

Is the “lactormone” a key-factor for exercise-related neuroplasticity? A hypothesis based on an alternative lactate neurobiological pathway

Renato Sobral-Monteiro-Junior^{a,b,c,d,*}, Pauline Maillot^e, Valeska Gatica-Rojas^f, Waldney Roberto M. Ávila^b, Alfredo M. Batista de Paula^a, André Luiz S. Guimarães^a, Sérgio Henrique S. Santos^a, Camila Castelo Branco Pupe^c, Andréa Camaz Deslandes^d

^a Post-graduate Program of Health Sciences, State University of Montes Claros, Montes Claros, Minas Gerais, Brazil

^b Physical Education and Sport Department, State University of Montes Claros, Montes Claros, Minas Gerais, Brazil

^c Post-Graduate Program of Medicine (Neurology/Neuroscience), Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

^d Psychiatry Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

^e Laboratoire Techniques et Enjeux du Corps (TEC) | EA 3625, Université Paris Descartes, Sorbonne Paris Cité, France

^f Human Motor Control Laboratory, Universidad de Talca, Talca, Chile

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ABSTRACT

For many years lactate was seen as a metabolite from glucose metabolism. However, since the last century researchers have shown that this molecule has an important role on liver, muscle, and brain metabolism. Lactate traffics along whole body mediating many biological processes depending on specific situations. For example, glucose is the main substrate used during exercise but lactate released by striated skeletal muscle is used by own muscle as secondary fuel. On the other hand, neuronal firing in the brain is almost totally lactate-dependent. In addition, lactate has an important role on BDNF-mediated neuroplasticity. As this molecule has a pleiotropic role in the body, it was called as “lactormone” in 2009. Here we show basic concepts on peripheral and central metabolism and discuss neurobiological pathways of lactate, including an alternative hypothesis on lactate released during exercise.

Introduction

Brain neuroplastic response has being target of many studies especially focused in preventive strategies and new neurodegenerative disease treatments. In the last two decades the exercise training was one of the most investigated low-cost interventions related to neuroplasticity [1,2]. While studies with animal models have shown evidences that exercise stimulates neuroplasticity in hippocampus, human studies has shown an increase of hippocampus volume of individuals with high physical fitness [3–6], as well as increased metabolism in precuneus and entorhinal cortex [7]. Furthermore, many studies showed an improved memory and executive functions in people who exercised [8–15].

Literature has shown that trophic factors are synthesized by active muscles during exercise, which would provide neural substrate for neuroplastic responses [1,2]. Furthermore, myokines released by muscle have anti-inflammatory and regenerative effects. Therefore, a lot of biological mechanisms are redundant in the body response. Additional substrates released through exercise may have potential

contributions for brain metabolism (e. g. lactate) [16]. For example, lactate is a substrate synthesized and used as fuel by muscle, heart, central nervous system (CNS), and other tissues [16–18]. Each cell from any of the aforementioned tissues can use its own lactate through a mechanism known as intracellular shuttle [16]. Additionally cells of the same tissue can oxidize the lactate released by their neighbors. In the CNS lactate is a molecule originated from glycolysis and glycogenolysis in the astrocytes, which traffics to neurons to be oxidized, supplying energy demand [19]. On the other hand, lactate released by muscle cells can be stored or oxidized in the hepatocytes [16]. Therefore, lactate is described by Brooks [16] as “lactormone” considering its blood distribution and systemic effects.

An interesting question arises from the exercise physiology and its perspective with neurobiology: is the “lactormone” a key-factor for neuroplasticity-related exercise? Our hypothesis is that peripheral lactate released through exercise is a signaling molecule in the brain through an alternative neurobiological pathway. To address this hypothesis we will approach different topics.

It is important to emphasize that there are many interactions among

* Corresponding author at: State University of Montes Claros, Av. Dr. Ruy Braga, S/N, Vila Mauriceia, Montes Claros, MG 39401-089, Brazil.

E-mail address: renatoprofedfis@hotmail.com (R. Sobral-Monteiro-Junior).

molecules in the human body. For instance, glucose-glycogen-lactate complex is modulated by zinc especially influenced by exercise [23,24]. In this article a special focus will be done to exercise-induced lactate and its role on human brain.

A brief overview of brain metabolism

Glucose is the preferred human body substrate to supply energetic demands because its feasibility to generate ATP [16]. Although brain represents 2% of body weight it has high energy demand. About 20% and 25% of oxygen and glucose, respectively, are addressed to cerebral activity [20]. When the neurons firing, the contribution of lactate to brain metabolism range from 7 to 60% [21,22]. Although peripheral glucose and glycogen traffic towards the brain, they are oxidized into the astrocytes via glycolysis and glycogenolysis, respectively [16,17,19]. Astrocytes cover synapses and detect their firing supplying neurons metabolic demand using lactate from glycolysis/glycogenolysis. Therefore, lactate is the preferred substrate used by active neurons [17–19].

