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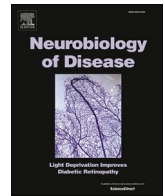
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## Review

## Lactate as a determinant of neuronal excitability, neuroenergetics and beyond

Bruno Cauli<sup>\*</sup>, Isabelle Dusart, Dongdong Li

Sorbonne Université, CNRS, INSERM, Neurosciences Paris Seine - Institut de Biologie Paris Seine (NPS-IBPS), 9 quai Saint Bernard, 75005 Paris, France

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## ABSTRACT

Over the last decades, lactate has emerged as important energy substrate for the brain fueling of neurons. A growing body of evidence now indicates that it is also a signaling molecule modulating neuronal excitability and activity as well as brain functions. In this review, we will briefly summarize how different cell types produce and release lactate. We will further describe different signaling mechanisms allowing lactate to fine-tune neuronal excitability and activity, and will finally discuss how these mechanisms could cooperate to modulate neuroenergetics and higher order brain functions both in physiological and pathological conditions.

## 1. Introduction

Lactate, first isolated in 1780 from sour milk by the Swedish chemist Carl Wilhelm Scheele (Oesper, 1931), is an end-product of carbohydrate fermentation occurring in some bacteria and yeasts under anaerobic conditions. It is also produced by animal cells when oxygen availability becomes limited, such as during intense muscle exercise (Li et al., 2022) or in pathological conditions like stroke (Henriksen et al., 1992), cancer (Hayes et al., 2021) and epilepsy (Slais et al., 2008). During anaerobic glycolysis, pyruvate is indeed converted into lactate instead of entering the Krebs cycle and producing ATP, the energy fuel of the cell. In the 1920s, Otto Warburg discovered that the "fermentation" of glucose into lactate occurred in cancer cells despite the presence of oxygen (Warburg et al., 1927). Since then, this metabolic pathway, referred to as aerobic glycolysis or "Warburg effect", has also been described under physiological conditions, notably in proliferating cells (Vander Heiden et al., 2009). More than a century ago, lactate was considered as a useless waste product, potentially toxic and responsible for muscle fatigue, soreness and *rigor mortis* (Schurr, 2014; Hall et al., 2016). Despite evidence that some organs, including the heart and the brain, are able to

consume an excess of lactate, this process was only considered as a means to remove lactate from the blood (Schurr, 2014). This "bad reputation" slowly began to change in the late 1920s when the Coris showed that d-lactate (former name of L-lactate), "when fed by the mouth or injected subcutaneously, leads to glycogen deposition in the liver" (Cori and Cori, 1929). Indeed, blood lactate recycled through gluconeogenesis and glycogenesis into liver glycogen can in turn lead to blood glucose, muscle glycogen and blood lactate again through glycolysis (see the Cori cycle).

In the 1950s, McIlwain demonstrated that lactate was as efficient as glucose to maintain respiration in human and monkey brain tissues (McIlwain, 1953). More recently, in the 1980s, lactate was found to support synaptic transmission (Schurr et al., 1988). A new game changer in brain lactate occurred in the 1990s when Pellerin and Magistretti demonstrated that glutamate, notably released by excitatory neurons (Fig. 1, point 1) and taken up by astrocytes via the excitatory amino-acid transporters 1 and 2 (EAAT1/2, point 1), stimulated not only glucose uptake via glucose transporter 1 (GluT1, Fig. 1, point 2) (Kacem et al., 1998; McEwen and Reagan, 2004) but also glycolysis and lactate release (Fig. 1, points 3, 4) (Pellerin and Magistretti, 1994; Voutsinos-Porche

**Abbreviations:** ANLS, astrocyte-neuron lactate shuttle; BOLD, blood oxygen-level-dependent; BDNF, brain-derived neurotrophic factor; EAAT1/2, excitatory amino-acid transporter 1/2; fMRI, functional magnetic resonance imaging; HCAR1, hydroxycarboxylic acid receptor 1; HK1, hexokinase 1; IEG, immediate early gene; GluT1/3, glucose transporter 1/3; K<sub>ATP</sub>, ATP-sensitive K<sup>+</sup>; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NVC, neurovascular coupling; PGE2, prostaglandin E2; PGT, prostaglandin transporter; PI3K, phosphatidylinositol 3'-kinase; P<sub>o</sub>, open probability; NMC, neurometabolic coupling.

<sup>\*</sup> Corresponding author.

E-mail address: [bruno.cauli@upmc.fr](mailto:bruno.cauli@upmc.fr) (B. Cauli).

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et al., 2003). Since then, other various by-products of excitatory transmission including glutamate,  $K^+$  and  $NH_4^+$  ions, were also found to stimulate blood glucose uptake, glycolysis and lactate release (Ruminot et al., 2011; Choi et al., 2012; Sotelo-Hitschfeld et al., 2015; Lerchundi et al., 2015). A growing number of evidence indicates that lactate is preferred over glucose as an energy substrate for neurons (Fig. 1, points 6,7) (Bouzier-Sore et al., 2003; Itoh et al., 2003; Bouzier-Sore et al., 2006; Karagiannis et al., 2021). The current view is that brain energy metabolism is partly compartmentalized in between astrocytes and neurons (Bonvento and Bolanos, 2021). Glycolysis in astrocytes consumes glucose and  $NAD^+$  to generate ATP, pyruvate and NADH (Fig. 1, points 2, 3). The reduction of pyruvate into lactate by lactate dehydrogenase (LDH) allows the regeneration of  $NAD^+$  and maintains an astrocytic glycolytic flux (Fig. 1, point 3). In neurons, the oxidation of lactate by LDH generates pyruvate and NADH (Williamson et al., 1967) which allows to fuel the Krebs cycle and respiratory chain to produce ATP (Fig. 1, point 7).

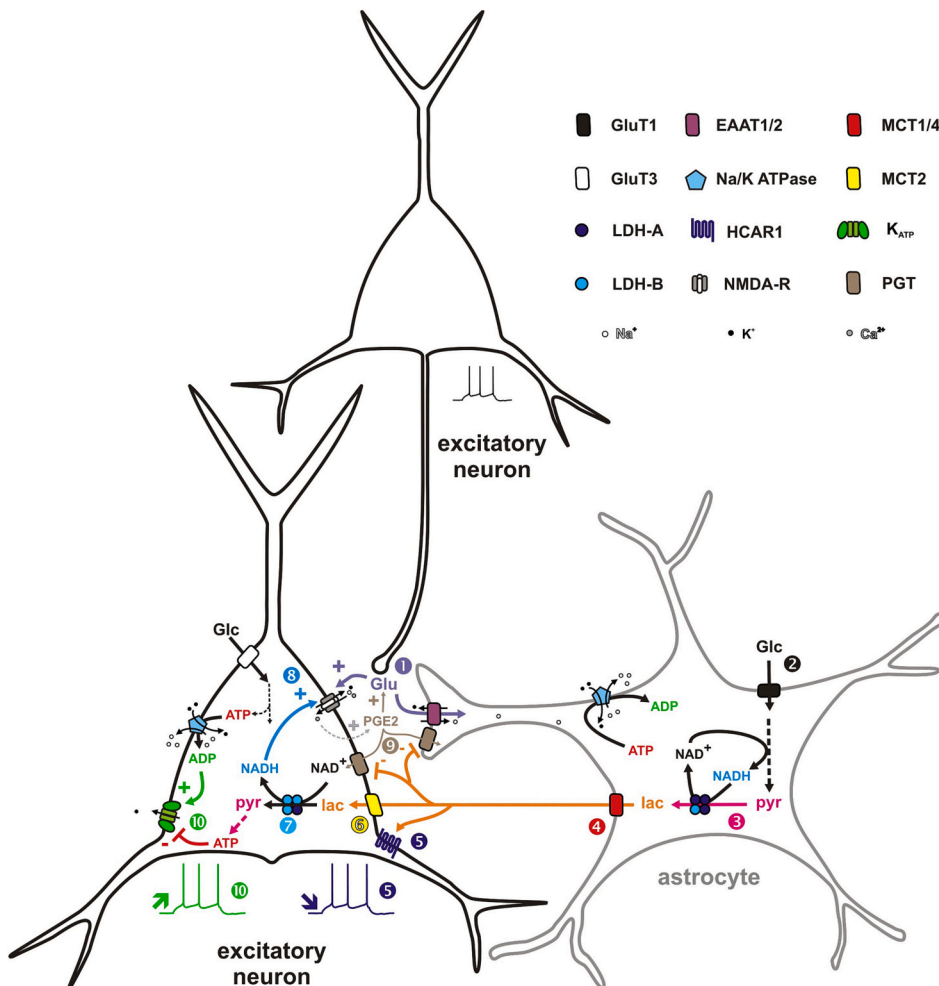
Brain extracellular lactate concentration, ranging under basal conditions from 1-2 mM in rodents (Abi-Saab et al., 2002; Horn and Klein, 2010) and up to 5 mM in humans (Abi-Saab et al., 2002; Zilberter et al., 2010), is almost doubled for several minutes following neuronal activity (Prichard et al., 1991; Hu and Wilson, 1997a). Thus, the so called astrocyte-neuron lactate shuttle hypothesis (ANLS) postulates that neuron activity stimulates lactate production by astrocytes and lactate in turn could be used as an energy substrate to feed neurons (Magistretti and Allaman, 2018)(Fig. 1, points 1-4, 6,7). Moreover, in addition to its metabolic role, the emerging view is that lactate is also a signaling molecule modulating various brain functions including cerebral

angiogenesis (Morland et al., 2017), neuroenergetics (Gordon et al., 2008; Roumes et al., 2021b), glucose homeostasis (Lam et al., 2005; Lhomme et al., 2021), sleep-wake cycle (Clasadonte et al., 2017), learning and memory (Suzuki et al., 2011; Zhou et al., 2021; Roumes et al., 2021b; Dembitskaya et al., 2022) or mood and social interactions (Carrard et al., 2018; Jimenez-Blasco et al., 2020; Yao et al., 2023).

This review therefore aims at providing an overview of the cellular and molecular mechanisms underlying the modulating impact of lactate on neuronal excitability and activity in cortical areas and integrated brain functions. Before getting to the heart of integrated brain functions, we will describe the sources of lactate as well as the mechanisms by which lactate modulates neuronal excitability and activity. Finally, we will discuss how these mechanisms contribute to integrated functions by presenting some examples: both in physiological conditions, including neurovascular and neurometabolic couplings (NVC and NMC) and learning and memory, and in pathological conditions.

## 2. Lactate originates from diverse sources

Brain lactate shows both cerebral and systemic origins. Under anaerobic conditions, as for intense physical exercise, muscle glycolysis generates ATP, pyruvate and NADH. In turn, pyruvate is reduced into lactate and released in the blood stream (Dalsgaard et al., 2004; Brooks, 2009; Li et al., 2022), which allows regenerating intracellular  $NAD^+$  and maintains the glycolytic flux in muscles. Nevertheless, under physiological conditions, even where cerebral oxygen supply is not limited (Mintun et al., 2001; Zhang et al., 2019; Drew, 2022), brain glucose is not fully oxidized into  $CO_2$  and  $H_2O$  to generate ATP, and



**Fig. 1.** ANLS and lactate signaling. During excitatory synaptic transmission ❶ the uptake of glutamate (Glu) by astrocytic EAAT1/2, ❷ stimulates glucose (Glc) uptake in astrocytes via GluT1, ❸ aerobic glycolysis and ❹ L-lactate (lac) via MCT1/4. Once released L-lactate can act on ❺ HCAR1 and decrease neuronal excitability and activity or ❻ be taken up by neuronal MCT2. Intracellular L-lactate is ❼ oxidized by neuronal LDH enriched in LDH-B subunit and produces NADH and pyruvate (pyr). ❸ NADH by potentiating NMDA receptor and  $Ca^{2+}$  entry increases neuronal activity. In COX-2 pyramidal cells, the increase in intracellular  $Ca^{2+}$  promotes PEG2 synthesis and release. ❹ Extracellular L-lactate favors PGE2 accumulation and presynaptic Glu release by inhibiting PGE2 reuptake via PGT. The ATP produced by pyruvate oxidative metabolism ❿ closes  $K_{ATP}$  channels and increases neuronal excitability and activity. Dashed arrows indicate multisteps reactions. Thinner arrows point out minor pathways. Adapted from (Karagiannis et al., 2021).

lactate is released in the extracellular space (Prichard et al., 1991; Hu and Wilson, 1997a; Machler et al., 2016; Zuend et al., 2020). This brain aerobic glycolysis is not evenly distributed and appears to be most prominent in specific cortical areas, such as parietal and prefrontal cortices (Vaishnavi et al., 2010). Furthermore, cerebral LDH, a tetrameric enzyme enabling interconversion of pyruvate and lactate, is composed of the LDH-A (or muscle isoform) and LDH-B (or heart isoform) isozymes. The relative distribution of these subunits varies across brain regions and differs among cell types (Bittar et al., 1996; Laughton et al., 2000; Cahoy et al., 2008; Zeisel et al., 2015; Tasic et al., 2016; Karagiannis et al., 2021), which contributes to determining their glycolytic (*i.e.*, LDH-A, Fig. 1, point 3) versus oxidative (*i.e.* LDH-B, Fig. 1, point 7) metabolic profile (Magistretti and Allaman, 2018; Bonvento and Bolanos, 2021).

Different brain cell types produce and release lactate. Astrocytes, notably enriched in the LDH-A (Fig. 1, point 3) subunit (Bittar et al., 1996; Yao et al., 2023), are the major producers of lactate (Pellerin and Magistretti, 1994; Almeida et al., 2001; Voutsinos-Porche et al., 2003; Choi et al., 2012; Lerchundi et al., 2015; Le Douce et al., 2020; Zuend et al., 2020). Astrocyte lactate may originate from their glycogen store (Sorg and Magistretti, 1991; Choi et al., 2012; Kilic et al., 2018) or more directly from glucose take up by GluT1 (McEwen and Reagan, 2004; Barros et al., 2013; Sotelo-Hitschfeld et al., 2015) through glycogenolysis and/or glycolysis, respectively. Lactate produced by astrocytes can be released by different mechanisms. The most documented one involves the monocarboxylate transporters (MCTs). MCT1 (or SLC16A1) (Broer et al., 1997; Pellerin et al., 2005; Chiry et al., 2006) and MCT4 (or SLC16A3) are prominently expressed in astrocytes (Fig. 1, point 4) (Rafiki et al., 2003; Pellerin et al., 2005; Rosafo et al., 2016). MCT2 (or SLC16A7) is only expressed by discrete astrocyte populations (Rafiki et al., 2003; Pellerin et al., 2005). Both MCT1 and MCT4 exhibit a lower affinity for lactate ( $K_m=3.5$  and 28 mM, respectively) (Broer et al., 1998; Manning Fox et al., 2000) than MCT2 ( $K_m=0.7$  mM) (Broer et al., 1999). However, the relatively high intracellular astrocytic lactate level (Machler et al., 2016) most likely saturates MCT2. Altogether, these observations indicate that astrocyte lactate release via MCTs is predominantly achieved by MCT1 and 4 (Schurr et al., 1999; Sotelo-Hitschfeld et al., 2015; Roumes et al., 2021b) (Fig. 1). Furthermore, astrocytes may also release lactate through a yet unidentified 37-pS ion channel (Sotelo-Hitschfeld et al., 2015) or by pannexin/connexin hemichannels (Karagiannis et al., 2016). In addition, lactate can diffuse across the astrocytic network through gap junctions (Rouach et al., 2008) and be released over a wider region than glutamate during synaptic transmission (Barros, 2013).

