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ORIGINAL PAPER

Expression of monocarboxylate transporter (MCT) 1 and MCT4 in overloaded mice plantaris muscle

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Abstract A number of studies have shown that changes in muscle contractile activity regulate the expression of monocarboxylate transporters (MCTs) in the skeletal muscle. The aim of this study was to investigate the effect of functional overload on MCT1 and MCT4 protein expression. Plantaris muscles were functionally overloaded for 15 days by ablation of the synergistic muscles. MCT1 and MCT4 mRNA abundance increased by 160–161% ($p < 0.01$) and 265–325% ($p < 0.05$), respectively, after 1–3 days of functional overload. MCT1 and MCT4 protein expression increased by 92 and 61%, respectively, after 12 days of functional overload ($p < 0.05$). AMP-activated protein kinase (AMPK) phosphorylation status [phospho-AMPK (Thr172)/total AMPK] was significantly elevated after 3–9 days of functional overload. Plasma testosterone concentration was elevated after 12 days of functional overload, while blood lactate concentration was not altered. Thus, the current study demonstrated that heavy mechanical loading induces increase in MCT1 and MCT4 protein expression in the muscles with increase in AMPK phosphorylation status and plasma testosterone concentration.

Keywords Lactate · Monocarboxylate transporter · Skeletal muscle · Overload

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Introduction

Lactate was initially considered as a metabolic waste product. However, it is now recognized that lactate can be oxidized in the skeletal muscle [1]. Lactate is primarily produced in fast-twitch fibers and oxidized in the heart and slow-twitch fibers [2]. Lactate transport across the plasma membrane is facilitated by a family of monocarboxylate transporters (MCTs) [3]. Among the 14 identified MCT isoforms, MCT1 and MCT4 are believed to be the key transporters in the skeletal muscle [4, 5]. As part of the lactate shuttle, MCT1 facilitates lactate uptake, while MCT4 facilitates lactate extrusion [2, 6]. MCT1 protein content, but not MCT4, was shown to increase by chronic muscle stimulation [7] or voluntary wheel running [8], while high-intensity interval training [9] and strength training [10] are known to increase MCT4 protein expression. Therefore, the intensity of muscle stimulus appears to be important for the regulation of MCT4 in skeletal muscle. However, although many studies have investigated changes in MCT1 and MCT4 following various forms of training, the cellular and molecular mechanisms regulating MCT1 and MCT4 protein expression are still at present unknown. Hashimoto et al. [11] demonstrated that incubation of cells with high lactate concentrations increased the intracellular levels of MCT1 protein. Moreover, Thomas et al. [12] showed the effects of training with metabolic alkalosis which has also been reported to increase muscle lactate accumulation on the increased MCT4 expression in rats. Enoki et al. [13] reported that injection of testosterone increased MCT1 and MCT4 protein expression concomitantly with muscle hypertrophy in rats. Triiodothyronine treatment, which has profound effects on growth and development as well as muscle metabolism, was also shown to increase MCT4 protein

content in rats [14]. Recently, Furugen et al. [15] reported that AMP-activated protein kinase (AMPK) activation by AICAR induced increases in MCT1 and MCT4 protein content in rats. Taken together, there seem to be at least three key factors inducing MCT expression in skeletal muscle; (1) lactate concentration, (2) the endocrine system and hormones, and (3) AMPK. In the current study, we sought to investigate changes in MCT1 and MCT4 protein expression by heavy mechanical loading with changes in these factors.

The most established animal model of mechanical loading is the synergist ablation (mechanical overload) model [16]. This model involves sectioning of the tendon and removal of the gastrocnemius and soleus muscle; as a result, the recruitment of the plantaris muscle is increased to compensate for the loss of its major synergistic muscles. The plantaris mass doubles following weeks of overload [17, 18]. Thus, the purpose of this study was to investigate the changes in MCT1 and MCT4 protein expression in overloaded mice plantaris muscle.

Materials and methods

Animals

Eight-week-old male ICR mice (CLEA Japan, Japan) were used. Animals were maintained in a temperature- and humidity-controlled environment (23 ± 2°C and 60 ± 5%) under a 12:12 h light:dark cycle. Food (Oriental Yeast, Japan) and water were provided ad libitum. Animals were randomly divided into seven experimental groups [pre (PRE) and at 1 day (D1), 3 days (D3), 6 days (D6), 9 days (D9), 12 days (D12) and 15 days of functional overload (D15)] and housed in the same standard cages for the duration of the experimental period. All protocols were approved by the Animal Experimental Committee of the University of Tsukuba and were in accordance with the Regulations for Animal Experiments at the University and Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science, and Technology.

