Effects of Captopril on Glucose Transport Activity in Skeletal Muscle of Obese Zucker Rats

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This study tested whether the angiotensin-converting enzyme (ACE) inhibitor captopril can modify the glucose transport system in insulin-resistant skeletal muscle. Obese Zucker (*fa/fa*) rats (~300 g)—a model of insulin resistance—were administered by gavage either a single dose (50 mg/kg body weight) or repeated doses (50 mg/kg/d for 14 consecutive days) of captopril. Corresponding groups of age-matched, vehicle-treated lean (*Fa/-*) littermates (~170 g) were also studied. Glucose transport activity in the epitrochlearis muscle was assessed by in vitro 2-deoxyglucose (2-DG) uptake. The increase in 2-DG uptake due to insulin (2 mU/mL) in muscles from vehicle-treated obese rats was less than 50% ($P < .05$) of the increase observed in muscles from lean rats. Short-term captopril treatment improved insulin-stimulable 2-DG uptake in muscles from obese rats by 46% ($P < .05$), and this enhanced insulin action due to captopril was completely abolished by pretreatment with the bradykinin antagonist HOE 140 (100 μg/kg). Long-term treatment with captopril produced a 60% improvement in insulin-stimulated 2-DG uptake ($P < .05$). Contraction-stimulated 2-DG uptake was significantly impaired (−31%, $P < .05$) in the obese rat, but was not altered by long-term captopril treatment. These findings indicate that both short- and long-term treatments with captopril significantly improve insulin-stimulated glucose transport activity in skeletal muscle of the obese Zucker rat, and that this improvement involves bradykinin metabolism. These data therefore support the hypothesis that captopril-induced improvements in glucose disposal result in part from an enhancement of the skeletal muscle glucose transport system.

HYPERTENSION is frequently accompanied by several other unfavorable metabolic conditions such as hyperinsulinemia, obesity, hyperlipidemia, and insulin resistance, a clustering of symptoms variously referred to as the "metabolic syndrome" or "syndrome X."[1-3] Approximately 40% of individuals with non–insulin-dependent diabetes mellitus (NIDDM) are also hypertensive and are at increased risk for cardiovascular and renal disease.[4,5] Angiotensin-converting enzyme (ACE) inhibitors have well-documented effects on reducing blood pressure and improving other cardiovascular parameters in hypertensives.[6-8] The influence of ACE inhibitors such as captopril on glucose metabolism has also been studied. Several groups have reported in clinical studies that the short- and long-term administration of captopril results in an increased insulin-stimulated glucose disposal in diabetic or hypertensive humans using the euglycemic clamp technique.[9-12] Even short-term oral administration of captopril at lower doses, which have no effect on blood pressure, improves peripheral glucose disappearance.[13] However, it is currently unclear whether this captopril-induced improvement in whole-body glucose disposal results from an alteration in the skeletal muscle glucose transport system, improved muscle blood flow, or a combination of the two effects.

Skeletal muscle, which comprises approximately 40% of the body mass of humans and other mammalian species, is the major tissue responsible for glucose disposal in the periphery in the face of a glucose or insulin challenge or during an exercise bout.[14,15] Skeletal muscle glucose transport, which is normally rate-limiting for glucose utilization, is activated via two separate pathways: one that is insulin-dependent and one that is contraction-dependent.[16-21] To date, no definitive study has addressed whether one possible site of action of short- or long-term captopril treatment in improving glucose disposal is the skeletal muscle glucose transport system. Furthermore, it is not known whether ACE inhibitors such as captopril might improve glucose transport in insulin-resistant skeletal muscle by enhancing the insulin-dependent pathway, the contraction-dependent pathway, or both pathways. Finally, ACE is identical to kininase II,[22] which degrades bradykinin. The involvement of bradykinin (and prostaglandins, one of its metabolites) in insulin action has been implicated.[23] However, the role of bradykinin in the action of ACE inhibitors on the skeletal muscle glucose transport system is currently unknown.

