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Am J Physiol Regulatory Integrative Comp Physiol 292:1970-1976, 2007. First published Feb 15, 2007; doi:10.1152/ajpregu.00503.2006

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Divergent response of metabolite transport proteins in human skeletal muscle after sprint interval training and detraining

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Submitted 17 July 2006; accepted in final form 12 February 2007

Burgomaster KA, Cermak NM, Phillips SM, Benton CR, Bonen A, Gibala MJ. Divergent response of metabolite transport proteins in human skeletal muscle after sprint interval training and detraining. *Am J Physiol Regul Integr Comp Physiol* 292: R1970–R1976, 2007. First published February 15, 2007; doi:10.1152/ajpregu.00503.2006.—Skeletal muscle primarily relies on carbohydrate (CHO) for energy provision during high-intensity exercise. We hypothesized that sprint interval training (SIT), or repeated sessions of high-intensity exercise, would induce rapid changes in transport proteins associated with CHO metabolism, whereas changes in skeletal muscle fatty acid transporters would occur more slowly. Eight active men (22 ± 1 yr; peak oxygen uptake = 50 ± 2 ml·kg⁻¹·min⁻¹) performed 4–6 × 30 s all-out cycling efforts with 4-min recovery, 3 days/wk for 6 wk. Needle muscle biopsy samples (vastus lateralis) were obtained before training (Pre), after 1 and 6 wk of SIT, and after 1 and 6 wk of detraining. Muscle oxidative capacity, as reflected by the protein content of cytochrome *c* oxidase subunit 4 (COX4), increased by ~35% after 1 wk of SIT and remained higher compared with Pre, even after 6 wk of detraining ($P < 0.05$). Muscle GLUT4 content increased after 1 wk of SIT and remained ~20% higher compared with baseline during detraining ($P < 0.05$). The monocarboxylate transporter (MCT) 4 was higher after 1 and 6 wk of SIT compared with Pre, whereas MCT1 increased after 6 wk of training and remained higher after 1 wk of detraining ($P < 0.05$). There was no effect of training or detraining on the muscle content of fatty acid translocase (FAT/CD36) or plasma membrane associated fatty acid binding protein (FABPpm) ($P > 0.05$). We conclude that short-term SIT induces rapid increases in skeletal muscle oxidative capacity but has divergent effects on proteins associated with glucose, lactate, and fatty acid transport.

GLUT4; monocarboxylate transporters; fatty acid translocase; plasma membrane fatty acid binding protein

TO GENERATE THE HIGH-POWER OUTPUTS achieved during short bursts of “all-out” maximal exercise, skeletal muscle primarily relies on muscle glycogen for energy provision. For example, a single 30-s bout of maximal cycling exercise can use almost one-quarter of the glycogen content in muscle, the majority of which is converted to lactate, to fuel nonoxidative ATP provision (26, 30, 33). Although the rate of muscle glycogenolysis is reduced during repeated sprinting, large amounts of lactate accumulate and the associated increase in [H⁺] poses a challenge to systems that regulate muscle pH (22). It is therefore not surprising that high-intensity sprint interval training (SIT) or repeated sessions of brief, intense exercise for several weeks, induces changes in monocarboxylate transporter (MCT)

proteins that regulate lactate and H⁺ exchange in human skeletal muscle (3, 23, 32). Although the early time course is unknown, relatively rapid increases in MCT1 and MCT4 could contribute to the reduced rate of muscle lactate accumulation and improved high-intensity exercise performance that have been documented after short-term (≤ 2 wk) SIT (7, 8, 12).

