Progress in study of exercise, monocarboxylate transporter 1 and lactic shuttle

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Abstract

Study have already discovered that the monocarboxylate transporter family (MCTs) has now fourteen members of MCTs, the MCT1 organization distribute very breadth, distribute particularly in muscle fiber of oxidize the type. The MCT1 content and mitochondrial densities are related very well. The MCT1 and MCT4 carry out "Cell-cell" and "intracellular lactate shuttle" in the cells to wear the shuttle together, delivering to have the special function for the lactic acid. The researchers think that the MCT1 belongs to one of the choice metabolism gene, adjusting in exercising to stimulate ascends very quickly and the muscle contracting increased proper activity of MCTs. It is proposed that MCT1 expression may be important for blood lactate removal after supramaximal exercise based on the existence of lactate shuttles and, in turn, in favor of a better tolerance to muscle fatigue. Exercise increasing the translation efficiency of the MCT1 and the stability of protein, that make MCT1 of change also is complicated, not only depend on the sport accumulate quantity, but also depend on the athletic stage. The meaning lies in the MCT1 of up adjust with sport train combine to guide the training. [Life Science Journal. 2007; 4(3): 57 – 63] (ISSN: 1097 – 8135).

Keywords: exercise; MCT1; MCT4; lactate shuttle; up-regulate; MCT1 mRNA; muscle

1 Introduction

Monocarboxylates such as lactate and pyruvate play a central role in cellular metabolism and metabolic communication between tissues. Essential to these roles is their rapid transport across the plasma membrane, which is catalyzed by a recently identified family of proton-linked monocarboxylate transporters (MCTs)[1]. The stereo selective transport of L-lactic acid across the plasma membrane of muscle fibers has been shown to involve a proton-linked MCT[2]. Currently, 14 mammalian members of the MCT family have been cloned and sequenced[3]. The kinetics and tissue distribution of only a few are known. These MCTs exited in a large number of rat tissues (heart, skeletal muscle, skin, brain, testes, vas deferens, adipose tissue, liver, kidney, spleen, and pancreas), as well as inhuman skeletal muscle. Unexpectedly, many tissues coexpressed 4 – 5MCTs, which only the first four (MCT1 – MCT4) have been demonstrated experimentally to catalyze the proton-linked transport of metabolically important monocarboxylates such as lactate, pyruvate and ketene bodies. The training intensity may affect the monocarboxylate transporters MCT1 and MCT4 in skeletal muscle. This article made a summary on the MCT1 this domain recent years research results, and forecast future development direction.

2 Simple Introduce about MCT1

The research demonstrated that, MCT1 produces in the skeletal muscle and the cardiac muscle, the MCT1 quantity along with the skeletal muscle, the cardiac muscle, the energy metabolism change which occurs by the movement changes, is extremely sensitive regarding the muscle active change. For example, after the muscle goes to the nerve, the MCT1 protein content reduces, when muscle activeness increases, MCT also along with increase. Study have shown that MCT1 expression in muscle is highly correlated with the oxidative capacity of different types

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of muscles (r = 0.91), citrate synthase (r = 0.82), heart-type lactate dehydrogenate (H-LDH; r = 0.83), and with the rate of lactate uptake from the circulation (r = 0.90). When the oxidative capacity of muscles is increased by chronic electrical stimulation or exercise training, the expression of MCT1 is also increased[26].

3 Identification of MCT1

Using covalent labeling of the protein with 4,4′-diisothiocyanatostilbene-2,2′-disulphonate(DIDS) showed MCT1 to have a molecular mass of about 45 kDa. Human MCT1 has been mapped to chromosome band 1p13.2-p12. MCT1s from human, rat and mouse have now been cloned and share about 95% sequence identity with the Chinese-hamster ovary MCT1. However, there is evidence for alternative splicing of the 5′- and 3′- untranslated regions and the use of alternative promoters for some isoforms. In addition, MCT1 and MCT4 have been shown to interact specifically with OX-47 (CD147), a member of the immunoglobulin super family with a single Tran membrane helix. This interaction appears to assist MCT expression at the cell surface[1].

