Clinical and Experimental Pharmacology and Physiology (2002) **29**, 381–385

QUINAPRIL TREATMENT RESTORES THE VASODILATOR ACTION OF INSULIN IN FRUCTOSE-HYPERTENSIVE RATS

Takanori Uchida,* Kenji Okumura,* Takayuki Ito,† Hiroki Kamiya,* Yasuhiro Nishimoto,* Michiharu Yamada,* Takahito Tomida,* Hideo Matsui* and Tetsuo Hayakawa*

**Department of Internal Medicine II and †Health Sciences, Nagoya University School of Medicine, Nagoya, Japan*

SUMMARY

1. Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve insulin-resistance both experimentally and clinically. We therefore investigated the effects of quinapril, which has high tissue specificity for ACE, regarding the contribution of insulin to vascular contractions, as well as insulin sensitivity in a dietary rat model of insulin resistance.

2. Male Sprague-Dawley rats were divided into three groups: (i) rats fed normal chow (normal diet group); (ii) rats fed fructose-rich chow containing 40% fructose and 7% lard (fructose diet group); and (iii) rats fed fructose-rich chow plus quinapril (10 mg/kg per day; quinapril-treated group).

3. After 2 weeks, we evaluated systolic blood pressure, insulin sensitivity as assessed by steady state plasma glucose (SSPG) levels, response of aortic rings to phenylephrine (10^{-9} to 10^{-6} mol/L) in the presence or absence of insulin and the response of aortic rings to acetylcholine.

4. Feeding rats fructose-rich chow resulted in an elevation of blood pressure ($P < 0.01$) and SSPG levels ($P < 0.01$). Quinapril treatment significantly prevented increases in both blood pressure and SSPG, with a return to the levels seen in the normal diet group.

5. In the absence of insulin, the maximal contractile response to phenylephrine did not differ between the three groups. However, in the presence of insulin (100 mU/mL), the contractile response to phenylephrine (10^{-6} mol/L) was reduced by 22.8 ± 1.2% in the normal diet group, although no insulin effects were observed in the fructose diet group ($P < 0.01$). Quinapril restored the inhibitory effect of insulin on phenylephrine-induced contractions.

6. In addition, the reduction in relaxation induced by acetylcholine in the fructose diet group was significantly reversed by quinapril treatment.

7. It is concluded that the fructose diet impairs the vasodilator effects of insulin as well as acetylcholine-induced relaxation in rat thoracic aortas. Quinapril prevented deterioration in the responses of the aortic rings, suggesting that ACE inhibitors may be useful for treating vascular insulin resistance.

Key words: angiotensin-converting enzyme inhibitor, aortic rings, insulin resistance, phenylephrine.

Correspondence: Dr Kenji Okumura, Department of Internal Medicine II, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Email: kenji@med.nagoya-u.ac.jp

Received 19 June 2001; revision 17 October 2001; accepted 17 October 2002.

INTRODUCTION

Impairment of insulin action (insulin resistance) is centrally involved in diseases such as type 2 diabetes mellitus, obesity, hypertension and cardiovascular disease.[1–3] However, the precise mechanisms linking insulin resistance to hypertension are not understood. In addition to its effects on glucose metablism, insulin has been demonstrated to be a vasodilator.[4] Insulin resistance states have also been reported to be associated with defective insulin-mediated vasodilation.[5] In recent years, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, have been reported to improve insulin resistance in both hypertensive subjects and several rat models of hypertension.[6–9] Therapy with ACE inhibitors has been shown to improve vascular function in a range of subjects with diabetes mellitus,[10] congestive heart failure[11] and smoking habitus.[12] So far, however, there have been few reports on vascular responses to insulin as a result of ACE inhibitor treatment.

