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Effects of Trandolapril and Verapamil on Glucose Transport in Insulin-Resistant Rat Skeletal Muscle

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We have used an animal model of insulin resistance—the obese Zucker (*fa/fa*) rat—to test whether oral administration of the non–sulfhydryl-containing angiotensin-converting enzyme (ACE) inhibitor, trandolapril, alone or in combination with the Ca^{2+}-channel blocker, verapamil, can induce a beneficial effect on insulin-stimulated glucose transport and metabolism in skeletal muscle. Insulin-stimulated 2-deoxyglucose (2-DG) uptake in the isolated epitrochlearis muscle was less than 50% as great in obese animals compared with lean (*Fa/-*) controls ($P < .05$), but was significantly improved in the obese group by both short-term (6 hours, +33%) and long-term (14 days, +70%) oral treatment with trandolapril. Verapamil treatment alone did not alter insulin-stimulated 2-DG uptake in muscle, but simultaneous administration of verapamil and trandolapril resulted in the most pronounced effect on insulin-stimulated 2-DG uptake (+106%). Long-term treatment with trandolapril alone and in combination with verapamil significantly increased muscle glycogen (+26% to 27%), glucose transporter GLUT-4 protein (+27% to 31%), and hexokinase activity (+21% to 49%), and decreased plasma insulin levels (−23% to −29%). Muscle citrate synthase activity was enhanced only when trandolapril and verapamil were administered in combination (+24%). We conclude that the long-acting, non–sulfhydryl-containing ACE inhibitor, trandolapril, alone and in combination with the Ca^{2+}-channel blocker, verapamil, can significantly improve insulin-stimulated glucose transport activity in skeletal muscle of the insulin-resistant obese Zucker rat, and that this improvement is associated with favorable adaptive responses in GLUT-4 protein levels, glycogen storage, and activities of relevant intracellular enzymes of glucose catabolism.

ESSENTIAL HYPERTENSION has been shown by several investigators to be frequently associated with a decreased insulin sensitivity of whole-body glucose disposal.[1-3] The hypertensive patient often shows a clustering of atherogenic risk factors, refered to as the "metabolic syndrome" or "syndrome X,"[4] and insulin resistance and the accompanying hyperinsulinemia are thought to play major roles in the etiology of this condition.[2,4-6] Some of the commonly used antihypertensive agents modify insulin sensitivity.[7] Whereas the β-adrenergic blockers and thiazides further decrease insulin sensitivity,[8-11] α_1-adrenergic blockers[12] and angiotensin-converting enzyme (ACE) inhibitors slightly improve insulin sensitivity in short-term[13-15] and long-term[8,16-22] studies. We have also found an acute metabolic effect of the sulfhydryl-containing ACE inhibitor, captopril, at doses that do not significantly affect blood pressure.[23] In addition, we have shown, using an in vitro assay system, that captopril significantly increases insulin action on glucose transport activity in insulin-resistant rat muscle.[24] However, it is not clearly established whether these metabolic changes caused by ACE inhibitors are reliant on the sulfhydryl components of the agent, or whether this is a general characteristic of this class of pharmaceutical agents.

Trandolapril, a novel long-acting ACE inhibitor (see the review[25] of pharmacologic properties and hemodynamic effects), has been recently introduced for clinical use. Unlike captopril, trandolapril does not contain sulfhydryl groups, and it was therefore of interest to see whether this agent would also improve insulin-stimulated glucose transport activity. Since Ca^{2+}-channel blockers such as verapamil are at times administered in combination with ACE inhibitors in the treatment of hypertension, we also as-

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sessed the interactive effects of verapamil and trandolapril. To analyze the actions of these agents on the skeletal muscle glucose transport system independently of hemodynamic factors, we used the isolated epitrochlearis muscle of the obese Zucker (*fa/fa*) rat, an animal model of insulin resistance. In addition, to assess associated cellular adaptive responses, we determined muscle levels of the glucose transporter GLUT-4 protein, total hexokinase activity, and citrate synthase activity.

MATERIALS AND METHODS

Animals

Female obese Zucker rats (*fa/fa*) and lean littermates (*Fa/-*) were purchased at 7 to 8 weeks of age from Harlan (Indianapolis, IN). Animals were housed two per cage and maintained on chow (Purina, St Louis, MO) and water ad libitum. All procedures described herein were approved by the University of Arizona Animal Use and Care Committee.