4 Location of MCT1 in Muscle

MCT1 was found in the mitochondria, as well as in the sarcolemma and whole muscle homogenates. Lactic acid transport across the plasma membrane is fundamental for the metabolism of and pH regulation of all cells, removing lactic acid produced by glycolysis and allowing uptake by those cells utilizing it for gluconeogenesis (liver and kidney) or as a respiratory fuel (heart and red muscle). In rodents, the properties of the different MCT isoforms and their tissue distribution and regulation reflect these roles. Regulation of MCT1 has been demonstrated in a variety of tissues under various conditions[4]. Muscles that are composed of predominantly oxidative fibers (e.g. soleus) express considerable quantities of MCT1 and very little MCT4, whereas muscles with a large proportion of fast-twitch, glycolytic fibers (e.g. white gastrocnemius) express primarily MCT4 and very little MCT1. Muscles composed of fast-twitch oxidative glycolytic fibers (e.g. red gastrocnemius) express both MCT1 and MCT4 in appreciable quantities[7]. MCT1 and 4 are also co expressed in human muscle, with MCT1 being more prevalent in type I fibers and MCT4 in type II fibers[5,6,27]. Kinetics data suggest that MCT1 (Km, 5 mM) and MCT4 (Km, 20 mM) are key transporters for lactate, the most prominent of the monocarboxylates, since their Km values are consistent with lactate concentrations that occur physiologically[15]. In addition, the sub cellular distribution of MCT1 and MCT4 in muscle differs. Both MCT1 and MCT4 are located in the plasma membrane and transverse tubules[7], and MCT1 is also found in the mitochondrial membrane[8], whereas MCT4, but not MCT1, is also present in an intracellular (endosomal) pool[7]. It has been proposed that the expression of MCT1 is most closely associated with muscle characteristics favoring the uptake of lactate for oxidative disposal, whereas MCT4 expression is related to the need for lactate extrusion. Therefore, it is likely that the expression of MCT1 and MCT4 is regulated independently in skeletal muscle.

Mitochondria in rat cardiac and skeletal muscle contain MCT1, Western blots indicated presence of MCT1 in sarcolemmas and in subsarcolemma and interfibrillar mitochondria. In contrast to autographs of Western blots did not indicate presence of MCT4 in mitochondria. Similar results obtained on human vastus lateralis biopsies lead us to conclude that in muscle MCT1 occupies sarcolemmal and mitochondrial domains, whereas MCT4 is the constitutive sarcolemmal lactate transporter. MCT1 is known to be abundant in both erythrocytes and sarcolemmal membranes[8]. This may indicate that lactate taken up into the muscle cell can also be readily taken into the mitochondria *via* MCT1, whereas the intracellular pool of MCT4 may represent a reservoir of transporters that may possibly be trans located to the plasma membrane with the appropriate stimulus, such as muscle contraction[9], and have suggested that its expression may be regulated in concert with that of other enzymes of the glycolytic pathway.

MCT1 was used to study the precise cellular and sub cellular distribution of this transporter in rat heart. MCT1 concentrated along the plasma membrane, including the transverse tubules and occurred with highest densities in intercalated disks, where they avoided desmosomes and gap junctions. Labeling was also associated with plasmalemmal invaginations having ultrastructural features typical of caveolae. The distribution of MCT1 across the plasma membrane was nearly symmetrical, indicating that the C-terminus of the transporter is situated very close to the cell membrane. It can be concluded that even under basal conditions the majority of the MCT1 molecules in heart is present in the myocyte plasma membrane, implying that there is a constitutive functional expression of this transporter. It follows that the increased transmembrane flux of lactate during exercise or in pathological conditions such as ischemia must be a result of altered substrate gradients rather than of translocation of MCT1 molecules to the plasma membrane[10].

