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Blockade of angiotensin converting enzyme but not of angiotensin AT_1 receptors improves glucose tolerance

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Abstract

This study compared the effect of benazepril, an angiotensin converting enzyme inhibitor to valsartan, an angiotensin AT_1 receptor antagonist, on glucose tolerance in the conscious, spontaneously hypertensive rat. Intraperitoneal infusion of benazepril or valsartan at 1, 3 and 10 mg/kg per day produced equivalent dose-related reductions in systolic blood pressure for 12 weeks. Body weight gain during the treatment period was significantly reduced by all infusion rates of benazepril. In contrast, only the highest infusion rate of valsartan significantly affected body weight gain. At the end of the 12-week treatment period, neither benazepril nor valsartan significantly affected glucose disposal during intravenous glucose tolerance tests. The insulin response to glucose challenge was unaffected by valsartan whereas following the highest infusion rate of benazepril the plasma insulin levels were significantly reduced. The results demonstrate that benazepril but not valsartan reduces the insulin required to dispose of a glucose load.

Keywords: Spontaneously hypertensive rat (SHR); Glucose tolerance; Blood pressure; Angiotensin-converting enzyme inhibitor; Angiotensin AT_1 receptor antagonist; Valsartan

1. Introduction

In epidemiological studies essential hypertension is often found closely related to insulin resistance (Ferrannini et al., 1990). Insulin resistance has been postulated not only as a cause of essential hypertension but also as the reason why this disorder is so often associated with metabolic abnormalities such as hyperinsulinemia, glucose intolerance, and disturbances of plasma lipids. The abnormal metabolic profile associated with essential hypertension, commonly referred to as syndrome X, is believed to play a major role in the development of atherosclerosis (Reaven, 1990, 1994).

Of the classes of antihypertensive drugs currently recommended for the therapy of essential hypertension only α-adrenoceptor antagonists and angiotensin converting enzyme inhibitors are thought to improve insulin sensitivity (Pollare et al., 1988; Osksa et al., 1994). In the case of angiotensin converting enzyme inhibitors, the evidence is mixed. Some studies show a mild improvement while others suggest that inhibition of angiotensin converting enzyme has no effect on insulin sensitivity (Osksa et al., 1994; Ferrannini et al., 1994; De Feo et al., 1992). A recent review of the literature has suggested that improved glucose tolerance is a more consistent finding following inhibition angiotensin converting enzyme than is increased insulin sensitivity (Ferrannini et al., 1994). These findings have been interpreted to suggest that potentiation of glucose-induced insulin release rather than increased peripheral insulin sensitivity is the primary response to chronic inhibition of angiotensin converting enzyme in human essential hypertension (Berne, 1991; Santoro et al., 1992; Ferrannini et al., 1994).

The increasing popularity of angiotensin converting enzyme inhibitors in the treatment of essential hypertension has stimulated interest in the development of other inhibitors of the renin-angiotensin system, such as angiotensin AT_1 receptor antagonists (Timmermans et al., 1993). The few studies that have been conducted suggest that angiotensin AT_1 antagonism may increase insulin sensitivity in humans (Moan et al., 1994, 1995). However, to date the effect of angiotensin AT_1 antagonism on endogenous insulin release in response to a glucose challenge remains largely unexplored either in the hypertensive human or in animal models of essential hypertension.

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Therefore, in the studies described here, the effect of the selective angiotensin AT_1 receptor antagonist, valsartan, has been compared to the effect of the angiotensin converting enzyme inhibitor, benazepril, on intravenous glucose tolerance in the spontaneously hypertensive rat. The spontaneously hypertensive rat was chosen for these studies as an animal model of essential hypertension with coexistent insulin resistance (Bursztyn et al., 1992).

2. Materials and methods

2.1. Animals

These experiments were performed with male, spontaneously hypertensive rats (SHR/NIco; Iffa Credo, Lyon, France), weighing on average 235 g and aged 8 weeks. Upon arrival at our facilities, the rats were housed in groups of 5 in wire-topped plastic cages ($35 \times 18 \times 57$ cm) with sawdust litter. The cages were maintained in a room with a 12-h light/dark cycle (6 a.m.–6 p.m. light) at a temperature of 20–24°C and 55% relative humidity. The animals were allowed access to a normal diet (NAFAG, Gossau, Switzerland) and given tap water to drink. Before use in the following experiments, each animal was allowed to adapt to the above conditions for at least 7 days to ensure a standard state of Na^+ intake and hydration.