Insulin resistance and hyperinsulinaemia have been induced in normotensive Sprague-Dawley rats by sucrose or fructose feeding.[13,14] This rat model is characterized by hypertriglyceridaemia and mild hypertension, similar to characteristics of syndrome X in humans. In previous studies, the fructose-hypertensive rat model has been used to study the interrelationship between insulin resistance and hypertension.[15,16] In the present study, we investigated whether quinapril treatment improves vascular responses to insulin in thoracic aortic rings from fructose-hypertensive rats with insulin resistance.

METHODS

Animals and treatments

Male Sprague-Dawley rats (approximately 180 g; aged 6 weeks) were used. Rats were divided into three groups according to diet: (i) a normal diet group fed normal chow; (ii) a fructose diet group fed fructose-rich chow (containing 40% fructose as a percentage of calories and 7% lard);[17] and (iii) a quinapril-treated group fed fructose-rich chow plus quinapril at 10 mg/kg per day (n = 12 for each group) for 2 weeks. The mineral, protein, fat and vitamin content in the three groups was matched. Quinapril was suspended in distilled water (0.2 mL) and was administered at a dose of 10 mg/kg per day orally by gastric gavage in the morning. Both the normal diet and fructose-fed groups were administered vehicle. Rats were allowed free access to the assigned diet and to water and were maintained on a 12 h light–dark cycle. All procedures were approved by the animal ethics committee of Nagoya University.

Blood pressure measurement procedures

Two weeks after the start of the special diet, systolic blood pressure (SBP) was determined in each animal 1 day prior to death. The tail-cuff method

was used to determine SBP with a photoelectric tail cuff detection system (Softron BP-98A; Softron, Tokyo, Japan) after external preheating for 5 min at 50°C.

Steady state plasma glucose and steady state plasma insulin measurements

Two weeks after the start of the diets, we determined the steady state plasma glucose (SSPG) and steady state plasma insulin (SSPI) levels according to the method of Mondon and Reaven[18] in the three groups ($n = 6$ in each group). In brief, rats anaesthetized with pentobarbital received a continuous infusion (1 mL/h) of adrenaline (0.08 μg/kg per min), propranolol (1.7 μg/kg per min), glucose (8 mg/kg per min) and insulin (1.25 mU/kg per min) through a catheter inserted into a femoral vein. Two hours after the start of infusion, blood samples were collected from the abdominal aorta for the measurement of plasma glucose levels and insulin concentrations in order to determine SSPG and SSPI levels.

Preparation of thoracic aortas

After rats were decapitated, the thorax was opened and the thoracic aorta was then removed rapidly and placed immediately in an ice-cold Krebs'–Henseleit solution of the following composition (in mmol/L): NaCl 118; KCl 4.7; $CaCl_2$ 2.55; $MgSO_4$ 1.18; $NaHCO_3$ 24.88; glucose 11.1; EDTACa-2Na 0.026. Fat and connective tissue on the aortic surface were removed and the aorta was then cut into rings (5 mm in length) with scissors. After two stainless-steel wires were inserted into the aortic lumen, the aortic ring was suspended in an organ bath filled with 30 mL Krebs'–Henseleit solution plus 0.05% albumin-containing antifoam agents (0.02%), with one of the wires connected to a force transducer (model TB-612T; Nihon Kohden, Tokyo, Japan) to measure isometric tension using a Flatbed Recorder (model FBR-252A; TOA Electronics, Tokyo, Japan). The buffer was maintained at 37°C and bubbled with a mixture of 95% O_2–5% CO_2. During these procedures, maximum care was taken to not apply unnecessary tension to the rings or to damage their luminal surface. Rings were allowed to equilibrate for 60 min at a resting tension of 1.0 g.

Response of aortic rings to phenylephrine in the presence or absence of insulin

In the first step, cumulative concentration–response curves to phenylephrine (10^{-9} to 10^{-6} mol/L) in the absence of insulin were constructed and the rings were then washed with buffer. After washing, each ring was incubated with buffer for 60 min. Human insulin (Humulin R; 100 mU/mL; Eli Lilly Japan, Kobe, Japan) was then added to the medium and rings were further incubated for 30 min. In the second step, cumulative concentration–response curves to phenylephrine (10^{-9} to 10^{-6} mol/L) were constructed in the presence or absence of insulin (100 mU/mL). Contraction responses were expressed as a percentage of the maximum contraction to 10^{-6} mol/L phenylephrine in the absence of insulin.

