Long-Term Effects of Perindopril on Metabolic Parameters and the Heart in the Spontaneously Hypertensive/NIH-Corpulent Rat With Non–Insulin-Dependent Diabetes Mellitus and Hypertension

John S. Striffler, Sam J. Bhathena, Otho E. Michaelis IV,† Joaquin D. Campbell, Carl T. Hansen, Elizabeth Scalbert, Nancy Thibault, and Manuel T. Velasquez

The spontaneously hypertensive/NIH-corpulent (SHR/N-cp) rat is a genetic model that exhibits both non–insulin-dependent diabetes mellitus (NIDDM) and hypertension. To determine the impact of long-term treatment with the long-acting angiotensin-coverting enzyme (ACE) inhibitor perindopril (PE) on the glucose metabolism, lipid levels, and heart in this model, studies were performed in three groups of SHR/N-cp rats maintained on a diet containing 54% carbohydrate with 18% sucrose and 36% starch. One group of obese rats received PE (0.5 to 1.0 mg/kg body weight/d) for 3 to 4 months, a second group of obese rats received no treatment, and a third group of lean rats were used as controls. The mean systolic blood pressure (SBP) increased gradually in both untreated obese and lean rats, with lean animals showing slightly higher levels compared with untreated obese rats. By contrast, SBP was reduced to normal levels in PE-treated obese rats throughout the treatment period. Compared with lean rats, obese rats showed significantly higher body weight and fasting serum levels of glucose, insulin, total cholesterol (TC), and triglyceride (TG). However, no significant differences were observed in these metabolic parameters between PE-treated and untreated obese rats. Plasma renin activity measured at the end of the treatment period was significantly higher in PE-treated rats compared with untreated obese and untreated lean rats. The mean heart weight and left ventricular weight, expressed in absolute terms or indexed to body weight, were significantly lower in PE-treated versus untreated obese and untreated lean rats. To further determine whether glucose metabolism is directly affected by PE treatment, in vitro glycogen synthesis was evaluated in isolated soleus muscles obtained from three additional groups of animals. The basal rate of muscle glycogen synthesis was significantly lower in obese compared with lean rats ($P < .05$), but did not differ between PE-treated and untreated obese rats. Maximal insulin-stimulated glycogen synthesis increased threefold in PE-treated obese rats, but this increase did not differ from the increases observed in untreated obese and lean rats. In conclusion, the present study shows that long-term PE treatment in obese SHR/N-cp rats with NIDDM and hypertension effectively controlled systemic arterial pressure and resulted in a significant reduction in left ventricular weight. However, these favorable effects of PE were not associated with significant improvement in glucose tolerance, hyperinsulinemia, and hyperlipidemia in this model. PE also had no direct stimulatory effects on either basal or insulin-mediated glycogen synthesis in the isolated soleus muscle of obese rats, perhaps because of the severe insulin-resistant state of the animals. Our results support the clinical observations that antihypertensive therapy with ACE inhibitors has neutral effects on glucose metabolism and insulin sensitivity in patients with combined hypertension and NIDDM.

HYPERTENSION and non–insulin-dependent diabetes mellitus (NIDDM) are two common conditions that often occur in the same individual, each predisposing to increased cardiovascular morbidity and mortality.[1-3] These two conditions also have in common the metabolic features of glucose intolerance, hyperinsulinemia, and insulin resistance,[4-7] which have been shown in epidemiologic studies to be independent predictors of coronary heart disease.[8-12] In addition, both hypertensive and diabetic patients frequently have associated lipid and cardiovascular abnormalities, including dyslipidemia, atherosclerosis, and left ventricular hypertrophy, which further increase the risk of cardiovascular events. Therefore, current strategies in the treatment of both hypertension and diabetes have placed great emphasis on not only the normalization of blood pressure or blood glucose but also the impact of therapy on glucose metabolism, insulin resistance, and coexistent risk factors.

Angiotensin-converting enzyme (ACE) inhibitors have become established agents in the treatment of hypertension and are increasingly used in both hypertensive and diabetic patients with complications such as congestive heart failure and diabetic renal disease. However, controversy exists as to whether ACE inhibitors have additional beneficial effects on glucose metabolism in patients with hypertension and diabetes. Some studies have shown that ACE inhibitors improve glucose control and/or insulin sensitivity in hypertensive and diabetic patients,[13-19] but other studies do not show such effects.[20-29] The reasons for these conflicting reports are not entirely clear. It is also uncertain whether the influence of ACE inhibitors on glucose control and insulin resistance is related to their direct action on glucose metabolism in skeletal muscle tissue or their vasodilatory effect on muscle blood flow.

