Persistence of Glucose Metabolism After Exercise in Trained and Untrained Soleus Muscle

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We tested the hypothesis that increments in glucose metabolism in muscles from trained animals are caused by training adaptations in skeletal muscle and not by the residual effects of the last training session. The effects of a single bout of exercise on glucose metabolism (glycolysis and glycogenesis) were compared, against appropriate controls, in untrained (experiment 1) and trained (experiment 2) rat soleus muscles immediately (t = 0) and 3, 6, 24, 48, and 96 h after a standardized bout of exercise. [^{3}H]Glucose incorporation into glycogen and glycolysis was measured in vitro in the absence and presence of insulin (0.1 and 10 nM). Experiment 1: A single bout of exercise provoked an increase in glycogenesis in the exercised, untrained muscles compared with the nonexercised, untrained muscles (0–96 h; P = 0.006). Glycolysis was not altered (0–96 h; $P > 0.05$). Experiment 2: In the exercised trained soleus, rates of glycolysis were greater than in the exercised, untrained soleus, at insulin concentrations of 0.1 nM (0–96 h; P = 0.005) and 10 nM (0–96 h; P = 0.01), but not in the absence of insulin (0–96 h; $P > 0.05$). No differences were observed in the rates of glycogenesis (0–96 h; $P > 0.05$). Therefore, acute exercise provokes increments in glycogenesis, whereas training increases glycolysis, in the presence of insulin, for some time after exercise. We speculate that insulin-dependent increments in glycolysis in trained muscles are a consequence of increased glucose transport caused by a greater pool of insulin-translocatable, intracellular glucose transporters.

It is well known that glucose uptake and metabolism in skeletal muscle are increased after acute exercise (1–6). Garretto et al. (7) have shown that the postexercise increase in glucose uptake occurs in two phases. The first phase, immediately after exercise, is an insulin-independent phase, and the second phase is an insulin-dependent phase that occurs 2.5 h after exercise when glycogen levels have been restored. However, exercise-induced increments in glucose transport may persist as long as 18 h after exercise in carbohydrate-deprived rat muscle (8). In humans, an increased disposal of glucose to glycogen remains well above the preexercise rates as long as 12–16 h after exercise (9,10). These studies suggest that exercise-induced increments in glucose utilization can persist for almost a full day.

Chronic exercise (training) also increases glucose transport and metabolism in rodent muscles (11–13). But, it is widely believed that training-induced improvements in glucose metabolism are lost within 2 days of ceasing training (14,15), and that training-induced increments in glucose metabolism reflect the persistent effects of the last exercise bout, and not training adaptations in glucose metabolism in trained animals (16). However, several studies (3,13,17,18) suggest that, in the presence of insulin, trained muscles have an increased capacity to metabolize glucose, which may not simply be a residual effect from the last exercise bout. Indeed, studies by Rodnick et al. (19) show an increase in glucose transporters in adipocytes from trained animals. This is compelling evidence to suggest that if similar effects occur in muscle, then glucose metabolism may well be increased in response to training rather than being simply a residual effect remaining from the last exercise bout, as has been suggested by others (16). Furthermore, the increase in low-density microsomal glucose transporters in adipocytes from trained animals (19) suggests that, if training-induced changes in glucose metabolism are present, they may well be more easily observable in the presence of insulin, which can translocate these transporters from the low-density microsomal compartment to the plasma membrane in skeletal muscles (20–22).

To determine whether glucose metabolism is increased in trained skeletal muscles beyond the first few hours after exercise, we examined the effects of acute exercise and chronic exercise (training) on glycolysis and glycogenesis in isolated soleus muscle strips in untrained rats (i.e., rested vs. exercised) (experiment 1), and in soleus strips from exercised rats (i.e., trained + exercise vs. untrained + exercise) (experiment 2).

