Endurance training reduces the contraction-induced interleukin-6 mRNA expression in human skeletal muscle

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Endurance training reduces the contraction-induced interleukin-6 mRNA expression in human skeletal muscle. Am J Physiol Endocrinol Metab 287: E1189–E1194, 2004. First published August 10, 2004; doi:10.1152/ajpendo.00206.2004.—Contracting skeletal muscle expresses large amounts of IL-6. Because 1) IL-6 mRNA expression in contracting skeletal muscle is enhanced by low muscle glycogen content, and 2) IL-6 increases lipolysis and oxidation of fatty acids, we hypothesized that regular exercise training, associated with increased levels of resting muscle glycogen and enhanced capacity to oxidize fatty acids, would lead to a less pronounced increase of skeletal muscle IL-6 mRNA in response to acute exercise. Thus, before and after 10 wk of knee extensor endurance training, skeletal muscle IL-6 mRNA expression was determined in young healthy men (n = 7) in response to 3 h of dynamic knee extensor exercise, using the same relative workload. Maximal power output, time to exhaustion during submaximal exercise, resting muscle glycogen content, and citrate synthase and 3-hydroxyacyl-CoA dehydrogenase enzyme activity were all significantly enhanced by training. IL-6 mRNA expression in resting skeletal muscle did not change in response to training. However, although absolute workload during acute exercise was 44% higher (P < 0.05) after the training period, skeletal muscle IL-6 mRNA content increased 76-fold (P < 0.05) in response to exercise before the training period, but only 8-fold (P < 0.05, relative to rest and pretraining) in response to exercise after training. Furthermore, the exercise-induced increase of plasma IL-6 (P < 0.05, preand posttraining) was not higher after training despite higher absolute work intensity. In conclusion, the magnitude of the exercise-induced IL-6 mRNA expression in contracting human skeletal muscle was markedly reduced by 10 wk of training. However, regular training also augments the basal skeletal muscle mRNA levels of important metabolic enzymes such as hexokinase II (HKII), citrate synthase (CS), and 3-hydroxyacyl-CoA dehydrogenase (HAD), as well as resting muscle transcriptional activity of the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) gene (31).

Interestingly, previous studies have also demonstrated that interleukin-6 (IL-6) is highly responsive to exercise (reviewed in Refs. 6, 24–26): the transcriptional activity (19) as well as the mRNA content (7, 18, 20, 22, 36, 37) of IL-6 in skeletal muscle is markedly increased by exercise. Moreover, IL-6 protein is accumulated in contracting muscle fibers (27) as well as released in large amounts into the circulation during exercise (37). Interestingly, exercise performed with reduced preexercise muscle glycogen content results in a greater transcriptional activity of the IL-6 gene (19) than exercise performed with normal preexercise muscle glycogen content. Thus preexercise intramuscular glycogen content appears to be an important modulator of the exercise-induced IL-6 gene expression. Accordingly, IL-6 in skeletal muscle responds the same way to reduced muscle glycogen content as a number of other important genes within the contracting skeletal muscle: pyruvate dehydrogenase kinase-4 (10, 29), hexokinase (29), and heat shock protein 72 (8). Furthermore, IL-6 appears to be a potent modulator of lipid metabolism in humans by increasing whole body lipolysis and fatty acid oxidation without causing hypertriacylglyceridemia (14).

Because IL-6 gene expression is enhanced by low preexercise muscle glycogen content, and IL-6 released into the circulation increases lipolysis, we hypothesized that regular endurance exercise training, causing elevated skeletal muscle glycogen levels and increased activity of mitochondrial enzymes, would lead to a less pronounced increase in IL-6 mRNA in working muscle. Thus we measured skeletal muscle IL-6 mRNA levels at rest and in response to an acute bout of exercise before and after 10 wk of endurance training.

