

Critical Review

The Monocarboxylate Transporter Family—Role and Regulation

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Summary

Monocarboxylate transporter (MCT) isoforms 1–4 catalyze the proton-linked transport of monocarboxylates such as L-lactate across the plasma membrane, whereas MCT8 and MCT10 are thyroid hormone and aromatic amino acid transporters, respectively. The importance of MCTs is becoming increasingly evident as their extensive physiological and pathological roles are revealed. MCTs 1–4 play essential metabolic roles in most tissues with their distinct properties, expression profile, and subcellular localization matching the particular metabolic needs of a tissue. Important metabolic roles include energy metabolism in the brain, skeletal muscle, heart, tumor cells, and T-lymphocyte activation, gluconeogenesis in the liver and kidney, spermatogenesis, bowel metabolism of short-chain fatty acids, and drug transport. MCT8 is essential for thyroid hormone transport across the blood–brain barrier. Genetic perturbation of MCT function may be involved in disease states such as pancreatic β -cell malfunction (inappropriate MCT1 expression), chronic fatigue syndromes (impairment of muscle MCT function), and psychomotor retardation (MCT8 mutation). MCT expression can be regulated at both the transcriptional and post-transcriptional levels. Of particular importance is the upregulation of muscle MCT1 expression in response to training and MCT4 expression in response to hypoxia. The latter is mediated by hypoxia inducible factor 1 α and often observed in tumor cells that rely almost entirely on glycolysis for their energy provision. The recent discovery of potent and specific MCT1 inhibitors that prevent proliferation of T-lymphocytes confirms that MCTs may be promising pharmacological targets including for cancer chemotherapy. © 2011 IUBMB

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Abbreviations AICAR, aminoimidazole-4-carboxamide-1- β -D-ribo-nucleoside; AMPK, AMP-activated protein kinase; HIF-1 α , hypoxia inducible factor-1 α ; HRE, hypoxia response elements; MCT, monocarboxylate transporter; PSD, postsynaptic density; RPE, retinal pigment epithelium; TM, transmembrane helix; UTR, untranslated region.

INTRODUCTION

The rapid transport of monocarboxylates such as pyruvate, lactate, and the ketone bodies (acetoacetate and β -hydroxybutyrate) across the plasma membrane of cells is essential for carbohydrate, fat, and amino acid metabolism and is facilitated by proton-linked monocarboxylate transporters (MCTs) (1, 2). Figure 1 summarizes the key metabolic pathways requiring such monocarboxylate transport. As described in the preceding article (3), these MCTs form part of the solute carrier (SLC)16 solute carrier family that contains 14 members in total. However, only four members of the family (MCTs1–4) have actually been demonstrated to facilitate proton-linked monocarboxylate transport. The function of only two other members of the family have been characterized; MCT10 (SLC16A10) is an aromatic amino acid transporter, also known as T-type amino acid transporter 1 (TAT1) and MCT8 (SLC16A2) is a thyroid hormone transporter. In the previous review (3), the structure and functional characteristics of the different MCT family members was described, whereas this article focuses on their physiological roles and regulation. As noted previously (3), there are also two members of the SLC5 solute transporter family that act as sodium-linked monocarboxylate transporters (SMCTs). These play a key role in endothelial monocarboxylate transport in the gut and kidney but will not be discussed further here.

PHYSIOLOGICAL ROLES OF THE DIFFERENT MCT ISOFORMS

At the outset, it is important to recognize that MCTs1–4 each catalyze the net proton-linked transport or exchange of short-chain monocarboxylates, usually substituted on the two or three carbons with a keto group (e.g., pyruvate and acetoacetate) or

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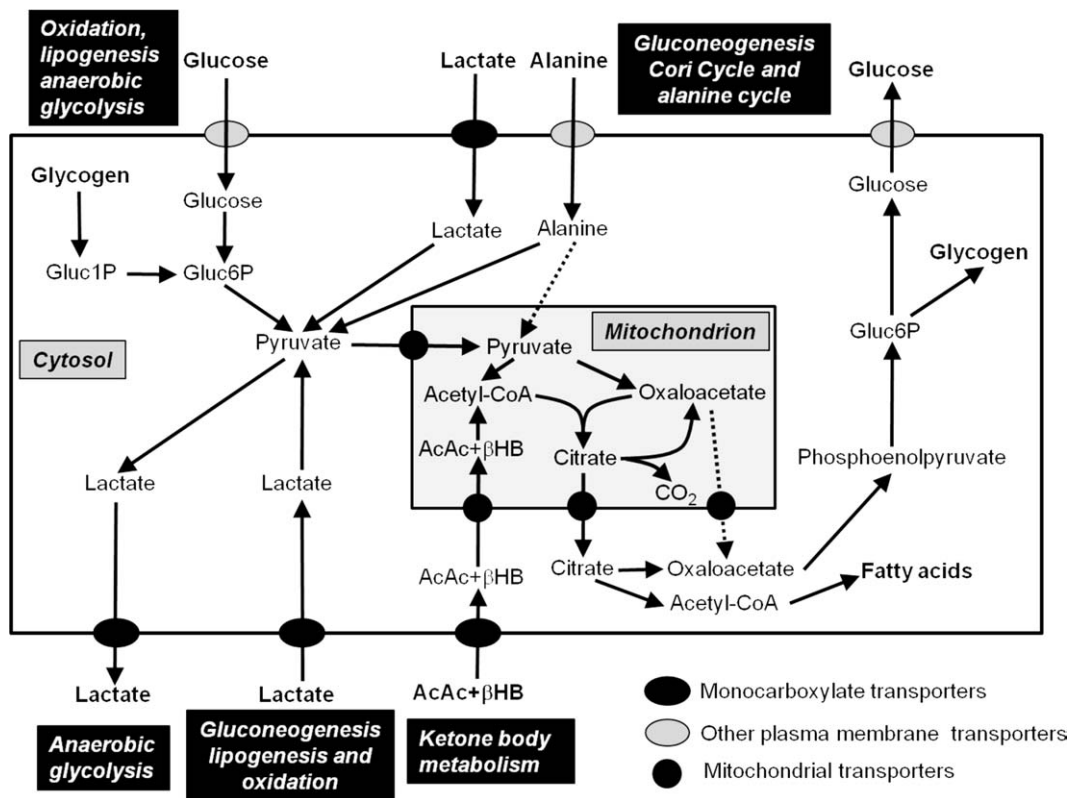