SIT may induce changes in other metabolite transport proteins, such as those associated with glucose and fatty acid metabolism; however, this has not been studied in humans. Although the contribution from blood glucose during sprint exercise is modest (23), an increased GLUT4 protein content could facilitate higher glucose uptake during recovery and explain in part the higher muscle glycogen content observed after SIT (7, 8, 12). Similarly, while extramuscular lipid is not a major source of energy during sprint exercise (21), several weeks of high-intensity training may increase the capacity for skeletal muscle lipid oxidation, as evidenced by an increased maximal activity of β -hydroxyacyl CoA dehydrogenase (HAD) (29, 34, 35). Other studies have reported no change in HAD after short-term SIT (7), which suggests pathways associated with fatty acid metabolism may adapt more slowly than those involved in carbohydrate metabolism.

The primary purpose of the present study was to examine the early time course for changes in metabolite transport proteins in human skeletal muscle in response to SIT. We speculated that proteins associated with glucose and lactate transport would adapt more quickly than proteins associated with fatty acid transport. Specifically, we hypothesized that 1 wk (3 sessions) of SIT would increase the muscle content of GLUT4, MCT1, and MCT4, as well as cytochrome *c* oxidase subunit 4 (COX4), which was used as a marker of oxidative capacity. In contrast, we hypothesized that changes in fatty acid translocase (FAT/CD36) and plasma membrane associated fatty acid binding protein (FABPpm) would occur more slowly and not be evident until after 6 wk of training. Muscle tissue was also harvested after 1 and 6 wk of detraining to examine the time course for changes in metabolite transport proteins upon cessation of the SIT stimulus.

METHODS

Subjects and General Design

Eight healthy men (22 ± 1 yr, 176 ± 3 cm, 80 ± 4 kg) volunteered to take part in the main experiment. The subjects were active students

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at McMaster University, who participated in some form of physical activity several times per week. The specific activities included jogging, bicycling for transportation, and intramural sports such as soccer and water polo. None of the subjects were specifically engaged in a regular program of exercise training for a particular sport or event. The study design consisted of a 6-wk SIT program followed by a 6-wk period of detraining. Given the generally active lifestyle of the subjects, this meant that the detraining phase of the study was characterized by a loss of the SIT stimulus but not complete sedentariness. Subjects were tested prior to training, after 1 and 6 wk of training, and 1 and 6 wk after the cessation of training. As described further below, measurements included a resting needle biopsy sample for the determination of metabolite transport proteins, and a 250-kJ cycling time trial to assess changes in exercise capacity. To more rigorously evaluate the validity of the performance data, eight other men drawn from the same population (26 ± 1 yr, 180 ± 2 cm, 76 ± 3 kg) served as a control group. The control group performed a series of time trials at intervals equivalent to the SIT group but without any training intervention or muscle biopsy sampling. Following routine medical screening and explanation of potential risks, all subjects provided written informed consent before their participation. The study was approved by the McMaster University and Hamilton Health Sciences Research Ethics Board.

Experimental Protocol

Subjects initially made several visits to the laboratory to become oriented with the testing procedures and training devices. All subjects performed a peak oxygen uptake ($\dot{V}O_{2\text{ peak}}$) test and a familiarization 250-kJ time trial, and subjects in the training group also performed a Wingate test (see *Wingate test*). Approximately 1 wk after the familiarization procedures, all subjects performed a baseline (pretraining) time trial. Subjects in the training group also underwent a needle biopsy procedure, which was always performed 1 h before the time trial. All subsequent time trials for a given subject were performed at the same time of day to minimize potential diurnal variations in exercise performance. The sprint training protocol consisted of 3 sessions per week on alternate days (i.e., Monday, Wednesday, Friday) over 6 wk. Each training session consisted of 4–6 \times 30-s Wingate tests separated by 4 min of recovery. Recovery consisted of cycling at 30 W to reduce venous pooling in the legs and potential feelings of dizziness or nausea. The number of intervals performed during each training session increased from 4 during the first 2 wk of training, to 5 during the middle 2 wk, and finally 6 intervals were performed per session during the final 2 wk of training. Subjects in the training group underwent a muscle biopsy procedure and performed a time trial after 1 and 6 wk of training. The biopsy was obtained \sim 72 h after the previous training session and was followed 1 h later by the time trial to match the timing of measurements performed during baseline testing. To obtain the 1-wk data, the normal Monday training session was eliminated and replaced by the testing procedures. Subjects also underwent a muscle biopsy procedure and performed a time trial after 1 and 6 wk of detraining. As previously indicated, subjects in the control group performed a series of time trials over the course of the study that coincided with the timing of exercise tests performed in the training group.