METHODS AND MATERIALS

Volunteers. Seven healthy untrained young men were recruited to the study: mean age 26 yr (range 23–29 yr), mean weight 86 kg (range 53–126 kg), and mean height 180 cm (range 171–189 cm). The purpose of the study and possible risks and discomforts were explained to the participants before obtaining written consent. The study protocol was approved by the local Ethical Committee of Copenhagen

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Exercise performance tests. Before (pretraining) and after the endurance training period (posttraining), the maximal power output ($P_{\text{max}}$) was determined during dynamic one-legged knee extensor exercise with the use of a modified ergometer, as described earlier (1). Each leg was tested individually to exclude possible differences between the dominant and nondominant leg. The $P_{\text{max}}$ test consisted of a short warm-up session with 60 knee extensions/min at 30 W. This was followed by an incremental increase of the workload by 10 W every 2 min until volitional exhaustion. The highest workload that was maintained for at least 1 min was defined as $P_{\text{max}}$.

In addition, each $P_{\text{max}}$ test was followed by a second test using a workload corresponding to 90% of $P_{\text{max}}$ to determine the time to exhaustion ($T_{\text{exh}}$) during submaximal exercise.

Training protocol. After completion of the first set of performance tests and the first acute-exercise experiment, the 10-wk training period commenced: for 10 wk, the participants trained each leg 5×/wk using dynamic one-legged knee extensor exercise, with each training session lasting 1 h. All training sessions were performed after an overnight fast. Water was consumed ad libitum during the training sessions. Although food was not permitted until the cessation of the training session, the participants received a sandwich at the laboratory immediately after each training session throughout the training period. Furthermore, the participants were asked not to change their diet during the training period, including the day before the acute-exercise experiments. The workload at the onset of the training period was 75% of $P_{\text{max}}$, determined for each participant before the training period. The workload during the 10 wk of exercise training was increased by 5–10% every fortnight depending on the progress of each participant.

Acute-exercise experiment. After completion of the tests for determination of $P_{\text{max}}$ and $T_{\text{exh}}$, the participants performed an acute-exercise experiment using the dynamic knee extensor exercise mode described earlier. Consequently, the acute-exercise experiment was performed before as well as after the 10 wk of endurance training. On the experimental days, participants reported to the laboratory at 0800 after an overnight fast. Furthermore, the participants were instructed to refrain from exercise for at least 48 h before the experiment. Accordingly, the acute-exercise experiment was performed >48 h after the last set of performance tests. After the arrival, subjects rested in a supine position. Under sterile conditions and after application of local anesthesia (lidocaine, 20 mg/ml; SAD, Copenhagen, Denmark), an indwelling 20-gauge catheter (Arrow, Reading, PA) was placed in the femoral artery using the Seldinger guide wire technique. The femoral artery was cannulated ~2 cm below the inguinal ligament, and the catheter was advanced ~10 cm in the proximal direction.

The exercise bout consisted of 3 h of dynamic two-legged knee extensor exercise at 60 extensions/min, with the workload per leg set to 50% of the individual and actual $P_{\text{max}}$.

After the exercise bout, the subjects rested in the supine position in the laboratory for a 2-h recovery period. Water was consumed ad libitum throughout the exercise and recovery period, but food was not permitted until the cessation of the recovery period.

Blood samples. During the two acute-exercise experiments, blood samples were drawn from the arterial catheter at rest (0 h), at the end of the exercise period (3 h), and after 2 h of recovery (5 h). Plasma for measurement of glucose, free fatty acids (FFA), and glycerol was obtained by drawing blood into precooled EDTA-containing glass tubes that were immediately centrifuged at 2,200 g for 15 min at 4°C. Blood samples for measurement of epinephrine and norepinephrine concentrations were drawn into ice-cold glass tubes containing glutathione and EGTA and spun immediately. The plasma was stored at −80°C until further analysis.

Plasma concentrations of epinephrine and norepinephrine were measured using HPLC, and plasma concentrations of glucose, FFA, and glycerol were determined using an automatic analyzer (Cobas Fara, Roche, France); both methods are described elsewhere (38).

Plasma IL-6 concentration was measured using a high-sensitivity ELISA kit (no. HS600B; R&D Systems, Minneapolis, MN), which detects total IL-6 independent of binding to soluble receptors, with sensitivity of ~0.04 pg/ml and intra- and interassay coefficients of variation of <8%.

In addition, a blood sample at each time point was analyzed using automated standard laboratory procedures for determination of hemoglobin concentration and hematocrit to correct for possible changes in plasma volume, using the method described by Dill and Costill (3).