Figure 1. The key metabolic pathways involving members of the MCT family. It should be noted that no single cell will carry out the full spectrum of pathways shown and further details of tissue-specific roles are given in the text. Adapted from ref. 2.

hydroxyl group (e.g., L-lactate and D- β -hydroxybutyrate). Both influx and efflux of monocarboxylates are facilitated, with the direction of net transport being determined purely by the concentration gradients of protons and monocarboxylate across the plasma membrane. The major differences between the isoforms are their relative substrate and inhibitor affinities, the regulation of their expression, and their tissue distribution and intracellular localization. These relate to the particular metabolic role of each isoform in each tissue, although the same role can be fulfilled by different MCT isoforms in different tissues and species. It is also important to note that cotransport of lactate with a proton is entirely consistent with the metabolic pathways producing or utilizing this monocarboxylate. Thus, it is lactic acid rather than lactate that is produced as a result of glycolysis and that is utilized as a substrate for oxidation, gluconeogenesis, or lipogenesis (4). It is also worth noting that in cells such as the heart glycolysis can play an important role in providing adenosine triphosphate (ATP) in the subsarcolemmal membrane to drive and/or regulate ion channels (5). However, MCTs are unlikely to be important in this process under normoxic conditions as the pyruvate will be oxidized by the mitochondria rather than be exported as lactic acid. Indeed, as noted below (MCT1 section), hearts are normally net users rather than producers of lactic acid.

MCT1

MCT1 is expressed in almost all tissues, sometimes in conjunction with other MCT isoforms whose distribution within and between cells can be quite distinct from MCT1 (see refs. 1 and 6). The major physiological role of MCT1 is to facilitate L-lactic acid entry into or efflux out of cells depending on their metabolic state. In liver parenchymal cells and the proximal convoluted tubule cells of the kidney, MCT1 may be used to transport L-lactate into the cells for gluconeogenesis for which it is a major substrate, especially after exercise (see ref. 1). However, as discussed below, in some species, the higher affinity MCT2 may fulfill this role (MCT2 section). In the heart and red skeletal muscle, MCT1 is required for lactate and ketone bodies to enter the myocytes and be oxidized as a major respiratory fuel under conditions when their concentrations are elevated (7, 8). Indeed, in skeletal muscle, there is a strong correlation between the amount of MCT1 expressed in muscle fibers and their oxidative capacity (mitochondrial content) (7, 8). MCT1 also facilitates the transport of these same monocarboxylates across the blood brain barrier for uptake into neurons (via MCT1 or MCT2) which, like red skeletal muscle, use them as respiratory fuels (9). In both muscle and the brain, there is cooperation between MCT isoforms involved in lactic acid efflux and influx by different cell types within the same tissue,

and this will be discussed further below (MCT Isoforms are Involved in Shuttling Lactate Between Different Cell Types Within Tissues section).

During hypoxia or anoxia, all cells become more dependent on glycolysis for their ATP production and thus require export of lactic acid which will usually be mediated by MCT1 as this is the predominant isoform in most tissues (1). It is lactic acid that is produced by glycolysis, and thus by transporting lactate with a proton MCT1 also acts to reduce intracellular acidification during conditions of high glycolytic flux. This means that lactic acid efflux via MCT1 also plays an important part in the restoration of intracellular pH during reperfusion or reoxygenation following a period of ischemia or hypoxia (6, 10). In tissues such as the red blood cell, T-lymphocytes, tumor cells and white muscle, energy metabolism is largely glycolytic even under aerobic conditions. Lactic acid efflux from these cells is mediated by MCT1 in some cases, (e.g., red blood cells and T-lymphocytes), whereas in other cells such as white muscle, MCT4 is the major transporter (see MCT4 section). Recent data has emphasized the importance of MCT1 during the activation and proliferation of resting T-lymphocytes, which is accompanied by a switch from aerobic to glycolytic metabolism and a massive increase in lactate production and export. Indeed, specific and potent MCT1 inhibitors developed by AstraZeneca block T-lymphocyte proliferation and act as potent immunosuppressant drugs (11). Likewise, tumor cells are also highly dependent on glycolysis for their ATP synthesis (the Warburg effect), and this may be an Achilles' heel that MCT inhibitors could exploit as chemotherapeutic agents (12). Some tumor cells use MCT1 for this purpose, whereas others, especially more invasive tumors, have upregulated MCT4 activity probably induced by overexpression of hypoxia inducible factor 1 α (HIF-1 α) as discussed further below (MCTs in Disease States section).