Short-Term Treatment Groups

Lean and obese animals at 10 to 11 weeks of age were randomly assigned either to a placebo control group or to a group receiving a single administration of trandolapril (Knoll, Ludwigshafen, Germany). Lean animals were restricted to 4 g chow after 5 PM of the evening before the experiment, and obese animals received 6 g chow at this time. At 6 AM on the day of the experiment, lean and obese placebo groups received water (3.0 mL/kg body weight) by gavage. Lean and obese trandolapril groups received by gavage 3.0 mg/kg body weight of a stock solution (1.0 mg/mL in distilled water). Since the time to peak plasma concentration of the active metabolite of trandolapril (trandolaprilat) is approximately 6 hours and the half-life of trandolapril is 24 hours,[25] we chose to study the acute metabolic effects of trandolapril 6 hours after administration. After this 6-hour period, animals were weighed and deeply anesthetized with pentobarbital sodium (50 mg/kg body weight intraperitoneally). Both epitrochlearis muscles were then surgically removed and prepared for in vitro incubation as described later.

Long-Term Groups

Obese animals at 8 to 9 weeks of age received one of the following treatments by gavage for 14 consecutive days: vehicle (water, 3.0 mL/kg body weight), low-dose trandolapril (0.1 mg/kg), high-dose trandolapril (1.0 mg/kg), verapamil (20 mg/kg), combined low-dose trandolapril and verapamil, and combined high-dose trandolapril and verapamil. In addition, lean animals were treated for 14 consecutive days with either water only (3.0 mL/kg) or high-dose trandolapril (1.0 mg/kg). All animals received the same volume relative to body weight. Animals were food-restricted the evening before the experiment as described earlier for the short-term treatment groups. Between 9 and 10 AM, approximately 20 hours after the final treatment, blood was drawn from a cut at the tip of the tail, mixed with EDTA (final concentration, 18 mg/mL), and centrifuged at 13,000 *g* to separate the plasma for determination of glucose[26] and insulin (by radioimmunoassay; Linco Research, St Charles, MO). Animals were then deeply anesthetized with pentobarbital sodium, and both epitrochlearis muscles were surgically removed and prepared for in vitro incubation. In separate groups of obese animals only, epitrochlearis muscles were removed, frozen, and weighed, and then prepared for determination of glycogen,[27] GLUT-4 protein,[28] total hexokinase activity,[29] and citrate synthase activity.[30] In addition, the heart was removed, quickly trimmed of blood vessels and visible fat, blotted free of blood, frozen, and weighed.

In vitro Insulin Treatments

Epitrochlearis muscles were initially incubated (without tension throughout) for 60 minutes in 3 mL oxygenated Krebs-Henseleit buffer (KHB) containing 8 mmol/L glucose, 32 mmol/L mannitol, and 0.1% bovine serum albumin ([BSA] radioimmunoassay grade). One muscle from each animal was incubated in the absence of insulin, and the contralateral muscle was incubated in medium containing a maximally effective concentration of pork insulin (2 mU/mL; Eli Lilly, Indianapolis, IN). The flasks were shaken in a Dubnoff incubator at 37°C and had a gas phase of 95% O_2:5% CO_2.

Muscle 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% BSA, and, if present previously, insulin. The muscles were then transferred to flasks containing 2 mL oxygenated KHB, 0.1% BSA, 1 mmol/L 2-deoxy[1,2-^{3}H]glucose ([2-DG] 300 mCi/mol) and 39 mmol/L [U-^{14}C]mannitol (0.8 mCi/mol) (ICN Radiochemicals, Irvine, CA), and insulin, if present previously. After this final 20-minute incubation period at 37°C, muscles were trimmed of fat, extraneous muscle, and connective tissue, frozen between aluminum blocks cooled to the temperature of liquid N_2, weighed, and dissolved in 0.5 mL 0.5N NaOH. Glucose transport activity was then calculated as described by Henriksen and Ritter.[31] This method for assessing glucose transport activity in epitrochlearis muscles of this size has been thoroughly studied and validated.[32]

Statistical Analysis

All data are presented as the mean ± SE. The significance of differences between multiple groups was assessed by ANOVA with a post hoc Scheffé F test (Statview II; Abacus Concepts, Berkeley, CA). A P value less than .05 was considered significant.