Details of Experimental Procedures

$\dot{V}O_{2\text{ peak}}$ test. Subjects performed an incremental test to exhaustion on an electronically braked cycle ergometer (Lode Excalibur Sport V2.0, Groningen, The Netherlands) to determine $\dot{V}O_{2\text{ peak}}$ using an online gas collection system (Moxus modular oxygen uptake system, AEI Technologies, Pittsburgh, PA). The initial workload was set at 50 W and was increased by 1 W every 2 s until fatigue. The value used for $\dot{V}O_{2\text{ peak}}$ corresponded to the highest value achieved over a 30-s collection period.

Time trial. Subjects were instructed to complete a 250-kJ self-paced laboratory time trial on an electronically braked cycle ergometer (Lode), as quickly as possible with no temporal, verbal, and physiological feedback. Time required to complete the test and average power output were recorded upon completion of each test. Method error reproducibility for the time trial (coefficient of variation) was 2.6% when eight individuals were tested 1 wk apart with no sprint training intervention (7).

Wingate test. This test consisted of a 30-s, “all-out” sprint on an electronically braked cycle ergometer (Lode) against a resistance set at 0.075 kg/kg body mass. Subjects were instructed to begin cycling as fast as possible, and the application of resistance was immediately applied by a computer interfaced with the ergometer and loaded with appropriate software (Wingate software version 1.11, Lode).

Muscle biopsy. The area over one thigh was prepared for the extraction of a resting biopsy sample from the vastus lateralis muscle. An incision was made through the skin and underlying fascia under local anesthetic (1% wt/vol xylocaine hydrochloride, AstraZeneca Canada, Mississauga, ON), and the biopsy sample was immediately frozen in liquid nitrogen after excision. A separate incision site was used for each biopsy sample, and incisions were spaced \geq 1 cm apart. All samples were stored at -86°C before analyses.

Dietary Controls

To minimize any potential diet-induced variability in measurements, subjects were instructed to document their dietary intake and refrain from using alcohol and caffeine for 48 h before the baseline muscle biopsy procedure and time trial. Dietary records were subsequently duplicated and returned to the subjects 2 days before each subsequent testing session, and subjects were instructed to replicate their individual patterns of food intake. Subsequent dietary analyses (Nutritionist Five, First Data Bank, San Bruno, CA) of the food records revealed no differences in total energy intake or macronutrient composition between testing sessions (data not shown).

Muscle Analyses

Frozen muscle samples were initially homogenized and protein concentrations were determined using a BCA assay (Sigma, St. Louis, MO). Proteins were separated using SDS-PAGE followed by Western blot analysis to detect the presence of GLUT4, MCT1, MCT4, COX4, FABPpm, and FAT/CD36 using routine procedures that we have previously described (5, 6). Equal quantities of protein were loaded into each lane, and a common standard was included in all blots. Blots were detected using enhanced chemiluminescence (Perkin Elmer Life Science, Boston, MA) and subsequently quantified using Gene Tool densitometry (SynGene, ChemiGenius2, Perkin-Elmer, Woodbridge, ON, Canada). Commercial suppliers were used for GLUT4 (Chemicon, Temecula, CA) and COX4 (Invitrogen Canada, Burlington, ON). The other antibodies were gifts from Dr. H. Hata, University of Tokyo, Tokyo, Japan (MCT1 and MCT4), Dr. Calles-Escandon, Wake Forest School of Medicine, Winston-Salem, NC (FABPpm) and Dr. N. Tandon, Thrombosis Research Laboratory, Otsuka Maryland Medicinal Laboratories, Rockville, MD (FAT/CD36).

