Effect of high-intensity exercise training on lactate/H\(^+\) transport capacity in human skeletal muscle

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The present study examined the effect of high-intensity exercise training on muscle sarcolemmal lactate/H\(^+\) transport and the monocarboxylate transporters (MCT1 and MCT4) as well as lactate and H\(^+\) release during intense exercise in humans. One-legged knee-extensor exercise training was performed for 8 wk, and biopsies were obtained from untrained and trained vastus lateralis muscle. The rate of lactate/H\(^+\) transport determined in sarcolemmal giant vesicles was 12% higher (P < 0.05) in the trained than in untrained muscle (n = 7). The content of MCT1 and MCT4 protein was also higher (76 and 32%, respectively; n = 4) in trained muscle. Release of lactate and H\(^+\) from the quadriceps muscle at the end of intense exhaustive knee-extensor exercise was similar in the trained and untrained leg, although the estimated muscle intracellular-to-interstitial gradients of lactate and H\(^+\) were lower (P < 0.05) in the trained than in the untrained muscle. The present data show that intense exercise training can increase lactate/H\(^+\) transport capacity in human skeletal muscle as well as improve the ability of the muscle to release lactate and H\(^+\) during contractions.

THE DECLINE in muscle force during development of muscle fatigue during high-intensity exercise is associated with accumulation of lactate and a concomitant lowering of pH in the muscle. Several studies have demonstrated that reduced muscle pH can interfere with the excitation-contraction coupling process (9). Therefore, the removal of lactate and H\(^+\) from skeletal muscle is likely to be of importance for the ability to maintain force during high-intensity exercise.

It is well known that the main part of the sarcolemmal lactate flux is mediated by the lactate/H\(^+\) transport systems in both animal (13, 14, 32, 35) and human (17) skeletal muscle, and the lactate/H\(^+\) transporters have been shown to be the muscle membrane transport systems with the highest capacity for H\(^+\) removal in rat muscle (15). Several monocarboxylate transporter (MCT) proteins have been identified and cloned (10–12, 31). In rat skeletal muscle, MCT1 has been found predominantly in oxidative muscles and only in small amounts in glycolytic muscles (22, 36), whereas MCT2 seems to be absent or present only in low concentrations in rat skeletal muscle (10, 12). Recently, MCT3 to MCT7 were cloned and sequenced (31), and the MCT4 isoform (formerly called MCT3) has been demonstrated in both oxidative and glycolytic rat muscle (31).

The lactate/H\(^+\) transport capacity of rat skeletal muscle has been reported to be enhanced by training (24, 28) as well as by chronic low-frequency stimulation (21). MCT1 was also found to be increased with chronic electrical stimulation and high-intensity training in rats (23) and after training in humans (6). Furthermore, a cross-sectional study showed that speed endurance-trained athletes have a higher capacity to transport lactate than untrained and less trained subjects (27). The latter finding suggests that lactate/H\(^+\) transport can be improved by training also in humans, but it cannot be excluded that the higher lactate/H\(^+\) transport capacity observed in the athletes was due to biological selection.

Thus the purpose of the present study was to examine whether training can induce changes in muscle lactate/H\(^+\) transport capacity and lactate/H\(^+\) transporter proteins in humans and furthermore to evaluate to what extent such alterations will affect lactate and H\(^+\) release during intense exercise.

METHODS

Subjects

Seven male subjects, aged from 20 to 24 yr, with an average height and weight of 183 cm (range: 174–187) and 81.8 kg (range: 55.0–107.7), respectively, participated in the study. The body mass was similar before and after the training period. The subjects were habitually physically active without taking part in competitive sports, and they maintained their normal activity pattern during the training period. The subjects were informed about the experimental procedure before they gave their informed consent, and the study was approved by the Copenhagen Ethics Committee.

The mass of the quadriceps femoris muscle of the untrained and the trained leg was estimated from anthropometric and skinfold measurements of the thigh (3), and no difference in the mass of the quadriceps muscle of the trained (3.3 ± 0.1 kg) and the untrained leg (3.3 ± 0.2 kg) was observed.