In this context, the obese Zucker (*fa/fa*) rat, an animal model of obesity and insulin resistance,[24] was used to further investigate these issues. Glucose transport activity was assessed in vitro using the isolated epitrochlearis to circumvent the possible influence of blood flow on this process. The specific aims of the present study were (1) to assess the suitability of the isolated epitrochlearis muscle from obese Zucker rats as a model of skeletal muscle insulin resistance of glucose transport; (2) to determine the effect of a single oral administration of captopril on insulin-stimulated glucose transport activity in the isolated epitrochlearis muscle of obese Zucker rats; (3) to investigate whether bradykinin plays a role in the action of captopril on insulin-stimulated glucose transport activity in insulin-resistant muscle; and (4) to determine the effect of long-term treatment with captopril on both insulin-

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stimulated and contraction-stimulated glucose transport activity in the epitrochlearis muscle.

MATERIALS AND METHODS

Animals

Female obese Zucker rats (*fa/fa*) and lean littermates (*Fa/-*) were purchased from Harlan (Indianapolis, IN) at 7 to 8 weeks of age. All animals were housed two per cage under controlled temperature conditions (21°C) with a 12-hour light:dark cycle (lights on at 6 AM). Animals had free access to standard rat chow and water until the evening before the experiment (see below). All procedures were reviewed and approved by the University of Arizona Animal Care and Use Committee.

Short-Term Treatment Groups

At 10 to 11 weeks of age, lean animals were assigned to a vehicle-treated control group. Age-matched obese animals were randomly assigned to either a vehicle-treated control group or a group receiving a single administration of captopril (Capoten; Bristol-Myers Squibb, Munich, Germany). All lean animals were restricted to 4 g chow and all obese animals received 6 g chow after 5 PM of the evening before the experiment. At 8 AM on the day of the experiment, lean and obese short-term vehicle-treated groups were weighed and received water by gavage (2.8 mL/kg body weight). The obese short-term captopril-treated group was also weighed and received by gavage 50 mg/kg body weight captopril from a stock solution (18 mg/mL in distilled water). After exactly 1 hour, animals were deeply anesthetized with pentobarbital sodium (50 mg/kg body weight intraperitoneally [IP]), and both epitrochlearis muscles were surgically removed and prepared for in vitro incubation.

In a separate experiment, three groups of obese animals were studied to test the effect of the bradykinin antagonist HOE 140 (kindly provided by Hoechst-Roussel Pharmaceuticals, Somerville, NJ) on captopril action. One group received by IP injection the bradykinin antagonist HOE 140 (100 μg/kg body weight administered in a 0.9% saline solution) 1 hour before captopril administration (50 mg/kg). A second group received an IP injection of vehicle 1 hour before receiving captopril. A third group received vehicle only at both treatment times. Muscle dissections commenced as described above.

Long-Term Treatment Groups

At 8 to 9 weeks of age, obese animals received one of the following treatments by gavage for 14 consecutive days: vehicle (water) at 2.8 mL/kg body weight or captopril at 50 mg/kg body weight. In addition, a group of lean animals were treated for 14 consecutive days with water only (2.8 mL/kg body weight). All animals were food-restricted the evening before the experiment as described above for the short-term treatment groups. Between 9 and 10 AM, approximately 20 hours after the final treatment, animals were weighed and then deeply anesthetized with pentobarbital sodium IP, and both epitrochlearis muscles were surgically removed and prepared for in vitro incubation. In addition, the heart was then excised, trimmed of blood vessels and fat, blotted free of blood, and weighed.

Insulin Treatments

All muscles were initially incubated for 60 minutes in 3 mL oxygenated Krebs-Henseleit buffer (KHB)[25] containing 8 mmol/L glucose, 32 mmol/L mannitol, and 0.1% bovine serum albumin (radioimmunoassay grade, Sigma Chemical, St Louis, MO). The medium in which the right muscle from each animal was incubated contained no insulin, whereas the medium in which the contralateral muscle was incubated contained 2 mU/mL porcine insulin (Eli Lilly & Co, Indianapolis, IN). The gas phase in each flask was 95% O_2:5% CO_2. The flasks were shaken in a Dubnoff incubator at 37°C.