Response of aortic rings to acetylcholine

Aortic rings were precontracted with 10^{-7} mol/L L-noradrenaline bitartrate. After the contractions reached a plateau, the rings were relaxed by acetylcholine (10^{-9} to 10^{-5} mol/L) and relaxation responses were recorded. Relaxation responses were expressed as a percentage of the tension developed in response to 10^{-7} mol/L noradrenaline. The concentrations used in the present study are in accordance with those used in other studies.[19,20]

Statistical analysis

Results are expressed as the mean ± SEM. Statistical differences were determined by one-way analysis of variance (ANOVA) for repeated measurements followed by the Student's modified *t*-test with Bonferroni's correction for multiple comparisons. $P < 0.05$ was considered statistically significant.

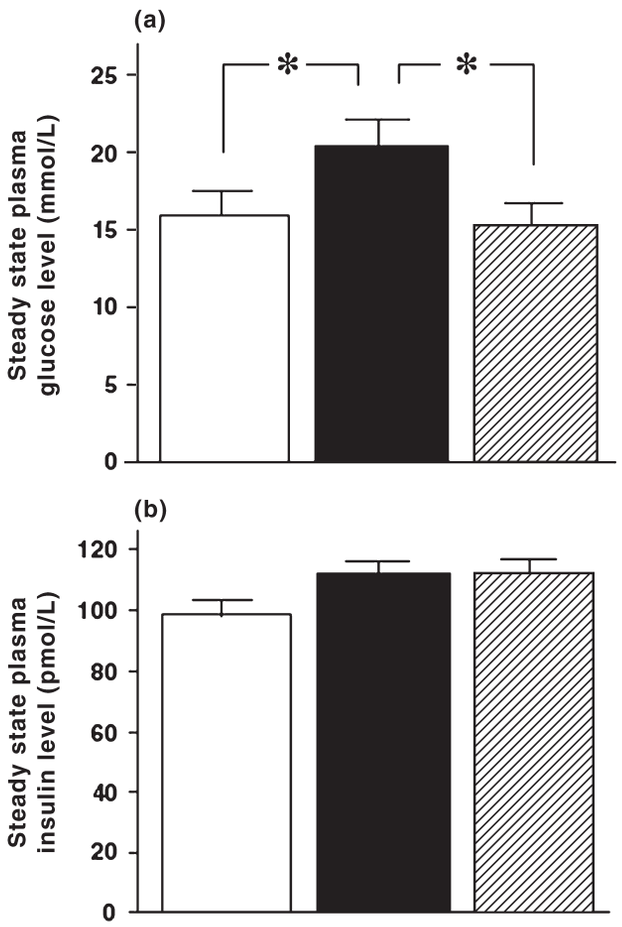

Fig. 1 (a) Steady state plasma glucose (SSPG) and (b) steady state plasma insulin (SSPI) levels in rats fed either a normal diet (□), a fructose-rich diet (■) or a fructose-rich diet with quinapril treatment (▨). The fructose diet group exhibited a significant increase in SSPG levels, but there was no difference in SSPI levels among the three groups ($n = 6$ in each group). Data are the mean ± SEM. *$P < 0.01$.

Table 1 Bodyweight, blood pressure and pulse rate in rats fed a normal diet, a fructose-rich diet and a fructose-rich diet with quinapril treatment

	Normal diet group	Fructose diet group	Quinapril-treated group
Bodyweight (g)	255 ± 7	253 ± 6	224 ± 5*
Systolic blood pressure (mmHg)	112 ± 5	123 ± 4†	109 ± 7**
Pulse rate (b.p.m.)	374 ± 17	379 ± 19	378 ± 19

Data are the mean ± SEM. *$P < 0.01$ compared with the normal diet and fructose diet groups; **$P < 0.01$ compared with the fructose diet group; †$P < 0.01$ compared with the normal diet group.