Training

The training consisted of dynamic one-legged knee extensor exercise in the supine position on a modified Krogh bicycle.
ergometer (2). Before initiating the training period, the subjects carried out three different one-legged performance tests with each leg as described in One-Legged Performance Tests. Before training, there was no difference in performance between the legs, and the leg to be trained was selected randomly.

The training lasted for 8 wk, and the frequency of training increased from 3 days/wk in the first week to 5 days/wk in the fifth week. The subjects performed three sets of intermittent exercise consisting of 2 × 30-s and 3 × 1-min bouts interspersed with 2-min rest periods per session in the first 2 wk, four sets in the following 2 wk, and five sets in the last 4 wk. The exercise bouts were performed with the flywheel preset (flying start) at kicking frequencies of 80 and 60 rpm for the 30-s and 1-min exercise bouts, respectively. The resistance was set at 100–120 N for the 30-s bouts, and, to exhaust the subjects at the end of the 1-min bouts, a resistance of 50–100 N was selected. Each training session was preceded by a 10-min warm-up period at 10 W.

One-Legged Performance Tests

Before and at the end of the training period the subjects performed three different performance tests with both the untrained and trained leg. Each test was performed on a separate day and was preceded by a 10-min warm-up period at an intensity of 10 W.

Maximal kicking. In the supine position, the subjects exercised maximally for 30 s, with flying start at 80 rpm and resistance of 120 N. Kicking frequency was recorded continuously during the test. Peak power (the highest power output in a 5-s interval) and mean power (average power during the 30-s period) were determined.

Endurance test. In the supine position, subjects performed one-legged knee-extensor exercise at a power output of 73.5 (55.0–93.5) W to exhaustion. The work rates were selected individually based on a number of preexperiments to obtain an exercise time of ~3 min.

Maximal isometric contraction. In the supine position, the subjects performed three one-legged knee-extensor maximal isometric contractions separated by 1-min rest periods, and peak isometric force was determined.

Muscle Sampling

For three of the subjects, muscle biopsies were obtained from the experimental leg before and 48 h after the last training session. For the other four subjects, muscle biopsies were obtained both from the trained and the untrained leg 48 h after completion of the training period. The subjects reported to the laboratory, and after 30 min of rest in the supine position three to four needle muscle biopsies were obtained from the same site of the trained and the untrained muscle. About 250 mg were used for sarcolemmal giant vesicle formation; one part of the biopsies was prepared for histochemical analyses, and the remaining portion (10–50 mg) was frozen in liquid N2.

Muscle Analyses

Sarcolemmal giant vesicle transport. The rate of lactate transport was determined in sarcolemmal giant vesicles produced by collagenase treatment of muscle biopsies as previously described (14, 17). Vesicles were inspected by phase contrast microscopy, and the diameters measured ranged from 2 to 25 μm with a median diameter of 4.4 μm, which is similar to previous findings for human skeletal muscle (27). Average vesicle diameter distributions were determined for the untrained and the trained muscles, and there was no difference between the distributions. The lactate efflux was determined during zero-trans conditions with 30 mM lactate. Briefly, vesicles were preloaded with lactate and radiolabeled lactate. The efflux was measured upon transferring the vesicles to a lactate-free medium. Fourteen samples were collected from the medium within the first 10 minutes, and the initial rate of efflux was calculated from a curve fit, as previously described (27). The carrier-mediated lactate transport was estimated by subtracting the flux, which previously has been found to occur via simple diffusion, from the total lactate transport (27) assuming that the diffusion component was similar in the trained and untrained muscle.

MCT isofrom determination. In four of the subjects, MCT isoforms were determined in samples from untrained and trained legs. Total crude homogenate samples were prepared and loaded in equal amounts of protein in each lane on the same gel. Subsequently, sodium dodecyl sulfate-polyacryl-

amide gel electrophoresis was run, and proteins were trans-

ferred to an Immobilon P-polyvinylidene difluoride mem-

brane (Millipore IPVH 00010) as previously described (28).

Polyconal antibodies were raised to human MCT1 and MCT4 in rabbits using the protocol previously described (30). These antibodies contained the COOH-terminal 16 residues of MCT1 (12) and MCT4 (31), respectively, supplemented with an NH2-terminal cysteine for coupling to keyhole limpet hemocyanin. A horsearadish peroxidase-labeled goat anti-rabbit antibody was used as secondary antibody, and antibody-antigen complexes were visualized by the enhanced chemiluminescence detection method. Densitometric scanning (SigmaGel) of the blots was performed for quantification of the content of MCT1 and MCT4 in the muscle samples.

