Effect of Antihypertensive Treatment With Alacepril on Insulin Resistance in Diabetic Spontaneously Hypertensive Rats

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Recent clinical reports have described the close relationship between insulin resistance and hypertension. Previous reports from our laboratory documented that spontaneously hypertensive rats (SHR) have mild insulin resistance, and that this insulin resistance is more intense in SHR with diabetes induced by streptozotocin (STZ). The aim of this study was to elucidate the effect of antihypertensive treatment with alacepril on insulin resistance in these diabetic SHR. Animals were divided into four groups as follows: group A, nondiabetic SHR; group B, diabetic SHR; group C, diabetic SHR treated with 0.05% alacepril; and group D, diabetic SHR treated with 0.1% alacepril. Diabetes was induced by intravenous (IV) injection of STZ (35 mg/kg bodyweight [BW]). Alacepril was given orally by mixing in laboratory chow. Mean (±SD) blood pressure was lowered in the alacepril-treated groups (A 212 ± 7 mm Hg and B 213 ± 8 *v* C 184 ± 6 and D 167 ± 9; $P < .01$). Total integrated plasma glucose levels were different among all the groups by oral glucose tolerance test (OGTT) (B 53.6 ± 3.3 mmol/L > C47.2 ± 4.5 > D 42.3 ± 1.4 > A 34.2 ± 1.2; $P < .01$). Steady-state plasma glucose (SSPG) during the insulin suppression test was higher in group B than in group A (15.7 ± 1.5 mmol/L *v* 10.4 ± 0.8; $P < .001$). The SSPG level (12.9 ± 0.7) was significantly ($P < .001$) lower in group D than in untreated group B. In the diabetic groups, blood pressure was positively correlated with integrated plasma glucose (PG) ($r = .79$, $P < .001$), SSPG ($r = .53$, $P < .02$), and plasma triglyceride ($r = .70$, $P < .001$), and negatively with high-density lipoprotein (HDL)-cholesterol ($r = -.74$, $P < .001$). Alacepril treatment not only dose-relatedly lowered mean blood pressure, but also dose-relatedly improved abnormalities in carbohydrate and lipid metabolism in STZ-induced diabetic SHR. These results suggest that an angiotensin-converting enzyme inhibitor, alacepril, has an antihypertensive effect, but also improves insulin resistance in hypertension with diabetes mellitus.

RECENT CLINICAL STUDIES have shown that there is a close relationship between insulin resistance and hypertension.[1-3] Spontaneously hypertensive rats (SHR) are known to be a good experimental model of hypertension.[4-6] We have shown that SHR have impaired glucose tolerance[7,8] and insulin resistance.[9] However, the degree of insulin resistance was so mild that we could not demonstrate the beneficial effects of antihypertensive treatment on glucose intolerance in SHR.[10-12] On the other hand, we have shown that SHR are more susceptible to induction of insulin resistance by a high-calorie sucrose-enriched diet or streptozotocin (STZ)-induced diabetes.[13] Alacepril (Dainippon Pharmaceutical, Osaka, Japan), a prodrug of captopril, is a long-acting angiotensin-converting enzyme (ACE) inhibitor[14,15] that has a dose-related hypotensive effect in SHR.[16] Pollare et al[17] reported that captopril improved insulin sensitivity in hypertensive patients. The aim of the present study was to elucidate the effect of antihypertensive treatment with alacepril on insulin resistance in diabetic SHR.