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Studies in both experiments were performed from 0–96 h after a standardized 45-min exercise bout, in the absence and presence of submaximal and maximal levels of insulin. We chose the soleus muscle because thin strips of rat soleus muscles are suitable for studies of insulin-stimulated glucose metabolism in vitro (4,23) and, during exercise, the activity of this muscle is now known to be greatly increased, as measured by computer analyses of complex electromyographic interference patterns in vivo (24,25).

METHODS — Male Sprague-Dawley rats were used in these studies. They were maintained at a constant temperature (23°C) with a fixed 12-h reversed artificial light cycle. They were fed a standard laboratory rat chow and were provided with water ad libitum. Before the standardized exercise bout and before training commenced, all animals were familiarized with treadmill exercise for 5–10 min at low speeds (15 m/min) for 4 days/wk before training commenced or the week before the standardized exercise bout, when untrained animals were used.

Experiment 1

In this experiment, untrained animals were used, and the effects of one bout of exercise (45-min treadmill run, 20 m/min, 8% grade) on glucose metabolism (glycolysis and glycogenesis) were compared with soleus muscle strips (<15 mg) in vitro (4,23) immediately after exercise (t = 0) and at 3, 6, 24, 48, and 96 h after exercise. A control group of untrained animals was not exercised, but their soleus muscle strips were studied at the same time points. Food intake was not controlled after exercise.

Experiment 2

In this second experiment, the effects of one bout of exercise on glucose metabolism (glycolysis and glycogenesis) were compared with soleus muscle strips from exercised, trained rats and exercised, untrained rats. For training purposes, rats ran for 6 wk on a motor-driven treadmill for 4 days/wk at progressively increasing speeds and grades (i.e., wk 1 = 20 m/min, 9% grade for 30 min; wk 6 = 25 m/min, 15% grade for 60 min). This running program has been used in previous studies and is known to increase insulin binding, glucose uptake, and metabolism in rat skeletal muscle (11).

In this experiment, both the trained and untrained rats performed the same 45-min standardized exercise bout (see experiment 1). In the trained animals, this standardized bout of exercise occurred 48 h after the last training session. Glycolysis and glycogenesis were determined again, immediately after this standardized exercise bout (t = 0) and 3, 6, 24, 48, and 96 h later. Food intake was not controlled during training or after the 45-min standardized exercise bout.

Analytical procedures

At the designated time points in both experiments, strips of the soleus muscles (4,23) were obtained for determination of glycogenesis and glycolysis in the absence and presence of submaximal (0.1 nM insulin) and maximal (10 nM) concentrations of insulin. Procedures for obtaining muscles strips are similar to those reported in a previous study (23). Measurements of glycolysis and glycogenesis have been published in detail elsewhere (1,2,12,26). Briefly, muscles were incubated at 37°C for 60 min in the presence of [5-^{3}H]glucose (5 mM, 0.5 μCi/vial). The appearance of ^3H_2O provided an index of the [^{3}H]glucose that entered the glycolytic pathway. The ^3H_2O was selectively trapped in calcium chloride by placing the incubating buffer in a center well and evaporating this buffer in a closed vessel. The calcium chloride was then redissolved in water. For the measurement of glycogen, muscles were washed in ice-cold saline (3 × 5 min), digested, and the glycogen precipitated in ethanol (4 times) with carrier glycogen at 0°C.

In both experiments, the time periods after exercise were randomized. Muscles from both groups in each experiment were always included in the same assays for determinations of glycolysis and glycogenesis.

Statistical analyses

Data were analyzed using a two-way analysis of variance for each of the two experiments. This permitted us to make comparisons between groups (*experiment 1*: untrained rested vs. untrained exercised; *experiment 2*: trained exercised vs. untrained exercised) across all time points simultaneously in each experiment (0–96 h). In this manner, we were able to: 1) assess the effects of insulin irrespective of time and group membership, 2) compare whether there were differences between the groups in each of the two experiments irrespective of insulin and time, 3) determine whether there were changes over time (0–96 h) after exercise irrespective of the groups and insulin concentrations used, and 4) establish whether there were interactions among these three main effects (i.e., four interactions were examined: group × insulin, group × time, insulin × time, and insulin × group × time). This approach provided the most comprehensive and statistically most powerful analyses of all of the data for the experimental design of the present investigation. All data are reported as means ± SE.