Astrocytes select glucose/glycogen from intraparenchymal vasculature and blood brain barrier (BBB), which come from periphery. Furthermore, glutamate released by neurons is uptake by astrocytes through specific transporters. When glutamate is captured by astrocytes it also stimulates glucose's uptake [17,19]. Glutamate transporters are activated by a gradient that stimulates Na^+ K^+ pump to triggers a signaling cascade for glycolysis, resulting in lactate production in astrocytes. Each glutamate molecule caught results in one uptake glucose molecule that generates two ATPs (used by Na^+ K^+ pump and glutamine synthetase) and two lactate molecules, respectively. Lactate is transported through monocarboxylate transporters (MCT1, MCT2, AND MCT4) and oxidized at Krebs cycle (via pyruvate) then via oxidative

phosphorylation in neuronal mitochondria [17–19] (See Fig. 1).

Experimental animal studies showed the increase of the pool of lactate in extracellular space when synapses are electrically stimulated in the rats' hippocampus, suggesting substrate release from astrocytes and its metabolism in neurons [18–20]. Therefore, lactate supplies the major metabolic demands in neuronal circuitry. Although lactate is our target in this paper, it is important to highlight that glucose is also used (less than lactate) by neurons [19].

A brief view of lactate as a signaling molecule into the brain

Although lactate participates mainly in metabolic pathways several molecular signals are triggered for it. There are many specific lactate receptors in neurons, such as hydrocarboxylic acid receptor 1 (HCAR1) that is coupled to inhibitory G protein (Gi). Gi deactivates adenylyl cyclase (AC), reducing neuronal activity and gene regulation. On the other hand, noradrenergic neurons have an unidentified lactate receptor coupled to G protein, which positively regulates AC promoting an excitatory potential and gene expression [19].

Lactate shuttle from astrocyte-to-neuron triggers oxidation which modulates redox mechanism through NADH^+ , stimulating NMDA receptors. Therefore a Ca^{2+} influx occurs promoting a lot of neuroplasticity-associated signaling pathways, which encode genes as activity-regulated cytoskeleton-associated protein (ARC), early growth response protein 1 (EGR1) and brain-derived neurotrophic factor (BDNF) [19,25]. Neurons from locus coeruleus are linked to memory consolidation in rats hippocampus, thus lactate appears having a main role on long-term potentiation (LTP) [19].

Lactate can be a supplemental fuel for the injured brain. People with traumatic brain injury who received lactate infusion improved brain