Muscle Contractions

For electrical stimulation of in vitro muscle contractions, the distal end of the muscle preparation was attached to a vertical Lucite (E.I. du Pont de Nemours & Co, Wilmington, DE) rod containing two platinum electrodes.[26] The proximal end was clipped to a jeweler's chain and attached to a Grass model FTO3 isometric force transducer (Grass Instrument, Quincy, MA). The mounted muscle was immersed in 25 mL KHB containing 8 mmol/L glucose and 32 mmol/L mannitol and continuously oxygenated with 95% O_2:5% CO_2 at 37°C. The muscle was then stimulated with supramaximal square-wave pulses of 0.2 milliseconds' duration using a Grass S11 stimulator. Ten tetanic contractions were produced by stimulating at 50 Hz for 10 seconds at a rate of one contraction per minute for 10 minutes. This protocol maximally activates the insulin-independent pathway for glucose transport in the epitrochlearis muscle.[21]

Measurement of Glucose Transport Activity

Following the initial treatments, all muscles were rinsed for 10 minutes at 37°C in 3 mL oxygenated KHB containing 40 mmol/L mannitol, 0.1% bovine serum albumin, and if present previously, 2 mU/mL insulin. The muscles were then transferred to flasks containing 2 mL oxygenated KHB, 0.1% bovine serum albumin, 1 mmol/L 2-deoxy[1,2-^{3}H]glucose (300 μCi/mmol [2-DG]), and 39 mmol/L [U-^{14}C]mannitol (0.8 μCi/mmol; ICN Radiochemicals, Irvine, CA), and insulin, if present previously. After this final 20-minute incubation at 37°C, muscles were blotted on a filter moistened with ice-cold medium, trimmed of fat, extraneous muscle tissue, and connective tissue, and frozen between aluminum blocks cooled to the temperature of liquid N_2. The frozen muscle was immediately weighed on an electronic balance and then dissolved in 0.5 mL 0.5N NaOH. After complete solubilization, 5 mL scintillant was added and samples were analyzed for radioactivity in the ^{3}H and ^{14}C channels. Radioactivity in the ^{14}C channel and the specific activity of the incubation medium were used to determine the extracellular space, and the specific uptake of 2-DG was calculated by subtracting the ^{3}H activity in the extracellular space from the total ^{3}H activity in each sample. This method for assessing glucose transport activity in epitrochlearis muscles of this size has been thoroughly studied and validated.[27]

Statistical Analysis

Data are expressed as the mean ± SE. The significance of differences between groups was assessed by one-way ANOVA with a post hoc Scheffé F test.

RESULTS

Effect of Short-Term Captopril Treatment on Insulin-Stimulated Glucose Transport Activity

The final average body weight of the obese vehicle-treated group was significantly greater than that of the age-matched lean controls, but was not different as compared with the obese short-term captopril-treated group (Table 1). However, there was no significant difference among groups for epitrochlearis wet weight. This is an important consideration, since we have shown previously

Table 1. Effect of Short-Term Captopril Treatment on In Vitro Stimulation of Skeletal Muscle Glucose Transport Activity by Insulin

Group	n	Final Body Weight (g)	Epitrochlearis Weight (mg)	2-DG Uptake (pmol · mg muscle^{-1} · 20 min^{-1})		
				Basal	+Insulin	ΔDue to Insulin
Lean vehicle-treated	11	160 ± 2	31.7 ± 1.4	123 ± 8	363 ± 20	240 ± 24
Obese vehicle-treated	9	303 ± 7*	31.9 ± 1.2	99 ± 6	209 ± 14*	111 ± 15*
Obese short-term captopril-treated	11	290 ± 5*	33.4 ± 1.4	102 ± 7	264 ± 18*†	162 ± 16*†

NOTE. Values are the mean ± SE for number (n) of animals shown. Captopril was administered by gavage at 50 mg/kg body weight. Insulin was present at 2 mU/mL.

*$P < .05$ *v* lean vehicle-treated group.

†$P < .05$ *v* obese vehicle-treated group.

that differences in muscle size and wet weight can independently alter in vitro glucose transport activity.[28]

In the absence of insulin, glucose transport activity as assessed by 2-DG uptake did not differ significantly in muscles from the three groups studied (Table 1). In the presence of a maximally effective concentration of insulin, the rate of 2-DG uptake was 42% lower ($P < .05$) in the obese vehicle-treated group compared with the lean control group. Likewise, the increase in 2-DG uptake above basal due to insulin was only 46% as great in the obese vehicle-treated group compared with lean controls ($P < .05$). A single administration of captopril enhanced the rate of 2-DG uptake in the presence of insulin by 26% and the insulin-mediated increase in 2-DG uptake above basal by 46% as compared with values in the obese vehicle-treated group (both $P < .05$). Insulin-stimulated 2-DG uptake in muscle from the captopril-treated obese group still remained 33% lower than in lean control muscle ($P < .05$).