METHODS

Animal Preparation

Male SHR were obtained from the Izumo colony (Shimane Institute of Health Science, Izumo, Kyoto, Japan). They had free access to tap water and commercial laboratory show (Funabashi SP, Funabashi Farm, Chiba, Japan), and were maintained on a 12-hour light-dark cycle (lights on 7:00 AM to 7:00 PM). Fifty-four SHR, 16 weeks old at the beginning of the study, were divided into four groups as follows: group A, nondiabetic SHR (n = 18); group B, diabetic SHR (n = 12); group C, diabetic SHR treated with 0.05% alacepril (n = 12); and group D, diabetic SHR treated with 0.1% alacepril (n = 12). Diabetes was induced by intravenous (IV) injection of STZ, diluted in 0.01 mol/L citrate buffer (pH 4.5). The dose of 35 mg/kg body weight (BW) was used; preliminary studies with this dosage have shown a moderate diabetic action with nonfasting blood glucose levels of approximately 250 mg/dL without frank ketosis or insulin dependence. Blood was obtained from the tail vein 1 week later and analyzed for glucose (BM TEST Blood Sugar 20-800R and Reflolux IIM; Boehringer-Mannheim, Mannheim, Germany). Animals with blood glucose levels ≥200 mg/dL were selected for the diabetic groups. Alacepril was given orally by mixing with laboratory chow.

Blood pressure and BW were measured 1 day before the oral glucose tolerance test (OGTT). Blood pressure was indirectly measured without anesthesia by a tail-cuff method (UR-1000; Ueda Electric Works, Tokyo, Japan).[18] The tail-cuff method was performed as follows: initially a rat was warmed in a hot box at 38°C for 10 minutes, and then placed in a restraining apparatus that was also kept at 38°C. The tail was inserted through the cuff, which contained a photoelectric pulse detector, and systolic blood pressure was recorded when the first oscillation appeared during the gradual reduction of the cuff pressure.

Insulin Secretion

After 6 weeks, OGTT was performed on each group of rats. OGTT was performed after a 24-hour overnight fast. Glucose solution (2 g/kg BW) was administered by stomach gavage through a metal catheter attached to a syringe, and blood was collected into heparinized hematocrit tubes after cutting the tip of the tail without anesthesia. Plasma glucose (PG) and immunoreactive insulin (IRI) levels were determined at fasting, and 30, 60, and 120 minutes after glucose administration. The total integrated PG and IRI were calculated from values obtained during the 120-minute OGTT.

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Plasma total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride values were obtained from fasting samples. PG was determined by a glucose-oxidase method.[19] IRI was determined by a double-antibody radioimmunoassay.[20] Plasma total cholesterol and triglyceride levels were measured by enzymatic methods.[21,22] HDL-cholesterol was measured after precipitating other lipoproteins.[23]

Insulin Resistance

Insulin sensitivity was evaluated using the insulin suppression test,[24,25] which was performed 2 weeks after OGTT. The procedure started with the withdrawal of food at 8:00 AM in the morning of the experiment. All infusions were begun at midday, after an intraperitoneal injection of sodium thiamylal (6.0 mg/100 g BW) to initiate anesthesia. Subsequently, the right jugular vein was exposed and cannulated for infusion. Rats received a continuous infusion (0.848 mL/h) of epinephrine (0.08 μg/kg/min), propranolol (1.7 μg/kg/min), glucose (8 mg/kg/min), and insulin (2.5 mU pork insulin/kg/min). Blood samples were withdrawn from the tip of the tail at 0, 60, 120, 130, 140, 150, and 160 minutes. Steady-state plasma glucose (SSPG) and steady-state plasma insulin (SSPI) concentrations were calculated from the plasma collected between 130 and 160 minutes, and studies in which the coefficient of variation was greater than 10% were excluded. For insulin radioimmunoassays, rat insulin was used as the standard when determining insulin concentrations in the basal state, and porcine insulin for measurement of insulin levels during the infusion. Hypothermia was prevented with a heat lamp.

Statistical Analysis

All values are expressed as the mean ± SD. Statistical analysis was evaluated by one-way analysis of variance (ANOVA), Fisher's multiple comparison test and linear regression analysis were performed using the Statview 512+ package (Brainpower, Calabasas, CA) on an Apple Macintosh SE computer (Cupertino, CA).