Muscle biopsies. Muscle biopsies were obtained from the vastus lateralis using the Bergström percutaneous needle method with suction. Before each biopsy, local anesthesia (lidocaine, 20 mg/ml; SAD) was applied to the skin and fascia superficial of the biopsy site. A new incision site was made for each biopsy, and all incision sites were at minimum 3 cm apart. Only biopsies obtained from the same leg of each participant were compared. Time points for the biopsies were preexercise (0 h), immediately postexercise (3 h), and at the end of recovery (5 h). Visible connective tissue and blood contamination were removed before the biopsies were frozen in liquid nitrogen and subsequently stored at −80°C until further analysis.

Skeletal muscle glycogen content was analyzed with the use of enzymatic reactions with fluorometric detection (4). In addition, biopsies were analyzed for CS and HAD activity (5).

Skeletal muscle IL-6 mRNA expression. Total RNA was extracted from the muscle tissue with the use of TRIZol, according to the manufacturer’s directions (Invitrogen, Grand Island, New York). The resulting RNA pellet was dissolved in diethylpyrocarbonate-treated water. Reverse transcription (RT) reactions were performed on 11 μl of RNA (~2 μg RNA) using an RT kit (Applied Biosystems, Foster City, CA) in a reaction volume of 170 μl. The resulting cDNA product was stored at −20°C until further analysis.

Primers and probes were designed (Primer Express version 1.0, Applied Biosystems) from the gene sequences for human IL-6 (35). An 81-base-long fragment was amplified using the forward primer 5'-GGTACATCCTCGACGGCATCT-3', the reverse primer 5'-GTGCCTTTGCTGCTTTCAC-3', and the TaqMan fluorescent probe 5'-FAM-TGTTACTCTTGTTACATGTCTCCTTTCTCAGGGCT-TAMRA-3' (Applied Biosystems).

GAPDH mRNA was used as an endogenous control to normalize the content of IL-6 mRNA in each sample and was amplified using a 5'-VIC- and 3'-TAMRA-labeled predeveloped assay reagent (Applied Biosystems). GAPDH has previously been evaluated as an endogenous control in contracting skeletal muscle (32).

The diluted RT product (template) was mixed with 2× TaqMan Universal Master Mix (Applied Biosystems), forward primer, reverse primer, and probe. The final reaction volume of 10 μl was obtained by adding RNase-free water. Approximately 50 ng of IL-6 cDNA and 8 ng of GAPDH cDNA were amplified (ABI PRISM 7900 sequence detector, Applied Biosystems) following standard conditions using 50 cycles. In addition to the samples of interest, standardized dilutions of either IL-6 cDNA or GAPDH cDNA originating from the same RT product were amplified on all plates.

The relative contents of IL-6 and GAPDH in the samples were quantified on the basis of the standard curve method (12), using the standardized cDNA samples on each PCR plate for the standard curve. All samples were run in triplicate. For each subject, all samples were run together, allowing relative comparison of the samples from a given subject.

Statistics. All data were tested for normality in distribution before further statistical analysis: $P_{\text{max}}$, $T_{\text{exh}}$, and CS and HAD activity were normally distributed without transformation. Skeletal muscle glycogen content and plasma concentrations of IL-6, epinephrine, norepinephrine, glucose, FFA, and glycerol were normally distributed after log transformation. IL-6-to-GAPDH mRNA ratios and fold changes in skeletal muscle IL-6 mRNA expression were normally distributed.
Results in the text are presented as means, with 95% confidence interval (CI), unless stated otherwise.

**RESULTS**

The exercise performance increased markedly in response to the 10-wk endurance training period: the $P_{\text{max}}$ during one-legged knee extensor exercise increased ~44% ($P < 0.05$) as a result of the training (74 W, CI 60–89 W, pretraining, vs. 107 W, CI 94–121 W, posttraining), and $T_{\text{exh}}$ during submaximal exercise (90% of $P_{\text{max}}$) increased ~300% ($P < 0.05$) after the training (5.0 min, CI 3.5–6.4 min, pretraining, vs. 19.7 min, CI 14.9–24.5 min, posttraining). Because of the combined training-induced increase of workload and $T_{\text{exh}}$ during the submaximal exercise performance test, the total work (time multiplied by workload) was more than fivefold higher ($P < 0.05$) during submaximal exercise after the endurance training. Of note, the weight of the participants did not change in response to the training ($P = 0.92$, when comparing the weight pretraining and posttraining).