Experimental design

The plantaris muscle was overloaded by surgically removing the soleus and gastrocnemius muscles as in a previous study [19]. At each sampling time [before the operation (PRE), and 1–15 days after the operation (D1–D15)], six mice in each group were sacrificed by cervical dislocation. The plantaris muscle was quickly dissected, weighed, frozen in liquid nitrogen, and stored at −80°C until further analysis.

Real-time RT-PCR

cDNA synthesized by SuperScript VILO (Invitrogen, USA) from total RNA isolated using TRIZOL (Invitrogen) was analyzed using 7500 Real-time PCR System (Applied Biosystems, USA) with Power SYBR Green PCR Master Mix (Applied Biosystems) as described previously [20]. Total RNA isolation and cDNA synthesis were performed according to the manufacturer's protocol. The primers synthesized by (Operon Biotechnologies, Japan) were as follows: MCT1 forward primer (5′-TTGTCTGTCTGG TTGCGGCTTGATCG-3′); reverse primer (5′-GCCCAAG ACCTCCAATAACACCAATGC-3′); MCT4 forward primer (5′-TGCCACAGCCACACAATAGCCCA-3′); reverse primer, (5′-GTCCAGCCTACTCGTCTCTCTCCACA-3′). The PCR conditions for MCT1 and MCT4 consisted of denaturing at 95°C for 15 s, followed by annealing and elongation at 60°C for 1 min. At the end of PCR, samples were subjected to dissociation curve analysis. The relative amounts of mRNA were determined by standard curve method. Signals were normalized to GAPDH. All samples for each gene were run in duplicate.

Western blotting

Proteins from muscles were separated using SDS-PAGE, and then MCT1 and MCT4 proteins were detected using western blotting as previously described [8, 13]. Protein concentrations of homogenate samples were measured using a BCA protein assay kit (Pierce, Pittsburgh, PA, USA). Antibodies against MCT1 and MCT4 were raised in rabbits against the oligopeptide corresponding to the C-terminal region of the respective MCT (Qiagen, Japan) and have been used in previous studies [8, 13]. Total AMPK-α, phospho-AMPK-α (Thr172) antibodies were obtained from Cell Signaling. Anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antibody was obtained from ABcam. For western blots, equal quantities of protein were loaded (10 μg). Also, a standard was included with each western blot. This permitted normalization of the data to the standard across the different blots. Proteins were visualized by chemiluminescence detection system according to the manufacturer's instructions (Amersham, UK). Blots were quantified using the ChemiDoc system (Bio-Rad, Japan). GAPDH was used as a loading control among the experimental conditions.

Blood sampling

In additional mice anesthetized with carbon dioxide, blood was collected by heart puncture at pre (PRE), and at 3 days (D3) and 12 days (D12) of functional overload. The

centrifugally separated plasma was stored at −80°C until analysis. Plasma total testosterone was measured using the Elecsys Testosterone II Assay (Roche Diagnostics). Blood was also taken from the tail vein before the anesthesia to measure the lactate concentration. Lactate concentration was measured using an auto analyzer (Lactate-Pro, Arkray).

Statistical analysis

All data were expressed as mean ± SE. Multi-group comparisons were performed by one-way analysis of variance (ANOVA), followed by the Tukey post hoc test. For all comparisons, statistical significance was defined as $p < 0.05$.

Results

No difference in body weight was observed between any of the experiment groups (Table 1). Compared to PRE expression, the absolute and relative plantaris weights increased after both 1 day ($p < 0.05$) and 3 days ($p < 0.01$) of overload (Table 1). MCT1 and MCT4 mRNA abundance in plantaris muscle increased by 160% ($p < 0.01$) and 325% ($p < 0.05$), respectively, after 1 day of functional overload, and by 161% ($p < 0.01$) and 265% ($p < 0.05$), respectively, after 3 days of functional overload, compared to PRE expression (Fig. 1). MCT1 and MCT4 protein expression in plantaris muscle increased by 92% ($p < 0.05$) and 61%, respectively, after 12 days ($p < 0.05$) and by 73 and 60%, respectively, after 15 days of functional overload, compared to PRE expression ($p < 0.05$) (Figs. 2, 3). AMPK phosphorylation status [phospho-AMPK (Thr172)/total AMPK] in plantaris muscle was significantly elevated after 3–9 days of functional overload (Fig. 4). Plasma testosterone concentration was elevated after 12 days of functional overload, while blood lactate concentration was not altered (Table 2).

