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Lactate metabolism and histone lactylation in the central nervous system disorders: impacts and molecular mechanisms

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Abstract

Brain takes up approximately 20% of the total body oxygen and glucose consumption due to its relatively high energy demand. Glucose is one of the major sources to generate ATP, the process of which can be realized via glycolysis, oxidative phosphorylation, pentose phosphate pathways and others. Lactate serves as a hub molecule amid these metabolic pathways, as it may function as product of glycolysis, substrate of a variety of enzymes and signal molecule. Thus, the roles of lactate in central nervous system (CNS) diseases need to be comprehensively elucidated. Histone lactylation is a novel lactate-dependent epigenetic modification that plays an important role in immune regulation and maintaining homeostasis. However, there's still a lack of studies unveiling the functions of histone lactylation in the CNS. In this review, we first comprehensively reviewed the roles lactate plays in the CNS under both physiological and pathological conditions. Subsequently, we've further discussed the functions of histone lactylation in various neurological diseases. Furthermore, future perspectives regarding histone lactylation and its therapeutic potentials in stroke are also elucidated, which may possess potential clinical applications.

Keywords Lactate, Histone lactylation, CNS diseases, Inflammation

Introduction

Brain is an organ with high demand of energy in the body due to complex activities in the CNS. Representing only 2% of the body weight, however, brain consumes 20% of the resting total body O_2 consumption and glucose [1, 2]. Moreover, continuous energy supply of ATP is needed for brain given the lack of sufficient energy reserve [1, 3].

Glucose serves as the main source of ATP in the CNS, which fuels 95% of ATP in the brain [3]. In the CNS, glucose can be processed in the following ways: oxidative phosphorylation (OXPHOS) and glycolysis for ATP generation, pentose phosphate pathway for anabolic and antioxidant reactions as well as glycogenesis for energy storage [4–6]. For ATP supply, glucose is first converted into Glucose-6-Phosphate via hexokinase. After a serious of enzymic reactions, pyruvate is generated. This process is termed glycolysis, in which two ATP molecules are generated (Fig. 1). Pyruvate is then converted to acetyl coenzyme A (acetyl-CoA), which undergoes tricarboxylic acid (TCA) cycle and OXPHOS in mitochondria, generating 30–36 ATP molecules eventually. Alternatively, under hypoxia/anoxia or in specific cell types, pyruvate is transformed into lactate via lactate dehydrogenase

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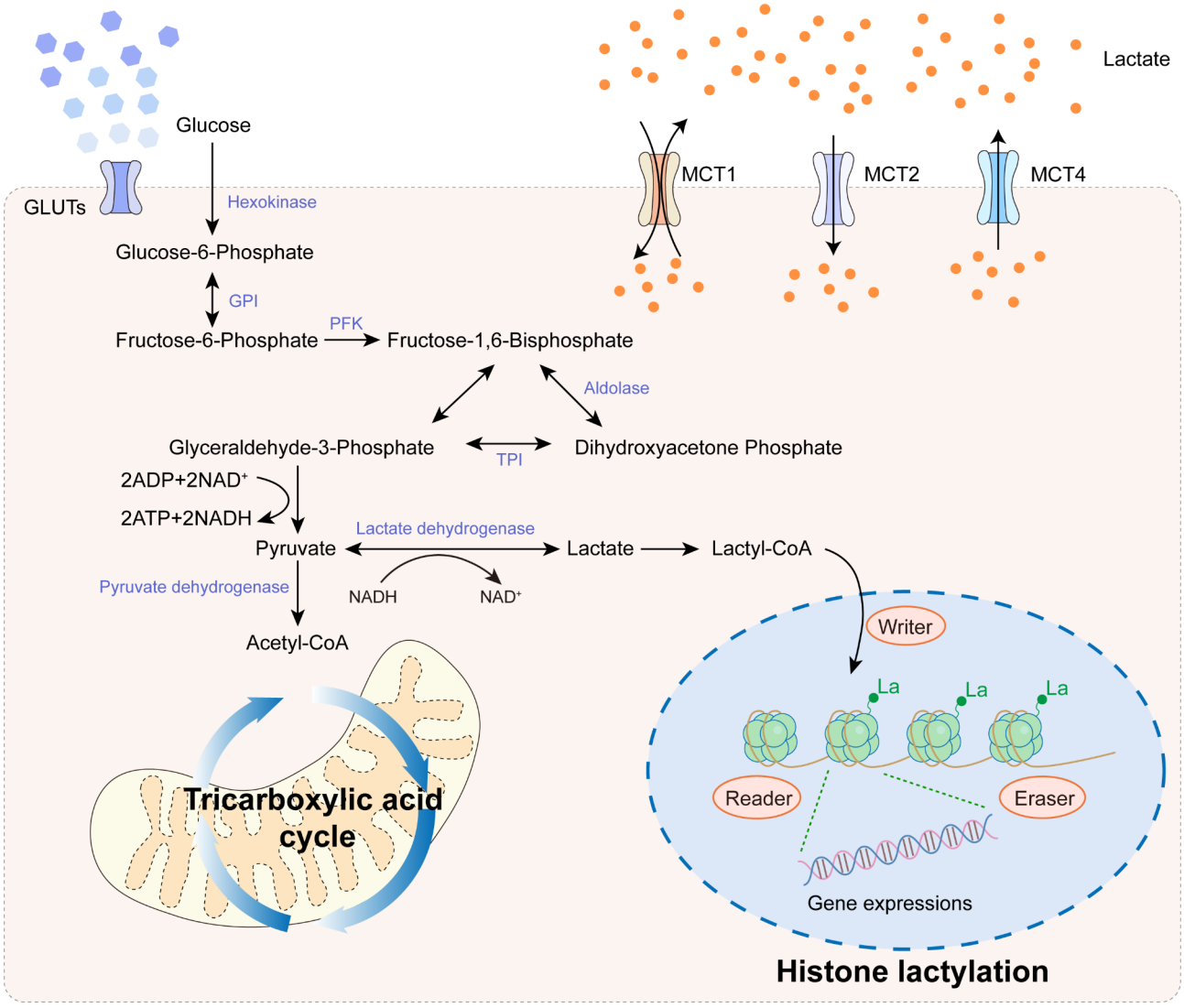

Fig. 1 The process of lactate metabolism and histone lactylation. For ATP generation, glucose can be processed in both OXPHOS and glycolysis. Firstly, glucose is transported into cells by glucose transporters (GLUTs) and metabolized into Glucose-6-Phosphate via hexokinase. After a serious of enzymatic reactions, Glucose-6-Phosphate is transformed to pyruvate, which is further transformed into acetyl-CoA via pyruvate dehydrogenase to fuel TCA or into lactate as the end-product of glycolysis via lactate dehydrogenase. Besides, lactate can be transported by multiple monocarboxylate transporters (MCTs) on cell membrane. In histone lactylation, lactate is firstly transformed into lactyl-CoA, which enters nucleus and adds lactyl group to lysine residues of histones. Diverse enzymes, known as writers, erasers and readers, are involved in this process. Notably, by being enriched in the promoter region of target genes, histone lactylation has been proved to participate in regulating gene expressions of cells. GPI: glucose-6-phosphate isomerase; PFK: phosphofructokinase; TPI: triose phosphate isomerase

(LDH), accompanied by generation of only 2 ATP molecules (Fig. 1) [3]. In normal conditions, OXPHOS is utilized for sustained and sufficient ATP production in the brain [3]. However, under certain circumstances, such as functional activation or facing acute stimuli in the brain, even when the oxygen supply is abundant, glucose could also be converted into lactate for rapid ATP generation. This process is termed aerobic glycolysis, also known as Warburg effect, which was first observed in cancer cells [6–8]. Another important function of glycolysis is to generate intermediates for anabolic reactions in the body including biosynthesis of nucleotide, lipid and amino acids [9].

Lactate, as the end-product of glycolysis, has been considered as a waste product in metabolism in the past. However, recently lactate has been proven to participate in energy supplementation and signal transmission, thus playing an important role in the regulation of brain function. In CNS, lactate has been viewed as an energy substrate and maybe the preferred substrate in neurons under aerobic conditions [1, 4]. Lactate taken up by neurons is able to be converted into pyruvate via LDH1,

which fuels into TCA cycle and OXPHOS to supply ATP for neurons, and this process is especially active during neuronal activities [10]. Moreover, lactate may serve as the substrate of histone lactylation, a newly defined post-translational modification (PTM). Histone lactylation was first found by Zhang et al. in macrophages exposed to hypoxia and bacterial stimulation [11]. PTMs of histones are common epigenetic changes which can regulate the transcription of target genes by altering the structure of chromosomes [12]. There are various kinds of PTMs, including methylation, phosphorylation, acetylation, glycosylation, ubiquitination and so on. Similar to the aforementioned PTMs, recent studies have found that histone lactylation participates in regulating the expressions of various genes in diversified types of cells and shed new light on therapeutics in multiple diseases [13].

In this review, we aimed to elaborate the functions of lactate/histone lactylation in pathophysiological conditions in CNS. We firstly detailed lactate metabolism in CNS and the roles of lactate in physiological and pathological circumstances in CNS. Thereafter, we discussed the process and functions of histone lactylation in various neurological diseases. At last, we elucidated the future perspectives regarding histone lactylation and its therapeutic potentials in stroke.

Lactate metabolism in neurons and glia in CNS

The metabolism patterns of glucose differ between neurons and glia in CNS, which may be ascribed by the discrepancies in mitochondria, expressions of metabolic enzymes and monocarboxylate transporters (MCTs) in these cells [2, 10].

Structure and action mechanism of MCTs

MCTs contains 14 protein members, which are encoded by the *SLC16A* genes family [14]. Among these MCTs, MCTs1-4 have been identified to transport monocarboxylates in humans [15]. MCTs possess highly conserved motifs and consist of 12 transmembrane helices with intracellular C- and N-termini, among which there's a large cytosolic loop between helices 6 and 7 (Fig. 2) [14]. MCTs are lactate-H^+ symporters. The molecular mechanism of lactate transport has been depicted in MCT1 [16]. In short, MCT1 is predicted to contain two different states. In the "outside-open" conformation, proton can bind to the uncharged lysine, thereafter leading to a binding site available for monocarboxylate anion to form an ionic pair. Then the lactate and proton are transported to intracellular binding sites and an "inside-open" status starts, during which period lactate and proton can be released into cytoplasm (Fig. 2) [14, 16]. Therefore, both the concentration gradients of monocarboxylate ions and protons between inside and outside of cells will have an influence on transport directions of MCTs [17].

In the CNS, MCTs are responsible for lactate transport, which are differentially expressed between neurons and glia (Fig. 2), more details are discussed below [18]. Previous studies have indicated the correlations between MCTs and glucose metabolism. MCT1 inhibition decreased lactate production under hypoxia in glioma cells [19]. Similarly, MCT1 silencing effectively reversed the increased lactate levels in macrophages under hypoxia, accompanied by downregulating histone lactylation levels too [20]. However, there exists some different opinions. MCT1 inhibition by AZD3965 was found to increase glycolysis and glycolytic enzymes in tumor cells, while Lopez et al. observed that MCT1 blockade increased mitochondrial metabolism in CAR T cells [21, 22]. On the other hand, Blaszczak et al. pointed out that MCT activity was irrelevant with lactic acid production, as MCT inhibitors cannot impede lactic acid production in cells [23]. In turn, lactate levels also have an impact on MCTs expressions, which may differ among different MCTs. Increased extracellular lactate after exercise has been reported to induce MCT1 mRNA and protein expressions probably via reactive oxygen species (ROS) generation [24, 25]. However, in another study, Sangsuwan et al. found that lactate upregulated MCT4 while downregulated MCT1/2 gene expressions in vitro [26]. Overall, the relationship between lactate metabolism and MCTs expressions seems to be conflicted and needs further investigation.