RESULTS — We attempted to keep the animals at approximately the same weight in these studies. However, for management of these studies, experiments 1 and 2 were conducted on two separate batches of animals. The untrained rats weighed 323 ± 3.3 g in the exercised group and 327 ± 4.1 g in the nonexercised group. The difference in body weights at the end of the training period in this study between trained (312 ± 5.5 g) and untrained rats (347.3 ± 5.2 g) ($P < 0.01$) is characteristically observed with training in male rats. The training program used in exper-

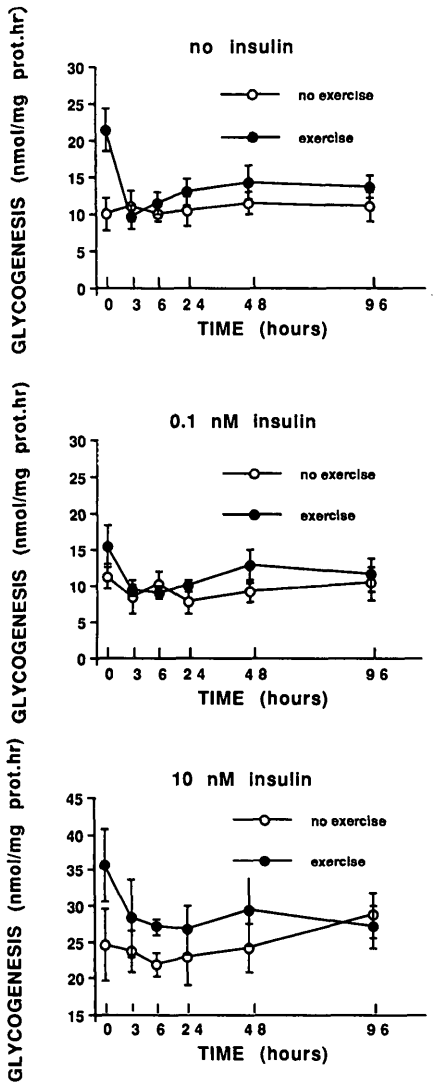

Figure 1—*Comparisons of glucose incorporation into glycogen at selected insulin concentrations in strips of soleus muscle obtained from untrained, exercised rats at specific times after exercise, and in soleus muscles obtained from untrained, rested rats at the same time points (means ± SE).*

Table 1—*Statistical summary of experiments 1 and 2*

Dependent variable	Independent variables (α levels): Insulin (nM)	Groups (G) [UEx] vs. [UnoEx]	Time (T) (0–96 h)	G × T
Experiment 1: (Untrained + exercise [UEx] vs. untrained no exercise [UnoEx])				
Glycogenesis	0	0.008	0.08	0.08
	0.1	0.07	0.047	0.65
	10	0.047	0.74	0.75
Glycolysis	0	0.79	0.23	0.11
	0.1	0.10	0.73	0.93
	10	0.64	0.67	0.21

Dependent variable	Independent variables (α levels): Insulin (nM)	Groups (G) [TEx] vs. [UTEx]	Time (T) (0–96 h)	G × T
Experiment 2: (Trained + exercise [TEx] vs. untrained + exercise [UTEx])				
Glycogenesis	0	0.42	<0.0001	0.34
	0.1	0.43	<0.0001	1.00
	10.0	0.41	0.042	0.99
Glycolysis	0	0.27	0.0015	0.98
	0.1	0.005	0.31	0.63
	10.0	0.01	0.36	0.65

Analyses of variance were used to examine rates of glycolysis and glycogenesis over a 96-h period after the last exercise bout in trained and untrained soleus muscle strips.

iment 2 was identical to one that resulted in significant increments in rat soleus muscle succinate dehydrogenase activity and rat insulin binding to soleus muscles in our previous studies (11).

In experiments 1 and 2, insulin increased the rates of glycolysis and glycogenesis ($P < 0.05$).