The endurance training also caused increased resting skeletal muscle levels of CS activity by ~36% ($P < 0.05$; 44 μmol·g$^{-1}$·min$^{-1}$, CI 32–56 μmol·g$^{-1}$·min$^{-1}$, pretraining), vs. 60 μmol·g$^{-1}$·min$^{-1}$, CI 51–69 μmol·g$^{-1}$·min$^{-1}$, posttraining), and HAD increased by ~47% ($P < 0.05$; 24 μmol·g$^{-1}$·min$^{-1}$, CI 21–27 μmol·g$^{-1}$·min$^{-1}$, pretraining, vs. 35 μmol·g$^{-1}$·min$^{-1}$, CI 32–39 μmol·g$^{-1}$·min$^{-1}$, posttraining).

The effect of the training and acute exercise on muscle glycogen content is shown in Fig. 1. The resting skeletal muscle glycogen content had increased ~74% ($P < 0.05$) in response to the training. However, the skeletal muscle glycogen content decreased to the same level in response to the acute-exercise bout. Thus there was no difference in skeletal muscle glycogen content between pretraining and posttraining at 3 and 5 h. Consequently, the exercise-induced utilization of muscle glycogen (calculated as the difference between muscle glycogen content at 0 and 3 h) was higher ($P < 0.05$) after the training period.

In response to the acute exercise, the plasma levels of epinephrine and norepinephrine (Table 1) increased markedly only after the training (effect of acute exercise $P < 0.05$, effect of training $P < 0.05$). This corresponded with a borderline-significant difference ($P = 0.15$) in the average heart rate during the acute exercise between pretraining and posttraining [117 beats/min (bpm), CI 101–132 bpm, pretraining, vs. 131 bpm, CI 124–138 bpm, posttraining].

Furthermore, the endurance training resulted in decreased resting plasma glycerol concentrations ($P < 0.05$) and a borderline-significant decrease of resting plasma glucose levels ($P = 0.08$). There was no effect of the endurance training on resting plasma FFA levels. Both before and after the training period, plasma glucose concentration decreased, whereas plasma FFA and glycerol concentrations increased in response to the acute exercise (Table 1). However, despite the higher

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**Table 1. Arterial plasma concentrations of epinephrine, norepinephrine, glucose, FFA, and glycerol**

<table>
<thead>
<tr>
<th>Plasma Concentration</th>
<th>Pretraining</th>
<th>Posttraining</th>
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<tbody>
<tr>
<td>Epinephrine, nmol/l</td>
<td></td>
<td></td>
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<tr>
<td>0 h</td>
<td>0.45 (0.26–0.86)</td>
<td>0.84 (0.55–1.36)</td>
</tr>
<tr>
<td>3 h</td>
<td>0.96 (0.47–2.43)</td>
<td>2.58 (1.18–7.53)*</td>
</tr>
<tr>
<td>5 h</td>
<td>0.43 (0.25–0.80)</td>
<td>0.82 (0.44–1.74)</td>
</tr>
<tr>
<td>Norepinephrine, nmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>1.26 (0.89–1.84)</td>
<td>1.10 (0.79–1.57)</td>
</tr>
<tr>
<td>3 h</td>
<td>2.81 (1.82–4.67)</td>
<td>6.68 (5.11–8.95)*†</td>
</tr>
<tr>
<td>5 h</td>
<td>1.63 (1.36–1.96)</td>
<td>1.35 (0.94–2.03)</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>5.75 (5.37–6.16)</td>
<td>5.15 (4.85–5.45)</td>
</tr>
<tr>
<td>3 h</td>
<td>3.97 (3.49–4.53)*</td>
<td>3.85 (3.58–4.14)*</td>
</tr>
<tr>
<td>5 h</td>
<td>4.40 (3.93–4.94)*</td>
<td>4.76 (4.36–5.21)</td>
</tr>
<tr>
<td>FFA, μmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>789 (560–1,160)</td>
<td>734 (575–958)</td>
</tr>
<tr>
<td>3 h</td>
<td>1,290 (949–1,815)*</td>
<td>1,920 (1,457–2,602)*</td>
</tr>
<tr>
<td>5 h</td>
<td>1,084 (798–1,523)</td>
<td>1,792 (1,522–2,129)*†</td>
</tr>
<tr>
<td>Glycerol, μmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>119 (83–181)</td>
<td>55 (39–81)†</td>
</tr>
<tr>
<td>3 h</td>
<td>225 (138–401)</td>
<td>260 (165–447)*</td>
</tr>
<tr>
<td>5 h</td>
<td>114 (82–163)</td>
<td>150 (116–198)*</td>
</tr>
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</table>