MCT1 (sometimes in conjunction with MCT2 and MCT4) may be important in communicating changes in the nicotinamide adenine dinucleotide reduced (NADH)/nicotinamide adenine dinucleotide oxidized (NAD⁺) redox state between cells and tissues (1, 6). The mechanism behind this involves cytosolic lactate dehydrogenase (LDH) and mitochondrial β -hydroxybutyrate dehydrogenase, both of which catalyze reactions that are close to equilibrium in most cells. This means that shifts in the cytosolic NADH/NAD⁺ ratio cause changes in the [lactate]/[pyruvate] ratio and vice-versa. Similarly, shifts in the mitochondrial NADH/NAD⁺ ratio cause changes in the [β -hydroxybutyrate]/[acetoacetate] ratio and vice-versa. As these monocarboxylates are rapidly transported into and out of cells by MCT1, their extracellular concentration ratio in the blood matches their intracellular concentration ratio. Thus, tissues can communicate their redox state through the concentration of these monocarboxylates in the blood.

There are data to suggest that MCT1 plays a vital role in the uptake of short-chain fatty acids such as acetate, propionate, and butyrate from the gut where they are produced in large

amount by bacteria (see refs. 1 and 6). Thus, MCT1 is present on the basolateral membrane of the gut epithelium whereas the SMCTs SLC5A8 and SLC5A12 are present on the apical membrane of the gut epithelial cells. It would seem probable that these transporters work together to enable net uptake of such short-chain fatty acids from the gut to the blood (13). However, while there is no doubt that MCT1 can facilitate the transport of these monocarboxylates, in most cells the free diffusion of the undissociated acid will occur sufficiently fast to make the additional transport provided by MCT1 less important (6).

In the insulin secreting β cell of the islets of Langerhans, all MCT isoforms, including MCT1, are conspicuous by their absence. This is essential to ensure that insulin secretion does not occur in response to elevated blood lactate during exercise (14). What represses MCT1 expression in β cells is not known, but the promoter of MCT1 contains multiple CpG sequences (termed CpG islands) typical of many genes that exhibit tissue-specific expression patterns (15). Tissue-specific DNA methylation often occurs within these CpG islands preventing some transcription factors from binding to the DNA resulting in tissue specific patterns of gene expression (15). Thus, if appropriate sites on the MCT1 promoter were specifically methylated in β cells, stimulatory transcription factors would not bind leading to greatly reduced expression.

A Role for MCT1 in Drug and Water Transport. MCT1 has been proposed to mediate the transport of some drugs across the plasma membrane of epithelial cells in the intestine and kidney and across the blood brain barrier. These include salicylate, valproic acid, atorvastatin, nateglinide, gamma-hydroxybutyrate, and nicotinic acid (see ref. 6). Another suggested role for MCT1 in some tissues is the movement of water as it has been shown that water moves across the plasma membrane with the monocarboxylate anion during the translocation cycle of MCT1 (see ref. 6). Such coordinated transport of lactate and water by MCT1 in the retinal pigment epithelium (RPE) may be important in maintaining osmotic balance of the eye where water and lactic acid are transported from the retina to the choroid. This is an essential process for the maintenance of retinal adhesion and the pH of the subretinal space as discussed further below (MCT3 section).

MCT1 is Not Responsible for Pyruvate Transport into Mitochondria. There are several reports that MCT1 is present in mitochondria of the heart, skeletal muscle, and brain, and it has been suggested that this provides a mechanism for these tissues to oxidize lactate as a respiratory fuel (see refs. 6 and 16). It is proposed that lactate rather than pyruvate is transported directly into the mitochondria where an intramitochondrial LDH may oxidize it to pyruvate before completing oxidation around the citric acid cycle. This "lactate shuttle" hypothesis might appear attractive as it avoids the need to use mitochondrial NADH shuttles for the oxidation of cytosolic NADH produced by LDH. However, there are strong theoretical arguments against

the hypothesis. Oxidation of lactate by LDH within the mitochondrial matrix is both energetically unfavorable and incompatible with the known NADH redox compartmentation within cells which usually maintain a much higher NADH/NAD⁺ ratio in the mitochondria than the cytosol (see ref. 6). In addition, mitochondria express a large family of 6-TM transporters (the SLC25 family) that are quite distinct from the 12-TM solute carriers of the plasma membrane, and one of these is thought to be the pyruvate carrier (17) which exhibits a very different inhibition profile and substrate affinity to MCT1 (18, 19). Furthermore, we and others have shown that careful density gradient centrifugation removes all significant MCT1 and LDH from the mitochondrial fraction (see ref. 6). To our knowledge, no studies have been reported in which the MCT1 detected within mitochondrial fractions has been shown to be protease insensitive as would be predicted for an inner membrane transporter. The reader is referred elsewhere to a fuller account of the arguments in favor and against the intracellular lactate shuttle hypothesis (5, 16, 20, 21).

MCT2

MCT2 has a higher affinity for pyruvate and lactate than MCT1 and its expression is primarily confined to those tissues that take up lactic acid in significant quantities for use as a respiratory fuel (*e.g.*, neurons) or for gluconeogenesis (liver parenchymal cells and kidney proximal convoluted tubules). However, there are considerable species differences in its expression profile (see refs. 1, 22, and 23). Both Northern blot analysis and inspection of the human expressed sequence tag (EST) database suggest little expression of MCT2 in human tissues, but in mouse, rat, and the hamster, Northern and Western blot analysis together with immunofluorescence microscopy show the protein to be expressed in liver, kidney, brain, and sperm tails, whereas in hamster, there is also evidence for its presence in skeletal muscle and heart (22, 23). Where MCT2 is expressed together with MCT1 its exact location within the tissue is different (22) and this appears to be especially important in the brain (see refs. 1 and 9) as discussed further below (MCT Isoforms and Lactate Shuttling Between Cells).

MCT3

Expression of MCT3 is confined to the RPE and choroid plexus epithelia where it is located on the basal membrane in contrast to MCT1 which is found on the apical membrane (24, 25). Together with MCT1, it is thought to play an important role in facilitating the transport of glycolytically derived lactic acid out of the retina as discussed above (A Role for MCT1 in Drug and Water Transport section). However, mice in which MCT3 was genetically deleted were healthy with no significant abnormalities in retinal histology, although electrophysiological studies of retinal function did reveal modest changes in behavior. This would be consistent with a decrease in the pH of the

subretinal space leading to a reduction in the magnitude of the light suppressible photoreceptor current (26).