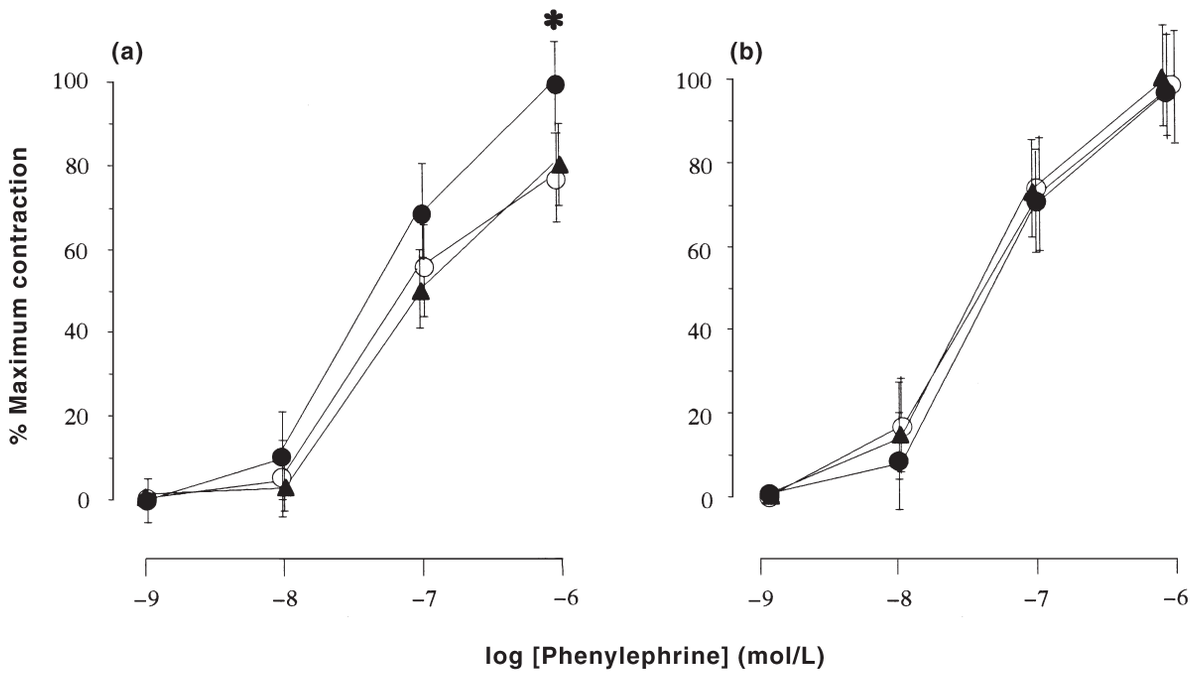

Fig. 2 Response of aortic rings to phenylephrine in the (a) presence or (b) absence of insulin (100 mU/mL). Contraction is expressed as a percentage of the maximum contraction in response to 10^{-6} mol/L phenylephrine in the absence of insulin. Insulin reduced the phenylephrine-induced contractile response in rats fed a normal diet (○) and quinapril-treated rats fed a fructose-rich diet (▲), whereas it had no effect in rats fed the fructose diet only (●). Data are the mean ± SEM ($n = 6$ in each group). *$P < 0.01$ compared with the normal diet and quinapril-treated groups.

