Glucose transporter content and enzymes of metabolism in nerve-repair grafted muscle of aging Fischer 344 rats

LISA LARKIN,1 ERIC R. LEIENDECKER,1 MARK SUPIANO,1,2,3 AND JEFFREY HALTER1,2,3
1 Division of Geriatric Medicine, Department of Internal Medicine, and 2 Institute of Gerontology, University of Michigan; and 3 Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs Medical Center, Ann Arbor, Michigan 48109

Larkin, Lisa, Eric R. Leiendecker, Mark Supiano, and Jeffrey Halter. Glucose transporter content and enzymes of metabolism in nerve-repair grafted muscle of aging Fischer 344 rats. J. Appl. Physiol. 83(5): 1623–1629, 1997.—Aging and grafting are associated with decreased ability of muscle to sustain power, likely reflecting diminished fuel availability. To assess mechanisms that may contribute to availability of glucose, we studied GLUT-1 and GLUT-4 protein as well as mRNA contents and enzymes of glucose metabolism in grafted and control medial gastrocnemius (MG) muscles of 6-, 12-, and 24-mo-old male Fischer 344 rats. There was no effect of age or grafting on MG GLUT-4 content. There was both an age- and graft-associated increase in GLUT-1 content (P = 0.0044 and 0.0063, respectively). There was no effect of aging or grafting on hexokinase and phosphofructokinase activity or on protein and glycogen content. Muscle mass and citrate synthase activity were significantly diminished with grafting. Citrate synthase activity was significantly greater in the 12-mo-old compared with the 6- and 24-mo-old animals. Grafting in combination with aging had no impact on any of the parameters measured. We conclude that diminished glucose transporter expression cannot explain the decreased ability of aged muscle to sustain power. In addition, we conclude that the diminished ability of the grafted MG muscle to sustain power may be explained, in part, by a decrease in energy available from oxidative metabolism.

glucose transporter protein; messenger ribonuclease content; muscle regeneration

AGING AND NERVE-REPAIR muscle grafting are associated with a decrease in the ability of skeletal muscle to sustain power during repetitive stimulation (21). One potential explanation for this decrease in the ability of the muscle to function during a bout of endurance exercise is alterations in glucose delivery to the muscle. Glucose enters skeletal muscle via a facilitated transport system involving two isoforms of glucose transporters: GLUT-1, which is responsible for uptake during basal conditions (16, 28), and GLUT-4, which is responsible for insulin- and contraction-stimulated glucose uptake (6, 23). Decreased expression of either isoform of glucose transporter may lead to diminished fuel availability to muscle during endurance exercise. In addition, alterations in the metabolic integrity of the grafts, such as decreased glycogen or decreased oxidative capacity, may contribute to the inability of the grafted muscle to sustain power, and aging may be associated with further decreases in metabolic capacity.

Denervation is associated with elevated basal glucose transport (5, 11) and diminished insulin-stimulated glucose transport (5, 11). In accordance, denervation is associated with altered expression of skeletal muscle glucose transporter protein isoforms: upregulation of GLUT-1 protein and mRNA content (3, 5, 11) and downregulation of GLUT-4 protein and mRNA content (3, 5, 11). To date, no studies have examined the effect of reinnervation after a nerve-repair grafting procedure on glucose transporter content. It is possible that continued alteration in the expression of glucose transporters may lead to diminished fuel availability during a bout of endurance exercise.