RESULTS

Short-Term Trandolapril Treatment

The obese vehicle-treated group had a significantly higher final body weight than the age-matched lean control group, whereas no differences were seen between the control group and the trandolapril-treated group for lean and obese animals, respectively (Table 1). However, the wet weight of the epitrochlearis was the same in all four groups. Therefore, differences in glucose transport activity between groups described herein cannot be attributed to differences in diffusion distance.[33]

Table 1. Body Weight and Epitrochlearis Muscle Wet Weight for the Short-Term Treatment Groups (n = 6)

Group	Body Weight (g)	Epitrochlearis Wet Weight (mg)
Lean vehicle-treated	160 ± 4	30.4 ± 1.9
Lean short-term trandolapril–treated (3 mg/kg)	159 ± 3	28.6 ± 1.6
Obese vehicle-treated	302 ± 2*	29.9 ± 1.2
Obese short-term trandolapril–treated (3 mg/kg)	301 ± 1*	28.9 ± 2.1

NOTE. Values are the mean ± SE.
*P < .05 v lean groups.

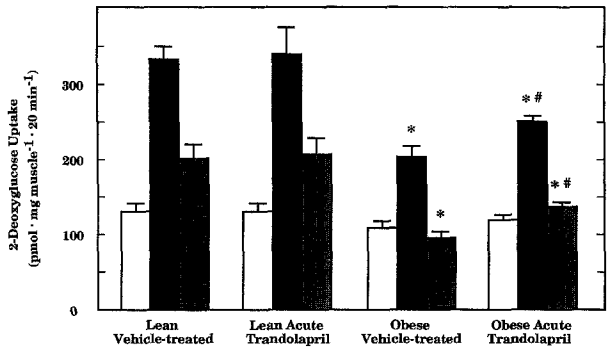

Fig 1. Effect of short-term trandolapril treatment on in vitro skeletal muscle 2-DG uptake in the absence (□) or presence (■) of insulin (2 mU/mL). (▨) Net increase in 2-DG uptake above basal due to insulin. Data are the mean ± SE for 6 animals per group. *P < .05 v lean vehicle-treated group. #P < .05 v obese vehicle-treated group.

Glucose transport activity in the absence of insulin did not differ between the four groups (Fig 1). However, the rate of insulin-stimulated 2-DG uptake in the obese vehicle-treated group was only 62% of the rate in the lean control group, and the net increase due to insulin was only 49% of the insulin-induced increase in the lean controls, indicating a severe insulin resistance in the muscle of the obese animals. However, following short-term trandolapril treatment, the rate of insulin-stimulated 2-DG uptake was 22% higher than in the obese control group and the net increase above basal due to insulin was 33% greater than in the obese controls. Short-term trandolapril treatment did not affect insulin-stimulated 2-DG uptake in muscle from lean animals.

Long-Term Treatments With Trandolapril and Verapamil

Final body weights for the vehicle-treated obese group and the various trandolapril- and verapamil-treated groups were significantly greater than for the lean vehicle-treated group, but were not different from one another (Table 2). Weight gain in all obese animals was similar (data not shown). Wet weight of the epitrochlearis muscle was similar in all groups investigated. Obese animals were slightly hyperglycemic compared with lean controls, with a 27% higher (P < .05) plasma glucose level. Treatments with trandolapril and verapamil individually and in combination did not significantly affect plasma glucose levels in obese animals.

The obese animals were markedly hyperinsulinemic compared with lean animals (Table 2). Verapamil treatment did not affect this parameter. However, a significant reduction in plasma insulin in obese animals was observed following long-term treatment with trandolapril (1.0 mg/kg/d) alone (−29%) or in combination with verapamil (−23%).

Absolute heart wet weight was significantly higher in obese vehicle-treated animals versus lean controls, whereas long-term treatment with trandolapril at the higher dose of 1.0 mg/kg and even at the lower dose of 0.1 mg/kg resulted in significant reductions in heart wet weight of approximately 8% (Table 2). This finding is in accordance with the known effect of ACE inhibitors on slowing or reversing cardiac hypertrophy[34] and is similar to the effect seen in obese Zucker rats after long-term captopril treatment.[24] In the verapamil-treated obese group and in rats receiving combined low-dose trandolapril and verapamil, there was no significant effect on heart wet weight. However, the combination of verapamil and high-dose trandolapril caused the most pronounced reduction (12%) in heart wet weight as compared with that of obese control rats.