5 MCT1 and Lactate Shuttle

High rates of glycolysis in skeletal muscle make it the main producer of lactic acid in the body, lactic acid can also be taken up by skeletal muscle and heart and used as a respiratory fuel. "Cell-cell" and "intracellular lactate shuttle" concepts describe the roles of lactate in the delivery of oxidative and gluconeogenic substrates, as well as in cell signaling[12].

Cell-cell lactate exchanges are facilitated by membrane-bound monocarboxylate transporters. In skeletal muscle, two MCT isoforms (MCT1 and MCT4) with different kinetic properties have been described[12]. Direct lactate oxidation by mitochondria is dependent on the presence of mitochondrial lactate dehydrogenize (LDH) and a pyruvate/lactate transporter. Dubouchaud et.al suggests MCT1 and MCT4 participate in the cell-cell lactate shuttle, whereas MCT1 facilitates operation of the intracellular lactate shuttle. Hashimoto is by using a rat-derived L6 skeletal muscle cell line and confocal laser-scanning microscopy, showed that LDH, MCT1, and CD147 are colocalized with the mitochondrial reticulum, and are abundant in mitochondrial fractions[7]. So support the presence of a mitochondrial lactate oxidation complex associated with the COX end of the electron transport chain that might explain the oxidative catabolism of lactate and, hence, mechanism of the intracellular lactate shuttle[13].

Some studies believe that the presence of MCT1 muscle fractions and its sensitivity to endurance training imparts a role of this isoform as a mitochondrial and sarcolemmal lactate transporter necessary for the cell-cell and intracellular lactate shuttles. MCT4 appears to be a constitutive sarcolemmal MCT isoform more likely involved in cell-cell lactate exchange than in intracellular lactate oxidation. The MCT4 member of this family has recently been identified as the major isoform of white muscle cells, under physiological conditions; rat MCT will therefore preferentially transport lactate. Lactate is the referred substrate of MCT4. MCT4 make Lactate mediating efflux out of glycolytically active myocytes[14,15]. Manning Fox *et al* argued that this is appropriate for the key role that MCT4 plays in lactic acid efflux from muscle. The very low affinity of MCT4 for pyruvate (Km, 150 mM) may be particularly important since it prevents the loss of pyruvate from the muscle in order being converted to lactate. In contrast, MCT1 has a ubiquitous distribution and can serve a role in either lactic acid efflux or influx depending on the required balance between oxidative metabolisms. The relatively low affinity of MCT4 for L-lactate (Km, 28 mM) might not have been predicted since it will lead to less efficient loss of lactic acid from the muscle and thus cause lactic acid accumulation[15]. Science also suggests that Both MCT1 and MCT4 participate in the cell-cell lactate shuttle, whereas MCT1 facilitates operation of the intracellular lactate shuttle[23]. So MCT1 and MCT4 role in lactic acid shuttle function, the current development is a subject area.

6 MCT1 and Lactate Clearing

The etiology of muscle fatigue remains incompletely solved especially *in vivo*. The causes of muscle fatigue vary according to the type, duration and intensity of exercise, and to the physical fitness and health status of the subjects. Since the transport of lactate across the sarcolemma is mediated mainly by the lactate-H^+ co transport *via* the monocarboxylate transporters MCT1 and MCT4. C. Thomas' study investigated whether muscular monocarboxylate transporter (MCT) 1 and 4 contents are related to the blood lactate removal after supramaximal exercise, the results showed that the blood lactate removal ability after a 1-min all-out test was significantly related to MCT1 content but not to MCT4. However, greater MCT1 and MCT4 contents were negatively related with a reduction of blood lactate concentration at the end of 1-min all-out exercise. Result concluded that skeletal muscle MCT1 expression was associated with the velocity constant of net blood lactate removal after a 1-min all-out test and with the fatigue indexes. It is proposed that MCT1 expression may be important for blood lactate removal after supramaximal exercise based on the existence of lactate shuttles and, in turn, in favor of a better tolerance to muscle fatigue[16]. MCT1 is ubiquitously expressed but is especially prominent in heart and red muscle where it is up regulated in response to increased work, suggesting an important role in lactic acid oxidation.