Accordingly, we have used the spontaneously hypertensive/NIH-corpulent (SHR/N-cp) rat, a genetic animal model that expresses both hypertension and NIDDM,[30,31] to further address some of these issues. Specifically, we determined the long-term effects of antihypertensive treatment with perindopril (PE), a

From the Department of Medicine, George Washington University Medical Center, Washington, DC; Beltsville Human Nutrition Research Center, Agricultural Research Service, US Department of Agriculture, Beltsville, MD; Veterinary Research Program, National Institutes of Health, Bethesda, MD; and Institut de Recherches Internationales Servier & Compagnie-Developpement, Paris, France.

†Deceased.

Submitted October 11, 1997; accepted April 2, 1998.

Supported in part by a research grant from Institut de Recherches Internationales Servier, Paris, France.

Current address for J.S.S.: Department of Diabetes, Endocrinology and Metabolism, City of Hope Medical Center, Duarte, CA 91010.

Address reprint requests to Manuel T. Velasquez, MD, Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University Medical Center, 2150 Pennsylvania Ave NW, Washington, DC 20037.

0026-0495/98/4710-0006$03.00/0

long-acting ACE inhibitor, on glucose metabolism and lipid and cardiac abnormalities in this model. To obviate the possible influence of blood flow on glucose metabolism, we also examined the effects of PE treatment on basal and insulin-stimulated glucose metabolism in the isolated soleus muscle of these animals.

MATERIALS AND METHODS

Animals

Male obese SHR/N-cp rats and lean littermates were obtained from the National Institutes of Health (Bethesda, MD) at approximately 5 to 6 weeks of age. All procedures were approved by the Institutional Animal Care and Use Committee of George Washington University and the Agricultural Research Service, US Department of Agriculture. Animals were housed individually in stainless steel wire cages in laminar airflow enclosures with a controlled temperature (21° to 25°C) and relative humidity (40% to 50%) and were maintained on a reverse 12-hour dark (9 AM to 9 PM)-light (9 PM to 9 AM) cycle. Rats were fed a 54% carbohydrate diet containing 36% starch and 18% sucrose plus the following: 10% casein, 10% lactalbumin, 5.9% cellulose, 4% beef tallow, 4% lard, 4% corn oil, 4% hydrogenated coconut oil, 3.1% AIN 76A (American Institute of Nutrition, Rockville, MD) salt mix (prepared without sucrose), and 1% vitamin fortification mix (no. 40060; Teklad Test Diets, Madison, WI). Animals were maintained on this diet throughout the study.

Long-Term Studies

After 2 months on the diet, obese rats were randomly assigned to treatment (n = 11) or no treatment (n = 11) with the ACE inhibitor PE for 3 months (12 to 14 weeks). PE is an orally active, long-acting, nonthiol ACE inhibitor, with its active metabolite perindoprilat having an elimination half-life of longer than 30 hours in humans.[32] In preliminary studies using SHR/N-cp rats, we found that oral administration of PE at a dose of 0.25 to 0.5 mg/kg body weight effectively decreased the systolic blood pressure (SBP) for at least 24 hours after dosing (Striffler JS and Velazquez MT, unpublished observations, April 1992). Lean rats were assigned to no treatment and served as controls (n = 8). PE was provided in the drinking water at a set concentration. The PE dose was adjusted to maintain SBP below 140 but above 110 mm Hg. This amounted to a dose range of 0.5 to 1.0 mg/kg body weight/d for the treated group, due to different requirements for individual rats. Food intake, body weight, and SBP by the tail-cuff method[33] using a Physiograph MK IV (Narco BioSystems, Houston, TX) were measured biweekly in each animal throughout the study. Blood samples were obtained by tail bleeding at 4- to 6-week intervals with the animals in the fasting state for determinations of glucose, insulin, total cholesterol (TC), and triglyceride (TG) in the serum. Blood pressure measurements and blood sampling were performed in the morning from 9 AM to noon during the dark period of the cycle, when rats are normally active.

Oral Glucose Tolerance Test

An oral glucose tolerance test was performed in both untreated and PE-treated obese rats before and during treatment. After an overnight fast of 12 to 14 hours, blood samples for basal and response levels of serum glucose and insulin were obtained before and 1 hour after an oral glucose load of 250 mg/kg body weight.[34] Tolerance tests were also performed in the morning between 9 AM and noon (dark period).

At the end of the 12- to 14-week drug treatment period, all animals were decapitated and an additional blood sample was obtained for determination of plasma renin activity. The heart was immediately removed and dissected free of blood vessels and surrounding fat. The atria, right ventricle, and left ventricle (LV) were separated, blotted free of blood, and weighed. Heart weight and LV weight in grams were indexed to body weight.

Glucose Metabolism in Soleus Muscle

In separate experiments, in vitro studies were performed in isolated soleus muscles obtained from additional groups of untreated lean (n = 5) and obese (n = 5) rats, and obese rats treated with PE 0.5 to 1.0 mg/kg body weight/d (n = 7) for 6 weeks. Glycogen synthesis in the basal state and in response to insulin was measured in soleus muscle harvested from the three groups of rats.