2.2. Experimental protocols

After adaptation, the rats were weighed to the nearest g and systolic blood pressure was measured by the tail cuff method (Ugo Basile, Comerio, Italy). Body weight and systolic pressure were always measured between 8 a.m. and 10 a.m. The measurement of body weight and systolic blood pressure was repeated on 2 further occasions, over the next 7 days, to establish baseline values. To facilitate accurate tracking over time, the rats were studied in groups of 12. Within 5 days of the last baseline measurement, equal numbers of rats in an experimental group were randomly assigned to treatment with either the isotonic saline vehicle or a single infusion rate of benazepril or valsartan. Over the course of the experiments body weight and systolic blood pressure were determined the day before removal of the mini-pumps. At the end of the treatment period, an intravenous glucose tolerance test was performed in each animal.

2.3. Surgical procedures

2.3.1. Implantation of mini-pumps

Benazepril and valsartan were given by osmotic mini-pumps implanted into the abdominal cavity. The rats were anesthetized with a mixture of 1.5% gaseous halothane (Hoechst-Pharma, Zurich, Switzerland) in oxygen. Once immobile, the rats were placed on their back, on a metal operating table and kept at a temperature of 36 ± 0.5°C. After a surgical plane of anesthesia had been reached, defined as a loss of both blink and pedal reflexes, a small opening was made through the ventral midline just above the head of the bladder and an Alzet osmotic mini-pump (model 2ML4; Alza, Palo Alto, CA, USA) containing either benazepril, valsartan or vehicle was inserted into the abdominal cavity. After implantation of the mini-pump, the body wall and skin were sutured closed and the animal was returned to its home cage. The mini-pumps delivered benazepril or valsartan at 1, 3, or 10 mg/kg per day or vehicle at 2.5 μl/h for 28 days. Over the 12-week infusion period, the pumps were changed every 28 days.

2.3.2. Implantation of catheters

At the end of the infusion period, the rats were anesthetized as described above and catheters were implanted into the right femoral artery and vein. The vessel catheters were 56 cm in length and made of polyethylene tubing (0.58 mm i.d. × 0.96 mm o.d.; Portex, Hythe, Kent, UK). A 2.5 cm length of smaller polyethylene tubing (0.40 mm i.d. × 0.80 mm o.d.) was attached to the end of the catheter inserted into the vessel. To minimize vessel damage during the implantation period, a 1 cm piece of Silastic tubing (0.012′ i.d. × 0.025′ o.d.; Dow Corning, Midland. MI, USA) was attached to the tip of the smaller catheter. The vessel catheters were filled with heparinized (10 IU/ml; Liquemine, Roche-Pharma, Basel, Switzerland) isotonic saline, plugged with stainless-steel pins and tunneled subcutaneously to exit dorsally in the interscapular region.

After recovery from surgery, the animals were placed singly in small plastic cages ($19 \times 23 \times 30$ cm). The arterial and venous catheters passed to the outside of the cage through a 31-cm stainless-steel spring attached to the animal through a Silastic collar. The venous catheter remained plugged while the arterial catheter was connected through a single-channel infusion swivel (Instech Labs, Horsham, PA, USA) to a computerized data collection system (Buxco Electronics, Sharon, CT, USA). The arterial catheter was kept patent by the continuous infusion of 17 μl/h heparinized (10 IU/ml) saline. The rats were allowed to recover from surgery for 48 h before the intravenous glucose tolerance tests were done.

2.4. Glucose tolerance tests

Rats were fasted overnight and allowed free access to water. With each animal resting quietly, mean arterial pressure was determined. Thereafter, 0.35 ml of arterial blood was quickly withdrawn into an ice-cold 1-ml syringe and placed in a heparin-coated microcentrifge tube maintained on ice. Each rat then received an intravenous injection of 500 mg/ml dextrose flushed in by a 0.5-ml bolus of isotonic saline. The duration of the injection was less than 10 s. The volume of the dextrose solution injected (0.5–0.6 ml) was adjusted to deliver glucose at a dose of

700 mg/kg. Blood samples (0.35 ml) were taken at 2, 5, 10, 20, 30 and 40 min after injection of the glucose solution and were replaced with an equivalent volume of isotonic saline. At the end of the experiment, the rat was killed with Vetanarcol (Veterinaria, Zurich, Switzerland) and weighed. Plasma was separated from the blood cells at 4°C and plasma glucose concentrations were measured immediately. The remaining plasma was frozen and maintained at −80°C prior to the measurement of plasma insulin concentrations.