RESULTS

Figure 1 shows the effect of alacepril on BW and blood pressure in each group of rats after 6 weeks. The mean BW was similar among the groups after the experimental period of 6 weeks (left panel). Blood pressure was significantly ($P < .01$) lowered in the alacepril-treated groups (212 ± 7 mm Hg in group A and 213 ± 8 mm Hg in group B v 184 ± 6 mm Hg in group C and 167 ± 9 mm Hg in group D). Blood pressure in group D was significantly ($P < .01$) lower than in group C (right panel).

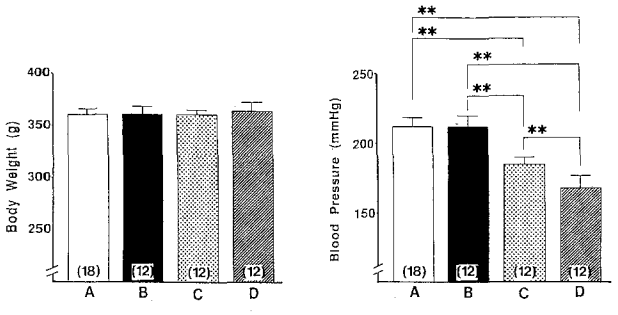

Fig 1. Mean (±SD) BW (left) and blood pressure (right) in 4 groups of rats after the experimental period of 6 weeks. Number of rats are shown in parentheses. (A) Nondiabetic SHR; (B) diabetic SHR; (C) diabetic SHR treated with 0.05% alacepril; and (D) diabetic SHR treated with 0.1% alacepril. *$P < .01$, **$P < .001$.

Figure 2 shows PG and insulin responses to oral glucose loading in four groups of animals after 6 weeks. As shown in the left panel, PG levels were higher in the diabetic groups than in the nondiabetic group. In contrast, as shown in the right panel, plasma insulin levels were lower in the diabetic groups than in the nondiabetic group.

Figure 3 shows the mean levels of integrated PG and insulin concentrations during the OGTT. As shown in the left panel, integrated PG levels were much higher in the diabetic group animals than in the nondiabetic animals. Alacepril treatment dose-relatedly lowered the mean integrated PG concentrations (group B 53.6 ± 3.3 mmol/L > group C 47.2 ± 4.5 mmol/L > group D 42.3 ± 1.4 mmol/L > group A 34.2 ± 1.2 mmol/L; $P < .01$). As shown in the right panel, the integrated plasma insulin concentrations were significantly lower ($P < .001$) in the diabetic groups than in the nondiabetic group, but were not affected by alacepril treatment.

Figure 4 shows plasma total cholesterol (left panel), HDL-cholesterol (middle panel), and triglyceride (right panel) concentrations in these animals. Diabetic groups showed decreased total and HDL-cholesterol levels and increased triglyceride levels. These abnormalities were significantly improved by alacepril treatment in a dose-related manner.

Figure 5 shows the mean SSPG and SSPI during the insulin suppression test. As shown in the right panel, the mean SSPI levels were not different among the four groups. Similar levels were achieved in all groups, and any differences in glucose disposal rates reflect differences in the ability of insulin to stimulate glucose utilization. As shown in the left panel, the mean SSPG concentrations were much higher in group B than in group A (15.7 ± 1.5 mmol/L v 10.4 ± 0.8 mmol/L; $P < .001$). The SSPG level was significantly ($P < .001$) lower in group D (12.9 ± 0.7 mmol/L) than in untreated group B.

Figure 6 shows the correlation of blood pressure with integrated plasma glucose (upper-left panel), SSPG (upper-right panel), plasma triglyceride (lower-left panel), and HDL-cholesterol (lower-right panel) in diabetic SHR treated with or without alacepril. In the diabetic groups, blood pressure was significantly correlated with integrated PG ($r = .79$, $P < .001$), SSPG ($r = .53$, $P < .02$), plasma triglyceride ($r = .70$, $P < .001$), and HDL-cholesterol ($r = -.74$, $P < .001$) levels.