Experiment 1: untrained, nonexercised muscles vs. untrained, resting muscles

Analyses of the data at each separate insulin concentration used in these experiments (i.e., no insulin, 0.1 and 10 nM insulin) indicated that an acute bout of exercise increased glycogenesis (Fig. 1 and Table 1). However, the rates of glycolysis were not altered (Fig. 2 and Table 1).

Experiment 2: trained, exercised muscles vs. untrained, exercised muscles

No differences in glycogenesis were found in this experiment between the trained and untrained muscles after exercise (Fig. 3 and Table 1). A greater rate of glycolysis occurred in the trained group, but this was evident only in the presence of insulin (0.1 and 10 nM), not in the absence of insulin (Fig. 4 and Table 1).

DISCUSSION— The experiments were designed to determine whether increased glucose disposal observed in trained animals is caused by training or the effects provoked by the last exercise bout. Therefore, we compared rates of glycolysis and glycogenesis: *1)* in untrained, exercised rats with those in untrained, nonexercised rats (experiment 1); and *2)* we compared rates of glycolysis and glycogenesis in trained, exercised rats with those in untrained, exercised rats (experiment 2). All comparisons were made in the absence of insulin, and at submaximal and maximal stimulating levels of insulin in strips of soleus muscle in vitro. Similar comparisons have been made immediately after exercise and again 2–3 h after exercise

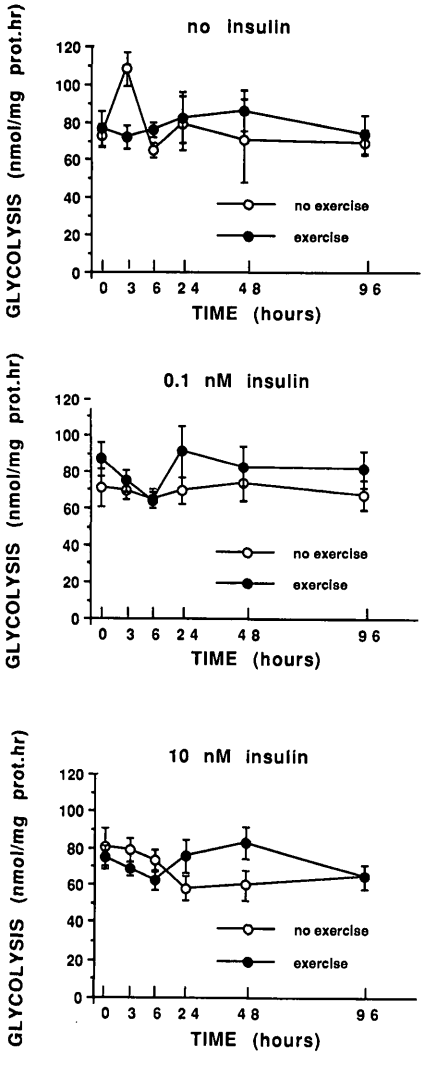

Figure 2—*Comparisons of glucose incorporation into glycolysis at selected insulin concentrations in strips of soleus muscle from untrained, exercised rats at specific times after exercise, and in soleus muscles obtained from untrained, rested rats at the same time points (means ± SE).*