Lactate metabolism in astrocytes and neurons

In CNS, astrocytes rely mainly on glycolysis while neurons rely predominantly on OXPHOS for energy supply [1]. Accumulating evidence has suggested that astrocytes serve as the major source of lactate in CNS [27]. The discrepancy of metabolism profiles between neurons and glia was first revealed in 1960s. Hyden et al. first found that the capacity of electron transporting system was increased after stimulation in neurons, whereas it was not altered in glia [28]. The differences in metabolism regulation between neurons and glia under vestibular stimulation were further confirmed by Hamberger et al., who observed upregulated activities of respiratory enzyme and downregulated anaerobic glycolysis in neurons, which were the opposite in glia [29]. Thereafter, transcriptome and mass spectrometric analysis revealed cell-specific metabolic profiles in the CNS [30, 31]. Notably, expressions of glycolytic enzymes including 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3 (Pfkfb3), pyruvate kinase (PK) and LDH vary between neurons and astrocytes. Zhang et al. found that more abundant expressions of *Pfkfb3*, *Pkm2* and *Ldhb* in astrocytes compared with neurons, collectively contributing to the preference for glycolysis in astrocytes [30]. However, pyruvate dehydrogenase (PDH), which promotes the flux

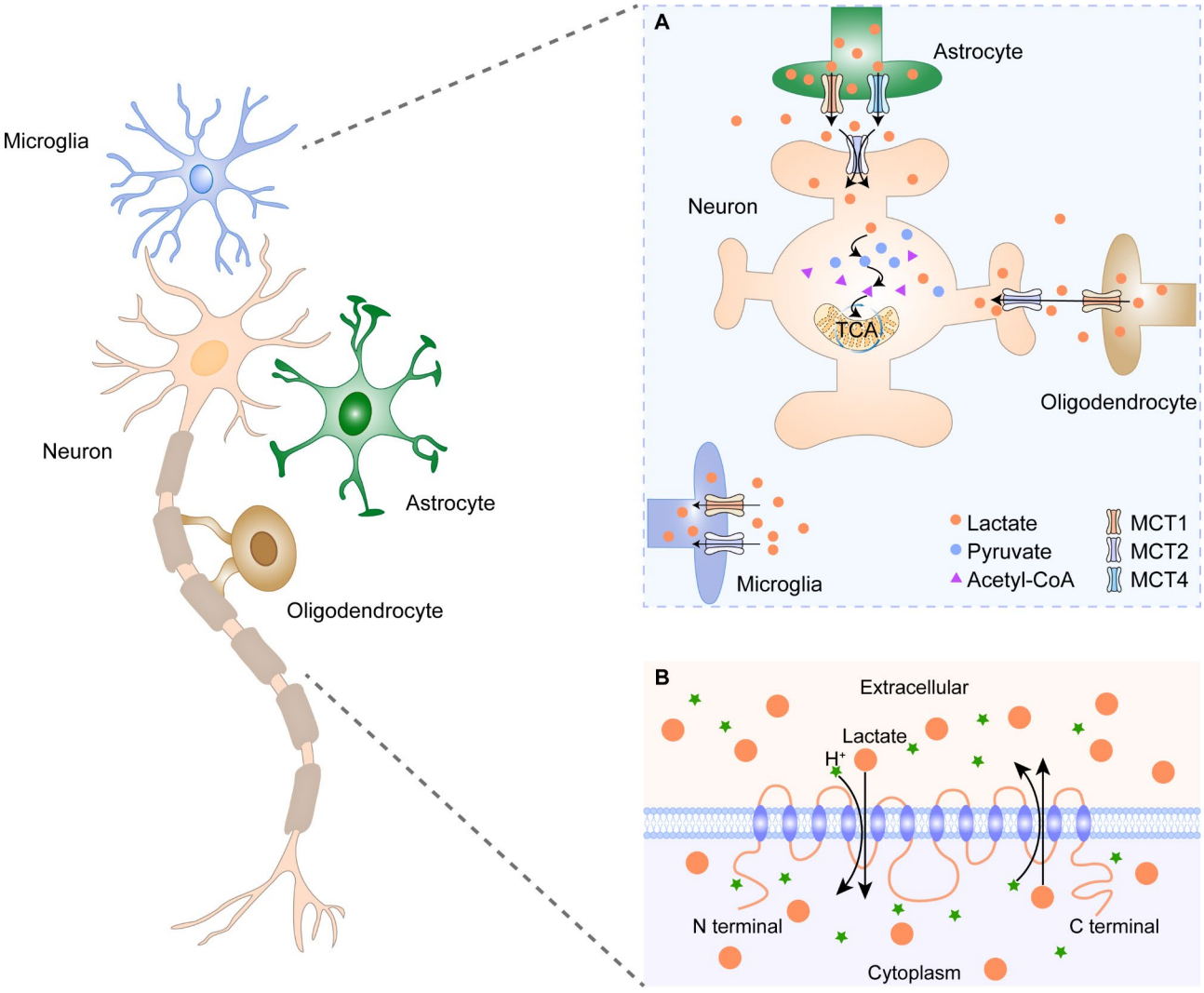

Fig. 2 Differential expressions and action mechanism of MCTs in the CNS. **(A)** MCTs expressions differ between neurons and glia. MCT1 and MCT4 in astrocytes are responsible for lactate efflux, which is then transported into neurons via MCT2. Similarly, lactate efflux via MCT1 in oligodendrocytes and uptake via MCT2 in neurons has also been observed. In microglia, lactate influx is mediated by MCT1 and MCT2. **(B)** Structure and action mechanism of MCTs. MCTs possess 12 transmembrane helices and intracellular C-, N-termini. Lactate and H^+ are co-transported via MCTs, which is determined on extracellular and intracellular concentrations of monocarboxylate ions and protons

of pyruvate into TCA cycle, is highly phosphorylated and less activated in astrocytes, thus promoting pyruvate shunted into glycolysis, while in neurons, PDH is more unphosphorylated and activated [3, 32]. The inactivation of PDH in astrocytes may be ascribed to more than 30-fold higher pyruvate dehydrogenase kinase 4 (Pdk4) transcripts than in neurons [30]. On the contrary, enzyme Pfkfb3 is degraded constantly in neurons, therefore limiting its glycolysis level [33]. Surprisingly, results from Lovatt et al. indicated that astrocytes were equipped with mitochondria and expressed most enzymes involved in TCA cycle [31]. However, mitochondrial respiratory chain (MRC) complexes are highly organized in neurons while mitochondrial free complex I is more abundant in astrocytes. As highly organized mitochondrial complexes are essential in regulating electron transfer efficiency, the disturbance of organization of respiratory complexes is responsible for poorer mitochondrial function in astrocytes. These discrepancies collectively result in decreased respiration rate and higher glycolysis in astrocytes than in neurons [34].

Astrocyte-neuron lactate shuttle (ANLS)

A large number of investigations have suggested metabolic cooperation between astrocytes and neurons, in which astrocytes modulate its metabolism to match neuronal activities [1]. It is believed that lactate released from astrocytes via MCT1/MCT4 can be taken up by neurons via MCT2 for generation of pyruvate and acetyl-CoA to fuel OXPHOS, thus ensuring necessary ATP

production during neuronal activation, which is called ANLS [10, 35, 36]. This transformation from lactate to pyruvate relies on LDH1, which is expressed by lactate-consuming cells, such as neurons in CNS [4]. The concept of ANLS was first raised in 1994 by Pellerin L. and Magistretti PJ, which proposed that glutamate released from synapses was taken up by astrocytes and stimulated astrocytic glucose uptake and aerobic glycolysis, subsequently, lactate derived from aerobic glycolysis in astrocytes was transferred into neurons for energy supply [37, 38]. Mechanistically, in astrocytes, glutamate is co-transferred with sodium ions, which leads to the disruption of sodium gradient and activation of Na^+/K^+ ATPase. On the other hand, a proportion of glutamate in astrocytes is transformed to glutamine via glutamine synthase, which also consumes ATP. ATP loss stimulates glucose uptake, glycolysis and lactate generation in astrocytes [10]. Thereafter, lactate is transported into neurons via lactate transporters.

The shuttle of lactate relies on MCTs on cells [35]. Previous studies have confirmed heterogeneous expressions of MCTs in the CNS. Among which, MCT2 is primarily expressed in neurons and is responsible for the uptake of lactate, which has also been found to be expressed in microglia, while lactate efflux from astrocytes relies on MCT1 and MCT4 [3, 39]. MCT1 can transport lactate bi-directionally [2]. In the CNS, MCT1 is also found to be expressed in oligodendrocytes, microglia and endothelial cells [6, 40, 41], while MCT4 is exclusively expressed in astrocytes [6].

Except for the differences in expressions of metabolic genes and cellular components between astrocytes and neurons, various studies have further supported the hypothesis of ANLS [4, 42, 43]. An early research proved accelerated uptake of glucose in astrocytes, which was unchanged in neurons during whisker stimulation, indicating the primary glucose uptake in astrocytes during neuronal activity [44]. In another study, glutamate boosts glucose uptake by astrocytes while inhibits glucose transport in neurons, which is consistent to the ANLS [45]. Moreover, it has also been verified that glycolysis in glia is vital for neuronal survival. Volkenhoff et al. showed that Trehalase or PK depletion in glia resulted in neuronal death in drosophila [46]. A recent study applied genetically encoded lactate sensor and in vivo two-photon laser scanning microscopy to detect lactate and found less lactate increase in astrocytes than in neurons in response to exogenous lactate. Furthermore, under stimulation of pyruvate (trans-acceleration of the MCT), reduced lactate was also observed in astrocytes but not in neurons [47]. These results collectively suggest a lactate gradient between astrocytes and neurons, which is a prerequisite of ANLS [47]. Another study from Sada et al. revealed that selectively inhibition of LDH in astrocytes resulted in hyperpolarized in pyramidal cells due to reduced lactate shuttle from astrocytes into neurons, indicating the important role of ANLS in neuronal activity [48].

Still, there are controversies against ANLS. First of all, there lacks direct evidence for glutamate-evoked lactate shuttle between astrocytes and neurons in vivo or in vitro [8]. Besides, the stoichiometry of ANLS has not been appropriately proposed. Daniel et al. pointed out that the rates of glycolysis and lactate release, the oxygen consumption of lactate oxidation and oxygen-glucose index were mismatched respectively [8, 49]. Moreover, lactate in CNS may be not exclusively from astrocytes during neuronal activation, and studies have confirmed rapid release of lactate to blood and perivascular lymphatic drainage while not retained in activated brain regions [49, 50]. In addition, a previous study by Díaz-García et al. revealed that neurons upregulated glucose consumption and glycolysis but did not require lactate supply from astrocytes during stimulation. Instead, they propose ANLS functions at resting states but not under stimulation [51]. In summary, there still exist vigorous debates on ANLS, which warrants further delicate studies to draw a conclusion.