MCT4

MCT4 is quite widely expressed but especially so in tissues that rely on glycolysis such as white skeletal muscle fibers, astrocytes, white blood cells, chondrocytes, and some mammalian cell lines (1, 3, 7, 8). The key role of MCT4 in exporting lactic acid from skeletal muscle is reflected in its expression pattern relative to MCT1 in different muscle fiber types. Highly glycolytic muscle fibers such as those predominating in white gastrocnemius muscle express more MCT4, whereas highly oxidative fibers, such as those predominating in the soleus muscle, express more MCT1 (1, 7, 8). The properties of MCT4 are well suited for its role in exporting lactic acid derived from glycolysis because its very K_m for pyruvate (at 150 mM) ensures that pyruvate is not lost from the cell. This is essential in a cell that relies on glycolysis because removal of the NADH produced in glycolysis requires that the pyruvate be reduced to lactate which would not be possible if the pyruvate were to be lost from the cell (see refs. 1 and 7). At first glance, the high K_m for lactate is not what one might predict for a lactic acid efflux pathway, but there is a good physiological rationale for this relatively low affinity. By restricting lactic acid efflux from skeletal muscle as levels of exercise increase, the pH of the muscle will drop and further enhance lactic acid efflux. However, if lactic acid production becomes excessive, the pH drops more and fatigue will occur. This will prevent further lactic acid production which might have dangerous repercussions by causing systemic lactic acidosis (1, 7).

MCT8 and MCT10

MCT8 is a thyroid hormone transporter with high affinity (K_m 2–5 μ M) for T4 and T3 (27). Although widely expressed (27), it appears to play a particularly important role in the brain where it is required for the thyroid hormone uptake that is essential for normal brain development (28). Indeed, mutation of MCT8 is a cause of severe X-linked psychomotor retardation (29). In other tissues, alternative thyroid hormone transporters appear to compensate for loss of MCT8 activity, including organic anion-transporting polypeptide (OATP)1C1 and MCT10 (see ref. 28). The latter is a sodium-independent transport system that selectively transports aromatic amino acids with K_m values of about 1 mM. It is strongly expressed on the basolateral membrane of epithelia in kidney, intestine, and the sinusoidal side of perivenous hepatocytes where it is thought to be crucial for the efficient (re)-absorption of these amino acids (see ref. 28).

MCT ISOFORMS AND LACTATE SHUTTLING BETWEEN CELLS

The existence of MCT isoforms in almost all tissues, allows lactate, pyruvate, and the ketone bodies produced in one tissue to be used in another. Thus, depending on the prevailing meta-

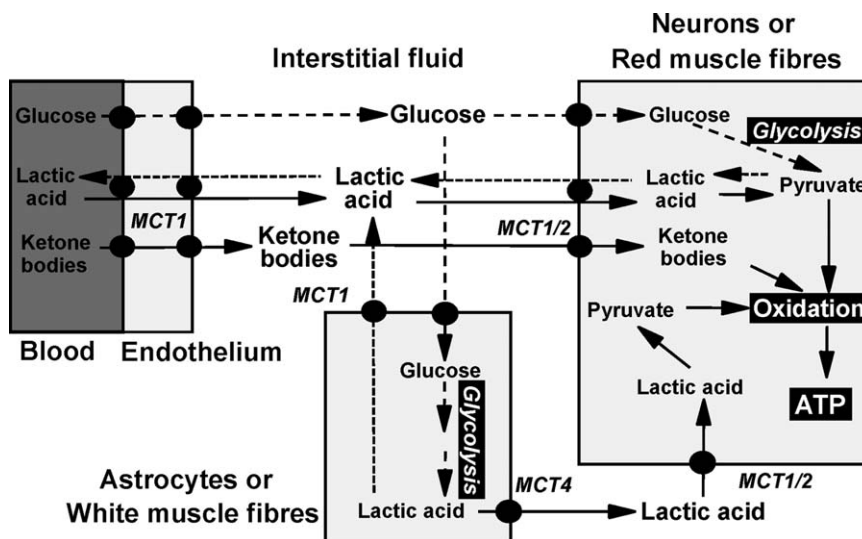


Figure 2. The roles of MCTs in brain and muscle to shuttle lactate between different cell types within the tissue. Adapted from ref. 1. See also Fig. 1.

bolic state, lactic acid produced by skeletal muscle can be taken up by the liver and kidney for gluconeogenesis, fat tissue for lipogenesis, and the heart and brain for oxidation. Similarly, ketone bodies are produced in the liver under conditions of high fatty acid oxidation (*e.g.*, starvation and diabetes) and exported into the blood via MCT1 or MCT2 to be taken up via MCT1 or MCT2 by neurons, skeletal, and cardiac muscle and used as a respiratory fuel (1, 4, 7, 9). As noted above and in the preceding review (3), the expression pattern of the different MCT isoforms in each tissue matches their normal metabolic role in that tissue. In addition to their role in shuttling monocarboxylates between tissues, there is now increasing evidence that MCTs are involved in shuttling lactic acid between different cell types within a tissue. Different MCT isoforms are used to export the lactic acid from a cell that is glycolytic even under normoxic conditions and then to import it into another cell type where it is used as a respiratory fuel. This is best established in skeletal muscle and brain as illustrated in Fig. 2. Most muscles contain a mixture of fibers, those that are primarily glycolytic (white fibers) and those that are primarily oxidative (red fibers) with each muscle having a different balance depending on whether its use is primarily rapid high-intensity exercise (glycolytic) or endurance exercise (oxidative) (7, 8). As noted above (MCT4 section), the glycolytic fibers express primarily MCT4 whose properties are appropriate for lactic acid efflux, whereas the oxidative fibers express primarily MCT1 (together with MCT2 in some species) that is well suited for lactic acid influx (6–8). There is also evidence for lactate shuttling within some tumors where the hypoxic centre of the tumor is glycolytic and produces lactic acid that is exported by MCT4 and taken up by peripheral tumor cells that are more oxidative and express MCT1 (30). In the brain, lac-