Oligodendrocytes also express LDH-A and MCT1 (Cahoy et al., 2008; Zeisel et al., 2015; Tasic et al., 2016), and release lactate from their own glycolysis or via their gap junction-coupling with astrocytes to fuel myelinated axons (Lee et al., 2012). As some cortical neurons express LDH-A and MCT1/2 transcripts, although at a low level, (Cahoy et al., 2008; Zeisel et al., 2015; Tasic et al., 2016; Karagiannis et al., 2021), they may also produce and release lactate through neuronal glycolysis (Bittner et al., 2010; Diaz-Garcia et al., 2017; Piquet et al., 2018; Karagiannis et al., 2021) from glucose take up by GluT3 (McEwen and Reagan, 2004). However their glycolytic capacity is limited by hexokinase 1 (HK1), the major hexokinase isoform that they express (Cahoy et al., 2008; Zeisel et al., 2015; Tasic et al., 2016; Piquet et al., 2018). Indeed, HK1, which catalyzes the first step of glycolysis, exhibits a micromolar affinity for glucose and is inhibited by its product glucose-6-phosphate (Wilson, 2003). HK1 is thus likely to be saturated under normoglycaemia. Moreover, neuronal glycolysis is maintained at a low flux (Fig. 1) by constantly degrading the 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase-3 (Herrero-Mendez et al., 2009), which produces fructose 2,6-bisphosphate, the most potent positive allosteric modulator of glycolysis. This post-translational regulation of glycolysis preserves the mandatory pentose phosphate pathway for long-term neuronal survival (Vaughn and Deshmukh, 2008; Herrero-Mendez

et al., 2009). Lastly, the high affinity of the neuronal MCT2 transporter (Fig. 1, point 6) (Rafiki et al., 2003; Pierre and Pellerin, 2005; Bergersen et al., 2005; Pellerin et al., 2005) makes it more easily saturated by intracellular lactate while only a few cortical neurons express MCT1 (Pierre and Pellerin, 2005; Pellerin et al., 2005; Pierre et al., 2007; Lee et al., 2012). Altogether, neuronal lactate release is expected to be very limited.

Lactate is also produced by skeletal muscles during physical exercise (Dalsgaard et al., 2004; Morland et al., 2017; Li et al., 2022), and in particular by the fast-twitch glycolytic fibers, which shuttle lactate to the slow-twitch oxidative fibers (Brooks, 2009). Skeletal muscle lactate is also released in the blood via MCT1 and MCT4 (Manning Fox et al., 2000; Bonen et al., 2000). Blood-borne lactate can cross the blood-brain barrier via MCT1 (Bergersen et al., 2002; Pierre and Pellerin, 2005; Chiry et al., 2006), which is present at both the luminal and the abluminal membranes of endothelial cells (Zlokovic, 2008). When its plasma concentration exceeds that of the brain extracellular space (Machler et al., 2016; Carrard et al., 2018; Roumes et al., 2021b), following an intense physical exercise for example (Dalsgaard et al., 2004; Morland et al., 2017; Li et al., 2022), it can be transported along its gradient and reach brain parenchyma.

In summary, the main sources of lactate in the brain parenchyma are astrocytes and blood.

### 3. How lactate modulates neuronal excitability

Once extracellular lactate is increased in the cortical parenchyma, it may affect neuronal excitability and activity mainly through three non-exclusive mechanisms that are summarized below: i) lactate receptor, ii) N-methyl-D-aspartate (NMDA) receptors and iii) ATP-sensitive  $K^+$  ( $K_{ATP}$ ) channels (Fig. 1, points 5, 8, 10).

#### 3.1. Lactate receptor

Hydroxycarboxylic acid receptor 1 (HCAR1, previously termed G protein receptor 81, GPR81) is a  $G_i$  protein-coupled receptor that is activated by the metabolically relevant enantiomer L-lactate with an  $EC_{50}$  of 1-7 mM, and less efficiently by its partial agonist D-lactate, but not by pyruvate (Cai et al., 2008; Liu et al., 2009; Ahmed et al., 2010) (Table 1). HCAR1 transcripts are mostly expressed in white adipose tissue (Regard et al., 2008) but are also observed in hippocampus and neocortex, although to a much lesser extent (Lauritzen et al., 2014; Briquet et al., 2022). HCAR1 mRNAs are barely detectable in mouse cortical neurons by either single-cell RNAseq (Zeisel et al., 2015; Tasic et al., 2016) or RNAscope<sup>TM</sup> (Briquet et al., 2022), indicating low expression at the cellular level. Consistently, because of the lack of specific antibodies (de Castro Abrantes et al., 2019), its cellular expression at the protein level has been indirectly reported in pial fibroblast-like and pericyte-like cells as well as in neurons using mice

**Table 1**  
Pharmacological properties and effects of different L-lactate targets.

	L-lactate	D-lactate	pyruvate	MCT dependence
HCAR1 receptor	⬇ excitability	⬇ excitability	No effect	No
NMDA receptors	⬇ activity ⬆ activity	⬇ activity No effect	No effect	Yes
$K_{ATP}$ channels	⬆ excitability	No effect	⬆ excitability	Yes
	⬆ activity		⬆ activity	

expressing the monomeric red fluorescent protein under the *Hcar1* promoter (Morland et al., 2017; de Castro Abrantes et al., 2019; Briquet et al., 2022).

When applied on primary cultures of embryonic cortical neurons, L-lactate decreased calcium transients, assessed as a surrogate of spiking activity, with an  $IC_{50}$  of 4.2 mM (Bozzo et al., 2013). D-lactate, which is much less efficiently transported than L-lactate (Nedergaard and Goldman, 1993) and poorly metabolized by mammalian cells (Cori and Cori, 1929; Ewaschuk et al., 2005), decreased cortical neuron spiking activity with an efficacy ( $IC_{50} = 4.6$  mM) similar to that of L-lactate (Fig. 1, point 5 and Table 1). The HCAR1 specific full agonist 3,5-dihydroxybenzoic acid (Liu et al., 2012), but not pyruvate (Table 1) or glucose, mimicked this effect suggesting that HCAR1 was indeed responsible for this modulation (Bozzo et al., 2013). The involvement of this receptor in decreased excitability was confirmed by showing that L-lactate and HCAR1 agonists lowered the spontaneous calcium activity of embryonic cortical neurons from wild-type but not from HCAR1 knockout mice (de Castro Abrantes et al., 2019). Using whole-cell patch-clamp recording in hippocampal slices from young male rats, HCAR1 agonists were also found to decrease the excitability of CA1 neurons through a  $G_{\alpha i}$  subunit independently of MCTs blockade (Herrera-Lopez and Galvan, 2018). Similar inhibitory effects of HCAR1 activation on neuronal activity were confirmed in embryonic cortical neurons and extended to the presynaptic regulation of glutamate release (de Castro Abrantes et al., 2019). Whole-cell patch-clamp recording of dentate gyrus slices from young rodents revealed that HCAR1 activation decreased the excitability of granule neurons with similar pre- and post-synaptic mechanisms, while this modulation was not detected in mice lacking HCAR1 (Briquet et al., 2022). Likewise, the activity of cortical neurons recorded from epileptic patient brain tissues was decreased by an HCAR1 agonist as revealed by patch-clamp recording and  $Ca^{2+}$  imaging (Briquet et al., 2022).

In summary, the activation of the lactate receptor HCAR1 decreases the activity and excitability of cortical neurons via pre- and post-synaptic mechanisms (Table 1). Further studies would be necessary to generalize this effect of lactate. Due to the lack of specific antibodies, the precise expression and localization of HCAR1 remains to be confirmed in neurons (de Castro Abrantes et al., 2019; Briquet et al., 2022). However, the use of HCAR1 knockout mice attests for the functional expression of HCAR1 in cortical neurons. Besides, the use of whole-cell patch-clamp recording (Herrera-Lopez and Galvan, 2018; de Castro Abrantes et al., 2019; Briquet et al., 2022), may have altered intracellular metabolism (Horn and Marty, 1988) and thereby the relative contribution of lactate receptors and metabolism on neuronal excitability. Investigating neuronal activity with  $Ca^{2+}$  imaging is an alternative approach to preserve intracellular metabolism (Bozzo et al., 2013). The role of HCAR1 should be considered in a condition-dependent manner such as in embryonic neurons (Bozzo et al., 2013; de Castro Abrantes et al., 2019) or in epileptic tissues (Briquet et al., 2022).

### 3.2. Modulation of NMDA receptors by lactate signaling

NMDA receptors represent a subtype of glutamate-gated ion channels with unique properties distinguishing them from other ionotropic glutamate receptors. In particular they display a high  $Ca^{2+}$  permeability (MacDermott et al., 1986), a voltage-dependent  $Mg^{2+}$  block (Nowak et al., 1984), a slow gating kinetics (Lester et al., 1990) and are specifically activated by both glutamate and glycine (Johnson and Ascher, 1987) or D-serine (Mothet et al., 2000) as co-agonists.

In primary cultures of mouse neocortical neurons, co-application of glutamate and a saturating concentration of glycine (Priestley et al., 1995) induced NMDA currents and the associated intracellular  $Ca^{2+}$  increase (MacDermott et al., 1986). Both responses were potentiated in the presence of 10 mM L-Lactate (Yang et al., 2014; Jourdain et al., 2018). Similar concentrations of D-lactate or pyruvate, or even an isoenergetic glucose concentration did not increase (Table 1), but instead decreased this calcium response (Yang et al., 2014; Jourdain et al.,

2018). This lack of enhancement by pyruvate and isoenergetic glucose ruled out the possibility that the effect of L-lactate on NMDA-induced  $Ca^{2+}$  response was mediated by energy metabolism. The decreased  $Ca^{2+}$  response by D-lactate could involve HCAR1 receptor, as shown in cultured cortical neurons (Bozzo et al., 2013; de Castro Abrantes et al., 2019). However, the opposite effects of lactate and pyruvate suggest the contribution of redox state modulation (Fig. 1, point 8). Indeed, exogenous application of 4 mM NADH, which is generated by LDH during L-lactate oxidation (Williamson et al., 1967), also enhanced NMDA-dependent intracellular  $Ca^{2+}$  increase (Yang et al., 2014). Consistently, LDH inhibition by stiripentol (Sada et al., 2015) prevented the enhancing effect of L-lactate (Jourdain et al., 2018).

Seven different NMDA receptor subunits have been identified: the NR1 (GluN1) subunit, four distinct NR2A-D (GluN2A-D) subunits and two NR3 (GluN3A-B) subunits, which determine receptor properties (Paoletti et al., 2013). NMDA receptors are heterotetramers typically associating the mandatory NR1 subunit with NR2 subunits or a mixture of NR2 and NR3 subunits. NR1, NR2A and B are massively expressed in cortical neurons whereas the expression of NR2C and D is mostly restricted to cortical interneurons (Monyer et al., 1994; Cauli et al., 2000; Cahoy et al., 2008; Zeisel et al., 2015; Tasic et al., 2016).

The potentiating effect of L-lactate, but not the basal  $Ca^{2+}$  response induced by glutamate/glycine co-application, was found to recruit NR2B-containing NMDA receptors (Jourdain et al., 2018). Supporting a redox-state effect of lactate on NMDA receptors, dithiothreitol, a reducing agent which potentiates NMDA currents (Sullivan et al., 1994; Kohr et al., 1994), also enhanced the intracellular  $Ca^{2+}$  increase induced by glutamate and glycine in a NR2B-dependent manner (Jourdain et al., 2018). Conversely, the oxidizing agent 5,5'-dithiobis(2-nitrobenzoic acid) prevented the effect of L-lactate (Jourdain et al., 2018). In addition to this mechanism, L-Lactate may also indirectly contribute to glutamatergic transmission. Indeed, L-lactate has been shown to promote extracellular prostaglandin E2 (PGE2) accumulation through prostaglandin transporter (PGT) modulation (Gordon et al., 2008). Given that PGE2 is a retrograde lipid messenger facilitating glutamatergic transmission (Sang et al., 2005), lactate may also indirectly potentiate glutamatergic transmission (Fig. 1, point 9), and thus NMDA receptor activity.

In summary, the enhancing effect of L-lactate on neuronal activity via NMDA receptors appears to mostly involve the redox regulation of NR2B-containing receptors by NADH produced intracellularly by LDH. This process thus requires L-lactate uptake (Fig. 1, point 8 and Table 1) and potentially the glutamatergic transmission via PGE2 at the presynaptic terminals (Fig. 1, point 9).

### 3.3. The Janus regulation of $K_{ATP}$ channels by lactate

Before addressing whether and how L-lactate influences energy metabolism-dependent homeostatic regulation, we will introduce the key players of this regulation, the  $K_{ATP}$  channels, and will discuss how this homeostatic regulation modulates neuronal excitability and activity. Finally we will report on how L-lactate may either close or open  $K_{ATP}$  channels.

*$K_{ATP}$  channels modulate neuronal activity:*  $K_{ATP}$  channels act as metabolic sensors controlling various cellular functions (Babenko et al., 1998). Their open probability ( $P_o$ ) is regulated by the energy charge of the cell (*i.e.*, the ATP/ADP ratio). While ATP mediates a tonic background inhibition of  $K_{ATP}$  channels, cytosolic increases of ADP concentrations that occur as a sequel to enhanced energy demands increase the  $P_o$  of  $K_{ATP}$  channels. In neurons, electrical activity is accompanied by enhanced sodium influx, which in turn activates the  $Na^+/K^+$  ATPase (Fig. 1). Activity of this pump sufficiently alters the submembrane ATP/ADP ratio to activate  $K_{ATP}$  channels (Tanner et al., 2011).  $K_{ATP}$  channels are activated ( $P_o > 0.1$ ) when ATP/ADP ratio is  $\leq 5$  (Tantama et al., 2013). These channels are heterooctamers (Moreau et al., 2005; Puljung, 2018) composed of four inwardly rectifying  $K^+$  channel subunits, Kir6.1

(or KCNJ8) or Kir6.2 (or KCNJ11), and four regulatory subunits, SUR1 (or ABCC8) or SUR2 (or ABCC9). A large majority of cortical neurons express functional  $K_{ATP}$  channels (Zawar et al., 1999; Cunningham et al., 2006; Molnar et al., 2014; Sada et al., 2015; Karagiannis et al., 2021) mostly composed with Kir6.2 and SUR1 subunits (Zawar et al., 1999; Cahoy et al., 2008; Doyle et al., 2008; Zeisel et al., 2015; Tasic et al., 2016; Karagiannis et al., 2021; Medel et al., 2022). Since this molecular composition confers the highest sensitivity to intracellular ATP-decrease (Liss et al., 1999), cortical neurons act as metabolic sensors and translate an increase in energy demand (i.e., decreased ATP/ADP ratio) into membrane hyperpolarization and decreased firing rate, and reciprocally (Fig. 1, point 10).