Lactate metabolism in microglia

Microglia are the resident immune cells in CNS and energy metabolism in microglia largely depends on the activation and phenotypes of microglia [52]. Microglia may adapt different phenotypes in response to various stimulations, which can be roughly classified as pro- or anti-inflammatory phenotypes [53]. Although this kind of binary classification has been considered oversimplified, it is clear that microglia modulate their metabolism patterns under pro-inflammatory and anti-inflammatory stimuli [54]. Microglia are able to metabolize glucose, amino acids and fatty acids due to the expressions of diverse transporters and enzymes [30, 54, 55]. Moreover, they express most genes involved in OXPHOS and glycolysis [54]. In resting microglia, OXPHOS is the primary way for energy supply. However, emerging evidence has suggested a shift of metabolism in microglia under stimulation, in which pro-inflammatory microglia prefer glycolysis while anti-inflammatory microglia rely more on OXPHOS and fatty acid oxidation [6, 54, 56]. Rapid lactate production in glycolysis supplies the necessary energy for the activation processes including proliferation, migration and secretion [6]. Previous studies have found that LPS increased glycolysis while suppressed mitochondrial function of microglia, and co-treatment with LPS and IFN-γ increased lactate production as well as the activities of PFK1 and LDH in microglia, reflecting the potentiation of glycolysis under pro-inflammatory stimulus [57, 58]. As extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) are

now considered as indicators for glycolysis activity and OXPHOS activity, recent studies have applied Seahorse system to monitor cellular energy metabolism and shown that IFN-γ, LPS both increased glycolysis in microglia reflected by increased ECAR, which indicated upregulated levels of glycolysis [59, 60]. Recent studies have further explored the link between metabolic reprogramming, the process in which cells flexibly reprogram cellular metabolic pathways in response to stimuli in the environment, and cellular functions in immune cells [61]. Similarly, glycolysis preference in microglia under pro-inflammatory environment promotes phenotype switch into pro-inflammatory phenotype [52, 54]. Furthermore, Monsorno et al. recently raised the possibility that lactate might influence microglial functions by regulating transcriptional profiles in microglia via lactylation [62].

Lactate metabolism in oligodendrocytes

Oligodendrocytes are the major cells responsible for myelin forming in the CNS. Previous studies have found that both mitochondrial metabolism of glucose and lactate production in oligodendrocytes were active [63], and oligodendrocytes rely more on aerobic glycolysis for ATP supply [3]. It has been confirmed that lactate plays an important regulatory role in development of oligodendrocyte and myelination [64]. Lactate in oligodendrocytes functions not only as an energy substrate but also to support myelination and lipid synthesis [63, 65]. Recently, the scope of ANLS has also been expanded to include oligodendrocytes. Emerging studies have indicated that oligodendrocytes produce lactate to support axons [2, 66]. Lactate in oligodendrocytes is transferred into neurons for ATP synthesis via MCTs and gap junctions [6]. Aerobic glycolysis in oligodendrocytes is regulated by axonal activity. Stimulation of N-methyl-d-aspartate (NMDA) receptors in oligodendrocytes by glutamate derived from adjacent neurons enhances GLUT1 expression, glucose uptake and aerobic glycolysis in oligodendrocytes, which in turn provide more lactate for neurons [67]. In addition, TCA cycle and ATP generation in mitochondrial metabolism in oligodendrocytes are also regulated by neurons, which is mediated by N-acetylaspartate derived from neurons [3]. Meanwhile, disruption of MCT1 on oligodendrocytes resulted in axon damage and neuronal loss, addressing the importance of MCT1 in metabolic coupling between oligodendrocytes and neurons [40].

Multiple physiological functions of lactate in CNS

Lactate sustains energy needs of neuronal activation and serves as a signal molecule to participate in multiple physiological activities and pathological processes in CNS [27, 68]. Lactate is related to CNS homeostasis. Previous studies have suggested the important regulatory roles of lactate in memory, neuronal activity and blood flow supply in the CNS [27, 69, 70] (Fig. 3).

Lactate participates in learning and memory formation

In 1994, O'Dowd et al. found that glycolysis and glycogenolysis were involved in energy supply for memory consolidation of long-term memory [69]. In a passive avoidance task of chicks, they observed that glycolytic inhibitor iodoacetate resulted in retention deficits in chicks. Furthermore, glycogenolysis was observed in the forebrains after learning [69]. Thereafter, studies confirmed glycogenolysis and lactate release in the hippocampus in rats after learning and during spatial working memory task [71, 72]. Suzuki et al. found that inhibition of glycogenolysis suppressed long-term potentiation (LTP) in hippocampus, which was rescued by lactate. Similarly, MCTs knockdown on astrocytes or neurons both abolished long-term memory. Collectively, Suzuki et al. verified the essential role of lactate transport from astrocytes to neurons for long-term memory formation [71]. Meanwhile, Newman et al. found that lactate supplementation improved spatial working memory, while it was impaired by glycogenolysis inhibition and MCT block on neurons [72]. Consistently, another study showed memory impairment in the inhibitory avoidance task in MCT1 deficient mice [73]. When studying the link between diabetes and memory defect, Shima et al. observed higher levels of hippocampal glycogen and lower levels of hippocampal MCT2 in diabetic rats, suggesting that abnormal lactate metabolism and transport may underlie memory dysfunction in diabetic patients [74]. In Morris water maze test, dichloroacetate (DCA) treatment in acquisition period impairs learning and memory while treatment after acquisition period has no influence on memory in probe trial in mice, implying that lactate is vital for memory acquisition-related synaptic plasticity but marginal in memory retrieval [75]. In addition, lactate is also involved in drug memory of cocaine, representing a new therapeutic strategy for drug addiction [76, 77].

The possible mechanisms underlying the vital role of lactate in long-term memory may be ascribed to the effect on the regulation of synaptic plasticity. It has been proved that glucose and lactate serve as energy substrate in presynaptic metabolism [78]. Besides, studies have implied that lactate is involved in genes expressions related to synaptic plasticity including *Arc*, *c-Fos*, and *Zif268* [79, 80]. Moreover, dynamic aerobic glycolysis through a lifetime seems to be correlated to synaptic plasticity. That is, increased aerobic glycolysis is observed during early development with the highest synaptic growth rates, while in adults, relatively higher aerobic glycolysis is found in neotenous regions, and during aging, aerobic glycolysis is downregulated,

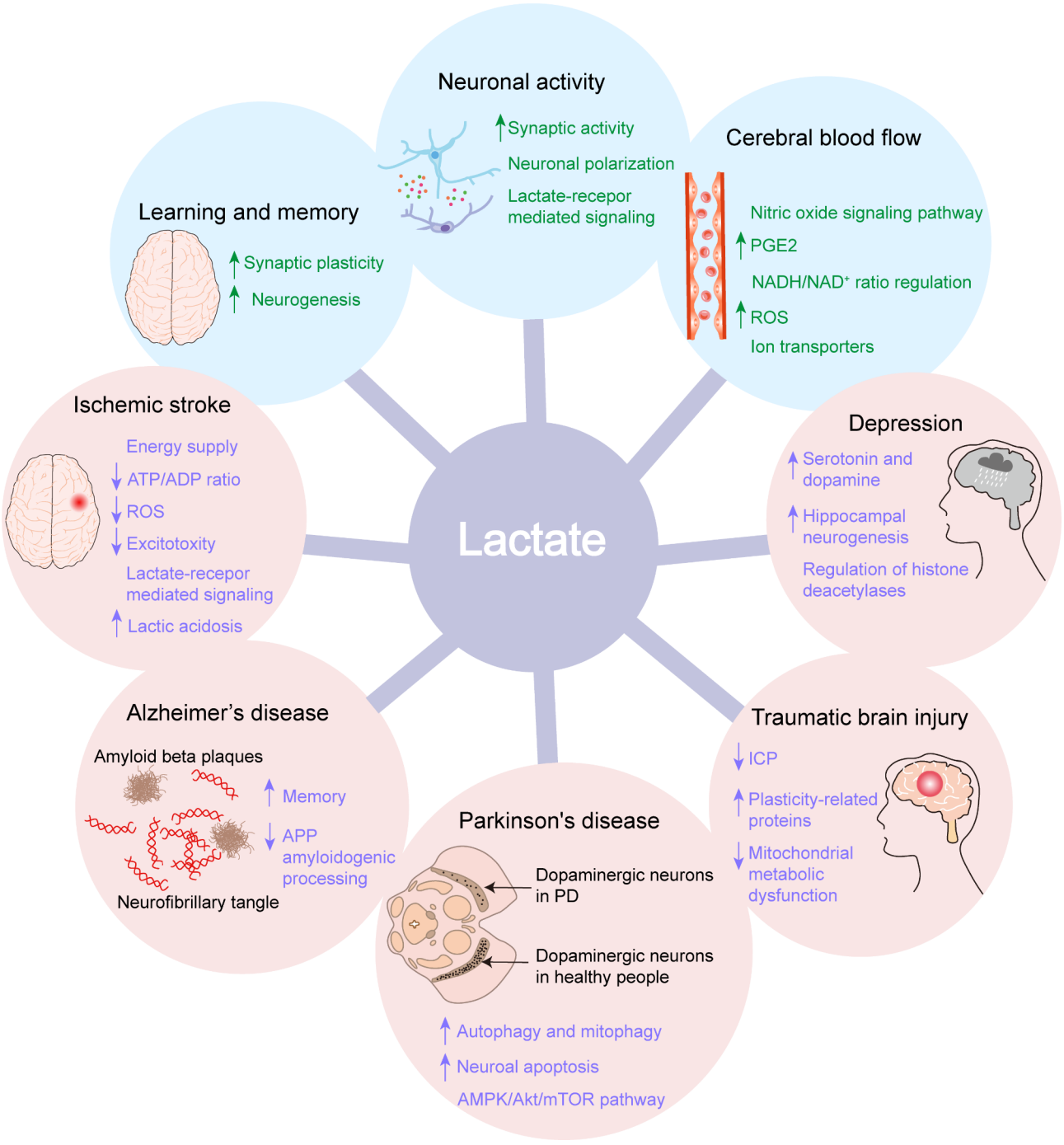

Fig. 3 Functions of lactate in physiological activities and pathological processes in CNS. Previous studies have revealed that lactate is involved in multiple physical functions in CNS including learning and memory, neuronal activity and cerebral blood flow regulation. In addition, lactate also plays roles in CNS disorders including ischemic stroke, Alzheimer's disease, Parkinson's disease, traumatic brain injury and depression

accompanied by decreased plasticity in the brain [81, 82]. A previous study by Hayek et al. revealed that lactate derived from muscles during exercise could cross the blood-brain barrier (BBB) and induce expressions of genes such as *Bdnf*, thus benefiting learning and memory [83]. Meanwhile, recent studies also showed that lactate or exercise contributed to increased neurogenesis in a hydroxycarboxylic acid receptor 1 (HCAR1)-dependent or MCT2-dependent manner, which may rescue memory defect during aging [84, 85].

Lactate is involved in regulating neuronal activity

It has been reported that glucose and lactate delivery from astrocytes to neurons via gap junctions sustains

glutamatergic synaptic activity under glucose deprivation [70]. Moreover, even with sufficient glucose and ATP, lactate transport at excitatory synapses via MCTs is essential for synaptic transmission, as evidenced by decreased excitatory postsynaptic current (EPSC) amplitude with MCT inhibition [86]. Similar results were also observed in orexin neurons, in which spontaneous activity was inhibited by MCT blocker [87]. Consistently, Sada et al. showed that LDH inhibition in astrocytes resulted in hyperpolarization in pyramidal cells when exposed to medium containing glucose, while in contrast, medium containing lactate reserved cellular membrane potential, indicating that extracellular lactate was transferred into neurons and modulated neuronal excitation [4, 48]. Besides, exogenous lactate can also induce neuronal depolarization in locus coeruleus without entering neurons, but rather relying on an undefined Gs receptor and intracellular cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling [88].