Muscle enzyme and buffer capacity. A part of the muscle samples was freeze-dried and analyzed fluorometrically for citrate synthase, L-3-hydroxyacyl-CoA-dehydrogenase (HAD), phosphofructokinase, total lactate dehydrogenase (LDH), and LDH1,4,5 activities (18). Muscle pH was measured by a small glass electrode (Radiometer GK 2801) after homogenization of freeze-dried samples in a nonbuffered solution containing 145 mM KCl, 10 mM NaCl, and 5 mM sodium fluoride (19, 26). After having adjusted pH of the sample to 7.1 with 0.01 M NaOH, the sample was titrated to pH 6.0 by serial additions of 0.01 M HCl followed by titration back to pH 7.1 by serial additions of 0.01 M NaOH. The pH was measured after each addition. The non-HCO3- physiochemical buffer capacity was determined from the number of moles of H+ required to change pH from 7.1 to 6.5 and was expressed as millimoles H+ per kilogram wet weight per pH (19, 26).

Histochemical analysis. The part of the muscle biopsies that was used for histochemical analyses was mounted in embedding medium, frozen in isopentane precooled in liquid N2, and stored at −80°C until analyzed. Serial transverse sections were cut in a cryostat and either stained to characterize fibers as type I, type IIA, and type IIB (7) or to visualize the capillaries (1). Fiber areas, fiber types, and capillary density were determined using a COMMAS image scanner (SBsysCOMFAS; Scan Beam, Hadsund, Denmark).

In Vivo Experiments

Protocols. To determine lactate and H+ release during intense exercise, five of the subjects carried out one out of two one-legged knee-extensor protocols 2 days after the last training session. In both protocols the subjects arrived at the laboratory after a light breakfast, and after 15 min of supine rest catheters were inserted in a femoral artery and vein of
each leg. After another 30 min of rest in the supine position, the subjects performed one-legged (the leg was randomly selected) exercise at 10 W for 10 min as warm-up and then rested for another 10 min.

Two of the subjects performed continuous incremental (20–70 W) one-legged exercise until exhaustion, and after 1 h of rest the protocol was repeated with the other leg. The average exercise duration was 698 (690 and 705) and 793 (715 and 870) s for the untrained and the trained leg, respectively. The other three subjects performed one-legged knee-extensor exercise at a constant power output until exhaustion with both the untrained [78.5 (range: 52.0–93.9) W] and trained [78.0 (range: 54.1–91.5) W] leg separated by 105 min. The duration of the exercise for the untrained and trained leg was 165 (130–217) and 260 (203–301) s, respectively.

Arterial and venous blood samples were drawn simultaneously from the exercising leg at the end of exercise. The samples were instantly placed on ice, a portion of each sample was centrifuged rapidly (<15 s), and plasma was collected. Femoral venous blood flow during exercise was measured by the thermodilution technique (3) immediately before blood sampling. Muscle biopsies were obtained from the middle portion of the vastus lateralis muscle at exhaustion, and the samples were frozen rapidly in liquid N2.

BLOOD ANALYSIS. Oxygen saturation and hemoglobin (Hb) concentration of the blood samples were determined using an OSM-3 (Radiometer, Copenhagen, Denmark). Blood pH and partial pressures of oxygen and carbon dioxide (PCO2) were measured as described in OSM-3 (Radiometer, Copenhagen, Denmark). Blood pH and partial pressures of oxygen and carbon dioxide (PCO2) were measured with the Astrup technique, and from these the actual base excess (ABE) was calculated (ABL 30; Radiometer; see Ref. 33). The ABE values were adjusted (ABEadj) by taking into account saturation of Hb as described by Siggaard-Andersen (33). Whole blood and plasma lactate concentrations were measured on a YSI analyzer (Yellow Springs Instruments, Yellow Springs, OH).

