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Effects of acute and chronic exercise on sarcolemmal MCT1 and MCT4 contents in human skeletal muscles: current status

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Exercise and Active Living and ⁵School of Sport and Exercise Science, Victoria University, Melbourne, Australia; ⁶Le Centre Hospitalier Universitaire, Montpellier, France; and ⁷Integrative Biology, University of California, Berkeley, California, USA

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Thomas C, Bishop DJ, Lambert K, Mercier J, Brooks GA. Effects of acute and chronic exercise on sarcolemmal MCT1 and MCT4 contents in human skeletal muscles: current status. *Am J Physiol Regul Integr Comp Physiol* 302: R1–R14, 2012. First published October 19, 2011; doi:10.1152/ajpregu.00250.2011.—Two lactate/proton cotransporter isoforms (monocarboxylate transporters, MCT1 and MCT4) are present in the plasma (sarcolemmal) membranes of skeletal muscle. Both isoforms are symports and are involved in both muscle pH and lactate regulation. Accordingly, sarcolemmal MCT isoform expression may play an important role in exercise performance. Acute exercise alters human MCT content, within the first 24 h from the onset of exercise. The regulation of MCT protein expression is complex after acute exercise, since there is not a simple concordance between changes in mRNA abundance and protein levels. In general, exercise produces greater increases in MCT1 than in MCT4 content. Chronic exercise also affects MCT1 and MCT4 content, regardless of the initial fitness of subjects. On the basis of cross-sectional studies, intensity would appear to be the most important factor regulating exercise-induced changes in MCT content. Regulation of skeletal muscle MCT1 and MCT4 content by a variety of stimuli inducing an elevation of lactate level (exercise, hypoxia, nutrition, metabolic perturbations) has been demonstrated. Dissociation between the regulation of MCT content and lactate transport activity has been reported in a number of studies, and changes in MCT content are more common in response to contractile activity, whereas changes in lactate transport capacity typically occur in response to changes in metabolic pathways. Muscle MCT expression is involved in, but is not the sole determinant of, muscle H⁺ and lactate anion exchange during physical activity.

lactate transport capacity; monocarboxylate transporters; training

SEVERAL LACTATE/PROTON COTRANSPORTER [monocarboxylate (lactate/pyruvate) transporter: MCT] isoforms are expressed in mammalian skeletal muscle, but, of those, MCT1 and MCT4 are the most prevalent. Since 1996, interest has focused on the effects of acute and chronic exercise on the membrane content of these two isoforms. This article will review recent progress in our understanding of the importance of lactate/proton cotransporters in the regulation of skeletal muscle metabolism and the effects of acute and chronic exercise on MCT content. In addition, we will review evidence investigating the cellular and molecular mechanisms responsible for changes in MCT content in response to contractile activity and changes in metabolic pathways.

Sarcolemmal Lactate/Proton Cotransporters in Skeletal Muscle

Metabolism and exchange of lactate. During heavy exercise, the rapid increase in the energy demand of contracting skeletal muscles is associated with an increase in glycolysis and the subsequent production and accumulation of lactate and proton (for review, see Ref. 128). To maintain a fast glycolytic flux during exercise, lactate production is catalyzed by the M-enriched lactate dehydrogenase isoforms (i.e., M4, M3H isoforms of LDH), which prevents pyruvate accumulation and, more importantly, maintains the supply of the proton-electron transporter nicotinamide adenine dinucleotide (NAD⁺) to glycolysis (see Ref. 68). Thus, lactate production favors the recycling of NADH from glycolysis, allowing the production of two ATP molecules per molecule of glucose utilized in glycolysis.

Although lactate was originally considered a “waste product,” oxidative muscle fibers can take up lactate from the circulation, or lactate released from neighboring fibers. Hence,

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the subsequent metabolic use of intramuscular lactate results in ATP production without conversion to glucose in the liver. The pathway of intramuscular lactate disposal involves conversion to pyruvate and subsequent entry into the Krebs cycle, in which pyruvate can be oxidized (27, 141). Glyconeogenesis from lactate has been observed in human skeletal muscles (for review, see Ref. 47), in IIa and IIb rabbit (38) and rat (101) muscle fibers, but this conversion is negligible in type I fibers. Lactate also competes successfully with glucose as a carbohydrate fuel source in skeletal muscle, thus sparing blood glucose for use by other tissues during exercise (91, 107). Because of the difficulty in accessing the intracardiac circulation, there are limited data on the metabolic use of lactate by the heart. However, the available data (53) clearly show that during leg exercise in humans, lactate becomes the major fuel source for the heart. Indeed, net carbohydrate fuel is transferred from the legs to the heart during human exercise.

Because of the widely acknowledged importance of lactate as an energy source, contemporary reviewers often overlook the first demonstrated example of lactate use during exercise, that of Cori cycle activity to support glycemia via gluconeogenesis from lactate (22). However, by means of dual isotope tracers (49), monitoring of secondary labeling of glucose from infused ^{13}C -labeled lactate (12), and mass isotopomer discrimination analysis (146), it is clear that during exercise lactate is by far the most important gluconeogenic precursor in humans during exercise, as it is in fasting (106). Thus, lactate is not only a compound that accumulates in various compartments during intense muscle activity, but it is also an important intermediary metabolite serving as an important link between energy metabolism in different tissues.

Lactate/proton cotransporters. In the 1970s, a saturation phenomenon was observed for lactate transport from exercising human skeletal muscle to the blood compartment (62, 66); it was subsequently reported that muscle lactate uptake also displayed a saturation effect (67, 68, 129, 130). A monocarboxylate transporter family, which mediates the 1:1 transmembrane cotransport of lactate and protons via a facilitated diffusion mechanism was first identified in red blood cells in the early 70 s by Halestrap and Denton (57), and later in skeletal frog muscle (93) and cardiac myocytes (121). Subsequently, different studies have determined the molecular identity of these MCTs (51, 120, 123, 150). The MCT family currently comprises 14 members (58, 102, 109). MCT distribution is ubiquitous, but intracellular distribution varies among the different cell types (e.g., plasma membrane, mitochondrial membrane, peroxisome) (23, 95), although this distribution is not universally accepted (34). In skeletal muscle, the most important and well-described isoforms are MCT1 and MCT4 (19).

Lactate/proton cotransport is bidirectional, which means that these transporters facilitate lactate flux, relative to lactate concentration and the proton gradient, either into or out of the skeletal muscle (30, 68, 70, 100), according to the cell-to-cell "lactate shuttle" (27). This cell-to-cell lactate shuttle (27) provides the basic framework for the understanding of lactate metabolism and exchange. In the context of this review, MCTs play crucial roles in the lactate shuttle by facilitating the release and uptake of lactate by diverse tissues. Without the MCTs, lactate could not be as rapidly exchanged between tissue compartments, under conditions ranging from postprandial to sustained exercise (31, 37, 58, 149). In addition to lactate,

MCTs can also transport other monocarboxylates (pyruvate, acetate, propionate, and butyrate) and keto acids derived by transamination (α -ketovalerate and α -ketoisocaproate), which have important metabolic roles (120). These transporters are, therefore, important for the regulation of cellular pH and lactate exchange, and play a significant role in the coordination of metabolism.

MCT1 has been found predominantly in oxidative human muscles ($r = 0.66$, $P < 0.01$), and only in small amounts in glycolytic human muscles (119), whereas MCT4 has not been demonstrated to be correlated with fiber type, and to present large interindividual variations in humans (39, 119). The K_m value (an indicator of the affinity of the transporter protein for lactate; a low K_m value suggests a high affinity) of MCT1 [3.5–8.3 mM (21, 25, 37)] is lower than that of MCT4 [25–31 mM (25, 37)], indicating a higher affinity of MCT1 for lactate compared with MCT4. With high lactate transport capacity and low affinity, MCT4 seems suited to play a role in the extrusion of lactate from glycolytic fibers (150). In addition, a high K_m (>100 mM) for pyruvate in glycolytic tissues (37) has to be mentioned. Indeed, this prevents loss of pyruvate, which would be a disaster for glycolytic fibers, since NAD^+ could no longer be regenerated by conversion of pyruvate to lactate, and thus, glycolysis would stop. Furthermore, in contrast, its high affinity for lactate and greater expression in more oxidative fibers strongly suggests that a key physiological role of MCT1 is to take up lactate from the circulation (24).