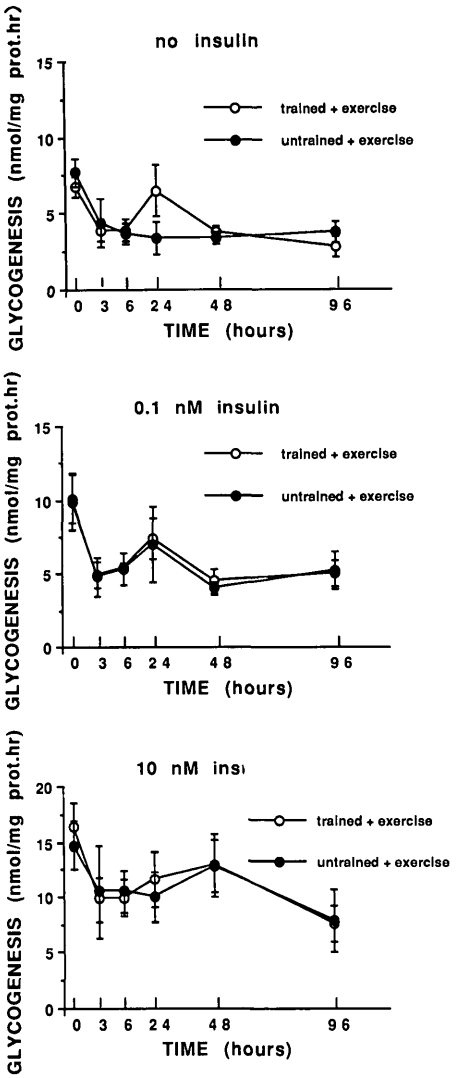

Figure 3—*Comparisons of glucose incorporation into glycogen at selected insulin concentrations in strips of soleus muscle obtained from untrained rats and trained rats at specific times after a standardized 45-min exercise work bout on the treadmill (means ± SE).*

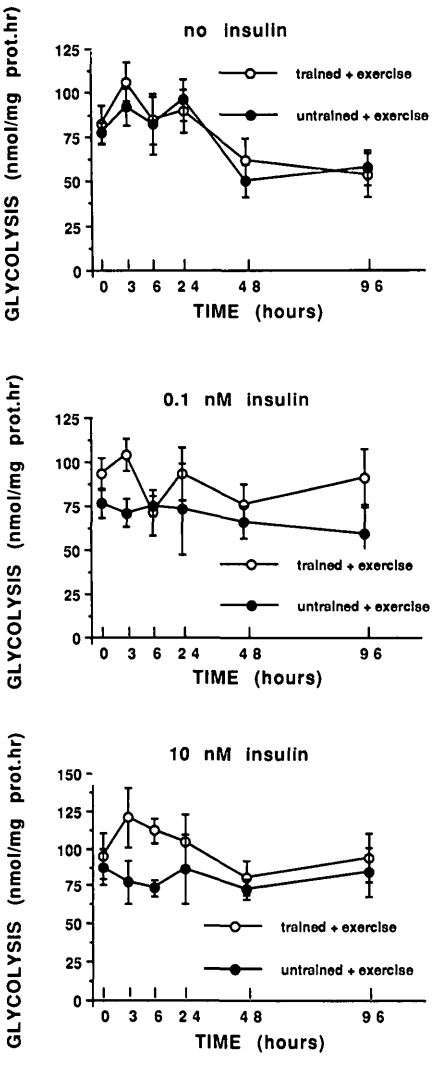

Figure 4—*Comparisons of glucose incorporation into glycolysis at selected insulin concentrations in strips of soleus muscle obtained from untrained rats and trained rats at specific times after a standardized 45-min exercise work bout on the treadmill (means ± SE).*

(3). We have extended these observations by studying the effects of exercise and training at selected time points for up to 4 days after the last exercise bout (i.e., 0, 3, 6, 24, 48, and 96 h after exercise). The primary findings in this study were that an acute bout of exercise increases glycogenesis, whereas training increased glycolysis, but only in the presence of insulin. These data suggest that there is a training-induced adaptation in skeletal muscle glucose metabolism, an effect that is not simply a residual phenomenon that can be ascribed to the last exercise bout.

Our results of increased rates of glycogenesis after an acute bout of exercise in untrained muscles and increased rates of glycolysis in trained muscles are remarkably congruent, with studies by Davis et al. (3). Although their studies were only taken to 3 h after exercise, they also reported that the increase in glucose uptake after exercise in untrained, exercised muscles was directed to glycogen synthesis, but that in trained muscles the postexercise increase in glu-

Table 2—*Comparisons of increments in glucose uptake determined by arteriovenous differences in 3-O-methylglucose ([^{3}H]MOG) with increments in [^{3}H]MOG transport in individual muscles in hindlimb-perfused rats*

