Rapid Publication

Acute Exercise Induces GLUT4 Translocation in Skeletal Muscle of Normal Human Subjects and Subjects With Type 2 Diabetes

John W. Kennedy, Michael F. Hirshman, Ernest V. Gervino, Jeffrey V. Ocel, R. Armour Forse, Stephen J. Hoenig, Doron Aronson, Laurie J. Goodyear, and Edward S. Horton

Total GLUT4 content in skeletal muscle from individuals with type 2 diabetes is normal; however, recent studies have demonstrated that translocation of GLUT4 to the plasma membrane is decreased in response to insulin stimulation. It is not known whether physical exercise stimulates GLUT4 translocation in skeletal muscle of individuals with type 2 diabetes. Five subjects (two men, three women) with type 2 diabetes and five normal control subjects (5 men), as determined by a standard 75-g oral glucose tolerance test, were recruited to determine whether an acute bout of cycle exercise activates the translocation of GLUT4 to the plasma membrane in skeletal muscle. Each subject had two open biopsies of vastus lateralis muscle; one at rest and one 3–6 weeks later from the opposite leg after 45–60 min of cycle exercise at 60–70% of Vo_{2max}. Skeletal muscle plasma membranes were prepared by subcellular fractionation, and GLUT4 content was determined by Western blotting. Plasma membrane GLUT4 increased in each subject in response to exercise. The mean increase in plasma membrane GLUT4 for the subjects with type 2 diabetes was 74 ± 20% above resting values, and for the normal subjects the increase was 71 ± 18% above resting values. Although plasma membrane GLUT4 content was ~32% lower at rest and after exercise in the muscle of the subjects with type 2 diabetes, the differences were not statistically significant. We conclude that in contrast to the previously reported defect in insulin-stimulated GLUT4 translocation in skeletal muscle of individuals with type 2 diabetes, a single bout of exercise results in the translocation of GLUT4 to the plasma membrane in skeletal muscle of individuals with type 2 diabetes. These data provide the first direct evidence that GLUT4 translocation is an important cellular mechanism through which exercise enhances skeletal muscle glucose uptake in individuals with type 2 diabetes. *Diabetes* 48:xxx-xxx, 1999

From the Research Division (J.W.K., M.F.H., D.A., L.J.G., E.S.H.), Joslin Diabetes Center; the Department of Medicine, Division of Cardiology (E.V.G., J.V.O.), and the Department of Surgery (R.A.F., S.J.H.), Beth Israel Deaconess Medical Center; and Harvard Medical School (J.W.K., E.V.G., R.A.F., S.J.H., D.A., L.J.G., E.S.H.), Boston, Massachusetts.

Address correspondence and reprint requests to Edward S. Horton, MD, Metabolism Section, Joslin Diabetes Center, One Joslin Pl., Boston, MA 02215. E-mail: ehorton@joslin.harvard.edu.

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AMPK, 5′ AMP-activated protein kinase; IRS, insulin receptor substrate; PI, phosphatidylinositol; TNA, Tris-NaCl buffer containing 0.01% sodium azide.

Skeletal muscle is the major tissue responsible for insulin-mediated glucose utilization (1,2) and contributes greatly to the postprandial hyperglycemia observed in individuals with type 2 diabetes (3,4). Glucose transport is rate limiting for glucose utilization under most physiologic conditions in skeletal muscle (5). Glucose is transported into the cell through the plasma membrane and T-tubules via facilitated transport using glucose transporter proteins. The GLUT4 glucose transporter is abundant in skeletal muscle (6–9), and in the resting/basal condition it is predominantly located intracellularly. Many studies in rat skeletal muscle have shown that GLUT4 translocates to the plasma membrane from intracellular storage sites in response to both insulin (10–12) and exercise/contraction (13–15). The plasma membrane GLUT4 content is correlated with glucose transport activity in both rat (16,17) and human (18) skeletal muscle. The GLUT1 and GLUT5 transporters are present in low levels in skeletal muscle, are located at the plasma membrane (19,20), and do not translocate in response to insulin or exercise (21–23). Therefore, GLUT4 translocation is considered to be the major mechanism responsible for the increased rate of glucose transport after insulin or exercise stimulation.