DISCUSSION

Experimental data from humans have shown that lowering of blood pressure in patients with hypertension is not necessarily associated with any improvement in insulin resistance or hyperinsulinemia. On the other hand, a decrease in blood pressure associated with antihypertensive treatment has also been accompanied by an improvement in insulin-stimulated glucose uptake and a decrease in plasma insulin concentrations. We have previously demon-

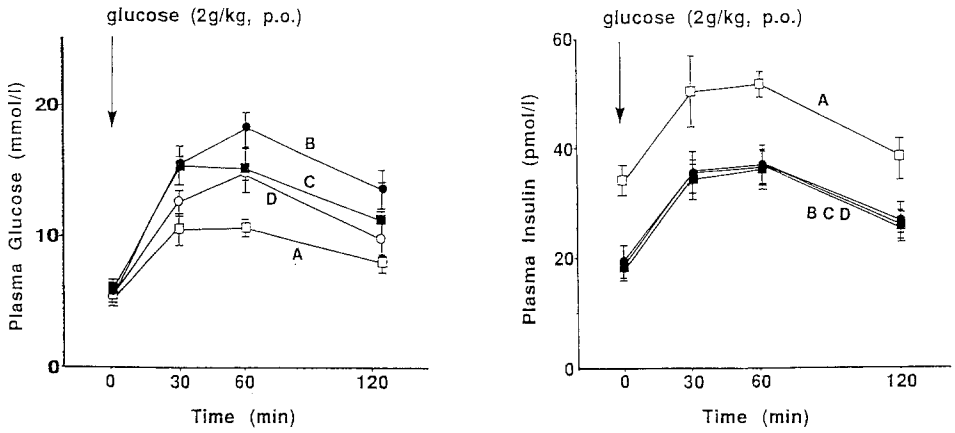

Fig 2. Mean (±SD) PG (left) and insulin (right) responses to oral glucose load in 4 groups of rats after 6 weeks. (A) Nondiabetic SHR; (B) diabetic SHR; (C) diabetic SHR treated with 0.05% alacepril; and (D) diabetic SHR treated with 0.1% alacepril.

strated that SHR are insulin-resistant when compared with normotensive Wistar-Kyoto (WKY) rats. However, the degree of insulin resistance was so mild that we could not find any beneficial effects of antihypertensive treatment with alacepril on insulin resistance in the nondiabetic SHR in preliminary study. Hypoinsulinemia induced in experimental animals is followed by an insulin-resistant state.[26-28] In the present study, we used the diabetic SHR whose insulin resistance was aggravated by STZ treatment. As a result, we were able to clearly demonstrate that alacepril treatment improved insulin resistance in diabetic SHR in a dose-related manner.

Several recent placebo-controlled intervention studies in hypertensive patients have demonstrated the effects of antihypertensive agents on insulin sensitivity measured by the euglycemic clamp technique.[17,29-31] An α_1-blocker, prazosin, improved insulin sensitivity and lowered insulin and glucose levels during a glucose tolerance test.[29] Selective β-blockers such as metoprolol and atenolol reduced insulin sensitivity.[30] These drugs also caused elevated fasting insulin levels, increased insulin levels during an intravenous glucose tolerance test, and increased HbA_{1c} concentrations. Calcium channel blockers, such as diltiazem, did not alter insulin sensitivity, insulin levels in the OGTT, or change HbA_{1c} levels.[31] Treatment with an ACE inhibitor, captopril, improved insulin sensitivity.[17] Both insulin and glucose concentrations were reduced in the OGTT. Other types of ACE inhibitors, such as enalapril, quinapril, ramipril, and lisinopril, also improved insulin sensitivity.[32] These studies of drug effects on insulin sensitivity have mostly dealt with hypertensive patients without manifest diabetes mellitus. However, the α_1-blocker, doxazosin,[33] and the ACE inhibitor, captopril,[34] also improved insulin sensitivity in hypertensive non–insulin-dependent diabetic patients. The reasons for the different effects on insulin sensitivity of these antihypertensive agents are not clear.

