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Lactate in the brain: an update on its relevance to brain energy, neurons, glia and panic disorder

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Abstract: Lactate is considered an important metabolite in the human body, but there has been considerable debate about its roles in brain function. Research in recent years has suggested that lactate from astrocytes may be crucial for supporting axonal function, especially during times of high metabolic demands or hypoglycemia. The astrocyte-neuron lactate transfer shuttle system serves a protective function to ensure a supply of substrates for brain metabolism, and oligodendrocytes appear to also influence availability of lactate. There is increasing evidence for lactate acting as a signaling molecule in the brain to link metabolism, substrate availability, blood flow and neuronal activity. This review will attempt to connect evidence to the relationship lactate has to panic disorder (PD), which suggests that its transporters, receptors or metabolism warrant investigation as potential therapeutic targets in PD.

Keywords: fuel, glia, lactate, lactate dehydrogenase, monocarboxylate transporters, neurons, panic disorder, pyruvate

Lactate in the periphery

Lactate and its role in the human body has been a topic of great interest and controversy for years. Traditionally, lactate has been considered a product of anaerobic metabolism. More recently it has become clear that lactate is both created and consumed in aerobic conditions and serves as a link between glycolytic and oxidative metabolism [Brooks, 2009]. The lactate dehydrogenase enzyme (LDH) converts lactate into pyruvate in the cytosol of a cell [Kraut and Madias, 2014]. Pyruvate can be shuttled from the cytosol to the mitochondria of a cell, and after formation from lactate, pyruvate can also be converted into glucose and thus is a substrate for gluconeogenesis [Brooks, 2009].

Muscles generate the greatest amount of lactate in the body [Andersen *et al.* 2013]. Lactate is moved within and between organs by monocarboxylate transporters (MCTs). At rest, the heart, kidneys, and liver take in lactate [Andersen *et al.* 2013]. The heart uses lactate as fuel. The kidneys and liver perform gluconeogenesis through the Cori cycle [van Hall, 2010; Andersen *et al.* 2013]. Under resting conditions the amount of lactate produced is normally equal to the amount consumed, resulting in a blood lactate level of 0.5–1 mmol/l [Smith *et al.* 2003; van Hall, 2010]. High lactate concentrations are considered to be >4 mmol/l; this can occur under many conditions including high intensity exercise, hypoxia, and shock [Andersen *et al.* 2013]. However, training increases lactate clearance rate through changes in MCT1 [Brooks, 2009].

When pyruvate is converted to lactate there is a change in oxidation state as lactate is more reduced than pyruvate. The redox change acts as a signal within the cell and inhibits the consumption of other substrates. It is also possible that lactate has an effect on gene expression as it is also linked with mitochondrial biogenesis and modification of MCTs [Brooks, 2009].

Importance of lactate in the brain

Traditionally, glucose has been considered to be the primary energy source for the brain, with some use of ketone bodies in hypoglycemic states. Boumezbeur and colleagues in a study on young

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healthy volunteers and using^{13} C-L-lactate and magnetic resonance spectroscopy, suggested that at normal physiological peripheral levels L-lactate may contribute 10% to brain metabolism, but that this could go up to 60% at supra-physiologic plasma L-lactate levels [Boumezbeur *et al.* 2010]. It has been speculated that when neurons are firing at high frequencies, lactate may be a preferred substrate [Baltan, 2015]. However, Dienel proposed lactate as an 'opportunistic' glucose-sparing substrate when it is present in high concentrations, but indicated that most research evidence supports the proposal that glucose is the major energy source in normal activated brain [Dienel, 2012].

Different types of MCTs are found in different cells in the brain. MCT1s, which have an intermediate affinity for lactate, are found in oligodendrocytes and tend to export lactate from a cell [Smith *et al.* 2003; van Hall *et al.* 2009; Barros and Deitmer, 2010; Halestrap, 2012; Barros, 2013; Tarczyluk *et al.* 2013; Rinholm and Bergersen, 2014; Vijay and Morris, 2014; Mosienko *et al.* 2015; Baltan, 2015; Bergersen, 2015]. Astrocytes contain MCT4s, which have a low affinity but high transport rate of lactate [Smith *et al.* 2003; van Hall *et al.* 2009; Barros and Deitmer, 2010; Halestrap, 2012; Tarczyluk *et al.* 2013; Barros, 2013; Rinholm and Bergersen, 2014; Vijay and Morris, 2014; Mosienko *et al.* 2015]. Neurons possess MCT2s [Smith *et al.* 2003; van Hall *et al.* 2009; Barros and Deitmer, 2010; Halestrap, 2012; Mosienko *et al.* 2015; Barros, 2013; Tarczyluk *et al.* 2013; Rinholm and Bergersen, 2014; Vijay and Morris, 2014; Bergersen, 2015]; these transporters have a high affinity for lactate, allowing neurons to bring in lactate as fuel efficiently even in substrate-poor conditions [Smith *et al.* 2003; Barros and Deitmer, 2010; Mosienko *et al.* 2015; Baltan, 2015]. There are also different types of LDH present in different cells in the brain [Barros and Deitmer, 2010; Vijay and Morris, 2014; Mosienko *et al.* 2015; Baltan, 2015]. Neurons contain LDH1, which preferably catalyzes the production of pyruvate while astrocytes contain LDH5 which makes lactate from pyruvate [Barros and Deitmer, 2010; Vijay and Morris, 2014; Mosienko *et al.* 2015; Baltan, 2015]. Of note, a recent study in slices from several brain areas by Karagiannis and colleagues used blockers of MCTs and pannexin and connexin hemichannels to demonstrate that lactate transport across membranes can occur by mechanisms independent of MCTs [Karagiannis *et al.* 2016]. They identified pannexin and connexin hemichannels as conduits of lactate transport, and in their study these hemichannels were recruited during times of hypoxia or increased neuronal activity.