Both MCT1 and MCT4 contents have been reported to be associated with net muscle lactate release during submaximal exercise in humans (21, 39). Although MCT1 and MCT4 are coexpressed in muscle (10, 39), only MCT1 appears to contribute to increased metabolic use of lactate after muscle activity, by facilitating lactate influx into myocytes and cardiocytes (39). This conclusion is supported by studies reporting correlations between maximal muscle oxidative capacity and MCT1 content in both rats (98) and humans (39); however, this relationship between muscle oxidative capacity and MCT expression has not been observed in all studies (144). This trend for a dissociation between oxidative metabolism and lactate transport exchange is also in agreement with results obtained after high-intensity training (77, 116, 131), endurance training (131), or a single, prolonged exercise bout in humans (55). For further information on the role and characterization of the different isoforms of MCT, and the integration of lactate metabolism in the lactate shuttle, the reader is referred to previous reviews (26, 27, 54, 68, 74).

Cellular regulation: role of the pH gradient in regulating lactate transport activity during exercise. During high-intensity exercise, the production of lactate is associated with an increase in protons (H^+) (i.e., a decrease in muscle pH) (64, 92). The management of muscle H^+ produced during exercise occurs via intracellular buffering (proteins and phosphates, and metabolic buffering) (16), and also via a number of different transport systems (71) (Fig. 1). MCT1 and MCT4 play important roles in the regulation of intracellular pH during high-intensity exercise (75), since they mediate most, but not all, of the H^+ efflux (69, 71, 72); other systems, such as the sarcolemmal sodium-hydrogen exchanger, are also activated during exercise. Nonetheless, during exercise, the lactate/ H^+ removal via MCTs exceeds the sum of the H^+ removal via the Na^+/H^+ exchanger and the bicarbonate-dependent system (68, 72, 117).

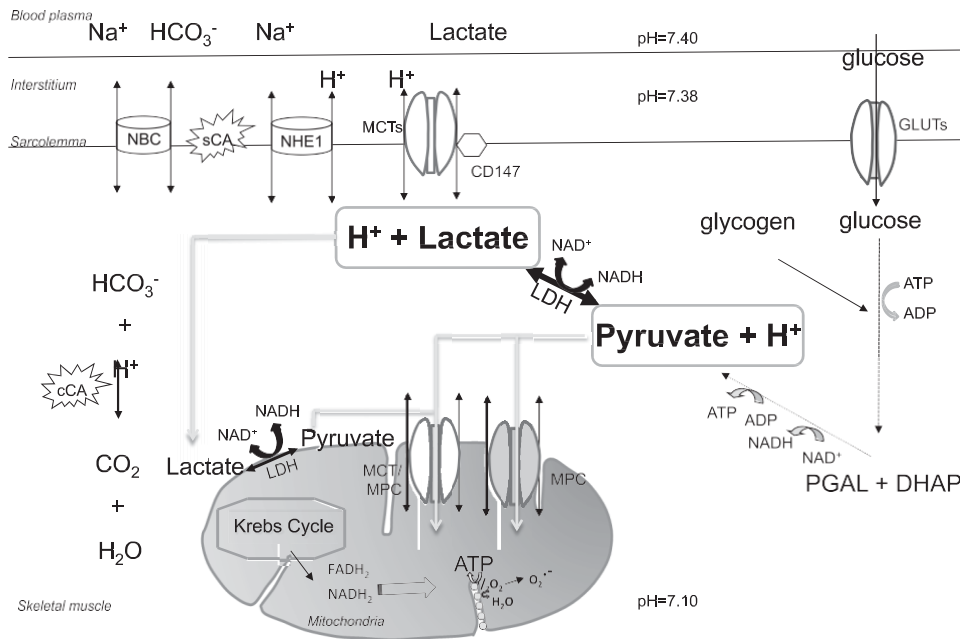


Fig. 1. Presentation of muscle lactate and proton regulation. Carbonic anhydrase (CA) exists as cytosolic (cCA) and membrane-bound (sCA) CA isoforms. NBC, sodium-bicarbonate cotransporter; NHE1, Na⁺-H⁺ exchanger isoform 1; MCTs, monocarboxylate transporters (lactate-proton co-transporter); GLUTs, glucose transporters; CD147, cluster of differentiation 147; PGAL, phosphoglycerate; DHAP, dihydroxyacetonephosphate; LDH, lactate dehydrogenase; MPC, mitochondrial pyruvate carrier. pH values in blood plasma, interstitium, and skeletal muscle are values at rest.

In working muscle, MCTs have a role in facilitating H⁺ efflux and thus preventing major decrements in intracellular pH during vigorous exertion (68, 71, 72). For example, a decrease in intracellular pH of 0.5 units accelerates the lactate/H⁺ flux by ≈50%. The subsequent increase in lactate and proton efflux from working myocytes reduces lactate accumulation and limits the decline of intracellular pH. The proton-coupled lactate efflux from Type II fibers, and concomitant decrease in both interstitium and plasma pH, will promote lactate (and proton) uptake by adjacent Type I muscle fibers (71). Therefore, the direction of this cotransport appears to be a function of the pH and lactate gradients, as lactate transport capacity in giant vesicles has been demonstrated to be identical in both directions (73).

Other proteins expressed in the sarcolemmal membrane, such as the carbonic anhydrase enzyme (CA) (52), and the sodium-bicarbonate cotransporter (NBC) (5), also influence extracellular H⁺ exchange and concentration (Fig. 1) and, therefore, complement the actions of the MCT isoforms (5, 7, 8). For example, CA helps to establish a fast equilibria between carbonic acid and CO₂, HCO₃⁻, and H⁺ (52). The activity of CA in muscle is mediated by different isoenzymes, which are located in the extracellular sarcolemmal [sCA isoform, CAIV (52)], or cytosolic [cCA isoform, CAII (52, 79)] compartment. Extracellular sCA facilitates lactate/proton transport across the sarcolemma by acting as an interstitial proton acceptor, and, therefore, maintaining the pH gradient (52, 149). Furthermore, sCA has been shown to facilitate lactate/proton exchange in rat skeletal muscles (149), and when MCT1 and cCA are coexpressed in oocytes, they cooperate with a binding of CA to the MCT1 in the cell membrane of the oocyte that greatly enhances the H⁺ flux via the MCT1 (7); it should be noted, however, that the effect of carbonic anhydrase on MCT1 is independent of its catalytic activity. Similar results have recently been observed between MCT4 and cCA (8). In humans, inhibition of extracellular and intracellular CA has been demonstrated to be

associated with a lower plasma lactate concentration during incremental exercise (135), presumably due to less lactate efflux via MCT.

Different isoforms of NBC have also been detected and quantified in human (79, 82) and rat (82, 143) skeletal muscles. Furthermore, we have reported a significant correlation between NBC and MCT1 relative abundance ($r = 0.50$, $P < 0.01$) in oxidative, but not glycolytic, rat muscle (143). For example, in rats an increase in bicarbonate concentration of the outer medium increased the activity of the NBC (82). As a consequence, it may be that the regulation of muscle pH via NBC may promote MCT transport activity during high-intensity exercise. Indeed, when MCT1 is coexpressed in frog oocytes with isoform one of NBC (NBC1), lactate transport influx in this isolated system is enhanced (5) as a result of the increased proton buffer capacity in the presence of NBC1 expression, i.e., once again by maintaining the pH gradient. Further research is required to determine whether there is a colocalization and coupling in activity of the different isoforms of NBC with MCT1 and MCT4 in human skeletal muscle.