Whereas individuals with type 2 diabetes have decreased insulin-stimulated glucose uptake in muscle (3,4), normal sensitivity of skeletal muscle in response to moderate exercise has been demonstrated with glucose turnover studies (24) and, most recently, by the arteriovenous leg balance technique (25). Thus, although skeletal muscle in type 2 diabetes is insulin resistant, it appears to remain sensitive to exercise. In individuals with type 2 diabetes, GLUT1 and GLUT4 are expressed normally in skeletal muscle (26–28). Therefore, a mechanism other than total muscle GLUT4 content must cause the decrease in insulin-stimulated glucose uptake in skeletal muscle from these individuals (29–31). In the obese Zucker rat, a rodent model of type 2 diabetes that demonstrates muscle insulin resistance (32,33), impaired glucose uptake is predominantly due to the failure of GLUT4 to translocate normally to the plasma membrane in response to insulin stimulation (11,34). In contrast to insulin stimulation, acute exercise promotes normal glucose uptake (35) and GLUT4 translocation in obese Zucker rat muscle (34,36).

Alterations in insulin signaling may be responsible for the defect in insulin-stimulated GLUT4 translocation. Decreased

glucose transport and GLUT4 translocation in incubated muscle strips from subjects with type 2 diabetes have been associated with decreased insulin-stimulated insulin receptor substrate (IRS)-1 tyrosine phosphorylation, phosphatidylinositol (PI) 3-kinase activity, and protein kinase B activity (37,38). While the insulin signaling pathway has been extensively examined (39), the cellular signaling mechanisms leading to GLUT4 translocation due to exercise still remain poorly defined. However, it is well established that insulin and exercise act on the glucose transport system through different signaling pathways in skeletal muscle (40). Additionally, it has also been suggested that GLUT4 may be stored intracellularly in two separate pools, one that is sensitive to insulin stimulation and another that is sensitive to contractile activity (40). It is possible that the distribution of these intracellular pools of GLUT4 is altered or that the t-/v-snares proteins involved in insulin-stimulated trafficking and docking of GLUT4-enriched vesicles to the plasma membrane may also be inhibited or downregulated in individuals with type 2 diabetes (41). Understanding the cellular mechanisms that explain the apparent paradox of how skeletal muscle may be simultaneously insulin resistant and exercise sensitive will be important for determining the pathophysiology of type 2 diabetes.

To date, three studies have demonstrated the failure of GLUT4 to translocate normally in response to insulin in skeletal muscle of subjects with type 2 diabetes (42–44). However, it is still not known whether exercise-stimulated GLUT4 translocation is normal in these patients. The purpose of this study was to determine whether an acute bout of cycle ergometry exercise stimulates GLUT4 translocation in skeletal muscle from individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subject selection. The protocol was approved by the Joslin Diabetes Center Committee on Human Subjects and the Beth Israel Deaconess Medical Center Committee on Clinical Investigations. Volunteers were recruited from the Boston area, and written informed consent was obtained from each subject after the nature of the study and all procedures were explained. Volunteers with evidence of cardiovascular disease or other conditions that would preclude their ability to exercise on a cycle ergometer were excluded. Volunteers were also excluded if they had clinically significant hepatic, renal, or hematologic disease based on routine laboratory panels obtained during the screening visit. Volunteers were excluded if they were <30 years of age or taking certain antihypertensive medications (β-blockers, ACE inhibitors, or thiazide diuretics). Volunteers with a history of diabetes were excluded if they had onset of their disease before age 30 or had a fasting C-peptide level <0.33 nmol/l. Volunteers with diabetes were also excluded if they were currently taking insulin, metformin, or troglitazone. Volunteers on glyburide or glipizide were continued on their current dose of the medicine throughout the study.

Experimental protocol. Written informed consent was obtained after all procedures were explained to each subject meeting the inclusion criteria. Volunteers were admitted to the Beth Israel Deaconess Clinical Research Center in the morning for a screening visit after a 12-h overnight fast. All volunteers with a fasting plasma glucose <7.7 mmol/l underwent a 2-h 75-g oral glucose tolerance test to determine if they had normal glucose tolerance or type 2 diabetes according to previously defined criteria (45). Volunteers with impaired glucose tolerance were excluded from the study. BMI and body fat content were determined by anthropometry by a certified anthropometrist. Body fat content was also determined by bioelectric impedance (BodyComp II Software; RJL Systems, Detroit, MI).