Astrocytes contain glycogen stores that can be metabolized when glucose levels are low and restored when glucose levels are high. This is considered an energy buffer and serves a protective function by ensuring that there is always a supply of substrates for metabolism in the brain [Baltan, 2015]. According to the Astrocyte-Neuron Lactate Transfer Shuttle hypothesis, astrocytes metabolize glucose or glycogen to lactate and this lactate is transferred to neurons *via* juxtasynaptic processes at nodes along the axon [Smith *et al.* 2003; Barros and Deitmer, 2010; Halestrap, 2012; Barros, 2013; Tarczyluk *et al.* 2013; Rinholm and Bergersen, 2014; Vijay and Morris, 2014; Mosienko *et al.* 2015, Bergersen, 2015; Morland *et al.* 2015]. The neurons then convert lactate into pyruvate which enters oxidative metabolism, resulting in the formation of adenosine triphosphate (ATP) [Tarczyluk *et al.* 2013]. Astrocytes also have a lactate reservoir that can be triggered to release lactate through ion channels in response to potassium. This reservoir is developed through transport of lactate *via* an anion channel that does not couple the movement of lactate with hydrogen ions [Mosienko *et al.* 2015; Morland *et al.* 2015; Sotelo-Hitschfeld *et al.* 2015].

Oligodendrocytes consume both glucose and lactate as fuel [Rinholm and Bergersen, 2014; Baltan, 2015]. As they form myelin around the axons, they tend to import lactate as an energy source. Once they mature, they export lactate [Bergersen, 2015]. Oligodendrocytes also play an important role in supplying neurons with an energy source, as they are able to provide lactate to the myelinated compartments of axons [Rinholm and Bergersen, 2014; Baltan, 2015].

Further, lactate may act as a signaling molecule in the brain through hydroxycarboxylic acid receptor 1 (HCAR1) [Mosienko *et al.* 2015; Baltan, 2015; Morland *et al.* 2015]. This particular receptor is found mainly in neurons of the hippocampus, neocortex and cerebellum [Baltan, 2015; Morland *et al.* 2015]. When HCAR1 is activated, neuronal activity decreases as a result of a decrease in cyclic adenosine monophosphate (cAMP) concentration [Mosienko *et al.* 2015; Baltan, 2015; Morland *et al.* 2015]. Lactate has the ability to

diffuse away from where it was released, which allows it to act as a volume transmitter [Rinholm and Bergersen, 2014; Baltan, 2015]. It is able to link energy metabolism, substrate availability, blood flow and neuronal activity throughout the brain [Rinholm and Bergersen, 2014; Baltan, 2015; Morland *et al.* 2015]. It is also of interest that increased blood lactate levels may be an early biomarker of development of extrapyramidal side effects in patients on long-term antipsychotics [Elmorsy *et al.* 2016].

Lactate and the blood–brain barrier

Lactate is transported across the blood–brain barrier (BBB) by MCT1s *via* facilitated diffusion [Smith *et al.* 2003; Halestrap, 2012; Halestrap and Wilson, 2012; Vijay and Morris, 2014]. The BBB, comprising endothelial cells of cerebral blood vessels, contains mRNA for MCTs [Bergersen, 2015]. The MCTs are regulated through transcription and post-transcriptional modifications [Wemmie, 2011; Vijay and Morris, 2014]. In order to function, MCTs require a glycosylated ancillary protein. For MCT1, this protein is basigin [Halestrap, 2012; Vijay and Morris, 2014; Bergersen, 2015]. When compared with the transport of glucose across the BBB, the transport of lactate achieves 50% efficiency [Smith *et al.* 2003]. The brain produces its own lactate from the metabolism of glycogen and tends to export lactate at rest [Paulson, 2002; Boumezbeur *et al.* 2010; Dienel, 2012; Overgaard *et al.* 2012; Andersen *et al.* 2013; Bergersen, 2015]. Lactate is brought into the brain across the BBB to be used as fuel when plasma lactate is high or plasma glucose is low [Boumezbeur *et al.* 2010; Dienel, 2012; Barros, 2013].

