a Sep-Pak C18 cartridge (Waters, Milford, MA), as described by Xuan et al. (43), and assayed using an ET-1 RIA kit (Peninsula Laboratories, Belmont, CA). To extract arterial ET-1, the frozen blood vessels were homogenized in 5 ml of extraction buffer (1 N HCl, 1% formic acid, 1% trifluoroacetic acid, and 1% NaCl), using a Polytron for 30 s on an ice bath (40). The homogenate was centrifuged at 2,000 g, 4°C for 30 min. The supernatants were further extracted with Sep-Pak C18 cartridges and then assayed by ET-1 RIA, as described above.

Statistical analysis. All results are expressed as means ± SD. Differences between the two groups were analyzed either by Student’s t-test or by two-way ANOVA with a post hoc t-test when multiple measurements were made. The correlation between two categorical variables was analyzed using Pearson’s correlation. Statistical significance was defined as a P value <0.05.

RESULTS

Changes in plasma levels of insulin and glucose and systolic blood pressure. Figure 1 shows plasma insulin and glucose levels in control rats and insulin-infused rats, with or without BQ-610 treatment. Plasma insulin levels doubled within 2 days of the start of insulin infusion and remained significantly higher than in saline-infused controls throughout the experiment, showing a chronic state of hyperinsulinemia. Plasma glucose levels in insulin-infused rats were significantly decreased at 2 days of infusion and then returned to control levels. BQ-610 injection had no significant effect on plasma insulin and glucose levels in insulin-infused rats. Figure 2 shows the changes in systolic blood pressure in saline-infused and insulin-infused rats, with or without BQ-610 treatment. No significant change was seen in either of the saline-infused control groups during the entire experimental period. Chronic infusion of insulin resulted in a significant increase in systolic blood pressure after 2 wk of infusion, and this hypertensive status was maintained until the end of the experiment (133 ± 3.1 vs. 113 ± 1.1 mmHg, P < 0.05); this effect was blocked by BQ-610 injection (117 ± 1.2 vs. 117 ± 1.8 mmHg).

Oral glucose tolerance. The results of the oral glucose tolerance test in the four groups are shown in Fig. 3 and Table 1. Baseline plasma glucose levels were slightly lower (nonsignificant difference) in hyperinsulinemic rats than in controls, and levels in all four groups increased similarly after oral glucose loading. Hyperinsulinemic rats had significantly higher baseline plasma insulin levels than controls. In response to oral glucose challenge, both hyperinsulinemic and control rats responded with an increase in plasma insulin levels, but the levels in the hyperinsulinemic rats were significantly higher than in controls. These results indicated that insulin-stimulated glucose utilization was impaired in insulin target tissues in the hyperinsulinemic rats. The values for the changes of the area under the glucose tolerance curve and 2-h insulin also suggested that the hyperinsulinemic rats were insulin resistant. There was no significant difference in the changes of the area under the insulin profile curve during the oral glucose tolerance test between the hyperinsulinemic and control groups, indicating that insulin secretion in the hyperinsulinemic group was normal. BQ-610 treatment did not ameliorate the insulin resistance in the hyperinsulinemic rats.

Plasma ET-1 concentration. As shown in Fig. 4, plasma ET-1 levels were significantly higher in both hyperinsulinemic groups than in the controls (2.5 ± 0.6 and 2.5 ± 0.8 vs. 1.8 ± 0.4 and 1.7 ± 0.3 pmol/l, P < 0.05). BQ-610 treatment had no effect on plasma ET-1 levels in either the hyperinsulinemic or control group. The systolic blood pressure also showed a positive correlation with plasma insulin levels (r = 0.565, P < 0.05; Fig. 5A) and ET-1 levels (r = 0.776, P < 0.01; Fig. 5B) in the saline-injected groups but not in the BQ-610-injected groups (Fig. 5, C and D).

Time series of elevation of arterial ET-1, plasma ET-1, and blood pressure. A separate study was performed to clarify the time courses of insulin-induced hypertension and ET-1 profiles in plasma and mesenteric arteries. As indicated in Fig. 6, insulin infusion induced the increase in arterial ET-1 content, plasma ET-1 levels, and blood pressure in rats. Besides, the onset time of hypertension (Fig. 6A) and the increase in arterial ET-1 content (Fig. 6B) was earlier than that of plasma ET-1 elevation (Fig. 6C).