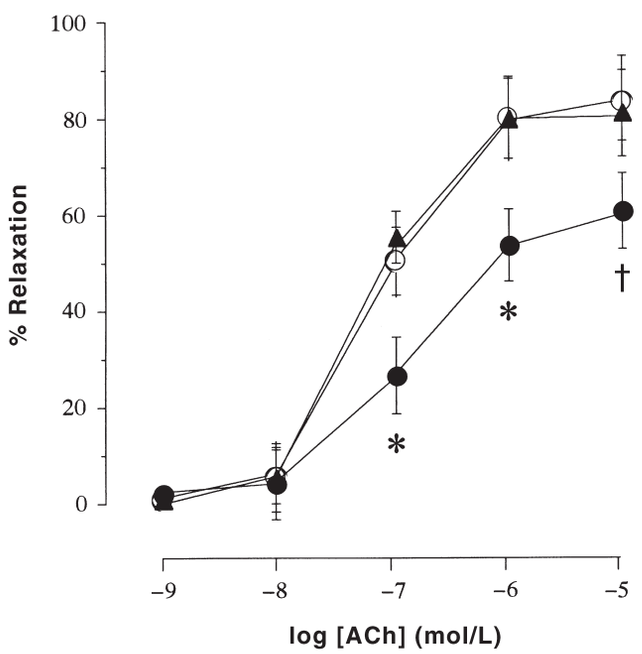

Fig. 3 Response of aortic rings to acetylcholine. Relaxation is expressed as a percentage of the tension developed in response to 10^{-7} mol/L noradrenaline. Fructose-rich chow (●) reduced acetylcholine-induced relaxation, which was reversed by quinapril treatment (▲). *$P < 0.01$ compared with the the normal diet (○) and quinapril-treated groups; †$P < 0.01$ and $P < 0.05$ compared with the normal diet group and the quinapril-treated group, respectively.

RESULTS

General features of animals

Bodyweight was significantly lower for the quinapril-treated group than for the other two groups (Table 1). Fructose-rich chow raised SBP to a small, but significant ($P < 0.01$), extent. The administration of quinapril completely prevented the rise in blood pressure induced by the feeding of a high-fructose diet ($P < 0.01$). There were no differences in SBP between the normal diet and quinapril-treated groups. There were no differences in pulse rate between the three groups (Table 1).

SSPG and SSPI levels

The fructose-fed group exhibited a significant increase in SSPG levels (20.2 ± 0.8 *vs* 15.8 ± 0.6 mmol/L in the normal diet group; $P < 0.01$), but there was no difference in the SSPI levels between the two groups (Fig. 1). These results are consistent with previous results[13,16] indicating that the feeding of a high-fructose diet significantly impairs insulin activity; that is, it causes insulin resistance. The administration of quinapril reduced the increased SSPG levels to those seen in the normal diet group (15.3 ± 0.9 mmol/L; $P < 0.01$), although there was no difference in SSPI levels. Quinapril treatment improved the insulin sensitivity impaired by the feeding of a high-fructose diet.

Response of aortic rings to phenylephrine in the presence or absence of insulin

Figure 2a shows the response of aortic rings to phenylephrine in the presence of insulin. Insulin reduced the contractile response to phenylephrine (10^{-6} mol/L) by 22.8 ± 1.2% in the normal diet group, whereas it had no effect in the fructose diet group. Quinapril

treatment of rats fed fructose-rich chow restored the vasodilator action of insulin on phenylephrine-induced contractions.

Figure 2b shows the response of aortic rings to phenylephrine in the absence of insulin. The maximum contractile response to phenylephrine did not differ among the three groups. The results shown in Fig. 2 indicate that quinapril treatment reverses the attenuation of contraction induced by insulin in aortas in response to phenylephrine in fructose-hypertensive rats.

Response of aortic rings to acetylcholine

Fructose-rich chow reduced acetylcholine-induced relaxation (82.9 ± 3.2 and 59.8 ± 5.4% relaxation in the normal and fructose diet groups, respectively; $P < 0.01$), effects that were nearly completely reversed by quinapril treatment (79.4 ± 4.5% relaxation; $P < 0.01$; Fig. 3).

