Effect of an Insulin Sensitizer, Pioglitazone, on Hypertension in Fructose-Drinking Rats

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ABSTRACT—To determine whether insulin resistance is responsible for the development of hypertension, we examined whether blood pressure changes in an insulin-resistant animal that was given a fructose solution as their drinking water. Wistar Kyoto rats that drank a 10% fructose solution for 10 weeks showed significant increases not only in plasma triglyceride and insulin levels but also in systolic blood pressure. The decrease in blood glucose in response to the intraperitoneal injection of insulin (0.2-1.0 U/kg) was slight in these fructose-drinking rats. To confirm whether insulin resistance contributes to the observed hypertension, we examined the effect of pioglitazone, an insulin sensitizer, on blood pressure in rats given a 10% fructose solution. When pioglitazone was administered to the rats at a dose of 10 mg/kg/day for 4 weeks from 12 weeks of age, plasma triglyceride and insulin levels and systolic blood pressure decreased, and blood glucose reduction in response to insulin was normalized. These results suggest that insulin resistance is responsible for the development of hypertension in fructose-drinking rats.

Keywords: Hypertension, Pioglitazone, Fructose, Insulin resistance, Hyperinsulinemia

It is well-known that non-insulin dependent diabetes mellitus patients frequently develop hypertension (1-4), and essential hypertension has often been associated with obesity and/or glucose intolerance (5-8). Therefore, hypertension and non-insulin dependent diabetes mellitus seem to share the common physiological characteristic of insulin resistance. Hyperinsulinemia caused by the insulin resistance has been thought to enhance sodium reabsorption from the kidneys (9, 10) and to activate the sympathetic nervous system (11, 12), resulting in an increase in blood pressure.

Fructose has been reported to induce insulin resistance in the liver (13). To determine whether insulin resistance is responsible for the development of hypertension, we examined whether blood pressure changes in an insulin-resistant animal that was given a fructose solution as their drinking water.

Pioglitazone is an insulin sensitizer that improves insulin sensitivity of peripheral tissues and the liver and lowers the plasma glucose and insulin levels in animal models of diabetes (14, 15). To confirm whether insulin resistance contributes to the observed hypertension, we examined the effect of pioglitazone on blood pressure in rats given a 10% fructose solution.

MATERIALS AND METHODS

Animals

Male Wistar Kyoto (WKY) rats were bred in the laboratory animal unit of our division and weaned at 4 weeks of age. These rats were maintained on a standard chow diet (CE-2; Clea Japan Inc., Tokyo) and water ad libitum. Throughout the experiment, these rats were housed in metal cages under controlled temperature (23±1℃) and humidity (55±5%), with a 12-hr light /dark cycle.

Fructose induced insulin resistance in WKY rats

At 6 weeks of age, these rats were divided into two groups. One group continued to receive the diet and water, and the other was given the diet and a 10% fructose solution for 6 weeks. Body weight, plasma components, systolic blood pressure (SBP) and pulse rate of the rats were measured every 3 weeks.

Effect of pioglitazone on blood pressure in fructose-drinking WKY rats

At 12 weeks of age, the WKY rats that drank a 10% fructose solution from 6 weeks of age were divided into

non-treated and pioglitazone-treated (10 mg/kg per day, p.o.) groups. The drug was suspended with a 0.5% methylcellulose solution and orally administered (2 ml/kg) to rats everyday for 4 weeks. Non-treated rats were given a 0.5% methylcellulose solution alone. Body weight, plasma components, SBP and pulse rate of the rats were measured every 2 weeks. At the end of the experiment, the kidneys, liver, epididymal adipose tissue and mesenteric adipose tissue were dissected out and weighed.

Biochemical analyses

Blood samples were obtained from the tail vein. The glucose and triglyceride concentrations in the plasma were determined enzymatically by a Hitachi Automatic Analyzer 7070 (Hitachi Ltd., Ibaragi). Plasma insulin was measured by a double-antibody method with a commercially available kit (Shionogi Pharmaceutical Co., Osaka).