Maximal cycle ergometer test ($V_{O_{2max}}$ determination). Each subject performed a continuous incremental (2-min stages) cycle ergometry protocol to exhaustion on a Corival 400 electromagnetically braked isokinetic cycle ergometer (Gronigen, Netherlands). Ventilation and pulmonary gas exchange were continuously measured with a Quinton QMC metabolic cart (Bothell, WA) for determination of ventilation, V_{O_2}, CO_2 production (V_{CO_2}), and the respiratory exchange ratio. $V_{O_{2max}}$ was defined as the highest V_{O_2} achieved during the test. Before each test, gas analyzers were calibrated with two commercial tanks of gases certified to within ± 0.03%. One tank had a composition of 25% O_2:5% CO_2:balance N_2. The other had a composition of 10% O_2:0% CO_2:balance N_2. Flow (pneumotachometer) was calibrated utilizing a 3-l syringe.

Cycle ergometry exercise session. From the maximal cycle ergometer test, a power output designed to elicit an intensity between 60 and 70% of $V_{O_{2max}}$ (range 57–70) was calculated for each subject. All subjects completed a 5-min warm-up period at an intensity of 40–50% of the subject's $V_{O_{2max}}$. After the warm-up period, subjects cycled at the designated power output for a duration of 45–60 min (range: 35–65 min).

Muscle biopsy. There were 10 subjects, 5 normal control subjects and 5 subjects with type 2 diabetes, who completed the protocol. Each subject had two muscle biopsies: one at rest, and one 3–6 weeks later after a single bout of cycle exercise at 60–70% of each subject's predetermined $V_{O_{2max}}$. For 3 days before the biopsy, subjects were instructed to consume at least 150 g of carbohydrate and to avoid strenuous exercise. Subjects underwent the biopsy at ~8:00 A.M. after an overnight fast. The skin overlying the vastus lateralis muscle was cleaned with iodine, and a sterile field was established. Some 10–15 ml of 1% lidocaine local anesthetic was infiltrated subcutaneously down to, but not below, the muscle fascia. Using a standard surgical technique, the vastus lateralis muscle was identified, and ~1 g of muscle tissue was removed. The fascia and skin were sutured and covered with a sterile pressure dressing. One patient developed a hematoma that resolved without incident. Otherwise, there were no serious complications encountered with the biopsies.

Skeletal muscle fractionation and marker enzyme analyses. Muscle samples were immediately washed in saline, blotted dry, and weighed. The muscle was minced and then homogenized in a buffer containing 250 mmol/l sucrose and 20 mmol/l HEPES, pH 7.4, and immediately frozen in liquid N_2. Plasma membranes were isolated by minor modifications of our fractionation procedure, which has been previously described (46). Briefly, the frozen homogenate was thawed at 37°C, and an aliquot was removed for protein and enzyme analyses. All subsequent steps were performed at 4°C. KCl and sodium pyrophosphate were added to the

TABLE 1
Subject characteristics

	Normal subjects	Type 2 diabetic subjects
n (M/F)	5/0	2/3
Age (years)	44 ± 3	49 ± 6
Fasting plasma glucose (mmol/l)	4.7± 0.2	11.4 ± 2.1*
HbA_{1c}	5.2 ± 0.2	8.8 ± 0.7*
Fasting plasma insulin (pmol/l)	43 ± 12	84 ± 20
$V_{O_{2max}}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	37 ± 4	25 ± 2*
Body weight (kg)	69.6 ± 2.3	73.5 ± 6.6
BMI (kg/m^2)	23.4 ± 0.8	27.2 ± 1.8
Body fat (%)		
Bioelectric impedance	20.2 ± 2.4	32.6 ± 2.3*
Anthropometry	21.2 ± 2.9	31.8 ± 1.7*
Waist-to-hip ratio	0.85 ± 0.03	0.90 ± 0.08

Data are means ± SE. *$P < 0.05$ compared with the normal group, unpaired Student's *t* test.

thawed homogenate to final concentrations of 225 and 18.75 mmol/l, respectively. After centrifugation and DNase treatments (13), the pellet was resuspended in 5 ml of 34% sucrose and layered in a discontinuous sucrose gradient (45, 34, 32, 30, 27, and 12% sucrose solutions). The sucrose gradient was centrifuged at 69,000g_{max} for 16–18 h, and the 12–30% fractions were pooled, pelleted, then resuspended to 0.3–0.5 mg/ml protein, and an aliquot was removed for protein and enzyme analyses. Protein concentrations in the homogenate and plasma membrane fractions were determined by the Bradford method (47). The plasma membrane marker 5′-nucleotidase was measured in the homogenate and the plasma membrane fraction to determine purity and recovery of plasma membranes (48).