Full NBC activity has been reported to depend on the cooperation of sCA (79) and cCA (1, 6, 52). Therefore, although the colocalization of MCT1, NBC, and CA has not yet been demonstrated in skeletal muscle, we can hypothesize that the cooperation of these proteins may be of physiological importance for lactate/proton exchange during high-intensity exercise. These interactions could act to suppress the buildup of intracellular H⁺ and to maintain the pH gradient that is required for continued MCT activity (75). Future studies should verify these hypotheses for lactate influx and efflux in mammalian muscles. Future research should also determine whether there is a coexpression of these proteins in the sarcolemmal membrane and to evaluate the lactate/proton transport capacity in human sarcolemmal vesicles, as currently performed (78), with and without the presence of inhibitors of NBC and CAs activity.

Implications for performance. A high muscle lactate/proton transport capacity may help to limit the accumulation of lactate and protons in the cytosolic compartment. This could counteract the negative consequences of cellular acidification, which has been proposed to contribute to the appearance of muscle fatigue (140). Despite contrasting views in the literature (87, 112, 114), it has been demonstrated that both protons (133) and lactate (63) may contribute to the appearance of muscle fatigue during muscle contractile activity. Indeed, an improved ability to extrude H^+ from the muscle will reduce the decrease in muscle pH for a given lactate production, which may delay the development of fatigue (103, 115, 144). Similarly, the accumulation of lactate ion per se within skeletal muscle may affect excitation-contraction coupling and, consequently, reduces muscle force independent of any pH changes; this suggests another mechanism by which a higher lactate transport capacity can delay fatigue appearance (63, 83, 139). These notions are supported by the observation of a low, but significant relationship between lactate transport capacity and the fatigue index ($r = 0.33$; $P < 0.05$) measured during 50 s of one-legged, maximal, knee-extensor exercise (115). Similarly, Thomas et al. (144) have reported that fatigue indices measured during continuous, 1-min, all-out and intermittent (repeated 10-s cycling sprints interspersed with 30 s of recovery) supramaximal exercise, were inversely related to MCT1 content ($r = 0.54$, $P < 0.05$ and $r = 0.58$, $P < 0.05$, respectively), but not MCT4 content, in 15 humans with different training status. Nevertheless, this result is in contrast to that obtained for lower-intensity exercise, since both MCT1 and MCT4 content in a homogeneous group of trained athletes was not correlated with performance when subjects were required to cycle at the highest sustainable power output for 2 and 10 min (9). As limited data are available in humans regarding MCT content and exercise performance, further research is required to investigate the effects of the population studied (homogeneous or heterogeneous, trained or untrained) and exercise intensity on the relationship between MCT content and exercise performance.

Regulation of MCT Content with Acute Exercise

There is a paucity of research on the effects of acute exercise on muscle membrane lactate transporter content. It is known that increased transmembrane lactate flux during exercise results from both increased transmembrane lactate and proton gradients (20, 68), in cooperation with regulatory proteins (5, 7, 8); an increased intrinsic activity of the transporters, measured in giant vesicles, has also been observed in one study (72). However, how lactate transport is altered as a function of exercise intensity, during and immediately after exercise, is not clear, and the effects of an acute exercise bout on human skeletal muscle lactate transporter content have only been investigated in a few experiments.

Effects of acute exercise on MCT content. Despite limited research, it appears that both MCT1 and MCT4 belong to a class of proteins that can be rapidly affected by an acute bout of exercise. Prolonged low-intensity exercise has been reported to acutely increase MCT content in both humans (55) and rats (35), with increases in MCT1 and MCT4 observed 2–6 days after a 5- to 6-h cycle training session at 60% of $\dot{V}O_{2\max}$ in untrained humans (55). During 16 h of heavy, intermittent,

cycle exercise (6 min of exercise at 90% of $\dot{V}O_{2\max}$ per h for 16 h) in untrained subjects, a rapid increase of MCT4 content has been reported (24%), with no change in MCT1 (56). Surprisingly, the opposite results (no change in MCT4 and increase of MCT1) were observed in moderately trained endurance runners 2 h after a time-to-fatigue test performed at 110% of $v\dot{V}O_{2\max}$ (the minimal velocity to elicit $\dot{V}O_{2\max}$) (14). Recently, Bishop et al. (18) have observed a significant decrease in both MCT1 (24%) and MCT4 (26%) content in total membrane preparations immediately after very exhaustive exercise (45 s at 200% of $\dot{V}O_{2\max}$) in six active women. This is in line with the results of Tonouchi et al. (145), who reported a decrease in the plasma membrane content of both MCT1 (10%) and MCT4 (25%) immediately following 10 min of high-intensity electrical stimulation in rats. Because of the limited number of studies, it is difficult to reconcile these contrasting findings. However, they may be the result of several factors, such as the type of exercise (duration, intensity, continuous vs. intermittent) and the type of subjects (trained vs. untrained, male vs. female). Alternatively, taken together, these contrasting findings may also be due to the timing of the muscle biopsy samples.

If we focus on the time course of the protein content measured after the start of exercise, rather than once exercise ended (Fig. 2), one can observe a rapid decrease in membrane MCT1 and MCT4 content (20 to 25%) between 45 s (18) and 10 min (145), no change from 30 min to 1 h 20 min (45, 46), and an increase in MCT1 content (+50–60%) 2 h after the beginning of exercise (14, 35). MCT1 content has been reported to remain elevated 7, 12, and 26 h after the onset of exercise in the red (RG) and white (WG) gastrocnemius, and in the soleus (Sol) of rats (35). Whereas no change was reported for human MCT4 content 2 h after the onset of a time-to-fatigue test at 110% of $v\dot{V}O_{2\max}$, increases in MCT4 content have been observed in the RG and Sol 2 h after the onset of exercise in rats, with a peak occurring after 12 h (35); MCT4 protein was also still upregulated after 26 h (35). Thus, it appears that 5–24 h after the start of exercise, there is an increase in membrane MCT content, after a previous and brief

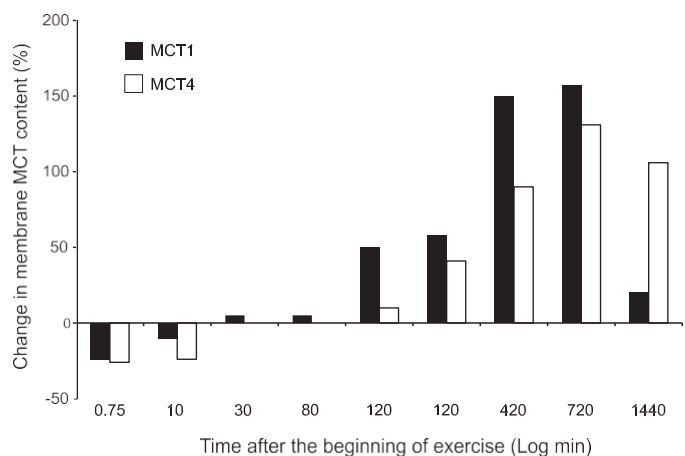


Fig. 2. The kinetics of MCT content measured during the recovery from exercise, but taking into account the time from the beginning of exercise to when the biopsy was performed. [Data in figure from studies of Bishop et al. (18), Tonouchi et al. (145), Eyedoux et al. (45, 46), Bickham et al. (14), and Coles et al. (35).]

decrease in membrane protein content. This proposed time course for the response of MCT to acute exercise needs to be confirmed, as it is based on a small number of studies performed with different types of exercises and different populations. Further study is also required to determine whether the decrease in MCT content immediately after exercise results from the intensity of exercise and/or the short exercise time until the collection of the biopsy and whether this decrease could be an acute response to exercise by which training leads to chronic increases in muscle MCT content. These findings also have important implications for the design of training studies, e.g., it may be important for researchers to avoid training in the 24–48 h before the biopsy to try and ensure that any observed changes are not due to the acute effects of the last training session.

Potential mechanisms involved in the reported changes in MCT content with acute exercise. The decrease in MCT1 and MCT4 content after high-intensity exercise may be expected to decrease rates of lactate and proton removal from the cell. Consistent with this, a decrease in sarcolemmal lactate transport capacity has been observed after time to fatigue exercise in both untrained [72 ± 19 min (40) and 80 ± 9 min (46)] and trained [204 ± 11 min (46)] rats. However, a decrease in lactate transport capacity has also been observed after 30 min of submaximal exercise (45), without changes in MCT1 content (45, 46). Although the physiological significance of these findings is unclear, these alterations are also in agreement with the slower blood lactate appearance (I_1) and removal (I_2) rate constants observed immediately following high-intensity exercise in humans (48, 113). These studies reveal the complexity of the effects of acute exercise on the exchange of lactate measured during recovery.