Blood pressure measurement

SBP of conscious rats was measured with a tail-cuff sphygmomanometer (UR-1000; Ueda Co., Ltd., Tokyo) between 2 and 5 PM. The average of two readings was taken.

Insulin tolerance test

Rats were fasted for 20 hr before this test. The rats were subjected to an intraperitoneal injection of insulin at a dose of 0.2, 0.5 and 1.0 U/kg every 90 min. Blood samples were obtained from a tail vein every 45 min, and the blood glucose concentration was measured.

Materials

Pioglitazone ((±)-5-[4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl]-thiazolidine -2,4-dione monohydrochloride) was synthesized in the chemical division of our research laboratories (16). Insulin (Novolin ®R 40) was purchased from Novo Nordisk A/S Co. (Bagsvaerd, Denmark). Other reagents were purchased from Wako Pure Chemical Industries, Ltd. (Osaka).

Statistical analyses

Data are expressed as the mean±S.D. The statistical analysis of differences was performed by Student's *t*-test and Dunnett's test. Differences were considered significant at a value of $P<0.05$.

RESULTS

WKY rats that drank a 10% fructose solution from the age of 6 weeks (WKY-F) showed a significant increase in the plasma triglyceride level after 3 weeks and significant

Table 1. Effects of fructose on body weight, plasma components, systolic blood pressure and pulse rate in male WKY rats

	Week	10% fructose (n)	WKY − (8)	WKY + (17)
Body weight (g)	0		152±17.2	152±13.0
	3		257±23.0	252±18.2
	6		311±21.0	309±22.5
Plasma glucose (mg/dl)	0		136±5.18	135±4.72
	3		135±7.37	137±7.81
	6		125±4.92	134±8.41*
Plasma triglyceride (mg/dl)	0		60.1± 9.1	61.4± 6.0
	3		83.4±11.5	235±33.1**
	6		79.3±9.34	198±26.2**
Plasma IRI (μU/ml)	0		25.9±10.8	23.1± 7.8
	3		121±26.6	113±40.0
	6		76.2±18.0	134±42.9**
SBP (mmHg)	0		117±7.65	118±5.12
	3		121±4.85	124±3.78
	6		128±8.61	142±4.68**
Pulse rate (/min)	0		398±17.5	400±17.8
	3		384±22.6	399±13.4
	6		390±21.3	404±15.1

Six-week-old male WKY were supplied with tap water or a 10% fructose solution. The significance of differences versus control rats was determined by Student's *t*-test (*$P<0.05$, **$P<0.01$). Mean±S.D. SBP, systolic blood pressure; IRI, immuno-reactive insulin.

Table 2. Effects of pioglitazone on body weight, plasma components, systolic blood pressure and pulse rate in fructose-drinking WKY (WKY-F) rats

	Week	Dose (mg/kg) (n)	WKY-F 0 (8)	WKY-F 10 (9)
Body weight (g)	0		308±18.2	311±27.9
	2		334±17.7	370±30.4**
	4		370±21.4	405±37.1*
Plasma glucose (mg/dl)	0		133±8.95	135±8.21
	2		128±6.15	128±4.76
	4		131±7.58	125±5.78
Plasma triglyceride (mg/dl)	0		207±31.3	189±16.3
	2		160±29.0	86.7±16.7**
	4		146±26.2	49.0±21.4**
Plasma IRI (μU/ml)	0		134±42.1	134±46.7
	2		171±43.0	136±34.6
	4		182±39.7	90.3±23.9**
SBP (mmHg)	0		142±4.92	142±4.74
	2		141±4.02	129±4.09**
	4		144±5.80	129±3.38**
Pulse rate (/min)	0		408±14.3	401±16.1
	2		408±12.2	398±15.6
	4		405±14.3	403±11.6

Twelve-week-old, 10% fructose-drinking WKY (WKY-F) rats were given pioglitazone (10 mg/kg/day, p.o.) everyday. The significance of differences versus control rats was determined by Student's *t*-test (*$P<0.05$, **$P<0.01$). Mean±S.D. SBP, systolic blood pressure; IRI, immuno-reactive insulin.