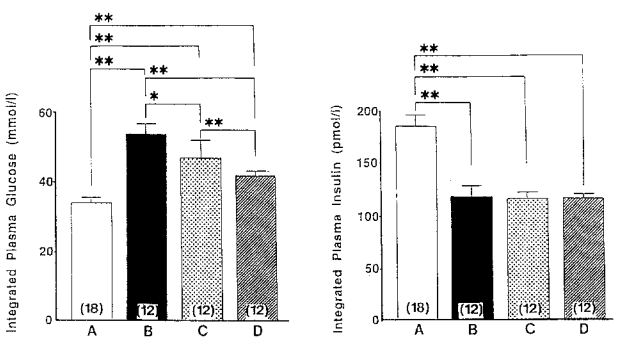

Fig 3. Mean (±SD) integrated PG (left) and insulin (right) during a 120-minute OGTT in 4 groups of rats after 6 weeks. Numbers of rats are shown in parentheses. (A) Nondiabetic SHR; (B) diabetic SHR; (C) diabetic SHR treated with 0.05% alacepril; and (D) diabetic SHR treated with 0.1% alacepril. *$P < .01$, **$P < .001$.

Although the present study does not permit us to identify the exact mechanism by which ACE treatment induced an increase in insulin sensitivity, the vasodilation could partly account for this phenomenon, since vasodilation may promote an enhanced access of glucose and insulin into skeletal muscle tissue, the main target organ for insulin action. Recent studies have indicated an important role for blood flow as a determinant of glucose uptake in skeletal muscle in both insulin-dependent diabetes mellitus[35,36] and non–insulin-dependent diabetes mellitus.[37,38] ACE inhibition would enhance insulin action through arterial vasodilation and increased blood flow. A similar mechanism has been invoked to explain the increased insulin sensitivity after prazosin.[29]

In this study, decreased total and HDL-cholesterol levels, and increased triglyceride levels, were observed in diabetic SHR. Although the main part of cholesterol in rats consisted of HDL-cholesterol, in most cases, changes in total cholesterol levels were parallel to changes in HDL-cholesterol levels. Abnormal lipid metabolism in diabetic SHR was significantly improved by alacepril treatment in a dose-related manner. Blood lipids are usually unaffected or even worsened by antihypertensive treatment. Insulin is invovled in triglyceride and very–low-density lipoprotein (VLDL) synthesis. The alteration of triglyceride levels with antihypertensive treatment might indirectly be due to the effects on the insulin levels described earlier. In previous short-term studies on the correlation of insulin sensitivity with conventional antihypertensive agents, blood lipid levels were also reported.

During treatments with selective β-blockers, metoprolol, and atenolol, serum triglyceride levels increased.[30] Proprano-