Lactate in psychiatry: panic disorder

Lactate infusion is one of several successful methods used to induce panic attacks in humans in a research setting [Pitts and McClure, 1967; Bourin *et al.* 1998; Freire *et al.* 2010; Wemmie, 2011]. This method results in the patient experiencing symptoms very similar to those experienced by individuals with panic disorder (PD) [Freire *et al.* 2010; Wemmie, 2011]. These symptoms include, but are not limited to: fear of dying, fear of losing control, fear of choking, sweating, shaking, nausea, temperature change sensations, paresthesias, derealization, depersonalization, dyspnea, palpitations, chest pain, and feeling dizzy [Freire *et al.* 2010; Wemmie, 2011; American Psychiatric Association, 2013]. The exact mechanism of this phenomenon remains unknown. Tang and colleagues activated astrocytes in the locus coeruleus optogenetically and measured electrophysiological responses and norepinephrine release [Tang *et al.* 2014]. The result was that L-lactate released by astrocytes excited locus coeruleus neurons similar to the effect of L-glutamate and acted like a transmitter rather than simply a substrate. The authors suggested that lactate-mediated effects could be due to stimulation of possible lactate receptors on locus coeruleus neurons that are yet to be confirmed.

There is a genetic component to PD as evidenced by familial and twin studies, but there are also environmental causes such as traumatic experiences [Freire *et al.* 2010; Maddock *et al.* 2013]. It has been reported that PD patients who show panic symptoms in response to infusion of lactate have higher than normal brain lactate levels before, during and after infusion [Dager *et al.* 1994, 1995]. Further, Maddock and colleagues reported that patients with PD accumulate higher levels of lactate in brain regions activated by sensory stimulation and that this effect is independent of end-tidal pCO_2 [Maddock *et al.* 2009]. These findings suggest a mechanism of metabolic disturbance involving either excessive lactate production or inefficient lactate removal rather than the previously proposed hypoxia model [Maddock *et al.* 2009]. In a clinical study on activity-dependent brain lactate and glutamate + glutamine responses, Maddock and colleagues concluded that the increased activity-dependent brain lactate accumulation is a trait feature of PD [Maddock *et al.* 2013]. This increased level may be related to altered function of acid-sensitive fear circuits and is consistent with a model of brain metabolic and pH dysfunction in PD.

Phenelzine (PLZ) is a monoamine oxidase-inhibiting antidepressant that also causes marked elevation of brain gamma-aminobutyric acid (GABA) and alanine levels [Tanay *et al.* 2001] and is also effective in treating PD [Ballenger, 1986; Johnson *et al.* 1995]. Although it has been assumed that the increased GABA levels contribute to its antipanic effects [Paslawski *et al.* 1996], it could be speculated that the increased alanine levels could be causing a decrease in lactate levels through a feedback effect on the

known lactate-to-pyruvate-to-alanine conversion that occurs in the body.

Acid-sensitive circuits in the brain are potential sites from which the symptoms of a panic attack may originate [Maddock *et al.* 2013]. The movement of lactate through MCTs is paired with hydrogen ions [Maddock *et al.* 2013; Vijay and Morris, 2014; Morland *et al.* 2015], and this affects local pH and buffering mechanisms [Halestrap and Wilson, 2012]. When the MCTs are inhibited, an accumulation of brain lactate and a change in pH dynamics would be expected [Maddock *et al.* 2013], probably triggering pH-sensitive chemoreceptors in the brain [Freire *et al.* 2010; Wemmie, 2011]. For example, respiratory chemoreceptors located in the brainstem are activated when there is a decrease in pH and stimulate breathing in order to raise the pH [Maddock *et al.* 2013]. This would result in the symptom of dyspnea. The amygdala has chemoreceptors as well, which are likely associated with the symptom of fear in PD [Wemmie, 2011].

Implications for therapeutic psychopharmacology

Although lactate historically has been thought of as an alternate energy source, recent evidence indicates that it may be more important in this regard than originally thought. Interestingly, recent evidence suggests that increased investigation into its role as a signaling molecule in the brain warrants further attention. MCTs, HCAR1s and metabolism of lactate should be considered as potential targets when developing new drugs for treating PD and perhaps preventing extrapyramidal side effects resulting from chronic use of antipsychotics.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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