MUSCLE ANALYSIS. The water content of the muscle samples was determined by weighing the samples before and after freeze-drying. Muscle lactate concentrations of freeze-dried samples were determined fluorometrically (18). Muscle pH was measured as described in Muscle enzyme and buffer capacity.

Calculations. Lactate and H+ release across the thigh was determined by multiplying blood flow by the venous-arterial concentration difference.

The cellular lactate concentration (mmol/l cell water) was calculated as ([Lac]m - 0.15·[Lac]pl)/(H2Om - 0.15), where [Lac]m is the wet weight lactate concentration in the biopsy, [Lac]pl is the venous plasma lactate concentration corrected for an assumed 6% protein content in venous plasma, H2Om is the fractional water content in the biopsy, and 0.15 is the assumed fractional interstitial volume of total muscle water content during exercise (34). The venous plasma lactate concentration was considered to be the best estimate of the interstitial lactate concentration. The measured H+ concentration in the homogenized biopsy was assumed to represent the cellular H+ concentration. Lactate and H+ gradients between the cellular space and the interstitium were estimated as the differences between the muscle cellular concentrations and the venous plasma concentrations.

Statistics

Data are presented as means ± SE. The results from the untrained and trained leg were compared using the Wilcoxon ranking test for paired data. A significance level of 0.05 was chosen.

Table 1. Peak and mean power during 30-s maximal one-legged knee-extensor exercise, and peak knee-extensor isometric force for UT and T leg

<table>
<thead>
<tr>
<th></th>
<th>UT</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 s Maximum</td>
<td>185 ± 10</td>
<td>214 ± 12*</td>
</tr>
<tr>
<td>Peak power, W</td>
<td>164 ± 6</td>
<td>198 ± 10*</td>
</tr>
<tr>
<td>Mean power, W</td>
<td>9.1 ± 1.5</td>
<td>21.1 ± 6.1*</td>
</tr>
<tr>
<td>Endurance test, kJ</td>
<td>566 ± 36</td>
<td>657 ± 46*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects. UT, untrained; T, trained. *Significantly different from untrained leg, P < 0.05.

RESULTS

Performance

For the trained leg, peak and mean power during the 30-s maximal knee extensor exercise test was 16 and 15%, respectively, higher (P < 0.05) than for the untrained leg (Table 1). In addition, the work performed during the endurance exercise test was 132% greater (P < 0.05), and peak isometric force was 16% higher (P < 0.05) for the trained than for the untrained leg.

Lactate Transport and MCT Expression

The rate of lactate transport in sarcolemmal giant vesicles obtained from the trained muscle was higher (P < 0.05) than in vesicles from the untrained muscle (64.3 ± 4.2 vs. 57.2 ± 2.6 pmol·cm⁻²·s⁻¹).

Representative Western blots showing the expression of MCT1 and MCT4 in the untrained and trained muscle of two subjects are given in Fig. 1. The average contents of MCT1 and MCT4 protein in the trained muscle were 70 ± 32 and 33 ± 10% higher (P < 0.05), respectively, than in the untrained muscle.

Muscle Buffer Capacity and Enzymes

The non-HCO₃ physicochemical buffer capacity was the same for the trained and untrained muscle (45.9 ± 4.1 vs. 44.9 ± 4.8 mmol·kg wet wt⁻¹·pH⁻¹). The activity of HAD in the trained muscle was 20% higher (P < 0.05) than in the untrained muscle, whereas there were no significant differences in the activity of citrate synthase, phosphofructokinase, or LDH (Table 2).

Fig. 1. Representative Western blots showing the content of monocarboxylate transporters MCT1 and MCT4 in homogenized muscle samples made from untrained (UT) and trained (T) muscle of two subjects. Subscript nos. 1 and 2 indicate subjects 1 and 2, respectively.
Table 2. PFK, HAD, CS, and LDH activities in UT and T vastus lateralis muscles as well as MCT1 and MCT4 expression in relation to UT muscle