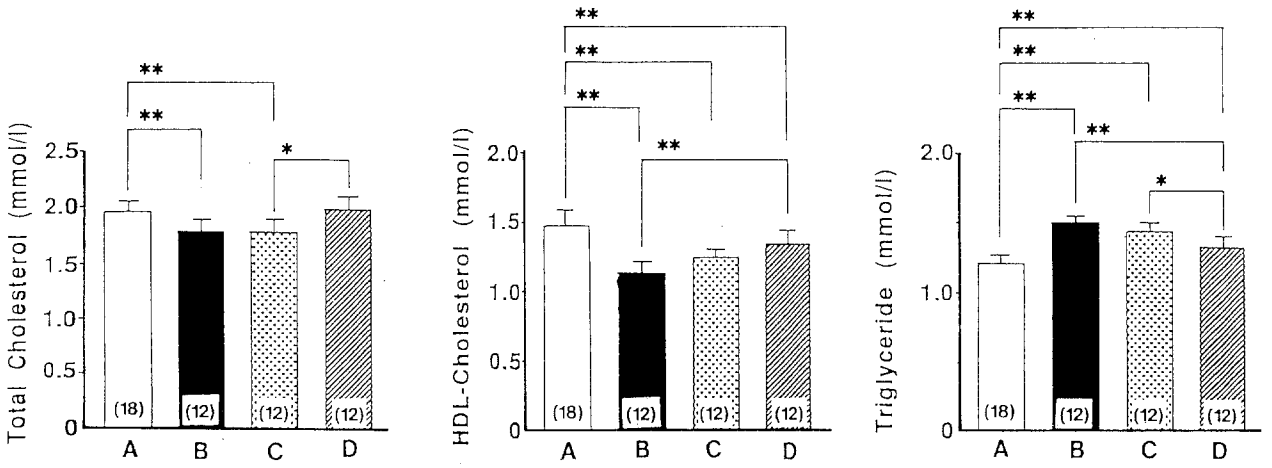

Fig 4. Mean (±SD) plasma total cholesterol (left), HDL-cholesterol (middle), and triglyceride (right) levels in 4 groups of rats after 8 weeks. Numbers of rats are shown in parentheses. (A) Nondiabetic SHR; (B) diabetic SHR; (C) diabetic SHR treated with 0.05% alacepril; and (D) diabetic SHR treated with 0.1% alacepril. *$P < .01$, **$P < .001$.

lol induced an increase in triglyceride levels, whereas pindolol did not affect triglyceride levels.[39,40]

All four β-blockers reduced HDL-cholesterol levels. Hydrochlorothiazide treatment increased both total cholesterol and triglyceride levels.[16] HDL-cholesterol was unaffected by thiazide treatment. Captopril, diltiazem, and prazosin did not cause any change in blood lipids.[17,29,31,41] The long-term effects of antihypertensive treatment must be considered in view of the fact that hypertension is accompanied by metabolic disturbances. Our results indicate that alacepril may directly or indirectly improve insulin resistance and abnormalities of lipid metabolism in hypertension with diabetes mellitus.

It was previously reported that STZ treatment induced not only diabetes, but also hypertension in rats,[42,43] while STZ had a hypotensive effect on SHR.[44-46] Somani et al reported that STZ treatment lowered blood pressure in SHR, but raised it in WKY.[44] Fluckiger et al reported that STZ treatment attenuated the development of hypertension in SHR and had a mild hypotensive effect in WKY.[45] In our previous study, weight loss, overt hyperglycemia, and the reduction of blood pressure were observed in SHR injected with high-dose STZ.[46] Therefore, low-dose STZ (35 mg/kg BW) was used in this study; preliminary study with this dosage showed a moderate diabetic action and mild hypotensive effect in SHR.[13] The diabetogenic effect of STZ is not completely the same in every experiment. Delicate differences may be brought on by a difference in lot of STZ or a fine difference in buffer condition. Blood glucose levels in this study were slightly lower than those in the same dosage used in the previous study. As a result, BW loss and reduction of blood pressure were not observed in the present study.

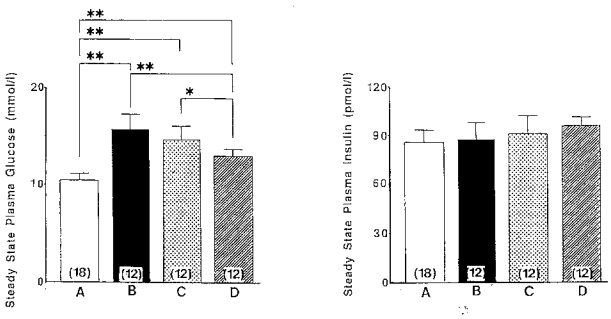

Fig 5. Mean (±SD) SSPG (left) and SSPI (right) in 4 groups of rats after 8 weeks. Numbers of rats are shown in parentheses. (A) Nondiabetic SHR; (B) diabetic SHR; (C) diabetic SHR treated with 0.05% alacepril; and (D) diabetic SHR treated with 0.1% alacepril. *$P < .01$, **$P < .001$.