Nevertheless, lactate has also been reported to decrease the activity of primary neurons through Gi protein-coupled receptor HCAR1, a receptor for lactate, and the inhibitor or agonist of HCAR1 reserves or diminishes neuronal activity respectively [89]. Other studies also confirmed that activation of HCAR1 decreased mEPSC frequency, neuronal excitability and calcium spiking frequency, which may be mediated by Giα subunit and intracellular inhibition of adenylate cyclase (AC)/cAMP/PKA [27, 90, 91]. In summary, the previous studies indicate that the effects of lactate on neuronal activity are dependent on specific neuron populations and downstream signaling pathway activated by lactate receptors [4, 27].

Lactate regulates cerebral blood flow (CBF)

Accumulating studies have revealed that lactate is also involved in CBF regulation in the CNS [27, 92, 93]. Alessandri et al. found that lactate treatment decreased lesion volume of controlled cortical impact, an animal model simulating traumatic brain injury (TBI), by augmenting CBF [94]. Moreover, in a model of recurrent antecedent hypoglycemia, a more profound increase in CBF by lactate was observed [95]. In human visual cortex, Lin et al. also found that task-induced CBF increase was positively related with lactate production, which is possibly mediated by nitric oxide signaling pathway [96]. Similarly, in another study, Hein et al. validated that lactate in vascular cells stimulated NO synthase and activation of guanylyl cyclase/cGMP signaling/ATP-sensitive potassium channels, eventually leading to vasodilation [97]. In addition, lactate may augment CBF under hypoxia by inhibiting prostaglandin E2 (PGE2) uptake into cells via prostaglandin transporters, thus leaving PGE2 extracellularly to induce vasodilation [98]. The engagement of NADH/NAD^+ ratio and ROS production in lactate-mediated CBF regulation has also been indicated [99]. Notably, the influences of lactate on vessels may differ in different cell types or under different conditions. While extracellular lactate led to the relaxations of smooth muscle-encircled vessels, in rat retinal pericyte-containing microvasculature, it was found that extracellular lactate induced pericytes to contract and vasoconstriction, in which Na^+/H^+ exchangers, Na^+-K^+ pumps, Na^+/Ca^{2+} exchangers and pericyte calcium levels were possibly involved. On the contrary, under hypoxia, lactate promoted pericytes to relax and vasodilation [100]. All these findings collectively indicate the strong potential of lactate in blood flow regulation, which warrants further detailed explorations.

Functions of lactate in neurological disorders

As an energy substrate and a signal molecule, emerging evidence has indicated that lactate plays pivotal roles in the pathology of a variety of cerebrovascular disease and degenerative diseases in CNS, in which energy metabolism is disrupted (Fig. 3). The levels of lactate are increased in kinds of CNS diseases, thus holding the potential to be a candidate biomarker in diseases [27, 101].

Lactate in stroke

Stroke is one of the leading causes of death and disability in the world, which brings severe challenges to society and medical treatment, in which ischemic stroke is the main type. During ischemic stroke, neuronal deaths, brain edema and neuroinflammation concurrently contribute to severe neurological deficits. Mechanically, excitotoxicity induced by glutamate release, oxidative stress caused by ROS and neuroinflammation mediated by glial cells and peripheral immune cells are the main causes of primary and secondary brain injury in ischemic stroke [102, 103].

In ischemic stroke, TCA cycle and ATP production in mitochondria are disrupted, glycolysis and generation of lactate are upregulated. Previous studies have shown increased levels of lactate in the acute phase of ischemic stroke [104, 105]. More recently, the neuroprotective effects of lactate in ischemic stroke have been proved in vivo and in vitro. A study by Berthet et al. showed that 4 mmol/L lactate protected against neuronal death in oxygen glucose deprivation (OGD) of organotypic hippocampal slices. Moreover, lactate administration intracerebroventricularly or intravenously both decreased lesion size and protected neurological function in a model of middle cerebral artery occlusion (MCAO) [106, 107]. They also pointed out that the protective effects depended on quantity of lactate and time of intervention [106]. On the other hand, effective lactate transport between glia cells and neurons is also essential in

ischemic stroke. Expressions of MCTs in CNS during ischemic stroke differ from that under physiological conditions. Intense MCT1 expression in astrocytes has been observed in rats undergoing transient global ischemia [108]. Consistently, in MCAO model of spontaneous hypertension rats, increased MCT1 mRNA and protein expressions were found in astrocytes and endothelial cells in peri-infarct area, which were possibly mediated by hypoxia-inducible transcription factor (HIF1) [109]. Moreover, while microglia are activated rapidly after cerebral ischemia, enhanced expressions of MCT1 and MCT2 have also been found in activated microglia in a rat ischemia model induced by unilateral extradural compression [110]. However, in stroke-prone spontaneously hypertensive rats, lactate production and MCTs expressions in astrocytes are both decreased, which may partially contribute to neuronal damage [18]. Another study has reported that inhibition of MCTs by alpha-cyano-4-hydroxycinnamate aggravated hippocampal delayed neuronal damage [111]. On the contrary, while neuronal expression of MCT2 is significantly decreased, overexpression of MCT2 protects against cognitive dysfunction after MCAO in rats [112]. Nevertheless, there are still some controversies on neuroprotective effects of lactate in ischemic stroke. High levels of lactate after brain ischemia may result in lactic acidosis and eventually aggravate neurological injury [113, 114]. Besides, GPR81, a known receptor for lactate, binds to a G protein (Gi), which inhibits adenylate cyclase and the second messenger cAMP [68]. A study by Shen et al. found that antagonist of GPR81 decreased neuronal deaths and alleviated brain injury after MCAO in vivo and OGD in vitro, partly via ERK signaling pathway, while cotreatment with lactate significantly reversed these neuroprotective effects [115]. Altogether, although the beneficial effects of lactate in ischemic stroke have been verified by more and more studies, the dural roles exhibited in previous researches cannot be ignored. Explorations to delineate the concrete influences of lactate on brain ischemia and to explain the discrepancies regarding the functions of lactate in ischemic stroke are warranted in the future.

Mechanistically, lactate benefits neurofunction in ischemic stroke mainly in two ways. First of all, it serves as an energy substrate for ATP supplementation for neuronal cells during oxygen and glucose deficiency. In addition, lactate is able to downregulate ATP/ADP ratio and reduce ROS production in mitochondria, thus promoting neuronal survival [18]. Secondly, lactate may function as a signal molecule. Regarding to neuronal excitotoxity, which is induced by excess glutamate release and occurs during ischemic stroke, lactate has been proved to attenuate excitotoxity as a signal molecular by generating ATP and activating PI3-kinase pathway/ K_{ATP} channels via purinergic receptors [103, 116]. Besides, lactate has also been reported to protect against neurological damage via receptor GPR81-mediated signaling pathway. It has been verified that GPR81 agonist decreased neuronal deaths in rat organotypic hippocampal slices exposed to OGD [117].

Lactate in CNS degenerative diseases

Alzheimer's disease (AD) is the leading cause of dementia worldwide, which leads to heavy economic burden [118, 119]. As a degenerative disease in CNS, impaired glucose metabolism has been observed in AD [120]. The concentrations of cerebrospinal fluid (CSF) lactate have been reported to be elevated at first, and then decreased along with higher disease severity, but remaining constantly higher than healthy controls yet [121]. Consistently, in another study, Liguori et al. found higher CSF lactate levels and hypometabolism of glucose in AD patients [122]. Moreover, the lactate contents are decreased along with diagnosis time [123]. Expressions of MCTs including MCT1, MCT2 and MCT4 were also found to be decreased in the CNS in AD mice [124]. Correspondingly, levels of both total tau protein and phosphorylated tau protein in CSF were negatively associated with levels of lactate [121]. These results potentially suggest the negative correlation between lactate levels and AD, which may also be parallel in experimental animal models [125]. However, the changes in lactate contents and the link between lactate and AD remain disputable. In a more recent study, Zebhauser et al. compared CSF lactate contents in AD patients at the stage of mild cognitive impairment and dementia with healthy controls in 312 individuals. Surprisingly, they observed comparable CSF lactate levels between patients with dementia and healthy individuals, while CSF lactate levels in mild cognitive impairment patients were higher than healthy controls. In addition, they also indicated that lactate in CSF did not correlate with severity of disease in AD [126]. Similarly, the elevation of CSF lactate was found to be irrelevant to Aβ aggravation in monkeys [127]. The differences in conclusions among these studies may be attributed to different sample sizes, screening criteria and course of AD [126]. Sample sizes are key factors in these studies. Different from most studies which conducted their researches in smaller sample sizes, Zebhauser et al. included more AD patients and healthy controls of 312 samples [126, 128, 129]. Besides, the inclusion criteria of AD rely largely on distinct cut-off values for Aβ42 or tau-proteins, the diagnostic criteria and classification of cognitive dysfunction in AD continuum have been constantly optimized in recent years. Therefore, inevitable differences in inclusion criteria of AD may help explain the conflicting results [126, 129]. Likewise, both volunteers with or without neurological symptoms were included in healthy controls in previous studies, which may result

in inconsistent conclusions too [121, 126, 130]. Notably, lactate contents in CSF have been indicated to be influenced by age and BBB integrity, which should be taken into consideration in further researches [126, 131]. Nevertheless, preclinical researches have explored the effects of lactate in AD and suggested lactate as a potential therapy for AD. For example, Lu et al. applied APP/PS1 mice to simulate AD model and proved that curcumin benefited memory in AD mice by upregulating lactate and MCT2 [132]. Similarly, vestigial-like family member 4 (VGLL4) was found to boost the production of lactate by upregulating the expression of lactate dehydrogenase A (LDHA), thus protecting against amyloid-β precursor protein (APP) amyloidogenic processing in AD [133].

The potential roles of lactate in amyotrophic lateral sclerosis (ALS) have also been investigated, as in $SOD1^{G93A}$ mice, an animal model of ALS, enhanced glycolytic influx was observed, which potentially led to increase of lactate [134].

Metabolism dysfunction also occurs in Parkinson's disease (PD), and to sustain energy supply, upregulated levels of aerobic glycolysis and lactate have been observed in PD patients [135, 136]. Previous studies have shown that lactate is neuroprotective in PD via activating autophagy and mitophagy [137, 138]. In contrast, a study from Li et al. applied MPTP-induced mouse PD model and showed that elevated lactate boosted apoptosis of dopaminergic neurons while lactate downregulation by inhibiting hexokinase 2 alleviated apoptosis of dopaminergic neurons and protected motor function of PD mice [139]. These effects probably rely on activation of AMPK and inhibition of Akt phosphorylation as well as mTOR phosphorylation by lactate, given that the activation of AMPK and inactivation of Akt by PD toxins have been reported to inhibit mTOR-mediated S6K1 and 4E-BP1 pathways, eventually inducing dopaminergic neurons deaths in vitro [139, 140].

A number of studies also demonstrate that concentrations of lactate in the brain are closely associated with metabolic dysfunction diseases, such as diabetes, but the results vary among different experimental disease models [141, 142].