An elevated lactate transport capacity delays both muscle lactate accumulation and intracellular pH decrease and seems to favor muscle activity. This makes an elevated sarcolemmal lactate (and proton) transport capacity an advantage during muscle activity. The single exercise session also resulted in elevations in the monocarboxylate transporters MCT1 and MCT4 throughout the 6 days after 59% VO2 peak prolonged cycle exercise (5 – 6 h). These results indicate that regulation of cellular lactate levels occurs rapidly and independently of other metabolic adaptations. It is proposed that increases in MCT and plasma volume are at least partly involved in the lower muscle lactate content observed after the training session by increasing lactate membrane transport and removal, respectively[17].

Experiments results believe endurance training decreases muscle lactate concentrations by increasing lactate clearance and by decreasing lactate production at low but not high power outputs. And MCT1 expression increases after short-term training in humans and chronic electrical stimulations in rats and decreases after denervation in rats.

7 Exercise and MCT1

Muscle lactate release and oxidation were associated with training-induced changes in MCT expression. One-legged knee-extensor exercise training, the content of MCT1 and MCT4 protein was also higher (76% and 32%, respectively)[18]. MCT1 was also found to be increased with chronic electrical stimulation and high-intensity training in rats and after training in humans. After 7 days of short-term bicycle ergometry training the MCT1 content in muscle was increased 18%. The concentrations of both muscle lactate and femoral venous lactate were reduced during exercise that was performed after training. These results suggest that lactate extrusion from exercising muscles is increased after training, and this may be associated with the increase in skeletal muscle MCT1[24]. Differences in MCT expression after training could, therefore, be dependent on the intensity of training.

The mitochondrial MCT1 pool is sensitive to endurance training because a 78% increase was measured after leg cycle training. Dubouchaud suggest the increase in the absolute mitochondrial MCT1 content is therefore the result of an increase in both mitochondrial density and intrinsic mitochondrial MCT1 content. Results suggest that endurance training increases expression of MCT1 in muscle because of insertion of MCT1 into both sarcolemma and mitochondria membranes. And those training programs affected only the working muscles but did not induce the physiological modifications observed in the present study[12].

20 elite cross-country skiers trained hard for 5 months, the concentration of MCT1 did not change for moderate intensity (60% – 70% VO2max) but fell 12% for high intensity (80% – 90% VO2max); the concentration of MCT4 did not change during the training period. The blood lactate concentration after long-lasting exhausting treadmill running correlated with the concentration of MCT1 but not with that of MCT4. Thus, the training response differed between moderate intensity and high intensity both in terms of performance and of the effect on MCT1. MCT1 may be important for releasing lactate to the blood during long-lasting exercise[19]. Experiments of rat results indicate that a single bout of sub maximal exercise, which did not induce an increase in muscle MCT1 content and apparent oxidative stress, decreased lactate transport capacity at low physiological concentration. Although the changes are small and independent of a MCT1-facilitated lactate transport regulation, results suggest that another MCT isoform with different kinetic properties from MCT1 could be present in the sarcolemma and responsible for lactate exchange alterations[20].

Forty male Wistar rats in the trained groups, MCT1 content increased in soleus and heart muscle. endurance training does not alter lactate transport capacity[21], Endurance training improves muscle capacity for lactate utilization and increases membrane transport of lactate probably *via* an increase in Type I monocarboxylate transport protein (MCT1) and perhaps other MCT isoforms as well[22]. Nine weeks of leg cycle endurance training Results support the conclusions that endurance training increases expression of MCT1 in muscle because of insertion of MCT1 into both sarcolemmal and mitochondrial membranes. Training has variable effects on sarcolemmal MCT4. Both MCT1 and MCT4 participate in the cell-cell lactate shuttle, whereas MCT1 facilitates operation of the intracellular lactate shuttle[23].

Muscle activity also exerts a strong influence on the expression of MCTs. MCTs may also be rapidly up-regulated by exercise. Baker et al. observed that the training-induced increase in MCT1 occurred quite rapidly, as MCT1 was increased +30% after only a few exercise bouts[23]. And Green et al observed, in human muscle, MCT1 and 4 proteins were increased by 20% – 40%, 2 and 4 days after a prolonged exercise bout[26], presumably, earlier and larger changes in these MCTs had occurred shortly after exercise. They have observed that MCT1 and 4 proteins were already considerably up-regulated 24 h after an exercise bout. a single bout of treadmill exercise increased the expression of both MCT1 and MCT4.

In chronically stimulated white muscle, there was only a small increase in MCT1 mRNA (30%), whereas MCT1 protein concentrations were increased far more (191%). And similarly, in stimulated red muscle, MCT1 protein was increased (78%) In conclusion, chronic contractile activity induces the expression of MCT1 but not MCT4. This increase in MCT1 alone was sufficient to increase lactate uptake from the circulation. In this report demonstrate that muscle contractile activity regulates the expression of MCT1 and MCT4 in an isoform-specific manner[26].

MCT1 through campaigns to improve not only depend on the excise intensity and the movement degree level, but the energy expenditure.

8 Exercise and MCT1mRNA

MCT1 and MCT4, mRNA for other MCT isoforms have been found in human skeletal muscle, and the protein quantity of these may also have been altered[18]. There were large changes in both MCT1 and MCT4 proteins during the first 24 h after a single exercise bout in most muscles examined, the increases in MCT1and MCT4 were maximal 5 – 10 h after exercise, but these MCT4 protein levels remained elevated up to 24 h after exercise, based on the post-exercise changes in MCT1 and 4 mRNA, the changes in MCT1 and 4 protein expression appeared to be mediated by transcriptional and post-transcriptional mechanisms. E.g. an increase in MCT4 mRNA has recently been observed within the first 100 min of exercise, with a decrease in this transcript occurring during the next 100 min of exercise[28]. Others have shown qualitatively that MCT4 mRNA in rat muscle was transiently increased during exercise[28]. And others have reported modest, exercise-induced increments in MCT1 and 4 proteins[25], although it was not clear why these exercise-induced increments were examined 2 – 6 days after completing exercise, rather than in the immediate hours or first day after exercise. From the present studies it is clear that the exercise-induced increments in MCT1 and 4 proteins had at times already occurred during exercise, and attained a maximum 5 – 10 h after exercise[29].

After one week of chronic muscle stimulation, MCT1 protein was increased but there were either no changes in MCT1 mRNA or only very modest accumulations in MCT1 mRNA (30%). In contrast to MCT1, low-frequency chronic muscle stimulation activity did not affect the expression of MCT4 in either red or white muscles. Only a slight transient reduction (15%) in MCT4 mRNA occurred in the red and white muscles after 1 wk of stimulation. Interestingly, the isoform-specific regulation of the MCT1 and MCT4 occurred independently of changes in muscle fiber composition. This appears to occur largely via posttranscriptional mechanisms, posttranscriptional mechanisms regulate the expression of MCT1 in muscle. It has been proposed that pools of MCT1 mRNA may be in messenger rib nucleoprotein, thus facilitating rapid translation when more protein is required. The very long 3' -untranslated region of MCT1 (1.6 kb) may be involved in the translational repression. With chronic muscle stimulation, translational capacity and efficiency are enhanced, as evidenced by the early (2 – 3 days) increase (~2 fold) in monosomes, polysomes, and ribosomal RNA[26].

These studies speculate that these rapid exercise-induced increments in MCTs could contribute to the well known reductions in the post-exercise muscle lactate and circulating lactate concentrations that are one of the earliest adaptive responses observed with the onset of an exercise training programmed. These studies have shown that MCT1 and 4 proteins are transiently up-regulated by a single bout of exercise, involving post-transcriptional and transcriptional mechanisms. Thus, MCT1 and MCT4 belong to a class of selected metabolic genes that are very rapidly up-regulated with an exercise stimulus.

These studies examined the effect of exercise on the protein and mRNA expression of the monocarboxylate transporters MCT1 and MCT4 in muscles. The intensity and duration of exercise, as well as the muscle fiber composition, can influence the increased rates of transcription in the post-exercise period. In the present study, the patterns of change in the mRNAs after exercise differed somewhat within and between muscles. Others have shown that MCT4 mRNA can increase and decrease during the same prolonged exercise bout[28]. Thus, the variable MCT mRNA patterns in muscle, induced by exercise, may not be unusual, particularly as studies by Hildebrandt, Pilegaard and Neufer[30] have recently shown that gene-specific and muscle fiber type-specific responses to exercise can occur. It was clear that not all genes are up-regulated by exercise. Recently, they[30] have postulated that genes, which are rapidly up-regulated by exercise, may not be expressed in sufficient quantities to meet the needs of the contracting muscle. Hence, these types of genes are thought to be the most susceptible to exercise-activated signaling/regulatory mechanisms that acutely activate transcription.

9 Distance and MCT1

The running behavior and biochemical markers of oxidative and glycolytic activities associated with voluntary running activity were studied in male Sprague-Dawley rats after 6 weeks of training in exercise wheel cages. The first group, low-activity runners averaged 2 – 5 km/day, the second, medium runners 6 – 9 km/day, and the third, high runners greater than 11 km/day. Voluntary running depressed the most increased biochemical markers of oxidative and glycolytic activities for the third group[31].

Yuko Yoshida examined whether the quantity of exercise performed influences the expression of monocarboxylate transporter (MCT) 1 in mouse skeletal muscles and heart. Wheel running exercise (1, 3, and 6 wk) was used which results in marked variations in self-selected running activity. There is a threshold of the accumulated running distance, more modest amounts of running increase MCT1 either after 1 wk of running or 3 wks of

running. Finally, in week 6, when MCT1 was increased in the tibialis anterior and plantaris muscles, there were no correlations with the accumulated running distances. These studies have shown that mild exercise training fails to increase MCT4 and those changes in MCT1 are complex, depending not only on the accumulated exercise but also on the stage of training[32].

10 Conclusion

Less prolonged and/or less intense exercise may not provoke changes in MCTs and lactate metabolism after a single exercise bout, whereas repetition of such bouts (i.e. training) may over time increase MCT protein expression and alter lactate metabolism. Clearly, until we have a better understanding as to what type of exercise up-regulates MCT protein expression rapidly, future studies may have to distinguish between acute, exercise-induced effects and training-induced effects on MCTs and lactate metabolism. The previous studies have shown that the rate of lactate flux into and out of muscle is correlated with the content of MCT1 and MCT4 in muscle. Thus, the increase in MCT1 and MCT4 in the present study may well be expected to affect the rates of lactate flux. Results believe that the observed increases in MCT1 and MCT4 expressions in the present study will result in increased rates of lactate flux; it appears that MCT1 and MCT4 belong to a class of metabolic genes that are very rapidly up-regulated by a single exercise session. The exercise-induced regulation of protein expression is complex.

11 Outlook

Based on the above, the lactic acid and H^+ transport capacity can improve through training, but also found that lactic acid-transport capacity have difficulties, such as high-capacity sports athletes have high lactic acid transport capacity, which is not reflected in the content of training is also reflected in the ability of the athletes themselves. Excessive movement caused muscle MCT1 and MCT4 concentrations decline, but more reasonable physical movements can cause both rise. For athletes, the key question is: which types of physical activity on the rise MCTs are positive; Movement which campaigns load or intensity more appropriate to the extent possible, to maintain or increase MCT1. The significance of the study, lactic acid faster how to go into muscle cell and remove it, to further enhance athletes lactic acid threshold and enhance athletic performance, up-regulates MCT protein and training in combination with exercise intensity and energy expenditure are for the training services together.

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