The effect of age on GLUT-4 expression has been studied in humans and in several rat models. In the female Fischer 344 (F-344) rat, there is no significant age-associated decline in GLUT-4 protein content (2), and in the female Long-Evans rat there is no age-associated decline in glucose uptake or GLUT-4 protein content (10). In contrast, in male F-344 control (nonexercised) rats, Kern et al. (15) have shown a trend toward an age-associated decline in GLUT-4 content in gastrocnemius and extensor digitorum longus muscles. A recent study in aging humans suggests an age-associated decline in GLUT-4 content in the vastus lateralis but not in the gastrocnemius muscle in both men and women (14). In a study of male F-344 × Brown Norway F1 hybrid rats (F-334 × BN), ages 9, 20, and 31 mo, there was no age-associated alteration in GLUT-1 expression in the soleus and epitrochlearis muscles (4). Several studies have shown an age-associated increase in the number of denervated skeletal muscle fibers (1, 17). Therefore, an alteration in the content of glucose transporters caused by an increase in the number of denervated muscle fibers may play a role in the decreased ability of senescent muscle to function during a bout of endurance exercise.

Like disuse atrophy, denervation in skeletal muscle is associated with a shift to a more glycolytic metabolism in which glycogen stores are utilized as the major fuel for energy (24). Aging is also associated with a shift to a more glycolytic metabolism, as indicated by an age-related decline in skeletal muscle citrate synthase, an indicator of the oxidative capacity, with no age-associated alteration in glycogen content (20); in hexokinase, the key enzyme in the conversion of cellular free glucose to glucose 6-phosphate (13); or in phosphofructokinase, the key enzyme in glycolysis (13). It is possible that the diminished ability of both grafted and senescent muscle to perform a bout of endurance exercise may be explained by a decrease in oxidative capacity of the muscle.

In this study, we investigated the effect of age and nerve-repair grafting on GLUT-4 and GLUT-1 protein

http://www.jap.org

1623

Downloaded from http://jap.physiology.org/ by 10.220.33.1 on June 12, 2017
and mRNA content. We tested the hypothesis that the medial gastrocnemius (MG) muscle of senescent male F-344 rats would have a metabolic profile similar to denervated muscle. Thus, with age, GLUT-1 protein and mRNA content would be upregulated and GLUT-4 protein and mRNA content would be downregulated. In addition, we tested the hypothesis that, in senescent muscle, the shifts in glucose transporter protein and mRNA content would be exacerbated by a nerve-repair grafting procedure. We also tested the hypothesis that aging and nerve-repair grafting of MG would be associated with diminished glycogen stores and diminished activity of enzymes of both glycolysis and the tricarboxylic acid cycle.

**METHODS**

Animal model and animal care. Studies were carried out in male F-344 rats obtained from the National Institute on Aging's animal colony maintained by Harlan Sprague-Dawley Laboratory (Indianapolis, IN). Thirty rats underwent a nerve-repair grafting procedure of the MG muscle at ages 2, 8, and 20 mo (10 from each age group). Either the right or left MG was randomly selected. All grafted animals were allowed to recover for 120 days before measurements were made of GLUT-4 and GLUT-1 protein and of mRNA content. All rats were acclimated to our colony conditions, i.e., light cycle and temperature, for 1 wk before the grafting procedure. Rats were housed individually in hanging plastic cages (28 cm × 30 cm × 19 cm) and kept on a 12:12 h light-dark cycle at a temperature of 20–22°C. The rats were fed Purina rodent chow 5001, laboratory chow, and water ad libitum. All surgical procedures were performed in an aseptic environment, with animals in a deep plane of anesthesia induced by injections of pentobarbital sodium (65 mg/kg body weight ip). Supplemental doses of pentobarbital sodium were administered as required to maintain an adequate depth of anesthesia.

All animal care and animal surgery were in accordance with the NIH Guide for Care and Use of Laboratory Animals (DHEW Publication No. 85–23). The experimental protocol was approved by the University Committee for the Use and Care of Animals. Although necropsy and microbiological examinations were not performed routinely, animals were inspected daily for external signs of disease. Only rats with no external signs of disease were used in this study.