2.5. Biochemical analyses

Plasma glucose concentrations were measured using a Beckman glucose analyzer (Beckman Instruments, Brea, CA, USA). Plasma insulin concentrations were measured by the double antibody dilution method using a commercially available kit for human insulin (INS15-SB; Medipro, Teufen, Switzerland). Rat insulin cross-reacted 100% with the human insulin antibody supplied with the kit and was used as the standard (Novo-Nordisk).

2.6. Determination of body composition

After killing, animals treated with either vehicle, benazepril (10 mg/kg per day) or valsartan (10 mg/kg per day) were placed on an operating table and the mini-pumps removed. The entire gastrointestinal tract was also removed, emptied and then returned to the animal. After opening every body cavity and sectioning the major muscle groups, each rat was heated in an oven at 70°C to constant weight. The water content of the intestinal contents was determined in the same way. Total body water was calculated as the initial wet weight − the final dry weight. The water content of the intestinal contents was added to the total body water. Total body fat was determined by a previously described method (Cox et al., 1985). Lean body mass was taken as total body water − total body fat.

2.7. Drugs used

The angiotensin converting enzyme inhibitor, benazepril ([*S*-(*R**,*R**)]-3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo), and the angiotensin AT_1 receptor antagonist, valsartan (valeryl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl-valine), were synthesized by Ciba-Geigy. Benazepril was dissolved in distilled water. Valsartan was dissolved in distilled water alkalinized with NaOH and neutralized with hydrochloric acid (Criscione et al., 1993).

2.8. Statistical analysis

Statistical analysis was done by one-way analysis of variance followed by the Least Significant Difference procedure. Where parameters were followed as a function of time, the data were analyzed using the multivariate analysis of variance for repeated measures with the Wilks' lambda in place of the *F* values (Armitage and Berry, 1987). In all analyses *P* values less than 0.05 were regarded as statistically significant. Areas under the curves were calculated by trapezoid integration.

3. Results

3.1. Benazepril and valsartan on systolic blood pressure, body weight gain and body composition

3.1.1. Systolic blood pressure

Compared to effects in the time control animals, both the angiotensin I converting enzyme inhibitor, benazepril, and the angiotensin AT_1 receptor antagonist, valsartan, produced significant and similar dose-related falls in systolic blood pressure (Fig. 1).

3.1.2. Body weight gain

During the treatment period, body weight increased significantly from baseline values in the control, benazepril and valsartan treatment groups (Fig. 1). The increase in body weight in animals treated with valsartan at either 1 or

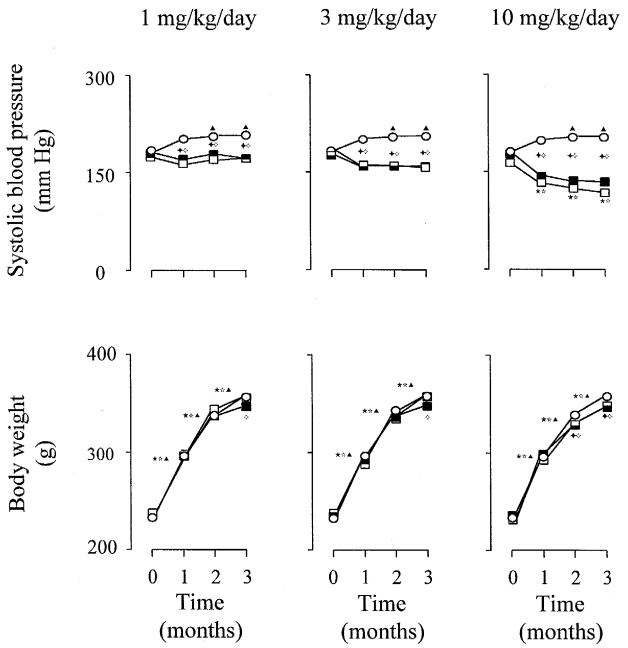

Fig. 1. Benazepril and valsartan on systolic blood pressure and body weight. Vehicle (○), benazepril (■), valsartan (□). Results expressed as means ± S.E.. In all cases, the symbols are larger than the S.E. bars. Numbers of experiments are the same as in Table 2. Statistical analyses by multivariate analysis of variance for repeated measures, followed by the Least Significant Difference test. Significant comparisons to time 0 in vehicle (▲), benazepril (solid 5-point star) or valsartan (open 5-point star) treatment groups. Significant comparisons at each time point to control group from benazepril (◇) and valsartan (◆) treatment groups.