tate is generated by glycolysis within astrocytes, and exported via MCT1 or MCT4 to the neurons where it is taken up via MCT1 and MCT2 for use as a respiratory fuel (9). Consistent with this, MCT2 expression in the brain is largely confined to the postsynaptic density (PSD) of the neurons, a region rich in mitochondria and thought to oxidize lactate as a preferred respiratory fuel (9). Targeting of MCT2 specifically to the PSD is thought to be mediated by a PDZ binding motif on the C-terminus of MCT2 that may allow it to bind to PSD95, a scaffolding protein found in the PSD. Furthermore, it has been suggested that MCT2 may in turn influence the trafficking of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor within neurons by modulating sorting of its GluR2 subunit to this compartment (31). The importance of the astrocyte/neuron lactate shuttle in normal brain function and the roles of the different MCT isoforms has recently been confirmed in some elegant *in vivo* studies (32). Disruption of astrocytic MCT4 or MCT1 expression in the hippocampus of rats was achieved by microinjection of antisense oligodeoxynucleotide and knockdown of either isoform prevented long-term potentiation resulting in the loss of memory of learned tasks. However, the memory could be rescued by localized infusion of L-lactate but not equicaloric glucose. Knockdown of MCT2 expression led to similar amnesia, but in this case, the effect could not be reversed by either L-lactate or glucose consistent with the MCT2 being required to enable the lactate to enter the neuron.

There is also evidence that lactate metabolism in the retina is subject to a complex interplay between photoreceptor cells and other neurons which oxidize lactate and glial cells (Müller cells) which export lactate through MCT4. Here, as noted above (A Role for MCT1 in Drug and Water Transport and MCT3

sections), lactic acid must cross the RPE as an accumulation of lactate within the subretinal space would cause osmotic swelling, resulting in the retina becoming detached from the RPE. This is prevented by the ability of MCT1 in association with MCT3 to transport both lactic acid and water rapidly across the RPE and into the blood. MCT1 is exclusively located on the apical surface of the RPE and transports lactate and water from the subretinal space into the RPE, whereas MCT3 is exclusively located on the basolateral surface of the RPE and is responsible for lactate efflux into the choroidal blood supply (24, 25).

ROLES OF THE MCT ANCILLARY PROTEIN, BASIGIN

MCTs1-4 require an ancillary protein, either basigin or embigin, for correct translocation to the plasma membrane where the proteins remain associated (see refs. 1, 3, and 6). MCT3 and MCT4 contain a dominant targeting sequences and direct basigin to the basolateral membrane. However, in the case of MCT1, it is the basigin that targets MCT1 to the basolateral membrane of most polarized cells, including the epithelia of the kidney, liver, gut, and thyroid. Indeed, a single L252A mutation of basigin redirects MCT1 to the apical surface (33). In the RPE, basigin-mediated targeting of MCT1 is ignored, and MCT1 is expressed with basigin at the apical membrane (33).

Although we have been unable to detect any change in the kinetic properties of MCT1 when it is bound to embigin rather than basigin, the associated ancillary protein does affect the ability of AR-C155858 and para-chloromercuriphenylsulfonic acid (*p*CMBS) to inhibit MCT activity (see ref. 3). This allows for the possibility that MCT activity might be regulated physiologically through binding of natural ligands to the ancillary proteins. Although such ligands have yet to be identified, some antibodies against extracellular epitopes of basigin have been reported to inhibit lactate transport and induce intracellular acidosis and cell death in basigin-expressing cancer cell lines (34). Interestingly, basigin plays a key role in tumor cell proliferation, migration, and invasiveness (35) which may reflect its involvement in extracellular metalloproteinases activation (36). Basigin has also been implicated in signaling pathways in inflammation, and as a receptor for viruses, including for HIV (36). Whether these interactions involve changes in MCT1 activity is not known.

REGULATION OF MCT ACTIVITY

Short-Term Regulation

Evidence for short-term regulation of MCT activity is very limited. Rapid stimulation of MCT1 activity via cyclic AMP has been reported in rat brain endothelial cells suggesting that the protein may be regulated by phosphorylation but our own data have failed to confirm this (see ref. 6). Both MCT1 and MCT4 have been shown to interact with intracellular carbonic anhydrase II, and this interaction enhances transport activity independently of the catalytic activity of the enzyme perhaps by acting as a

“proton-collecting antenna” (37). By contrast, transport activity of MCT2 is enhanced by extracellular carbonic anhydrase IV but not by intracellular carbonic anhydrase II (38). It is not known whether these interactions between MCTs and carbonic anhydrase isoforms are subject to any acute regulation.