MG neurovascular grafting procedure. Orthotopic neurovascular grafts of the MG muscle were performed as previously described by Miller et al. (26). Briefly, the left or right MG was isolated from surrounding muscle and connective tissue, the distal and proximal tendons were severed, and the muscle was removed from its bed. The muscle was then placed back into its original position, and the tendons were repaired by using 8-0 nylon sutures. The branch of the tibial nerve innervating the MG was isolated, severed, and then repaired by using epineurial sutures of 11-0 nylon. Care was taken to leave the blood supply intact. The incision was closed in layers by using 4-0 nylon sutures. The animals were allowed to recover for 120 days before measurements of contractile properties were made. Previous work has demonstrated that this recovery period is sufficient to allow stabilization of whole muscle maximal tetanic tension of neurovascular muscle grafts (9).

Analytic procedures. Control and grafted MG samples were analyzed for glycogen content (mmol/g muscle) via the method of Hassid and Abraham (12). Muscle homogenates (from a 700-g supernatant) were used to determine citrate synthase activity (µmol·µg protein−1·min−1) by using the method of Serre (30). Hexokinase activity (U/mg protein) was measured by using the method of Eysterby and Qadri (7). Phosphofructokinase activity (µmol·mg protein−1·min−1) was measured by using the method of Dansour et al. (22). Protein content (mg/g tissue) was determined by using a Bradford protein assay kit from Bio-Rad (Richmond, CA).

GLUT-1 and GLUT-4 Western blotting. Total membranes were isolated from 100 mg of frozen gastrocnemius muscle as follows. Frozen tissues (200 mg) were powdered in a mortar and pestle that were cooled in liquid N2. Powdered tissues were suspended in 5.0 ml of ice-cold SSS buffer (10 mM NaHCO3, 0.25 M sucrose, and 5.0 mM NaN3) and homogenized twice for 10 s by using a Brinkman polytron (setting 7). Homogenates were centrifuged at 1,200 g for 10 min at 4°C. Pellets were resuspended in 5 ml of ice-cold SSS buffer and centrifuged at 1,200 g for 10 min at 4°C. Supernatants were combined and centrifuged at 190,000 g for 66 min at 4°C. Pellets were then resuspended in 500 µl ice-cold SSS buffer and stored at −70°C.

Western analysis of GLUT-1 and GLUT-4 was performed by using vertical slab polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate (SDS) on molecular weight markers (Amersham, Arlington Heights, IL) and aliquots of muscle membrane proteins each containing 30 μg protein. An internal control sample was run on all gels; the sample consisted of an aliquot (30 mg protein) of a muscle membrane pool obtained from combined muscle homogenates. Duplicate samples from each animal were separated on a 10% polyacrylamide resolving gel and then eletrophoretically transferred onto Immobilon polyvinylidifluoride membrane (Millipore, Milford, MA). Immobilon polyvinylidifluoride membranes were then blocked for 60 min with tris(hydroxymethyl)aminomethane-buffered saline with Tween-20 (100 mM tris(hydroxymethyl)aminomethane, 0.9% NaCl, 2.0 ml Tween-20, pH 7.5) and 5% Carnation nonfat dry milk. Immunoblotting was performed by using a rabbit polyclonal antibody against rat brain GLUT-1 or insulin-regulatable GLUT-4 protein (East Acres Biologicals, Southbridge, MA), followed by 125I-labeled anti-rabbit immunoglobulin G (Amersham) and exposure of the transfer membrane to Kodak X-OMAT film at −80°C for 24 h. 125I-labeled transfer membranes were then cut and counted on a gamma counter (Tm Analytic, Elk Village, IL). Total counts per minute were corrected for background, and then specific counts were normalized for the internal standard. There was a single band for both GLUT-1 and GLUT-4 protein at a molecular mass of 45 kDa.