Indeed, in adult rat entorhinal cortical slices, metabolically sensitive slow wave oscillations have been recorded with sharp electrodes in both excitatory neurons and inhibitory interneurons (Cunningham et al., 2006). The frequency of these oscillations, which consisted in up (depolarization) and down (hyperpolarization) phases, was decreased by lowering the extracellular glucose from 10 mM, a classically used *ex vivo* concentration, to a physiologically relevant concentration of 2.5 mM (Silver and Erecinska, 1994; Hu and Wilson, 1997b). Down states were prolonged in 2.5 mM glucose, whereas the up states duration, relying on excitatory recurrent activity, remained unaffected. This observation indicated that only the down phase was metabolically sensitive (Cunningham et al., 2006). It also suggested that the decreased energy charge (i.e., ATP/ADP ratio) of neurons during up states, which involved highly energy-demanding excitatory transmission (Attwell and Laughlin, 2001; Tantama et al., 2013; Baeza-Lehnert et al., 2019), drove the transition to the down phase by activation of  $K_{ATP}$  channels. Consistently, up states and down states were mimicked by  $K_{ATP}$  blocker and opener, respectively. Moreover, intracellular recording of single neurons with a high ATP concentration in the recording pipette, to block  $K_{ATP}$  channels, prolonged the up phase and suppressed the hyperpolarization of the down phase in the recorded neurons, without affecting population activity. Hence, this pioneering work disclosed an energy metabolism-dependent homeostatic regulation of cortical activity (Cunningham et al., 2006).

**Lactate-induced neuronal depolarisation via  $K_{ATP}$  channels closure:** The importance of L-lactate, LDH, the downstream pyruvate and  $K_{ATP}$  channels has been shown in the control of neuronal excitability in different brain areas (Sada et al., 2015). Using whole-cell patch-clamp recording in hippocampal slices, CA1 pyramidal cells were hyperpolarized by glucose depletion or showed impaired L-lactate metabolism by LDH inhibition (Sada et al., 2015). As discussed below, it was not the case of fast spiking interneurons despite a functional expression of  $K_{ATP}$  channels. This hyperpolarization induced by LDH inhibition was reversed by extracellular pyruvate, and was accompanied by a decrease in membrane resistance, indicative of hyperpolarizing conductance activation and decreased excitability. Consistent with a neuron-type specific effect of LDH inhibition, excitatory postsynaptic currents were more strongly reduced than inhibitory postsynaptic currents. Furthermore, paired whole-cell and cell-attached recording between CA1 pyramidal cells and nearby astrocytes were used to selectively inhibit LDH in astrocytes upon rupture of the cell-attached membrane patch. This treatment induced a progressive hyperpolarisation in pyramidal cells and was prevented by extracellular L-lactate, thereby supporting the ANLS (Sada et al., 2015). The lack of effect in fast spiking interneurons was attributed to a missing link between downstream LDH metabolite and  $K_{ATP}$  channels. Of note, intracellular ATP delivered through the patch pipette did not revert the hyperpolarization induced by LDH inhibition in neurons of the basal ganglia subthalamic nucleus.

In contrast with neurons of the entorhinal cortex (Cunningham et al., 2006), the evoked firing of single neurons from the barrel cortex, which were recorded in slices of juvenile rodents using the perforated patch configuration that preserves intracellular metabolism (Horn and Marty, 1988), was found to be insensitive to a decrease in glucose concentration from 10 mM to 2.5 mM. Under 2.5 mM extracellular glucose, L-lactate

dose-dependently enhanced the spiking activity of both pyramidal cells and cortical GABAergic interneurons (Karagiannis et al., 2021). This enhancing effect was observed at a concentration of L-lactate up to 15 mM, an isoenergetic condition with 10 mM glucose, which doubled the firing rate. 15 mM pyruvate induced a similar enhancing effect, ruling out the involvement of HCAR1 (Ahmed et al., 2010) and a redox-state dependence (Table 1). Lactate-induced increase in firing rate was abolished by MCT blockade implying the facilitated transport of L-lactate for its enhancing effect on spiking activity. As evidenced by NADH intrinsic fluorescence imaging (Chance et al., 1962), cortical neurons were found to uptake and oxidize L-lactate by LDH (Williamson et al., 1967; Karagiannis et al., 2021)(Table 1). Consistent with a high oxidative metabolism of cortical neurons (Itoh et al., 2003; Gulyas et al., 2006), the majority of the produced ATP was found to massively derive from oxidative metabolism and poorly from glycolysis (Karagiannis et al., 2021)(Fig. 1, point 7), as shown by the use of an intracellular fluorescent ATP biosensor (Imamura et al., 2009) and metabolic inhibitors. These observations suggested that the L-lactate enhancing effect was mediated by the downstream oxidative metabolism of pyruvate in mitochondria to produce ATP and blockade of  $K_{ATP}$  channels (Fig. 1, point 10). Indeed, the firing-rate enhancement by L-lactate was suppressed by a  $K_{ATP}$  channel opener, while this effect was reversed by a  $K_{ATP}$  channel blocker. L-lactate occluded the effect of the blocker, indicating the closure of all  $K_{ATP}$  channels. Furthermore, cortical neurons of Kir6.2 knockout mice were insensitive to L-lactate, thereby implying closure of  $K_{ATP}$  channels in lactate sensing.

**Lactate-induced neuroprotection via  $K_{ATP}$  channels opening.** In primary cultures of cortical neurons, application of glutamate in a  $Mg^{2+}$ -free medium (Jourdain et al., 2016), or co-application with glycine at saturating concentrations, induced a massive NMDA-dependent  $Ca^{2+}$  entry followed by an irreversible cell swelling (Jourdain et al., 2018), as imaged by digital holography microscopy (Jourdain et al., 2011), which preceded cell death. L-lactate dose-dependently protected against this NMDA-receptor-dependent excitotoxicity (Jourdain et al., 2016; Jourdain et al., 2018). This neuroprotection was mimicked with a similar concentration of pyruvate, but not by 10 mM D-lactate (Jourdain et al., 2016; Jourdain et al., 2018), suggesting that the effect of L-lactate was independent of redox state and HCAR1 receptor (Ahmed et al., 2010) (Table 1). The absence of effect using an isoenergetic condition with 5 mM glucose indicated that neuroprotection did not rely on glucose energy metabolism (Jourdain et al., 2016). The observations that i) L-lactate is preferred over glucose as an energy substrate in cultured neurons (Bouzier-Sore et al., 2003; Itoh et al., 2003), ii) L-lactate is converted into pyruvate by LDH, and iii) L-lactate and pyruvate have similar neuroprotective effects, suggested a neuroprotection mediated by the oxidative metabolism of pyruvate in mitochondria to produce ATP. Indeed, L-lactate-induced neuroprotection was abolished by the blockade of the mitochondrial pyruvate carrier (Jourdain et al., 2016). Furthermore, extracellular application of ATP $\gamma$ S, a non metabolisable ATP analogue and a stable purinergic receptor, but not of an adenosine receptor agonist, mimicked the neuroprotective effect of L-lactate, suggesting that it was not mediated by ATP consumption but rather by the release of ATP and the activation of extracellular purinergic receptors (Jourdain et al., 2016). The neuroprotection conferred by L-lactate was abolished by the blockade of pannexins, which act as ATP-releasing channels (Bao et al., 2004; Whyte-Fagundes and Zoidl, 2018), as well as by the presence of an extracellular ATP-degrading enzyme, thereby ruling out the involvement of adenosine receptors (Jourdain et al., 2016; Jourdain et al., 2018). Molecular observations and pharmacological manipulations respectively identified P2Y2 receptor and its downstream phosphatidylinositol 3'-kinase (PI3K) pathway, as the purinergic receptor and its signalling cascade responsible for L-lactate-induced neuroprotection (Jourdain et al., 2016). Since the activation of  $K_{ATP}$  channels is neuroprotective by reducing neuronal activity and energy demand (Soundarapandian et al., 2007) and the PI3K pathway has been shown to open these channels (Mirshamsi et al.,

2004; Plum et al., 2006), their contribution to L-lactate-induced neuroprotection was evaluated using a  $K_{ATP}$  channel blocker. This treatment indeed reverted the protection conferred by both L-Lactate and the direct pharmacological activation of purinergic receptors (Jourdain et al., 2016; Jourdain et al., 2018), thereby implying the opening of  $K_{ATP}$  channels via a L-Lactate/P2Y2/PI3K pathway.

These studies indicated that L-Lactate can modulate  $K_{ATP}$  channel closure or opening depending on the context. On the one hand, L-lactate may enhance neuronal excitability and activity via  $K_{ATP}$  channel closure (Sada et al., 2015; Karagiannis et al., 2021), whereas it promotes neuronal survival via  $K_{ATP}$  channel opening (Jourdain et al., 2016; Jourdain et al., 2018). Although both effects modulate  $K_{ATP}$  channels in opposite direction, they share some common features. Indeed, both enhancement of spiking activity and neuroprotection are mimicked by pyruvate (Table 1), which is also an intermediate in their signalling cascade. While the contribution of MCTs and LDH has not been evaluated on L-Lactate-induced neuroprotection *per se* (Jourdain et al., 2016; Jourdain et al., 2018), the observation that mitochondrial pyruvate carrier was mandatory strongly suggests that MCTs and LDH are indeed involved in neuroprotection. The mechanisms underlying both L-lactate effects start to diverge downstream of pyruvate: spiking enhancement involves an intracellular modulation of  $K_{ATP}$  channels whereas neuroprotection entails a  $K_{ATP}$  channel autocrine regulation.

But how could these signalling pathways deviate? A possible explanation could arise from the experimental designs leading to dramatic differences in intracellular  $Ca^{2+}$  load and/or cell swelling. Indeed, the ATP release by pannexins is both  $Ca^{2+}$ -sensitive and mechanosensitive (Bao et al., 2004; Whyte-Fagundes and Zoidl, 2018). In neuronal cultures, the rapid and strong intracellular  $Ca^{2+}$  increase induced by excitotoxic challenges was followed by cellular swelling (Jourdain et al., 2016; Jourdain et al., 2018) and may have promoted pyruvate-derived ATP release via pannexins as well as its autocrine action on purinergic receptor. By contrast, in hippocampal slices, the effect of both glucose depletion and LDH inhibition on resting neurons was analyzed and resulted in a hyperpolarisation through  $K_{ATP}$  channel opening (Sada et al., 2015). Under these conditions, both intracellular  $Ca^{2+}$  and cell swelling are expected to be minimal (Andrew and MacVicar, 1994). Thus, the intracellular inhibition of  $K_{ATP}$  channels induced by L-lactate or pyruvate should have been promoted. In spiking neocortical neurons (Karagiannis et al., 2021), intracellular  $Ca^{2+}$  is increased by activating voltage-gated  $Ca^{2+}$  channels. However, neuronal swelling is likely to be modest since increased neuronal volume is mostly observed under extreme conditions such as cordial spreading depression (Zhou et al., 2010). Altogether, these observations suggest that autocrine regulation by pyruvate-derived ATP may be favored over intracellular inhibition of  $K_{ATP}$  channels under substantial increases in both intracellular  $Ca^{2+}$  and cell volume.

Since enhancement and/or promotion of spiking activity by L-lactate is mediated by  $K_{ATP}$  channel closure, in order to be effective this effect implicitly requires that some  $K_{ATP}$  channels are open. This has been achieved through metabolic impairment or evoked firing (Sada et al., 2015; Karagiannis et al., 2021). Indeed, under resting conditions the neuronal ATP/ADP ratio is far above 10 and  $K_{ATP}$  channels are already closed (Tantama et al., 2013). Metabolically-induced ATP depletion is a well established means to activate  $K_{ATP}$  channels (Liss et al., 1999; Zawar and Neumcke, 2000; Sada et al., 2015; Karagiannis et al., 2021). However it remains unclear how continuous moderate neuronal firing (*i.e.*, 2-4 Hz) affects  $K_{ATP}$  channels. Indeed, in hippocampal slices brief pulses of action potentials at a frequency of up to 20 Hz resulted in an increase in  $P_o$  of neuronal  $K_{ATP}$  channels in a  $Na^+/K^+$  ATPase-dependent manner, which was correlated with a drop in cytosolic ATP (Tanner et al., 2011; Toloe et al., 2014). By contrast, a decrease in intracellular ATP of layer 5 pyramidal cells was only observed *in vivo* at stimulation frequency of 100 Hz and above (Baeza-Lehnert et al., 2019). Whether these differences relate to the preparations, the cortical areas and/or the difficulty of measuring submembrane ATP remains to be solved.

Whether ATP is the intracellular mediator of L-Lactate-inducing increase in spiking activity is also an open question. In contrast to oxaloacetate, intracellular ATP was found to be ineffective for reverting  $K_{ATP}$  channel opening induced by LDH inhibition (Sada et al., 2015). Interestingly, hippocampal interneurons are insensitive to glucose deprivation in whole-cell configuration (Sada et al., 2015) but not in perforated patch configuration (Zawar and Neumcke, 2000), whereas the almost opposite was observed in CA1 pyramidal cells. Whether altered intracellular metabolism by whole-cell recording accounted for the apparent lack of ATP sensitivity also remains to be determined.

In summary, L-Lactate can modulate neuronal activity and excitability via different mechanisms controlling  $K_{ATP}$  channels which depend on the metabolic context, the cell volume as well as the level of neuronal activity. In a recent study, L-lactate was also found to promote neuronal excitability in the dorsomedial prefrontal cortex via MCT2 and inhibition of large conductance  $Ca^{2+}$ -activated  $K^+$  channels (Yao et al., 2023). Whether both mechanisms could coexist or depend on cortical areas and developmental stages is another open question. Interestingly, in human cerebral cortex, MCT2, Kir6.2 and SUR1 expression patterns are tightly correlated, and all enriched in caudal sensory areas (Medel et al., 2022).

#### 4. Integrated effect of L-lactate on neurophysiology

In the previous section, we have described different molecular mechanisms by which L-lactate modulates neuronal excitability and activity (Table 1). In the next subsections we will discuss how these different mechanisms could contribute to brain functions, namely NVC and NMC, as well as learning and memory.

##### 4.1. NVC and NMC

The tight coupling between neuronal activity and local cerebral blood flow has been recognized more than a century ago (Roy and Sherrington, 1890). Since then, this neurovascular coupling (NVC) has been the subject of intense debates and two main contradictory hypotheses emerged. While the "metabolic" hypothesis postulated that NVC was a feedback response to an increased energy demand by neuronal activity, the "neurogenic" hypothesis attributed the neurovascular response to a feedforward process involving the release of specific vasoactive messengers (Attwell et al., 2010). The observations that: i) baseline blood flow was adequate to meet oxygen needs, even during increased neuronal activity (Mintun et al., 2001; Zhang et al., 2019; Drew, 2022), and ii) NVC persisted in an excess of blood oxygen or glucose (Wolf et al., 1997; Lindauer et al., 2010) indicated that NVC was not a response to an increase of energy demand. As a consequence, the "metabolic" hypothesis has been progressively disregarded. Nonetheless astrocyte metabolism is essential for the full process of NVC (Lecrux et al., 2011).