Values are means, with 95% confidence intervals in parentheses. Arterial plasma concentrations of epinephrine, norepinephrine, glucose, free fatty acids (FFA), and glycerol at rest (0 h), at the end of the acute exercise (3 h), and after 2 h of recovery (5 h) from 3 h of 2-legged knee extensor exercise performed before (pretraining) and after (posttraining) 10 wk of endurance training ($n = 7$). *$P < 0.05$, difference from rest. †$P < 0.05$, difference between pre- and posttraining.

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Fig. 1. Skeletal muscle glycogen content (glycogen concentration; [glycogen]) (n = 6) at rest (0 h), at the end of the acute exercise (3 h), and after 2 h of recovery (5 h) from 3 h of 2-legged knee extensor exercise performed before (pretraining) and after (posttraining) the 10-wk endurance training period, expressed as mmol glycogen/kg skeletal muscle (dry weight; dw). Data are geometric means ± geometric SE. Open bars, results from the 3-h exercise experiment performed before the endurance training; filled bars, results from the 3-h exercise experiment after the training period. *$P < 0.05$, difference from rest (0 h). SP $P < 0.05$, difference between pre- and posttraining.
absolute workload during the acute exercise after the training period, plasma glucose concentration (Table 1) only decreased significantly from 0 to 3 h posttraining, and pretraining plasma glucose concentration was lower than rest at 3 h as well as 5 h ($P < 0.05$ at both time points). In contrast, plasma FFA concentration was markedly higher at 5 h posttraining compared with pretraining ($P < 0.05$), and plasma glycerol concentration increased to the same level at 3 and 5 h before and after the training.

The endurance training did not change IL-6 mRNA expression of resting skeletal muscle (Fig. 2). However, skeletal muscle IL-6 mRNA content (Fig. 2) increased 76-fold (CI 20–210-fold, $P < 0.05$) relative to the preexercise level immediately after the acute-exercise bout before training, whereas IL-6 mRNA content only increased 8-fold (CI 3–17-fold, $P < 0.05$) from rest in response to the acute-exercise bout after training. Therefore, the skeletal muscle IL-6 mRNA expression after 3 h of exercise (Fig. 2) was markedly lower ($P < 0.05$) after the training period, despite the much higher workload employed during the acute-exercise posttraining. Of note, the resting muscle glycogen levels correlated negatively (Pearson correlation: $P < 0.05, R^2 = 0.34$) with the IL-6 mRNA amount immediately postexercise (Fig. 3). Thus high muscle glycogen content was associated with low IL-6 mRNA levels postexercise and vice versa. And in response to training, there was a tendency for a shift toward higher resting muscle glycogen content and lower postexercise IL-6 mRNA.

The basal plasma IL-6 concentration was not affected by the training period (Fig. 4). In response to the acute exercise, plasma IL-6 levels increased during both the pretraining and the posttraining bouts of acute exercise ($P < 0.05$ on both occasions), with no overall effect of training on plasma IL-6 levels.
the contraction-induced IL-6 mRNA expression was clearly attenuated.