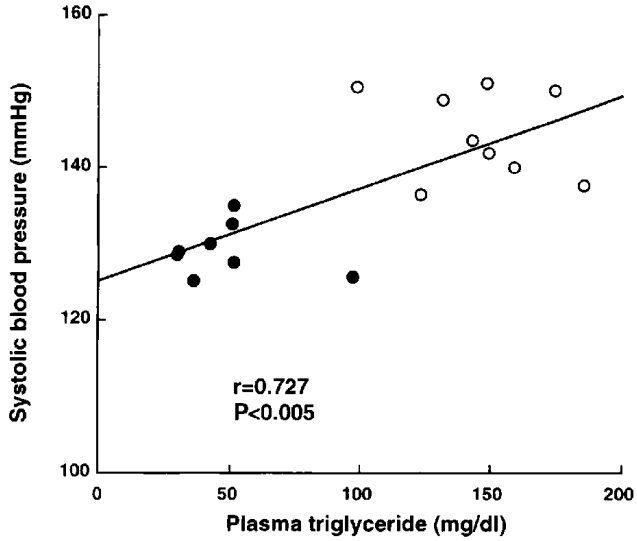

Fig. 1. Relationship between systolic blood pressure and plasma triglyceride in 10% fructose-drinking WKY (WKY-F) (○) and pioglitazone-treated WKY-F (●) rats at 16 weeks of age.

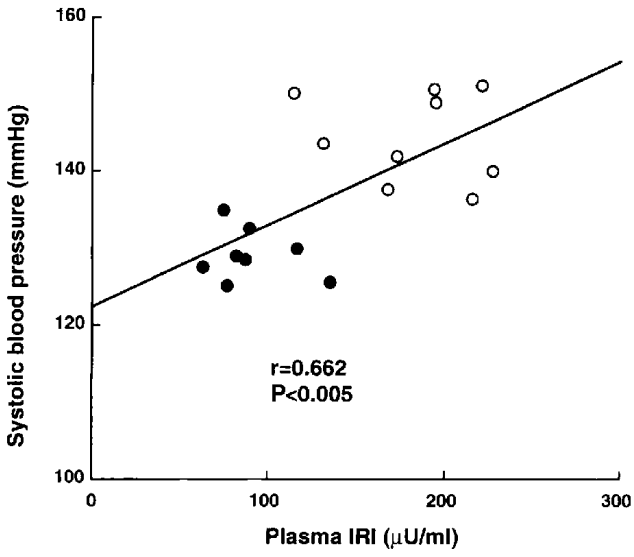

Fig. 2. Relationship between systolic blood pressure and plasma IRI in 10% fructose-drinking WKY (WKY-F) (○) and pioglitazone-treated WKY-F (●) rats at 16 weeks of age. IRI, immunoreactive insulin.

increases in the insulin level and SBP after 6 weeks (Table 1). The plasma glucose level at week 6 was increased significantly, but this level was normal (Table 1). Body weight and pulse rate did not change during this 6-week period (Table 1).

From the age of 12 weeks, WKY-F rats were given pioglitazone for 4 weeks. Pioglitazone significantly decreased the levels of plasma triglyceride and insulin at week 2 and/or week 4 (Table 2). In parallel with these reductions, SBP was significantly decreased without a change in the pulse rate. In WKY-F rats, both the plasma insulin and triglyceride levels correlate positively with the blood pressure by pioglitazone treatment (Figs. 1 and 2).

As compared with non-treated WKY-F rats, the liver weight tended to decrease, but the kidney and mesenteric adipose tissue weights did not change, and the epididymal adipose tissue weight increased in the pioglitazone-treated WKY-F rats (Table 3).

Table 3. Effects of pioglitazone on the weight of various tissues in fructose-drinking WKY (WKY-F) rats at 17 weeks of age

	Dose (mg/kg)	WKY-F 0	WKY-F 10
	(n)	(6)	(9)
Kidney (g)		2.96±0.21	2.93±0.29
Liver (g)		14.1±1.18	12.9±1.87
Epididymal adipose tissue (g)		6.98±0.94	8.85±2.00*
Mesenteric adipose tissue (g)		4.70±0.94	5.35±1.39

Twelve-week-old, 10% fructose-drinking WKY (WKY-F) rats were given pioglitazone (10 mg/kg/day, p.o.) everyday. The significance of differences versus control rats was determined by Student's *t*-test (*P<0.05). Mean±S.D.