Transcriptional Regulation

MCT1. In skeletal muscle, numerous studies have shown upregulation of MCT1 in response to chronic stimulation or exercise in rats and humans, whereas downregulation occurs in response to denervation or spinal injury (see refs. 6–8). The upregulation is thought to be through activation of gene expression and is likely to be mediated by elevated calcium and AMP that in turn may activate the calcium-dependent protein phosphatase, calcineurin, and AMP-activated protein kinase (AMPK) (see ref. 6). Calcineurin is thought to play a central role in muscle gene expression, and the calcineurin inhibitors cyclosporine A (CsA) and FK506 can both remodel skeletal muscle in favor of fast oxidative fibers (37). These fibers express less MCT1 as opposed to slow oxidative fibers that express more MCT1 and less MCT4 (7). CsA also inhibits cardiac hypertrophy (39), a process that is associated with upregulation of MCT1 (see refs. 1 and 6). Calcineurin is thought to act by dephosphorylation and activation of the transcription factor nuclear factor of activated T-cells (NFAT) (nuclear factor of activated T cells) and inspection of the MCT1 promoter reveals that it contains several consensus NFAT binding sequences ((T/A)GGAAA(A/N)(ATC)N) (6). Interestingly, the activation and proliferation of T-lymphocytes is a highly glycolytic process requiring rapid efflux of lactic acid and is accompanied by a large (several-fold) increase in MCT1 expression (11). This could be an important downstream target for the immunosuppressive action of CsA. In support of this hypothesis, the novel MCT1 inhibitors developed by AstraZeneca (*e.g.*, AR-C155858) are potent immunosuppressive drugs that inhibit T-lymphocyte proliferation (11). The transcriptional coactivator PGC1 α may also be involved the upregulation of MCT1 expression in response to increased muscle activity (reviewed in ref. 6). PGC1 α expression is increased in response to increased calcium concentrations and activation of AMPK and is capable of driving the formation of slow-twitch oxidative muscle fibers which primarily express MCT1 rather than MCT4 (6–8). Furthermore, as shown in Fig. 3, using an MCT1 promoter luciferase construct, we demonstrated that 2-mM 5-aminoimidazole-4-carboxamide-1- β -D-ribose nucleoside (AICAR), an activator of AMPK, stimulated MCT1 promoter activity in both L6 myoblasts and HepG2 hepatoma cells twofold while reducing the activity of the MCT4 promoter by more than 50%. However, in rat Sertoli cells, others have reported that AICAR downregulates MCT1 expression. Thyroid hormone (T3) has also been reported to upregulate MCT1 and MCT4 expression in skeletal muscle at the mRNA level although only MCT4 protein levels were found to be increased (see ref. 6).

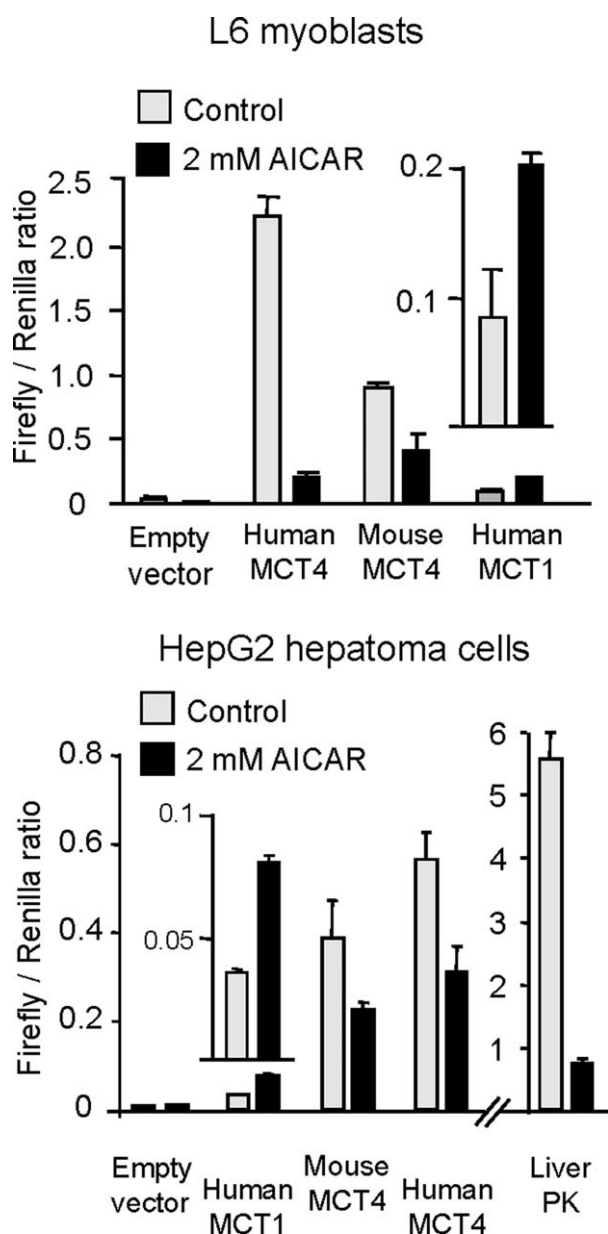


Figure 3. Activation of AMP-activated protein kinase (AMPK) with AICAR stimulates the MCT1 promoter but inhibits the MCT4 promoter in L6 myoblasts and HepG2 hepatoma cells. Promoter activity was measured using firefly luciferase MCT promoter constructs cotransfected with a constitutively active Renilla luciferase construct as described previously (40). Data are shown as the ratio of the luciferase to Renilla signal and as means \pm SEM (error bars) of four to six separate experiments. In the HepG2 cells, data for a human liver pyruvate kinase (PK) firefly luciferase promoter construct are also shown as a positive control for the effects of AMPK activation. These are previously unpublished data of Davies and Halestrap.

Expression of MCT1 in adipose tissue, heart, and skeletal muscle was reported to be reduced in streptozotocin-induced toxicity that results in a diabetic-like state, although others did not observe this effect in skeletal muscle despite a decrease in measured rates of lactate transport (see refs. 1 and 6). In obese rats, a decrease in skeletal muscle MCT1 expression has been described while an increase has been reported in the brain of obese mice or mice subject to ketosis and chronic hyperglycemia (see refs. 1 and 6). There is also evidence for changes in MCT isoform expression patterns during development in the heart, inner ear, and brain as well as during the development of the preimplantation embryo (see refs. 1 and 6).

MCT2. An early comparison of the expression levels of MCT2 mRNA and protein suggested that MCT2 may be subject to post-transcriptional control (23). Further evidence for this has been provided in the brain where noradrenaline as well as both insulin and IGF-1 were reported to enhance the expression of MCT2 by translational activation (see ref. 40). This activation was shown to be mediated by stimulation of the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway. Subsequent studies from the same laboratory demonstrated that brain-derived neurotrophic factor (BDNF) enhances MCT2 expression in mouse cultured cortical neurons by a similar mechanism and suggested that changes in MCT2 expression could participate in the process of synaptic plasticity induced by BDNF (40). Food deprivation (48 h) has been reported to induce MCT2 mRNA expression in the brainstem of female rats, consistent with enhanced utilization of ketone bodies as a respiratory fuel under these conditions (41). Surprisingly, other studies suggested that obesity also increases expression of MCT2 (and that of MCT1 and MCT4) in the brain, most prominently in the cortex and in the hippocampus (42). Recovery from a focal ischemic insult of the brain has also been reported to show an increase in MCT1 and MCT2 expression (43). However, in human adipocytes, hypoxia decreases expression of MCT2 mRNA MCT2 while increasing that of MCT1 and MCT4 (44).

MCT3 and MCT4. As noted above (MCT3 section), MCT3 expression is restricted to the RPE and choroid plexus but how such a restricted expression is regulated is not known. Interestingly, wounding of the RPE resulted in loss of MCT3 and the up-regulation of MCT4 expression in migrating cells at the edge of the wound (45). MCT4 expression in skeletal muscle has recently been reported to increase in response to the stimulation of AMPK with AICAR (46) but this observation conflicts with our own data on the regulation of the MCT4 promoter described above (Transcriptional Regulation section and Fig. 3). Upregulation of MCT4 expression under conditions of high-energy demand has only been reported in one study following high-intensity treadmill training of rats, and it was only modest compared with that of MCT1 (47). The major regulatory mechanism identified for MCT4 expression is hypoxia, and this is consistent with the proposed role of this iso-

form in exporting lactic acid derived from glycolysis (see MCT4 section). We demonstrated that hypoxia increases MCT4 mRNA and protein expression in a variety of cells and this effect could be mimicked by treatment with cobalt, implicating transcriptional regulation via HIF-1 α (48). The effects of cobalt and hypoxia were confirmed in human adipocytes by others where a parallel increase of MCT1 but a decrease in MCT2 expression was also described (44). Using luciferase promoter constructs, we were able to show that MCT4 promoter activity is stimulated by hypoxia, whereas no such effect was observed with the MCT1 or MCT2 promoter. The effect of hypoxia was abolished in cells lacking HIF-1 α , consistent with the presence of four potential hypoxia response elements (HRE) in the MCT4 promoter that are absent in the MCT1 and MCT2 promoters (48). Deletion analysis revealed that only the two HRE just upstream from the transcription start are essential for the hypoxia response. Thus MCT4 joins a large family of proteins, including several other key glycolytic enzymes, whose expression is regulated by HIF-1 α that coordinates an appropriate metabolic response of the cell to hypoxia. MCT4 is also upregulated in the neonatal heart (49). It is not known how this effect is mediated but neonatal hearts are more glycolytic in their energy metabolism than the adult heart which would be consistent with a role for HIF-1 α .

Post-Transcriptional Regulation

In addition to transcriptional regulation of MCT expression, parallel measurements of MCT1 and MCT2 mRNA and protein in several tissues suggest that post-transcriptional mechanisms may also play a role (21). In the heart, MCT1 protein expression increases in left ventricle hypertrophy following surgical ligation of a major branch of the left coronary artery, but there is little change in mRNA implying post-transcriptional regulation (50). It was suggested that this might involve translocation to the sarcolemma of a novel intracellular pool of MCT1 associated with cisternae close to the t-tubules. Interestingly, MCT1 possesses two acidic clusters and an LL motif in the C-terminus; these motifs are believed to be important in endosomal-lysosomal targeting of GLUT 4 (see refs. 1 and 6). Post-transcriptional regulation of MCT1 could also involve regulation of its translation. Such translational control of protein synthesis usually involves specific sequences and secondary structure in the 5' or, frequently, the 3' untranslated region (UTR). Initiation factors such as eIF4E and other regulatory factors such as Maskin or Cup are thought to interact with these regions to enhance or repress translation (see refs. 6 and 51 for details). As the 3' untranslated region of MCT1 is very long (some 1.2 kb longer than either MCT4 or MCT2 in rats), it could well be involved in such translational control of MCT1 expression (6). Our own studies have revealed a particularly striking example of post-transcriptional up-regulation of MCT1 expression during the cell cycle as shown in Fig. 4. MCT1 protein expression increased several fold during the postmitotic and G1 phases of the cell

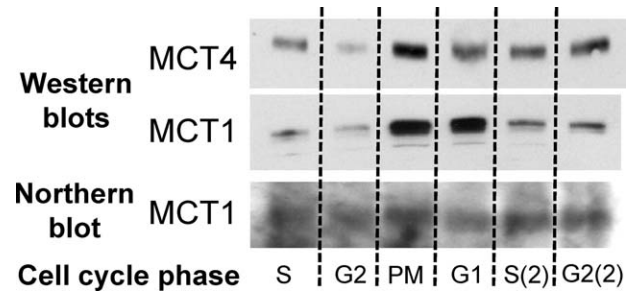


Figure 4. Increased MCT1 expression in HeLa cells during the cell cycle protein may involve regulation of translation rather than transcription. HeLa cells were synchronized by blocking the cell cycle at the G1/S boundary with thymidine and aphidicolin and then releasing the block with fresh medium (51). Samples were taken at the indicated times for Western and Northern blotting performed as described previously (22, 40). These are previously unpublished data of Wilson and Halestrap.