Statistical Analyses

All muscle data were analyzed using a 1-factor (time) repeated-measures ANOVA. Time trial performance data were analyzed using a two-factor mixed ANOVA with the between factor “group” and the repeated factor “time.” The level of significance for all analyses was set at $P < 0.05$, and significant main effects were subsequently analyzed using a Fisher’s least squares difference test. All values are reported as means \pm SD. Performance data are based on $n = 8$ per group, and muscle data for the training group are based on $n = 6$ due to inadequate muscle biopsy samples, which precluded a complete data set for two subjects.

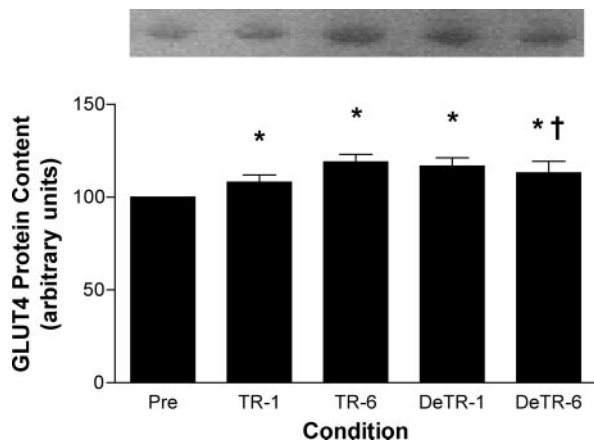


Fig. 1. GLUT4 protein content at baseline (Pre) and after 1 (TR-1) and 6 wk (TR-6) of sprint interval training, and 1 (DeTR-1) and 6 wk (DeTR-6) of detraining. Values are expressed as means \pm SD ($n = 6$). * $P < 0.05$ vs. Pre. † $P < 0.05$ vs. TR-6.

RESULTS

Skeletal Muscle

GLUT4. Muscle GLUT4 content was higher at all time points during training and detraining compared with Pre ($P < 0.05$) (Fig. 1). GLUT4 content was lower after 6 wk of detraining compared with 6 wk of training ($P < 0.05$).

COX4. Muscle COX4 content increased after 1 wk of training and remained higher at all other time points during training and detraining compared with Pre ($P < 0.05$) (Fig. 2).

MCT1 and MCT4. The muscle content of MCT1 was higher after 6 wk of training and remained elevated compared with Pre after 1 wk of detraining ($P < 0.05$) (Fig. 3). MCT4 protein content was elevated above Pre after 1 and 6 wk of training ($P < 0.05$) but was not different after 1 and 6 wk of detraining (Fig. 3). MCT4 content after 6 wk of detraining was lower ($P < 0.05$) compared with 6 wk of training.

FABPpm and FAT/CD36. The muscle content of the two measured fatty acid transport proteins remained unchanged

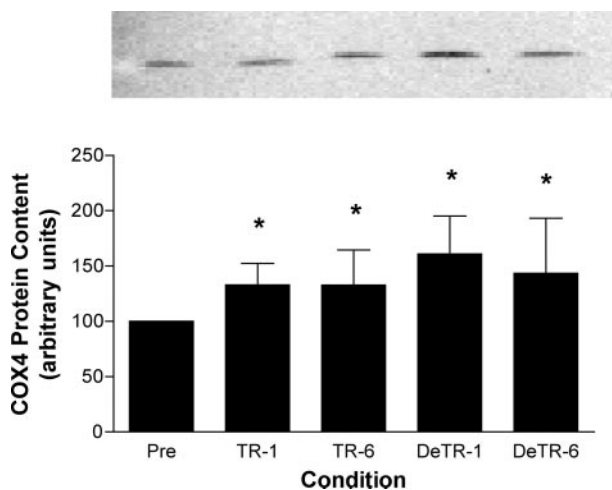


Fig. 2. COX4 protein content at baseline (Pre) and after 1 (TR-1) and 6 wk (TR-6) of sprint interval training, and 1 (DeTR-1) and 6 wk (DeTR-6) of detraining. Values are expressed as means \pm SD ($n = 6$). * $P < 0.05$ vs. Pre.

