The role of GRP81 lactate receptor in synaptic transmission regulation: does it enhance endocytosis?

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The brain is an expensive tissue in terms of energy consumption. It comprises about 2% of body mass and consumes about 20% of all oxygen and calories (Fedorovich and Waseem, 2018). For these reasons, glucose is the primary energy substrate, although they are able to use ketone bodies, pyruvate and lactate (Fedorovich and Waseem, 2018). All these compounds can be metabolized directly in the Krebs cycle, bypassing glycolysis. Hence, they are termed non-glycolytic energy substrates. Out of all potential non-glycolytic substrates, lactate is the most physiological (Magistretti and Allaman, 2018). Ketone bodies could reach concentrations in blood plasma and cerebrospinal fluid which are sufficient to meet metabolic demands of neurons only under specific non-physiological conditions, e.g., ketogenic diet and starvation, or during suckling. In contrast, the normal plasma level of lactate is about 1.5 mM and can reach 20 mM during intensive physical exercise. This is a very high value and this compound undoubtedly contributes to energy production (Mosienko et al., 2015). The lactate concentration in cerebrospinal fluid increases up to 3 mM during brain ischemia (Mosienko et al., 2015). Therefore, the action of lactate on neurons could have certain pathophysiological consequences. In addition, the concept of astrocyte-neuron lactate shuttle has been developed. According to this concept, glycolysis occurs mainly in astrocytes but not in neurons. Lactate is imported from astrocytes to neurons wherein it is further metabolized in mitochondria. Apart from its metabolic function, lactate possesses a signaling function (Morland et al., 2015; Mosienko et al., 2015; Magistretti and Allaman, 2018). Hence, the role of lactate in neurons could also regulate different physiological processes in the body (Morland et al., 2015; Mosienko et al., 2015; Magistretti and Allaman, 2018). As an example, lactate plays a role in neuronal plasticity andengrams formation and regulates calcium transport and neuronal plasma membrane potential (Magistretti and Allaman, 2018). At the level of particular physiological functions, lactate is important for breath control (Magistretti and Allaman, 2018).

Role of lactate in brain diseases: Lactate is implicated in both normal brain functioning and the pathogenesis of different brain diseases. As mentioned above, cerebral ischemia leads to an increase in extracellular lactate concentration. The mechanism of this phenomenon is very simple. In oxygen shortage, lactate fails to be oxidized in mitochondria and is effluxed from cells by the monocarboxylate transporter operating in reverse mode (Magistretti and Allaman, 2018). Moreover, lactate levels could rise after traumatic brain injury. Glucose metabolism impairment with potential changes in lactate concentrations has been demonstrated in several brain areas during depression, bipolar disorder or even in the case of schizophrenia (Dogan et al., 2018; Magistretti and Allaman, 2018). Interestingly, the acute administration of a moderate amount of lactate has an antidepressant effect (Carrard et al., 2018; Magistretti and Allaman, 2018). In contrast, the infusion of a hypertonic solution with a very high lactate concentration could provoke a panic attack (Magistretti and Allaman, 2018). Lactate in high concentrations would result in acidification followed by activation of acid-sensitive ion channels or an increase in osmolality. This fact could explain the lactate-induced panic attack.

Synaptic vesicle recycling: Neurotransmitters are stored in specialized organelles called synaptic vesicles. When an action potential arrives at neuronal presynaptic terminals, it leads to the opening of voltage-gated calcium channels followed by an increase in calcium level that provokes fusing of the plasma membrane and membranes of synaptic vesicles termed exocytosis. It induces neurotransmitter release into the synaptic cleft. However, synaptic vesicle recycling is not limited by exocytosis and includes endocytosis, priming and docking of synaptic vesicles, and their loading with neurotransmitters. Several of these steps are energy-dependent (Fedorovich and Waseem, 2018).

It has been demonstrated that in neurons two aspects have significant importance:

The total adenosine triphosphate (ATP) content and the spatiotemporal dynamics of biochemical processes which leads to the generation of ATP nano-domains close to ATP-synthesizing enzyme or organelles (Dhar-Chowdhury et al., 2007). This assumption is illustrated by an association of some glycolytic enzymes with synaptic vesicles (Ikemoto et al., 2003) which results in creating high local concentrations of ATP. Downregulation of glycolysis leads to insufficiency in synaptic vesicle neurotransmitter recycling. The failure in mitochondrial ATP synthesis does not affect this process (Ikemoto et al., 2003). Therefore, it is very important for neurons not only how much ATP they have received but also how exactly that ATP was obtained.