Table 1
Benazepril and valsartan on body composition of spontaneously hypertensive rats

	Body water (%)	Body fat (%)	Lean body mass (%)
Control	65.1 ± 0.3	12.6 ± 0.4	22.4 ± 0.1
Benazepril 10 mg/kg per day	65.2 ± 0.3	12.4 ± 0.4	22.4 ± 0.1
Valsartan 10 mg/kg per day	65.7 ± 0.3	11.8 ± 0.5	22.5 ± 0.2

Results are expressed as means ± S.E. Statistics compare the effect of benazepril and valsartan with control values by analysis of variance. The analysis of variance showed no significant differences between drug-treated and control groups for each parameter.

3 mg/kg per day was not significantly different from the increase in body weight observed in time control animals. In contrast, after 3 months of treatment with 1 and 3 mg/kg per day benazepril, a small but significant decrease in body weight gain relative to control animals was observed. Following infusion of either benazepril or valsartan at 10 mg/kg per day, the body weight gain was significantly reduced from that in the time controls after both 2 and 3 months of treatment.

3.1.3. Body composition

Infusion of either benazepril or valsartan at 10 mg/kg per day lowered blood pressure and slowed body weight gain but did not significantly affect the percentage of body water, body fat or lean body mass compared to those of the control animals (Table 1).

3.2. Benazepril and valsartan on components of the glucose tolerance test

3.2.1. Blood pressure

Mean blood pressure measured from the arterial catheter immediately prior to the glucose tolerance tests is shown in Table 2. The results show that both benazepril and valsartan produced dose-related and significant falls in mean blood pressure.

3.2.2. Glucose disappearance

Baseline plasma glucose in these fasting animals averaged 95.1 ± 1.7 mg/dl and was not affected by any infusion rate of benazepril (Table 2). In contrast, infusion rates of 3 and 10 mg/kg per day of valsartan significantly increased baseline glucose concentrations from control values. In the control group of animals, intravenous injection of 700 mg/kg dextrose produced the changes in plasma glucose shown in Fig. 2. None of the infusion rates of benazepril or valsartan significantly altered the glucose disappearance curves relative to those of the control animals.

3.2.3. Insulin disappearance

Baseline plasma insulin in these fasting animals averaged 1.41 ± 0.17 ng/ml and was not affected by any infusion rate of valsartan (Table 2). In contrast, infusion of benazepril at 10 mg/kg per day significantly reduced the fasting plasma insulin concentrations below control values. None of the infusion rates of valsartan significantly altered the area under the plasma insulin curves from control animals (Fig. 3). In contrast, after the infusion of benazepril at 10 mg/kg per day, the glucose-induced increase in plasma insulin was significantly less than that in control animals (Fig. 3).

When grouped together the areas under the insulin disappearance curves following both benazepril and valsar-

Table 2
Effect of benazepril and valsartan on mean blood pressure and fasting glucose and insulin levels in plasma

	Control	Infusion rate		
		1 mg/kg per day	3 mg/kg per day	10 mg/kg per day
Mean blood pressure (mmHg)				
	155.9 ± 2.6 (41)			
Benazepril		134.9 ± 2.9 [a] (15)	124.1 ± 3.7 [a] (11)	112.5 ± 3.4 [a] (15)
Valsartan		133.7 ± 2.5 [a] (16)	121.5 ± 3.7 [a] (11)	96.0 ± 2.9 [a] (15)
Fasting plasma glucose (mg / dl)				
	95.1 ± 1.7			
Benazepril		93.3 ± 1.6	100.1 ± 4.8	94.0 ± 2.3
Valsartan		99.5 ± 2.9	105.4 ± 4.6 [a]	103.6 ± 2.2 [a]
Fasting plasma insulin (ng / ml)				
	1.41 ± 0.17			
Benazepril		1.02 ± 0.17	1.44 ± 0.28	0.57 ± 0.15 [a]
Valsartan		1.18 ± 0.19	1.13 ± 0.36	1.18 ± 0.23

Results are expressed as means ± S.E. The number of experiments are in parentheses. The results for each infusion rate of benazepril or valsartan were compared with the control by analysis of variance. [a] Significantly different from control values by the least significant difference procedure.

