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REVIEW

IS LACTATE FOOD FOR NEURONS? COMPARISON OF MONOCARBOXYLATE TRANSPORTER SUBTYPES IN BRAIN AND MUSCLE

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Abstract—Intercellular monocarboxylate transport is important, particularly in tissues with high energy demands, such as brain and muscle. In skeletal muscle, it is well established that glycolytic fast twitch muscle fibers produce lactate, which is transported out of the cell through the monocarboxylate transporter (MCT) 4. Lactate is then taken up and oxidized by the oxidative slow twitch muscle fibers, which express MCT1. In the brain it is still questioned whether lactate produced in astrocytes is taken up and oxidized by neurons upon activation. Several studies have reported that astrocytes express MCT4, whereas neurons express MCT2. By comparing the localizations of MCTs in oxidative and glycolytic compartments I here give support to the idea that there is a lactate shuttle in the brain similar to that in muscle. This conclusion is based on studies in rodents using high resolution immunocytochemical methods at the light and electron microscopical levels.

Key words: immunocytochemistry, skeletal muscle, brain, electron microscopy, ischemia, exercise.

Contents

Lactate has long been considered as a mere waste product of cell metabolism. However, during the last 10–20 years it has been discovered that lactate can act as an energy substrate for skeletal muscle. Data that have emerged during the last years have shown that also neurons can use lactate to produce energy. In this review I will discuss the role of lactate as a source of energy for brain neurons.

Lactate is the end product of glycolysis and quantitatively the most important monocarboxylate. In glycolysis, glucose is enzymatically broken down to pyruvate, which in turn either enters the mitochondria for oxidation in the Krebs cycle or is reversibly converted to lactate by the enzyme lactate dehydrogenase. Export of lactate from the cell is important to maintain high rates of glycolysis in excess of what can be oxidized via the Krebs cycle. If the production of lactate is higher than the rate of its efflux from the cell, this will cause the pH to decrease the mechanism of this is debated (Robergs et al., 2004) which again will inhibit glycolysis.

Lactic acid, which has a pK_a of 3.9, exists almost entirely as the lactate anion at physiological pH. Both the proton and the lactate or other monocarboxylates require a specific transport mechanism to cross cell membranes. This is provided by proton linked monocarboxylate transporters (MCTs) (Poole and Halestrap, 1993; Juel, 1997; Halestrap and Meredith, 2004). A family of MCTs has been cloned and their distributions mapped (Poole and Halestrap, 1993; Garcia et al., 1994a, 1995; Jackson et al., 1995, 1997; Yoon et al., 1997; Price et al., 1998). Fourteen MCTs have been identified (Halestrap and Meredith, 2004). Six have been functionally characterized, but only MCT1–MCT4 are shown to catalyze proton coupled transport of lactate (Halestrap and Price, 1999; Manning Fox et al., 2000; Friesema et al., 2003; Kim et al., 2001; Wilson et al., 1998; Garcia et al., 1994a,b). MCT8 and MCT10 catalyze the sodium-independent transport of thyroid hormone and aromatic amino acids, respectively (Friesema et al., 2003; Kim et al., 2001). MCT1 (SLC16A) and MCT4 (SLC16A3) require a monotopic ancillary protein, CD147 (originally known as OX-47, Fossum et al., 1991), to form functional proteins in the plasma membrane (Kirk et al., 2000; Wilson et al., 2005). MCT2 (SLC16A7) does not interact with CD147, but does require a different ancillary protein named gp70 to be properly expressed at the cell surface (Wilson et al., 2005).

The MCTs transport lactate with different K_m values (Wilson et al., 1998; Bröer et al., 1999). MCT2 has the highest affinity with a K_m value of about 0.7 mM, whereas MCT4 has a lower affinity with K_m about 35 mM. The affinity of MCT1 is closer to that of MCT2 with a K_m of about 3.5 mM. These K_m values probably contribute to

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Abbreviations: FG, fast-twitch glycolytic; FOG, fast-twitch oxidative glycolytic; MCT, monocarboxylate transporter; SO, slow-twitch oxidative.

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determining whether the MCTs are expressed in cells that are predominantly oxidative or glycolytic and to whether they are more suited for transporting lactate out of or into these cells. However, it is important to point out that the direction of flux is decided by the combined electrochemical gradients of lactate and proton. The different K_m values are probably important for regulation of the lactate transport rate when the concentration of lactate varies. In this case it is important that the K_m value roughly match the lactate concentration on the side of the membrane from which lactate is transported. Thus, the low affinity transporter MCT4, which has a high capacity for lactate transport (Manning Fox et al., 2000), is more suited for regulating the transport rate than the low affinity transporter MCT1, which is likely to be saturated at relatively low lactate concentrations (for discussion see Hertz and Dienel, 2005). Besides MCT4 has been reported (Manning Fox et al., 2000) to have a much lower affinity for pyruvate, which could ensure that pyruvate does not leave the cell without first being converted to lactate. Even with similar K_m for lactate and pyruvate (Dimmer et al., 2000) the much lower concentration of pyruvate would favor the conversion of pyruvate to lactate before exit. This could be a measure to ensure that glycolysis is not halted by the build up of NADH (see discussion in Manning Fox et al., 2000).

