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Review Article

Glia-neuron energy metabolism in health and diseases: New insights into the role of nervous system metabolic transporters

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ABSTRACT

The brain is, by weight, only 2% the volume of the body and yet it consumes about 20% of the total glucose, suggesting that the energy requirements of the brain are high and that glucose is the primary energy source for the nervous system. Due to this dependence on glucose, brain physiology critically depends on the tight regulation of glucose transport and its metabolism. Glucose transporters ensure efficient glucose uptake by neural cells and contribute to the physiology and pathology of the nervous system. Despite this, a growing body of evidence demonstrates that for the maintenance of several neuronal functions, lactate, rather than glucose, is the preferred energy metabolite in the nervous system. Monocarboxylate transporters play a crucial role in providing metabolic support to axons by functioning as the principal transporters for lactate in the nervous system. Monocarboxylate transporters are also critical for axonal myelination and regeneration. Most importantly, recent studies have demonstrated the central role of glial cells in brain energy metabolism. A close and regulated metabolic conversation between neurons and both astrocytes and oligodendroglia in the central nervous system, or Schwann cells in the peripheral nervous system, has recently been shown to be an important determinant of the metabolism and function of the nervous system. This article reviews the current understanding of the long existing controversies regarding energy substrate and utilization in the nervous system and discusses the role of metabolic transporters in health and diseases of the nervous system.

1. Introduction

Neurons and glia are the primary cellular components that perform the functions of the central and peripheral nervous system (CNS and PNS, respectively). Glia maintain tissue homeostasis, form myelin, regulate development, and contribute to diverse neuropathophysiologies in the CNS and the PNS. Besides providing structural and metabolic support to neurons, glia also contribute to recovery following neuronal injuries. Neurons transmit signals over long distances through their axons; and these axons require an enormous energy supply to maintain their function. Axons are closely associated with glial cells that support their function and prevent degeneration.

Research over the last decades has shown that the brain is an organ of unusually high metabolic demand that utilizes 20% of the total glucose and 20% of the total oxygen in the human body (Magistretti and Allaman, 2015). Studies have reported glucose as the obligatory energy substrate for brain, where it is almost fully oxidized (Kety and Schmidt, 1948; Sokoloff, 1960). Similarly, further studies at the whole organ level have provided some refinements to this view, suggesting that ketone bodies fulfill the energy requirements of the brain under particular conditions, including fasting, uncontrolled diabetes and breast-fed newborn babies (Magistretti, 1999). Additionally, several studies over the last few years have illustrated the significance of lactate as an energy substrate for the brain (Baltan, 2015; Castillo et al., 2015; Machler et al., 2016; Matsui et al., 2017; Magistretti and Allaman, 2018). Specifically, findings from *in vitro* and *in vivo* studies demonstrate that lactate sustains neuronal activity during glucose deprivation (Wyss et al., 2011; Sobieski et al., 2018). The astrocyte-neuron lactate shuttle hypothesis (ANLSH) suggests that astrocyte-derived L-lactate is taken up by neurons via monocarboxylate transporters (MCTs), metabolic transporters for monocarboxylates, and used as an energy substrate, possibly in preference to glucose. Though it was proposed over twenty years ago (Magistretti et al., 1993; Pellerin and Magistretti, 1994), ANLSH remains controversial and not fully accepted. A recent study claims that during fasting conditions, glucose contributes indirectly (via circulating lactate) to tissue TCA metabolism in all tissues except the brain (Hui et al., 2017). Additionally, a study modeling the kinetic characteristics and cellular concentrations of the neuronal glucose and lactate transporters opposes the ANLSH primarily due to the fact that neuronal glucose transporter, GLUT3, has higher affinity for

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glucose than the astrocytic counterpart, GLUT1, an, indicating that glucose may be primarily transported to and consumed by neurons (Simpson et al., 2007). Finally, studies suggest that neurons have the capacity to boost their own glycolysis and potentially export rather than import lactate during brain activation or in response to stimulation (Diaz-Garcia et al., 2017; Yellen, 2018). This article addresses these controversies and reviews different aspects of glia-axon energy metabolism in health and diseases of the nervous system focusing on neural energy substrates consumption and metabolism, and their transporters.

2. Fuels to neural cells: glucose, its "by-product" lactate, and occasionally acetate too!

About 20% of our circulating glucose enters the brain, suggesting that glucose is the primary energy source for the brain. For some time, it had been accepted without reservation that all brain metabolic pathways are subsequent to glucose until the proposition of the ANLSH (Magistretti, 2008, Pellerin and Magistretti, 2012). The ANLSH challenged this precept, stating that activity-dependent uptake of glucose takes place in astrocytes that subsequently metabolize the glucose anaerobically to lactate and then transport lactate to neighboring neurons where it serves as the primary metabolic fuel. The ANLSH was proposed almost 25 years ago (Magistretti et al., 1993; Pellerin and Magistretti, 1994) and is still quite controversial (Simpson et al., 2007; Dienel, 2012; Diaz-Garcia et al., 2017; Yellen, 2018); as such, the exact metabolic fuel to neural cells remains highly debatable. At the same time, a recent study has also indicated acetate as an occasional energy substrate for the brain. This section provides an updated understanding about the fuels to neural cells (Fig. 1).