Antagonism of bradykinin by pretreatment with the compound HOE 140 completely abolished the acute improvement in insulin action on 2-DG uptake mediated by captopril (Table 2).

Effect of Long-Term Captopril Treatment on Insulin-Stimulated and Contraction-Stimulated Glucose Transport Activity

Body weights, epitrochlearis wet weights, and heart wet weights from the long-term treated groups are shown in Table 3. As in the short-term experiment, the final body weights of obese long-term vehicle-treated and obese captopril-treated groups were substantially greater than those of the age-matched lean controls, but were not different from one another. In addition, the net increase in body weight over the 14-day treatment period was similar between the two obese groups (28 ± 4 and 32 ± 2 g in the obese vehicle-treated and captopril-treated groups, respectively). Epitrochlearis wet weights were not different among the groups. Absolute heart wet weights in the obese vehicle-treated animals were 41% greater ($P < .05$) than in lean controls. Final heart wet weights were 8% to 9% smaller ($P < .05$) in the long-term captopril-treated obese animals as compared with the obese control group, irrespective of whether this weight was expressed in absolute terms or relative to final body weights. This decreased growth of the myocardium in the captopril-treated group is consistent with the known effect of ACE inhibition on reversing left ventricular hypertrophy,[29] and is further evidence for the positive systemic action of this agent.

Glucose transport activities in muscles from lean vehicle-treated, obese vehicle-treated, and obese captopril-treated groups are shown in Table 4. Basal 2-DG uptake rates did not differ in muscles from these groups. The rate of insulin-stimulated 2-DG uptake was significantly lower (−40%, $P < .05$) in muscles from obese vehicle-treated animals as compared with lean controls, and was 29% greater in the captopril-treated obese group as compared with the obese vehicle-treated group ($P < .05$). There was also evidence of an impairment of contraction-stimulated 2-DG uptake in the epitrochlearis muscle of obese animals, since this parameter was 31% less as compared with lean control values ($P < .05$). Moreover, long-term captopril treatment had no effect on contraction-stimulated 2-DG uptake in this muscle. The effects of insulin and contractions on 2-DG uptake were fully additive in all of the long-term treatment groups studied. There were no significant differences among the three groups in the maximal isometric force produced by the muscles in response to the electrical stimulation (19 ± 1, 16 ± 1, and 20 ± 2 g for lean vehicle-treated, obese vehicle-treated, and obese captopril-treated groups, respectively).

Table 2. Effect of Bradykinin Antagonism Preceding Short-Term Captopril Treatment on In Vitro Insulin-Stimulated Glucose Transport Activity in Skeletal Muscle of Obese Zucker Rats

Short-Term Treatments		n	Final Body Weight (g)	Epitrochlearis Weight (mg)	2-DG Uptake (pmol · mg muscle^{-1} · 20 min^{-1})		
HOE 140	Captopril				Basal	+Insulin	ΔDue to Insulin
No	No	5	286 ± 8	33.5 ± 1.0	91 ± 10	213 ± 14	122 ± 20
No	Yes	5	283 ± 9	30.7 ± 2.7	114 ± 8	276 ± 20*	162 ± 23
Yes	Yes	5	285 ± 3	33.4 ± 1.8	101 ± 6	204 ± 6†	103 ± 11†

NOTE. Values are the mean ± SE for number (n) of animals indicated. The bradykinin antagonist HOE 140 was administered IP at 100 μg/kg body weight, and captopril by gavage at 50 mg/kg. Insulin was present at 2 mU/mL.

*$P < .05$ *v* group receiving neither compound.

†$P < .05$ *v* group receiving captopril only.