Discussion

The major finding of the present study is that 2 weeks of functional overload on the plantaris muscle induced increases in MCT1 and MCT4 protein expression. Previous studies showed that MCT1 is increased by the most type of

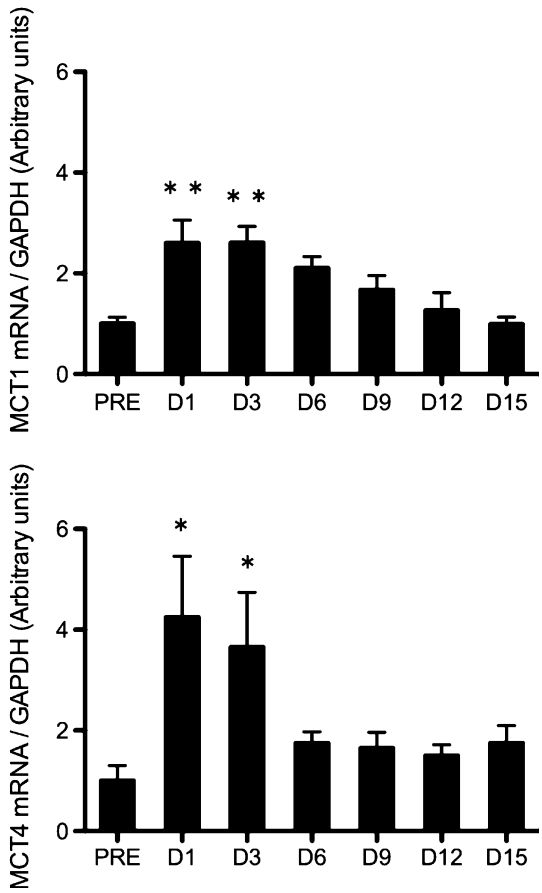

Fig. 1 MCT1 and MCT4 mRNA abundance in plantaris muscle in the pre group (*PRE*) and at 1 day (*D1*), 3 days (*D3*), 6 days (*D6*), 9 days (*D9*), 12 days (*D12*), and 15 days of functional overload (*D15*). All values are reported as mean ± SE ($n = 6$). *Significantly different from the PRE group ($p < 0.05$); **significantly different from the PRE group ($p < 0.01$)

Table 1 Changes in body and muscle weight over a time course of functional overload

	PRE	D1	D3	D6	D9	D12	D15
Body weight (g)	37.18 ± 0.49	35.18 ± 0.43	35.11 ± 0 42	36.75 ± 0.34	38 46 ± 0.69	38.36 ± 0.35	39.76 ± 0 62
Absolute plantaris weight (mg)	20.79 ± 0.22	33.65 ± 1.77	39.34 ± 1.58**	51.98 ± 2.44**	54.58 ± 6.93**	51.58 ± 3.71**	49.83 ± 1.25**
Relative plantaris weight (mg/g)	0.55 ± 0.01	0.95 ± 0.04*	1.12 ± 0.05**	1.41 ± 0.06**	1.41 ± 0.17**	1.34 ± 0.09**	1.25 ± 0.02**

All values are reported as mean ± SE ($n = 6$)

* Significantly different from the PRE group ($p < 0.05$)

** Significantly different from the PRE group ($p < 0.01$)

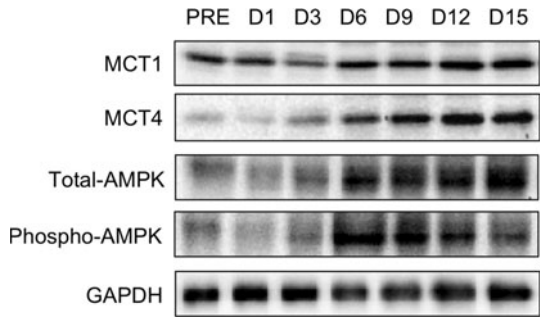

Fig. 2 Representative immunoblots of MCT1, MCT4, and total and phosphorylated AMPK (at Thr172). GAPDH was used as a loading control among the experimental conditions