Soleus muscles were excised and prepared for in vitro incubation using the method described by Cuendet et al,[35] except that muscle strips were not mounted. Briefly, isolated soleus muscles from each rat were rinsed in 0.9% physiological saline and then divided into strips of equal weight (50 to 60 mg) so that assays could be performed in duplicate for each muscle. Muscle strips were incubated in gassed (95% O_2/5% CO_2) Krebs-Ringer bicarbonate buffer containing 1% fatty acid–free bovine serum albumin (Intergen, Purchase, NY), 5 mmol/L glucose, and ^{14}C-glucose (0.5 μCi/mL) with or without insulin (10^{-7} mol/L) for 1 hour at 37°C with continuous shaking. Prior to incubation in complete medium, two 15-minute preincubations were performed in medium without ^{14}C-glucose to remove endogenous insulin. Following the 1-hour incubation, incorporation of ^{14}C-glucose (15.4 pCi/pmol; NEN, Dupont, Boston, MA) into ^{14}C-glycogen was measured using methods described by Cuendet et al.[35]

Analytical Measurements

The serum glucose concentration was measured by the hexokinase method described by Bondar and Mead.[36] The serum insulin level was measured by a radioimmunoassay using the double-antibody procedure (Linco Research, St Charles, MO). Plasma renin activity was determined by radioimmunoassay using a kit from Incstar (Stillwater, MN). Serum cholesterol and triglyceride concentrations were measured enzymatically in a Centrifichem 600 system (Serono-Baker Diagnostics, Allentown, PA).

Statistical Analysis

Results are expressed as the mean ± SEM. Comparisons among groups were made using two-way ANOVA. Differences between groups and in time-related measures were tested by paired or unpaired Student's *t* test as appropriate. Differences were considered significant at a P value less than .05.

RESULTS

Figure 1A and B shows serial measurements of body weight, food intake, SBP, and fasting serum levels of glucose, insulin, TC, and TG before and during treatment in untreated lean, untreated obese, and PE-treated obese SHR/N-cp rats. At baseline, all three groups (3 to 4 months of age) were hypertensive, with a SBP between 135 and 145 mm Hg. At this age, obese rats were already heavier (>400 g) than the lean littermates and showed significantly elevated fasting serum levels of glucose, insulin, TC, and TG, although food intake was comparable in all three groups.

After 4 to 6 weeks of treatment with PE in obese rats, mean SBP was reduced to a normal level and was significantly lower than the corresponding level in untreated obese rats. By contrast, SBP gradually increased in untreated rats, with lean animals showing slightly higher levels compared with untreated obese rats. Fasting serum levels of glucose and insulin measured during the treatment period did not differ between untreated obese and PE-treated obese rats. Fasting levels of TC