GLUT4 immunoblotting. To determine GLUT4 content, aliquots of homogenate protein (100 µg) and plasma membrane protein (10 µg) were separated using polyacrylamide minigels (SDS-PAGE). Proteins resolved by SDS-PAGE were transferred to nitrocellulose membranes using a wet transfer apparatus. For GLUT4, nonspecific antibody binding was reduced by blocking membranes with 5% albumin for 2 h at 37°C in a Tris-NaCl buffer (pH 7.8) containing 0.01% sodium azide (TNA). The membranes were incubated with α-GLUT4 (5 µg/ml) in TNA containing 5% albumin for 12–16 h at 4°C. α-GLUT4 is an affinity-purified polyclonal antibody produced from a synthetic peptide corresponding to a 15–amino acid COOH-terminal sequence in rat muscle GLUT4 (provided by Dr. R.J. Smith, Joslin Diabetes Center). The membranes were then washed twice for 10 min in TNA plus 0.05% Nonidet P-40 and once for 10 min in TNA plus 0.1% Tween 20. Antibody binding to the transfer membranes was visualized by incubation with ^{125}I-labeled protein A solution (0.2 µCi/ml) for 1 h at room temperature and washed as above. Quantification of specific protein bands was determined using a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).

Materials. Reagents for SDS-PAGE and protein assays were from Bio-Rad (Richmond, CA). DNase was purchase from Worthington (Freehold, NJ). ^{125}I–protein A was obtained from ICN (Costa Mesa, CA). Other chemicals and reagents were from Fisher (Lexington, MA) or Sigma (St. Louis, MO).

Statistical methods. Data are expressed as means ± SE for each group. Differences between rest and exercise values were determined with a two-tailed paired Student's t test for each group. Differences between the normal control subjects and those with type 2 diabetes were determined with a two-tailed unpaired Student's t test. $P < 0.05$ was considered statistically significant.

RESULTS

Subject characteristics. Subject characteristics are summarized in Table 1. Subjects with type 2 diabetes had higher fasting plasma glucose and HbA_{1c} concentrations, lower $V_{O_{2max}}$, and an increased percentage of body fat compared with normal control subjects.

Exercise data. Table 2 summarizes the data under which the two groups exercised. The duration of the exercise session and the relative level of exertion as a percentage of $V_{O_{2max}}$ were not significantly different between the normal and the type 2 diabetes groups. However, because the $V_{O_{2max}}$ of the normal subjects was significantly greater than that of the subjects with type 2 diabetes, the absolute work load and total amount of work performed during the exercise session by the normal subjects were significantly greater.

TABLE 2
Exercise session data

	Normal subjects	Type 2 diabetic subjects
Exercise (min)	54 ± 5	51 ± 3
Workload (W)	126 ± 27	61 ± 11*
Total work (W/session)	6,120 ± 931	3,020 ± 455*
% $V_{O_{2max}}$	66 ± 2	63 ± 2

Data are means ± SE. *P 0.05 compared with the normal group, unpaired Student's t test.

Plasma membrane preparations. Vastus lateralis muscle was obtained by open biopsy in the resting state and immediately after a single bout of cycle exercise. Characteristics of the muscle specimen, the homogenate, and the plasma membrane fraction are shown in Table 3. Muscle weight and total homogenate protein were similar among the normal and type 2 diabetes groups at rest and after exercise. To determine the plasma membrane purity and recovery in the plasma membranes fractionated from the muscle biopsy, we measured the activity of 5′-nucleotidase, an enzyme present predominantly in the surface membranes (48). The specific activity of 5′-nucleotidase in the homogenate and plasma membrane fractions was not significantly different among the groups or treatments, demonstrating that type 2 diabetes and/or exercise did not alter muscle 5′-nucleotidase activity or the purity of the fractionated plasma membranes. Approximately 9% of the plasma membrane marker was recovered from the muscle of the control subjects, while ~6% was recovered in the subjects with type 2 diabetes. This difference is due primarily to a greater plasma membrane protein recovered in the normal control subjects and is not a contributing factor when determining plasma membrane GLUT4 content within individuals at rest and after exercise. Overall, the plasma membrane fractions were purified by 30- to 40-fold over homogenate 5′-nucleotidase activity.