<table>
<thead>
<tr>
<th></th>
<th>PFK</th>
<th>HAD</th>
<th>CS</th>
<th>LDH total</th>
<th>LDH 1+2</th>
<th>LDH 3+4+5</th>
<th>MCT1, %</th>
<th>MCT4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT</td>
<td>106±6</td>
<td>41±3</td>
<td>38±2</td>
<td>556±60</td>
<td>185±26</td>
<td>371±35</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>T</td>
<td>121±15</td>
<td>48±3*</td>
<td>45±1</td>
<td>598±107</td>
<td>181±26</td>
<td>417±83</td>
<td>170±32</td>
<td>133±10</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects, except for MCT1 and MCT4, where n = 4. Phosphofructokinase (PFK), 3-hydroxyacyl-CoA dehydrogenase (HAD), citrate synthase (CS), and lactate dehydrogenase (LDH) activities (mmol·kg wet wt⁻¹·min⁻¹) in untrained (UT) and trained (T) vastus lateralis muscle as well as monocarboxylate transporter MCT1 and MCT4 expression in relation to UT muscle.

*Significantly different from untrained muscle, P < 0.05.

Fiber Type Distribution and Capillarization

There was no difference in the relative distribution of the three main fiber types in the trained and untrained muscle. The fiber area of each fiber type and the number of capillaries were also the same in the two muscles (Table 3).

Lactate Release During Exercise

Femoral arterial and venous blood and plasma lactate concentrations were higher (n = 5; P < 0.05) in the trained than in the untrained leg at the end of exercise (Fig. 2). The femoral venous-arterial lactate difference at the end of exercise was similar in trained compared to untrained muscle (2.33 ± 0.07 vs. 1.97 ± 0.21 mmol/l, n = 5). Leg blood flow was 5.64 ± 0.45 and 5.86 ± 0.31 l/min at the end of exercise in the untrained and trained leg, respectively. No difference in lactate release between the trained (13.7 ± 0.9 mmol/min) and untrained (11.7 ± 1.7 mmol/min) leg was observed.

Muscle lactate concentration at exhaustion was lower (P < 0.05) in the trained than in the untrained muscle (13.3 ± 2.6 vs. 17.7 ± 2.9 mmol/kg wet wt). Similarly, the estimated intracellular-to-interstitial gradient of lactate at the point of exhaustion was lower (P < 0.05) in the trained than in the untrained muscle (4.8 ± 3.3 vs. 17.4 ± 4.3 mmol/l).

H⁺ Release and Acid-Base Balance During Exercise

The femoral arterial and venous actual base excess corrected for degree of Hb saturation (ABE adj) was lower (P < 0.05) in the trained than in the untrained leg at the end of exercise (Fig. 2A), and the arterial-venous difference in ABE adj was similar in trained (4.93 ± 0.85 mmol/l) and untrained (4.56 ± 0.31 mmol/l) legs. The estimated H⁺ release in the trained and untrained legs was the same at the end of exercise (29.3 ± 5 vs. 26.1 ± 3.5 mmol/min).

Muscle pH at exhaustion was the same in the trained and untrained muscle (6.97 ± 0.04 vs. 6.86 ± 0.06). The estimated intracellular-to-interstitial H⁺ gradient was lower (P < 0.05) in the trained than in the untrained muscle (85.1 ± 19.9 vs. 129.6 ± 18.3 mmol/l).

Arterial and venous pH and P CO₂ were the same in the two legs at exhaustion, whereas the arterial blood HCO₃⁻ concentration was lower (P < 0.05) in the trained than in the untrained leg at the end of exercise (Fig. 3).

DISCUSSION

The main findings of the present study were that high-intensity training induced an increase in the sarcolemmal lactate/H⁺ transport capacity as well as an enhanced content of MCT1 and MCT4 protein in human skeletal muscle. These changes were associated with similar release rates of lactate and H⁺ during intense exercise before and after training, although the intracellular-to-interstitial gradients of lactate and H⁺ were lower after training. Combined, these results suggest that the muscle lactate/H⁺ transporters can be altered by intense training and that they play an important role in the regulation of lactate and pH in human skeletal muscle.