The reported decrease in membrane MCT content following an acute bout of exercise (18, 145) could be due to a number of factors that require further investigation, including lipid peroxidation, which may also lead to fluidity and permeability alterations in the membrane (36, 137), intracellular translocation, and protein carbonylation (4). One could hypothesize that protein carbonylation could affect the conformation of proteins inside the sarcolemmal membranes, due to changes in its interaction with residues, with consequences for the intrinsic activity of the transporter and/or the recognition by the anti-MCT1 or anti-MCT4 antibody using Western blot analysis. Alternatively, Tonouchi et al. (145), hypothesized that the decrease in MCT4 and MCT1 content that they observed after acute muscle contractions may have been due to translocation of the protein to an intracellular pool. Intracellular pools of MCT1 have been observed in cardiac myocytes during post-ischemic hypertrophy, which was associated with up-regulation of MCT1 (65). However, this phenomenon needs to be confirmed in skeletal muscle in response to acute exercise.

Concomitantly with the above described changes, it is likely that there is an increase in MCT protein synthesis. This would explain the time course illustrated in Fig. 2, whereby there is an initial decrease in MCT content, followed by no change and then a significant increase. Potential mechanisms controlling this increase in protein synthesis are described in *Which Cellular and Molecular Signals/Mechanism Regulate Muscle MCT Content?* Furthermore, on the basis of results of the few studies that have reported changes in both MCT mRNA and protein at different times postexercise, it can be concluded that

exercise-induced regulation of MCT protein expression is complex, since there is not a simple concordance between the rate of gene transcription, mRNA expression, and changes in protein levels after 2 X 5 min of intense muscle contractions induced by electrical stimulation (145) or following 2 h of exercise (35) in rat muscles. The results of studies on laboratory animals are, however, consistent with those of a human study that demonstrated an increase in MCT1 protein level, without any changes in mRNA content, 2 h following a bout of high-intensity exercise (time-limit test at 110% of $\dot{V}O_{2\max}$) (14). This suggests that MCT expression may be regulated primarily by posttranscriptional mechanisms, or by a combination of posttranscriptional regulation and pretranslational mechanisms (14, 23, 24), at least in skeletal muscle (23). Further studies are needed to clarify the role of transcriptional regulation on the acute expression of these proteins in response to exercise.

Regulation of MCT with Chronic Exercise

Changes in MCT1 and MCT4 content as a function of training status. When subjects with different training status are studied, well-trained endurance subjects present significantly higher MCT1 content ($P < 0.05$), compared with less-trained subjects, with a trend also for higher MCT4 content ($P = 0.10$) (144). Similarly, lactate transport activity measured in human skeletal muscle is significantly higher ($\blacklozenge 75$ pmol·cm⁻²·s⁻¹) in well-trained endurance athletes ($\dot{V}O_{2\max} = 70$ ml·min⁻¹·kg⁻¹) compared with sedentary ($\dot{V}O_{2\max} = 48$ ml·min⁻¹·kg⁻¹) and moderately trained subjects ($\dot{V}O_{2\max} = 62$ ml·min⁻¹·kg⁻¹), who both presented a lactate transport capacity of $\blacklozenge 57$ pmol·cm⁻²·s⁻¹ (115). It is interesting to note that the highest lactate transport capacities were observed in two track cyclists (>100 pmol·cm⁻²·s⁻¹), who competed in the 4-km pursuit (one obtained a bronze medal at the 1992 Olympic Games) and who combined training on the road with high-intensity track training ($\dot{V}O_{2\max} \blacklozenge 78$ ml·min⁻¹·kg⁻¹). The results of these two cross-sectional studies support the hypothesis that contractile activity is an important stimulus to increase MCT content.

Longitudinal studies. Few training studies have not observed an increase in either MCT1 (3, 17, 44) or MCT4 (17, 44, 108) content. For example, increases in MCT have been reported after endurance (21, 39, 44), strength (76), all-out sprint (14, 31, 108, 116), and interval training (17, 77). In contrast, 1 wk of detraining, after training in humans, leads to a lower MCT1 and MCT4 content (31). This is in agreement with the lower lactate transport capacity observed after extreme inactivity in laboratory animals (41, 96, 117). For example, significant decreases in lactate transport activity have been observed in sarcolemmal vesicles isolated from the hind limb skeletal muscles of tail-suspended rats (41) and from denervated rat skeletal muscle (96, 117). Thus, consistent with the observations from cross-sectional studies, the results from these longitudinal studies support the hypothesis that contractile activity is an important factor regulating the lactate transport system. Furthermore, analysis of the mean data from the 10 human training studies available in the literature suggests that the percentage increase in MCT1 and MCT4 content in response to contractile activity is related ($r = 0.81$, $P < 0.01$; Fig. 3). However, changes in MCT1 content following training are approximately twice those of MCT4, which suggest that MCT1

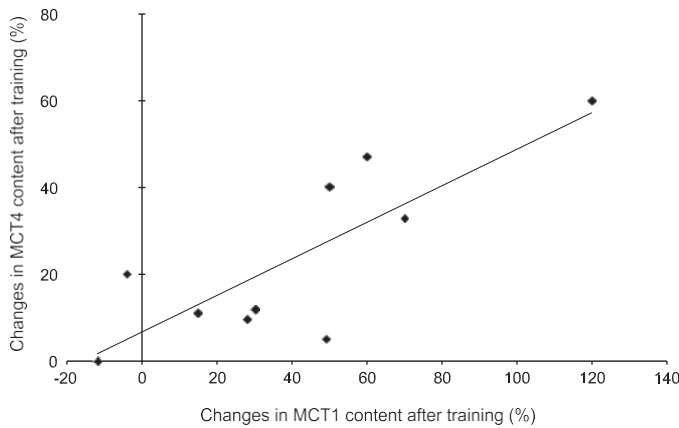


Fig. 3. Relationship between percentage changes in human MCT4 and MCT1 content ($r = 0.81$, $y = 0.42x + 6.7$, $P < 0.01$) from mean data of 10 studies available in the literature (14, 17, 21, 31, 39, 44, 76, 77, 108, 116).

protein expression is more sensitive to training than MCT4 protein expression.

Initial fitness of subjects. As summarized in Table 1, changes in MCT1 and MCT4 content with chronic contractile activity do not appear to be strongly influenced by the initial level of training since both sedentary (21, 39, 76, 77), active (108, 116), and moderately trained (14, 17, 31) subjects respond to increases in physical activity level by augmenting muscle MCT content. However, the results of one of the few studies conducted with elite

athletes suggest that daily training at a high intensity may be required to maintain, but not enhance, MCT protein content (44). In that study, moderate-intensity training (following a period of intensive training during the racing season) led to a decrease in MCT content in these elite, endurance-trained subjects (elite junior cross-country skiers with high $\dot{V}O_{2\max}$ values [73 and 58 ml·min⁻¹·kg⁻¹ in men and women, respectively]). In consequence, one can speculate that training above a certain intensity may be required to increase MCT content in elite athletes, but no further increase in MCT content appears after weeks or months of daily training at this intensity (44). In contrast, in less-trained subjects increases in chronic contractile activity may induce increases in MCT content without a strong effect of the initial fitness of subjects.

Training characteristics (intensity, duration, volume). An important question is how much and what kind of training is required to maximally increase MCT content? Training factors that could influence training-induced changes in MCT content, such as the type of training, the intensity and duration of individual training sessions, and the duration and total work of the training period, are now investigated to highlight the various factors that may be involved in the regulation of MCT content.