The rate of insulin-stimulated 2-DG uptake was 43% less and the absolute increase in 2-DG uptake due to insulin was 56% less in the obese vehicle-treated group compared with the age-matched lean control group (Fig 2). Trandolapril (1.0 mg/kg) administered to lean animals caused a small (15%) but nonsignificant increase in the net effect of insulin on 2-DG uptake. On the other hand, trandolapril administered at 0.1 mg/kg to obese animals resulted in a 28% greater, and at 1.0 mg/kg a 33% greater, increase in the rate of insulin-stimulated 2-DG uptake as compared with the obese vehicle-treated group. The net increase in 2-DG uptake due to insulin in the low-dose trandolapril group tended to be greater (28%, P < .1) compared with the obese vehicle control, but in the high-dose trandolapril

Table 2. Body Weight, Epitrochlearis Wet Weight, Heart Wet Weight, and Plasma Glucose and Insulin Levels for the Long-Term Treatment Groups

Group	Body Weight (g)	Epitrochlearis Wet Weight (mg)	Heart Wet Weight (mg)	Plasma Glucose (mmol/L)	Plasma Insulin (μU/mL)
Lean vehicle-treated	160 ± 3	31.8 ± 1.4	480 ± 8	8.3 ± 0.7	25 ± 3
Obese vehicle-treated	311 ± 7*	31.7 ± 1.5	677 ± 12*	10.5 ± 0.3*	203 ± 19*
Obese trandolapril-treated					
0.1 mg/kg	293 ± 8*	30.9 ± 1.8	621 ± 19*†	9.9 ± 0.5	ND
1.0 mg/kg	290 ± 6*	31.8 ± 1.2	622 ± 11*†	10.1 ± 0.3*	144 ± 16*†
Obese verapamil-treated					
20 mg/kg	308 ± 4*	33.0 ± 1.2	683 ± 14*	9.8 ± 0.5	199 ± 19*
Verapamil + trandolapril 0.1 mg/kg	308 ± 4*	33.2 ± 1.7	654 ± 16*	10.1 ± 0.3*	ND
Verapamil + trandolapril 1.0 mg/kg	295 ± 10*	30.8 ± 1.0	599 ± 16*†	9.6 ± 0.2	157 ± 12*†

NOTE. Values are the mean ± SE for 6 to 12 animals per group.
Abbreviation: ND, not determined.
*P < .05 v lean vehicle-treated group.
†P < .05 v obese vehicle-treated group.

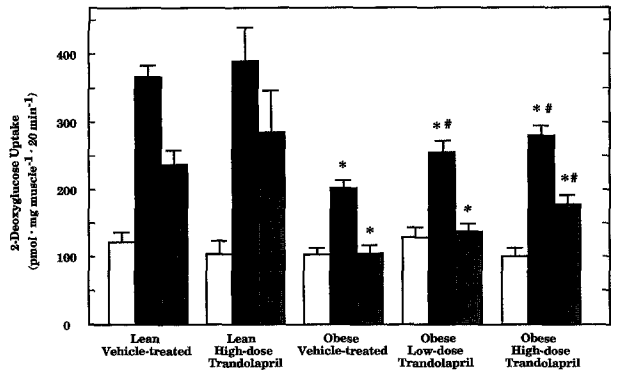

Fig 2. Effect of long-term trandolapril treatment on in vitro skeletal muscle 2-DG uptake in the absence (□) or presence (■) of insulin (2 mU/mL). (▨) Net increases in 2-DG uptake above basal due to insulin. Data are the mean ± SE for 10 to 12 animals per group. *P < .05 v lean vehicle-treated group. #P < .05 v obese vehicle-treated group.

group, this parameter was significantly greater (70%) compared with the obese control group.

Long-term treatment of obese animals with verapamil alone caused no significant change in muscle glucose transport activity (Fig 3). As before, low-dose trandolapril treatment resulted in a nonsignificant increase in insulin-stimulated 2-DG uptake. However, following combined verapamil/low-dose trandolapril treatment, there were significant increases in the rate of insulin-stimulated 2-DG uptake (26%), as well as in the net increase due to insulin (43%), as compared with values in vehicle-treated obese rats.

High-dose trandolapril treatment again caused significant increases in the rate of insulin-stimulated 2-DG uptake (35%) and in the net increase due to insulin (+69%) compared with vehicle treatment (Fig 3). However, when high-dose trandolapril was combined with verapamil, the most pronounced quantitative increases in insulin action were observed: the rate of insulin-stimulated 2-DG uptake was 45% greater than for obese vehicle-treated controls and 35% greater than for the group receiving verapamil alone, and the differences between these same groups for the net increase in 2-DG uptake due to insulin were 106% and 70%, respectively. However, it should be pointed out that the increase due to combined trandolapril/verapamil treatment was not statistically greater than the increase due to trandolapril treatment alone. In addition, in the verapamil/high-dose trandolapril group, the rate of insulin-stimulated 2-DG uptake and the net increase due to insulin were 83% and 90%, respectively, of the values seen in the lean vehicle-treated group (Fig 3; not statistically different).

Long-term verapamil administration to obese animals did not alter the muscle level of GLUT-4 protein or the activities of hexokinase and citrate synthase (Fig 4). In contrast, long-term treatment with high-dose trandolapril led to significantly elevated GLUT-4 protein (+27%) and hexokinase activity (+21%). With combined high-dose trandolapril and verapamil administration, GLUT-4 protein (+31%) and hexokinase activity (+49%) remained

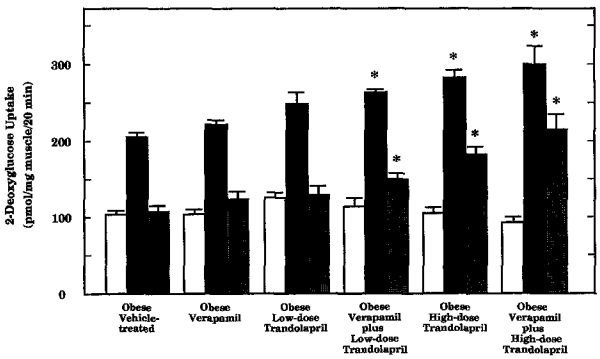

Fig 3. Interaction between long-term trandolapril and verapamil treatments on in vitro skeletal muscle 2-DG uptake in the absence (□) or presence (■) of insulin (2 mU/mL). (▨) Net increases in 2-DG uptake above basal due to insulin. Data are the mean ± SE for 4 to 12 animals per group. *P < .05 v vehicle-treated group.

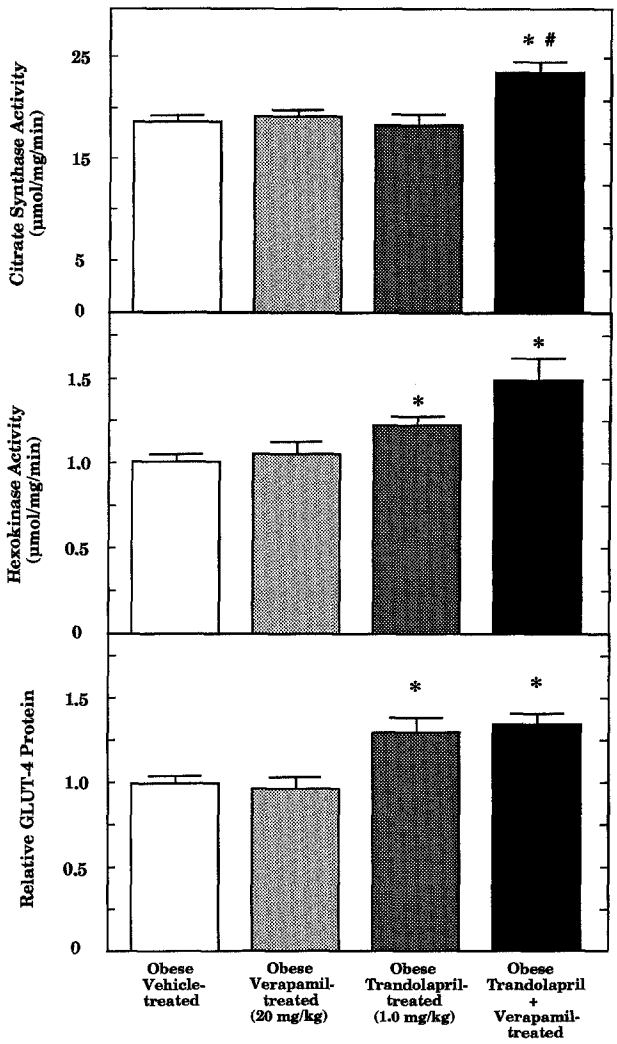

Fig 4. Effect of long-term trandolapril treatment with or without simultaneous verapamil administration on skeletal muscle GLUT-4 protein levels, hexokinase activity, and citrate synthase activity. Data are the mean ± SE for 5 to 7 animals per group. *P < .05 v obese vehicle-treated group. #P < .05 v obese trandolapril-treated group.

