Neuroscience 276 (2014) 109–116

REVIEW

WHITE MATTER LACTATE – DOES IT MATTER?

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Abstract—About half of the human brain is white matter, characterized by axons covered in myelin, which facilitates the high speed of nerve signals from one brain area to another. At the time of myelination, the oligodendrocytes that synthesize myelin require a large amount of energy for this task. Conditions that deprive the tissue of energy can kill the oligodendrocytes. During brain development, the oligodendrocytes may use lactate as an alternative source of energy and material for myelin formation. Mature oligodendrocytes, however, can release lactate through the myelin sheath as nutrient for axons. In addition, lactate carries signals as a volume transmitter. Myelin thus seems to serve as a provider of substrates and signals for axons, and not as a mere insulator. We review the fluxes of lactate in white matter and their significance in brain function.

This article is part of a Special Issue entitled: The CNS White Matter.

Key words: energy, lactate, development, myelination, volume transmitter.

Contents

INTRODUCTION

The complex functions and large size of the human brain require high speed interactions between distant brain regions. Our brain therefore has special needs for maintaining the performance of these long-distance connections. This need is illustrated by the abundance of myelinated axons; about half of the human brain mass is white matter (Gur et al., 1999). The CNS myelin has long been regarded solely as an insulator that helps speed up the neuronal action potentials by enabling saltatory conduction. New literature now suggests that the myelin sheath provides important energetic supply to the axons in the form of lactate (Funfschilling et al., 2012; Lee et al., 2012). Furthermore, the oligodendrocytes that synthesize myelin in the CNS seem to be particularly vulnerable to low energy conditions during myelination and may consume lactate for energy production, as well as for lipid synthesis (Sanchez-Abarca et al., 2001; Rinholm et al., 2011, see also Amaral et al., 2013, who recently reviewed several metabolic aspects of neuron–oligodendrocyte–astrocyte interactions). Although the white matter is less energetically demanding than gray matter, white matter axons and myelin are greatly affected by insults involving lack of energy such as in stroke and spinal cord injury. Finally, oligodendrocyte metabolism may also be involved in neurodegenerative diseases that were not initially associated with energy deficiency: recently, metabolic dysfunction of the oligodendrocytes was linked to Amyotrophic Lateral Sclerosis (ALS) (Lee et al., 2012) and X-linked adrenoleukodystrophy (X-ALD) (Kassmann et al., 2007). A better understanding of the metabolic fluxes and energy needs of the white matter is imperative for identifying the mechanisms leading to white matter damage.

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Abbreviations: ALS, Amyotrophic Lateral Sclerosis; ANLS, astrocyte-to-neuron lactate shuttle; cAMP, cyclic AMP; CAP, compound action potential; MCTs, monocarboxylate transporters; PEPCK, phosphoenolpyruvate carboxykinase; SOD1, superoxide dismutase.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.10.002

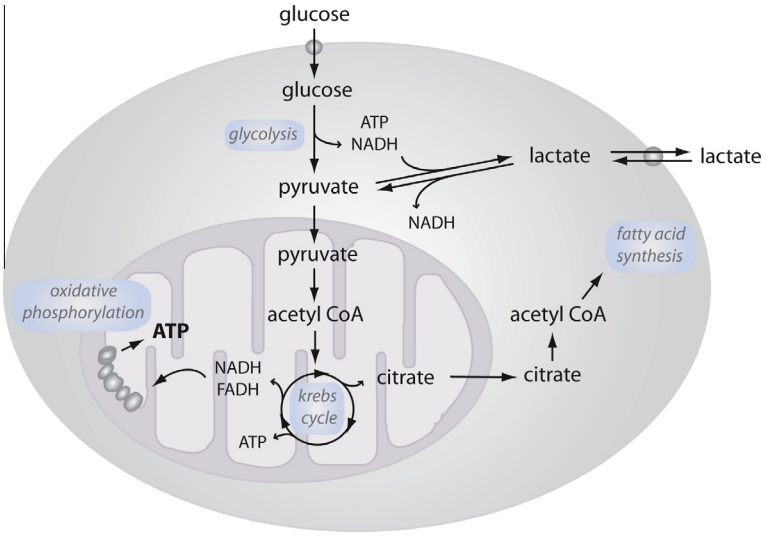

Fig. 1. Schematic of glucose metabolism in a cell. See main text for details.