DISCUSSION

In the present study, fructose-fed rats became insulin resistant, as manifested by significantly higher SSPG levels. In addition, a mild but significant rise in blood pressure was observed, although no obesity was observed in fructose-fed rats. These results are in accordance with those of previous studies.[13,21] The ACE inhibitor quinapril prevented the rise in blood pressure and the elevation in SSPG levels observed in the fructose diet group, suggesting that quinapril is useful for treating insulin resistance in fructose-hypertensive rats.

Insulin has a specific physiological action; namely, it vasodilates skeletal muscle vasculature in humans.[22,23] Insulin indirectly attenuates vascular contraction via enhancement of endothelium-dependent vasodilation.[24] In addition, it has recently been found that insulin vasodilation contributes, in part, to an inhibition of voltage-operated Ca^{2+} channels.[25] According to studies using aortas from rats fed a high-fructose diet, the responsiveness of vascular smooth muscles is not impaired because the vasodilator response to sodium nitroprusside is not decreased in insulin resistance.[26] The impairment of vasodilation induced by acetylcholine, which was reproduced in the present study, appears to be due to the decreased effects of nitric oxide, presumably via excess vascular oxidative stress.[26] In humans, obese/insulin-resistant subjects are characterized by endothelial dysfunction and endothelial resistance to the effects of insulin on the enhancement of endothelium-dependent vasodilation.[27]

Insulin resistance and the resultant hyperinsulinaemia are causally related to hypertension.[28,29] It has been demonstrated that insulin resistance, but not hyperinsulinaemia, induces endothelial dysfunction resulting in hypertension.[30,31] In the present study, insulin reduced the contractile response of aortic rings to phenylephrine in the normal diet group, implying that insulin does have vasodilator effects, as mentioned above, in thoracic aortic rings contracted by phenylephrine, although insulin produces no significant change in the basal tonus of rings (data not shown). This finding is in agreement with those of previous studies in which insulin has suppressed the vasoconstrictor actions of noradrenaline, phenylephrine and angiotensin II in isolated arteries and veins.[32–34] In addition, we observed that insulin does not reduce this contractile response to phenylephrine in fructose-hypertensive rats, indicating that the fructose diet significantly impairs the vasodilator effects of insulin in precontracted aortas. With regard to this phenomenon, Verma *et al*. have already observed that the vasodilator effects of insulin disappear in fructose-hypertensive rats because insulin does not reduce the contractile response to angiotensin II in rat aortas.[35]

Furthermore, the present study indicates that quinapril ameliorates vascular insulin resistance and inhibits the elevation of blood pressure in fructose-hypertensive rats. Quinapril itself is an antihypertensive drug and upregulates nitric oxide.[36] Angiotensin-converting enzyme inhibitors have also been reported to directly mediate vasodilation.[37] A prevention of the rise in blood pressure may be attributed to ameliorated insulin resistance[38,39] rather than the antihypertensive effects of quinapril, because the SSPG levels in quinapril were as low as those in the normal diet group and endothelium-derived nitric oxide plays an important role in maintaining basal blood pressure.[38] In fact, in the present study, quinapril improved the relaxation induced by acetylcholine, presumably via effects of nitric oxide, in noradrenaline-precontracted aortas. Recently, Feldman and Schmidt have shown that chronic quinapril therapy enhances vascular sensitivity to insulin without a significant change in blood pressure in subjects with borderline or mild hypertension.[40] However, the mechanism by which quinapril improves vascular insulin resistance in fructose-hypertensive rats was not revealed in the present study. Treatment of genetic hypertensive rats with insulin resistance with quinapril, not angiotensin II receptor antagonists, is known to enhance vascular sensitivity to insulin and to improve insulin resistance involving hypertension.[9] In the same way, chronic quinapril treatment enhances β-adrenoceptor-mediated relaxation,[40] but its effects are not associated with the endothelium. We did not evaluate β-adrenoceptor-mediated vasodilation in the present study. Based on our findings, it seems that the improvement of endothelial function, as indicated by the response to acetylcholine, may, at least in part, improve vascular insulin resistance. Further investigation of the mechanisms involved in the beneficial effects of quinapril remains to be performed.