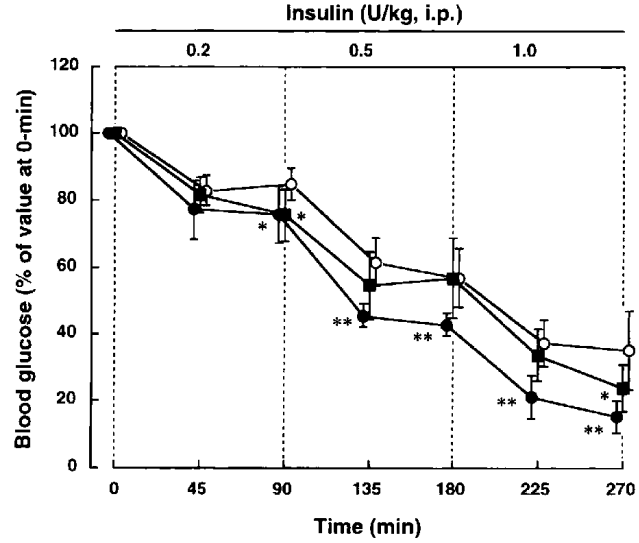

Fig. 3. Effect of pioglitazone on insulin sensitivity in 10% fructose-drinking WKY (WKY-F) rats. Sixteen-week-old, male WKY-F rats and 12-week-old control WKY rats were given intraperitoneal injections of insulin at doses of 0.2–1.0 U/kg. At 0-min, blood glucose concentrations were 84.5±4.77, 83.5±4.08 and 70.9±2.91 mg/dl in WKY-F (○), pioglitazone-treated WKY-F (●) and WKY (■) rats, respectively. The significance of differences versus WKY-F rats was determined by Dunnett's test (*P<0.05, **P<0.01). Mean±S.D., n=7–9.

The insulin tolerance test was performed to compare the insulin sensitivity between pioglitazone-treated and non-treated WKY-F rats. In this test, 12-week-old WKY rats that were not given the fructose solution and pioglitazone were used as the normal controls. At any dose of insulin (0.2, 0.5, 1.0 U/kg), blood glucose decreased rapidly to reach a steady level which was maintained until the end of the 90-min period in all groups (Fig. 3). The sensitivity to exogenous insulin in WKY-F rats was lower than that in WKY rats. When WKY-F rats were treated with pioglitazone, the sensitivity increased to more than the level in the WKY control group.

DISCUSSION

Recent studies have shown that the development of hypertension is associated with insulin resistance and/or hyperinsulinemia. In some epidemiological studies, patients with obesity and/or glucose intolerance frequently develop hypertension (1–4), and essential hypertension has often been associated with obesity and/or glucose intolerance (5–8). In this study, we tried to induce insulin resistance by dietary manipulation and change in blood pressure was investigated.

It is known that fructose induces insulin resistance mainly in the liver (13). In this study, we gave a fructose to WKY rats in a convenient way by giving it to them in their drinking solution and could obtain several characteristic features of insulin resistance such as hyperlipidemia and hyperinsulinemia. Especially, hyperinsulinemia was more prominent by fructose drinking than that by fructose diet feeding (13). In this study, plasma glucose and insulin decreased dependently on age, because these animals were so young (6 to 16 weeks of age) that their food intake and body weight were rapidly changing throughout the experiment. The insulin tolerance test also revealed the presence of insulin resistance in WKY rats given the fructose solution. Furthermore, the fructose solution drinking moderately but significantly increased the blood pressure like feeding a fructose diet did (17).