Here we review current knowledge on lactate fluxes in the white matter and their involvement in brain pathology. We then consider the non-metabolic functions of lactate, with special emphasis on oligodendrocytes and axons.

GLUCOSE AND LACTATE FUEL BRAIN CELLS

Glucose is the most important energy source in the adult brain (Sokoloff, 1992). Inside the cell cytoplasm, glucose can either be stored in the form of glycogen (presumably only in astrocytes), or be broken down via glycolysis (although some breakdown through the pentose phosphate pathway also occurs) to generate pyruvate and some ATP. Pyruvate can be further metabolized in mitochondria via the Krebs cycle and oxidative phosphorylation, where most of the ATP is produced (Fig. 1). Alternatively, the pyruvate from glycolysis can be converted into lactate and exported out of the cell. Lactate can then be imported by other cells where it is converted back to pyruvate and further metabolized in mitochondria. The major steps in a cell's glucose metabolism are summarized in Fig. 1.

THE ASTROCYTE–NEURON LACTATE SHUTTLE HYPOTHESIS

The shuttling of lactate between different cell types is substantial in tissues with high energy demands such as brain and skeletal muscle. In skeletal muscle tissue, glycolytic muscle fibers produce lactate that is subsequently consumed by oxidative muscle fibers (Brooks, 1991). Similarly in the brain, astrocytes with high glycolytic activity can transfer lactate to oxidative neurons. The astrocyte–neuron lactate shuttle was first demonstrated in cultured cells (Dringen et al., 1993a,b) and then proposed for gray matter where perisynaptic astrocyte processes were suggested to support synaptic activity by supplying lactate to postsynaptic spines (Pellerin and Magistretti, 1994; Pellerin et al., 1998; Magistretti and Pellerin, 1999; Bergersen et al., 2001, 2005). The Ransom group later found a similar shuttle in the white matter by studying the compound action potential (CAP) area in rat and mouse optic nerves. They showed that the CAP area, and thus axon function, could be maintained for a while in glucose-free medium, but not if lactate transport or glycogen breakdown was inhibited (Brown et al., 2003, 2004; Tekkok et al., 2005). These data all support the hypothesis that white matter astrocytes can transfer lactate to axons.

The astrocyte-to-neuron lactate shuttle (ANLS) is held to be important for maintaining neuronal function at low glucose levels and/or high neuronal activity (Brown et al., 2005) and for higher functions such as memory formation (Suzuki et al., 2011). In fact, neuronal activity seems to be tightly linked to astrocyte metabolism and lactate release since astrocytes increase their glycolytic activity in response to a rise in extracellular glutamate (so-called neurometabolic coupling, Pellerin and Magistretti, 1994, 1996). However, the ANLS is not unanimously accepted as a mechanism essential for neuronal function. The hypothesis has been severely criticized and the main lactate flux suggested to be small and even to go in the opposite direction, from neuron to glia (e.g. Mangia et al., 2011; Dienel, 2012a). In addition to several *in vitro* studies (including those mentioned above), the supporters of the ANLS base their arguments on a metabolic model showing that lactate will indeed flow from astrocytes to neurons (Aubert et al., 2007; Cloutier et al., 2009). This is contrary to another metabolic model that was proposed by Simpson et al. (2007) (see also Mangia et al., 2009). Simpson's model suggests that lactate flows in the opposite directions – from neurons to astrocytes. This model also predicts that astrocytes will not be able to increase their uptake of glucose sufficiently to produce significant amounts of lactate during high activity. Another point of disagreement is whether neurons are able to up regulate their glycolytic activity sufficiently during high activity. The two models have used data