Lactate in TBI

Lactate has been suggested not only to be a promising prognostic marker but also to represent a potential treatment in TBI. Previous studies have indicated lactate-pyruvate ratio in cerebral microdialysis as a positive predictor for poor outcome of TBI [143, 144]. Similarly, Wettervik et al. found that high arterial lactate was inversely related to pressure autoregulation and clinical outcomes of TBI [145]. The inverse correlation between lactate concentrations and outcomes of TBI may be explained by Carprnter's assumption that low lactate concentration suggests more lactate has been taken up by neurons, while high lactate concentration indicates that damaged neurons cannot uptake lactate efficiently [146]. On the other hand, lactate has been evidenced to reduce intracranial pressure (ICP), benefit cerebral perfusion in TBI patients, and protect against cognitive deficits in animal models [94, 147–149]. Uptake of lactate was observed in injured brain after TBI of rats by applying ^{14}C-lactate [150]. Moreover, increased uptake of lactate correlates with favorable outcomes of TBI [151]. More recently, lactate preconditioning was found to ameliorate neurological dysfunction by upregulating multiple plasticity-related proteins in TBI rats, which may be mediated by GPR81 signaling pathway [152]. Besides, hypertonic sodium lactate infusion after 30 min of injury manifested protective effects in mitochondrial metabolic dysfunction in TBI rats [153]. However, further researches are still warranted to delicately elucidate the roles and underlying mechanism that lactate functions in TBI.

Lactate in depression

Dysfunction of glucose metabolism in depressed patients has been proved in multiple previous studies [154, 155]. Notably, some antidepressant drugs are reported to reverse metabolic disorders in depression, such as paroxetine and fluoxetine [156, 157]. Allaman et al. revealed that paroxetine and fluoxetine can increase glucose metabolism and lactate release by astrocytes in cortical astrocyte culture [158]. Besides, there is increasing evidence indicating protective roles of lactate in psychiatric disorders. In Shaif's study, they found that lactate treatment augmented the levels of serotonin and dopamine in brain, thus exerting antidepressant effects in animal model of menopausal depression [159]. Moreover, Carrard et al. confirmed that lactate protected against depression by promoting hippocampal neurogenesis in mice model [160]. Lactate was also found to exert protective effects in depression by regulating histone deacetylases [161].

Taken together, besides ischemic stroke, lactate is also involved in a variety of diseases in the CNS, in which the mechanisms are related with different signaling pathways and remain to be further comprehensively explored (Fig. 3).

The process of histone lactylation

Histone lactylation was recently identified as an epigenetic modification that is regulated by lactate contents in cells [11]. Histone lysine lactylation can be directly derived from exogenous or endogenous lactate, which is able to generate lactyl-coenzyme A (lactyl-CoA). Zhang et al. proposed that lactyl-CoA was responsible for adding lactyl group to lysine residues [11, 162]. Thereafter,

the existence of lactyl-CoA was validated in mammalian cells and tissues via liquid chromatography mass spectrometry by Varner et al. in 2020 [163].

Histone lactylation is regulated by diverse enzymes known as writers, erasers and readers, responsible for addition, removal, recognition and interpretation of histone lactylation, respectively (Fig. 1). Zhang et al. first showed p53-dependent p300-mediated H3 and H4 lactylation in macrophages, suggesting p300, a known acetyltransferase, can catalyze both acetylation and lactylation, and is now considered as the writer of lactylation [11, 164, 165]. On the other hand, recent studies have identified histone deacetylase (HDAC1-3) and silent information regulator (SIRT1-3) as delactylases in vitro, serving as eraser enzymes of histone lactylation [166, 167]. Dai et al. further observed that inhibition of HDAC1-3 significantly increased H3K18la in vivo, confirming that HDAC1-3 can erase histone lactylation [168]. Besides enzymatic lysine lactylation, non-enzymatic lysine lactylation via acyl transfer from glycolytic intermediate, lactoylglutathione to protein Lys residues has also been found by Gaffney et al. They revealed that glyoxalase 2 was critical for this kind of lysine modification, which hydrolyzes lactoylglutathione in cells. In glyoxalase 2 knockout cells, the levels of lactoylglutathione and Lactoyl Lys modifications are both elevated. In addition, these PTMs are largely enriched on enzymes involved in glycolysis and regulate glycolysis in turn [169].

It has been proved that various PTMs are derived from metabolites in cells. Similarly, histone lactylation is also regulated by glucose metabolism and the levels of intracellular lactate. Metabolic reprogramming influences the balance between glycolysis and TCA cycle, which plays a vital role in histone lactylation and other acylations [170]. It has now been acknowledged that lactate metabolism is tightly related to histone lactylation. Zhang et al. first found that suppression of lactate production by LDH and PDH inhibition decreased intracellular lactate and thus downregulated histone lactylation. Moreover, genetically deletion of LDH resulted in decreased lactate production and histone lactylation in cells under normoxia. On the contrary, mitochondrial inhibitor and exposure to hypoxia increased lactate and histone lactylation levels in vitro [11]. These phenomena collectively indicates that histone lactylation is specifically dependent on lactate levels, which has been constantly confirmed in more and more studies recently [171–173]. Besides histone lactylation, the involvement of lactate and LDH in some other epigenetic alterations has also been suggested. A study from An et al. indicated lactate as major carbon source for histone acetylation in a LDH-dependent manner. They found that lactate treatment and LDH inhibition induced increased and decreased histone acetylation respectively [174]. Moreover, LDH in drosophila has also been reported to influence DNA methylation by regulating L-2-hydroxyglutarate generation [175].

Functions of histone lactylation

Histone lactylation is involved in genes regulation by being enriched in the promoter region of target genes in various cells, thus participating in the regulation of diverse systems in the body. The latest studies have implied that histone lactylation plays important roles in maintenance of homeostasis and regulation of multiple pathophysiological processes [168, 172, 176]. Existing studies have found that histone lactylation is involved in regulating embryogenesis and CNS development [168, 177, 178]. On the other hand, histone lactylation is also involved in regulating the functions of immune cells and inflammation, thus participating in tumor development and multiple diseases [11, 171, 179]. When it comes to the CNS, histone lactylation is reported to be involved in degenerative diseases and acute CNS injuries by regulating functions of glia and neuroinflammation [176]. The details are thoroughly discussed below (Fig. 4).

Histone lactylation in embryo development

Dynamic fluctuations of histone lactylation are often relevant to and play an important role in physiological and pathological changes. Recent studies have revealed that histone lactylation can regulate pregnancy and embryogenesis. Yang et al. applied proteomic atlas of ligand-receptor interactions and revealed that lactate-induced histone lactylation facilitated remodeling processes of endometrium for successful implantation [180]. A previous study by Yang et al. has found that reduced histone lactylation in embryos impaired embryonic development in mice, while another study proposed that lactate induced H3K18la accumulation on germline and cleavage embryo genes in mouse embryonic stem cells and promoted transcriptional elongation [177, 178]. Besides, histone lactylation is believed to function during development. Dai et al. have recently observed global changes in histone lactylation during neural development, while Li et al. demonstrated that Glis1 facilitated pluripotency of induced pluripotent stem cells by increasing H3K27Ac and H3K18la at pluripotency gene loci [168, 181]. In summary, present studies have suggested wide distributions of histone lactylation in healthy individuals, which is essential for development and various physiological functions.

Histone lactylation in inflammation

Histone lactylation may regulate expressions of target genes by enrichment in the promoter region of specific genes, therefore playing an important role in diverse diseases. A number of studies have confirmed the involvement of histone lactylation in inflammation and

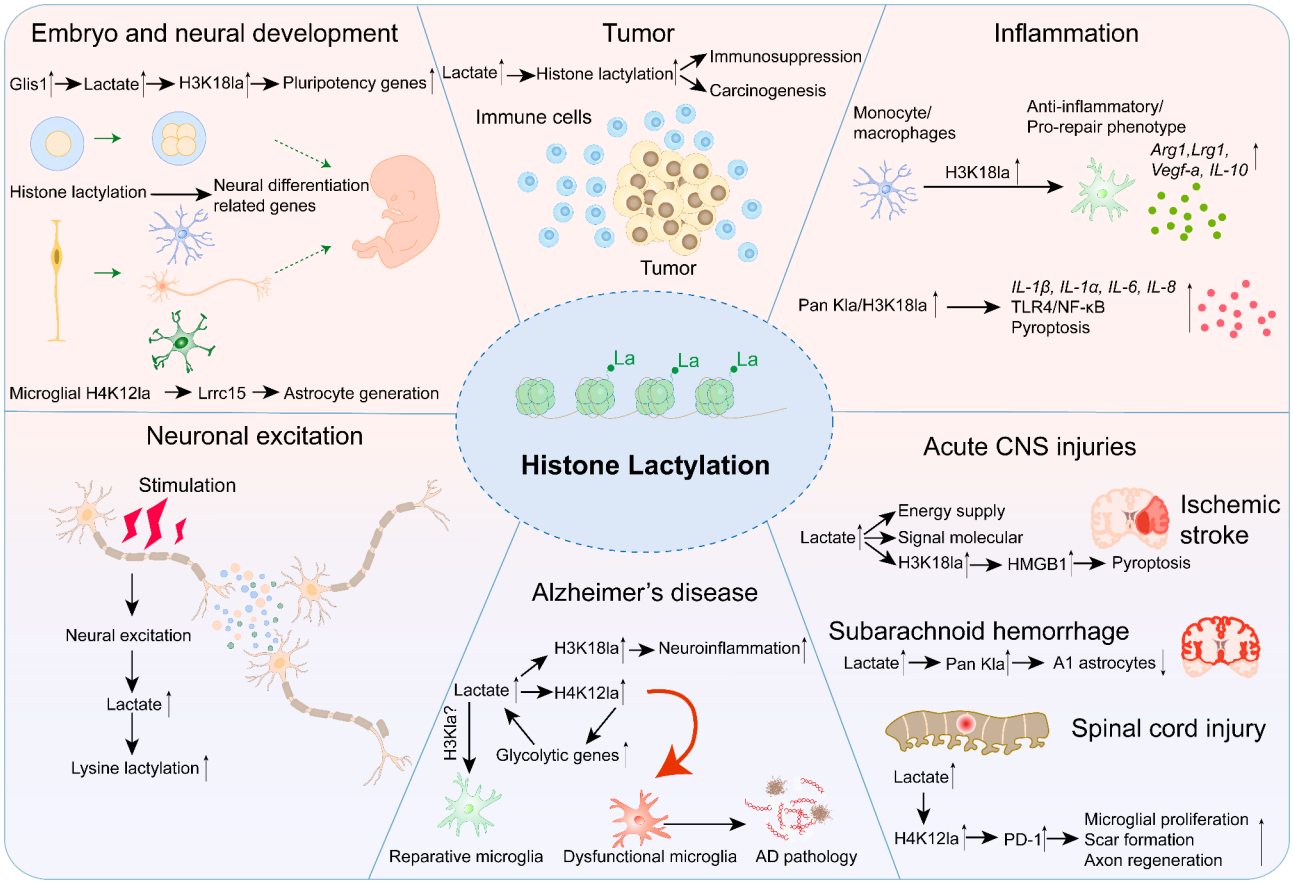

Fig. 4 Functions of histone lactylation in the regulation of homeostasis and pathophysiological processes. Histone lactylation has been shown to participate in regulation of embryo and neural development, tumor and inflammation. In CNS, histone lactylation is involved in regulation of neuronal excitation and diverse diseases including neurodegenerative diseases such as AD and acute CNS injuries such as SAH and SCI. Moreover, we speculate that histone lactylation plays an important role in ischemic stroke due to its regulatory effects on inflammation and reparative-related genes