As reported in Table 1, all types of training (endurance, speed endurance training, repeated-sprint training, and strength training) have been reported to increase MCT1 and MCT4 content, with a large variation in the response. For example, endurance training has been reported to increase MCT1 content

Table 1. A summary of the characteristics and results of training studies that have investigated changes in MCT content in humans

Subjects			Adaptations					
Study	Type	$\dot{V}O_{2max}$	Training Program	Blood La	MCT1	MCT4	$\dot{V}O_{2max}$	CS
Moderate Intensity								
(21)	7 UT ♂	45.1 ± 2.5	1 wk: 2 h/day at 65% $\dot{V}O_{2max}$	<4 mM	118%	nr	=	nr
(39)	9 UT ♂	43.5 ± 3.9	9 wk: 1 h at 75% $\dot{V}O_{2max}$, 6 days/wk	nr	161%	148%	115%	175%
(44)	20 E S! ♂	58–73	20 wk: 10–16 h/wk at 60–70% $\dot{V}O_{2max}$	<1.5 mM	212 ± 3%	=	=	26% ^{ns}
			20 wk: 10–16 h/wk at 80–90% $\dot{V}O_{2max}$	3–4 mM	=	=	=	26% ^{ns}
High Intensity								
(17)	6 MT S! ♂	43.2 ± 4.9	5 wk: 6–12X (2 min at 95–115% $\dot{V}O_{2max}$: 1 min rest), 3 days/wk	16 mM	24% ^{ns}	120% ^{ns}	110%	16% ^{ns}
(108)	6 Act ♂	50.2 ± 3.7	8 wk: 15X (6-s sprint: 1 min at 95% max), 3–5 days/wk	8 mM	128 ± 12%	110% ^{ns}	nr	nr
	7 Act ♂	49.0 ± 4.2	8 wk: 8X (30 s at 130% $\dot{V}O_{2max}$: 90 s rest), 3–5 days/wk	16 mM	130 ± 09%	112% ^{ns}	nr	
(77)	6 UT ♂	50.2 ± 3.0	7–8 wk: 15 X (1 min at 150% $\dot{V}O_{2max}$: 3 min rest), 3–5 days/wk	>8 mM	115 ± 5%	111 ± 11% ^{ns}	nr	nr
(14)	7MT ♂	58.1 ± 2.0	6 wk: 14–30 X 40–100 m at 90–100% $\dot{V}O_{2max}$: 5 min rest 3 days/wk	nr	150%	110% ^{ns}	=	nr
(116)	4 Act ♂	nr	8 wk: 3–5 X (5 X 30–60 s at 150–200% $\dot{V}O_{2max}$: 2 min rest), 3–5 days/wk	5–6 mM	170 ± 32%	133 ± 10%	nr	118% ^{ns}
(31)	8 MT ♂	50.0 ± 5.6	1 wk: 4–6X (30 s all-out: 240 s rest), 3 days/wk		157 ± 57%	139 ± 26%	=	138% after 2 wk with this type of training (32)
			6 wk: 4–6X (30 s all-out: 240 s rest), 3 days/wk	20 mM (59)	1120 ± 29%	160 ± 09%		
Resistance								
(76)	7 UT ♂	nr	6 wk: 3–4X (8–12 reps: 2 min rest), 3 days/wk	5 mM	148%	132%	nr	nr

Results are means ± SE. $\dot{V}O_{2\max}$ = ml·kg⁻¹·min⁻¹; MCT, monocarboxylate transporters; La, lactate; CS, citrate synthase; UT, untrained; Act, active; MT, moderately trained; E, elite; ♂, males; S!, females; nr, not reported; =, no change; ns, not significant.

by 18% [with a range of 0 to 62% in this study (21)] to 61% (39), and has also been reported to induce large interindividual variations (with increases or decreases in individual subjects) in MCT4 content (39). MCT1 and MCT4 content has been reported to increase by 15% (77) to 120% (31) and by 0 (108) to 60% (31), respectively, in response to high-intensity training, except for two human studies where no significant changes were observed for either protein (17, 44).

It has previously been suggested that the intensity of contractile activity during training is not of importance for the increase in skeletal muscle MCT1 content, whereas increases in MCT4 content seem to depend on a high intensity of contractile activity (76). However, if we focus on the program variables for the eight high-intensity training protocols, the increase in both MCT1 and MCT4 content is related to the intensity of the individual training sessions ($r = 0.59$ and $r = 0.71$, respectively, $P < 0.05$) (data from eight training protocols used in six studies in Table 1). Thus, the research to date suggests that the training intensity appears to be an important variable influencing changes in MCT content. As these conclusions are based on correlations using mean data, they need to be confirmed, especially as few protocols (only 8 in humans) have focused on high-intensity training-induced changes in both MCT1 and MCT4 content. In addition, we must be cautious in this interpretation since, at high intensity, two types of training induced similar changes in MCT1 and MCT4 content (108). Furthermore, it is very difficult to interpret the results of the small number of studies published to date due to differences in the initial fitness of subjects and the timing of the post-training biopsy (discussed below).

The duration of individual training sessions does not appear to be of importance for increasing muscle MCT protein expression. No correlations were found between the percentage increase in MCT1 and MCT4 content with training and the duration of the individual training sessions (Table 1). This suggests that a long-duration training session is not necessary to induce increases in MCT content. Instead, as discussed in the previous paragraph, the metabolic perturbations induced by short and high-intensity contractile activity appear to be more effective to stimulate increases in MCT content. Similarly, lactate transport capacity in humans appears unaffected by physical activity within a broad range of fitness levels (from sedentary to well trained). The finding that no subject with a $\dot{V}O_{2\max} < 68 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ had an elevated lactate-transport capacity indicates that a high volume of training, including frequent bouts of high-intensity exercise, is likely to be necessary to improve the lactate transport system (115). These results are confirmed by results of experiments on laboratory animals because, in rats, improved lactate transport capacity is detectable only in some muscles after high-intensity exercise training and only when measured with giant sarcolemmal vesicles (80, 118). In contrast, no change in lactate transport was observed with small sarcolemmal vesicles (131), which could be inherent in the vesicle model used in these studies, since small sarcolemmal vesicles are constituted with predominantly glycolytic hind limb muscles. Further research is clearly required to determine the optimal intensity and duration of a training session to promote improvements in both MCT content and lactate transport capacity.

It is a common observation that many adaptations to training are related to the duration of training and to the total work

performed during training. One could, therefore, hypothesize that the duration and/or the total work (number of repetitions \times exercise duration \times exercise intensity expressed as a percent of $\dot{V}O_{2\max}$) performed during the training period may affect the changes in skeletal muscle MCT1 and MCT4 content. To date, the duration of the training period used in studies has ranged from 1 wk (31) to 9 wk (39). However, analysis of the moderate- and high-intensity studies in the literature (Table 1) does not indicate any relationship between the duration or the total work of the training period and increases in MCT1 or MCT4 content ($P > 0.05$). The maximal response to training appears to be quickly reached as Juel et al. (77) observed no further increase in MCT content between 4 and 7–8 wk of training, and years of training, as performed by athletes, does not seem to produce further increases (44). Thus, total time of exercise appears to be less important than the intensity of exercise training for increasing MCT content.