GLUT-1 and GLUT-4 Northern blotting. RNA was isolated from 100 mg of frozen gastrocnemius muscle by using TRI reagent, a single-step method of RNA isolation by using acid guanidinium thiocyanate-phenol-chloroform extraction (Molecular Research Center, Cincinnati, OH). Then 10 µg per lane of RNA were electrophoresed in 1% formaldehydeagarose gels and transferred onto nylon Biotrans membranes (Boehringer Mannheim, Indianapolis, IN). Quality of RNA was confirmed by staining with methylene blue. RNA was fixed to the membrane by baking the membrane in a vacuum oven for 2 h at 80°C. GLUT-1 cDNA was obtained from Dr. Frank C. Brosius, and GLUT-4 cDNA was obtained from Dr. Jessica Schwartz, both at the University of Michigan, Ann Arbor, MI. Both cDNAs were used to synthesize a cRNA probe with the use of T7 polymerase and the Genius 4 RNA-labeling kit as described by the manufacturer (Boehringer Mannheim). Hybridization of the cRNA probe was carried out at 65°C in a hybridization solution consisting of 50% formamide, 5× saline sodium citrate (SSC), 0.2% SDS, 0.1% N-lauroysar-
cosine, and 2% blocking reagent (Genius System, Boehringer Mannheim). Membranes were washed twice for 15 min in 2× SSC, 0.1% SDS at 65°C and twice for 15 min in 0.5× SSC, 0.1% SDS at 65°C. Detection of digoxigenin-labeled GLUT-1 and GLUT-4 mRNA was performed by using the chemiluminescent substrate Lumi-Phos 530, Genius System (Boehringer Mannheim) and exposing the membrane to Kodak X-OMAT film at 25°C for 1.5 h. The abundance of GLUT-1 and GLUT-4 mRNA signal was determined by using a densitometer. Each membrane consisted of duplicate samples from one animal from each age group randomly loaded into inner lanes and duplicate samples of a control sample loaded into the two outside lanes. The average signal for each animal was corrected for the average control signal on the membrane. The signal was then expressed as a percentage of the 6-mo-old age group.

Statistics. Values are presented as means ± SE. Statistical analysis was performed by using Statview 4.01 (Abacus Concepts, Berkeley, CA). An analysis of variance was used to compare differences between rats at various ages and grafted groups. When a significant main effect was found, the Fisher’s least-significant difference post hoc test was used to determine differences between the age and grafted groups. Differences were considered significant at \( P < 0.05 \).

RESULTS

Metabolic characteristics. There was a significant age-associated increase in the body weights of the 12- and 24-mo-old rats compared with the 6-mo-old animals (\( P = 0.0001 \); Table 1). There was no age- or graft-associated effect on hexokinase (U/mg protein) and phosphofructokinase (\( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{mg protein}^{-1} \)) activity or protein (mg protein/g tissue) and glycogen (\( \mu \text{mol/g muscle} \)) content (Table 1). Muscle mass (g) and citrate synthase activity (\( \mu \text{mol} \cdot \text{mg protein}^{-1} \cdot \text{min}^{-1} \)) were both significantly lower in the grafted muscles (\( P = 0.0162 \) and \( P = 0.0004 \), respectively; Table 1). There was also a significant effect of age on muscle mass and citrate synthase activity (\( P = 0.0036 \) and \( P = 0.001 \), respectively). However, the age effect on citrate synthase activity was complex; it was significantly greater in the 12-mo-old compared with the 6- and 24-mo-old animals. There was no significant interaction of grafting with aging on any of the parameters measured. Thus the effect of grafting was not greater in older compared with younger animals.

GLUT-4 protein and mRNA content. There was no significant age- or graft-associated effect on GLUT-4 protein content (Fig. 1). After the grafting procedure, there was no change in GLUT-4 protein content in senescent grafted muscle compared with younger grafted muscles. There tended to be an age-associated decline in GLUT-4 mRNA content of control muscle (Fig. 2). However, this did not reach statistical significance. Similarly, there was a trend toward a graft-associated decline in GLUT-4 mRNA content in the 6- and 24-mo-old animals, but overall this effect was not significant. After the grafting procedure, there was no greater decrease in GLUT-4 mRNA content in senescent grafted muscle compared with younger grafted muscles.