immunosuppression by regulating specific target genes of immune cells. Firstly, Zhang et al. observed that histone lactylation was enriched in the promoters of homeostasis-related genes and promoted expressions of homeostatic genes including arginase1 (*Arg1*) at late stage of M1 macrophages polarization induced by LPS and IFN-γ, resulting in the transition into M2-like phenotype [11]. Moreover, Irizarry-Caro et al. revealed that B-cell adapter for PI3K (BCAP) was involved in aerobic glycolysis and histone lactylation in macrophages. Deficiency of BCAP impaired aerobic glycolysis as well as histone lactylation, thus impeding reparatory transition from inflammatory phenotype of macrophages [182]. Similarly, Wang et al. found elevated histone lactylation in monocytes post myocardial infarction, and they demonstrated that histone lactylation in monocyte-macrophages facilitated expressions of reparative genes including *Lrg1*, *Vegf-a*, and *IL-10* post myocardial infarction, validating both anti-inflammatory and pro-angiogenic effects of histone lactylation [172]. Nevertheless, there are still controversies over the effects of histone lactylation on inflammation. Recently, Chu et al. have shown that high H3K18la correlates with higher expressions of diverse inflammatory factors and *Arg1* in patients with septic shock, hence proposing H3K18la as a potential biomarker to diagnose and predict the severity of septic shock [183]. In dairy cows, high-concentrate diet leads to increased concentration of lactate, which upregulates histone lactylation via p300/CBP and activates TLR4/NF-κB signaling pathway, finally inducing higher expressions of various inflammatory factors including *IL-1β*, *IL-1α*, *IL-6* and *IL-8* [184]. However, in the above two studies, due to the lack of further investigation on the influence of histone lactylation regulation on inflammatory cytokines secretion, the phenomena that elevated histone lactylation accompanied by increased pro-inflammatory cytokines may be the results of pathological stimulus. Modulating histone lactylation and sequencing of lactylation-targeted genes is warranted to investigate the effects of histone lactylation on inflammation. On the other hand, the latest research by Yao et al. further extended the effects of histone lactylation on pyroptosis, a form of pro-inflammatory cell death. In this study, Yao et al. demonstrated that histone lactylation mediated by LDHA were enriched

on the promoter of HMGB1 in neurons, which induced neuronal pyroptosis in cerebral ischemia reperfusion injury in vivo and in vitro [185]. Collectively, as we can conclude, most existing studies have suggested that histone lactylation may target specific anti-inflammatory and pro-reparative genes in immune cells, therefore promoting anti-inflammatory microenvironment in diverse pathological conditions. However, the emerging divergent views indicate that the regulation of multi-target genes expressions in diverse cell types renders the vital and complicated roles of histone lactylation in inflammation, which awaits further detailed exploration [13, 186]. Besides the potential effects on inflammation and immunoregulation, emerging evidence has demonstrated the important roles of lactylation in carcinogenesis, which is tightly related to the immunosuppression induced by lactylation and has been thoroughly discussed in the latest reviews [187–189].

Histone lactylation in CNS development and diseases

Histone lactylation is believed to function during development in CNS. Li et al. demonstrated that Glis1 facilitates pluripotency of induced pluripotent stem cells by increasing H3K27Ac and H3K18la at pluripotency gene loci [168, 181]. Moreover, a recent delicate study by Dai et al. revealed wide distributions and global changes of histone lysine lactylation during neural development [168]. Compared with early stage of neurogenesis, the levels of overall H3-Kla and H3K18la are decreased at the late stage of neurogenesis of telencephalon. Besides, H3K18la are largely enriched in genes involved in cell proliferation-related pathways. By ChIP-seq and RNA-seq assays, Dai et al. discovered that increased H3K9cr or H3K18la upregulated genes engaged in neuronal differentiation and maturation, while reduced levels of H3K9cr or H3K18la downregulated genes involved in cell proliferation, suggesting the supportive role of global changes in histone lactylation for neural differentiation [168]. Moreover, lactylation in microglia has been found to be associated to astrogenesis during early brain development, which is mediated by LRRC15-CD248 axis and JAK/STAT signaling pathway [190]. In detail, Wang et al. found that conditional knockout of Bach1 induced decreased enrichment of H4K12la in the Lrrc15 promoter region in microglia, therefore impairing astrocyte generation [190]. In addition, lysine lactylation has been demonstrated to occur in the brain in adult mice and is regulated by neuronal excitation via neural-activity-induced lactate, while social defeat stress increases histone H1 Kla in neurons [191]. Similarly, increased histone lactylation was also observed in mice under conditions of cold stress [192]. However, the function of such a modification in CNS remains unclear and deserves further exploration.

On the other hand, the significant role of histone lactylation in AD has been highlighted by Pan et al. on 2022. At first, they found elevated levels of histone lactylation in both AD model of mice and AD patients, with increased H4K12la accumulated in microglia adjacent to Aβ plaque. As chronic neuroinflammation and abnormal activation of microglia are vital for AD development [193, 194], the authors further found that exacerbated microglial dysfunction and neuroinflammation were induced by a positive feedback loop of glycolysis/H4K12la/PKM2 axis, which eventually drove AD pathogenesis. Meanwhile, interruption of the loop inhibited microglial activation and ameliorated AD pathology [176]. Lately, another study from Wei et al. confirmed the correlation between H3K18la in senescent microglia and AD development [195]. They found elevated levels of Pan Kla and H3K18la in senescent microglia in aged mice, and in AD mice, the augmented H3K18la led to augmented neuroinflammation via the activation of NF-κB signaling pathway as well as the secretion of IL-6 and IL-8, thus aggravating AD pathology [195]. On the contrary, Han et al. revealed that lactate led to microglial H3 Kla and promoted anti-inflammatory/reparative phenotype of microglia, as shown by decreased pro-inflammatory cytokines while increased anti-inflammatory cytokines after lactate treatment, eventually improving cognitive functions in mice with cognitive decline induced by AlCl3/D-gal [196].

Furthermore, histone lactylation has also shown therapeutic potentials in cerebrovascular diseases and acute CNS injury recently. Zhou et al. proposed the possible involvement of histone lactylation in neonatal hypoxic-ischemic encephalopathy via regulating inflammation [186]. In hypoxic-ischemic encephalopathy, oxygen and nutrient deprivation induces lactic acidosis [197]. On the other hand, microglia and invading immune cells secrete inflammatory cytokines, chemokines and ROS, contributing to neuroinflammation in injured brain [198]. In consideration of regulatory effects of histone lactylation on inflammation and immune cells, it is plausible to speculate that histone lactylation may function in diseases such as neonatal hypoxic-ischemic brain injury and other acute brain injuries, in which neuroinflammation play pivotal roles. Indeed, a recent study from Zhang et al. implied the involvement of histone lactylation in regulation of astrocytes polarization in animal model of subarachnoid hemorrhage (SAH) [199]. They found that lactate supplementation increased histone lactylation in astrocytes, accompanied by restraining A1 polarization of astrocytes after SAH, while inhibition of lactate production induced the opposite effects [199]. Moreover, Hu er al. recently observed upregulated lactate and histone lactylation levels in spinal cord injury (SCI) model of mice, with elevated H4K12la level in microglia after surgery. Notably, they demonstrated that lactate-induced

H4K12la in microglia promoted neurological repair after SCI by promoting microglial proliferation, scar formation and axon regeneration via H4K12la/PD-1 axis [173].

Histone lactylation in stroke

Studies have been endeavored to further elucidate the roles that lactate plays in the pathogenesis of ischemic stroke. It has been proved that, the production of lactate is closely associated with progression of ischemic stroke [200]. Lactate is primarily deemed to be neuroprotective in ischemic stroke, as it has been reported to protect against neuronal death, which is possibly associated with enhanced energy supply via glycolysis or functioning as a signal molecule [201–203]. Mechanistically, along with elevated levels of lactate, the expression levels of MCTs are also up-regulated, which also participate in lactate transport in cerebral ischemic injury [18]. Besides, in experimental ischemic stroke, HIF-1 up-regulated the expression levels of a variety of genes that are related with glucose transportation and glycolysis, which eventually enhanced glucose metabolism and significantly elevated the production of lactate [204]. This enhanced glycolytic metabolism induced by HIF-1α may possibly be associated with its binding to the gene promoter of MCT4, and could potentially exert neuroprotective impacts on ischemic stroke [204, 205]. A latest study from Yao et al. has showed that LDHA knockdown declined the enrichment of histone lactylation on HMGB1 promoter and decreased the levels of IL-18, IL-1β, cleaved-caspase-1 and GSDMD-N protein in cerebral ischemia/reperfusion model in vivo and in vitro, thus reducing the infarction size and relieving neurological dysfunction in MCAO rats [185]. Their results suggest that histone lactylation mediated by LDHA induces pyroptosis and augments neurological injuries in MCAO model of rats. However, histone lactylation may target diverse genes in physical and pathological conditions, thus the functions and molecular mechanisms of histone lactylation in ischemic stroke are warranted to be further explored.

Taken together, researches investigating the role of histone lactylation in ischemic stroke are still in infancy. Considering the beneficial effects of lactate in ischemic stroke, it deserves further exploration whether histone lactylation is involved in pathology of ischemic stroke or mediates lactate-dependent protection against neurological damage in ischemic stroke.

Conclusions

In this review, we have comprehensively reviewed the roles both lactate itself and histone lactylation play in CNS. Previous studies have proved that lactate plays an important role in the physiology and pathology in CNS, which not only serves as an energy substrate, but also as a signal molecule involved in multiple signaling pathways [4, 27, 206]. Under normal conditions, lactate participates in diverse physical functions in CNS including memory formation, neuronal activity and CBF regulation [27, 69, 70]. Besides, lactate has also been verified to play a vital role in kinds of CNS injuries and degenerative diseases, by supplying energy as a substrate and transmitting signals as a signaling molecule [106, 107, 132, 152, 159]. Noteworthy, the discovery of histone lactylation represents a novel potential way for lactate to exert diverse effects. As indicated, histone lactylation is widely expressed in various cells on physical status in the body, which undergoes changes in different pathological processes. The pivotal role of histone lactylation relies on the regulatory function on target genes expressions via enrichment in the promoter regions. Different from previous findings that lactate is involved in certain signaling pathways, the latest findings indicate that lactate may stimulate transcription of multiple genes directly via histone lactylation [11, 172, 176]. Histone lactylation has been indicated to be involved in homeostasis maintenance and pathophysiological processes in the body [168, 172, 176]. Notably, histone lactylation not only participates in CNS development and stress responses, but also plays an important role in degenerative diseases by regulation of glial functions and neuroinflammation [176, 196]. From the limited investigations on histone lactylation, we can still find the giant potential of histone lactylation in therapies of diseases, especially in inflammatory diseases, cancers, regenerative and repair process of diseases [11, 171, 172, 179]. Given the regulatory effects of histone lactylation on immunity and reparative-related genes, histone lactylation holds promising therapeutic potentials in hypoxic-ischemic encephalopathy including ischemic stroke, which warrants more relevant researches. Besides, the effects of histone lactylation on glia and neurons awaits further investigation.

However, up to now, there is still a lack of methods to specifically regulate histone lactylation, and it is hard to distinguish the effects of histone lactylation from lactate on physiology and pathology of diseases. Therefore, further investigations on dynamic processes and involved enzymes of histone lactylation are warranted. Understanding the processes of histone lactylation more comprehensively and searching for the specific regulatory methods of histone lactylation will benefit elucidating the roles of histone lactylation in diverse diseases, and then shedding light on novel therapeutics for the CNS diseases based on histone lactylation.