Influence of the timing of the post-training biopsy. Part of the inconsistent response of MCT to training may be attributable to the timing of the post-training biopsy. For example, Fig. 2 (see *Sarcolemmal Lactate/Proton Cotransporters in Skeletal Muscle*) would suggest that the smallest changes in MCT content are likely to be observed when the posttraining biopsy is performed close to the last training session. Consistent with this observation, the lowest increase in MCT content is observed when biopsies are performed immediately at the end of the last training session (108) or following the posttraining test (77). Percentage changes in MCT1 and MCT4 content, compared with pretraining, progressively increase with a greater delay of the posttraining biopsy, i.e., from 24 h (21, 76), to 48 h (14, 39, 116) after the last training session, with the highest gain observed when the biopsy is performed 72 h after the last training session (31). This observation is consistent with the known time course for increase in protein synthesis, but also with studies reporting tapering to elicit greater physiological adaptations due to a supercompensation following a reduction in training before competition (110). Other physiological

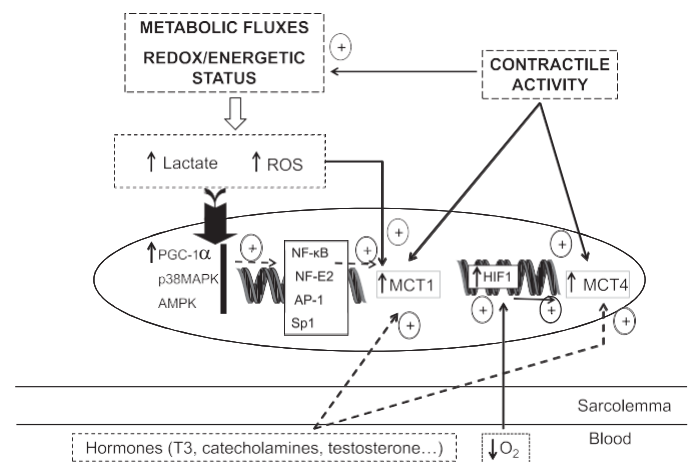


Fig. 4. Molecular and cellular factors known and suspected to affect MCT content and activity. Solid arrows denote factors known; dashed arrows denote factors suspected; + denotes stimulation. T3, thyroid hormone; ROS, reactive oxygen species; PGC-1 α , peroxisome proliferator-activated receptor-1 coactivator; p38MAPK, p38 mitogen-activated protein kinases; AMPK, 5' adenosine monophosphate-activated protein kinase; NF- κ B, nuclear factor- κ B; NF-E2, nuclear factor-erythroid-derived 2; AP-1, activated protein-1; Sp1, stimulating protein-1; HIF1, hypoxia-inducible factor 1.

changes during taper, such as an increase in citrate synthase activity and glycogen concentration, have also been reported (111, 138). Further studies are needed to confirm this potential kinetics of protein expression after low- and high-intensity training, and to test the effects of tapering on MCT1 and MCT4 content and lactate transport capacity. Indeed, to our knowledge, no studies have taken into account the importance of a taper after training, or the timing of the posttraining biopsies, when analyzing changes in MCT content following training.

Which Cellular and Molecular Signals/Mechanisms Regulate Muscle MCT Content?

The regulation of skeletal muscle MCT1 and MCT4 content by a variety of stimuli has been demonstrated, and evidence has been presented for both transcriptional and posttranscriptional regulation (24, 35, 43, 58, 75, 148). At present, the question is which signal(s) is(are) behind the training-induced changes in MCT1 and MCT4 content? However, because of the limited number of studies available to answer this question, we have chosen to summarize the potential role of intracellular factors (such as lactate), and other factors, which may alter muscle metabolism (such as hormonal factors, hypoxia, nutrition, and metabolic disturbances). We also specifically comment on cellular states that produce an increase in muscle and blood lactate concentration to help understand factors, which may regulate MCT content with exercise (Fig. 4).

Products of muscle glycolytic activity during exercise. Lactate is continuously produced even under fully aerobic conditions (28), especially during exercise when rates of glycogenolysis and glycolysis are elevated (29). As a consequence, high lactate concentrations could be involved in triggering adaptations in lactate/proton transport in response to high-intensity training. However, if we focus on the peak blood lactate concentration measured (or estimated) during training (Table 1), and the percentage increase in MCT content, no correlations were found in these longitudinal studies. Furthermore, Mohr et al. (108) have reported no significant differences in MCT1 and MCT4 content following two training programs that elicited very different blood lactate values (blood lactate concentrations of 8 and 16 mM). These observations are consistent with the finding that chronic, low-frequency stimulation of the rat tibialis muscle for 7 days produced a doubling of the lactate transport capacity despite minor increases in plasma lactate (97).

However, blood lactate levels can be low even though turnover in the blood and muscle lactate concentration are relatively high (13). In accordance with this statement, no relationship was reported between muscle and blood lactate concentration when subjects performed repeated intense exercise (33, 84, 85). In contrast, following continuous exercise, where the blood lactate concentrations are low, the muscle lactate concentrations are closely related to values observed in the blood (85, 86). Thus, we cannot conclude from the 10 studies published to date that there is evidence to support the local formation of lactate, during the training bouts, as an important factor stimulating increases in lactate/proton transport capacity. Equally, we cannot exclude the possible role of repeated increases in lactate concentration during high-intensity training session to stimulate both MCT expression and lactate transport activity (3, 77, 115, 116). This suggests that

factors associated with physical activity are also involved in the lactate transport rate increase when lactate concentration is low during training.

Other factors than muscle glycolytic activity during exercise potentially affecting muscle MCT regulation. Alteration of MCT content in response to exercise is not solely due to muscle contractile activity, even if this factor is the most studied and well known, but may also be attributable to other stressors such as hormonal factors, hypoxia, caloric restriction, altered metabolism, or factors related to muscle contractility, such as calcineurin pathway. These factors can act through specific pathways, certainly interconnected, to modify gene expression and induce muscle adaptations to training. Indeed, one thing that muscle contractile activity, oxygen tension, and insulin resistance have in common is an increase in muscle and blood lactate concentration, which has led to the suggestion that lactate may play a role in regulating MCT content.

Discrepancies exist concerning the hormonal regulation of MCT content, and each protein isoform seems to respond differently to hormonal stimulation, also at the posttranscriptional level. Following 7 days of thyroid hormone (T3) ingestion, rat sarcolemmal MCT4, but not MCT1, content increased, whereas mRNA expression of both transporters was increased (148). In this experimental protocol, rats were kept in a cage and did not perform exercise. In addition, testosterone administration in rats induces increases in both sarcolemmal lactate transport capacity and MCT1 and MCT4 protein content, but without affecting mRNA expression (43). These last results may help to explain the absence of training-induced changes in MCT content (17), and lactate-transport capacity (131), after high-intensity training in untrained women and in female rats, respectively. Despite limited research, sex has been reported to exert a strong influence on gene expression (132). Direct measurement of changes in MCT relative abundance in males and females, exposed to the same training stimulus, is required to test the hypothesis that sex hormones influence training-induced changes in MCT proteins. Nonetheless, different types of training may be required to alter MCT content in males and females.

Against the hypothesis that humoral factors during exercise may play an important role in regulating MCT content, Juel et al. (76) observed different changes in MCT content in trained and untrained legs with a one-legged training protocol. On the basis of these observations, they proposed that humoral, blood-borne factors can be excluded and that changes in MCT1 content must depend upon local, contraction-induced factors.

A decrease in muscle oxygen tension, due to exercise at altitude or due to alteration in O₂ diffusion, has been proposed to stimulate gene expression leading to muscle oxidative adaptations (2, 136). To date, however, the only published human study (79) has reported no changes in MCT1 and MCT4 content in European lowlanders after 2 and 8 wk at altitude (4,100 m, Bolivia), compared with muscle biopsy samples obtained at sea level. However, the authors did observe changes in sarcolemmal CA density, which may improve lactate and proton transport across the sarcolemma by regulating the pH gradient (see *Cellular regulation: role of the pH gradient in regulating lactate transport activity during exercise?*). To date, studies on laboratory animals have produced contrasting results regarding changes in MCT content in response to chronic hypoxia. Juel and Pilegaard (80) reported

that lactate transport capacities in both red and white rat muscles were unchanged after chronic hypoxic treatments, whereas McClelland and Brooks (94) observed a tissue-specific increase of MCT1 and MCT4 content in the skeletal muscles of rats exposed to a chronic high altitude of 4,300 m. In addition, Py et al. (124) observed an increase in lactate transport capacity following chronic exposure to 5,500 m, with an increase in MCT4, but not MCT1, in oxidative muscles only. In agreement with Py et al. (124), Ullah et al. (147) have reported that hypoxia increased the in vitro expression of MCT4 mRNA and protein, but not MCT1, through a hypoxia-inducible factor 1 α -mediated mechanism. Differences between these animal studies remain unexplained, but could be related to a sex hormone effect, the use of females (94) compared with males (80, 124), or to differences in type and duration of the altitude exposure [20 min a day 5 days/wk for 3 wk (80), 21 consecutive days (124), 8 wk (94)]. It is noteworthy that the only study presenting no increase in MCT content was also the study that contained the smallest exposure to altitude (80). Although the lowered oxygen tensions is the most likely factor explaining increases in MCT following long-term exposure of rat to hypoxia, it also needs to be considered that hypoxia is associated with a decrease in food consumption, compared with normoxic rats (15), and that caloric restriction may independently affect MCT content (see below).