Table 3. Body Weights, Epitrochlearis Wet Weights, and Heart Weights Following Long-Term Administration of Captopril

Group	n	Body Weight (g)		Epitrochlearis Wet Weight (mg)	Heart Wet Weight (mg)	Heart Wet Weight/Body Weight (mg/g)
		Initial	Final			
Lean vehicle-treated	12	148 ± 4	163 ± 3	32.0 ± 1.3	484 ± 8	2.98 ± 0.05
Obese vehicle-treated	14	287 ± 5	315 ± 5	32.7 ± 1.1	688 ± 11	2.21 ± 0.04
Obese captopril-treated	16	280 ± 8	312 ± 8	32.4 ± 1.1	631 ± 14*	2.02 ± 0.03*

NOTE. Values are the mean ± SE for number (n) of animals indicated. Captopril was administered by gavage at 50 mg/kg body weight for 14 consecutive days.

*$P < .05$, obese captopril-treated *v* obese vehicle-treated.

Net increases in 2-DG uptake due to insulin alone were calculated for muscle pairs from each animal and pooled for each of the three experimental groups (Table 4). The increase in 2-DG uptake due to insulin was only 49% as great in the obese vehicle-treated group as compared with the lean group ($P < .05$), but was improved to 79% of lean control values by long-term captopril treatment of the obese animals.

DISCUSSION

The present study provides several new insights regarding resistance to activation of skeletal muscle glucose transport activity in an animal model of NIDDM. The most important finding from the clinical standpoint is that the ACE inhibitor captopril improved insulin-stimulated glucose transport activity in skeletal muscle following either short-term (1-hour) or long-term (14-day) oral administration. Although previous investigations in humans have also demonstrated that captopril improves insulin-stimulated whole-body[9-13] or forearm[10,11] glucose removal, it was assumed by the investigators that the drug effect was mediated by enhanced skeletal muscle glucose uptake. We have assessed glucose transport activity in the isolated epitrochlearis muscle preparation, which allows for precise control of conditions under which glucose transport is measured and more importantly eliminates any influence of blood flow on muscle glucose transport. The present study is therefore the first to provide definitive evidence that the skeletal muscle glucose transport system is involved in the action of captopril.

Resistance to insulin for stimulation of glucose transport activity has been a consistent finding in studies using the obese Zucker rat, whether assessed by glucose uptake over the entire hindlimb[30,31] or by transport of glucose analogs into individual muscles during hindlimb perfusion[32,33] or into isolated soleus muscles.[34] We have confirmed these findings using an optimal isolated-muscle preparation—the epitrochlearis (Tables 1, 2, and 4). In addition, using this isolated-muscle preparation we have shown that contraction-stimulated glucose transport activity in the obese Zucker rat is also significantly impaired (Table 4). However, it is noteworthy that this impairment in the capacity of the epitrochlearis muscle from obese Zucker rats to respond to contractions for activation of glucose transport (65% of lean control) is not as severe as the impairment in insulin action (49% of lean control). Moreover, the contraction pathway for activation of glucose transport activity was unaffected by long-term captopril treatment, indicating that the beneficial effects of this agent are restricted to the insulin pathway.

In the present investigation, we have provided evidence that bradykinins are involved in the action of captopril in enhancing insulin-stimulated glucose transport activity in insulin-resistant muscle (Table 2). Whether bradykinin itself or some metabolite of bradykinin such as the prostaglandins acts as the mediator of captopril action cannot be ascertained from these results. In this context, it is known that ACE inhibition can lead to enhanced prostaglandin production[8] and that short-term treatment with prostaglandin E_2 can augment insulin-stimulated glucose transport activity in rat epitrochlearis muscle.[16,35] In addition, the short-term effect of captopril may have influenced insulin receptor tyrosine kinase activity or glucose transporter (GLUT-4) translocation, both of which are known to be

Table 4. Effect of Long-Term Captopril Administration on In Vitro Stimulation of Skeletal Muscle Glucose Transport Activity by INS and/or CON