Table 1. Plasma glucose and plasma insulin parameters after an oral glucose tolerance test in the 4 experimental groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Saline-Infused (n = 6)</th>
<th>Saline-Infused BQ-610-Injected (n = 6)</th>
<th>Insulin-Infused Saline-Injected (n = 7)</th>
<th>Insulin-Infused BQ-610-Injected (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCglucose, mmol/l·h⁻¹</td>
<td>15.2±0.8</td>
<td>15.2±1.0</td>
<td>15.7±1.1</td>
<td>15.5±0.7</td>
</tr>
<tr>
<td>ΔAUCglucose, mmol/l·h⁻¹</td>
<td>3.0±0.3</td>
<td>2.9±0.9</td>
<td>5.6±1.7*</td>
<td>4.6±1.9*</td>
</tr>
<tr>
<td>AUCinsulin, pmol/l·h⁻¹</td>
<td>359±65</td>
<td>330±47</td>
<td>602±132*</td>
<td>538±96*</td>
</tr>
<tr>
<td>ΔAUCinsulin, pmol/l·h⁻¹</td>
<td>84±33</td>
<td>65±59</td>
<td>111±84</td>
<td>121±57</td>
</tr>
<tr>
<td>2-h Insulin, pmol/l</td>
<td>122±10</td>
<td>107±20</td>
<td>218±65*</td>
<td>177±53*</td>
</tr>
</tbody>
</table>

Values are means ± SD. AUC, area under the curve during oral glucose tolerance tests; ΔAUC, changes in the area under the curve during oral glucose tolerance tests. *P < 0.05 compared with the saline-injected saline-infused group.
DISCUSSION

The results of the present study demonstrate that hyperinsulinemia caused by exogenous insulin infusion resulted in insulin resistance and subsequent hypertension in rats. These results are consistent with our previous findings (20) and those of another laboratory (24). In addition, plasma ET-1 levels were significantly increased in both insulin-infused groups. Several lines of evidence suggest that insulin may increase ET-1 release both in vitro (15) and in vivo (7). It is possible that hyperinsulinemia may continuously stimulate ET-1 release, which may cause an increase in blood pressure through an increase in plasma ET-1 levels. Besides, we cannot rule out the possibility that high plasma ET-1 is the result of decreased ET-1 degradation in insulin-infused rats. However, based on our knowledge, no study showed that insulin may interfere in ET-1 degradation in vivo. To determine whether the increased ET-1 levels seen in the insulin-infused groups were attributable to increased blood pressure, the effect of BQ-610, a selective ETAR antagonist, on the insulin-induced increase in blood pressure was tested. The results (Fig. 2) showed that BQ-610 normalized the blood pressure in insulin-infused rats and provided convincing evidence that ET-1 is an important mediator of insulin infusion-induced hypertension in rats. In addition, chronic treatment with an ETAR antagonist did not prevent the increase in plasma ET-1 levels in insulin-infused rats (Fig. 4). This strongly supports our hypothesis that chronic hyperinsulinemia provides a continuous stimulus for the production and secretion of ET-1, which results in increased circulating ET-1 levels and induces hypertension via the ETAR. The data in Fig. 4 also indicate that ETAR is not involved in the mechanism of insulin-induced ET-1 release from arterial endothelial cells.

However, chronic hyperinsulinemia does not consistently raise blood pressure in dogs (34). It was possible that chronic hyperinsulinemia does not elevate plasma ET-1 concentration in dogs. It was not easy to clarify the relationship between ET-1 and hypertension in hyperinsulinemic dogs because there was no report about the change of plasma ET-1 levels in this animal model. Another possibility is that a counterregulatory
mechanism may mask the pressor effect of chronic hyperinsulinemia in dogs. A study by Brands et al. (2) showed that long-term glucose administration and hyperinsulinemia combined with cyclooxygenase-2 inhibition can significantly increase mean arterial blood pressure in dogs. In human studies, subjects with insulinoma showed hyperinsulinemia but normal ET-1 levels and blood pressure compared with normal subjects. However, subjects with syndrome X showed higher ET-1 levels and hypertension than normal subjects and subjects with insulinoma (32). All these observations suggested that ET-1 may play a mediating role in hyperinsulinemia-induced hypertension.

Insulin was usually used for the treatment of diabetes. It was very interesting whether chronic insulin administration also induced plasma ET-1 elevation and hypertension in diabetic rats. Hu et al. (15) also demonstrated that a significant elevation of plasma ET-1 levels was induced by the subcutaneous implanted insulin pellet in streptozotocin-diabetic rats (15), but the changes of blood pressure in these animals were not evaluated in their study. Haak et al. (10) have reported that plasma ET-1 levels were elevated in diabetic patients with hypertension (10). Some studies also suggested that elevation of plasma ET-1 levels was observed in diabetic patients without hypertension (26, 36). However, there was not any follow-up study to investigate the incidence of hypertension in diabetic patients with high plasma ET-1. Although these observations cannot support the role of ET-1 in the development of diabetic hypertension, the changes in plasma ET-1 may precede vascular complications associated with diabetes. Additionally, the effects of long-term insulin therapy on blood pressure in diabetes needed further elucidation.

The role of ET-1 in hypertension and vascular diseases was well observed by Iglarz and Schiffrin (17, 35). They pointed out that ET-1 plays important roles in hypertension and vascular growth. Endothelial damage may activate expression of ET-1 in vessels and in heart as blood pressure increases. Recent studies have proposed the mechanisms involved in the vascular damage and atherosclerosis induced by ET-1, including increased oxidative stress, stimulation of nuclear factor-κB and activator protein S-1, and upregulation of vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and monocyte chemoattractant peptide-1. Together with the comitogenic effect with other growth factors, ET-1 may induce serial cell growth and inflammatory responses in the development and progression of atherosclerosis. These findings all suggested that ET-1 may contribute to hypertension and to progression of vascular damage and atherosclerosis.