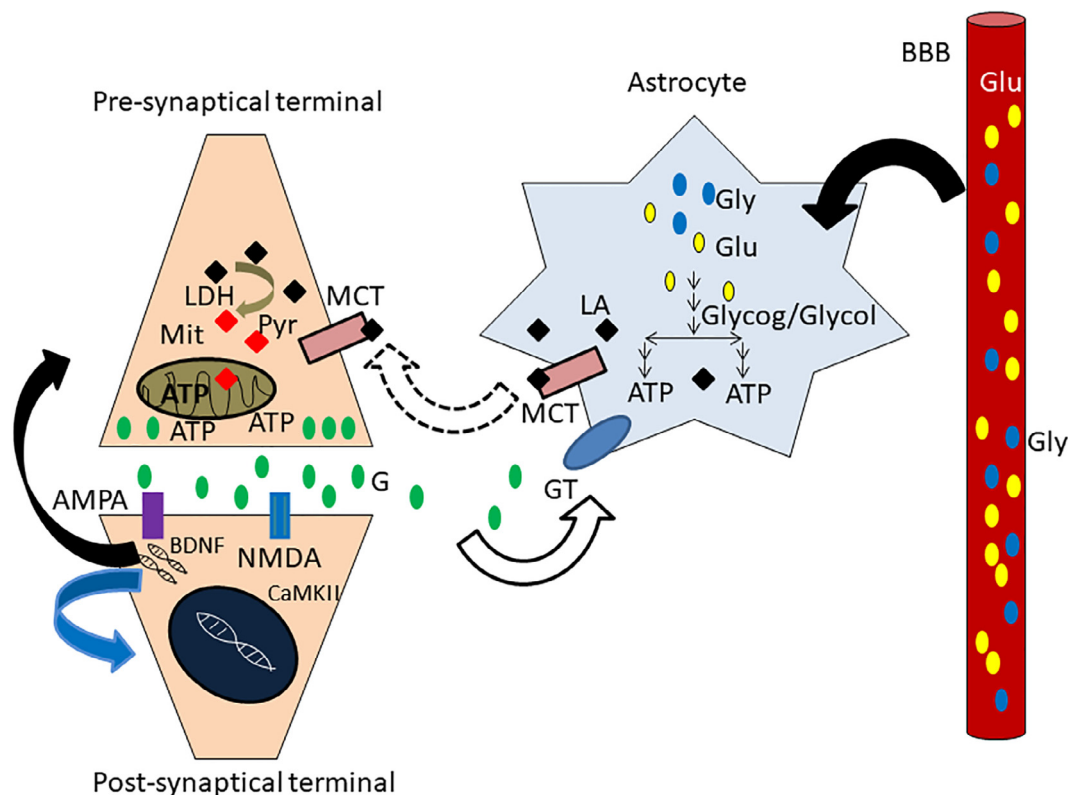


Fig. 1. Brain metabolism: Synapses activation. Glucose (Glu) and Glycogen (Gly) from circulation cross blood-brain-barrier (BBB) and are metabolized by astrocyte (Glycol – glycolysis/Glycog – glycogenolysis). Lactate (LA) is produced as a result of glycolysis and glycogenolysis and traffics to pre-synaptical neuron through monocarboxylate transporter (MCT) (dashed arrow). Lactate is converted in pyruvate (Pyr) through lactate dehydrogenase (LDH) into the mitochondria (Mit) resulting in adenosine triphosphate (ATP). Pre-synaptical terminal releases glutamate (G) that binds to AMPA and NMDA receptors, which increase post-synaptical activity and molecular expression (e. g. BDNF). Blue and black arrows indicate autocrine and paracrine BDNF signaling, respectively. G is partially conducted (continuous arrow) to the astrocyte through glutamate transporter (GT) to be converted in glutamine.

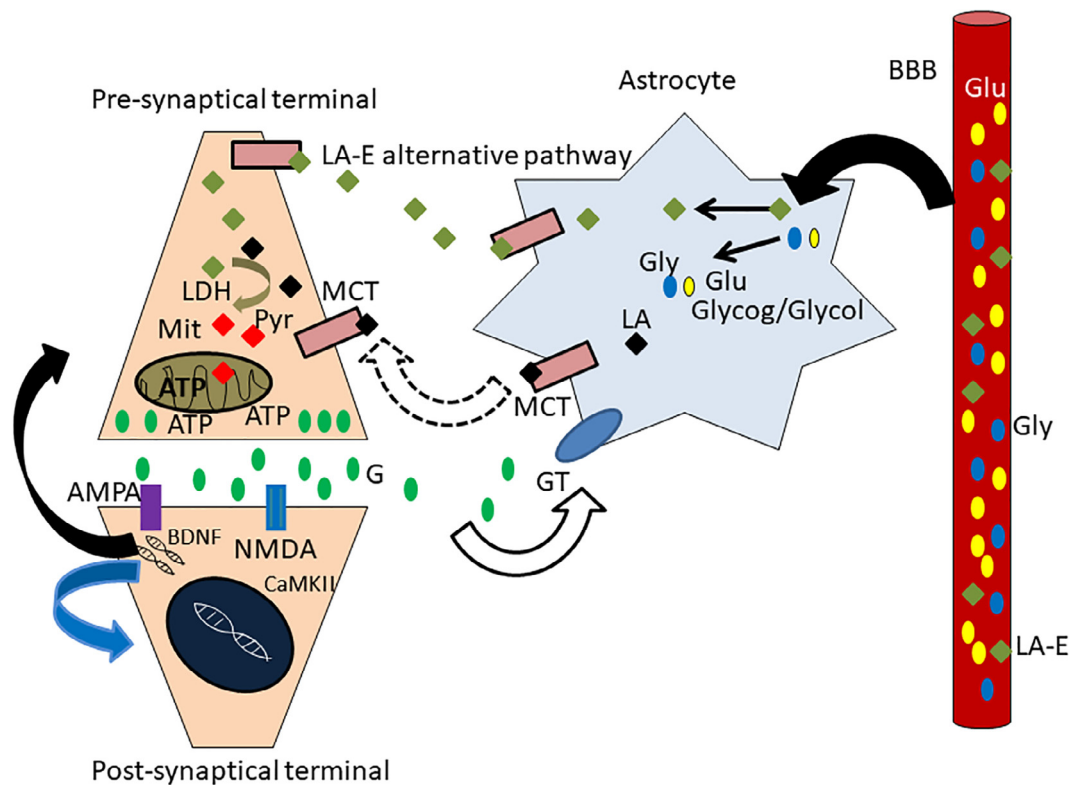


Fig. 2. Alternative neurobiological pathway. Brain metabolism remains unchanged but additional exercise-related lactate (LA-E) crosses blood–brain–barrier (BBB). Monocarboxylate transporter (MCT) transports LA-E from astrocyte to neuron that uses it as energy supply and signaling molecule for neuroplasticity. Blue and black arrows indicate autocrine and paracrine BDNF signaling, respectively. This figure is restricted to show only the alternative neurobiological lactate pathway.

energetic but it was related a baseline lactate-pyruvate ratio. Cerebral blood flow and glucose are modulated by lactate. Therefore, even exogenous lactate seems to be a metabolic role on nervous system [26].