Group	n	2-DG Uptake (pmol · mg muscle^{-1} · 20 min^{-1})					
		Basal	+INS	+CON	+INS, +CON	ΔDue to INS	Pooled Δ Due to INS
Lean vehicle-treated	6	133 ± 13	333 ± 19			200 ± 22	
	6			483 ± 49	679 ± 75	196 ± 59	198 ± 30 (n = 12)
Obese vehicle-treated	9	102 ± 9	201 ± 15*			98 ± 16*	
	5			331 ± 17*	428 ± 25*	97 ± 23	98 ± 13* (n = 14)
Obese captopril-treated	11	106 ± 9	260 ± 15*†			155 ± 14†	
	5			330 ± 21*	492 ± 44*	162 ± 27	157 ± 13† (n = 16)

NOTE. Values are the mean ± SE for number (n) of animals indicated. INS was present at 2 mU/mL. CON were 10 tetani. Captopril was administered by gavage at 50 mg/kg body weight for 14 consecutive days.

Abbreviations: INS, insulin; CON, contractions.

*$P < .05$ *v* lean vehicle-treated group.

†$P < .05$ *v* obese vehicle-treated group.

defective in skeletal muscle of the obese Zucker rat.[36,37] These same factors may also have been affected by long-term treatment with captopril, with the additional possibility that the muscle level of GLUT-4 may also have been increased. Interventions such as exercise training of obese Zucker rats can induce increases in muscle GLUT-4 protein levels[38,39] that are associated with enhanced insulin-stimulated glucose uptake.[39] Since circulating insulin or lipid levels (triglycerides, free fatty acids, and ketone bodies) are not markedly affected by captopril administration in human hypertensive[4] or NIDDM[10,11] patients, it is unlikely that these factors are directly involved in the mechanism of action of captopril.

In contrast to the present findings, two recent studies using the hindlimb perfusion technique have indicated that contraction-stimulated glucose uptake in muscle from obese Zucker rats is not significantly impaired.[31,33] However, in the study by Dolan et al,[33] a significant reduction in contraction-stimulated glucose uptake by the white gastrocnemius of obese Zucker rats was indeed seen. Interestingly, the white gastrocnemius and the epitrochlearis both consist predominantly of type IIb fibers.[15,40] In addition, smaller absolute increases above basal due to contractions were also found in the red gastrocnemius and the extensor digitorum longus of obese rats as compared with lean controls.[33] Therefore, our study and that of Dolan et al[33] are actually in agreement. One possible explanation for the discrepant findings of the present study (Table 4) and those of Brozinick et al[31] is that following electrical stimulation of the hindlimb muscles, one would expect capillaries in the previously contracting muscles to be dilated, thus enhancing substrate delivery to the muscle fibers. If a greater vasodilation occurred in the hindlimbs of the obese rats, the increased substrate delivery could overcome an impairment of the intrinsic activity of the glucose transport system in these muscles. In the present investigation, substrate delivery to the isolated muscles was accomplished entirely by diffusion, thus eliminating the influence of the vascular system and allowing for the determination of intrinsic glucose transport activity of the muscle. Alternatively, there may be a heterogeneity of adaptations in the contraction-dependent pathway among muscles of the obese rats, with the epitrochlearis showing a greater decrease than the hindlimb muscles. The resolution of these issues awaits further research.

These beneficial effects of captopril on the skeletal muscle glucose transport system have also been found for another ACE inhibitor, trandolapril.[41] Long-term treatment of obese Zucker rats with trandolapril led to a 69% increase in insulin-stimulatable glucose transport activity in the isolated epitrochlearis as compared with values in a vehicle-treated obese group. These similar findings for captopril and trandolapril are consistent with the interpretation that this likely represents a class effect of the ACE inhibitors on the glucose transport system in skeletal muscle.

In summary, we have demonstrated that both short- and long-term administrations of the ACE inhibitor captopril significantly enhance the insulin responsiveness of in vitro glucose transport activity in insulin-resistant skeletal muscle of obese Zucker rats. The enhancement of insulin action on glucose transport activity by captopril is dependent on bradykinin or one of its metabolites, since antagonism of bradykinin abolishes the short-term effect of captopril. The long-term effect of captopril is restricted to the insulin-dependent pathway for glucose transport, since the impaired contraction-induced glucose transport activity in the epitrochlearis muscle was not improved. These data support the idea that ACE inhibitors can affect the skeletal muscle glucose transport system and may help to explain the observed action of ACE inhibitors in improving glucose disposal in human NIDDM.

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