Verma et al. (41) had suggested the dual nature of insulin to synchronously stimulate ET and the nitric oxide system in rat aortas. At subthreshold concentrations of insulin, the absence of insulin-mediated vasodilation was uncovered by an ET receptor antagonist. In addition, the same dose of insulin evoked vasodilation in aortas isolated from rats after long-term ET receptor antagonist treatment. Miller et al. (27) also demonstrated that enhanced ET activity suppressed insulin-stimulated vasodilation in insulin-resistant mesenteric arteries, and the impaired vasodilation could be normalized in the presence of BQ-610. These data proposed the functional interaction between insulin and ET-1 in modulating vascular tone and also clarified that insulin can engender the production of ET-1 to affect vascular function preceding blood pressure elevation. These concepts were compatible with our observations that ET-1 played the mediating role in the development of insulin-associated hypertension.

In addition to the increase in blood pressure, chronic insulin infusion also caused insulin resistance, as estimated by the oral glucose tolerance test. Theoretically, insulin resistance can occur either by downregulation of insulin receptor or by signal impairment at the postreceptor level in this model. However, the relationship between increased ET-1 levels and insulin resistance in insulin-infused rats is not clear. The increased plasma levels of ET-1 might further increase insulin resistance by reducing flow-dependent insulin sensitivity (1), thereby contributing to continuous overstimulation of insulin resistance. Our previous studies also showed that ET-1 may induce insulin resistance in vitro (22) and in vivo (19). However, the results of the oral glucose tolerance test indicated that administration of BQ-610 did not ameliorate insulin resistance in insulin-infused rats (Fig. 3 and Table 1), suggesting that the contribution of elevated plasma ET-1 levels to the pathogenesis
of insulin resistance induced by chronic insulin infusion was minor.

Similar studies have been performed in the fructose-fed rat model. When rats are fed a fructose diet, they develop hyperinsulinemia, insulin resistance, hypertriglyceridemia, and hypertension, a profile reminiscent of syndrome X seen in patients with non-insulin-dependent diabetes mellitus. Expression of the ET-1 and ET₄R genes and the vasoconstrictor response to ET-1 are increased in the arteries of fructose-fed rats (18, 21). In this model, the nonselective ET antagonist bosentan (40) or the ET₄R antagonist BQ-610 (18) lowers the high blood pressure. In these studies, we were unable to directly address the question of whether ET-1 is a mediator linking hyperinsulinemia and hypertension. However, in the present study, infusion of exogenous insulin directly caused hyperinsulinemia, which, in turn, causes high expression of ET-1 and, consequently, hypertension. These results showing that BQ-610 caused a decrease in blood pressure in the insulin-infused rats without any change in plasma insulin levels suggest that hyperinsulinemia is the primary step causing hypertension in insulin-infused rats and that the increase in ET-1 levels is secondary. Our findings therefore suggest that ET-1 plays a mediating role linking hyperinsulinemia to hypertension.

The same experimental design has been used to explore the role of ANG II in the pathogenesis of insulin-induced hypertension in rats. Fang and Huang (5) demonstrated that an ANG II type 1 receptor antagonist blunts hyperinsulinemia-induced hypertension in rats. These observations raised the possibility of an interaction between ET-1 and ANG II. Both ET-1 and ANG II are important vasoconstrictor peptides and act as mitogens and trophic factors in vascular smooth muscle (12, 23, 48). ANG II induces expression and secretion of ET-1 in cultured vascular endothelial cells through its interaction with the ANG II type 1 receptor (8). Chronic ANG II administration increases tissue ET-1 content and induces vascular hypertrophy and hypertension in rats, and treatment with an ET₄R antagonist reduces blood pressure and prevents vascular structural changes (28). These experimental findings provide support for the idea that an interaction between ANG II and ET-1 is operative in vivo. Several lines of evidence also suggest an interaction between the renin-angiotensin system and ET-1 in diseases involving increased activation of the renin-angiotensin system, such as heart failure and hypertension (38, 46). Therefore, antagonists of the renin-angiotensin or ET system may be important in the therapy of cardiovascular diseases.

In summary, the present study demonstrates that chronic insulin infusion induces hyperinsulinemia, insulin resistance, elevation of arterial ET-1 content and plasma ET-1 level, and hypertension in rats and that, in insulin-infused rats, chronic BQ-610 treatment completely prevents the development of hypertension but not insulin resistance or hyperendothelium. Our data demonstrate that ET-1 is a mediator linking hyperinsulinemia to hypertension in insulin-infused hypertensive rats. These data also suggest that hyperinsulinemia and/or insulin resistance may create an environment resulting in activation of the ET system, thus causing hypertension. If this concept is true, this disordered environment may prove to be an important target for therapy using ET antagonists.

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