GLUT-1 protein and mRNA content. There was both a significant age- and graft-associated increase in GLUT-1 protein content (Fig. 3). After the grafting procedure, there was no greater increase in GLUT-1 protein content in senescent grafted muscle compared with younger grafted muscles. There tended to be an age-associated increase in GLUT-1 mRNA content of control muscle (Fig. 4). However, this did not reach statistical significance. There was a significant graft-associated increase in GLUT-1 mRNA content. After the grafting procedure, there was no greater increase in GLUT-1 mRNA content in senescent grafted muscle compared with younger grafted muscles.

DISCUSSION

Previous studies (3, 5, 11) have shown that after denervation of muscle, GLUT-1 protein content is increased and GLUT-4 protein content is decreased. The present study extends these previous observations by showing that 120 days after a nerve-repair graft in MG

| Table 1. Metabolic characteristics of nerve-repair grafted and control medial gastrocnemius muscle in 6-, 12-, and 24-mo-old male Fischer rats |
|----------------------|----------------------|----------------------|----------------------|----------------------|
|                      | 6 mo                 | 12 mo                | 24 mo                |
|                      | Control Graft        | Control Graft        | Control Graft        | Effect of Grafting   |
|                      |                      |                      |                      | Effect of Age        |
|                      |                      |                      |                      | Age × Grafting       |
| Body weight, g       | 351 ± 6              | 426 ± 7              | 416 ± 8              | 0.0001               |
| Muscle mass, mg      | 715 ± 36             | 659 ± 21             | 712 ± 18             | 631 ± 18†            |
| Protein content, mg  | 213 ± 11             | 220 ± 11             | 230 ± 23             | 254 ± 8              |
|                    | (10)                 | (9)                  | (7)                  | (7)                  |
| Hexokinase, units/mg | 25.4 ± 5.5           | 30.3 ± 1.2           | 30.9 ± 1.8           | 35.1 ± 2.8           |
|                    | (6)                  | (9)                  | (7)                  | (6)                  |
| Phosphofructokinase, | 1.70 ± 0.04          | 1.65 ± 0.04          | 1.65 ± 0.04          | 1.54 ± 0.15          |
|                      | (6)                  | (8)                  | (7)                  | (6)                  |
| Citrate synthase,    | 176 ± 14             | 211 ± 5             | 182 ± 13*            | 166 ± 11†            |
|                      | (6)                  | (8)                  | (7)                  | (7)                  |
| Glycogen, \( \mu \text{mol/g muscle} \) | 36.1 ± 1.8           | 34.2 ± 2.9           | 34.5 ± 4.2           | 0.9288               |

Values are means ± SE. Nos. in parentheses, no. of rats. *Significantly different from 6-mo-old group. †Significantly different from 12-mo-old group.
muscle, as in acute denervation, both GLUT-1 protein and mRNA content are significantly increased. However, unlike the case in denervation, GLUT-4 content and mRNA content were not significantly altered in stabilized nerve-repair graft MG muscles. In addition, the present study shows that in the MG muscle GLUT-1 protein content increased, whereas GLUT-4 protein content remained unchanged, with increasing age. The mRNA contents of the two glucose transporters followed the same trends as the respective protein contents. There was an age- and graft-associated decline in citrate synthase activity that suggests diminished oxidative capacity of these muscles. In addition, there was no age- or graft-associated alteration in glycogen content, hexokinase, or phosphofructokinase activity. This result suggests there is no alteration in the glycolytic capacity of these muscles. Grafting in combination with aging had no further impact on any of the parameters measured.