Source	Ratio	Arteriovenous increase in MOG uptake	Parameter measured in muscle	Muscles			
						Gastrocnemius	
				Soleus	Plantaris	Red	White
Megeney & Bonen (unpublished observations)	Exercise:control	2:1	MOG transport	2.1:1	2.5:1	2.4:1	1.5:1

Data are expressed as ratios, where the control data are set to 1.

cose metabolism was directed primarily to glycolysis (3). Therefore, the previous assertion that increased glucose metabolism in trained muscles is a residual effect from the last exercise bout (16) can no longer be seen to be tenable, in light of the results from this study and that of Davis et al. (3), both of which found an increased rate of glycolysis in trained muscles, when the effects of the last exercise bout were controlled. Our study also indicates that these training effects last considerably longer than simply a few hours past the last exercise bout.

The reason that training effects were seen to be a residual effect from the last exercise bout is most likely related to the reliance on data obtained from glucose uptake measurements based on arteriovenous (A-V) glucose differences in the perfused rat hindlimb (16). However, these measurements of A-V glucose differences in the perfused rat hindlimb preparation are not very sensitive and cannot reflect the known differences in glucose transport and disposal by individual muscles in the rat hindlimb provoked by exercise and insulin (2,27–30) (Table 2). The discrepancy between A-V glucose difference measurements and glucose uptake by different muscles can be attributed to the following facts: *1*) a considerable proportion of nonmuscle tissue is perfused in the rat hindlimb (31); 2) not all muscles are equally insulin-sensitive (2,27–30) (Table 2); and 3) not all hindlimb muscle fibers are necessarily recruited during exercise or endurance training, because by mass 76% of the hindlimb musculature of the rat is comprised of fast-twitch glycolytic muscle fibers (32) that are not necessarily recruited during endurance exercise or training. Because the venous perfusate drains a considerable amount of nonmuscle tissue and relatively inactive or even nonexercising muscles, the contributions of these tissues to glucose metabolism can mask an increase in glucose metabolism, especially if the previously exercised muscle mass is relatively small. This may explain why Ivy et al. (16) were not able to demonstrate training-induced effects in glucose metabolism using A-V glucose differences, whereas we were able to observe training-induced adaptations in glucose metabolism (glycolysis) when the experiments were done in the isolated muscles that are known to be very active during treadmill exercise (24,25).

The mechanism for the increased glucose utilization in trained animals in the presence of insulin remains speculative. The known differences in glycogen levels in trained and untrained animals (33) that might retard glucose uptake (34) would seem to be an unlikely explanation, since we used soleus strips from the same soleus muscle for the different incubation conditions (0, 0.1 and 10 nM insulin), but only in the presence of insulin was glycolysis increased in the trained muscle strips.

We can reasonably assume that, in our trained muscles, the increased rates of glycolysis, along with no changes in the rates of glycogenesis, must be preceded by an increase in glucose transport. Indeed, an increase in glucose transport in trained muscle has been reported (13). Therefore, our results in trained muscles (i.e., increased rates of glycolysis only in the presence of insulin) are most compatible with the idea that training increases the number of intracellular glucose transporters, which can then be translocated to the sarcolemmal membrane by insulin to increase glucose transport (20–22). Recently, such an increase in glucose transporters has been observed in muscles of trained rats (19). However, at present, we cannot discount the idea that the properties of the glucose transporters, rather than the absolute number of transporters, are altered in trained muscles. Evidence for altered glucose transporter activity has been proposed for heart muscle exposed to insulin (35) and in brown adipose tissue of cold-adapted rats (36).

In summary, this study demonstrates that after an acute bout of exercise glycogenesis is increased and that with training glycolysis is increased in the presence of insulin. We conclude, therefore, that training adaptations in glucose metabolism do occur in skeletal muscle and that these are distinct from the effects of a single bout of exercise on glucose metabolism. Presumably, these persistent increments in glucose metabolism in trained muscles are attributable, in part, to the greater number of insulin-

regulatable glucose transporters in trained muscles.

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