To confirm whether insulin resistance contributes to the observed hypertension, the next study was designed to examine the effect of pioglitazone on blood pressure in rats given the fructose solution (WKY-F rats). In the WKY-F rats, pioglitazone improved insulin resistance and ameliorated not only the metabolic abnormalities (hyperlipidemia and hyperinsulinemia) but also the hypertension. These results clearly demonstrated that the inhibition of the development of insulin resistance and/or hyperinsulinemia by pioglitazone led to a decrease in blood pressure. Indeed, both the plasma insulin and triglyceride levels in WKY-F rats correlated positively with the blood pressure after 4 weeks of pioglitazone treatment (Figs. 1 and 2). After 2 weeks of pioglitazone treatment, although the plasma triglyceride level correlated positively with the blood pressure ($r=0.810$, $P<0.001$), plasma IRI level did not correlate significantly with the blood pressure ($r=0.250$, $P=0.335$). The decrease in plasma IRI by the improvement of insulin resistance seems to need a longer period of time than plasma triglyceride.

Some mechanisms of hyperinsulinemia-induced hypertension are considered. Hyperinsulinemia has been reported to enhance sodium ion reabsorption from the kidneys (9, 10), activate the sympathetic nervous system (11, 12) or activate the sodium-proton pump and increase intracellular sodium and calcium ion (18), and proliferate the vascular smooth muscle cells (19, 20). We have also found that the growth of smooth muscle cells from the explanted thoracic aorta in pioglitazone-treated WKY-F rats was lower than that in non-reated WKY-F rats (data not shown). It is, therefore, suggested that pioglitazone suppressed vascular smooth muscle cell growth via improving hyperinsulinemia, resulting in a decrease in the blood pressure.

In studies on the effect of troglitazone, another insulin sensitizer, on hypertension, the drug slightly lowered the blood pressure in obese patients (21) or it lowered the fasting glucose level and blood pressure in hypertensive non-insulin dependent diabetes mellitus patients (22). In animals, troglitazone also showed an antihypertensive effect in insulin-resistant SHR (23) and Zucker fatty rats (24). On the other hand, the antihypertensive effect of pioglitazone was also reported in Dahl salt-sensitive rats with insulin resistance (25). Interestingly, pioglitazone lowered the blood pressure in one kidney, one clip hypertensive rats that did not develop insulin resistance (26). Therefore, it is suggested that pioglitazone exerts its antihypertensive effect by improving insulin sensitivity and also by another mechanism. In recent studies, pioglitazone showed a direct effect on vascular smooth muscle cells to inhibit calcium ion influx, resulting in the inhibition of blood vessel constriction and vascular cell growth and decreasing the blood pressure (27–29). In this study, however, the improvement of insulin resistance rather than the direct effect of pioglitazone on arterial cells seems to contribute much to the blood pressure reduction.

The liver weight in WKY-F rats tended to decrease with pioglitazone treatment. It is known that the lipid contents in the liver were increased insulin-resistant animals (30–32). Therefore, it is suggested that pioglitazone improved hyperinsulinemia and suppressed the lipid synthesis in the liver. Concerning the adipose tissues, the weight in mesenteric fat did not change, but the weight in epididymal fat was significantly increased. A previous

study showed that pioglitazone increased epididymal fat weight (33) because pioglitazone improved the insulin sensitivity to cause an increase in peripheral lipoprotein lipase activity and decreases in hormone sensitive lipase activity in adipose tissue and lipoprotein synthesis in the liver. On the other hand, the accumulation of mesenteric fat is known to be associated with the development of hypertension (34, 35). Moreover, it is well-known that the mesenteric fat is associated with glucose intolerance. As compared with other fat tissues, the mesenteric fat is more sensitive to catecholamines, which release fatty acid (FFA) (36). FFA enhanced the synthesis of very low density lipoprotein (VLDL) and induced insulin resistance in the liver and to suppress peripheral lipoprotein lipase activity and VLDL clearance, thereby increasing the blood triglyceride level. In this study, however, pioglitazone treatment did not result in any change in the mesenteric adipose tissue weight in WKY-F rats. It is suggested that pioglitazone did not aggravate glucose tolerance and hypertension via increasing the accumulation of mesenteric fat.

In conclusion, we revealed the close relationship between the development of insulin resistance and hypertension using the fructose-drinking rat model of insulin resistance and an insulin sensitizer, pioglitazone.

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