In conclusion, the fructose diet significantly impaired the vasodilator effects of insulin and attenuated acetylcholine-induced relaxation in rat thoracic aortas. Quinapril prevented the development of these impaired responses, suggesting that ACE inhibitors may be useful for treating vascular insulin resistance.

REFERENCES

1. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–607.
2. DeFronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; **14**: 173–94.
3. Morris AD, Petrie JR, Connell JM. Insulin and hypertension. *J. Hypertens.* 1994; **12**: 633–42.
4. Anderson EA, Mark AL. The vasodilator action of insulin. Implications for the insulin hypothesis of hypertension. *Hypertension* 1993; **21**: 136–41.
5. Feldman RD, Bierbrier GS. Insulin-mediated vasodilation: Impairment with increased blood pressure and body mass. *Lancet* 1993; **342**: 707–9.
6. Ferrannini E, Buzzigoli G, Bonadonna R *et al.* Insulin resistance in essential hypertension. *N. Engl. J. Med.* 1987; **317**: 350–7.
7. Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N. Engl. J. Med.* 1989; **321**: 868–73.

8. Kodama J, Katayama S, Tanaka K, Itabashi A, Kawazu S, Ishii J. Effect of captopril on glucose concentration. Possible role of augmented postprandial forearm blood flow. *Diabetes Care* 1990; **13**: 1109–11.
9. Nakagawa H, Daihara M, Tamakawa H, Nozue T, Kawahara K. Effects of quinapril and losartan on insulin sensitivity in genetic hypertensive rats with different metabolic abnormalities. *J. Cardiovasc. Pharmacol.* 1999; **34**: 28–33.
10. O'Driscoll G, Green D, Maiorana A, Stanton K, Colreavy F, Taylor R. Improvement in endothelial function by angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. *J. Am. Coll. Cardiol.* 1999; **33**: 1506–11.
11. Hornig B, Arakawa N, Haussmann D, Drexler H. Differential effects of quinaprilat and enalaprilat on endothelial function of conduit arteries in patients with chronic heart failure. *Circulation* 1998; **98**: 2842–8.
12. Chalon S, Moreno Jr H, Hoffman BB, Blaschke TF. Angiotensin-converting enzyme inhibition improves venous endothelial dysfunction in chronic smokers. *Clin. Pharmacol. Ther.* 1999; **65**: 295–303.
13. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. *Hypertension* 1987; **10**: 512–16.
14. Bunag RD, Tomita T, Sasaki S. Chronic sucrose ingestion induces mild hypertension and tachycardia in rats. *Hypertension* 1983; **5**: 218–25.
15. Bhanot S, McNeill JH. Vanadyl sulfate lowers plasma insulin and blood pressure in spontaneously hypertensive rats. *Hypertension* 1994; **24**: 625–32.
16. Reaven GM, Ho H, Hoffmann BB. Somatostatin inhibition of fructose-induced hypertension. *Hypertension* 1989; **14**: 117–20.
17. Matsui H, Okumura K, Kawakami K, Hibino M, Toki Y, Ito T. Improved insulin sensitivity by bezafibrate in rats: Relationship to fatty acid composition of skeletal-muscle triglycerides. *Diabetes* 1997; **46**: 348–53.
18. Mondon CE, Reaven GM. Evidence of abnormalities of insulin metabolism in rats with spontaneous hypertension. *Metabolism* 1988; **37**: 303–5.
19. Khan SA, Mathews WR, Meisheri KD. Role of calcium-activated K^+ channels in vasodilation induced by nitroglycerine, acetylcholine and nitric oxide. *J. Pharmacol. Exp. Ther.* 1993; **267**: 1327–35.