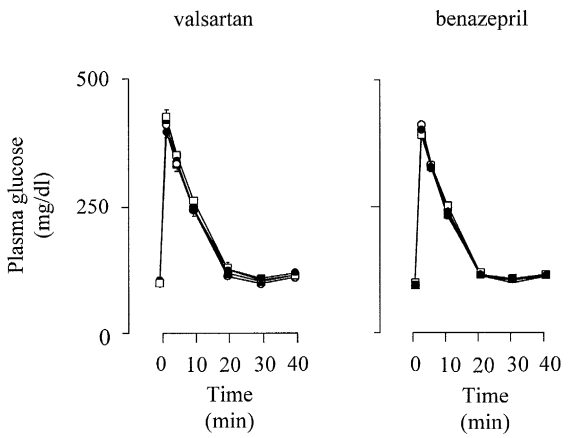

Fig. 2. Benazepril and valsartan on plasma glucose levels during the glucose tolerance tests. Glucose (700 mg/kg) injected i.v. at time 0 and plasma samples analyzed for glucose over the subsequent 40-min period. Vehicle (○), 1 mg/kg per day (●), 3 mg/kg day (□), 10 mg/kg per day (■). Results expressed as means ± S.E. In the majority of cases symbols are larger than the S.E. bars. Numbers of experiments are the same as in Table 2. Statistical analyses by multivariate analysis of variance for repeated measures which did not detect significant differences between the control, valsartan and benazepril groups of animals.

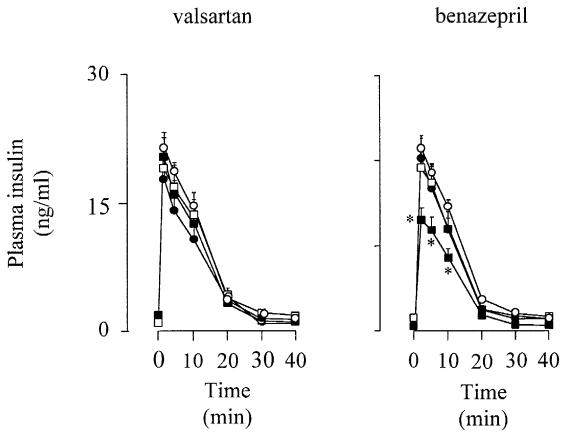

Fig. 3. Benazepril and valsartan on plasma insulin levels during the glucose tolerance tests. Glucose (700 mg/kg) injected i.v. at time 0 and plasma samples analyzed for insulin over the subsequent 40-min period. (○) Vehicle, (●) 1 mg/kg per day, (□) 3 mg/kg per day, (■) 10 mg/kg per day. Results expressed as means ± S.E. In some cases symbols are larger than the S.E. bars. Numbers of experiments are the same as in Table 2. Statistical analyses by multivariate analysis of variance for repeated measures followed by the Least Significant Difference test. * Significantly different from the corresponding time points for the control group of animals.

tan treatment did not correlate significantly with either mean arterial blood pressure ($R^2 = 0.056$) or body weight ($R^2 = 0.054$).

4. Discussion

The purpose of this study was to compare the effect of angiotensin converting enzyme inhibition with the effect of angiotensin AT_1 receptor antagonism on glucose disposal induced by endogenous insulin in the conscious spontaneously hypertensive rat.

Previous studies have shown that chronic blockade of both angiotensin I converting enzyme and angiotensin AT_1 receptors slows the body weight gain in spontaneously hypertensive rats (Harrap et al., 1990; Thybo et al., 1994; Vacher et al., 1995; Tufro-McReddie et al., 1994). The present studies suggest that valsartan was less potent in this regard than benazapril. Although the underlying mechanisms have not been elucidated, the results of the present studies demonstrated that changes in the growth process rather than alterations in body fluid volume must be involved since treatment with either benazepril or valsartan slowed body weight gain but did not affect the relative proportions of body water, fat or lean mass compared to those of the control.