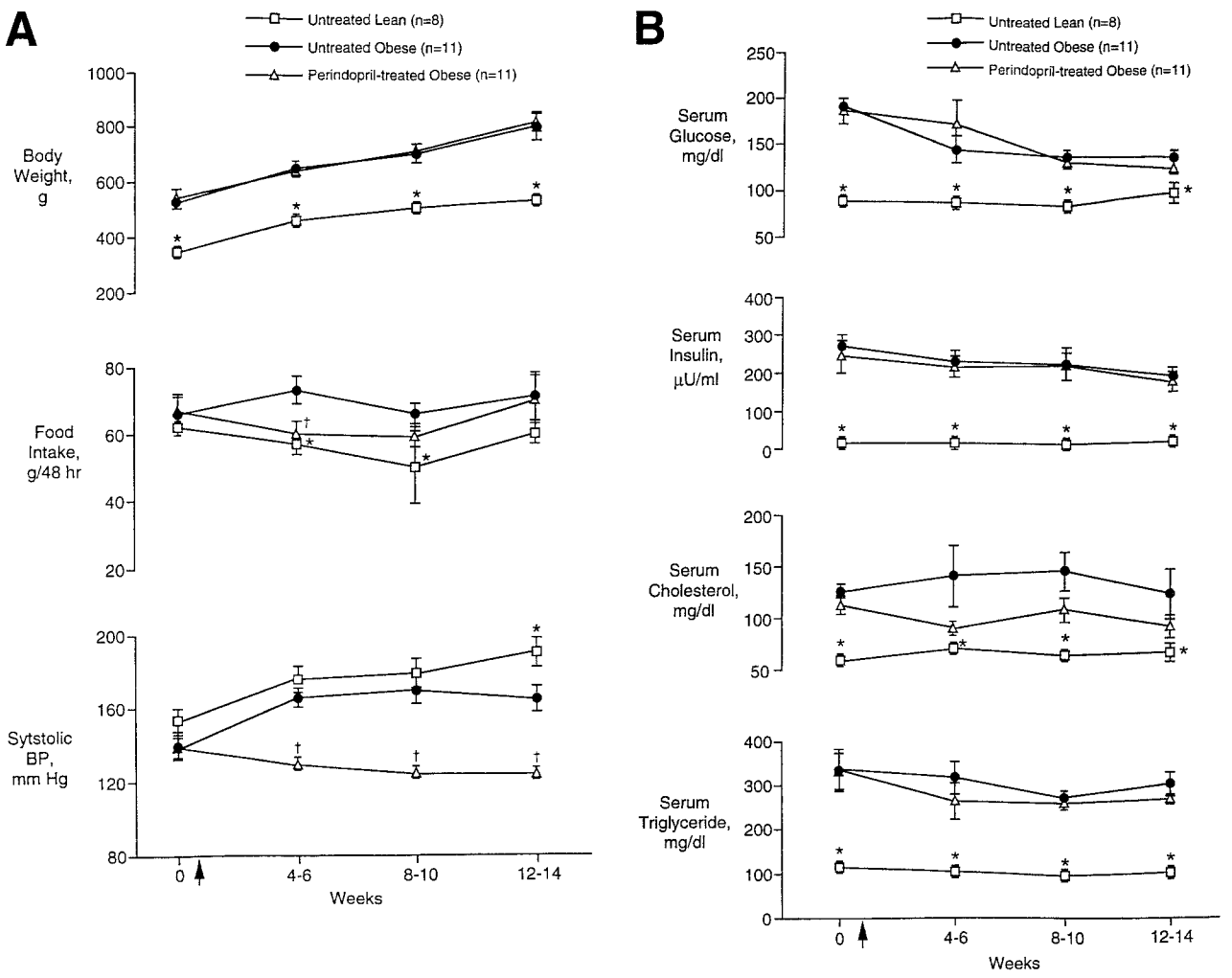

Fig 1. (A) Serial measurements of body weight, food intake, and systolic blood pressure in untreated lean, untreated obese, and perindopril-treated obese SHR/N-cp rats. Arrow denotes start of the drug treatment period, which began 1 to 3 days after baseline (time 0) measurements were made. *$P < .05$, lean *v* obese untreated rats; †$P < .05$, perindopril-treated *v* untreated obese rats. (B) Serial measurements of fasting serum glucose, insulin, total cholesterol, and triglyceride in untreated lean, untreated obese, and perindopril-treated obese SHR/N-cp rats. *$P < .05$, lean *v* obese untreated rats.

and TG were slightly lower in PE-treated versus untreated obese rats, but these differences were not statistically significant. Similarly, 1-hour response levels of serum glucose and insulin following an oral glucose load did not differ between the two groups of obese rats throughout the study (Table 1). At the end of the treatment period, final body weight and food intake were comparable in PE-treated and untreated obese rats.

Plasma renin activity measured at the end of the treatment period was significantly higher in PE-treated compared with untreated obese and untreated lean rats (Table 2). Both the mean heart weight and left ventricular weight were significantly lower in PE-treated versus untreated obese and untreated lean rats, regardless of whether the weights were expressed in absolute terms or indexed to body weight.

Table 3 summarizes the results for basal and maximal insulin-stimulated rates of glycogen synthesis in isolated soleus muscle from the three groups of animals. Basal rates of muscle glycogen synthesis were significantly lower in both untreated and PE-treated obese rats compared with the lean rats ($P < .05$). Basal rates in the two groups of obese rats were approximately the same. Maximal insulin-stimulated glycogen synthesis increased threefold in lean rats, whereas it increased fourfold in untreated obese rats (P = not significant). The increase in glycogenesis was slightly less in muscle from PE-treated obese rats compared with untreated obese and untreated lean rats, but the differences did not reach statistical significance.

DISCUSSION

Obese SHR/N-cp rats exhibited mild hyperglycemia and marked hyperinsulinemia and showed glucose intolerance when administered an oral glucose load, as demonstrated in previous studies.[30,31] Obese rats also exhibited hypercholesterolemia and hypertriglyceridemia, probably as a consequence of the marked hyperinsulinemia. Because of their genetic (SHR) background, obese SHR/N-cp rats and their lean counterparts also develop spontaneous hypertension that could have added to their insulin-resistant state, as previously documented in spontaneously hypertensive rats.[37,38]

Table 1. Fasting and 1-Hour Response Levels of Serum Glucose and Insulin After an Oral Glucose Load in Untreated (n = 11) and PE-Treated (n = 11) Obese SHR/N-cp Rats

Parameter	Baseline	Drug Treatment Period		
	−2-0 Weeks	4-6 Weeks	8-10 Weeks	12-14 Weeks
Serum glucose (mg/dL)				
C				
0-h	190 ± 23	145 ± 15	138 ± 8	137 ± 8
1-h	362 ± 32	256 ± 19	278 ± 26	267 ± 29
PE				
0-hr	182 ± 21	172 ± 27	130 ± 9	125 ± 10
1-h	354 ± 28	279 ± 34	218 ± 23	250 ± 17
Serum insulin (μU/mL)				
C				
0-h	220 ± 31	—	224 ± 42	191 ± 23
1-h	260 ± 45	—	312 ± 82	236 ± 39
PE				
0-h	243 ± 26	—	217 ± 35	178 ± 25
1-h	286 ± 64	—	291 ± 60	238 ± 25

NOTE. Values are the mean ± SE. Values are fasting levels; 1-h values are response levels obtained 1 hour following an oral glucose load of 250 mg/kg body weight.