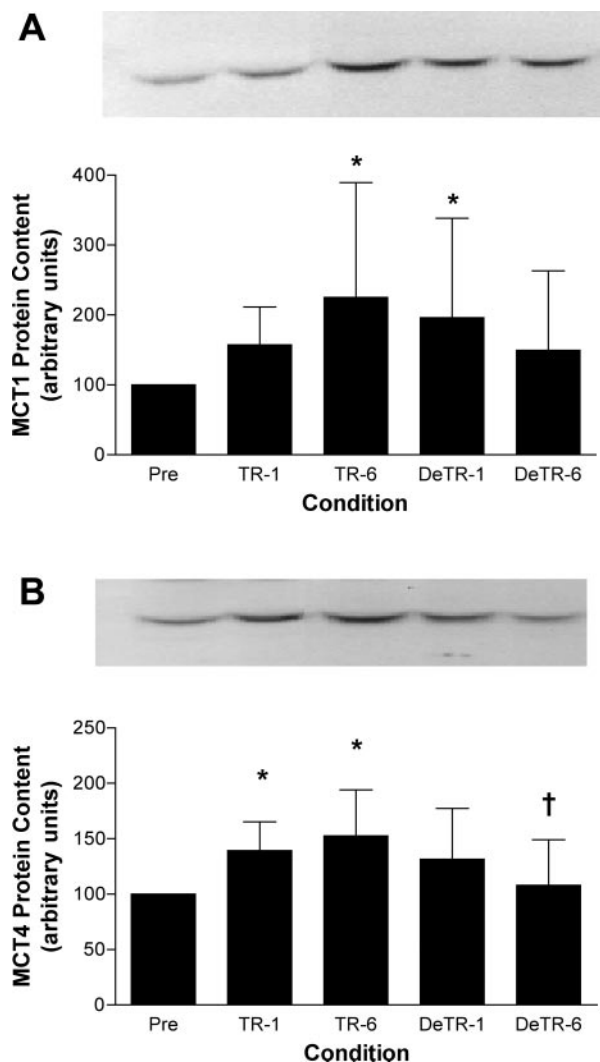


Fig. 3. Protein content of MCT1 (A) and MCT4 (B) at baseline (Pre) and after 1 (TR-1) and 6 wk (TR-6) of sprint interval training, and 1 (DeTR-1) and 6 wks (DeTR-6) of detraining. Values are expressed as means \pm SD ($n = 6$). * $P < 0.05$ vs. Pre. † $P < 0.05$ vs. TR-6.

during training and detraining compared with baseline (data not shown).

Exercise Performance

There was no difference between the training and control groups at baseline (Pre) in the time required to complete the 250 kJ cycling test (Fig. 4). However, in the SIT group, time trial performance was lower after 6 wk of training and after 1 and 6 wk of detraining compared with Pre ($P < 0.05$). The control group showed no change in performance over the course of the study (Fig. 4), and their time was slower vs. the training group after 6 wk of training and 1 and 6 wk of detraining ($P < 0.05$).

DISCUSSION

This was the first study to examine the effect of sprint interval training and detraining on metabolite transport proteins in human skeletal muscle. Muscle GLUT4 content, as well as the content of the mitochondrial marker COX4, were increased