Glucose disposal was assessed in the present studies with the intravenous glucose tolerance test (Lundbaek, 1962; Frankson et al., 1962). Across the range of infusion rates studied, neither benazepril nor valsartan significantly altered the shape of the glucose disappearance curves relative to the control values. Although the glucose disappearance rate was unchanged by benazepril or valsartan, a surprising difference in insulin requirement following infusion of the two inhibitors was observed. Thus, at an infusion rate which normalized blood pressure, benazepril reduced by 50% the quantity of insulin required to produce the same glucose disposal. In contrast, valsartan had no significant effect on the quantity of insulin released in response to glucose challenge, despite also normalizing blood pressure. This difference in insulin metabolism between the 2 compounds was also reflected in the basal fasting insulin concentrations, which were significantly lowered by 10 mg/kg per day benazepril but not by valsartan at an equivalent infusion rate.

Previous animal studies have also shown that inhibition of angiotensin converting enzyme improves the parameters of the glucose tolerance test in insulin resistant animal models (Zhang et al., 1994). Increased tissue insulin sensitivity is the most common explanation for these observations and could explain the reduced insulin requirement of benazepril treated animals obtained in these experiments. Supporting evidence comes from euglycemic-hyperinsulinemic clamp studies and insulin/glucose tolerance tests demonstrating that inhibition of angiotensin converting enzyme can improve tissue insulin sensitivity in animal models including the spontaneously hypertensive rat (Uehara et al., 1994; Tomiyama et al., 1994; Chow et al., 1995).

Animals treated with 1, 3 or 10 mg/kg per day benazepril lost weight. Although weight loss has been shown to decrease insulin resistance it is unlikely to explain the effects of benazepril since the glucose-stimulated insulin release did not correlate with body weight. Furthermore, at the lower infusion rates, benazepril affected body weight without affecting glucose tolerance.

Despite the wealth of information on the effects of angiotensin converting enzyme inhibition on glucose metabolism very little is known in this regard concerning blockade of angiotensin AT_1 receptors. The results of the present study demonstrated that, in contrast to benazepril, valsartan had no effect on plasma insulin release. The results of the two previous studies in which the effect of angiotensin AT_1 antagonism on glucose metabolism in animals was investigated, support the present results by demonstrating that neither losartan nor valsartan affect insulin sensitivity in the spontaneously hypertensive rat (Tomiyama et al., 1994; Chow et al., 1995). Although blockade of angiotensin AT_1 receptors does not appear to affect glucose metabolism in the spontaneously hypertensive rat this is not the case in the human where losartan has been shown to improve insulin sensitivity (Moan et al., 1994, 1995). The reason for the difference between the effects of angiotensin AT_1 receptor antagonism in human and animal hypertension is still unknown. This and previous studies do, however, show clearly that care should be taken when extrapolating the results of studies with inhibitors of angiotensin converting enzyme in sponta-

neously hypertensive rats to essential hypertension in man (Tomiyama et al., 1994; Chow et al., 1995).

The reason why the enhanced insulin sensitivity in response to inhibition of angiotensin converting enzyme was not seen after angiotensin AT_1 receptor inhibition in this animal model is still unclear. Bradykinin may be involved since, in addition to catalyzing the formation of angiotensin II, angiotensin converting enzyme inhibitors also mediate the breakdown of kinins. Endogenous bradykinin production may mediate the effects of benazepril observed in the present study, since the beneficial effects of angiotensin converting enzyme inhibition can be prevented by a kinin receptor antagonist (Pellacani et al., 1994; Uehara et al., 1994; Tomiyama et al., 1994). Bradykinin or other vasoactive mediators such as prostaglandins and nitric oxide released in response to bradykinin may improve glucose metabolism by enhancing muscle blood flow and thus enhance the rate of insulin and glucose delivery to target tissues. (McGiff et al., 1972; Dyer et al., 1992). Alternatively, other mechanisms may also be involved since it has recently been shown that bradykinin can facilitate the translocation of the glucose transport proteins GLUT 1 and GLUT 4 across cell membranes (Henriksen et al., 1996; Rett et al., 1996).

In summary, inhibition of angiotensin converting enzyme with benazepril lowered blood pressure, slowed body weight gain and reduced the insulin requirement for maintenance of glucose tolerance. Blockade of angiotensin AT_1 receptors with valsartan also lowered blood pressure and slowed the body weight gain but did not affect the insulin requirement. Thus, angiotensin AT_1 receptor antagonism and angiotensin converting enzyme inhibition have similar antihypertensive effects but appear to exert different effects on glucose/insulin metabolism in the spontaneously hypertensive rat.

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