Abbreviation: C, untreated obese rats; PE, perindropil-treated obese rats.

Long-term oral administration of PE in obese rats consistently decreased systemic arterial pressure to normal levels. However, the antihypertensive effect of PE was not associated with significant changes in either the fasting or 1-hour responses (to an oral glucose load) of serum glucose and insulin, suggesting that glucose metabolism and insulin responsiveness were not altered by the treatment. PE treatment in obese rats also had no significant effects on serum cholesterol and TG levels, in accordance with the lack of effect of the ACE inhibitor on hyperinsulinemia. These results support previous observations by Bak et al[39] in patients with hypertension and NIDDM that insulin sensitivity and secretion (as assessed by oral glucose tolerance and insulin tolerance tests) and serum lipid levels are unaffected by PE treatment. Our data in the SHR/N-cp rat with NIDDM and hypertension also complement other studies in humans showing no effect of ACE inhibitors on glucose control and serum lipid levels in hypertensive and diabetic patients.[21,24-26,40,41]

The effects of various ACE inhibitors on glucose metabolism

Table 2. Final Body Weight, Plasma Renin Activity, and Heart Weight in Untreated Lean, Untreated Obese, and PE-Treated Obese SHR/N-cp Rats

Parameter	Untreated Lean (n = 8)	Untreated Obese (n = 11)	PE-Treated Obese (n = 11)
Body weight (g)	533 ± 10	802 ± 45*	788 ± 33*
PRA (ng/Al/h)	8 ± 1	11 ± 2	53 ± 8*†
HW (g)	1.60 ± 0.1	1.76 ± 1.0	1.42 ± 0.6*†
LVW (g)	1.33 ± 0.03	1.46 ± 0.10	1.10 ± 0.05*†
HW/BW (g/kg)	2.68 ± 0.19	2.21 ± 0.05*	1.80 ± 0.09*†
LVW/BW (g/kg)	2.21 ± 0.14	1.83 ± 0.08*	1.40 ± 0.08*†

NOTE. Values are the mean ± SE.

Abbreviations: PRA, plasma renin activity; Al, angiotensin I; HW, heart weight; LVW, left ventricular weight; BW, body weight.

*$P < .05$ *v* untreated lean.

†$P < .05$ *v* untreated obese.

Table 3. Comparison of Basal and Maximal Insulin-Stimulated Glycogen Synthesis in Isolated Soleus Muscle of Untreated Lean, Untreated Obese, and PE-Treated Obese SHR/N-cp Rats

Rat Group	Rate of Glycogen Synthesis (nmol/h/mg)		
	Basal	Insulin Stimulated (10^{-7} mol/L)	Degree of Stimulation
Untreated lean (n = 5)	0.73 ± 0.05	2.31 ± 0.32	3.3-fold
Untreated obese (n = 5)	0.51 ± 0.08*	2.20 ± 0.26	4.3-fold
PE-treated obese (n = 7)	0.48 ± 0.04*	1.48 ± 0.1	3.1-fold

NOTE. Values are the mean ± SE.

*$P < .05$ *v* untreated lean.

in hypertensive and diabetic patients have been evaluated in many clinical trials. Some studies have shown that ACE inhibitors improve either glucose control, insulin sensitivity, or both in hypertensive and diabetic patients,[13-19] but other studies indicate no significant effects on glucose metabolism in patients treated with ACE inhibitors.[20-29] The differences in the metabolic effects of ACE inhibitors among these reports are difficult to interpret, but may relate to differences in the demographics, experimental design, degree of glycemia or insulinemia among diabetic patients, concomitant use of agents that influence glucose metabolism, potassium balance, and dose or duration of ACE inhibitor treatment. It has been suggested that the increased glucose disposal rate during ACE inhibition is related to vasodilation induced by ACE inhibitors. An increase in blood flow to skeletal muscle is thought to increase the availability of glucose to muscle, the prime target tissue for glucose uptake and disposal.[13,42,43] One recent study suggests that the improvement of insulin sensitivity produced by ACE inhibition is dependent on bradykinin production.[44]