The effects of caloric restriction have been highlighted by the results of Py et al. (124), since most of the effects of chronic hypobaric hypoxia on increases in lactate transport were mediated by the associated anorexia. This was demonstrated by the use of pair-fed rats that were exposed to normoxia and pair-fed quantities of food equivalent to those consumed by animals subjected to hypoxia. In agreement with this result, caloric restriction (88) or a high-sucrose diet (Lambert K, Thomas C, Metz L, Py G, Mercier J., unpublished data), increases sarcolemmal lactate transport capacity, compared with a control diet. Since expression of the transporters was unchanged after caloric restriction (80), lactate exchange improvement may have resulted from an increase in translocation inside the membrane, an increased affinity for lactate and/or conversion to another MCT isoform, such as MCT2 (which has also been detected in muscle). These results emphasize the importance of controlling and recording nutritional intake in studies seeking to investigate the effects of an exercise intervention on lactate transport or MCT content.

Another factor that may modify the effects of exercise training on MCT content is the existence of metabolic pathologies, such as diabetes, where both carbohydrate and lipid (the major substrate during submaximal exercise) metabolism is modified. In these situations of metabolic disturbances, rats with streptozotocin (STZ)-induced diabetes, present elevated resting blood lactate compared with healthy rats (42, 126). In contrast, obese insulin-resistant Zucker *fa/fa* rats do not present a systematic elevation in resting plasma lactate (105, 127); nonetheless, a reduction in lactate uptake has also been observed on sarcolemmal vesicles in these animals (105). The effects of training on MCT content in diabetic states have only been investigated in a few studies. Strength training in type 2 diabetic human subjects increased (76) and normalized MCT1 content. After endurance training, Zucker *fa/fa* rats showed an increase in both lactate uptake and sarcolemmal MCT1 expression (105). The type and intensity of training do not seem of

importance to normalize MCT1 content in type 2 diabetic subjects (76, 105), but, to date, training has been reported to have no effect on MCT4 content. This indicates a difference in the regulation of MCT1 and MCT4 with pathology and contractile activity. However, in type 2 diabetic patients, a 10-wk individualized training program, targeted at the power at which the highest rate of lipids are oxidized (LIPOXmax), did not change either MCT1 or MCT4 content (Metz L, Lambert K, Bordenave S, Mercier J., unpublished data). In contrast, in a type 1 diabetic rodent model, the reduction in the content of both MCT1 and MCT4 was alleviated by endurance treadmill training (42).

Time course studies are required to determine whether exercise training induces an increase or has no effect in MCT1 and MCT4 content in diabetic subjects (76) or whether exercise training prevents the continued decrease in MCT1 and MCT4 [as observed in sedentary control animals (42)]. Furthermore, the coupled effects of caloric restriction and training on skeletal muscle MCT content in humans, with and without insulin resistance, warrant further research. In addition, on the basis of previous studies, training can alter lactate transport capacity and MCT content, even when a skeletal muscle insulin resistant state exists. Zucker and STZ rats present "classical" sarcolemmal lactate transport adaptations to training, even though they present large differences in insulin levels. These results suggest that variations in MCT content and lactate transport are independent of insulin levels and that insulin state does not influence adaptations to training.

Inhibition of the calcineurin pathway is another factor related to contractile activity, which may affect MCT expression. Indeed, the serine/threonine phosphatase calcineurin plays a functional role in the hypertrophy and regeneration of skeletal muscle (134). It has been reported that a specific inhibitor of calcineurin by the administration of cyclosporine A increased MCT1 and MCT4 contents only in rat oxidative muscles, which suggests that calcineurin negatively regulates MCT contents with a fiber specificity (142).

Lactate as a cell-signaling molecule. In the only study to date, Hashimoto et al. (61) provided evidence that lactate formation may be a signal transduced to generate changes in MCT content in skeletal muscles. To examine this possibility, they used cultured L6 cells and chronically exposed these cells to high lactate levels (10 and 20 mM), similar to those found in muscles during high-intensity exercise. Hashimoto et al. (61) reported that after 1 h of incubation with lactate, there was increased mRNA and protein expression of MCT1, but not MCT4. Furthermore, CD147, a protein chaperone that facilitates the cell surface expression and the intrinsic activity of both MCT1 (58, 75, 81, 151) and MCT4 (58, 75, 151), was also increased following 1 h of lactate incubation (61). These authors proposed that a transient increase in lactate concentration and mitochondrial oxygen consumption could generate reactive oxygen species (ROS), which would activate a transcriptional signaling network leading to adaptive cell responses (61). In this context, in response to exercise, ROS have been reported to phosphorylate both p38MAPK and AMPK, which is also activated by alteration of the energy status, both of which activate peroxisome proliferator-activated receptor- γ coactivator (PGC)-1 α (90) (Fig. 4).

Recent research suggests that MCT1 and CD147 belong to a family of metabolic genes whose expression is regulated by

PGC-1 α (11, 61). It has also been demonstrated by comparing oxidative capacities among muscles and by increasing muscle oxidative capacities by PGC-1 α transfection and chronic muscle stimulation that there is a strong relationship between the expression of PGC-1 α and MCT1, and between the expression of PGC-1 α and CD147 proteins. Thus, in addition to being a metabolic intermediate, it has been proposed that lactate may also be a cell-signaling molecule, a “lactormone” (60), involving reactive oxygen species production, which can upregulate gene and protein expression [for review, see Brooks (26)].

However, one might ask why peak lactate concentration during training is not correlated with percentage changes in MCT content (Table 1), whereas in vitro study tends to demonstrate lactate as a cell-signaling molecule. Then, the peak value of lactatemia could not be the major factor of increase in MCT, but rather the changes in hyperlactatemia, and concomitantly in redox status and ROS during and after exercise. Acute repeated changes in glycolytic fl and metabolites concentration in skeletal muscles could affect MCT expression and transport activity, and chronic hyperlac-

tatemia associated with metabolic disturbances could lead to a downregulation of MCT content and activity. Further study is required to determine the different cellular and molecular factors involved in MCT1 and MCT4 expression in humans in response to chronic contractile activity.

Relationship Between Alteration of MCT Content and Lactate Transport Capacity

An important unresolved question is whether or not MCT content and lactate transport capacity are independently regulated in response to acute and chronic exercise. Initial studies reported that the rate of lactate flux into and out of the skeletal muscle was correlated with the content of MCT1 and MCT4 in the sarcolemmal membrane (23, 24, 98, 99). However, subsequent studies have shown a dissociation between changes in MCT content and lactate transport activity (Fig. 5). For example, lactate transport capacity has been reported to be altered without change in MCT content in response to hormonal