It seems that we are just in the beginning of mapping and understanding how monocarboxylates and their transporters influence muscle performance on one side, and synaptic transmission and nerve cell thriving on the other. In this review, I will compare existing data on the distributions of MCTs in skeletal muscle with similar data in the brain to enhance the understanding of how lactate can supply given cell types with energy.

MUSCLE

It is known that skeletal muscle has a high rate of glycolysis, making it the main producer of lactate in the body (Wilson et al., 1998; Pilegaard et al., 1999; Manning Fox et al., 2000; Bonen, 2001). Lactate can also be taken up by oxidative skeletal muscle and heart and used as a respiratory fuel (McCullagh et al., 1997). During exercise, lactate is transported out of the working glycolytic muscle cells. Lactate can then be taken up by neighboring oxidative muscle cells or enter the circulation to be metabolized in fibers of other skeletal muscles or heart. The experimental evidence for this cell-to-cell lactate shuttle hypothesis is based on several reports. Important is the findings that during exercise, lactate concentration is much higher in glycolytic type II fibers than in oxidative type I fibers (Baldwin et al., 1977) and that type II fibers produce lactate when stimulated, whereas type I fibers oxidize lactate during contraction (Peter et al., 1971; Baldwin et al.,1978). Next, lactate is also produced in fully oxygenated muscle (see Jöbsis and Stainsby, 1968; Connett et al., 1984, 1990; Ahlborg, 1985; Richter et al., 1988; Brooks et al., 1998) and released from stimulated muscles when contractions start, but consumed when contractions continues (Welch and Stainsby, 1967). Furthermore, supplying contracting muscles with lactate results in an uptake of lactate instead of release (Gladden and Yates, 1983; Gladden et al., 1994). Importantly, when blood lactate levels increase in arm to leg cycling exercise, working leg muscle switch from lactate release to consumption (Richter et al., 1988). Also heart muscles may utilize the elevations in blood lactate levels that occurs e.g. during exercise (Gertz et al., 1981, 1988).

Taken together, these studies suggest that lactate produced and released from type II muscle fibers could be directly taken up and oxidized by neighboring type I fibers, or lactate released into the blood could be taken up and oxidized by type I fibers at some distance from the release site or by heart muscle cells.

The lactate shuttle hypothesis is supported by the findings that MCT1 is present in the sarcolemma of oxidative skeletal muscle fibers (slow-twitch oxidative (SO) and fast-twitch oxidative glycolytic (FOG) fibers (Fig. 1B and 1A) and heart muscle cells (Jóhannsson et al., 1997; Fishbein et al., 2002; Bergersen et al., 2006), but not in fast-twitch glycolytic (FG) fibers (Wilson et al., 1998; Bergersen et al., 2006). In oxidative skeletal muscle as well as in the heart there is an activity dependent increase in the level of MCT1 protein (Baker et al., 1998; McCullagh et al., 1996, 1997; Coles et al., 2004). In fact, muscle contractions increase the rate of lactate uptake in direct proportion to the increase in MCT1 (McCullagh et al., 1997). MCT1 upregulation has also been observed in surviving heart muscle after induction of myocardial infarction (Jóhannsson et al., 2001).

In contrast to MCT1, MCT4 is exclusively localized in glycolytic cells, such as FG and FOG muscle fibers (Pilegaard et al., 1999; Wilson et al., 1998; Manning Fox et al., 2000; Bonen, 2001; Bergersen et al., 2006), and absent from the SO fibers (Fig. 1C and D) (Bergersen et al., 2006). The low affinity MCT4 is suited for export of lactate by glycolytic fibers, while MCT1 with its higher affinity is suited for import of lactate to oxidative fibers upon cross-reinnervation of soleus and extensor digitorum longus muscle fiber types and expression of MCT subtype switch (Bergersen et al., 2006). This indicates that nerve impulse activity is able to influence the type and level of the expressed MCT.

BRAIN

Like oxidative skeletal muscle and heart muscle, the brain may consume lactate, when it is in ample supply such as during exercise (Dalsgaard et al., 2004). The brain has been shown to express three different MCTs: MCT1, MCT2 and MCT4. Is there a selective distribution of the MCTs between cells with different oxidative/glycolytic properties in the brain, like there is in muscle?

The high affinity transporter MCT2 was first reported in astrocytes (Gerhart et al., 1997, 1998). However, using a highly specific antibody we have found by high resolution immunogold cytochemistry that MCT2 is present exclusively in neurons, more specifically in the postsynaptic density at glutamatergic synapses in the cerebellum (Berg-