2.1. Glucose

Elegant and pioneering *in vivo* studies in humans by Kety, Schmidt and Sokoloff conducted almost six decades ago identified glucose as the obligatory energy substrate for brain (Kety and Schmidt, 1948; Sokoloff, 1960). Glucose is the main source of energy for the brain, and its physiology is determined by tight regulation of glucose metabolism, suggesting the requirement for continuous delivery of glucose from blood (Mergenthaler et al., 2013). Despite the presumption that neurons would thus preferentially use glucose as their primary energy metabolite, several recent reports suggest that brain glucose is mostly consumed by astrocytes and oligodendrocytes and that neurons depend on glucose metabolites produced and released by these glial cells for their energy requirements (Chuquet et al., 2010; Funfschilling et al., 2012; Lee et al., 2012; Amaral et al., 2016; Saab et al., 2016). Despite the important role of glial cells, neurons clearly express GLUT3 (Simpson et al., 2008), which is a glucose transporter that allows the direct import of glucose into neurons. Glucose supply to the brain is regulated by neurovascular coupling, and it enters the brain from the blood by crossing the blood brain barrier through glucose transporters (primarily GLUT1). The rapid distribution of glucose in the brain is assisted by a highly coupled metabolic network of glial and neuronal cells interconnected by gap junctions (Froes et al., 1999; Parpura et al., 2012). Physiologic functions of the brain are fueled by ATP generated primarily by glucose metabolism. Glucose metabolism disturbances underlie many diverse neurological diseases, including neuroinflammation, neurodegenerative disorders, psychiatric disorders, and peripheral neuropathies. Glucose supply to brain is also crucial due to its potential conversion to lactate.

2.2. Lactate

A significant portion of glucose entering the brain is metabolized to lactate during aerobic glycolysis (Vaishnavi et al., 2010). The aerobic glycolysis accounts for up to 30% of brain glucose metabolism during development and 25% glucose metabolism in specific regions of the adult brain, such as the dorsolateral prefrontal cortex, the superior and medial frontal gyrus, or the precuneus and posterior cingulate cortex (Goyal et al., 2014; Magistretti and Allaman, 2015). At the cellular level, astrocytes are better equipped for aerobic glycolysis and lactate production than neurons (Belanger et al., 2011). Emerging evidence establishes astrocytes as naturally glycolytic cells (Supplie et al., 2017). Molecularly, GLUT1 expressed by both endothelial cells and astrocytes facilitates glucose uptake from the circulation. LDH5, which is primarily expressed by astrocytes in the CNS, converts pyruvate derived from glycolysis to lactate, which can then be shuttled to neurons through monocarboxylate transporters (primarily MCT1 and MCT4 in astrocytes and MCT2 in neurons). Neurons express LDH1 that facilitates the utilization of lactate as neuronal energy substrate by converting it to pyruvate. Neurons also have the capacity to take up glucose directly, however, since the glucose transporter, GLUT3, is expressed in neurons (Belanger et al., 2011). Due to the location of astrocytic endfeet surrounding blood vessels, however, it is likely that most of the glucose that enters the brain does so through astrocytes (Kacem et al., 1998; Belanger et al., 2011; Mergenthaler et al., 2013).

Glial cells were proposed to contribute to neuronal energy metabolism almost 50 years ago, and about two decades ago it was established that metabolite transfer occurs from glial cells to neuronal cells at least in honeybee retina (Tsacopoulos et al., 1994). Refined versions of the ANLSH assert that lactate is produced by astrocytes, and possibly active neurons, and is released into a lactate pool that is eventually used as energy substrate by neurons at rest or during active state (Baltan, 2015). A functional intercellular lactate shuttle, commonly called ANLSH in the CNS, exists in multiple CNS regions (Magistretti et al.,

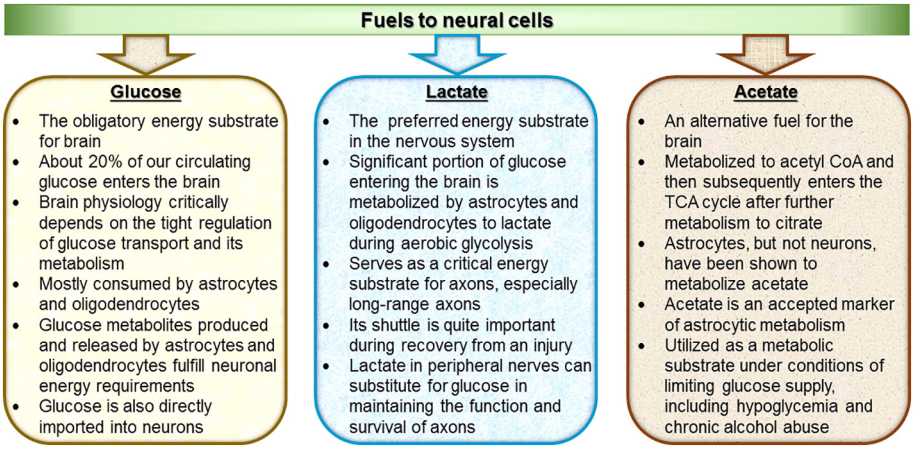

Fig. 1. Fuels to neural cells. Glucose, its "by-product" lactate, and occasionally acetate are fuels to neural cells.