significantly elevated, but with this treatment muscle citrate synthase activity was now significantly greater (+24%) than the activity in the obese control group. These parameters were not changed with long-term low-dose trandolapril treatment alone or in combination with verapamil (data not shown).

Glycogen concentrations in the epitrochlearis muscle of obese animals were not affected by verapamil treatment (Fig 5). However, there was a trend ($P < .1$) toward higher glycogen levels in the epitrochlearis muscle of obese animals treated either with trandolapril at 1.0 mg/kg (+27%) or with this dose of trandolapril in combination with verapamil (+26%). Glycogen concentration was not altered with the low-dose trandolapril treatment alone or in combination with verapamil (data not shown).

DISCUSSION

The present study provides new information regarding the effects of ACE inhibitors, Ca^{2+}-channel blockers, and their combined administration on the skeletal muscle glucose transport system. We have used the isolated epitrochlearis muscle preparation from the obese Zucker rat, an animal model of insulin resistance. By assessing muscle glucose transport activity in vitro, we have eliminated the potential confounding influence of blood flow on this measurement. Therefore, our findings are the first to demonstrate a beneficial effect of short- and long-term administration of the ACE inhibitor, trandolapril, on the glucose transport system of insulin-resistant skeletal muscle. In addition, this study provides the first assessment of the metabolic effects of combined treatment with an ACE inhibitor and a Ca^{2+}-channel blocker.

The 33% improvement in insulin-stimulated glucose transport activity following short-term treatment of obese Zucker rats with trandolapril is consistent with clinical studies of the acute effect of ACE inhibitor administration on improving whole-body glucose disposal in non–insulin-dependent diabetes mellitus (NIDDM) patients, assessed using the euglycemic, hyperinsulinemic clamp technique.[13-15,21,23] We have also demonstrated in the present study that long-term administration of trandolapril increased insulin-stimulated glucose transport activity in a dose-dependent fashion. We have previously found in this same experimental system that short- and long-term administration of the sulfhydryl-containing ACE inhibitor, captopril, caused a significant enhancement of insulin-stimulated glucose transport activity.[24] Therefore, it is likely that these findings present a class effect rather than a substrate-specific effect, and that the sulfhydryl groups of captopril are not essential for the metabolic effects of ACE inhibitors. This contention is supported by the study reported by Paolisso et al,[19] who in a placebo-controlled clinical trial demonstrated similar improvements in the insulin sensitivity of glucose disposal following treatment with five different ACE inhibitors.

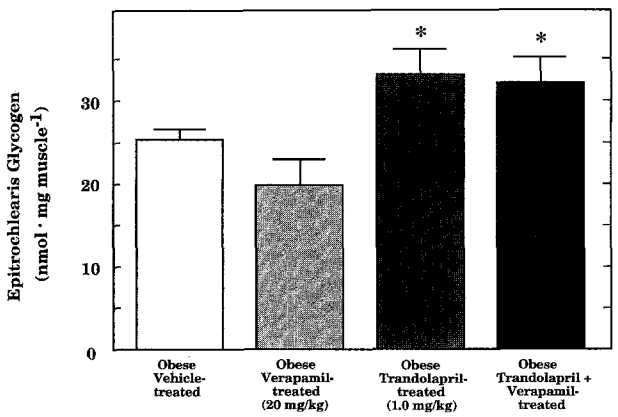

Fig 5. Effect of long-term trandolapril treatment with or without simultaneous verapamil administration on skeletal muscle glycogen levels. Data are the mean ± SE for 5 to 6 animals per group. *$P < .05$ v obese verapamil-treated group.