There are two common methods to estimate insulin sensitivity. One method, the insulin suppression test, is performed by continuously infusing epinephrine, propranolol, insulin, and glucose. Epinephrine and propranolol suppress endogenous insulin release, and steady-state plasma levels of exogenous insulin and glucose are reached in all individuals. Because the SSPI level is the same in all subjects, the height of the SSPG level provides a direct estimate of insulin resistance. The other method, the euglycemic clamp technique, produces a steady-state level of exogenous hyperinsulinemia by means of a primed and continuous insulin infusion. Glucose also infused at a rate sufficient to prevent an insulin-induced decrease in glucose concentration, and the amount of glucose required to maintain the basal plasma glucose level, provide the estimate of insulin resistance.

A high degree of correlation existed between assessment of insulin sensitivity with the insulin suppression test and the euglycemic clamp in the human study.[47] The preliminary study, which used diabetic SHR, SSPG in the insulin suppression test was significantly correlated with glucose infusion rate in the euglycemic clamp ($r = -.916$, $P < .0001$). As the euglycemic clamp is more difficult to perform, requiring considerably greater resources and personnel than the insulin suppression test, the insulin suppres-

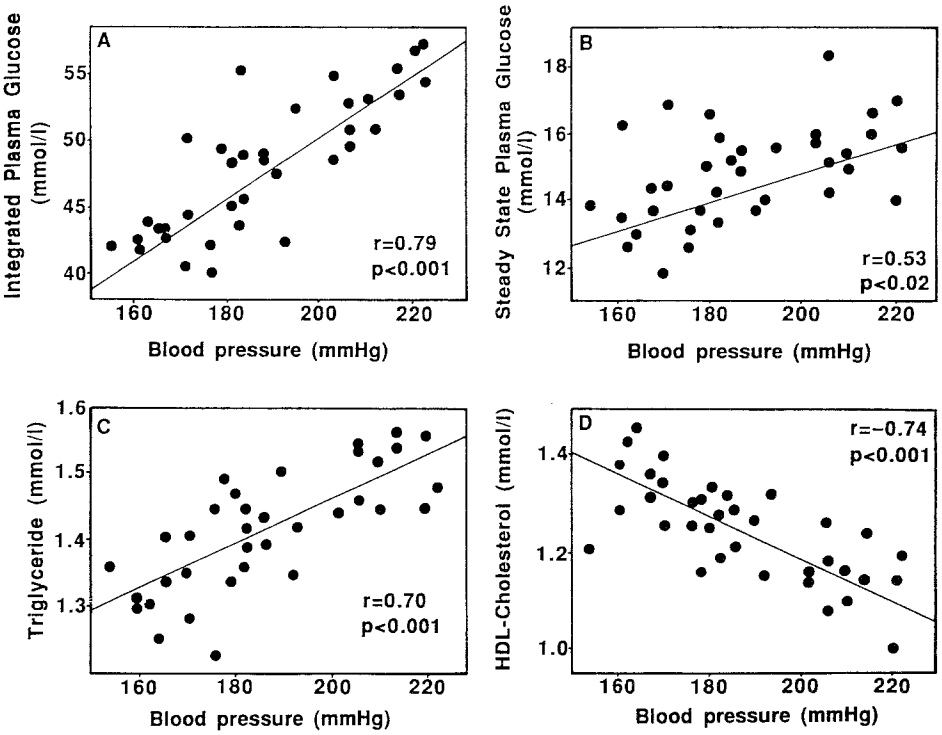

Fig 6. Correlation of blood pressure with integrated PG (upper left), SSPG (upper right), plasma triglyceride (lower left), and HDL-cholesterol (lower right) levels in diabetic SHR treated with or without alacepril.

sion test was used in our experiment to evaluate insulin sensitivity.

In summary, alacepril treatment dose-relatedly lowered mean blood pressure, and also dose-relatedly improved abnormalities in carbohydrate and lipid metabolism in STZ-induced diabetic SHR.

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