Abbreviations

CNS	Central nervous system
OXPHOS	Oxidative phosphorylation
Acetyl-CoA	Acetyl coenzyme A
TCA	Tricarboxylic acid
LDH	Lactate dehydrogenase
PTM	Post-translational modification

GLUTs	Glucose transporters
GPI	Glucose-6-phosphate isomerase
PFK	Phosphofructokinase
TPI	Triose phosphate isomerase
MCTs	Monocarboxylate transporters
ROS	Reactive oxygen species
Pfkfb3	6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3
PK	Pyruvate kinase
PDH	Pyruvate dehydrogenase
Pdk4	Pyruvate dehydrogenase kinase 4
MRC	Mitochondrial respiratory chain
ANLS	Astrocyte-neuron lactate shuttle
ECAR	Extracellular acidification rate
OCR	Oxygen consumption rate
NMDA	N-methyl-d-aspartate
LTP	Long-term potentiation
DCA	Dichloroacetate
BBB	Blood-brain barrier
HCAR1	Hydroxycarboxylic acid receptor 1
EPSC	Excitatory postsynaptic current
cAMP	Cyclic adenosine monophosphate
PKA	Protein kinase A
AC	Adenylate cyclase
CBF	Cerebral blood flow
TBI	Traumatic brain injury
PGE2	Prostaglandin E2
OGD	Oxygen glucose deprivation
MCAO	Middle cerebral artery occlusion
HIF1	Hypoxia-inducible transcription factor
AD	Alzheimer's disease
CSF	Cerebrospinal fluid
VGLL4	Vestigial-like family member 4
LDHA	Lactate dehydrogenase A
APP	Amyloid-β precursor protein
ALS	Amyotrophic lateral sclerosis
PD	Parkinson's disease
ICP	Intracranial pressure
Lactyl-CoA	Lactyl-coenzyme A
HDAC	Histone deacetylase
SIRT	Silent information regulator
Arg1	Arginase1
BCAP	B-cell adapter for PI3K
SAH	Subarachnoid hemorrhage
SCI	Spinal cord injury

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Author contributions
Minjie Xie and Wei Wang raised up the theme and designed the frame of this article. Yao Wang collected the data and wrote this review. Ping Li, Yuan Xu, Linyu Feng, Yongkang Fang, Guini Song, Li Xu, Zhou Zhu participated in collecting previous related articles. Minjie Xie and Qi Mei revised the manuscript carefully. The final version of the manuscript was approved by all the authors.

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Data availability
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Declarations

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Not applicable.

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References

1. Bonvento G, Bolanos JP. Astrocyte-neuron metabolic cooperation shapes brain activity. Cell Metab. 2021;33:1546–64.
2. Jha MK, Morrison BM. Glia-neuron energy metabolism in health and diseases: new insights into the role of nervous system metabolic transporters. Exp Neurol. 2018;309:23–31.
3. Cunnane SC, Trushina E, Morland C, Prigione A, Casadesus G, Andrews ZB, Beal MF, Bergersen LH, Brinton RD, de la Monte S, et al. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Nat Rev Drug Discov. 2020;19:609–33.
4. Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci. 2018;19:235–49.
5. Bordone MP, Salman MM, Titus HE, Amini E, Andersen JV, Chakraborti B, Diuba AV, Dubouskaya TG, Ehrke E, de Espindola A, et al. The energetic brain - A review from students to students. J Neurochem. 2019;151:139–65.
6. Zhang S, Lachance BB, Mattson MP, Jia X. Glucose metabolic crosstalk and regulation in brain function and diseases. Prog Neurobiol. 2021;204:102089.
7. Warburg O, Wind F, Negelein E. THE METABOLISM OF TUMORS IN THE BODY. J Gen Physiol. 1927;8:519–30.
8. Dienel GA. Brain glucose metabolism: integration of energetics with function. Physiol Rev. 2019;99:949–1045.
9. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol. 2011;27:441–64.
10. Magistretti PJ, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. Neuron. 2015;86:883–901.
11. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, et al. Metabolic regulation of gene expression by histone lactylation. Nature. 2019;574:575–80.
12. Chen R, Kang R, Fan XG, Tang D. Release and activity of histone in diseases. Cell Death Dis. 2014;5:e1370.
13. Chen AN, Luo Y, Yang YH, Fu JT, Geng XM, Shi JP, Yang J. Lactylation, a Novel Metabolic Reprogramming Code: current status and prospects. Front Immunol. 2021;12:688910.
14. Perez-Escuredo J, Van Hee VF, Sboarina M, Falces J, Payen VL, Pellerin L, Sonveaux P. Monocarboxylate transporters in the brain and in cancer. Biochim Biophys Acta. 2016;1863:2481–97.
15. Halestrap AP. The SLC16 gene family - structure, role and regulation in health and disease. Mol Aspects Med. 2013;34:337–49.
16. Halestrap AP. Monocarboxylic acid transport. Compr Physiol. 2013;3:1611–43.
17. Song W, Li D, Tao L, Luo Q, Chen L. Solute carrier transporters: the metabolic gatekeepers of immune cells. Acta Pharm Sin B. 2020;10:61–78.
18. Yamagata K. Lactate supply from astrocytes to neurons and its role in ischemic stroke-induced neurodegeneration. Neuroscience. 2022;481:219–31.
19. Miranda-Gonçalves V, Granja S, Martinho O, Honavar M, Pojo M, Costa BM, Pires MM, Pinheiro C, Cordeiro M, Bebiano G, et al. Hypoxia-mediated upregulation of MCT1 expression supports the glycolytic phenotype of glioblastomas. Oncotarget. 2016;7:46335–53.
20. Li M, Sun P, Tu B, Deng G, Li D, He W. Hypoxia conduces the glioma progression by inducing M2 macrophage polarization via elevating TNFSF9 level in a histone-lactylation-dependent manner. Am J Physiol Cell Physiol. 2024;327:C487–504.
21. Bola BM, Chadwick AL, Michopoulos F, Blount KG, Telfer BA, Williams KJ, Smith PD, Critchlow SE, Stratford IJ. Inhibition of monocarboxylate transporter-1 (MCT1) by AZD3965 enhances radiosensitivity by reducing lactate transport. Mol Cancer Ther. 2014;13:2805–16.
22. Lopez E, Karattil R, Nannini F, Weng-Kit Cheung G, Denzler L, Galvez-Cancino F, Quezada S, Pule MA. Inhibition of lactate transport by MCT-1 blockade improves chimeric antigen receptor T-cell therapy against B-cell malignancies. J Immunother Cancer 2023, 11.

23. Blaszczak W, Williams H, Swietach P. Autoregulation of H(+)/lactate efflux prevents monocarboxylate transport (MCT) inhibitors from reducing glycolytic lactic acid production. Br J Cancer. 2022;127:1365–77.
24. Doherty JR, Cleveland JL. Targeting lactate metabolism for cancer therapeutics. J Clin Invest. 2013;123:3685–92.
25. Hashimoto T, Hussien R, Oommen S, Gohil K, Brooks GA. Lactate sensitive transcription factor network in L6 cells: activation of MCT1 and mitochondrial biogenesis. Faseb j. 2007;21:2602–12.
26. Sangsuwan R, Thuamsang B, Pacifici N, Allen R, Han H, Miakicheva S, Lewis JS. Lactate exposure promotes immunosuppressive phenotypes in Innate Immune cells. Cell Mol Bioeng. 2020;13:541–57.
27. Cai M, Wang H, Song H, Yang R, Wang L, Xue X, Sun W, Hu J. Lactate is answerable for brain function and treating Brain diseases: Energy Substrates and Signal Molecule. Front Nutr. 2022;9:800901.
28. Hyden H, Lange PW. A kinetic study of the neuronglia relationship. J Cell Biol. 1962;13:233–7.
29. Hamberger A, Hyden H. Inverse enzymatic changes in neurons and glia during increased function and hypoxia. J Cell Biol. 1963;16:521–5.
30. Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'Keeffe S, Phatnani HP, Guarnieri P, Caneda C, Ruderisch N, et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci. 2014;34:11929–47.
31. Lovatt D, Sonnewald U, Waagepetersen HS, Schousboe A, He W, Lin JH, Han X, Takano T, Wang S, Sim FJ, et al. The transcriptome and metabolic gene signature of protoplasmic astrocytes in the adult murine cortex. J Neurosci. 2007;27:12255–66.
32. Halim ND, McFate T, Mohyeldin A, Okagaki P, Korotchkina LG, Patel MS, Jeoung NH, Harris RA, Schell MJ, Verma A. Phosphorylation status of pyruvate dehydrogenase distinguishes metabolic phenotypes of cultured rat brain astrocytes and neurons. Glia. 2010;58:1168–76.
33. Bolaños JP, Almeida A, Moncada S. Glycolysis: a bioenergetic or a survival pathway? Trends Biochem Sci. 2010;35:145–9.
34. Lopez-Fabuel I, Le Douce J, Logan A, James AM, Bonvento G, Murphy MP, Almeida A, Bolaños JP. Complex I assembly into supercomplexes determines differential mitochondrial ROS production in neurons and astrocytes. Proc Natl Acad Sci U S A. 2016;113:13063–8.
35. Proia P, Di Liegro CM, Schiera G, Fricano A, Di Liegro I. Lactate as a metabolite and a Regulator in the Central Nervous System. Int J Mol Sci 2016, 17.
36. Beard E, Lengacher S, Dias S, Magistretti PJ, Finsterwald C. Astrocytes as key regulators of Brain Energy Metabolism: New Therapeutic perspectives. Front Physiol. 2021;12:825816.
37. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci U S A. 1994;91:10625–9.
38. Pellerin L, Pellegri G, Bittar PG, Charnay Y, Bouras C, Martin JL, Stella N, Magistretti PJ. Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. Dev Neurosci. 1998;20:291–9.
39. Annoni F, Peluso L, Gouvea Bogossian E, Creteur J, Zanier ER, Taccone FS. Brain Protection after Anoxic Brain Injury. Is Lactate Supplementation Helpful? Cells; 2021. p. 10.
40. Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang PW, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487:443–8.
41. Nijland PG, Michailidou I, Witte ME, Mizee MR, van der Pol SM, van Het Hof B, Reijerkerk A, Pellerin L, van der Valk P, de Vries HE, van Horssen J. Cellular distribution of glucose and monocarboxylate transporters in human brain white matter and multiple sclerosis lesions. Glia. 2014;62:1125–41.
42. Pellerin L, Magistretti PJ. Sweet sixteen for ANLS. J Cereb Blood Flow Metab. 2012;32:1152–66.
43. Barros LF, Weber B. CrossTalk proposal: an important astrocyte-to-neuron lactate shuttle couples neuronal activity to glucose utilisation in the brain. J Physiol. 2018;596:347–50.
44. Chuquet J, Quilichini P, Nimchinsky EA, Buzsáki G. Predominant enhancement of glucose uptake in astrocytes versus neurons during activation of the somatosensory cortex. J Neurosci. 2010;30:15298–303.
45. Porras OH, Loaiza A, Barros LF. Glutamate mediates acute glucose transport inhibition in hippocampal neurons. J Neurosci. 2004;24:9669–73.
46. Volkenhoff A, Weiler A, Letzel M, Stehling M, Klämbt C, Schirmeier S. Glial glycolysis is essential for neuronal survival in Drosophila. Cell Metab. 2015;22:437–47.
47. Mächler P, Wyss MT, Elsayed M, Stobart J, Gutierrez R, von Faber-Castell A, Kaelin V, Zuend M, San Martín A, Romero-Gómez I, et al. In vivo evidence for a Lactate gradient from astrocytes to neurons. Cell Metab. 2016;23:94–102.
48. Sada N, Lee S, Katsu T, Otsuki T, Inoue T. Epilepsy treatment. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. Science. 2015;347:1362–7.
49. Dienel GA. Lack of appropriate stoichiometry: strong evidence against an energetically important astrocyte-neuron lactate shuttle in brain. J Neurosci Res. 2017;95:2103–25.
50. Dienel GA. Fueling and imaging brain activation. ASN Neuro 2012, 4.
51. Díaz-García CM, Mongeon R, Lahmann C, Koveal D, Zucker H, Yellen G. Neuronal stimulation triggers neuronal glycolysis and not Lactate Uptake. Cell Metab. 2017;26:361–e374364.
52. Yang S, Qin C, Hu ZW, Zhou LQ, Yu HH, Chen M, Bosco DB, Wang W, Wu LJ, Tian DS. Microglia reprogram metabolic profiles for phenotype and function changes in central nervous system. Neurobiol Dis. 2021;152:105290.
53. Qin C, Zhou LQ, Ma XT, Hu ZW, Yang S, Chen M, Bosco DB, Wu LJ, Tian DS. Dual functions of Microglia in ischemic stroke. Neurosci Bull. 2019;35:921–33.
54. Bernier LP, York EM, MacVicar BA. Immunometabolism in the brain: how metabolism shapes microglial function. Trends Neurosci. 2020;43:854–69.
55. Hammond TR, Dufort C, Dissing-Olesen L, Giera S, Young A, Wysoker A, Walker AJ, Gergits F, Segel M, Nemesh J, et al. Single-cell RNA sequencing of Microglia throughout the mouse lifespan and in the injured brain reveals Complex Cell-State changes. Immunity. 2019;50:253–e271256.
56. Lynch MA. Can the emerging field of immunometabolism provide insights into neuroinflammation? Prog Neurobiol. 2020;184:101719.
57. Voloboueva LA, Emery JF, Sun X, Giffard RG. Inflammatory response of microglial BV-2 cells includes a glycolytic shift and is modulated by mitochondrial glucose-regulated protein 75/mortalin. FEBS Lett. 2013;587:756–62.
58. Gimeno-Bayón J, López-López A, Rodríguez MJ, Mahy N. Glucose pathways adaptation supports acquisition of activated microglia phenotype. J Neurosci Res. 2014;92:723–31.
59. Holland R, McIntosh AL, Finucane OM, Mela V, Rubio-Araiz A, Timmons G, McCarthy SA, Gun'ko YK, Lynch MA. Inflammatory microglia are glycolytic and iron retentive and typify the microglia in APP/PS1 mice. Brain Behav Immun. 2018;68:183–96.
60. Nair S, Sobotka KS, Joshi P, Gressens P, Fleiss B, Thornton C, Mallard C, Hagberg H. Lipopolysaccharide-induced alteration of mitochondrial morphology induces a metabolic shift in microglia modulating the inflammatory response in vitro and in vivo. Glia. 2019;67:1047–61.
61. Sun L, Yang X, Yuan Z, Wang H. Metabolic reprogramming in Immune Response and tissue inflammation. Arterioscler Thromb Vasc Biol. 2020;40:1990–2001.
62. Monsorno K, Buckinx A, Paolicelli RC. Microglial metabolic flexibility: emerging roles for lactate. Trends Endocrinol Metab. 2022;33:186–95.
63. Amaral AI, Tavares JM, Sonnewald U, Kotter MR. Oligodendrocytes: development, physiology and glucose metabolism. Adv Neurobiol. 2016;13:275–94.
64. Rinholm JE, Hamilton NB, Kessaris N, Richardson WD, Bergersen LH, Attwell D. Regulation of oligodendrocyte development and myelination by glucose and lactate. J Neurosci. 2011;31:538–48.
65. Sánchez-Abarca LI, Tabernero A, Medina JM. Oligodendrocytes use lactate as a source of energy and as a precursor of lipids. Glia. 2001;36:321–9.
66. Fünfschilling U, Supplie LM, Mahad D, Boretius S, Saab AS, Edgar J, Brinkmann BG, Kassmann CM, Tzvetanova ID, Möbius W, et al. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature. 2012;485:517–21.
67. Saab AS, Tzvetavona ID, Trevisiol A, Baltan S, Dibaj P, Kusch K, Möbius W, Goetze B, Jahn HM, Huang W, et al. Oligodendroglial NMDA Receptors Regulate Glucose Import and Axonal Energy Metabolism. Neuron. 2016;91:119–32.
68. Kambe Y. Recent behavioral findings of pathophysiological involvement of lactate in the central nervous system. Biochim Biophys Acta Gen Subj. 2022;1866:130137.
69. O'Dowd BS, Gibbs ME, Ng KT, Hertz E, Hertz L. Astrocytic glycogenolysis energizes memory processes in neonate chicks. Brain Res Dev Brain Res. 1994;78:137–41.
70. Rouach N, Koulakoff A, Abudara V, Willecke K, Giaume C. Astroglial metabolic networks sustain hippocampal synaptic transmission. Science. 2008;322:1551–5.
71. Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, Alberini CM. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell. 2011;144:810–23.
72. Newman LA, Korol DL, Gold PE. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS ONE. 2011;6:e28427.