Effects of exercise on GLUT4 protein. To determine if GLUT4 translocates in response to an acute bout of exercise in normal control subjects and subjects with type 2 diabetes, plasma membranes purified from skeletal muscle obtained at rest and immediately after a single bout of exercise were immunoblotted for GLUT4 content. Figure 1 shows representative immunoblots from two normal individuals and two individuals with type 2 diabetes at rest and immediately after

TABLE 3
Muscle and plasma membrane characteristics

	Normal subjects		Type 2 diabetic subjects	
	Rest	Exercise	Rest	Exercise
Muscle weight (g)	1.04 ± 0.08	0.91 ± 0.07	1.19 ± 0.11	1.08 ± 0.05
Total protein (mg)				
Homogenate	134.7 ± 14.4	119.1 ± 4.5	124.7 ± 10.0	114.3 ± 6.1
Plasma membrane	0.40 ± 0.04	0.25 ± 0.04	0.20 ± 0.01	0.18 ± 0.01
5′-Nucleotidase activity (nmol · mg^{-1} · 2 h^{-1})				
Homogenate	57± 11	50 ± 12	59 ± 11	53 ± 10
Plasma membrane	1,670 ± 294	1,933 ± 182	1,915 ± 232	2,030 ± 156
5′-Nucleotidase recovery (%)				
Plasma membrane	8.9 ± 1.1	8.9 ± 1.3	5.5 ± 0.6	6.4 ± 0.6

Data are means ± SE. n = 5.

exercise. Figure 2 (two left bars) represents the relative abundance of plasma membrane GLUT4 in the five normal subjects expressed in arbitrary units. All normal subjects increased plasma membrane GLUT4 content in response to exercise, and the mean plasma membrane GLUT4 content was significantly greater after exercise than at rest ($P < 0.05$). Figure 2 also demonstrates that plasma membrane GLUT4 content in the muscle of all five subjects with type 2 diabetes increased after exercise. There was a significant increase in the mean plasma membrane GLUT4 content in skeletal muscle from subjects with type 2 diabetes after exercise ($P < 0.05$). Although plasma membrane GLUT4 content was ~31 and 33% lower at rest and after exercise, respectively, in the muscle of the subjects with type 2 diabetes compared with the normal subjects, the differences were not statistically significant. When the data from Fig. 2 were expressed as the percent increase in plasma membrane GLUT4 above the resting value, an acute bout of exercise increased GLUT4 translocation to the plasma membrane to the same relative extent in subjects with type 2 diabetes and in normal control subjects (74 ± 20 vs. 71 ± 18%, respectively).

To determine whether total muscle GLUT4 is different in subjects with type 2 diabetes compared with control subjects or is altered by an acute bout of exercise, the whole muscle homogenate was immunoblotted for GLUT4 content. No significant differences were observed in total homogenate GLUT4 content between the normal subjects and the subjects with type 2 diabetes. In addition, acute exercise had no effect on total homogenate GLUT4 content in either group. Total homogenate GLUT4 protein was 9.1 ± 2.3 and 9.0 ± 2.3 arbitrary units for normal control subjects at rest and after exercise, and 10.6 ± 1.2 and 9.5 ± 1.1 arbitrary units for subjects with type 2 diabetes at rest and after exercise, respectively.

Among the normal subjects, the amount of GLUT4 translocated with exercise correlated with the total amount of work performed during the exercise session, (i.e., workload in watts multiplied by the duration of exercise session, $r^2 = 0.82$, $P < 0.05$). In contrast, in the subjects with type 2 diabetes there was no significant correlation between the total amount of work performed and the amount of GLUT4 translocated. We also observed a negative correlation between BMI and resting plasma membrane GLUT4 content ($r^2 = 0.41$, $P < 0.05$) when all subjects were analyzed as a single group.