Training has been reported to enhance the lactate transport capacity of rat skeletal muscle (24, 28). Furthermore, the observation that athletes have a higher capacity to transport lactate than untrained and untrained subjects (27) indicates that training also can affect lactate/H⁺ transport in humans. The present findings demonstrate for the first time that high-intensity training can elevate the rate of sarcolemmal lactate/H⁺ transport in human skeletal muscle. It cannot be excluded that a difference in lactate/H⁺ transport capacity existed between the two legs already before the training was initiated, because for four of the subjects biopsies were obtained from both legs at the end of the training period. However, this possibility seems unlikely, since the performance ability was similar for the two legs before the training period for these...
Fig. 2. Femoral arterial (open bars) and venous (hatched bars) blood actual base excess (A) and plasma (B) and blood (C) lactate concentration at the end of intense knee-extensor exercise in untrained and trained leg. Values are means ± SE; n = 5 subjects. ABEadj, adjusted actual base excess. *Significantly different from untrained leg, P < 0.05.

Fig. 3. Femoral arterial (open bars) and venous (hatched bars) blood PCO2 (A), pH (B), and HCO3 (C) at the end of intense knee-extensor exercise in untrained and trained leg; n = 5 subjects. Values are means ± SE. *Significantly different from untrained leg, P < 0.05.
subjects, and the rate of sarcolemmal lactate transport was enhanced in all three subjects in whom biopsies were obtained from the same leg before and after training.

The higher content of MCT1 and MCT4 protein in the trained muscle can in part explain the observed increase in the sarcolemmal lactate/H\(^+\) transport. However, in addition to MCT1 and MCT4, mRNA for other MCT isoforms have been found in human skeletal muscle (31), and the protein quantity of these may also have been altered. In addition, the relative contributions of MCT1 and MCT4 to total lactate/H\(^+\) transport are not known. For these reasons, it is not to be expected that the relative changes in MCT1 and MCT4 are reflected in similar relative changes in vesicular lactate transport. In addition, it is likely that free diffusion of lactate at a given muscle lactate gradient is unaltered by training. Therefore, the relative change in carrier-mediated lactate transport was presumably larger than the observed percentage change in vesicular lactate transport.

Determination of MCT1 and MCT4 in various rat muscles have revealed that MCT4 exists in both oxidative and glycolytic muscles (36), whereas MCT1 predominantly exists in oxidative muscles (23). Therefore, it could be that the presently observed more marked increase in MCT1 compared with the change in MCT4 was due to a smaller basal content of MCT1 than of MCT4 in the muscle, since the relative contribution of fast-twitch fibers was ~35%. The training-induced increase in MCT1 and MCT4 was not caused by a general elevation in muscle proteins, since the MCT content is expressed per milligram of total muscle protein. On the other hand, the lactate/H\(^+\) transporter proteins were not the only membrane proteins that were affected, as evidenced by the number of Na\(^+\)-K\(^+\) pumps in the plasma membrane, which were 13% higher in the trained than in the untrained muscle in the present study (unpublished data). Furthermore, the higher HAD activity in the trained than in the untrained muscle shows that the training also elicited adaptations in mitochondrial proteins, whereas no significant changes were observed in other muscle enzymes.

To evaluate the importance of the training-induced improvement in lactate/H\(^+\) transport, release rates of lactate and H\(^+\) were examined during short-lasting, exhaustive exercise with the trained and untrained leg in five of the subjects. The finding of similar release rates of lactate and H\(^+\) in the two legs at the point of exhaustion, despite a lower intracellular-to-interstitial gradient of lactate and H\(^+\) in the trained than in the untrained muscle (Fig. 4), may be explained by the enhanced sarcolemmal lactate/H\(^+\) transport capacity in the trained muscle.

An additional reason for the need of a lower driving force to obtain a given transmembrane flux of H\(^+\) in the trained muscle could be that the capacity of the Na\(^+\)/H\(^+\) exchange system also increased in response to the high-intensity training, as has been demonstrated in rats (16). The training solely affected muscle pH regulation via changes in membrane transport systems, since the training had no influence on the physiochemical buffer capacity, which is in accordance with previous reports (20, 25).

In summary, the present data show that high-intensity training can enhance the sarcolemmal lactate/H\(^+\) transport capacity as well as the contents of MCT1 and MCT4 protein in human skeletal muscle. These changes were associated with reduced transmem-
brane gradients of lactate and H+ in the trained leg for a given release rate of lactate and H+. This suggests that the training-induced changes in lactate/H+ transport are of importance for the regulation of muscle lactate and pH in humans.

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