73. Tadi M, Allaman I, Lengacher S, Grenningloh G, Magistretti PJ. Learning-Induced Gene expression in the Hippocampus reveals a role of Neuron -Astrocyte metabolic coupling in Long Term Memory. PLoS ONE. 2015;10:e0141568.
74. Shima T, Matsui T, Jesmin S, Okamoto M, Soya M, Inoue K, Liu YF, Torres-Aleman I, McEwen BS, Soya H. Moderate exercise ameliorates dysregulated hippocampal glycometabolism and memory function in a rat model of type 2 diabetes. Diabetologia. 2017;60:597–606.
75. Harris RA, Lone A, Lim H, Martinez F, Frame AK, Scholl TJ, Cumming RC. Aerobic Glycolysis Is Required for Spatial Memory Acquisition But Not Memory Retrieval in Mice. *eNeuro* 2019, 6.
76. Boury-Jamot B, Carrard A, Martin JL, Halfon O, Magistretti PJ, Boutrel B. Disrupting astrocyte-neuron lactate transfer persistently reduces conditioned responses to cocaine. Mol Psychiatry. 2016;21:1070–6.
77. Zhang Y, Xue Y, Meng S, Luo Y, Liang J, Li J, Ai S, Sun C, Shen H, Zhu W, et al. Inhibition of Lactate Transport erases drug memory and prevents drug Relapse. Biol Psychiatry. 2016;79:928–39.
78. Lucas SJ, Michel CB, Marra V, Smalley JL, Hennig MH, Graham BP, Forsythe ID. Glucose and lactate as metabolic constraints on presynaptic transmission at an excitatory synapse. J Physiol. 2018;596:1699–721.
79. Margineanu MB, Mahmood H, Fiumelli H, Magistretti PJ. L-Lactate regulates the expression of synaptic plasticity and neuroprotection genes in cortical neurons: a transcriptome analysis. Front Mol Neurosci. 2018;11:375.
80. Yang J, Ruchti E, Petit JM, Jourdain P, Grenningloh G, Allaman I, Magistretti PJ. Lactate promotes plasticity gene expression by potentiating NMDA signaling in neurons. Proc Natl Acad Sci U S A. 2014;111:12228–33.
81. Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, Raichle ME. Aerobic glycolysis in the human brain is associated with development and neotenous gene expression. Cell Metab. 2014;19:49–57.
82. Goyal MS, Vlassenko AG, Blazey TM, Su Y, Couture LE, Durbin TJ, Bateman RJ, Benzinger TL, Morris JC, Raichle ME. Loss of Brain Aerobic glycolysis in normal human aging. Cell Metab. 2017;26:353–e360353.
83. El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, El-Ghandour R, Nasrallah P, Bilen M, Ibrahim P, et al. Lactate mediates the effects of Exercise on Learning and Memory through SIRT1-Dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). J Neurosci. 2019;39:2369–82.
84. Lambertus M, Øverberg LT, Andersson KA, Hjelden MS, Hadzic A, Haugen ØP, Storm-Mathisen J, Bergersen LH, Geiseler S, Morland C. L-lactate induces neurogenesis in the mouse ventricular-subventricular zone via the lactate receptor HCA(1). Acta Physiol (Oxf). 2021;231:e13587.
85. Lev-Vachnish Y, Cadury S, Rotter-Maskowitz A, Feldman N, Roichman A, Illouz T, Varvak A, Nicola R, Madar R, Okun E. L-Lactate promotes adult hippocampal neurogenesis. Front Neurosci. 2019;13:403.
86. Nagase M, Takahashi Y, Watabe AM, Kubo Y, Kato F. On-site energy supply at synapses through monocarboxylate transporters maintains excitatory synaptic transmission. J Neurosci. 2014;34:2605–17.
87. Parsons MP, Hirasawa M. ATP-sensitive potassium channel-mediated lactate effect on orexin neurons: implications for brain energetics during arousal. J Neurosci. 2010;30:8061–70.
88. Tang F, Lane S, Korsak A, Paton JF, Gourine AV, Kasparov S, Teschemacher AG. Lactate-mediated glia-neuronal signalling in the mammalian brain. Nat Commun. 2014;5:3284.
89. Bozzo L, Puyal J, Chatton JY. Lactate modulates the activity of primary cortical neurons through a receptor-mediated pathway. PLoS ONE. 2013;8:e71721.
90. de Castro Abrantes H, Briquet M, Schmuziger C, Restivo L, Puyal J, Rosenberg N, Rocher AB, Offermanns S, Chatton JY. The lactate receptor HCAR1 modulates neuronal network activity through the activation of G(α) and G(βγ) subunits. J Neurosci. 2019;39:4422–33.
91. Herrera-López G, Galván EJ. Modulation of hippocampal excitability via the hydroxycarboxylic acid receptor 1. Hippocampus. 2018;28:557–67.
92. Dienel GA. Brain lactate metabolism: the discoveries and the controversies. J Cereb Blood Flow Metab. 2012;32:1107–38.
93. Vafaee MS, Vang K, Bergersen LH, Gjedde A. Oxygen consumption and blood flow coupling in human motor cortex during intense finger tapping: implication for a role of lactate. J Cereb Blood Flow Metab. 2012;32:1859–68.
94. Alessandri B, Schwandt E, Kamada Y, Nagata M, Heimann A, Kempski O. The neuroprotective effect of lactate is not due to improved glutamate uptake after controlled cortical impact in rats. J Neurotrauma. 2012;29:2181–91.
95. Herzog RI, Jiang L, Herman P, Zhao C, Sanganahalli BG, Mason GF, Hyder F, Rothman DL, Sherwin RS, Behar KL. Lactate preserves neuronal metabolism and function following antecedent recurrent hypoglycemia. J Clin Invest. 2013;123:1988–98.
96. Lin AL, Fox PT, Hardies J, Duong TQ, Gao JH. Nonlinear coupling between cerebral blood flow, oxygen consumption, and ATP production in human visual cortex. Proc Natl Acad Sci U S A. 2010;107:8446–51.
97. Hein TW, Xu W, Kuo L. Dilation of retinal arterioles in response to lactate: role of nitric oxide, guanylyl cyclase, and ATP-sensitive potassium channels. Invest Ophthalmol Vis Sci. 2006;47:693–9.
98. Gordon GR, Choi HB, Rungta RL, Ellis-Davies GC, MacVicar BA. Brain metabolism dictates the polarity of astrocyte control over arterioles. Nature. 2008;456:745–9.
99. van Meijel LA, van Asten JJA, Grandjean J, Heerschap A, Tack CJ, van der Graaf M, