L-Lactate

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l-Lactate plays a role as a metabolic and signaling molecule, accordingly, Vaccari-Cardoso and co-workers developed a viral vector to express a modified version of lactate oxidase (LOx) originating from the bacteria Aerococcus viridans. Their results in vitro show that LOx expression in astrocytes reduced their intracellular lactate levels and its release to the extracellular space.

Keywords: lactate ; anls ; brain energy metabolism

1. Introduction

Brain energy metabolism is crucial to support cellular mechanisms at the base of brain functioning, such as the action potentials required for neuronal communication, maintenance of ionic gradients across the plasma membrane, protein synthesis, phospholipid metabolism, or neurotransmitter recycling [1]. The astrocyte-neuron lactate shuttle (ANSL) establishes that presynaptic glutamate, released from excitatory boutons, starts a chain of events leading up to L-Lactate synthesis that is finlally shuttled to neurons. Glutamate first is taken up by astrocytes, to enter the glutamate-glutamine cycle, together with Na^+ through specific astrocyte transporters, resulting in a dissipation of the Na^+ gradient which is reestablished through the activity of the Na/K-ATPase [2]. Both Na/K-ATPase activity and glutamine formation from glutamate are highly energy consumptive processes; astrocytes increase the glucose uptake from the bloodstream. Surprisingly, instead of using glucose through oxidative phosphorylation in mitochondria to produce ATP, astrocytes use the glycolysis pathway to produce a few ATP molecules; this process (also known as “aerobic glycolysis” since glycolysis is still happening despite the presence of oxygen, or “Warburg effect”) is accompanied by the synthesis of lactate, which is released via MCT1 and MCT4 and taken up by active neurons through MCT2. In neurons, lactate is transformed into pyruvate and is subsequently metabolized through oxidative phosphorylation, yielding between 14 and 17 ATPs per lactate molecule [3][4]. Lactate shuttle from astrocytes and further uptake by neurons has been shown to play an essential role in learning, memory consolidation and LTP [5][6][7][8].

One such study to confirm the importance of ANLS in LTP and hippocampal memory formation was performed by Suzuki and collaborators using electrophysiological and behavioral experiments. The electrophysiological studies showed that LTP could be triggered in CA1 neurons following Schaffer collateral stimulation with the increased fEPSP slope, a classic indication and monitor of increased synaptic efficacy. Behavioral trials were conducted on rats performing the inhibitory avoidance test, a strong learning paradigm. Rodents were either exposed to an MCT inhibitor or received a bilateral hippocampal injection of 1,4-dideoxy-1,4-imino-d-arabinitol (DAB), which is a glycogen phosphorylase inhibitor. Researchers found inhibition of L-Lactate transfer prevented LTP maintenance and hypothesized that the intrahippocampal application of additional lactate could bypass it. Interestingly, the effect of DAB points to the fact that glycogen granules, being glucose stores specifically located in astrocytes, are a major source of L-Lactate, together with glycolysis. These findings indicate that neurons require lactate uptake to meet the energy demands of LTP induction, even when displaying average concentrations of glucose. Therefore, lactate should be available for neurons during the conditioning phase of the behavioral test. Results show that the application of lactate after conditioning does not restore LTP. This indicates that ANLS plays a critical role in long-term synaptic plasticity, long-term memory, as well as molecular and synaptic changes [6].

A similar study by Duran et al. examined the learning capacities and electrophysiological properties of the hippocampal CA3-CA1 synapse using glycogen synthase knockout mice. The electrophysiological results show that paired-pulse facilitation (a form of short-term plasticity-related with short-term memory) is enhanced in the mice lacking glycogen synthase. Moreover, paired-pulse stimulation (an indirect measurement of the probability of neurotransmitter release) reflects a disturbance in the release of neurotransmitters at the presynaptic terminal in the knockout mice. This confirms the role of glycogen as a precursor of glutamate and its importance in short-term memory processes. Finally, the knockout mice did not show significant LTP after the stimulation session, suggesting that glycogen is a crucial energy source to

evoke this change in synaptic strength. The authors also conducted a behavioral test using the Skinner box. The results from his test reveal a significant impairment in the learning process of mice lacking glycogen synthase, which supports the previous results [9].

To support the idea that lactate regulates synaptic potentiation at central synapses and contributes to the process of memory formation, Herrera-López and co-workers carried out a series of electrophysiological experiments on hippocampal slices. They demonstrated that extracellular lactate induces glutamatergic potentiation on the recurrent collateral synapses of hippocampal CA3 pyramidal cells (CA3 PC). This potentiation occurs through a post-synaptic lactate receptor mechanism, calcium accumulation and NMDA receptor activation. The researchers found that lactate does not induce potentiation at the mossy fiber synapses of CA3 PC, concluding that lactate triggers an input-specific form of synaptic plasticity on the hippocampus and that it increases the output discharge of CA3 neurons when recurrent collaterals are repeatedly activated during lactate perfusion [10].

The degree to which long-term modifications in synaptic strength are complemented by modifications in lactate dynamics is still a matter of research. To understand it, Bingul et al. induced LTP of synapses in the dentate gyrus in freely behaving rats; this process was done through HFS of the medial perforant pathway. Before, during and up to 72 h after LTP induction, the extracellular lactate concentrations were measured using fixed potential amperometry, allowing the evaluation of how changes in synaptic strength modify local glycolytic activity. They found that synaptic potentiation was associated with persistent alterations in acute lactate dynamics following neuronal activation and observed chronic lactate availability within the dentate gyrus. These changes in lactate dynamics were only visible 24 h after HFS, whereas synaptic potentiation and altered lactate dynamics lasted up to 72 h. The authors conclude that these observations reflect a metaplastic effect that could regulate the memory consolidation process. Furthermore, these changes in extracellular lactate concentrations could support the increased energetic demands or play a neuroprotective role [11]. In order to monitor lactate dynamics Mächler and co-workers used a genetically encoded FRET sensor in combination with in vivo two-photon laser scanning microscopy. Following opening of MCTs in astrocytes and neurons using a transactivation process, they observed at first a decrease in lactate signal in astrocytes followed by an increase of it in neurons, demonstrating a lactate gradient between these two cell types that favor the flow of lactate from astrocytes to neurons, consistent with the ANLS [12].

The ANLS model establishes that lactate is released from astrocytes through MCT1 and MCT4 and taken up by neurons through MCT2, which makes these transporters critical in learning and memory formation [13]. To better understand their role, Netzahualcoyotzi and Pellerin used transgenic mice and a viral vector to decrease the expression of each transporter within the dorsal hippocampus. They demonstrate that both neuronal MCT2 and astroglial MCT4 are essential in spatial information acquisition and retention in different hippocampal-dependent tasks. After an intracerebral injection of lactate, mice with reduced levels of MCT4 exhibited improved spatial memory, but this manipulation did not affect mice with an MCT2 knockdown, supporting the idea that ANLS contributes to hippocampal-dependent learning. In contrast, MCT2 is shown to be required for long-term memory formation seven days after training, and plays an important role in mature neurons in the process of adult neurogenesis in the dentate gyrus [14].

Long-term memory formation is also affected by the release of noradrenaline and β-adrenergic signaling, which occurs in states of arousal because the coeruleo-cortical noradrenergic projection, results in noradrenaline release in the cortex. Noradrenaline has been shown to trigger glycogenolysis in astrocytes [15] resulting in aerobic glycolysis, consequently stimulating lactate production from glycogen [16]. Fink and collaborators studied single noradrenaline-stimulated astrocytes by measuring cytosolic lactate concentration using a FRET nanosensor; this process was done under different pharmacological conditions. First, they used 2-deoxy-d-glucose, a non-metabolizable form of d-glucose, to interfere with lactate metabolism; second, DAB, a potent inhibitor of glycogen phosphorylase and glycogen degradation; and finally, 3-nitropropionic acid (3-NPA), an irreversible inhibitor of succinate dehydrogenase, a Krebs cycle enzyme. Their findings reveal that d-glucose uptake is critical for the noradrenaline-induced increase in lactate concentration resulting from glycogen degradation, suggesting that most glucose molecules in the noradrenaline-stimulated cells transit through a glycogen shunt. In addition, it was observed that under these pharmacological conditions and a defined transmembrane glucose gradient, the glycolytic flux intermediates are used to produce lactate and support oxidative phosphorylation via pyruvate. This was demonstrated by an increase in lactate concentration during inhibition of the Krebs cycle [17].

To confirm the role of noradrenaline in lactate production, Zuend et al. investigated lactate dynamics in neurons and astrocytes in awake mice. They exposed the mice to isoflurane, which caused a strong arousal response, pupil dilatation and Ca^{2+} elevations in both neurons and astrocytes. These alterations in cortical activity triggered an extracellular lactate release which correlates with a fast and prominent lactate dip in astrocytes, followed by a delayed rise in neuronal and astrocytic lactate [16]. The work by Gao and collaborators also illustrates the role of adrenergic signaling in modulating

long-term memory consolidation by activating glycogenolysis and subsequent lactate release [18]. These changes altogether suggest activity-dependent glycogen mobilization and further lactate release from astrocytes, which are critical in the long-term memory formation and consolidation processes [12][16][18].

Lactate also plays an important role in supporting the expression of genes such as Arc, c-Fos, Bdnf and Zif268, which involved in plasticity and neuronal activity [19]. Yang and co-workers investigated this matter in vitro in primary cultures of neurons and in vivo in the mouse sensory-motor cortex. They found that lactate stimulates the expression of genes such as Arc, c-Fos and Zif268, which are related to synaptic plasticity, and that these effects were not replicable with glucose nor pyruvate. This upregulation is carried out through a mechanism involving NMDA receptor activity and its downstream signaling cascade Erk1/2. The researchers found that lactate potentiates NMDA receptor-mediated currents, which produces elevated intracellular calcium via an increased calcium influx. Furthermore, lactate increases the intracellular levels of NADH associated with changes in the redox state of neurons. NADH mimics the effects of lactate on NMDA signaling, leading to the idea that an increase in NADH directly affects the effects of lactate [20]. In another study Margineanu and collaborators used RNA-sequencing to identify synaptic plasticity promoting genes. In addition to those found by Yang et al., they identified that Erg2, Erg3, Erg4, Npas4, Nr4a3 and Rgs4 are modulated by L-lactate in cortical neurons. Moreover, they identified ten genes associated with the MAPK signaling pathway; those are: c-Fos Bdnf, Atf4, Nr4a1, Gadd45g, Map3k11, Dusp4, Dusp6 and Dusp10 [21]. These studies lead to the conclusion that lactate can be considered a signaling molecule in neuronal plasticity, in addition to its role in energy metabolism.

2. The Role of L-Lactate in Disease

Lactate production in astrocytes and its sequential shuttle to neurons is an essential process in learning, memory consolidation and LTP. Accordingly, anomalies in the brain energy metabolism can result in severe pathologies or aggravate pre-existing conditions. In particular, Alzheimer's Disease (AD), amyotrophic lateral sclerosis (ALS), depression, stress and schizophrenia show disruptive lactate signaling between astrocytes and neurons [22]. For instance, Positron Emission Tomography (PET) scans have documented reduced glucose utilization in brain regions affected by patients with Alzheimer, Parkinson and Huntington's disease, as well as with ALS [23].

AD is one of the most common forms of dementia. In its preclinical stage, brain glucose hypometabolism is recognized as a prominent anomaly and some studies suggest that glycogenolysis plays a critical role in the development of the disease [24]. Impairments in glycogen synthesis could reduce glycogen levels, impeding the physiological flux of glucose units through glycogen, consequently affecting learning and memory processes [25]. Research shows reduced levels of GLUT1 and GLUT3, which correlates with less glucose uptake, which translates into a subsequent cognitive decline. Furthermore, the enzymatic activity of phosphofructokinase, phosphoglycerate mutase, aldolase, glucose-6-phosphate isomerase and lactate dehydrogenase display a loss of activity in patients with AD in comparison with age-matched controls [23]. Ryu and collaborators compared neural progenitor cells and astrocytes differentiated from late-onset AD patients. The authors found a significant downregulation of lactate dehydrogenase A in both cell types and that astrocytes from late-onset AD have a reduced metabolism of lactate [26].

In the case of Parkinson's Disease (PD), glucose hypometabolism has been documented. Key enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase are expressed in lower levels in putamen and cerebellum of PD patients [23]. Other studies show an increase in lactate levels in the striatum of patients and animal models of advanced PD [27][28].

On the other hand, ALS is characterized in patients by loss of motor neurons in the brain and spinal cord, as well as glucose intolerance, insulin resistance and hyperlipidemia. At the cellular level is common to find altered endothelial transporter proteins and astrocyte end feet degradation [23]. Nonetheless, research has shown that lactate could be used directly as cerebral uptake or indirectly as gluconeogenic precursor to improve ALS symptoms [29][30].

Schizophrenia and bipolar disorders are common and severe psychiatric disorders. They characterize by overlapping genetic background, brain abnormalities and clinical presentations. Some research suggests that alterations in brain metabolism and mitochondrial function are evident in these disorders. A set if studies ex-vivo using mouse models of schizophrenia, bipolar disorder and autism spectrum disorders showed lower pH and higher lactate levels in all the models [31]. In vivo studies in animal models and in patients confirm this evidence. Lactate concentrations are elevated and negative correlated with general cognitive function and functional capacity [32][33][34]. In contrast, patients suffering from depression can benefit from lactate as a treatment option. It has been proved that lactate administration produces antidepressant-like effects, promotes resilience to stress and rescues social avoidance and anxiety behaviors [35][36].

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