Previous studies from our laboratory (19) have shown that, at 120 days after nerve-repair grafting, muscle contractile function has stabilized but has not returned to control values. The ability of the stabilized graft muscle to perform an endurance exercise protocol in
It is possible that altered glucose transporter expression could diminish fuel available to working muscle and, thereby, decrease the ability to perform an endurance-exercise protocol. In the present study, GLUT-4 protein, which is responsible for insulin- and contraction-stimulated glucose uptake (6, 23), is not diminished in nerve-repair grafted compared with control muscle. Therefore, it is not likely that decreased expression of GLUT-4 plays a role in the diminished ability of the MG to perform endurance exercise. In fact, data from a study in humans (25) showed that the increase in skeletal muscle GLUT-4 protein content observed with endurance training is associated with diminished exercise-stimulated glucose uptake, suggesting that glucose disposal may be inversely related to GLUT-4 protein content in some metabolic conditions. Although the content of GLUT-4 is correlated with the uptake of glucose into skeletal muscle during contractions, the translocation of the glucose transporter to the plasma membrane from intracellular pools and the intrinsic activity of the transporter once docked at the plasma membrane are also factors influencing the uptake of glucose into working muscle and must be investigated in future studies.

The observed increase in GLUT-1 content in the senescent and grafted muscle is compatible with the altered expression of glucose transporter isoforms observed in populations of denervated fibers. Block et al. (3) first noted that denervation was associated with reexpression of neonatal isoforms of glucose transporters. In the fetus, GLUT-1 is the primary isoform of glucose transporter in skeletal muscle, whereas GLUT-4 protein content is undetectable (29). At birth, GLUT-1 protein content diminishes and GLUT-4 protein content increases, both reaching adult levels at ~10 days of age (29). Several studies (3, 5, 11) have demonstrated that, at 3 days postdenervation in skeletal muscle, GLUT-1 protein and mRNA content are increased while GLUT-4 protein and mRNA content are diminished. The increased GLUT-1 protein content may improve the ability to recover after an injury by increasing basal glucose transport and by increasing available energy for tissue repair. Ren et al. (28) have demonstrated that overexpression of the GLUT-1 isoform is associated with a 10-fold increase in glycolgen concentration in the skeletal muscle that was not caused either by an increase in glycolgen synthase activity or by a decrease in glycolgen phosphorylase activity.

This being the case, the increase in GLUT-1 content in the MG muscle of grafted and aged animals could enhance glycolgen storage and increase substrate available for use during an endurance exercise bout. However, we observed no significant increase in glycolgen content in the grafted compared with control muscle. The increases in GLUT-1 protein content that we observed, ranging from 43 to 16% (6 and 24 mo, respectively), are substantially less than the changes seen by Ren et al. (28) in transgenic mice and therefore may not have been enough to enhance the storage of glycolgen. Furthermore, because limited tissue was available for study, we were unable to investigate the specific location (perineural vs. muscle plasma membrane) of the increased GLUT-1 protein. Thus it is possible that the increase was in neural rather than muscle tissue with negligible effect on muscle metabolism. Further studies need to be done to investigate this possibility.

A previous study (4) in male F-344 × BN rats reported no age-associated alteration in GLUT-1 expression in either the soleus or the epitrochlearis muscle. In contrast, in the present study, we observed an age-associated increase in GLUT-1 protein content in the MG muscle of male F-344 rats. The discrepancy between these two studies may possibly be explained by the different muscles, the age of the rats, and/or the strain of rats studied. In the F-344 × BN study, there was a tendency for increased GLUT-1 content in the epitrochlearis muscle, which is similar to the MG in fiber type; in the 9-mo-old compared with the 20-mo-old rats; and in the decline to 9-mo-old values in the 31-mo-old animals. The median life span for the F-344 × BN rat is 28 mo and for the F-344 rat is 24 mo. It is possible that GLUT-1 content in muscles with predominantly type IIb fibers (epitrochlearis and MG) is increased with age until the median life span is reached and that there is then an age-associated decline in GLUT-1 content concomitant with the age-associated decline in muscle weight.