Neuronal activity also stimulates blood glucose uptake and its use by brain cells, a process termed NMC (for neurometabolic coupling), which relies on the interplay between glutamatergic neurons, astrocytes and blood vessels (Bonvento et al., 2002; Bonvento and Bolanos, 2021). In the late 1980s, seminal positron emission tomography studies revealed that the local increase in cerebral blood flow and brain glucose uptake induced by neuronal activity far exceeded that of oxygen consumption (Fox and Raichle, 1986; Fox et al., 1988), questioning the functional relevance of increased oxygen delivery. Thus, NVC leads to an increase in blood oxygen availability (Buzsaki et al., 2007) in the activated area, which is the physiological basis of blood oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) (Ogawa et al., 1990) to map neuronal activity (Logothetis, 2008).

It is now widely admitted that this process is achieved by highly coordinated mechanisms that vary according to the vascular segments, leading to an increase in blood velocity within the capillary bed and a dilation of upstream pre-capillary, penetrating and pial arterioles (Cauli

and Hamel, 2018; Rungta et al., 2021; Schaeffer and Iadecola, 2021). NVC is controlled by spiking and synaptic activities (Devor et al., 2008; Logothetis, 2008) and involves the release of multiple vasoactive messengers produced by excitatory pyramidal cells, inhibitory interneurons, astrocytes and endothelial cells (Niwa et al., 2000; Cauli et al., 2004; Gordon et al., 2008; Girouard et al., 2010; Lecrux et al., 2011; Lacroix et al., 2015; Uhlirva et al., 2016; Mishra et al., 2016; Longden et al., 2017; Chow et al., 2020; Rungta et al., 2021).

A recent study has examined the role of brain L-lactate in NMC and NVC in the rat barrel cortex (Roumes et al., 2021b). It was found that down-regulation of either neuronal MCT2 or astroglial MCT4 abolished the L-lactate increase induced by whisker stimulation. The impairment of L-lactate surge is more easily interpretable in animals presenting a down-regulation of MCT4 than in those presenting a down-regulation of MCT2. Indeed, as mentioned earlier MCT4 is selectively expressed in astrocytes (Rafiki et al., 2003; Pellerin et al., 2005; Rosafio et al., 2016) and participates in L-lactate release (Fig. 1, point 4). It is thus not surprising that altering a pathway of L-lactate release impaired the ability of astrocytes to release it, although other release mechanisms (Sotelo-Hitschfeld et al., 2015; Karagiannis et al., 2016) remained unaltered. The impact of MCT2 down-regulation is however more intriguing since neuronal lactate release is expected to be very limited. An explanation might be that the uptake of L-lactate by neurons promotes the release of L-lactate by astrocytes. We indeed described before that L-lactate enhances neuronal activity via  $K_{ATP}$  channel closure (Fig. 1, point 10), and in particular, in glutamatergic pyramidal cells (Sada et al., 2015; Karagiannis et al., 2021). Thus, entry of L-lactate in neurons through MCT2 could favor glutamate release. Yet, glutamate via its uptake in astrocytes by EAAT1/2, stimulates glucose uptake, glycolysis and L-lactate release (Pellerin and Magistretti, 1994; Voutsinos-Porche et al., 2003)(Fig. 1, points 1-4). Thus, this would imply that feedback mechanism(s), which remain(s) to be elucidated, should exist to prevent an overproduction of L-lactate and a cortical hyperactivity.

In the same work (Roumes et al., 2021b), BOLD-fMRI-imaged NVC was also dramatically altered in rats down-regulated for MCT2, and to a lesser extent for MCT4. Impairment of the BOLD response was observed in about half of the animals with a down-regulation of MCT4. NVC could be rescued by peripheral L-lactate infusion. Conversely, the down-regulation of MCT2 induced an impairment of NVC resistant to systemic L-lactate in all rats (Roumes et al., 2021b). These observations question how MCT2 and MCT4 could also be involved in NVC. Spiking activity is essential for this process by allowing the release of vasoactive messengers directly by neurons or indirectly by astrocytes and endothelial cells (Cauli and Hamel, 2010; Attwell et al., 2010; Iadecola, 2017; Cauli and Hamel, 2018; Kaplan et al., 2020). Here again neuronal lactate sensing would have promoted the release of vasoactive messengers by enhancing spiking activity (Fig. 1, point 10). This idea is supported by the rescuing of NVC by systemic L-lactate in animals downregulated for MCT4 (Roumes et al., 2021b). In the latter, lactate enters the brain most likely by endothelial MCT1 (Bergersen et al., 2002; Pierre and Pellerin, 2005; Chiry et al., 2006; Zlokovic, 2008). Along this line, systemic L-lactate was found to increase motor cortex excitability in humans (Coco et al., 2010), and possibly NVC as well, which could have been mediated by neuronal lactate sensing. L-lactate could also participate in NVC by potentiating NMDA receptors (Fig. 1, point 8 and Table 1)(Yang et al., 2014; Jourdain et al., 2018). Indeed, these receptors respectively promote the release of PGE2 (Fig. 1, point 8) by cyclooxygenase-2 pyramidal cells (Niwa et al., 2000; Lecrux et al., 2011; Lacroix et al., 2015) and nitric oxide (NO) and by NO-producing interneurons (Cauli et al., 2004; Mishra et al., 2016; Lee et al., 2020), two key vasoactive messengers of NVC (Cauli and Hamel, 2010; Attwell et al., 2010; Cauli and Hamel, 2018). Furthermore, lactate-sensing and the enhancement of L-lactate mediated NMDA receptors may act synergistically. By depolarizing neurons, lactate-sensing could indeed promote the removal of the  $Mg^{2+}$  block from NMDA receptors (Nowak et al., 1984). In addition to the promoting effect of L-lactate on PGE2 release via  $K_{ATP}$  channel and

NMDA receptor regulation, L-lactate might also favor PGE2 accumulation by impairing its reuptake via PGT (Fig. 1, point 9), and thus enhance NVC (Gordon et al., 2008). Interestingly, systemic L-lactate potentiated the BOLD response in humans (Mintun et al., 2004), whereas the opposite was observed with systemic pyruvate (Vlaskenko et al., 2006). These opposite effects may have been mediated via redox-dependent modulation of NMDA receptors by L-lactate and pyruvate (Yang et al., 2014; Jourdain et al., 2018) which could have been potentiated in the case of L-lactate by lactate-sensing (Sada et al., 2015; Karagiannis et al., 2021)(Table 1).

In summary, L-lactate could fine-tune NVC in metabolic (*i.e.*  $K_{ATP}$ ) and redox (*i.e.* NMDA) dependent manners (Fig. 1 and Table 1), and may somehow reconcile the "neurogenic" and "metabolic" hypotheses of NVC. Although useful to infer neuronal activity with BOLD fMRI (Logothetis, 2008), the functional significance of NVC has been questioned (Moore and Cao, 2008; Drew, 2022). If NVC is not a response to the metabolic needs of active neurons, what other function(s) might it serve? A possible answer to this question could arise from a study showing in the rat barrel cortex that BOLD response induced by whisker stimulation was associated with the expression of c-Fos in neurons (Lu et al., 2004), an immediate early gene (IEG) whose expression correlates with neuronal activity but equally during synaptic plasticity and memory processing (Alberini, 2009). Interestingly, extracellular brain L-lactate is not only doubled following neuronal activity (Prichard et al., 1991; Hu and Wilson, 1997a) but also during training of long-term memory (Suzuki et al., 2011).

#### 4.2. Learning and memory: could L-lactate promote IEGs expression, synaptic plasticity and learning and memory?

A growing number of evidence has shown that astrocyte-derived L-lactate induces the expression of plasticity-related IEGs, and potentiates glutamatergic transmission, memory formation and/or retention (Suzuki et al., 2011; Netzahualcoyotzi and Pellerin, 2020; Zhou et al., 2021; Roumes et al., 2021b; Dembitskaya et al., 2022), identifying L-lactate as an important player of synaptic plasticity and memory. However, when uncoupled to memory formation L-lactate impaired memory retention (Zhou et al., 2021), thereby stressing the concept that its promoting effect on memory is time- and context-dependent (Suzuki et al., 2011; Zhou et al., 2021; Dembitskaya et al., 2022).

In both cultures of cortical neurons and the sensory-motor cortex of anesthetized adult mice, L-lactate induced the expression of the IEGs c-Fos, Zif268 and Arc (Yang et al., 2014). Similarly, glycogenolysis and L-lactate release induced by optogenetically-led cAMP increase in hippocampal astrocytes have promoted the neuronal expression of Arc and c-Fos (Zhou et al., 2021). Conversely, an impairment of glycogenolysis and/or ANLS, dramatically reduced the induction of Arc or c-Fos (Suzuki et al., 2011; Zhou et al., 2021). The *in vitro* and *in vivo* observations that similar concentrations of D-lactate, pyruvate or an isoenergetic concentration of glucose was inefficient at inducing IEGs expression (Yang et al., 2014) indicated that L-lactate effect was redox-sensitive and did not rely on HCAR1 or energy metabolism (Table 1). Consistently, D-lactate impaired memory retention (Suzuki et al., 2011). However, the enhancing effects of glycogen-derived L-lactate on synaptic plasticity and memory was only found to be critical for intense neuronal activity pattern and high-attention cognitive tasks, whereas less demanding forms of synaptic plasticity and memory could rely on glucose (Dembitskaya et al., 2022).

The fact that the transcriptional regulation by L-Lactate was i) dependent on NMDA receptors and its downstream Erk1/2 (*extracellular signal-regulated kinase 1/2*) signaling cascade and ii) mimicked by NADH (Yang et al., 2014), showed that NMDA receptors were the primary target (Yang et al., 2014; Jourdain et al., 2018). Along this line, the long-term potentiation underlying the promoting effect of L-lactate on memory relied on NMDA receptors (Suzuki et al., 2011; Zhou et al., 2021; Dembitskaya et al., 2022). Furthermore, the observation that the



impairment of long term potentiation by intracellular LDH inhibition was rescued by NADH but not by pyruvate, demonstrated that the effect of L-lactate was dependent on redox state and not on downstream pyruvate metabolism (Dembitskaya et al., 2022). Altogether, these findings indicated that the promoting effect of L-lactate on synaptic plasticity was primarily mediated by its action on NMDA receptors (Table 1). Nonetheless, as discussed earlier on NVC, the depolarization induced by  $K_{ATP}$  channel closure could have contributed to the effect of L-lactate by favoring the removal of the  $Mg^{2+}$  block of NMDA receptors (Nowak et al., 1984). Interestingly, the effect of L-lactate on synaptic plasticity was observed with high activity patterns (Dembitskaya et al., 2022), which notably induce intracellular ATP drops (Baeza-Lehnert et al., 2019) thereby favoring the opening of  $K_{ATP}$  channels (Tantama et al., 2013) which is essential for lactate-sensing (Sada et al., 2015; Karagiannis et al., 2021). Although, the effect of L-lactate on long term potentiation does not depend on pyruvate metabolism on (Dembitskaya et al., 2022), the use of whole-cell patch-clamp may have altered intracellular metabolism and render modulation of  $K_{ATP}$  channels ineffective.

In addition to inducing the expression of IEGs, L-lactate was also found to control adult hippocampal neurogenesis (Scandella and Knobloch, 2019; Nicola and Okun, 2021) that is key to the formation of spatial memories (Netzahualcoyotzi and Pellerin, 2020). Both adult hippocampal neurogenesis and memory formation involved the neuronal uptake of L-lactate via MCT2, but not HCAR1 (Lev-Vachnisch et al., 2019; Netzahualcoyotzi and Pellerin, 2020). Interestingly, L-lactate was also found to induce the expression of Brain Derived Neurotrophic Factor (BDNF) in neuronal cultures (Yang et al., 2014) : BDNF expression is importantly induced in the late transcriptional phase of plasticity processing (Caroni et al., 2012) as well as in neurogenesis (Lev-Vachnisch et al., 2019). The beneficial effect of physical exercise on learning and memory was also found to be mediated by blood-borne lactate and BDNF induction (El Hayek et al., 2019). It is worth noting that the production of BDNF is altered in Kir6.2 knockout mice and impaired by a  $K_{ATP}$  channel opener (Fan et al., 2016), both conditions compromising lactate-sensing. Furthermore, Kir6.2 knockout mice have an altered response to novelty (Deacon et al., 2006), which is at the basis of memories promoted by L-lactate (Zhou et al., 2021; Roumes et al., 2021b; Dembitskaya et al., 2022). Determining whether  $K_{ATP}$  channels indeed contribute to the promoting effect of L-lactate on memory would require further investigations.

## 5. Deregulation of L-lactate signaling in pathologies

In this section we will briefly report on how different mechanisms regulating neuronal excitability and activity by L-lactate are deregulated in some neurological diseases. We will first focus on two pathologies, epilepsy and stroke, in which neuronal, astroglial, metabolic and vascular deficits overlap, thereby altering the integrated functions modulated by L-lactate described in the previous sections. We will also discuss how the different mechanisms of L-lactate signaling could cooperate or oppose in pathogenesis. Finally, we will list some examples of other pathologies in which lactate dysregulation is involved.

### 5.1. Epilepsy

Brain L-lactate is dramatically increased in a rat model of status epilepticus (Slais et al., 2008).  $K_{ATP}$  channels and lactate-sensing were indeed found to be critically involved in epilepsy, and stiripentol, an antiepileptic drug, was revealed to be a LDH inhibitor (Sada et al., 2015). In addition, HCAR1 could also be involved in seizures (Briquet et al., 2022), although in an opposite manner compared to  $K_{ATP}$  channels. Whether both mechanisms co-exist and compete remains to be determined. In addition, a deleterious postictal hypoperfusion, which is used to infer the localization of seizure onset with perfusion MRI (Gaxiola-Valdez et al., 2017), was found to critically involve PGE2

derived from cyclooxygenase-2 activity and the activation of its EP1 vasoconstrictive receptor (Tran et al., 2020). Along this line plasma levels of PGE2 are elevated in epileptic patients (Rawat et al., 2020) suggesting an increased brain PGE2 synthesis. Increased parenchymal PGE2 concentration may indeed favor vasoconstriction over vasodilation by progressively recruiting the arteriolar vasoconstrictive receptor EP1 (Dabertrand et al., 2013; Czigler et al., 2020; Rosehart et al., 2021) that shows lower affinity than the EP2 and EP4 dilatory receptors of PGE2 (Boie et al., 1997; Lacroix et al., 2015; Mishra et al., 2016). In addition, an excess of PGE2 can also lead to EP4 receptor internalization (Desai et al., 2000), thereby decreasing its vasodilatory potency. As described in the NVC and MNC section, L-lactate could have contributed to PGE2 overproduction and accumulation by potentiating NMDA receptors (Yang et al., 2014; Jourdain et al., 2018), by enhancing neuronal activity via  $K_{ATP}$  channel closure (Sada et al., 2015; Karagiannis et al., 2021) and/or by impairing PGE2 clearance (Gordon et al., 2008).