DISCUSSION

These data are the first to demonstrate that plasma membrane GLUT4 is increased in skeletal muscle from individuals with type 2 diabetes in response to an acute bout of exercise. The ability of exercise to cause GLUT4 translocation is in contrast to studies demonstrating the inability of insulin to stimulate GLUT4 translocation in individuals with type 2 diabetes (42–44). The translocation of skeletal muscle GLUT4 with moderate exercise, but not insulin, in type 2 diabetes is consistent with studies showing normal glucose uptake in skeletal muscle of individuals with type 2 diabetes after exercise (24,25). These human studies are also in agreement with data obtained from the insulin-resistant Zucker (*fa/fa*) rat, which demonstrated that exercise stimulation, but not insulin stimulation, causes a normal translocation of GLUT4 to the plasma membrane (34,36).

Our data are consistent with previous work that has demonstrated that total muscle GLUT4 is not different between normal subjects and individuals with type 2 diabetes (26–28). Although we saw a trend for the subjects with type 2 diabetes to have a lower plasma membrane GLUT4 content at rest and after exercise than control subjects, no significant differences were observed. Lower resting plasma membrane GLUT4 content in insulin-resistant subjects has been observed in some studies (44,49), but not in others (42,43). In vitro experiments have also reported that skeletal muscle from subjects with type 2 diabetes is characterized by diminished basal glucose uptake (4). In this study, we observed that BMI was negatively correlated with resting plasma membrane GLUT4 content ($r^2 = 0.41$, $P < 0.05$) when all subjects were analyzed as a single group, suggesting that lower resting plasma membrane GLUT4 may be a function of adiposity. Even though the subjects with type 2 diabetes in our study had significantly higher body fat content and a lower $V\text{O}_{2max}$ than their normal counterparts, exercise increased the GLUT4 content of the plasma membrane to the same degree (~70% above resting levels) as it did in the leaner fitter control subjects.

We chose a physiologic exercise stimulus of 60–70% of the subjects $V\text{O}_{2max}$ for a duration of 45–60 min to determine whether moderate-intensity cycle ergometry exercise can induce a significant translocation of GLUT4 to the plasma membrane of normal control subjects or those with type 2 diabetes. A positive correlation between the total work per-

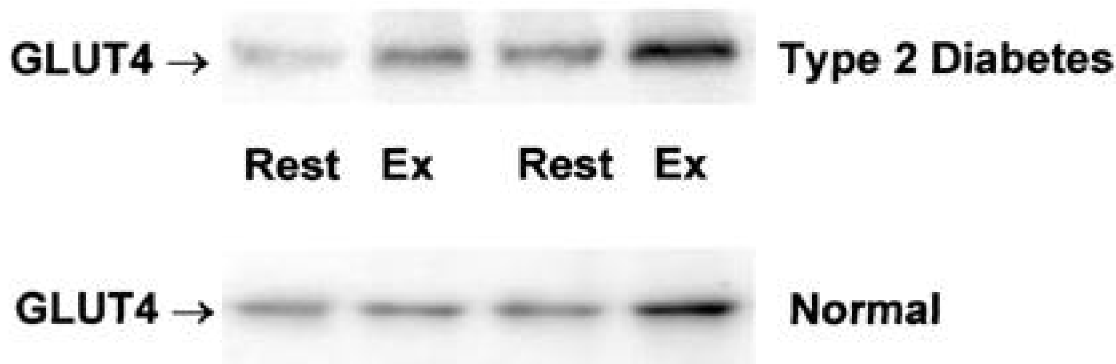

FIG. 1. GLUT4 protein content in plasma membranes isolated from skeletal muscle of subjects with type 2 diabetes and normal control subjects. The image shows immunoreactive GLUT4 from two subjects with type 2 diabetes and two normal control subjects studied in the resting state and after an acute bout of cycle exercise (Ex). Plasma membranes were fractionated and immunoblotted for GLUT4 protein as described in METHODS.

formed and amount of GLUT4 translocated was noted in the normal subjects (r^2 = 0.82, P < 0.05). We were unable to detect a similar trend in the group with type 2 diabetes. This may be explained by the difference in total work performed by the normal control subjects and those with type 2 diabetes. Although there was no significant difference with respect to exercise intensity (i.e., percentage of the subjects' Vo_{2max}) and the duration of the exercise session between the groups, the total amount of absolute work performed during the exercise session by the type 2 diabetic group was significantly lower. Subjects with type 2 diabetes had significantly lower Vo_{2max} values, thus these subjects also cycled at a lower absolute workload during the exercise session. In addition, the subjects with type 2 diabetes had a smaller range of workloads, making any significant correlation difficult to establish with only five subjects in the group. The correlation in normal subjects suggests that human skeletal muscle has the ability to respond in a graded fashion to varying workloads and matches GLUT4 translocation to the physiologic needs of the muscle for glucose uptake.