A similar training-induced attenuation of the acute exercise-induced mRNA expression has been observed for pyruvate dehydrogenase kinase-4 (21). On the other hand, it has been shown that both PGC-1α transcriptional activity and mRNA levels are higher in a trained compared with an untrained leg during recovery from prolonged exercise (31). Pilegaard et al. (31) also demonstrated that resting skeletal muscle mRNA levels of HKII, CS, and HAD are increased in a trained muscle compared with an untrained muscle. In the present study, we observed that basal levels of skeletal muscle IL-6 mRNA remained very low and were unaffected by exercise training. This is different from a previous study (11) showing that exercise training decreases basal skeletal muscle IL-6 mRNA expression in patients with chronic heart failure (CHF). However, the same study also showed that patients with CHF have much higher basal skeletal muscle IL-6 mRNA levels compared with healthy age- and sex-matched controls.

Previous studies have demonstrated that reduction of the skeletal muscle glycogen content has a marked influence on the exercise-induced gene expression of IL-6 within the contracting skeletal muscle. Thus exercise with lowered preexercise muscle glycogen content results in a greater transcriptional activation of IL-6 (19) compared with exercise with normal preexercise glycogen levels in the skeletal muscle. In the present study, resting muscle glycogen content increased with training, which is in accordance with numerous previous studies (15). However, immediately after 3 h of exercise and 2 h of recovery, muscle glycogen did not differ at trained and untrained conditions. Therefore, it appears that muscle glycogen content at the onset of exercise is a determining factor for the IL-6 mRNA expression in contracting skeletal muscle. This point of view is supported by our results showing that preexercise skeletal muscle glycogen content is negatively correlated with the IL-6 mRNA content immediately after exercise. Although speculative, it is possible that skeletal muscle IL-6 gene expression is enhanced as soon as muscle glycogen content decreases below a certain level reached earlier in the untrained state.

Furthermore, we observed that plasma IL-6 increased to the same extent during the 3-h exercise before and after the training. Although circulating IL-6 protein was not attenuated as skeletal muscle IL-6 mRNA in response to acute exercise, it is remarkable that IL-6 after the acute exercise was not higher after training, since the absolute workload had increased markedly. Of note, it has previously been shown that plasma IL-6 increases with increasing exercise intensity (23). Therefore, markedly higher plasma IL-6 levels would have been expected in response to the acute exercise in the trained state, if the IL-6 response to acute exercise was unaffected by the training per se. Because skeletal muscle is a major contributor to IL-6 in the circulation (9, 39), plasma IL-6 can act as a crude indirect marker of the IL-6 released from the skeletal muscle. Therefore, it is not likely that skeletal muscle synthesis of IL-6 protein was higher in response to the acute exercise after the training period. However, although IL-6 protein within skeletal muscle can be determined qualitatively with the use of immunohistochemistry (27), precise quantitative methods are not yet available.

In the present study, the attenuated decrease of plasma glucose levels and increased plasma FFA levels after acute exercise, as well as the increased resting skeletal muscle activity of CS and HAD, indicate a significant training adaptation. But in contrast to previous training studies (28), we observed increased plasma levels of catecholamines and FFA in response to acute exercise in the trained state. However, because the same relative workload was employed before and after exercise, the absolute workload was markedly higher after the training. When the same absolute workload is used before and after training (thus a lower relative workload in the trained state), it has been shown that the exercise-induced increase of catecholamines and FFA in plasma is attenuated after training (28). Of note, the same study showed that, despite the lower availability of FFA in the circulation in the trained state, the total fat oxidation is higher because of increased oxidation of intramuscular triglycerides. The absent attenuation of the catecholamine and FFA response to acute exercise in the trained state could, however, also be related to the use of dynamic knee extensor exercise as the training mode in the present study, because the muscle mass involved in the training may be too small to induce a major systemic training adaptation.

It has previously been shown that IL-6 derived from contracting skeletal muscle is sensitive to preexercise muscle glycogen content, and that circulating IL-6 can increase lipolysis and fat oxidation (14). Thus, from a teleological point of view, it seems reasonable that IL-6 derived from contracting skeletal muscle is required less in the trained state, since several other potent adaptations leading to decreased dependence on carbohydrates and increased utilization of fat as substrate have already taken place.

In conclusion, the present results show that the magnitude of the exercise-induced IL-6 mRNA response in contracting skeletal muscle was reduced by 10 wk of training, possibly related to the training-induced increase in basal muscle glycogen content.

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REFERENCES