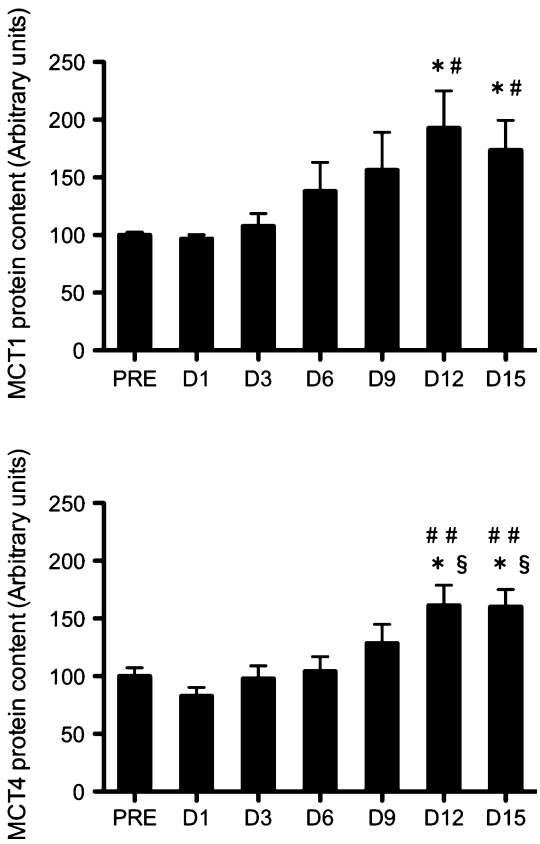

Fig. 3 MCT1 and MCT4 protein expression in plantaris muscle in the pre group (PRE) and at 1 day (*D1*), 3 days (*D3*), 6 days (*D6*), 9 days (*D9*), 12 days (*D12*), and 15 days of functional overload (*D15*). All values are reported as mean ± SE ($n = 6$). *Significantly different from the PRE group ($p < 0.05$); [#]significantly different from the D1 group ($p < 0.05$); [##]significantly different from the D1 group ($p < 0.01$); [§]significantly different from the D3 group ($p < 0.05$)

training, while sprint and strength training can up-regulate MCT4 expression [12]. Interestingly, we have previously found that increased MCT4 by high-intensity training could not be maintained by moderate-intensity training in horses [21]. However, it remains a challenge to understand the mechanisms determining which factor affects the expression of MCTs. In the present study, lactate concentration was not altered over a time course of functional overload. Thus, the result suggested that lactate production and accumulation is not necessarily needed to increase MCT1 and MCT4 expression. In the current study, we found increases in AMPK phosphorylation status in overloaded plantaris muscle, in accordance with the previous study [22]. High-intensity training has a substantial effect on AMPK activity [23]. Therefore, AMPK activity may be required to increase MCT expression. We also found the plasma testosterone level was increased over a time course of functional overload. Moreover, the androgen receptor is known to be increased after 7 days of functional overload [24]. Intense exercise induces the elevation of testosterone level and its receptor binding [25]. Since testosterone is known to increase MCT1 and MCT4 expression [13], these data may suggest that MCTs may be regulated not only by metabolic loading reflected by AMPK but also by the endocrine system and hormones related to muscle hypertrophy. When muscle activity is decreased by denervation [26] or hindlimb suspension [27], lactate transport is decreased with a concomitant decrease in the protein levels of MCT1 and MCT4. In addition, aging is known to induce a decline in MCT1 and MCT4 in skeletal muscle [28]. Reduced muscle activity such as unloading and aging induces decreases in AMPK [29, 30] and testosterone level [31, 32], supporting the importance of AMPK and hormone level for up-regulating MCT1 and MCT4 expression.

In the current study, MCT1 and MCT4 protein content increased after 12 days of overload, while their mRNA expression increased after 1–3 days. The reason for this difference in timing may be due to a greater up-regulation of other proteins synthesis by muscle hypertrophy, as loading induces gene expression related to structural damage, myofiber growth, satellite cell activation, and immune cell infiltration [16, 33–35]. Moreover, several reports suggest that MCTs are regulated at various points during gene expression. For example, it is reported that MCT1 protein expression increased by chronic electrical stimulation whereas mRNA does not [7]. Similarly, both acute exercise and training increased MCT1 protein, without the increases in the corresponding gene transcript level [36]. In contrast, triiodothyronine treatment up-regulated MCT1 mRNA, whereas protein expression remained unaltered [14]. In addition, MCT1 protein to mRNA ratios was observed to differ greatly among different tissues [37]. It was suggested that the relatively long (1.6 kb) 3′-UTR of MCT1 mRNA may allow translational control of expression [38]. Together, the regulation of MCT expression seems to be translational. In the current study, increases in plasma testosterone level and AMPK phosphorylation status preceded or coincided with increases in MCT1 and MCT4 protein but followed increases in MCT1 and MCT4