Previous studies have shown that the recovery of muscle functionality in grafted muscle is associated with the degree of reinnervation and revascularization of the muscle after the grafting procedure. In our model, incomplete revascularization cannot explain the diminished endurance capacity in the grafted MG muscle because the vasculature was left intact during the surgical procedure. On the other hand, the nerve to the MG muscle was severed and repaired during the grafting procedure, so incomplete reinnervation could be a contributing factor. One study has shown that disuse of skeletal muscle due to denervation leads to a decrease in the oxidative capacity of skeletal muscle (27). We found that citrate synthase activity, an indicator of oxidative capacity in skeletal muscle, was lower in the grafted compared with control muscle. Therefore, the diminished ability of the grafted muscle to perform an endurance-exercise bout may be caused in part by incomplete reinnervation of the MG muscle, thus leading to disuse and subsequent decreased activity of enzymes associated with oxidative metabolism. Further studies are needed to determine the completeness of the reinnervation of grafted MG muscles and to test this hypothesis.

In physiological conditions in which low oxidative capacity exists, such as disuse atrophy after denervation, skeletal muscle will shift to a more glycolytic metabolism and utilize glycolgen stores as the major fuel for energy (24). With recovery from denervation, oxidative enzymes increase and the muscle shifts back to a more oxidative energy metabolism. In the present study, GLUT-4 protein content and hexokinase activity did not significantly differ in grafted compared with...
control muscle. This result suggests that the capacity for glucose uptake into the muscle cell is unchanged. In addition, the activity of phosphofructokinase, the key regulatory enzyme for glycolysis, was unchanged after the grafting procedure, suggesting no impairment in the glycolytic pathway. In contrast, citrate synthase, an indicator of oxidative capacity, was diminished in the grafted compared with control muscle. It is possible that the stabilized grafted MG muscle has shifted toward glycolytic metabolism and could be relying on glycolytic metabolism because there was a significant decrease in the ability to spare glycogen. Lactate reached twofold higher levels, and glycogen fell significantly with increasing age in both slow-oxidative and fast-glycolytic muscles. Phosphofructokinase (the key enzyme in the conversion of cellular free glucose to glucose 6-phosphate, remains unchanged with age in both slow-oxidative and fast-glycolytic muscles). Phosphofructokinase (the key enzyme in glycolysis) has been shown to remain unchanged in slow-oxidative and to decrease in fast-glycolytic muscles of old (28-mo-old) rats (13). Citrate synthase, an indicator of oxidative capacity of muscle, has been shown to decrease with increasing age in gastrocnemius muscle of male F-344 rats (20). It is possible that, like denervated skeletal muscle, aging muscles metabolize carbohydrate via glycolytic rather than oxidative pathways to a greater degree than do younger muscles.

In conclusion, we have shown that a 120-day recovery period after a nerve-repair grafting procedure is associated with both continued upregulation of both GLUT-1 protein and mRNA content and with no alteration in the expression of GLUT-4 content and mRNA. In addition, aging is associated with a glucose transporter profile similar to that of denervated muscle, in that GLUT-1 protein content increased with increasing age. However, unlike the case with denervation, GLUT-4 protein content remained unchanged with increasing age. Aging is not associated with a decreased ability to express glucose transporters after a nerve-repair grafting procedure because there was no further impact on either GLUT-1 or GLUT-4 protein or mRNA contents. Furthermore, the decreased ability of grafted and senescent muscle to function during a bout of endurance exercise may not be explained by a decrease in GLUT-4 protein content. Finally, we conclude that the diminished ability of the aged and grafted MG muscle to sustain power may be explained, in part, by a decrease in energy available from oxidative metabolism.

This research was supported in part by National Institute on Aging Training Grant T32-AG-00114; the Core Facility for Aged Rodents of the Claude Pepper Older Americans Independence Center at the University of Michigan (AG-08808); National Institute on Aging Grant K01-AG-00710; the Medical Research Service of the Department of Veterans Affairs; and the Geriatric Research, Education, and Clinical Center, Ann Arbor Veterans Affairs Medical Center. Address for reprint requests: L. M. Larkin, Geriatrics Center, MSRB3, 6301, 1150 West Medical Center Dr., Univ. of Michigan, Ann Arbor, MI 48109-0642.

Received 4 April 1997; accepted in final form 8 July 1997.

REFERENCES