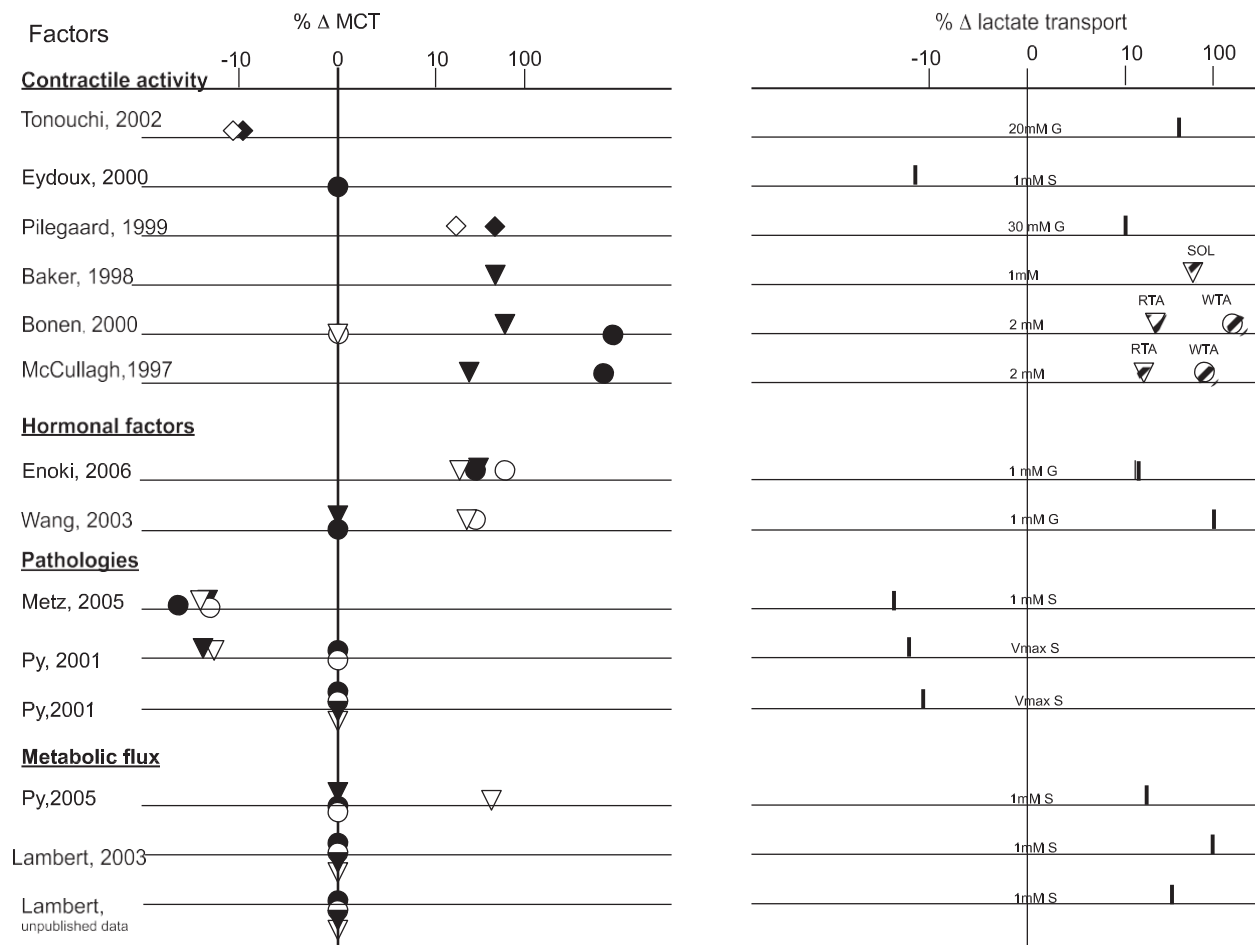


Fig. 5. Representation of MCT1 and MCT4 content (% of control) in skeletal muscles or sarcolemmal vesicles and lactate transport capacity in muscle or in sarcolemmal vesicles using either giant (= G) or small (= S) vesicle. \blacklozenge , MCT1 in oxidative muscle; \bullet , MCT4 in oxidative muscle; \blacksquare , MCT1 in glycolytic muscle; \blacktriangle , MCT4 in glycolytic muscle; \circ , MCT1 when there is not muscle typology; \emptyset , MCT4 when there is not muscle typology; ∇ denotes lactate transport measured in oxidative muscle; ∇ denotes lactate transport measured in glycolytic muscle; 1 denotes lactate transport measured in sarcolemmal muscles. Only studies that reported both MCT content and lactate-transport activity variations in response to contractile activity, hormonal factors, pathologies such as diabetes, and changes in metabolic fluxes are presented in this figure. % \blacklozenge MCT muscle denotes percentage change in MCT content measured in sarcolemmal membrane of skeletal muscle. % \blacklozenge lactate transport was measured in giant (G) or sarcolemmal (S) vesicles, or in perfused or isolated rat muscles, at different concentrations of unlabeled L(+)-lactate (1, 2, and 30 mM) or at the maximal rate of lactate influx (V_{max}). SOL, soleus muscle; RTA, red tibialis anterior muscle; WTA, white tibialis anterior muscle.

factors (148), pathologies (125, 127), and changes in metabolic pathways (Lambert K, Thomas C, Metz L, Py G, Mercier J., unpublished data; 124). Regrettably, the literature contains few reports on the effects of exercise and exercise training on blood lactate flux, lactate oxidation, or tissue exchange.

Although some studies have observed that changes in MCT content in response to training seem to vary in parallel with changes in the lactate transport capacity (21, 39, 77, 116), some have not (46, 145). A possible explanation for this last observation could be a change in the intrinsic activity of MCT, as has been reported for GLUT4 activity (50). This latter mechanism could explain why small increases in MCT content have been associated with large increases in lactate transport capacity and why decreases in MCT content have been associated with an increase in lactate exchange (Fig. 5). Thus, lactate transport capacity may be regulated independently of MCT content in the sarcolemmal membrane in response to different stimuli. However, from data presented in Fig. 5, altered metabolic demand associated with contractile activity by skeletal muscles could regulate MCT content and lactate/proton transport capacity. Indeed, it appears that increases in MCT1 and MCT4 content with training may result from increases in contractile activity, whereas increase in lactate transport capacity may result from changes in metabolic pathways.

MCT1 and MCT4 proteins are important, since these isoforms participate in the cell-to-cell lactate shuttle, to transport both lactate, as a metabolic intermediary, and protons to counteract muscle acidosis. According to the different results reported in the literature, it appears that high-intensity interval training should be recommended to improve lactate transport capacity (3, 71, 77, 115, 116), whereas high training volume is also necessary ($\dot{V}O_{2\max}$ superior to $60\text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$). Indeed, with acute repeated high-intensity training session, concomitant increases in contractile activity and lactate concentration may promote increases in MCT content, and changes in metabolic fluxes with high-intensity exercise and/or nutrition may contribute to an elevated lactate transport activity. These hypotheses need to be confirmed, along with the suggestion that the exercise-induced beneficial effects of ROS in muscle MCT expression should not be counteracted by taking antioxidants during training periods (122). Further research is required to determine the isoform-specific regulation of transporters, and the beneficial effect of ROS, as this has important implications for the design of interventions to improve these proteins in both health and disease.

Conclusions

It is clear that MCTs are important for regulating muscle pH and facilitating lactate exchange. Thus, MCTs play significant roles in the coordination of metabolism within and among tissues. During the last decade, interest has focused on the effects of acute and chronic exercise on the muscle content of these two isoforms. Despite limited research, it appears that both MCT1 and MCT4 belong to a class of proteins that can be rapidly altered by an acute bout of exercise. Further studies are needed to investigate the underlying mechanisms and to clarify the role of transcriptional regulation on the expression of these proteins in response to exercise. Such research has important implications for the design of an acute exercise stimulus to maximally increase MCT content.

The content of MCT1 and MCT4 in humans can also be affected by chronic activity levels, as indicated by the results of both cross-sectional and longitudinal studies. The type of training appears to be of little importance, as few studies have not observed an increase in MCT content or lactate transport capacity following training. However, further research is still required to determine the optimal intensity and duration of a training session to promote improvements in both MCT content and lactate transport capacity, although high-intensity appears to be more effective.

Perspectives and Significance

Further research is also required to confirm our observation that MCT1 protein expression is more sensitive to training than MCT4 protein expression. Once again, methodological limitations (and variations) limit the conclusions that can be drawn from the current literature. In particular, we note that the timing of the posttraining biopsy has not been standardized and that the smallest changes in MCT content are likely to be observed when the posttraining biopsy is performed close to the last training session. Finally, further studies are also needed to investigate the mechanisms responsible for increases in MCT content and lactate transport capacity in response to exercise training. Results of cross-sectional and longitudinal training studies show that like other important parameters of metabolism (e.g., $\dot{V}O_{2\max}$, muscle mitochondrial density, or GLUT4 expression), muscle MCT expression is one among many factors affecting physical performance.

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