Table 2 Changes in plasma testosterone and blood lactate concentration over a time course of functional overload

	PRE	D3	D12
Testosterone (ng/mL)	0.15 ± 0.02	0.28 ± 0.04	0.93 ± 0.29*
Lactate (mmol/L)	2.40 ± 0.15	2.45 ± 0.19	1.80 ± 0.18

All values are reported as mean ± SE ($n = 6$)

* Significantly different from the PRE group ($p < 0.05$)

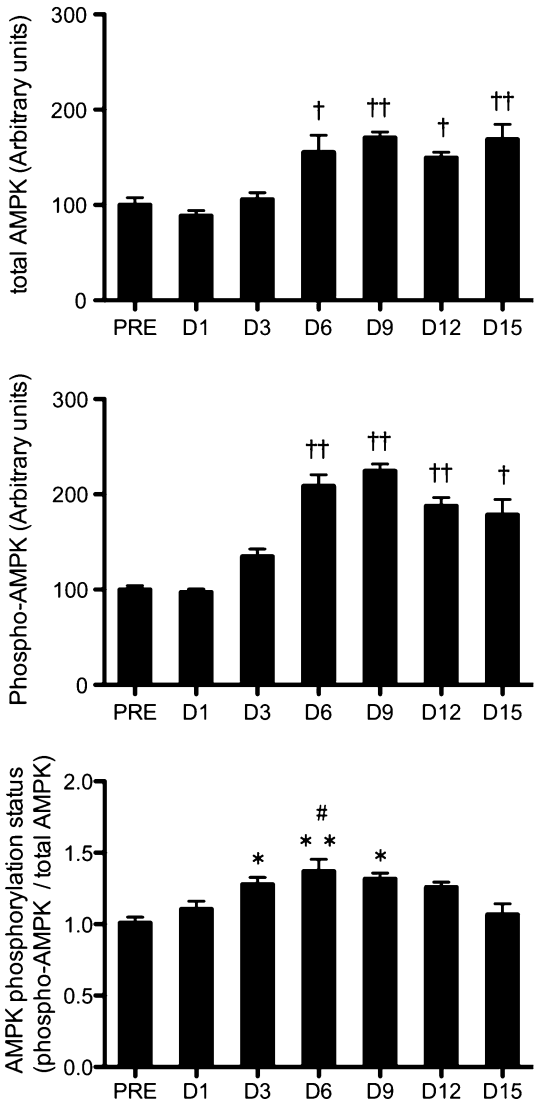

Fig. 4 Phosphorylated AMPK (at Thr172), total AMPK protein expression, and AMPK phosphorylation status [phospho-AMPK (Thr172)/total AMPK] in plantaris muscle in the pre group (PRE) and at 1 day (*D1*), 3 days (*D3*), 6 days (*D6*), 9 days (*D9*), 12 days (*D12*), and 15 days of functional overload (*D15*). All values are reported as mean ± SE ($n = 6$). †Significantly different from the PRE, D1, and D3 group ($p < 0.05$); ††significantly different from the PRE, D1, and D3 group ($p < 0.01$). *Significantly different from the PRE group ($p < 0.05$); **significantly different from the PRE group ($p < 0.01$). #Significantly different from the D1 group ($p < 0.05$)

mRNA. This result might suggest not only the importance of translational regulation of MCTs at least in skeletal muscle but also the existence of some other factors which induce transient increases in MCT1 and MCT4 mRNA at the onset of overload.

The changes at the level of protein are physiologically most relevant, and functional overload clearly induced the increases in MCT1 and MCT4 proteins in plantaris muscle in the present study. It is known that contractile capacity is increased in overloaded plantaris muscle [18]. Since lactate production during exercise depends on the muscle power output and the total working muscle mass in addition to ATP turnover rate [39], increases in lactate transport by MCT1 and MCT4 in overloaded muscle are likely to be important.

Conclusions

The current study showed that MCT1 and MCT4 protein expression increased after functional overload with increases in AMPK phosphorylation status and plasma testosterone concentration. Together with previous findings, it is suggested that heavy mechanical loading on the muscle might be required to increase MCT4 protein expression. Increased loading would induce MCT1 and MCT4 expression to facilitate the lactate influx and efflux to meet the increased energy demands in skeletal muscle.

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