The relatively normal translocation of skeletal muscle GLUT4 with moderate exercise, in contrast with impaired responses to insulin, in type 2 diabetes is consistent with the hypothesis that exercise and insulin signal GLUT4 translocation by separate and unique cellular mechanisms (40). Alterations in insulin signaling may be responsible for the defect in insulin-stimulated GLUT4 translocation in muscle of individuals with type 2 diabetes. Decreased glucose transport and GLUT4 translocation in muscle strips from subjects with type 2 diabetes incubated in vitro have been associated with decreased insulin-stimulated IRS-1 tyrosine phosphorylation and PI 3-kinase and AKT kinase activity (37,38). In contrast, exercise does not phosphorylate the insulin receptor or IRS-1, nor does it activate PI 3-kinase (50,51) or AKT (52,53). Therefore, exercise must activate GLUT4 translocation by an insulin-independent pathway. One possible candidate for a regulatory signal that may mediate exercise-stimulated glucose uptake is the 5′ AMP-activated protein kinase (AMPK) (54,55). A recent study by our laboratory (55) demonstrated that contraction of rat skeletal muscle in vitro activates AMPK activity and that pharmacologic activation of this kinase, similar to contraction, increases glucose transport by an insulin-independent and wortmanin-insensitive mechanism (55). This study supports the hypothesis that AMPK is a signaling intermediary for contraction-stimulated glucose uptake in skeletal muscle. Future studies are required to establish whether this hypothesis will hold up in human muscle.

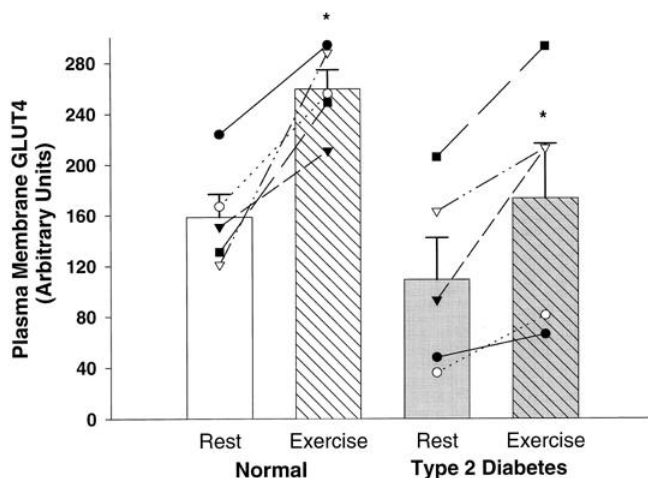

FIG. 2. Quantitation of skeletal muscle plasma membrane GLUT4 protein from subjects with type 2 diabetes and normal control subjects studied in the resting state and after an acute bout of cycle exercise. Immunoreactive GLUT4 was quantitated using a PhosphorImager, and the data are expressed as GLUT4 in arbitrary units. Plasma membrane GLUT4 protein in the resting state and after an acute bout of cycle exercise are shown for each subject (symbols connected by lines); the means ± SE for each group and treatment are shown as bars. Skeletal muscle plasma membrane GLUT4 increased with exercise in all individual subjects. After exercise, plasma membrane GLUT4 significantly increased in both the type 2 diabetes group and the normal control group (*P < 0.05 vs. resting state). Statistically significant differences were not detected in plasma membrane GLUT4 at rest or after exercise between the type 2 diabetic and normal groups (n = 5 per group).

The results of the current study show that normal glucose utilization in insulin-resistant muscle of subjects with type 2 diabetes after acute exercise is due, at least in part, to the translocation of GLUT4 to the plasma membrane. Whether an exercise signaling pathway interacts with the insulin signaling pathway to enhance glucose transport and improve insulin sensitivity is a major focus of ongoing research. Various therapies for individuals with type 2 diabetes, including exercise training, lead to an improvement in glucose utilization; whether these treatments act by restoring translocation of GLUT4 to the plasma membrane after insulin stimulation is also unknown. Elucidation of the exercise and insulin signaling pathways that regulate the glucose transport system in normal muscle and in muscle from individuals with type 2 diabetes is critical if we are to fully understand the pathophysiology of insulin resistance in skeletal muscle.

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