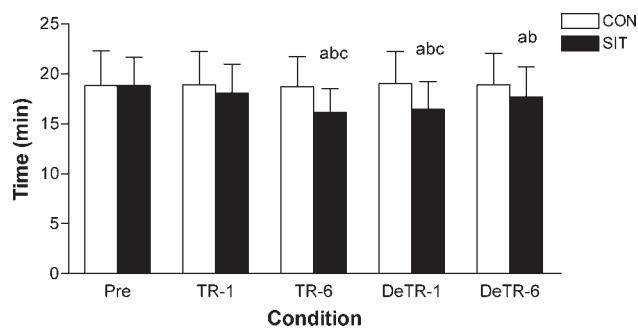


Fig. 4. Time to complete a 250-kJ cycling time trial before (Pre) and after 1 (TR-1) and 6 wk of sprint interval training (TR-6) and after 1 (DeTR-1) and 6 wk of detraining (DeTR-6). A control group (CON) performed the time trial on several occasions over the course of the study with no training intervention. Values are means \pm SD ($n = 8$ each) for the sprint interval training (SIT) and CON groups. ^a $P < 0.05$ vs Pre. ^b $P < 0.05$ vs. CON group at same time point. ^c $P < 0.05$ vs. TR-1.

after only 3 sessions of SIT, or a total of 6 min of very intense exercise over 1 wk. There was no further increase in GLUT4 and COX4 after 6 wk of SIT, but surprisingly, the training-induced increases in these proteins persisted for 6 wk after cessation of the SIT stimulus. The muscle content of MCT4 increased after 1 wk of training, whereas the increase in MCT1 content was more variable and not significant until after 6 wk. Both MCT1 and MCT4 declined upon cessation of the SIT stimulus and returned to baseline values after 6 wk of detraining. The muscle contents of the fatty acid transport proteins FAT/CD36 and FABPpm were unchanged by training and detraining.

GLUT4

This is the first study to demonstrate that brief, intense interval training increases the protein content of GLUT4 in human skeletal muscle. Our data are supported by work from Terada and colleagues (38), who showed that GLUT4 protein content in rat epitrocleus muscle was increased after a total of only 5 min of intense intermittent swim training over 8 days. Although the training-induced increase in GLUT4 content was consistent across subjects in the present study, the magnitude of the change was modest and peaked at $\sim 25\%$ above baseline values after 6 wk of SIT. In contrast, GLUT4 protein content can be increased by $\geq 100\%$ after 5–7 consecutive days of traditional endurance training, that is, 1–2 h per day at 60–75% $\dot{V}O_{2\text{ peak}}$ (15, 18, 31). It has also been reported that a single bout of moderate-intensity exercise can increase GLUT4 protein content 8–22 h after the bout (14). Therefore, it is possible that the “training”-induced increases in GLUT4 reported in the present study were due in part by residual “acute” effects from the previous exercise bout. We feel that any residual acute effect from the previous exercise bout was likely small given the 72-h period between the training session and the biopsy procedure. However, even if we assume that the increase in GLUT4 after 1 wk of training was solely attributable to the acute effect of the previous high-intensity interval session, this suggests that a total of 2 min of “all-out” cycling is sufficient to increase GLUT4 protein content in human skeletal muscle. Regardless of the time course for changes in GLUT4 after SIT, the present data confirm that exercise modes other than tradi-

tional moderate-intensity training can increase muscle GLUT4 content, as previously shown for resistance exercise (17, 36).

One of the most interesting findings from the present study was that the training-induced increase in GLUT4 persisted for 6 wk after the cessation of SIT. Several studies have reported that GLUT4 content decreases relatively quickly (within 1–2 wk) when previously endurance-trained individuals stop training (27, 42), although this is not a universal finding (19). Houmard et al. (20) showed that the training-induced increase in GLUT4 content was maintained for 2 wk in subjects who reduced their training volume by 50%, whereas the gains were lost if subjects stopped training completely. While speculative, it is possible that the persistent elevation in GLUT4 during detraining in the present study was related to our subjects’ return to their previously “active” lifestyle (i.e., which consisted of a few low-to-moderate-intensity sessions of physical activity per week as opposed to complete sedentariness). Alternatively, a recent study showed that long-term high-intensity exercise training provided more enduring benefits to insulin action compared with moderate- or low-intensity exercise (10), which lends credence to the notion that SIT may induce unique adaptations with respect to muscle GLUT4.