Different stages of synaptic vesicle recycling are energy-dependent. Therefore, it is hypothesized that the replacement of the energy substrate which feeds neurons might somehow influence this process. It should be mentioned that the maintenance of synaptic vesicle recycling by energy substrates other than glucose is not an immutable fact. The neuronal presynaptic role of lactate is a very complicated issue. Earlier, we showed that non-glycolytic energy substrates such as β-hydroxybutyrate, which is the main ketone body, and pyruvate are able to fuel synaptic vesicle recycling to some extent. However, a non-glycolytic energy substrate has modified the synaptic vesicle recycling through endocytosis inhibition (Hrynevich et al., 2016). Apparently, in normal physiological conditions, moderately decreased endocytosis does not interfere with synaptic transmission. However, it might deplete synaptic vesicles upon overstimulation. We suggest that depletion could at least partially explain the anticonvulsive properties of a ketogenic diet.

The key difference between lactate and pyruvate is the existence of a special receptor for lactate. At least one type of lactate receptor was characterized and termed GPR81 or HCAR1 (Mosienko et al., 2015). It is a G-protein coupled receptor that preferentially inhibits adenylyl cyclase (Magistretti and Allaman, 2018). This protein is widely expressed in different types of neurons and their parts such as presynaptic terminals and postsynaptic density (Morland et al., 2015). Therefore, in our experiments we have additionally used DHBA, an HCAR1 agonist. We have showed that this compound activated endocytosis in a normal glucose-containing incubation medium (Dubovsky et al., 2021). This effect was suggested to compensate for endocytosis inhibition during metabolism rebuilding which occurs under exposure to other non-glycolytic energy substrates (Hrynevich et al., 2016).

At the same time, not all lactate’s effects on synapses can be mediated or simulated by HCAR1. It was shown that lactate can act as a mild oxidative stress. Free radicals could have a signaling function that is independent of classical plasma membrane receptors. For
instance, in neuroblastoma cells, pyruvate and lactate were shown to induce mild oxidative stress which seems to have an adaptive rather than damaging action (Tauffenberger et al., 2019). Interestingly, an increase in free radical levels is not only to protect cells in vivo, but also to prolong the lifespan of C. elegans in vivo (Tauffenberger et al., 2019). We have shown that lactate, but not pyruvate, induced superoxide anion formation in the electron-transport chain of intrasynaptosomal mitochondria. In contrast, DHBA had no effect on free radical formation in synaptosomes (Dubovskaya et al., 2021). This indicates that in synaptosomes, oxidative stress is independent of HCAR1 activation unlike synaptic vesicle recycling. Why lactate and pyruvate have such drastically different effects on mitochondria in our experimental system is still not clear. The difference in action of two monocarboxylates on reactive oxygen species formation was demonstrated using two fluorescent dyes, 2′,7′-dichlorofluorescein diacetate and MitoSOX™ (Dubovskaya et al., 2021). Probes differ in their mechanisms of detection and range of detectable free radicals. Effects of lactate and HCAR1 on neuronal presynaptic endings are schematically depicted in Figure 1.

Figure 1 | Influence of lactate on neuronal presynaptic endings.

It can be transported into the cells through a monocarboxylate transporter (MCT). After that it is metabolized in mitochondria that negatively regulates endocytosis. Alternatively, lactate can interact with the specific hydroxycarboxylic acid receptor 1 (HCAR1) that positively regulates endocytosis.

It can be noted that not all lactate-induced changes in neurons would be reproduced in synaptosomes, e.g., lactate-induced plasma membrane depolarization in several types of neurons (Morland et al. and Allaman, 2018). In synaptosomes, substitution of glucose for lactate also led to a decrease in the plasma membrane potential but addition of lactate to a glucose-containing incubation medium failed to produce any depolarization (Dubovskaya et al., 2021). The question of how extracellular terminals, lactate-induced plasma membrane depolarization is mediated by energy shortage rather than by signaling events.

Conclusion: The physiological function of HCAR1 is being extensively studied but is still not completely clear. Recently, it was proposed that in some cases HCAR1 compensates for the action of lactate in excessive extracellular concentrations, for instance, during ischemia (Morland et al., 2015). The suggestion was supported by further experimental evidence showing the strengthening of neurogenesis (Lambertus et al., 2021), reduction in calcium influx in neurons and decreased neuronal excitability (de Castro Abrantes et al., 2019) upon activation of HCAR1 in neurons. These changes can be neuroprotective in some instances and probably facilitate the brain's adaptation to ischemia. HCAR1 activation also inhibits an increase in phosphorylation of tau protein which potentially could preserve synaptic function in Alzheimer's disease (Morland et al., 2015). In general, our experiments (Dubovskaya et al., 2021) confirm the concept described. Non-glycolytic energy substrates are considered impermeable because they do not completely maintain synaptic vesicle recycling. HCAR1 compensates for this disadvantage via endocytosis stimulation.

HCAR1 exerts its signaling function mainly through adenylyl cyclase inhibition (Mosienko et al., 2015). Moreover, the existence of another yet unidentified receptor activating adenylyl cyclase was predicted (Magistretti and Allaman, 2018). However, it can be noted that currently HCAR1 or GPR81 is the only known receptor for lactate. To summarize, future studies should focus on the role of cyclic adenosine monophosphate-dependent pathway of intracellular signaling in lactate's action on synapses and potential compensation for excessive lactate effects.

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