In the present study, we further evaluated the effects of PE on glucose metabolism in isolated soleus muscle from SHR/N-cp rats to exclude any possible influence of blood flow and circulating hormones on muscle glucose metabolism. Specifically, we measured basal and insulin-mediated glycogen synthesis in muscle, since a decrease in glycogenesis in skeletal muscle has been shown to be primarily responsible for the impaired glucose disposal in human NIDDM.[45,46] We found that the basal rate of muscle glycogen synthesis was significantly lower in obese compared with lean rats. In addition, it should also be noted that the basal and maximal insulin-stimulated rates of muscle glycogen synthesis observed in these lean and obese rats are lower than those reported by other investigators using soleus muscle from nondiabetic male Wistar rats[47] and male Sprague-Dawley rats.[48] In those studies, maximal insulin-stimulated rates of glycogen synthesis were 5 to 6 nmol/h/mg wet weight, approximately twofold to threefold higher than the rates observed in SHR/N-cp rats used in our study, consistent with the presence of severe insulin resistance in these obese animals. Although it is possible that the lower rates of muscle glycogen synthesis in our rats are also due to a limitation of glucose diffusion into strips of thicker muscle mass, this is unlikely, since muscle strips from the three groups of rats were of comparable weight and the length of incubation in glucose medium (1 hour) was sufficient to obviate diffusion effects. Our results further show that PE had no significant effect on either basal or maximal insulin-mediated glucose conversion into glycogen in soleus muscle.

Our findings differ from recent studies in other animal models. Henriksen and Jacob[49] have shown that both short-term and long-term treatment with captopril improves insulin-stimulated glucose transport activity (as assessed by 2-deoxyglucose uptake) in the epitrochlearis muscle of obese Zucker rats, and that pretreatment of the animals with a bradykinin antagonist abolishes this effect. More recently, Rosenthal et al[50] showed that long-term chronic treatment with enalapril decreases ambient blood glucose levels in the Cohen-Rosenthal diabetic hypertensive rat, an animal model with genetic hypertension and diabetes. However, the dosage for ACE inhibitors used in these studies was very high (eg, 50 mg/kg/d for captopril and 30 mg/kg/d for enalapril) compared with the PE dosage (0.5 to 1.0 mg/kg/d) used in our rats and the daily dosage usually used for antihypertensive treatment in patients, although the dosage for ACE inhibitors used in the cited studies may be equipotent for blood pressure reduction. Our in vitro studies in soleus muscle are consistent with our in vivo data indicating that treatment with PE at a dosage that effectively normalizes arterial blood pressure is not associated with improvement in glucose control or insulin resistance in obese rats. The lack of an effect of PE on glucose control in obese rats may be related to their severe insulin-resistant state, which is not easily improved by ACE inhibitors such as PE. It is possible that ACE inhibitors used in combination with antidiabetic agents that directly increase insulin sensitivity to treat NIDDM and hypertension may produce additive or synergistic effects to enhance glucose disposal in insulin-resistant tissues. Additional studies in animals or humans with both NIDDM and hypertension are needed to examine this point.

In the present study, the antihypertensive effect of PE treatment in obese rats was associated with a marked increase in plasma renin activity and a significant reduction in heart weight and left ventricular weight. The hyperreninemia is most likely due to a compensatory response to a decrease in angiotensin II formation caused by ACE inhibition.[51,52] The decrease in left ventricular weight produced by PE is consistent with the known favorable effect of ACE inhibitors in reversing left ventricular hypertrophy in experimental and human hypertension.[53-55]

In summary, the present studies show that long-term PE treatment in obese SHR/N-cp rats with NIDDM and hypertension effectively controls systemic arterial pressure and results in a significant reduction in left ventricular weight. However, these favorable effects of PE were not associated with significant improvement in glucose and insulin levels, glucose tolerance, or serum lipid levels, suggesting that glucose metabolism and insulin responsiveness are unaffected by PE treatment. These results are further supported by in vitro data showing that basal and insulin-mediated glycogen synthesis are not significantly improved in isolated soleus muscle of obese rats treated with PE. Our results support clinical observations that antihypertensive therapy with ACE inhibitors has no significant effects on glucose metabolism and insulin sensitivity in patients with combined hypertension and NIDDM.

ACKNOWLEDGMENT

We thank Dr David K. Kreutter for expert advice on performing the soleus muscle experiments.

REFERENCES

1. Fuller JH: Epidemiology of hypertension with diabetes mellitus. Hypertension 7:II113-II117, 1985 (suppl)

2. Panzram G: Mortality and survival in type 2 (non–insulin-dependent) diabetes mellitus. Diabetologia 30:123-131, 1987

3. Kannel WB, Wilson PWF, Zhang TJ: The epidemiology of impaired glucose tolerance and hypertension. Am Heart J 121:1268-1273, 1991

4. Olefsky JM, Kolterman OG, Scarlett JA: Insulin action and resistance in obesity and non–insulin dependent type II diabetes mellitus. Am J Physiol 243:E15-E30, 1982

5. DeFronzo RA, Ferrannini E: The pathogenesis of non–insulin-dependent diabetes: An update. Medicine (Baltimore) 61:125-140, 1982

6. Modan M, Halkin H, Almog S, et al: Hyperinsulinemia: A link between hypertension, obesity, and glucose intolerance. J Clin Invest 75:809-817, 1985

7. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

8. Pyorala K: Relationships of glucose intolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. Diabetes Care 2:131-141, 1979