### 5.2. Ischemia

Ischemia is another example of pathology in which the modulation of neuronal activity and excitability by L-lactate is involved. Indeed, L-lactate was found to be neuroprotective against ischemia at moderate levels in adult mice and neonatal rats (Berthet et al., 2009; Roumes et al., 2021a), but toxic at a higher doses (Berthet et al., 2009). This dual effect of L-lactate presumably involves opposite mechanisms in a dose-dependent manner. The beneficial effects were likely to be mediated by the activation of  $K_{ATP}$  channels (Jourdain et al., 2016; Jourdain et al., 2018) and/or HCAR1 receptor (Bozzo et al., 2013; de Castro Abrantes et al., 2019) which might have mitigated the deleterious stroke-induced energy demand through lowering neuronal excitability and/or activity. Along this line both  $K_{ATP}$  channels and HCAR1 receptor were found to be neuroprotective against ischemia (Sun et al., 2007; Castillo et al., 2015). Since pyruvate also conferred neuroprotection (Castillo et al., 2015), the beneficial effect of L-lactate could also be exerted by promoting ATP production, thereby counterbalancing stroke-induced energy shortage. On the other hand, the deleterious effects of L-lactate higher doses (Berthet et al., 2009) may involve lactate-sensing (Sada et al., 2015; Karagiannis et al., 2021), might aggravate the deleterious stroke-induced energy demand by enhancing neuronal activity.

### 5.3. Other neurological diseases involving L-lactate

L-Lactate signaling and integrated functions could also be altered in many other diseases, such as migraine with aura and its associated cortical spreading depression and hypoperfusion (Bolay et al., 2002; Schain et al., 2017), which critically involve astrocyte metabolism (Kilic et al., 2018; Smith et al., 2020), or Alzheimer's disease with its memory impairment, hyperactivity (Palop et al., 2007), hypoperfusion (Iturria-Medina et al., 2016), altered brain aerobic glycolysis (Vlaskenko et al., 2010) and astrocyte metabolism (Allaman et al., 2010).

## 6. Conclusion

In summary, L-lactate can modulate neuronal excitability and activity by acting on at least three main molecular mechanisms. While the activation by L-lactate of HCAR1 decreases neuronal activity, the modulation of NMDA receptors and  $K_{ATP}$  channels by L-lactate generally promotes neuronal activity and/or excitability (Fig. 1 and Table 1). Thus, L-lactate is able to contextually fine-tune various brain functions, depending on i) its systemic or cerebral source, the latter deriving from astrocyte glycolysis and/or glycogenolysis, ii) the relative distribution of its molecular targets across cortical areas, and iii) the level of neuronal activity. The effects of lactate rely on a delicate interplay between neurons, astrocytes, blood vessels and metabolism. The recent advances on the molecular and cellular mechanisms underlying L-lactate modulation of neuronal excitability and activity will allow to decipher how

these different mechanisms are altered in several neurological diseases. Determining how the different mechanisms of L-lactate signaling are altered in these pathologies could open new promising avenues for therapeutic targets.

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## CRedit authorship contribution statement

**Bruno Cauli:** Writing – original draft, Writing – review & editing. **Isabelle Dusart:** Writing – review & editing. **Dongdong Li:** Writing – review & editing.

## Declaration of Competing Interest

The authors declare no competing interests.

## Data availability

No data was used for the research described in the article.

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## References

- Abi-Saab, W.M., Maggs, D.G., Jones, T., Jacob, R., Srihari, V., Thompson, J., Kerr, D., Leone, P., Krystal, J.H., Spencer, D.D., Doring, M.J., Sherwin, R.S., 2002. Striking differences in glucose and lactate levels between brain extracellular fluid and plasma in conscious human subjects: effects of hyperglycemia and hypoglycemia. *J. Cereb. Blood Flow Metab.* 22, 271–279.
- Ahmed, K., Tunaru, S., Tang, C., Muller, M., Gille, A., Sassmann, A., Hanson, J., Offermanns, S., 2010. An autocrine lactate loop mediates insulin-dependent inhibition of lipolysis through GPR81. *Cell Metab.* 11, 311–319.
- Alberini, C.M., 2009. Transcription factors in long-term memory and synaptic plasticity. *Physiol. Rev.* 89, 121–145.
- Allaman, I., Gavillet, M., Belanger, M., Laroche, T., Viertl, D., Lashuel, H.A., Magistretti, P.J., 2010. Amyloid-beta aggregates cause alterations of astrocytic metabolic phenotype: impact on neuronal viability. *J. Neurosci.* 30, 3326–3338.
- Almeida, A., Almeida, J., Bolanos, J.P., Moncada, S., 2001. Different responses of astrocytes and neurons to nitric oxide: the role of glycolytically generated ATP in astrocyte protection. *Proc. Natl. Acad. Sci. U. S. A.* 98, 15294–15299.
- Andrew, R.D., MacVicar, B.A., 1994. Imaging cell volume changes and neuronal excitation in the hippocampal slice. *Neuroscience* 62, 371–383.
- Attwell, D., Laughlin, S.B., 2001. An energy budget for signaling in the grey matter of the brain. *J. Cereb. Blood Flow Metab.* 21, 1133–1145.
- Attwell, D., Buchan, A.M., Charpak, S., Lauritzen, M., MacVicar, B.A., Newman, E.A., 2010. Glial and neuronal control of brain blood flow. *Nature* 468, 232–243.
- Babenko, A.P., Aguilar-Bryan, L., Bryan, J., 1998. A view of sur/KIR6.X, KATP channels. *Annu. Rev. Physiol.* 60, 667–687.
- Baeza-Lehnert, F., Saab, A.S., Gutierrez, R., Larenas, V., Diaz, E., Horn, M., Vargas, M., Hosli, L., Stobart, J., Hirrlinger, J., Weber, B., Barros, L.F., 2019. Non-canonical control of neuronal energy status by the Na(+)-pump. *Cell Metab.* 29, 668–680.
- Bao, L., Locovei, S., Dahl, G., 2004. Pannexin membrane channels are mechanosensitive conduits for ATP. *FEBS Lett.* 572, 65–68.
- Barros, L.F., 2013. Metabolic signaling by lactate in the brain. *Trends Neurosci.* 36, 396–404.
- Barros, L.F., San, M.A., Sotelo-Hitschfeld, T., Lerchundi, R., Fernandez-Moncada, I., Ruminot, I., Gutierrez, R., Valdebenito, R., Ceballos, S., Alegria, K., Baeza-Lehnert, F., Espinoza, D., 2013. Small is fast: astrocytic glucose and lactate metabolism at cellular resolution. *Front. Cell. Neurosci.* 7, 27.
- Bergersen, L., Rafiki, A., Ottersen, O.P., 2002. Immunogold cytochemistry identifies specialized membrane domains for monocarboxylate transport in the central nervous system. *Neurochem. Res.* 27, 89–96.
- Bergersen, L.H., Magistretti, P.J., Pellerin, L., 2005. Selective postsynaptic co-localization of MCT2 with AMPA receptor GluR2/3 subunits at excitatory synapses exhibiting AMPA receptor trafficking. *Cereb. Cortex* 15, 361–370.
- Berthet, C., Lei, H., Thevenet, J., Gruetter, R., Magistretti, P.J., Hirt, L., 2009. Neuroprotective role of lactate after cerebral ischemia. *J. Cereb. Blood Flow Metab.* 29, 1780–1789.
- Bittar, P.G., Chamay, Y., Pellerin, L., Bouras, C., Magistretti, P.J., 1996. Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. *J. Cereb. Blood Flow Metab.* 16, 1079–1089.
- Bittner, C.X., Loaiza, A., Ruminot, I., Larenas, V., Sotelo-Hitschfeld, T., Gutierrez, R., Cordova, A., Valdebenito, R., Frommer, W.B., Barros, L.F., 2010. High resolution measurement of the glycolytic rate. *Front. Neuroenerg.* 2.
- Boie, Y., Stocco, R., Sawyer, N., Slipetz, D.M., Ungrin, M.D., Neuschäfer-Rube, F., Puschel, G.P., Metters, K.M., Abramovitz, M., 1997. Molecular cloning and characterization of the four rat prostaglandin E2 prostanoid receptor subtypes. *Eur. J. Pharmacol.* 340, 227–241.
- Bolay, H., Reuter, U., Dunn, A.K., Huang, Z., Boas, D.A., Moskowitz, M.A., 2002. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat. Med.* 8, 136–142.
- Bonen, A., Tonouchi, M., Miskovic, D., Heddle, C., Heikkilä, J.J., Halestrap, A.P., 2000. Isoform-specific regulation of the lactate transporters MCT1 and MCT4 by contractile activity. *Am. J. Physiol. Endocrinol. Metab.* 279, E1131–E1138.
- Bonvento, G., Bolanos, J.P., 2021. Astrocyte-neuron metabolic cooperation shapes brain activity. *Cell Metab.* 33, 1546–1564.
- Bonvento, G., Sibson, N., Pellerin, L., 2002. Does glutamate image your thoughts? *Trends Neurosci.* 25, 359–364.
- Bouzier-Sore, A.K., Voisin, P., Canioni, P., Magistretti, P.J., Pellerin, L., 2003. Lactate is a preferential oxidative energy substrate over glucose for neurons in culture. *J. Cereb. Blood Flow Metab.* 23, 1298–1306.
- Bouzier-Sore, A.K., Voisin, P., Bouchaud, V., Bezancon, E., Franconi, J.M., Pellerin, L., 2006. Competition between glucose and lactate as oxidative energy substrates in both neurons and astrocytes: a comparative NMR study. *Eur. J. Neurosci.* 24, 1687–1694.
- Bozzo, L., Puyal, J., Chatton, J.Y., 2013. Lactate modulates the activity of primary cortical neurons through a receptor-mediated pathway. *PLoS One* 8, e71721.
- Briquet, M., Rocher, A.B., Alessandri, M., Rosenberg, N., de Castro, A.H., Wellbourne-Wood, J., Schmuziger, C., Ginet, V., Puyal, J., Pralong, E., Daniel, R.T., Offermanns, S., Chatton, J.Y., 2022. Activation of lactate receptor HCAR1 downmodulates neuronal activity in rodent and human brain tissue. *J. Cereb. Blood Flow Metab.* 42, 1650–1665.
- Broer, S., Rahman, B., Pellegrini, G., Pellerin, L., Martin, J.L., Verleysdonk, S., Hamprecht, B., Magistretti, P.J., 1997. Comparison of lactate transport in astroglial cells and monocarboxylate transporter 1 (MCT 1) expressing *Xenopus laevis* oocytes. Expression of two different monocarboxylate transporters in astroglial cells and neurons. *J. Biol. Chem.* 272, 30096–30102.
- Broer, S., Schneider, H.P., Broer, A., Rahman, B., Hamprecht, B., Deitmer, J.W., 1998. Characterization of the monocarboxylate transporter 1 expressed in *Xenopus laevis* oocytes by changes in cytosolic pH. *Biochem. J.* 333 (Pt 1), 167–174.
- Broer, S., Broer, A., Schneider, H.P., Stegen, C., Halestrap, A.P., Deitmer, J.W., 1999. Characterization of the high-affinity monocarboxylate transporter MCT2 in *Xenopus laevis* oocytes. *Biochem. J.* 341 (Pt 3), 529–535.
- Brooks, G.A., 2009. Cell-cell and intracellular lactate shuttles. *J. Physiol.* 587, 5591–5600.
- Buzsáki, G., Kaila, K., Raichle, M., 2007. Inhibition and brain work. *Neuron* 56, 771–783.
- Cahoy, J.D., Emery, B., Kaushal, A., Foo, L.C., Zamanian, J.L., Christopherson, K.S., Xing, Y., Lubischer, J.L., Krieg, P.A., Krupenko, S.A., Thompson, W.J., Bares, B.A., 2008. A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. *J. Neurosci.* 28, 264–278.
- Cai, T.Q., Ren, N., Jin, L., Cheng, K., Kash, S., Chen, R., Wright, S.D., Taggart, A.K., Waters, M.G., 2008. Role of GPR81 in lactate-mediated reduction of adipose lipolysis. *Biochem. Biophys. Res. Commun.* 377, 987–991.
- Caroni, P., Donato, F., Muller, D., 2012. Structural plasticity upon learning: regulation and functions. *Nat. Rev. Neurosci.* 13, 478–490.
- Carrard, A., Elsayed, M., Margineanu, M., Boury-Jamot, B., Fragniere, L., Meylan, E.M., Petit, J.M., Fiumelli, H., Magistretti, P.J., Martin, J.L., 2018. Peripheral administration of lactate produces antidepressant-like effects. *Mol. Psychiatry* 23, 392–399.
- Castillo, X., Rosafio, K., Wyss, M.T., Drandarov, K., Buck, A., Pellerin, L., Weber, B., Hirt, L., 2015. A probable dual mode of action for both L- and D-lactate neuroprotection in cerebral ischemia. *J. Cereb. Blood Flow Metab.* 35, 1561–1569.
- de Castro Abrantes, H., Briquet, M., Schmuziger, C., Restivo, L., Puyal, J., Rosenberg, N., Rocher, A.B., Offermanns, S., Chatton, J.Y., 2019. The lactate receptor HCAR1 modulates neuronal network activity through the activation of Galpha and Gbeta subunits. *J. Neurosci.* 29, 4422–4433.
- Cauli, B., Hamel, E., 2010. Revisiting the role of neurons in neurovascular coupling. *Front. Neuroenerg.* 2, 9.
- Cauli, B., Hamel, E., 2018. Brain perfusion and astrocytes. *Trends Neurosci.* 41, 409–413.
- Cauli, B., Porter, J.T., Tsuzuki, K., Lambalez, B., Rossier, J., Quenet, B., Audinat, E., 2000. Classification of fusiform neocortical interneurons based on unsupervised clustering. *Proc. Natl. Acad. Sci. U. S. A.* 97, 6144–6149.
- Cauli, B., Tong, X.K., Rancillac, A., Serluca, N., Lambalez, B., Rossier, J., Hamel, E., 2004. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. *J. Neurosci.* 24, 8940–8949.
- Chance, B., Cohen, P., Jobsis, F., Schoener, B., 1962. Intracellular oxidation-reduction states in vivo. *Science* 137, 499–509.
- Chiry, O., Pellerin, L., Monnet-Tschudi, F., Fishbein, W.N., Merezinskaya, N., Magistretti, P.J., Clarke, S., 2006. Expression of the monocarboxylate transporter MCT1 in the adult human brain cortex. *Brain Res.* 1070, 65–70.

- Choi, H.B., Gordon, G.R., Zhou, N., Tai, C., Rungta, R.L., Martinez, J., Milner, T.A., Ryu, J.K., McLarnon, J.G., Tresguerres, M., Levin, L.R., Buck, J., MacVicar, B.A., 2012. Metabolic communication between astrocytes and neurons via bicarbonate-responsive soluble adenylyl cyclase. *Neuron* 75, 1094–1104.
- Chow, B.W., Nunez, V., Kaplan, L., Granger, A.J., Bistrong, K., Zucker, H.L., Kumar, P., Sabatini, B.L., Gu, C., 2020. Caveolae in CNS arterioles mediate neurovascular coupling. *Nature* 579, 106–110.
- Clasadonte, J., Scemes, E., Wang, Z., Boison, D., Haydon, P.G., 2017. Connexin 43-mediated astroglial metabolic networks contribute to the regulation of the sleep-wake cycle. *Neuron* 95, 1365–1380.
- Coco, M., Alagona, G., Rapisarda, G., Costanzo, E., Calogero, R.A., Perciavalle, V., Perciavalle, V., 2010. Elevated blood lactate is associated with increased motor cortex excitability. *Somatosens. Mot. Res.* 27, 1–8.
- Cori, C.F., Cori, G.T., 1929. Glycogen formation in the liver from d- and l-lactic acid. *J. Biol. Chem.* 81, 389–403.
- Cunningham, M.O., Pervouchine, D.D., Racca, C., Kopell, N.J., Davies, C.H., Jones, R.S., Traub, R.D., Whittington, M.A., 2006. Neuronal metabolism governs cortical network response state. *Proc. Natl. Acad. Sci. U. S. A.* 103, 5597–5601.
- Czigler, A., Toth, L., Szarka, N., Szilagyi, K., Kellermayer, Z., Harci, A., Vecsernyes, M., Ungvari, Z., Szolics, A., Koller, A., Buki, A., Toth, P., 2020. Prostaglandin E2, a postulated mediator of neurovascular coupling, at low concentrations dilates whereas at higher concentrations constricts human cerebral parenchymal arterioles. *Prostaglandins Other Lipid Mediat.* 146, 106389.
- Dabertrand, F., Hannah, R.M., Pearson, J.M., Hill-Eubanks, D.C., Brayden, J.E., Nelson, M.T., 2013. Prostaglandin E(2), a postulated astrocyte-derived neurovascular coupling agent, constricts rather than dilates parenchymal arterioles. *J. Cereb. Blood Flow Metab.* 33, 479–482.
- Dalsgaard, M.K., Quistorff, B., Danielsen, E.R., Selmer, C., Vogelsang, T., Secher, N.H., 2004. A reduced cerebral metabolic ratio in exercise reflects metabolism and not accumulation of lactate within the human brain. *J. Physiol.* 554, 571–578.
- Deacon, R.M., Brook, R.C., Meyer, D., Haecckel, O., Ashcroft, F.M., Miki, T., Seino, S., Liss, B., 2006. Behavioral phenotyping of mice lacking the K ATP channel subunit Kir6.2. *Physiol. Behav.* 87, 723–733.
- Dembitskaya, Y., Piette, C., Perez, S., Berry, H., Magistretti, P.J., Venance, L., 2022. Lactate supply overtakes glucose when neural computational and cognitive loads scale up. *Proc. Natl. Acad. Sci. U. S. A.* 119, e2121004119.
- Desai, S., April, H., Nwaneshiudu, C., Ashby, B., 2000. Comparison of agonist-induced internalization of the human EP2 and EP4 prostaglandin receptors: role of the carboxyl terminus in EP4 receptor sequestration. *Mol. Pharmacol.* 58, 1279–1286.
- Devor, A., Hillman, E.M., Tian, P., Waeber, C., Teng, I.C., Ruvinskaya, L., Shalinsky, M. H., Zhu, H., Haslinger, R.H., Narayanan, S.N., Ulbert, I., Dunn, A.K., Lo, E.H., Rosen, B.R., Dale, A.M., Kleinfeld, D., Boas, D.A., 2008. Stimulus-induced changes in blood flow and 2-deoxyglucose uptake dissociate in ipsilateral somatosensory cortex. *J. Neurosci.* 28, 14347–14357.
- Diaz-Garcia, C.M., Mongeon, R., Lahmann, C., Koveal, D., Zucker, H., Yellen, G., 2017. Neuronal stimulation triggers neuronal glycolysis and not lactate uptake. *Cell Metab.* 26, 361–374.
- Doyle, J.P., Dougherty, J.D., Heiman, M., Schmidt, E.F., Stevens, T.R., Ma, G., Bupp, S., Shrestha, P., Shah, R.D., Dougherty, M.L., Gong, S., Greengard, P., Heintz, N., 2008. Application of a translational profiling approach for the comparative analysis of CNS cell types. *Cell* 135, 749–762.
- Drew, P.J., 2022. Neurovascular coupling: motive unknown. *Trends Neurosci.* 45, 809–819.
- El Hayek, L., Khalifeh, M., Zibara, V., Abi, A.R., Emmanuel, N., Karnib, N., El-Ghandour, R., Nasrallah, P., Bilen, M., Ibrahim, P., Younes, J., Abou, H.E., Barmo, N., Jabre, V., Stephan, J.S., Sleiman, S.F., 2019. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). *J. Neurosci.* 39, 2369–2382.
- Ewaschuk, J.B., Naylor, J.M., Zello, G.A., 2005. D-lactate in human and ruminant metabolism. *J. Nutr.* 135, 1619–1625.
- Fan, Y., Kong, H., Ye, X., Ding, J., Hu, G., 2016. ATP-sensitive potassium channels: uncovering novel targets for treating depression. *Brain Struct. Funct.* 221, 3111–3122.
- Fox, P.T., Raichle, M.E., 1986. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc. Natl. Acad. Sci. U. S. A.* 83, 1140–1144.
- Fox, P.T., Raichle, M.E., Mintun, M.A., Dence, C., 1988. Nonoxidative glucose consumption during focal physiological neural activity. *Science* 241, 462–464.
- Gaxiola-Valdez, I., Singh, S., Perera, T., Sandy, S., Li, E., Federico, P., 2017. Seizure onset zone localization using postictal hypoperfusion detected by arterial spin labelling MRI. *Brain* 140, 2895–2911.
- Girouard, H., Bonev, A.D., Hannah, R.M., Meredith, A., Aldrich, R.W., Nelson, M.T., 2010. Astrocytic endfoot Ca2+ and BK channels determine both arteriolar dilation and constriction. *Proc. Natl. Acad. Sci. U. S. A.* 107, 3811–3816.
- Gordon, G.R., Choi, H.B., Rungta, R.L., Ellis-Davies, G.C., MacVicar, B.A., 2008. Brain metabolism dictates the polarity of astrocyte control over arterioles. *Nature* 456, 745–749.
- Gulyas, A.I., Buzsaki, G., Freund, T.F., Hirase, H., 2006. Populations of hippocampal inhibitory neurons express different levels of cytochrome c. *Eur. J. Neurosci.* 23, 2581–2594.
- Hall, M.M., Rajasekaran, S., Thomsen, T.W., Peterson, A.R., 2016. Lactate: friend or foe. *PM. R.* 8, S8–S15.
- Hayes, C., Donohoe, C.L., Davern, M., Donlon, N.E., 2021. The oncogenic and clinical implications of lactate induced immunosuppression in the tumour microenvironment. *Cancer Lett.* 500, 75–86.
- Henriksen, O., Gideon, P., Sperling, B., Olsen, T.S., Jorgensen, H.S., rlien-Soborg, P., 1992. Cerebral lactate production and blood flow in acute stroke. *J. Magn. Reson. Imaging* 2, 511–517.
- Herrera-Lopez, G., Galvan, E.J., 2018. Modulation of hippocampal excitability via the hydroxycarboxylic acid receptor 1. *Hippocampus* 28, 557–567.
- Herrero-Mendez, A., Almeida, A., Fernandez, E., Maestre, C., Moncada, S., Bolanos, J.P., 2009. The bioenergetic and antioxidant status of neurons is controlled by continuous degradation of a key glycolytic enzyme by APC/C-Cdh1. *Nat. Cell Biol.* 11, 747–752.
- Horn, T., Klein, J., 2010. Lactate levels in the brain are elevated upon exposure to volatile anesthetics: a microdialysis study. *Neurochem. Int.* 57, 940–947.
- Horn, R., Marty, A., 1988. Muscarinic activation of ionic currents measured by a new whole-cell recording method. *J. Gen. Physiol.* 92, 145–159.
- Hu, Y., Wilson, G.S., 1997a. A temporary local energy pool coupled to neuronal activity: fluctuations of extracellular lactate levels in rat brain monitored with rapid-response enzyme-based sensor. *J. Neurochem.* 69, 1484–1490.
- Hu, Y., Wilson, G.S., 1997b. Rapid changes in local extracellular rat brain glucose observed with an in vivo glucose sensor. *J. Neurochem.* 68, 1745–1752.
- Iadecola, C., 2017. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron* 96, 17–42.
- Imamura, H., Nhat, K.P., Togawa, H., Saito, K., Iino, R., Kato-Yamada, Y., Nagai, T., Noji, H., 2009. Visualization of ATP levels inside single living cells with fluorescence resonance energy transfer-based genetically encoded indicators. *Proc. Natl. Acad. Sci. U. S. A.* 106, 15651–15656.
- Itoh, Y., Esaki, T., Shimoi, K., Cook, M., Law, M.J., Kaufman, E., Sokoloff, L., 2003. Dichloroacetate effects on glucose and lactate oxidation by neurons and astroglia in vitro and on glucose utilization by brain in vivo. *Proc. Natl. Acad. Sci. U. S. A.* 100, 4879–4884.
- Iturria-Medina, Y., Sotero, R.C., Toussaint, P.J., Mateos-Perez, J.M., Evans, A.C., 2016. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat. Commun.* 7, 11934.
- Jimenez-Blasco, D., Busquets-Garcia, A., Hebert-Chatelain, E., Serrat, R., Vicente-Gutierrez, C., Ioannidou, C., Gomez-Sotres, P., Lopez-Fabuel, I., Resch-Beuscher, M., Resel, E., Arnouil, D., Saraswat, D., Varilh, M., Cannich, A., Julio-Kalajzic, F., Bonilla-Del, R., Almeida, A., Puente, N., Achicallende, S., Lopez-Rodriguez, M.L., Jolle, C., Deglon, N., Pellerin, L., Josephine, C., Bonvento, G., Panatier, A., Lutz, B., Piazza, P.V., Guzman, M., Bellocchio, L., Bouzier-Sore, A.K., Grandes, P., Bolanos, J. P., Marsicano, G., 2020. Glucose metabolism links astroglial mitochondria to cannabinoid effects. *Nature* 583, 603–608.
- Johnson, J.W., Ascher, P., 1987. Glycine potentiates the NMDA response in cultured mouse brain neurons. *Nature* 325, 529–531.
- Jourdain, P., Pavillon, N., Moratal, C., Boss, D., Rappaz, B., Depuersinge, C., Marquet, P., Magistretti, P.J., 2011. Determination of transmembrane water fluxes in neurons elicited by glutamate ionotropic receptors and by the cotransporters KCC2 and NKCC1: a digital holographic microscopy study. *J. Neurosci.* 31, 11846–11854.
- Jourdain, P., Allaman, I., Rothenfusser, K., Fiumelli, H., Marquet, P., Magistretti, P.J., 2016. L-Lactate protects neurons against excitotoxicity: implication of an ATP-mediated signaling cascade. *Sci. Rep.* 6, 21250.
- Jourdain, P., Rothenfusser, K., Ben-Adiba, C., Allaman, I., Marquet, P., Magistretti, P.J., 2018. Dual action of L-Lactate on the activity of NR2B-containing NMDA receptors: from potentiation to neuroprotection. *Sci. Rep.* 8, 13472.
- Kacem, K., Lacombe, P., Seylaz, J., Bonvento, G., 1998. Structural organization of the perivascular astrocyte endfeet and their relationship with the endothelial glucose transporter: a confocal microscopy study. *Glia* 23, 1–10.
- Kaplan, L., Chow, B.W., Gu, C., 2020. Neuronal regulation of the blood-brain barrier and neurovascular coupling. *Nat. Rev. Neurosci.* 21, 416–432.
- Karagiannis, A., Sylanteyev, S., Hadjihambi, A., Hosford, P.S., Kasparov, S., Gourine, A.V., 2016. Hemichannel-mediated release of lactate. *J. Cereb. Blood Flow Metab.* 36, 1202–1211.
- Karagiannis, A., Gallopin, T., Lacroix, A., Plaisir, F., Piquet, J., Geoffroy, H., Hepp, R., Naude, J., Le, G.B., Egger, R., Lambolez, B., Li, D., Rossier, J., Staiger, J.F., Imamura, H., Seino, S., Roeper, J., Cauli, B., 2021. Lactate is an energy substrate for rodent cortical neurons and enhances their firing activity. *Elife* 10, e71424.
- Kilic, K., Karatas, H., Donmez-Demir, B., Eren-Kocak, E., Gursoy-Ozdemir, Y., Can, A., Petit, J.M., Magistretti, P.J., Dalkara, T., 2018. Inadequate brain glycogen or sleep increases spreading depression susceptibility. *Ann. Neurol.* 83, 61–73.
- Kohr, G., Eckardt, S., Luddens, H., Monyer, H., Seeburg, P.H., 1994. NMDA receptor channels: subunit-specific potentiation by reducing agents. *Neuron* 12, 1031–1040.
- Lacroix, A., Toussay, X., Anenberg, E., Lecrux, C., Ferreiros, N., Karagiannis, A., Plaisir, F., Chausson, P., Jarlier, F., Burgess, S.A., Hillman, E.M., Tegeder, I., Murphy, T.H., Hamel, E., Cauli, B., 2015. COX-2-derived prostaglandin E2 produced by pyramidal neurons contributes to neurovascular coupling in the rodent cerebral cortex. *J. Neurosci.* 35, 11791–11810.
- Lam, T.K., Gutierrez-Juarez, R., Poca, A., Rossetti, L., 2005. Regulation of blood glucose by hypothalamic pyruvate metabolism. *Science* 309, 943–947.
- Laughton, J.D., Charnay, Y., Belloir, B., Pellerin, L., Magistretti, P.J., Bouras, C., 2000. Differential messenger RNA distribution of lactate dehydrogenase LDH-1 and LDH-5 isoforms in the rat brain. *Neuroscience* 96, 619–625.
- Lauritzen, K.H., Morland, C., Puchades, M., Holm-Hansen, S., Hagelin, E.M., Lauritzen, F., Attramadal, H., Storm-Mathisen, J., Gjedde, A., Bergersen, L.H., 2014. Lactate receptor sites link neurotransmission, neurovascular coupling, and brain energy metabolism. *Cereb. Cortex* 24, 2784–2795.
- Le Douce, J., Maugard, M., Veran, J., Matos, M., Jegou, P., Vigneron, P.A., Faivre, E., Toussay, X., Vandenbergh, M., Balbastre, Y., Piquet, J., Guiot, E., Tran, N.T., Taverna, M., Marinesco, S., Koyanagi, A., Furuya, S., Gaudin-Guerif, M., Goutal, S., Ghetta, A., Pruvost, A., Bemelmans, A.P., Gaillard, M.C., Cambon, K., Stimmer, L., Sazdovitch, V., Duyckaerts, C., Knott, G., Herard, A.S., Delzescaux, T., Hantraye, P.,

- Brouillet, E., Cauli, B., Oliet, S.H.R., Panatier, A., Bonvento, G., 2020. Impairment of glycolysis-derived l-serine production in astrocytes contributes to cognitive deficits in Alzheimer's disease. *Cell Metab.* 31, 503–517.
- Lecrux, C., Toussay, X., Kocharyan, A., Fernandes, P., Neupane, S., Levesque, M., Plaisier, F., Shmuel, A., Cauli, B., Hamel, E., 2011. Pyramidal neurons are "neurogenic hubs" in the neurovascular coupling response to whisker stimulation. *J. Neurosci.* 31, 9836–9847.
- Lee, Y., Morrison, B.M., Li, Y., Lengacher, S., Farah, M.H., Hoffman, P.N., Liu, Y., Tsingalia, A., Jin, L., Zhang, P.W., Pellerin, L., Magistretti, P.J., Rothstein, J.D., 2012. Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature* 487, 443–448.
- Lee, L., Boorman, L., Glendenning, E., Christmas, C., Sharp, P., Redgrave, P., Shabir, O., Bracci, E., Berwick, J., Howarth, C., 2020. Key aspects of neurovascular control mediated by specific populations of inhibitory cortical interneurons. *Cereb. Cortex* 30, 2452–2464.
- Lerchundi, R., Fernandez-Moncada, I., Contreras-Baeza, Y., Sotelo-Hitschfeld, T., Machler, P., Wyss, M.T., Stobart, J., Baeza-Lehnert, F., Alegria, K., Weber, B., Barros, L.F., 2015. NH4<sup>+</sup> triggers the release of astrocytic lactate via mitochondrial pyruvate shunting. *Proc. Natl. Acad. Sci. U. S. A.* 112, 11090–11095.
- Lester, R.A., Clements, J.D., Westbrook, G.L., Jahr, C.E., 1990. Channel kinetics determine the time course of NMDA receptor-mediated synaptic currents. *Nature* 346, 565–567.
- Lev-Vachnisch, Y., Cadury, S., Rotter-Maskowitz, A., Feldman, N., Roichman, A., Illouz, T., Varvak, A., Nicola, R., Madar, R., Okun, E., 2019. L-lactate promotes adult hippocampal neurogenesis. *Front. Neurosci.* 13, 403.
- Lhomme, T., Clasadonte, J., Imbernon, M., Fernadois, D., Sauve, F., Caron, E., da Silva, L.N., Heras, V., Martinez-Corral, I., Mueller-Fielitz, H., Rasika, S., Schwanger, M., Nogueiras, R., Prevot, V., 2021. Tancytic networks mediate energy balance by feeding lactate to glucose-insensitive POMC neurons. *J. Clin. Invest.* 131.
- Li, V.L., He, Y., Contrepres, K., Liu, H., Kim, J.T., Wiggenhorn, A.L., Tanzo, J.T., Tung, A. S., Lyu, X., Zushin, P.H., Jansen, R.S., Michael, B., Loh, K.Y., Yang, A.C., Carl, C.S., Voldstedlund, C.T., Wei, W., Terrell, S.M., Moeller, B.C., Arthur, R.M., Wallis, G.A., Stahl, A., Kiens, B., Richter, E.A., Banik, S.M., Snyder, M.P., Xu, Y., Long, J.Z., 2022. An exercise-inducible metabolite that suppresses feeding and obesity. *Nature* 606, 785–790.
- Lindauer, U., Leithner, C., Kaasch, H., Rohrer, B., Foddiss, M., Fuchtemeier, M., Offenhauser, N., Steinbrink, J., Royl, G., Kohl-Bareis, M., Dirnagl, U., 2010. Neurovascular coupling in rat brain operates independent of hemoglobin deoxygenation. *J. Cereb. Blood Flow Metab.* 30, 757–768.
- Liss, B., Bruns, R., Roeper, J., 1999. Alternative sulfonyleurea receptor expression defines metabolic sensitivity of K-ATP channels in dopaminergic midbrain neurons. *EMBO J.* 18, 833–846.
- Liu, C., Wu, J., Zhu, J., Kuei, C., Yu, J., Shelton, J., Sutton, S.W., Li, X., Yun, S.J., Mirzadegan, T., Mazur, C., Kamme, F., Lovenberg, T.W., 2009. Lactate inhibits lipolysis in fat cells through activation of an orphan G-protein-coupled receptor, GPR81. *J. Biol. Chem.* 284, 2811–2822.
- Liu, C., Kuei, C., Zhu, J., Yu, J., Zhang, L., Shih, A., Mirzadegan, T., Shelton, J., Sutton, S., Connelly, M.A., Lee, G., Carruthers, N., Wu, J., Lovenberg, T.W., 2012. 3, 5-Dihydroxybenzoic acid, a specific agonist for hydroxycarboxylic acid 1, inhibits lipolysis in adipocytes. *J. Pharmacol. Exp. Ther.* 341, 794–801.
- Logothetis, N.K., 2008. What we can do and what we cannot do with fMRI. *Nature* 453, 869–878.
- Longden, T.A., Dabertrand, F., Koide, M., Gonzales, A.L., Tykocki, N.R., Brayden, J.E., Hill-Eubanks, D., Nelson, M.T., 2017. Capillary K<sup>+</sup>-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow. *Nat. Neurosci.* 20, 717–726.
- Lu, H., Patel, S., Luo, F., Li, S.J., Hillard, C.J., Ward, B.D., Hyde, J.S., 2004. Spatial correlations of laminar BOLD and CBV responses to rat whisker stimulation with neuronal activity localized by fBx expression. *Magn. Reson. Med.* 52, 1060–1068.
- MacDermott, A.B., Mayer, M.L., Westbrook, G.L., Smith, S.J., Barker, J.L., 1986. NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones. *Nature* 321, 519–522.
- Machler, P., Wyss, M.T., Elsayed, M., Stobart, J., Gutierrez, R., von Faber-Castell, A., Kaelin, V., Zuend, M., San, M.A., Romero-Gomez, I., Baeza-Lehnert, F., Lengacher, S., Schneider, B.L., Aebischer, P., Magistretti, P.J., Barros, L.F., Weber, B., 2016. In vivo evidence for a lactate gradient from astrocytes to neurons. *Cell Metab.* 23, 94–102.
- Magistretti, P.J., Allaman, I., 2018. Lactate in the brain: from metabolic end-product to signalling molecule. *Nat. Rev. Neurosci.* 19, 235–249.
- Manning Fox, J.E., Meredith, D., Halestrap, A.P., 2000. Characterisation of human monocarboxylate transporter 4 substantiates its role in lactic acid efflux from skeletal muscle. *J. Physiol.* 529 (Pt 2), 285–293.
- McEwen, B.S., Reagan, L.P., 2004. Glucose transporter expression in the central nervous system: relationship to synaptic function. *Eur. J. Pharmacol.* 490, 13–24.
- McIlwain, H., 1953. Substances which support respiration and metabolic response to electrical impulses in human cerebral tissues. *J. Neurol. Neurosurg. Psychiatry* 16, 257–266.
- Medel, V., Crossley, N., Gajardo, I., Muller, E., Barros, L.F., Shine, J.M., Sieralta, J., 2022. Whole-brain neuronal MCT2 lactate transporter expression links metabolism to human brain structure and function. *Proc. Natl. Acad. Sci. U. S. A.* 119, e2204619119.
- Mintun, M.A., Lundstrom, B.N., Snyder, A.Z., Vlassenko, A.G., Shulman, G.L., Raichle, M. E., 2001. Blood flow and oxygen delivery to human brain during functional activity: theoretical modeling and experimental data. *Proc. Natl. Acad. Sci. U. S. A.* 98, 6859–6864.
- Mintun, M.A., Vlassenko, A.G., Rundle, M.M., Raichle, M.E., 2004. Increased lactate/pyruvate ratio augments blood flow in physiologically activated human brain. *Proc. Natl. Acad. Sci. U. S. A.* 101, 659–664.
- Mirshamsi, S., Laidlaw, H.A., Ning, K., Anderson, E., Burgess, L.A., Gray, A., Sutherland, C., Ashford, M.L., 2004. Leptin and insulin stimulation of signalling pathways in arcuate nucleus neurones: PI3K dependent actin reorganization and KATP channel activation. *BMC Neurosci.* 5, 54.
- Mishra, A., Reynolds, J.P., Chen, Y., Gourine, A.V., Rusakov, D.A., Attwell, D., 2016. Astrocytes mediate neurovascular signaling to capillary pericytes but not to arterioles. *Nat. Neurosci.* 19, 1619–1627.
- Molnar, G., Farago, N., Kocsis, A.K., Rozsa, M., Lovas, S., Boldog, E., Baldi, R., Csajbok, E., Gardi, J., Puskas, L.G., Tamas, G., 2014. GABAergic neurogliaform cells represent local sources of insulin in the cerebral cortex. *J. Neurosci.* 34, 1133–1137.
- Monyer, H., Burnashev, N., Laurie, D.J., Sakmann, B., Seeburg, P.H., 1994. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron* 12, 529–540.
- Moore, C.I., Cao, R., 2008. The hemo-neural hypothesis: on the role of blood flow in information processing. *J. Neurophysiol.* 99, 2035–2047.
- Moreau, C., Prost, A.L., Derand, R., Vivaudou, M., 2005. SUR, ABC proteins targeted by KATP channel openers. *J. Mol. Cell. Cardiol.* 38, 951–963.
- Morland, C., Andersson, K.A., Haugen, O.P., Hadzic, A., Kleppa, L., Gille, A., Rinholm, J. E., Palibrk, V., Diget, E.H., Kennedy, L.H., Stolen, T., Hennestad, E., Moldestad, O., Cai, Y., Puchades, M., Offermanns, S., Vervaeke, K., Bjoras, M., Wisloff, U., Storm-Mathisen, J., Bergersen, L.H., 2017. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCARI1. *Nat. Commun.* 8, 15557.
- Mothet, J.P., Parent, A.T., Wolosker, H., Brady Jr., R.O., Linden, D.J., Ferris, C.D., Rogawski, M.A., Snyder, S.H., 2000. D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. *Proc. Natl. Acad. Sci. U. S. A.* 97, 4926–4931.
- Nedergaard, M., Goldman, S.A., 1993. Carrier-mediated transport of lactic acid in cultured neurons and astrocytes. *Am. J. Phys.* 265, R282–R289.
- Netzahualcoyotzi, C., Pellerin, L., 2020. Neuronal and astroglial monocarboxylate transporters play key but distinct roles in hippocampus-dependent learning and memory formation. *Prog. Neurobiol.* 194, 101888.
- Nicola, R., Okun, E., 2021. Adult hippocampal neurogenesis: one lactate to rule them all. *NeuroMolecular Med.* 23, 445–448.
- Niwa, K., Araki, E., Morham, S.G., Ross, M.E., Iadecola, C., 2000. Cyclooxygenase-2 contributes to functional hyperemia in whisker-barrel cortex. *J. Neurosci.* 20, 763–770.
- Nowak, L., Bregestovski, P., Ascher, P., Herbet, A., Prochiantz, A., 1984. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* 307, 462–465.
- Oesper, R.E., 1931. The collected papers of Carl Wilhelm Scheele. *J. Chem. Educ.* 8, 2304.
- Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc. Natl. Acad. Sci. U. S. A.* 87, 9868–9872.
- Palop, J.J., Chin, J., Roberson, E.D., Wang, J., Thwin, M.T., Bien-Ly, N., Yoo, J., Ho, K.O., Yu, G.Q., Kreitzer, A., Finkbeiner, S., Noebels, J.L., Mucke, L., 2007. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron* 55, 697–711.
- Paoletti, P., Bellone, C., Zhou, Q., 2013. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci.* 14, 383–400.
- Pellerin, L., Magistretti, P.J., 1994. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proc. Natl. Acad. Sci. U. S. A.* 91, 10625–10629.
- Pellerin, L., Bergersen, L.H., Halestrap, A.P., Pierre, K., 2005. Cellular and subcellular distribution of monocarboxylate transporters in cultured brain cells and in the adult brain. *J. Neurosci. Res.* 79, 55–64.
- Pierre, K., Pellerin, L., 2005. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. *J. Neurochem.* 94, 1–14.
- Pierre, K., Parent, A., Jayet, P.Y., Halestrap, A.P., Scherrer, U., Pellerin, L., 2007. Enhanced expression of three monocarboxylate transporter isoforms in the brain of obese mice. *J. Physiol.* 583, 469–486.
- Piquet, J., Toussay, X., Hepp, R., Lerchundi, R., Le, D.J., Faivre, E., Guiot, E., Bonvento, G., Cauli, B., 2018. Supragranular pyramidal cells exhibit early metabolic alterations in the 3xTg-AD mouse model of Alzheimer's disease. *Front. Cell. Neurosci.* 12, 216.
- Plum, L., Ma, X., Hampel, B., Balthasar, N., Coppari, R., Münzberg, H., Shanabrough, M., Burdakov, D., Rother, E., Janoschek, R., Alber, J., Belgardt, B.F., Koch, L., Seibler, J., Schwenk, F., Fekete, C., Suzuki, A., Mak, T.W., Krone, W., Horvath, T.L., Ashcroft, F. M., Bruning, J.C., 2006. Enhanced PIP3 signaling in POMC neurons causes KATP channel activation and leads to diet-sensitive obesity. *J. Clin. Invest.* 116, 1886–1901.
- Prichard, J., Rothman, D., Novotny, E., Petroff, O., Kuwabara, T., Avison, M., Howseman, A., Hanstock, C., Shulman, R., 1991. Lactate rise detected by 1H NMR in human visual cortex during physiologic stimulation. *Proc. Natl. Acad. Sci. U. S. A.* 88, 5829–5831.
- Priestley, T., Laughton, P., Myers, J., Le, B.B., Kerby, J., Whiting, P.J., 1995. Pharmacological properties of recombinant human N-methyl-D-aspartate receptors comprising NR1a/NR2A and NR1a/NR2B subunit assemblies expressed in permanently transfected mouse fibroblast cells. *Mol. Pharmacol.* 48, 841–848.
- Puljung, M.C., 2018. Cryo-electron microscopy structures and progress toward a dynamic understanding of KATP channels. *J. Gen. Physiol.* 150, 653–669.

- Rafiki, A., Boulland, J.L., Halestrap, A.P., Ottersen, O.P., Bergersen, L., 2003. Highly differential expression of the monocarboxylate transporters MCT2 and MCT4 in the developing rat brain. *Neuroscience* 122, 677–688.
- Rawat, C., Shivangi, Kushwaha, S., Sharma, S., Srivastava, A.K., Kukreti, R., 2020. Altered plasma prostaglandin E2 levels in epilepsy and in response to antiepileptic drug monotherapy. *Prostaglandins Leukot. Essent. Fatty Acids* 153, 102056.
- Regard, J.B., Sato, I.T., Coughlin, S.R., 2008. Anatomical profiling of G protein-coupled receptor expression. *Cell* 135, 561–571.
- Rosafio, K., Castillo, X., Hirt, L., Pellerin, L., 2016. Cell-specific modulation of monocarboxylate transporter expression contributes to the metabolic reprogramming taking place following cerebral ischemia. *Neuroscience* 317, 108–120.
- Rosehart, A.C., Longden, T.A., Weir, N., Fontaine, J.T., Joutel, A., Dabertrand, F., 2021. Prostaglandin E2 dilates intracerebral arterioles when applied to capillaries: implications for small vessel diseases. *Front. Aging Neurosci.* 13, 695965.
- Rouach, N., Koulakoff, A., Abudara, V., Willecke, K., Giaume, C., 2008. Astroglial metabolic networks sustain hippocampal synaptic transmission. *Science* 322, 1551–1555.
- Roumes, H., Dumont, U., Sanchez, S., Mazuel, L., Blanc, J., Raffard, G., Chateil, J.F., Pellerin, L., Bouzier-Sore, A.K., 2021a. Neuroprotective role of lactate in rat neonatal hypoxia-ischemia. *J. Cereb. Blood Flow Metab.* 41, 342–358.
- Roumes, H., Jolle, C., Blanc, J., Benkhaled, I., Chatain, C.P., Massot, P., Raffard, G., Bouchaud, V., Biran, M., Pythoud, C., Deglon, N., Zimmer, E.R., Pellerin, L., Bouzier-Sore, A.K., 2021b. Lactate transporters in the rat barrel cortex sustain whisker-dependent BOLD fMRI signal and behavioral performance. *Proc. Natl. Acad. Sci. U. S. A.* 118.
- Roy, C.S., Sherrington, C.S., 1890. On the regulation of the blood-supply of the brain. *J. Physiol.* 11, 85–158.
- Ruminot, I., Gutierrez, R., Pena-Munzenmayer, G., Anazco, C., Sotelo-Hitschfeld, T., Lerchundi, R., Niemeyer, M.I., Shull, G.E., Barros, L.F., 2011. NBCE1 mediates the acute stimulation of astrocytic glycolysis by extracellular K<sup>+</sup>. *J. Neurosci.* 31, 14264–14271.
- Rungta, R.L., Zuend, M., Aydin, A.K., Martineau, E., Boido, D., Weber, B., Charpak, S., 2021. Diversity of neurovascular coupling dynamics along vascular arbors in layer II/III somatosensory cortex. *Commun. Biol.* 4, 855.
- Sada, N., Lee, S., Katsu, T., Otsuki, T., Inoue, T., 2015. Epilepsy treatment. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. *Science* 347, 1362–1367.
- Sang, N., Zhang, J., Marcheselli, V., Bazan, N.G., Chen, C., 2005. Postsynaptically synthesized prostaglandin E2 (PGE2) modulates hippocampal synaptic transmission via a presynaptic PGE2 EP2 receptor. *J. Neurosci.* 25, 9858–9870.
- Scandella, V., Knobloch, M., 2019. Sensing the environment: extracellular lactate levels control adult neurogenesis. *Cell Stem Cell* 25, 729–731.
- Schaeffer, S., Iadecola, C., 2021. Revisiting the neurovascular unit. *Nat. Neurosci.* 24, 1198–1209.
- Schain, A.J., Melo-Carrillo, A., Strassman, A.M., Burstein, R., 2017. Cortical spreading depression closes paravascular space and impairs glymphatic flow: implications for migraine headache. *J. Neurosci.* 37, 2904–2915.
- Schurr, A., 2014. Cerebral glycolysis: a century of persistent misunderstanding and misconception. *Front. Neurosci.* 8, 360.
- Schurr, A., West, C.A., Rigor, B.M., 1988. Lactate-supported synaptic function in the rat hippocampal slice preparation. *Science* 240, 1326–1328.
- Schurr, A., Miller, J.J., Payne, R.S., Rigor, B.M., 1999. An increase in lactate output by brain tissue serves to meet the energy needs of glutamate-activated neurons. *J. Neurosci.* 19, 34–39.
- Silver, I.A., Erecinska, M., 1994. Extracellular glucose concentration in mammalian brain: continuous monitoring of changes during increased neuronal activity and upon limitation in oxygen supply in normo-, hypo-, and hyperglycemic animals. *J. Neurosci.* 14, 5068–5076.
- Slais, K., Vorisek, I., Zoremba, N., Homola, A., Dmytrenko, L., Sykova, E., 2008. Brain metabolism and diffusion in the rat cerebral cortex during pilocarpine-induced status epilepticus. *Exp. Neurol.* 209, 145–154.
- Smith, S.E., Chen, X., Brier, L.M., Bumstead, J.R., Rensing, N.R., Ringel, A.E., Shin, H., Oldenborg, A., Crowley, J.R., Bice, A.R., Dikranian, K., Ippolito, J.E., Haigis, M.C., Papouin, T., Zhao, G., Wong, M., Culver, J.P., Bonni, A., 2020. Astrocyte deletion of alpha2-Na/K ATPase triggers episodic motor paralysis in mice via a metabolic pathway. *Nat. Commun.* 11, 6164.
- Sorg, O., Magistretti, P.J., 1991. Characterization of the glycogenolysis elicited by vasoactive intestinal peptide, noradrenaline and adenosine in primary cultures of mouse cerebral cortical astrocytes. *Brain Res.* 563, 227–233.
- Sotelo-Hitschfeld, T., Niemeyer, M.I., Machler, P., Ruminot, I., Lerchundi, R., Wyss, M.T., Stobart, J., Fernandez-Moncada, I., Valdebenito, R., Garrido-Gerter, P., Contreras-Baeza, Y., Schneider, B.L., Aebischer, P., Lengacher, S., San, M.A., Le, D.J., Bonvento, G., Magistretti, P.J., Sepulveda, F.V., Weber, B., Barros, L.F., 2015. Channel-mediated lactate release by K<sup>+</sup>-stimulated astrocytes. *J. Neurosci.* 35, 4168–4178.
- Soundarapandian, M.M., Zhong, X., Peng, L., Wu, D., Lu, Y., 2007. Role of K(ATP) channels in protection against neuronal excitatory insults. *J. Neurochem.* 103, 1721–1729.
- Sullivan, J.M., Traynelis, S.F., Chen, H.S., Escobar, W., Heinemann, S.F., Lipton, S.A., 1994. Identification of two cysteine residues that are required for redox modulation of the NMDA subtype of glutamate receptor. *Neuron* 13, 929–936.
- Sun, H.S., Feng, Z.P., Barber, P.A., Buchan, A.M., French, R.J., 2007. Kir6.2-containing ATP-sensitive potassium channels protect cortical neurons from ischemic/anoxic injury in vitro and in vivo. *Neuroscience* 144, 1509–1515.
- Suzuki, A., Stern, S.A., Bozdagi, O., Huntley, G.W., Walker, R.H., Magistretti, P.J., Alberini, C.M., 2011. Astrocyte-neuron lactate transport is required for long-term memory formation. *Cell* 144, 810–823.
- Tanner, G.R., Lutas, A., Martinez-Francois, J.R., Yellen, G., 2011. Single K ATP channel opening in response to action potential firing in mouse dentate granule neurons. *J. Neurosci.* 31, 8689–8696.
- Tantama, M., Martinez-Francois, J.R., Mongeon, R., Yellen, G., 2013. Imaging energy status in live cells with a fluorescent biosensor of the intracellular ATP-to-ADP ratio. *Nat. Commun.* 4, 2550.
- Tasic, B., Menon, V., Nguyen, T.N., Kim, T.K., Jarsky, T., Yao, Z., Levi, B., Gray, L.T., Sorensen, S.A., Dolbeare, T., Bertagnoli, D., Goldy, J., Shapovalova, N., Parry, S., Lee, C., Smith, K., Bernard, A., Madisen, L., Sunkin, S.M., Hawrylycz, M., Koch, C., Zeng, H., 2016. Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nat. Neurosci.* 19, 335–346.
- Toloe, J., Mollajew, R., Kugler, S., Mironov, S.L., 2014. Metabolic differences in hippocampal 'Rett' neurons revealed by ATP imaging. *Mol. Cell Neurosci.* 59, 47–56.
- Tran, C.H.T., George, A.G., Teskey, G.C., Gordon, G.R., 2020. Seizures elevate gliovascular unit Ca<sup>2+</sup> and cause sustained vasoconstriction. *JCI Insight* 5.
- Uhlirova, H., Kilic, K., Tian, P., Thunemann, M., Desjardins, M., Saisan, P.A., Sakadzic, S., Ness, T.V., Mateo, C., Cheng, Q., Weldy, K.L., Razoux, F., Vanderberghe, M., Cremonesi, J.A., Ferri, C.G., Nizar, K., Sridhar, V.B., Steed, T.C., Abashin, M., Fainman, Y., Masliah, E., Djurovic, S., Andreassen, O., Silva, G.A., Boas, D.A., Kleinfeld, D., Buxton, R.B., Einevoll, G.T., Dale, A.M., Devor, A., 2016. Cell type specificity of neurovascular coupling in cerebral cortex. *Elife* 5, e14315.
- Vaishnavi, S.N., Vlassenko, A.G., Rundle, M.M., Snyder, A.Z., Mintun, M.A., Raichle, M.E., 2010. Regional aerobic glycolysis in the human brain. *Proc. Natl. Acad. Sci. U. S. A.* 107, 17757–17762.
- Vander Heiden, M.G., Cantley, L.C., Thompson, C.B., 2009. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324, 1029–1033.
- Vaughn, A.E., Deshmukh, M., 2008. Glucose metabolism inhibits apoptosis in neurons and cancer cells by redox inactivation of cytochrome c. *Nat. Cell Biol.* 10, 1477–1483.
- Vlassenko, A.G., Rundle, M.M., Raichle, M.E., Mintun, M.A., 2006. Regulation of blood flow in activated human brain by cytosolic NADH/NAD<sup>+</sup> ratio. *Proc. Natl. Acad. Sci. U. S. A.* 103, 1964–1969.
- Vlassenko, A.G., Vaishnavi, S.N., Couture, L., Sacco, D., Shannon, B.J., Mach, R.H., Morris, J.C., Raichle, M.E., Mintun, M.A., 2010. Spatial correlation between brain aerobic glycolysis and amyloid-(beta) (A(beta)) deposition. *Proc. Natl. Acad. Sci. U. S. A.* 107, 17763–17767.
- Voutsinos-Porche, B., Bonvento, G., Tanaka, K., Steiner, P., Welker, E., Chatton, J.Y., Magistretti, P.J., Pellerin, L., 2003. Glial glutamate transporters mediate a functional metabolic crosstalk between neurons and astrocytes in the mouse developing cortex. *Neuron* 37, 275–286.
- Warburg, O., Wind, F., Negelein, E., 1927. The metabolism of tumors in the body. *J. Gen. Physiol.* 8, 519–530.
- Whyte-Fagundes, P., Zoidl, G., 2018. Mechanisms of pannexin1 channel gating and regulation. *Biochim. Biophys. Acta Biomembr.* 1860, 65–71.
- Williamson, D.H., Lund, P., Krebs, H.A., 1967. The redox state of free nicotinamide-adenine dinucleotide in the cytoplasm and mitochondria of rat liver. *Biochem. J.* 103, 514–527.
- Wilson, J.E., 2003. Isozymes of mammalian hexokinase: structure, subcellular localization and metabolic function. *J. Exp. Biol.* 206, 2049–2057.
- Wolf, T., Lindauer, U., Villringer, A., Dirnagl, U., 1997. Excessive oxygen or glucose supply does not alter the blood flow response to somatosensory stimulation or spreading depression in rats. *Brain Res.* 761, 290–299.
- Yang, J., Rucht, E., Petit, J.M., Jourdain, P., Grenningloh, G., Allaman, I., Magistretti, P.J., 2014. Lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons. *Proc. Natl. Acad. Sci. U. S. A.* 111, 12228–12233.
- Yao, S., Xu, M.D., Wang, Y., Zhao, S.T., Wang, J., Chen, G.F., Chen, W.B., Liu, J., Huang, G.B., Sun, W.J., Zhang, Y.Y., Hou, H.L., Li, L., Sun, X.D., 2023. Astrocytic lactate dehydrogenase A regulates neuronal excitability and depressive-like behaviors through lactate homeostasis in mice. *Nat. Commun.* 14, 729.
- Zawar, C., Neumcke, B., 2000. Differential activation of ATP-sensitive potassium channels during energy depletion in CA1 pyramidal cells and interneurons of rat hippocampus. *Pflügers Arch.* 439, 256–262.
- Zawar, C., Plant, T.D., Schirra, C., Konnerth, A., Neumcke, B., 1999. Cell-type specific expression of ATP-sensitive potassium channels in the rat hippocampus. *J. Physiol.* 514 (Pt 2), 327–341.
- Zeisel, A., Machado, A.B., Codeluppi, S., Lonnerberg, P., La, M.G., Jureus, A., Marques, S., Munguba, H., He, L., Betsholtz, C., Rolny, C., Castelo-Branco, G., Hjerling-Leffler, J., Linnarsson, S., 2015. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. *Science* 347, 1138–1142.
- Zhang, Q., Roche, M., Gheres, K.W., Chaigneau, E., Kedarasetti, R.T., Haselden, W.D., Charpak, S., Drew, P.J., 2019. Cerebral oxygenation during locomotion is modulated by respiration. *Nat. Commun.* 10, 5515.
- Zhou, N., Gordon, G.R., Feighan, D., MacVicar, B.A., 2010. Transient swelling, acidification, and mitochondrial depolarization occurs in neurons but not astrocytes during spreading depression. *Cereb. Cortex* 20, 2614–2624.
- Zhou, Z., Okamoto, K., Onodera, J., Hiragi, T., Andoh, M., Ikawa, M., Tanaka, K.F., Ikegaya, Y., Koyama, R., 2021. Astrocytic cAMP modulates memory via synaptic plasticity. *Proc. Natl. Acad. Sci. U. S. A.* 118, e2016584118.
- Zilberter, Y., Zilberter, T., Bregestovski, P., 2010. Neuronal activity in vitro and the in vivo reality: the role of energy homeostasis. *Trends Pharmacol. Sci.* 31, 394–401.
- Zlokovic, B.V., 2008. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* 57, 178–201.
- Zuend, M., Saab, A.S., Wyss, M.T., Ferrari, K.D., Hosli, L., Looser, J.Z., Stobart, J.L., Duran, J., Guinovart, J.J., Barros, L.F., Weber, B., 2020. Arousal-induced cortical activity triggers lactate release from astrocytes. *Nat. Metab.* 2, 179–191.