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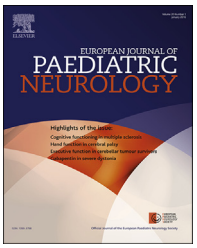

Review Article

Lactate and its many faces

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ABSTRACT

Background: Lactate is traditionally seen as a marker of ischemia and a waste product of anaerobic glycolysis. In the last thirty years a more beneficial side of lactate as an alternative 'glucose sparing' fuel has been demonstrated. However, the translation of these growing insights to clinical practice seems to appear with great delay.
Methods: A review of the literature was performed, focusing on glucose and lactate in relation to cerebral energy metabolism, in the context of four typical clinical situations, namely (transient states of) low glucose availability for the brain due to hypoglycemia, combined with high blood lactate concentrations; permanent neuroglycopenia; lactic acidosis in mitochondrial disorders; and ischemic as well as traumatic brain injury.
Results: Lactate is thought to be an alternative fuel in the brain of patients with glucose transporter type 1 deficiency syndrome and glycogen storage disease, and it has been demonstrated that lactate might have a protective role in ischemic and traumatic brain injury.
Conclusion: Lactate has an apparently largely ignored, but potential beneficial role in the clinical management of several neurologic disorders.

Contents

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1. Introduction

Lactate is traditionally seen as a marker of ischemia and a waste product of anaerobic glycolysis. The negative connotation of lactate can easily be understood from everyday clinical practice, since increases of serum or tissue lactate concentrations are often encountered and generally associated with severe disease states or poor outcome.[1] Interestingly, however, in the last decades, a more beneficial side of lactate as an alternative 'glucose sparing' fuel of the brain has also been demonstrated.[2–6] Experimental and clinical research shows that lactate can be used as an alternative fuel for brain metabolism in circumstances of a low brain glucose.[7] It is also hypothesized that lactate might be used as an alternative source of energy in some inborn errors of metabolism. In patients with glucose transporter type 1 deficiency syndrome (GLUT1DS), for example, it is assumed that lactate is used as an alternative fuel in the brain to compensate for defective glucose transport across the blood brain barrier.[8–10]

In order to gain more insight in the possible beneficial role of lactate in inborn errors of metabolism, as well as the potential role of lactate in the treatment and prognosis of acquired brain injury, we have performed an extensive review of the literature. Our aim was to summarize our findings from a clinical point of view.

2. Methods

We have performed a systematic review of the literature, focusing on glucose and lactate in relation to cerebral energy metabolism, with four different clinical situations in our minds. These four situations are: [1] (transient states of) low glucose availability for the brain due to hypoglycemia, combined with high blood lactate concentrations as typically occur in diabetes mellitus, glycogen storage disease type 1, and fructose-1,6-biphosphatase deficiency; [2] permanent neuroglycopenia (due to decreased glucose transport into brain) in glucose transporter type 1 deficiency syndrome (GLUT1DS); [3] (isolated) lactic acidosis in mitochondrial disorders; and [4] ischemic as well as traumatic brain injury, as situations with acquired, local or systemic lactate increases.

Since we aimed to focus on (above mentioned) clinical situations in which "low glucose" or "high lactate" are the only or the dominant metabolic abnormalities, we excluded ketolysis defects (characterized by (hypoglycemia with) very high concentrations of serum ketones), and organic acidurias and fatty acid oxidation defects (dominated by the presence of high amounts of organic acids, while lactic acidosis is generally not very prominent).

Pubmed was searched until June 2014 using the relevant MeSH and 'Title and Abstract' terms. Limits were used for "English". Abstracts were screened for articles describing the role of lactate in metabolism, diagnosis, treatment and prognosis.

3. Physiology of brain energy metabolism

Glycolysis is the first stage of brain energy metabolism. It provides two adenosine triphosphate (ATP) and two pyruvate molecules at the expense of two nicotinamide adenine dinucleotide (NAD^+) and two adenosine diphosphate (ADP). Pyruvate can either enter oxidative metabolism in mitochondria generating more ATP or it can be converted to lactate regenerating 2 NAD^+ for glycolysis.[11] Traditionally, it was believed that conversion to lactate only occurred in case of an oxygen deficit in an attempt to maintain production of energy through glycolysis. However, there is growing evidence that the production of lactate also occurs in fully oxygenated circumstances, i.e. 'aerobic glycolysis'.[11] With this respect, energy metabolism of the brain has been studied and discussed extensively during the past years. According to the astrocyte neuron lactate shuttle theory (ANLS),[12] astrocytes use glycolysis to produce lactate, which is subsequently shuttled to neurons for oxidative metabolism. Neurons have a high expression of monocarboxylate transporters (MCT), allowing lactate to enter the cell. In the neurons, lactate can be converted to pyruvate through lactate dehydrogenase (LDH) and enter oxidative metabolism.[12] This would mean that not glucose, but lactate is the major fuel for energy metabolism in neurons. Although the theory is strongly supported by experimental evidence, it still remains controversial.[12,13]

Besides lactate derived from astrocytes, the circulating blood can also be a source of lactate for neurons. Experimental research has revealed that lactate derived from blood is an important metabolic fuel for the brain during the pre-suckling period in neonates.[4] Furthermore, physical exercise may – due to a mismatch between oxygen need and delivery in skeletal muscles – cause an impressive release of lactate into