cycle in the absence of a change in MCT1 mRNA. MCT4 showed no significant change in expression at either the protein or mRNA levels. Importantly, the 3'-UTR of MCT1 contains a potential cytosolic polyadenylation element and hexanucleotide elements, sequences thought to be critical in the regulation of polyadenylation at the exit from the mitotic phase in the cell cycle that in turn may relieve Maskin or Cup inhibition of eIF4E (51). Furthermore, the phosphorylation states of eIF4E and 4E-BP1 change greatly during the cell cycle in parallel with rates of translation. Indeed, the time of maximal 4E-BP1 phosphorylation corresponds with the peak of MCT1 expression (52).

MCTS IN DISEASE STATES

Fatigue

In a rare condition known as cryptic exercise intolerance, otherwise healthy individuals suffer severe chest pain and muscle cramping on vigorous exercise. This would be consistent with a defect in lactate efflux pathways from muscle, and measurements of lactate uptake by the erythrocytes of such patients was reported to show a reduction in transport that was attributed to an MCT defect. Furthermore, RT-PCR of MCT1 from muscle biopsies from these patients identified a number of amino acid differences that were not attributable to polymorphisms (53). Of these, only a lysine to glutamate mutation in the large cytoplasmic loop between transmembrane domains (TMDs) 6 and 7 was considered a likely candidate, but we have expressed the K204E mutant in *Xenopus* oocytes and been unable to demonstrate any difference in its properties from wild-type MCT1 (see refs. 1 and 6). Thus, it remains unclear whether mutations in MCT1 are responsible for cryptic exercise intolerance or whether other factors (such as mutations in embigin or basigin) might be involved.

Mice in which basigin has been knocked out are sterile, show various neurological abnormalities and exhibit retinal dysfunction. This is consistent with disruption of correct MCT expression in the testes, brain and retina where they play essential metabolic roles (36). The natural ligand(s) of basigin remain uncertain but some antibodies against extracellular epitopes of basigin can inhibit lactate transport and induce intracellular acidosis and cell death in basigin-expressing cancer cell lines (34). It is intriguing to speculate whether autoantibody interactions with basigin may underlie some chronic fatigue syndromes that are known to be associated with autoantibody production. For example, patients with primary biliary cirrhosis who experience chronic muscle fatigue have abnormalities in muscle pH regulation consistent with impaired lactate transport mediated by autoantibodies against basigin (or MCT) (54).

Cancer

Tumor cells usually depend on glycolysis for their energy metabolism (12), and thus, it is not surprising that they exhibit high levels of MCT expression to maintain an appropriate pH environment for tumor growth (55, 56). However, there is considerable variation in the MCT isoforms expressed in different tumors and in their associated ancillary protein (57). In metastatic tumors, which frequently show upregulation of HIF-1 α and MCT4 expression, there is also an increased plasma membrane expression of basigin (55, 56). This may be significant because another function of basigin is to activate extracellular metalloproteinases (36) that play a key role in tumor cell proliferation, migration, and invasiveness (35).

Exercise-Induced Hyperinsulinemia

In individuals of three separate pedigrees, each displaying exercise-induced hyperinsulinemia (EIHI) with hypoglycemia, mutations have been identified in the MCT1 promoter that enhance its activity (58). This leads to inappropriate MCT1 expression in the insulin secreting β cells of the islets of Langerhans which are normally devoid of MCT1 (14). The presence of MCT1 in these β cells enables lactate to be oxidized during exercise and thus provide increased ATP levels to signal insulin secretion which in turn leads to the observed hypoglycemia.

Severe X-Linked Psychomotor Retardation

Another disease in which an MCT mutation has been implicated is severe X-linked psychomotor retardation mutation. Here, a mutation in the MCT8 gene (located on the X chromosome) has been established and the lack of MCT8 activity in the brain prevents thyroid hormone uptake and thus normal brain development (29).

FUTURE PERSPECTIVES

Recently, it has become apparent just how extensive and important are the roles played by members of the MCT family under both physiological and pathological conditions. No doubt

there are further roles to be discovered, including those played by members of the family whose properties have yet to be characterized. Indeed, clues to the identity of these orphan members of the MCT family may emerge as disease states are recognized that are associated with their mutations.

An important recent development is the discovery by Astra-Zeneca of a class of potent MCT1 inhibitors that act as powerful immunosuppressive agents by inhibiting T-lymphocyte proliferation (11). These represent a valuable tool for further dissecting the metabolic roles of MCT1 and illustrate the promise of MCTs as pharmacological targets. Thus targeting of MCTs becomes a potential strategy for chemotherapy, especially in view of the emerging concept that the altered metabolism of tumor cells may be their Achilles' heel (12). Inhibiting tumor cell proliferation and inducing death by treatment with an MCT inhibitor has already been described (see ref. 30), although the inhibitor used (α -cyano-4-hydroxy cinnamate (CHC)) is not isoform specific and is actually more potent at inhibiting the mitochondrial pyruvate carrier than any MCT (see ref. 6). Clearly, drugs that are specific and potent inhibitors of the other MCT isoforms would also be desirable, both for probing their roles in normal metabolism and as potential therapeutic agents. For example, a specific MCT4 inhibitor might have particular merit for targeting metastatic tumor cell lines in which MCT4 predominates as a result of HIF-1 α over-expression (56).

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