9. Fuller JH, Shipley MJ, Rose G, et al: Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall Study. Lancet 1:1373-1376, 1980

10. Eschwege P, Richard JL, Thibault N, et al: Coronary heart disease mortality in relation with diabetes, blood glucose, and plasma insulin levels. The Paris Prospective Study, ten years later. Horm Metab Res 15:41-46, 1985 (suppl)

11. Zavaroni I, Bonora E, Pagliara M, et al: Risk factors for coronary artery disease with hyperinsulinemia and glucose tolerance. N Engl J Med 320:702-706, 1989

12. Inchiostro S, Bertoli G, Zanette G, et al: Evidence of higher insulin resistance in NIDDM patients with ischemic heart disease. Diabetologia 37:597-603, 1994

13. Jauch KW, Hartl W, Guenther B, et al: Captopril enhances insulin responsiveness of forearm muscle tissue in non–insulin-dependent diabetes mellitus. Eur J Clin Invest 17:448-454, 1987

14. 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 321:868-873, 1989

15. Ferrier C, Ferrari P, Weidmann P, et al: Antihypertensive therapy with Ca^{+2} antagonist verapamil and/or ACE inhibitor enalapril in NIDDM patients. Diabetes Care 14:911-914, 1991

16. Moore MP, Elliott TW, Nichols MG: Hormonal and metabolic effects of enalapril treatment in hypertensive subjects with NIDDM. Diabetes Care 11:397-401, 1988

17. Paolliso G, Gambardella A, Verza M, et al: ACE inhibition improves insulin-sensitivity in aged insulin-resistant hypertensive patients. J Hum Hypertens 6:175-179, 1992

18. Santoro D, Natali A, Palombo C, et al: Effects of chronic angiotensin converting enzyme inhibition on glucose tolerance and insulin sensitivity in essential hypertension. Hypertension 20:181-191, 1992

19. Donnelly R: Angiotensin-converting enzyme inhibitors and insulin sensitivity: Metabolic effects in hypertension, diabetes, and heart failure. J Cardiovasc Pharmacol 20:S38-S44, 1992 (suppl 11)

20. Corcoran JS, Perkins JE, Hoffbrand BI, et al: Treating hypertension in non–insulin-dependent diabetes: A comparison of atenolol, nifedipine, and captopril combined with bendrofluazide. Diabet Med 4:164-168, 1987

21. Bilo HJG, Westerman RF, Nicolas-Mercus AM, et al: Effect of enalapril with and without hydrochlorothiazide in hypertensive patients

with non–insulin-dependent diabetes mellitus. Diabetes Res 9:21-25, 1988

22. Prince MJ, Stuart CA, Padia M, et al: Metabolic effects of hydrochlorothiazide and enalapril during treatment of the hypertensive diabetic patient: Enalapril for hypertensive diabetics. Arch Intern Med 148:2363-2368, 1988

23. Seefeldt T, Orskov L, Mengel A, et al: Lack of effect of angiotensin-converting enzyme (ACE)-inhibitors on glucose metabolism in type 1 diabetes. Diabet Med 7:700-704, 1990

24. Reneland R, Andersson PE, Haenni A, et al: Metabolic effects of long-term angiotensin-converting enzyme inhibition with fosinopril in patients with essential hypertension: Relationship to angiotensin-converting enzyme inhibition. Eur J Clin Pharmacol 46:431-436, 1994

25. Haenni A, Andersson PE, Lind L, et al: Electrolyte changes and metabolic effects of lisinopril/bendrofluazide treatment. Am J Hypertens 7:615-622, 1994

26. Andersson PE, Lithell H: Metabolic effects of doxazosin and enalapril in hypertriglyceridemic, hypertensive men: Relationship to changes in skeletal muscle blood flow. Am J Hypertens 9:323-333, 1996

27. Shionoiri H, Miyakawa T, Takasaki I, et al: Glucose tolerance during chronic captopril therapy in patients with essential hypertension. J Cardiovasc Pharmacol 9:160-164, 1987

28. Shionoiri H, Sugimoto K, Minamisawa K, et al: Glucose and lipid metabolism during long-term treatment with cilazapril in hypertensive patients with or without impaired glucose metabolism. J Cardiovasc Pharmacol 15:933-938, 1990

29. Ludvik B, Kueenburg E, Brunnbauer M, et al: The effects of ramipril on glucose tolerance, insulin secretion, and insulin sensitivity in patients with essential hypertension. J Cardiovasc Pharmacol 18:157-159, 1991

30. Michaelis OE IV, Ellwood KC, Judge JM, et al: Effect of dietary sucrose on the SHR/N-corpulent rat: A new model for insulin-independent diabetes. Am J Clin Nutr 39:612-618, 1984

31. Michaelis OE IV, Patrick DH, Hansen CT, et al: Spontaneous hypertensive/NIH-corpulent rat. Animal model for insulin-independent diabetes mellitus (type II). Am J Pathol 123:398-400, 1986