COX4

Another major finding from the present study was that muscle oxidative capacity, as reflected by the muscle content of COX4, was increased after only three sessions of SIT over 1 wk. Previously, we have reported increases in mitochondrial enzymes after six sessions of SIT over 2 wk (7, 8), and Gibala et al. (12) recently showed that the increase in citrate synthase maximal activity after this protocol was comparable to a group who performed the same number of endurance training sessions (90–120 min of cycling at 65% $\dot{V}O_{2\text{ peak}}$ per day). The potency of high-intensity exercise is also supported by work in animals that showed rapid increases in citrate synthase maximal activity after short-term swim training (8 days of 15 \times 20 s intervals with 10 s of rest) (38). The potency of SIT to elicit rapid changes in skeletal muscle phenotype is likely related to its high level of muscle fiber recruitment, and the potential to stress type II fibers, in particular (13). Animal studies have shown that differences in contraction intensity result in selective activation of specific intracellular signaling pathways, which may determine the specific adaptations induced by different forms of exercise training (28, 37). In this regard, Terada and colleagues (37, 38) have shown rapid increases in mitochondrial biogenesis after short-term, high-intensity swim training in rats, which the authors attributed to exercise-induced changes in the expression of peroxisome proliferator-activated receptor coactivator-1.

Similar to the change in GLUT4, the training-induced increase in COX4 persisted after 6 wk of detraining in the present study. It is believed that mitochondrial capacity decreases relatively quickly after cessation of endurance training (9, 16), but data regarding changes in muscle oxidative capacity after high-intensity intermittent training and detraining are limited and equivocal (11, 25, 35). The estimated rate of change in muscle oxidative capacity during detraining may depend on the specific mitochondrial enzyme that is measured. For example, Simoneau et al. (35) reported that oxoglutarate dehydrogenase remained elevated 7 wk after the cessation of a 15-wk SIT

program, whereas β -hydroxyacyl CoA dehydrogenase returned to pretraining levels. Persistent increases in muscle oxidative capacity have also been reported several weeks after the cessation of aerobic exercise training (43), specifically the maximal activity of COX, a subunit of which was measured in the present study. Thus, the elevated muscle COX4 content observed during detraining in the present study may be specific to that protein or could represent a unique adaptation induced by the SIT stimulus, influenced in part by the habitual activity of the subjects.

MCT 1 and 4

The present data are consistent with the findings of Pilegaard et al. (32) and indicate that several weeks of intense, interval-based training can increase both MCT1 and MCT4 content in human muscle. A novel finding from the present work was that the increase in MCT4 occurred relatively quickly after only three sessions of SIT. This observation is supported by a preliminary report by Yoshida and colleagues (44) that showed 3 wk of daily sprint-run training in rats increased the muscle content of both MCT 1 and MCT4. Although the mean changes during training were larger for MCT1 compared with MCT4 in the present study, the individual responses were more variable. Compared with baseline, peak individual increases over the 6-wk training period ranged from ~30 to 530% for MCT1 and ~15–200% for MCT4. We attribute this mainly to individual differences in the response to the SIT stimulus (i.e., physiological variability) since the intra-assay variability for MCT proteins is comparable to other proteins routinely measured by Western blot analysis in our laboratory (i.e., coefficient of variation of $\leq 10\%$ for replicates from the same homogenate run on the same gel). Previous work from our laboratory has shown less variable changes in MCTs after electrical stimulation in animals (2) and aerobic-based training in humans (4). For example, seven consecutive days of aerobic-based training increased MCT1 content by 18% in human skeletal muscle; however, the range (0–62%) was considerably smaller than in the present study (4). Other groups have also reported larger mean changes and higher variability for MCT1 compared with MCT4 after high-intensity exercise training (32). Muscle fiber composition has been shown to influence the adaptive response of MCT1 to exercise training in rodents (2), and this may explain, in part, the variability associated with the human adaptive response to SIT.