When high-dose trandolapril and verapamil were administered in combination, the data suggest that the positive metabolic effects of trandolapril were more pronounced, with the increase in 2-DG uptake due to insulin in the combined trandolapril/verapamil group being 22% higher than in the high-dose trandolapril group. One can at least conclude that long-term verapamil treatment at the dose administered does not negatively affect the beneficial metabolic action of trandolapril on insulin-stimulated glucose transport activity. This contrasts with the finding of Cartee et al,[35] who showed that in vitro incubation of skeletal muscle with high concentrations of verapamil markedly inhibited insulin-stimulated glucose transport activity. However, verapamil levels used in that study were likely much higher than those achieved in the present investigation. Indeed, most clinical studies to date have reported that Ca^{2+}-channel blocker administration does not adversely affect whole-body glucose metabolism.[7,10,36,37]

The results of this study suggest that increases in the cellular expression of the glucose transporter protein GLUT-4 may be associated with the improved insulin-stimulated glucose transport capacity of the epitrochlearis muscle following long-term trandolapril administration alone or in combination with verapamil. We have demonstrated previously that the muscle level of GLUT-4 protein is one important factor determining the glucose transport capacity of that muscle.[38] The enhanced levels of hexokinase following these treatment regimens would also be consistent with the idea that the glucose phosphorylation capacity in vivo would not be a limiting factor for intracellular glucose metabolism. In addition, there was a strong tendency for increased glycogen storage in the epitrochlearis muscle of animals treated long-term with 1.0 mg/kg trandolapril, indicating that at least some of the increased amount of glucose entering the cell was deposited as this polysaccharide. This is in agreement with the clinical findings of Vuorinen-Markkola and Yki-Järvinen.[22] However, despite an increased capacity for insulin-stimulated glucose transport and glucose phosphorylation in muscle from animals treated with both trandolapril and verapamil, no further increase in glycogen storage was observed. One explanation for this observation is that the increased glucose transported into the muscle from the combined-therapy group was oxidized rather than stored as glycogen.

Consistent with this hypothesis is our finding that the oxidative capacity of the epitrochlearis, as reflected by citrate synthase activity, was increased only in trandolapril/verapamil-treated animals.

The present study does not address other potential cellular mechanisms responsible for the effects of trandolapril and verapamil on glucose transport. For example, the translocation of GLUT-4 protein to the plasma membrane in response to insulin in muscle from obese Zucker rats is defective,[39] and the possibility exists that trandolapril may improve this process. In addition, the role of kinins, such as bradykinin, and prostaglandins in the improved insulin-stimulated glucose transport activity is currently not well described. Since ACE is identical to kininase II,[40] its inhibition should increase the level of kinins and prostaglandins. We have previously shown in this system that bradykinin antagonism prevents the captopril-mediated increase in insulin action on glucose transport,[24] a finding confirmed in human NIDDM patients.[21] Additionally, intraarterial infusion of PGE_1 enhances muscle glucose uptake while only slightly increasing blood flow.[41] Finally, in vitro studies indicate that PGE_2 significantly increases insulin-stimulated glucose transport activity in rat skeletal muscle.[42,43] The role of the kinins in the metabolic actions of ACE inhibitors in insulin-resistant muscle should be the focus of future investigations.

The effects of ACE inhibitors on glucose disposal have previously been attributed to improved capillary blood flow and the accompanying increased delivery of insulin and glucose to the muscle.[13-15,44,45] The antihypertensive action of ACE inhibitors appears to involve a kinin-induced vasodilation.[46,47] Additionally, Hirooka et al[45] found an improvement of endothelium-dependent vasodilation after administration of captopril, and Kodama et al[44] reported an improvement of glycemic control in human NIDDM subjects, accompanied by an increase in forearm blood flow. Although the potential contribution of hemodynamic influences of ACE inhibitors on glucose disposal cannot be ruled out, our present and previous findings[24] provide strong support for an additional effect of ACE inhibitors on the skeletal muscle glucose transport system.

In conclusion, our findings provide evidence that, like captopril, both short- and long-term administration of the ACE inhibitor, trandolapril, improve the insulin-sensitive glucose transport system in insulin-resistant skeletal muscle of obese Zucker rats. Since glucose transport activity was assessed in an isolated muscle preparation, these improvements in insulin action cannot be attributed to hemodynamic effects, and must therefore represent an adaptive response of the muscle itself. We observed the greatest improvement in insulin action following long-term treatment with trandolapril and the Ca^{2+}-channel blocker, verapamil, in combination. The significance of this latter finding, as well as elucidation of the cellular mechanisms responsible for the observed improvements in insulin action following trandolapril treatment, require further investigation.

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