32. MacFadyen RJ, Lees KR, Reid JL: Perindopril. A review of its pharmacokinetics and clinical pharmacology. Drugs 39:49-63, 1990 (suppl 1)

33. Bunag RD: Validation in awake rats of a tail-cuff method for measuring systolic pressure. J Appl Physiol 34:279-282, 1973

34. Carswell N, Michaelis OE IV, Prather E: Effect of acarbose (BAY-g-5421) on expression of noninsulin-dependent diabetes mellitus in sucrose-fed SHR/N-corpulent rats. J Nutr 119:388-394, 1989

35. Cuendet GS, Loten EG, Jeanrenaud B, et al: Decreased basal, noninsulin-stimulated glucose uptake and metabolism by skeletal soleus muscle isolated from obese-hyperglycemic (ob/ob) mice. J Clin Invest 58:1078-1088, 1976

36. Bondar RJ, Mead DC: Evaluation of glucose-6-phosphate dehydrogenase from *Leuconostoc mesenteroides* in the hexokinase method for determining glucose in the serum. Clin Chem 20:586-590, 1974

37. Mondon CE, Reaven GM: Evidence of abnormalities of insulin metabolism in rats with spontaneous hypertension. Metabolism 37:303-305, 1988

38. Reaven GM, Chang H, Hoffman BB, et al: Resistance to insulin-stimulated glucose uptake in adipocytes isolated from spontaneously hypertensive rats. Diabetes 38:1155-1160, 1989

39. Bak JF, Gerdes LU, Sorensen NS, et al: Effect of perindopril on insulin sensitivity and plasma lipid profile in hypertensive non–insulin-dependent diabetic patients. Am J Med 92:69S-72S, 1992 (suppl 4B)

40. Baba T, Neugebauer S: The link between insulin resistance and hypertension: Effects of antihypertensive and antihyperlipidaemic drugs on insulin sensitivity. Drugs 47:383-404, 1994

41. Gall M-A, Rossing P, Skott P, et al: Placebo-controlled comparison of captopril, metoprolol, and hydrochlorothiazide therapy in non–insulin-dependent diabetic patients with primary hypertension. Am J Hypertens 5:257-265, 1992

42. Lillioja S, Young AA, Culber CL, et al: Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. J Clin Invest 80:415-424, 1987

43. Laakso M, Edelman SV, Brechtel G, et al: Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. A novel mechanism for insulin resistance. J Clin Invest 85:1844-1852, 1990

44. Tomiyama H, Kushior T, Abeta H, et al: Kinins contribute to the improvement of insulin sensitivity during treatment with angiotensin converting enzyme inhibitors. Hypertension 23:450-455, 1994

45. Meyer HU, Curchod B, Maeder E, et al: Modifications of glucose storage in nonobese diabetics, measured by continuous indirect calorimetry. Diabetes 29:752-756, 1980

46. Young AA, Bogardus C, Wolfe-Lopez D, et al: Muscle glycogen synthesis and disposition of infused glucose in humans with reduced rates of insulin-mediated carbohydrate storage. Diabetes 37:303-308, 1988

47. Leighton B, Cooper GJS: Pancreatic amylin and calcitonin gene–related peptide cause resistance to insulin in skeletal muscle in vitro. Nature 335:632-635, 1988

48. Kreutter DK, Orena SJ, Torchia AJ, et al: Amylin and CGRP induce insulin resistance via a receptor distinct from cAMP-coupled CGRP receptor. Am J Physiol 264:E606-E613, 1993 (suppl)

49. Henriksen EJ, Jacob S: Effects of captopril on glucose transport activity in skeletal muscle of obese Zucker rats. Metabolism 44:267-272, 1995

50. Rosenthal T, Erlich Y, Rosenmann E, et al: Effects of enalapril, losartan, and verapamil on blood pressure and glucose metabolism in the Cohen-Rosenthal diabetic hypertensive rat. Hypertension 29:1260-1264, 1997

51. Vander AJ, Geelhoed GW: Inhibition of renin secretion by angiotensin II. Proc Soc Exp Biol Med 120:399-403, 1965

52. Kostis JB, Raia JJ Jr, DeFelice EA, et al: Comparative clinical pharmacology of ACE inhibitors, in Kostis JB, DeFelice EA (eds): Angiotensin Converting Enzyme Inhibitors. New York, NY, Liss, 1987, pp 19-54

53. Dunn FG, Oigman W, Ventura HO: Enalapril improves systemic and renal hemodynamics and allows regression of left ventricular mass in essential hypertension. Am J Cardiol 53:105-108, 1984

54. Frohlich ED: Pathophysiological considerations in left ventricular hypertrophy. J Clin Hypertens 3:54-65, 1987

55. Devereux RB, Pickering TG, Cody RS: Relation of renin-angiotensin system activity to left ventricular hypertrophy and function in experimental and human hypertension. J Clin Hypertens 3:87-103, 1987