20. Hamaguchi M, Ishibashi T, Imai S. Involvement of charybdotoxin-sensitive K^+ channel in the relaxation of bovine tracheal smooth muscle by glyceryl trinitrate and sodium nitroprusside. *J. Pharmacol. Exp. Ther.* 1992; **262**: 263–70.
21. Chen S, Kashiwabara H, Kosegawa I, Ishii J, Katayama S. Bradykinin may not be involved in improvement of insulin resistance by angiotensin converting enzyme inhibitor. *Clin. Exp. Hypertens.* 1996; **18**: 625–36.
22. Laakso M, Edelman SV, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. *J. Clin. Invest.* 1990; **85**: 1844–52.
23. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J. Clin. Invest.* 1991; **87**: 2246–52.
24. Wu HY, Jeng YY, Yue CJ, Chyu KY, Hsueh WA, Chan TM. Endothelial-dependent vascular effects of insulin and insulin-like growth factor I in the perfused rat mesenteric artery and aortic ring. *Diabetes* 1994; **43**: 1027–32.
25. Goud C, Pitt B, Webb RC, Richey JM. Synergistic actions of insulin and troglitazone on contractility in endothelium-denuded rat aortic rings. *Am. J. Physiol.* 1998; **275**: E882–7.
26. Shinozaki K, Kashiwagi A, Nishio Y *et al.* Abnormal biopterin metabolism is a major cause of impaired endothelium-dependent relaxation through nitric oxide/O_2^- imbalance in insulin-resistant rat aorta. *Diabetes* 1999; **48**: 2437–45.
27. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J. Clin. Invest.* 1996; **97**: 2601–10.
28. Mark AL, Anderson EA. Genetic factors determine the blood pressure response to insulin resistance and hyperinsulinemia: A call to refocus the insulin hypothesis of hypertension. *Exp. Biol. Med.* 1995; **208**: 330–6.
29. Landsberg L. Insulin sensitivity in the pathogenesis of hypertension and hypertensive complications. *Clin. Exp. Hypertens.* 1996; **18**: 337–46.
30. Shinozaki K, Suzuki M, Ikebuchi M *et al.* Insulin resistance associated with compensatory hyperinsulinemia as an independent risk factor for vasospastic angina. *Circulation* 1995; **92**: 1749–57.
31. Shinozaki K, Suzuki M, Ikebuchi M, Hara Y, Harano Y. Demonstration of insulin resistance in coronary artery disease documented with angiography. *Diabetes Care* 1996; **19**: 1–7.
32. Grover A, Padginton C, Wilson JF, Sung BH, Izzo Jr JL, Dandona P. Insulin attenuates norepinephrine-induced venoconstriction. An ultrasonographic study. *Hypertension* 1995; **25**: 779–84.
33. Alexander WD, Oake RJ. The effect of insulin on vascular reactivity to norepinephrine. *Diabetes* 1977; **26**: 611–14.
34. Yagi S, Takata S, Kiyokawa H *et al.* Effects of insulin on vasoconstrictive responses to norepinephrine and angiotensin II in rabbit femoral artery and vein. *Diabetes* 1988; **37**: 1064–7.
35. Verma S, Bhanot S, Yao L, McNeill JH. Vascular insulin resistance in fructose-hypertensive rats. *Eur. J. Pharmacol.* 1997; **322**: R1–2.
36. Bachetti T, Comini L, Pasini E, Cargoni A, Curello S, Ferrari R. ACE-inhibition with quinapril modulates the nitric oxide pathway in normotensive rats. *J. Mol. Cell. Cardiol.* 2001; **33**: 395–403.
37. Zarnke KB, Feldman RD. Direct angiotensin converting enzyme inhibitor-mediated venodilation. *Clin. Pharmacol. Ther.* 1996; **59**: 559–68.
38. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. *J. Clin. Invest.* 1994; **94**: 1172–9.
39. Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. *J. Clin. Invest.* 1994; **94**: 2511–15.
40. Feldman RD, Schmidt ND. Quinapril treatment enhances vascular sensitivity to insulin. *J. Hypertens.* 2001; **19**: 113–18.