Fatty Acid Transporters

This is the first study to examine the effect of SIT on fatty acid transport proteins in human skeletal muscle, and in contrast to our hypothesis, we found no effect of training or detraining on the muscle protein content of FABPpm or FAT/CD36. Our hypothesis was based on the fact that several weeks of SIT have been shown to increase the maximal activity of HAD, which is a commonly used marker for fat oxidation in muscle (29, 34). However, the relationship between fatty acid transporters and the maximal capacity for fatty acid oxidation in skeletal muscle is unclear. Aerobic-based training increases the maximal capacity for fat oxidation (1); however, there are limited and conflicting data regarding the effect of this type of training on muscle FABPpm and FAT/CD36 content (24, 40). For example, Tunstall et al. (40) reported the muscle content of

FAT/CD36, but not FABPpm, was increased by short-term aerobic training (1 h at 63% $\dot{V}O_{2\text{peak}}$ per day for 9 days), whereas Kiens and colleagues (24) showed that 3 wk of endurance training increased muscle FABPpm. The rate-determining step in skeletal muscle lipid oxidation appears to be the activity of carnitine palmitoyl transferase (1), and thus it is possible that SIT increases the maximal capacity for lipid oxidation during exercise; however, an increased skeletal muscle content of fatty acid transport proteins is not obligatory for this to occur.

Exercise Performance

Finally, although the major focus of this study was metabolite transport proteins, we also rigorously evaluated the effect of sprint training and detraining on exercise performance using a task that closely resembles athletic competition. Time trial performance improved progressively over the 6-wk training period, and while the absolute performance times slowed during detraining, performance remained better than at baseline (pretraining). The performance data are bolstered by the fact that all subjects performed extensive familiarization procedures to minimize any potential “learning effect,” and the control group showed no change in performance over the course of the study. It is unclear whether the observed changes in metabolite transport proteins directly contributed to, or merely occurred in conjunction with, the improvement in exercise tolerance. Obviously, factors responsible for training-induced improvements in performance are complex and are determined by numerous physiological (e.g., cardiorespiratory, metabolic, neural, thermoregulatory) and psychological attributes (e.g., mood, motivation, perception of effort).

In summary, the results from the present study demonstrate that SIT rapidly increased muscle oxidative potential and the proteins associated with glucose and lactate/H⁺ transport. Upon cessation of the training stimulus, the muscle content of MCT1 and MCT4 declined to pretraining levels; however, the training-induced increases in GLUT4 and COX4 persisted after 6 wk of detraining. The muscle content of fatty acid transport proteins was unchanged throughout the study, which suggests proteins associated with carbohydrate (CHO) metabolism are more responsive to the initiation and cessation of SIT in humans. Future studies should examine the signaling pathways and regulatory mechanisms responsible for the training-induced increases in muscle oxidative capacity and carbohydrate transport proteins, as well as the physiological/health-related consequences of these adaptations. The present data add novel insights to the growing body of evidence that shows the potency of SIT to elicit rapid metabolic adaptations in human skeletal muscle, despite a relatively small training time commitment and total exercise volume.

ACKNOWLEDGMENTS

The authors thank the subjects for their time and effort, and John Moroz and Todd Prior for technical assistance.

GRANTS

This study was supported by an American College of Sports Medicine Foundation Research Endowment Grant (to M. J. Gibala), and operating grants from the Natural Sciences and Engineering Research Council of Canada (NSERC; to M. J. Gibala and A. Bonen), the Canadian Institutes of Health Research (A. Bonen) and the Canada Research Chair program (to A. Bonen). K. A. Burgomaster was supported by a NSERC Canada Graduate Scholarship

and a Gatorade Sports Science Institute Student Research Award. C. R. Benton held an Ontario Graduate Scholarship. A. Bonen is the Canada Research Chair in Metabolism and Health at the University of Guelph.

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