Lactate released through exercise and its relationship with neuroplasticity

In the beginning of the last century lactate was seen as a metabolite from glycolysis/glycogenolysis and a precursor of fatigue through exercise [16]. However, since the last quarter of the 20th century the lactate reuse as substrate was discovered. Nowadays it is considered not only a substrate, but also a signaling molecule [16–19,25]. In other words the pleiotropic role of lactate is still not clearly understood.

Exercise requires energy from ATP that is provided through three main pathways: ATP-CP, glycolysis/glycogenolysis, and oxidative phosphorylation [27]. Lactate is produced as a result of glucose oxidation in glycolysis/glycogenolysis under low oxygen uptake. This production is originated since a reduction of H^+ ions from $NADH^+$ and some pyruvate, through lactate dehydrogenase (LDH). This molecular pathway has a main target: to buffer acidosis [27]. This mechanism is the main (predominant) pathway that provides energy during moderate to vigorous intense exercise. However, muscle cell uses the produced lactate mitochondrial fuel to generate ATP. Moreover, other myocytes, cardiomyocytes, and hepatocytes can use or restore lactate. It is possible due to intracellular and extracellular lactate shuttles [16]. If this molecule has a peripheral pleiotropic role, is it possible the lactate produced during exercise traffic from muscles to brain and trigger neuroplasticity? The answer for this question is possibly yes.

A recent brief communication wrote by Coco [28] argued that brain behaves as muscle, considering that lactate from myocytes could reach the brain after an intense exercise being used as fuel. The main focus of this communication was the central fatigue therefore the lactate consumed by brain would preserve the activity of motor and sensory

regions. It may be partially supported by the Quintard et al (2016) who showed that an exogenous lactate administration in patients who suffered of traumatic brain injury improved brain metabolism. In complement, Dennis et al (2015) showed an increased availability of brain lactate after a 15 min of an intense cycle ergometer. According to this context, if the peripheral lactate can reach the brain working as fuel, it can also trigger molecular signaling.

As aforementioned, lactate regulates HCAR1 coupled to G protein. According with neuronal sources (ex. noradrenergic neurons) the lactate modulation of G protein could stimulates AC, triggering molecular cascades for gene expression and upregulation of NMDA glutamate receptors promoting LTP on hippocampus [19]. In this context, a memory formation and consolidation would occur improving learning. Marston et al [29] investigated the effect of two different bouts of resistance training on serum lactate and BDNF. Individuals who exercised at high-intensity with short rest showed elevated serum lactate, which was correlated with increased BDNF. It makes sense when we analyze the fact that lactate signaling in NMDA receptors increases the influx of Ca^{2+} , which regulates the synthesis of BDNF, ARC, and EGR1 [19]. Therefore, it is reasonable to suggest a link between exercise-related lactate and neuroplasticity in the brain (Fig. 2). In addition, exercise promotes an increase of PGC1- α synthesis that triggers a FNDC5 activation, which modulates cell metabolism and increases BDNF realizing [30]. We speculated an alternative neurobiological pathway of exercise-induced lactate on brain neuroplasticity. Lactate produced by exercised muscle would traffic to blood brain barrier reaching astrocytes, which would deliver it via MCT directly to neurons (details in Fig. 2)

Although lactate is one of the molecules which trigger neuroplasticity, it is reasonable highlight its use as a biomarker in hypoxic pathological conditions (e. g. cardiac failure, and cancer) [31,32]. As the many tissues need of oxygen, when hypoxia occurs lactate is released as a result of anaerobic metabolism. In these conditions lactate is a useful marker related to tissue damage instead neuroplasticity. Therefore,

health professionals need knowledge to distinguish applications of lactate dosage and any other molecule which may influence many signaling pathways in different cases.

Final considerations

Besides lactate is produced as a result of glucose/glycogen metabolism, it is obvious that lactate is not only a metabolite but it is probably a hormone, as postulated by Brooks (2009) as “lactormone”. Lactormone has different cellular and molecular targets such as energy supply and neuroplasticity signaling, respectively. Therefore, lactormone produced as a result of exercise with moderate intensity (such as strength training, cycling, and running) may have an important role to sustain brain activity and neuroplasticity through an alternative pathway modulated by astrocyte-neuron coupling. These mechanisms may be associated to neurofunctional findings such as memory and executive improvements. The present hypothesis is based on molecular and clinical findings and presents an alternative neurobiological pathway of exercise, which could elucidate neuroprotection against neurodegenerative diseases as well the amelioration of symptoms in dementia, Parkinson’s disease and depression.

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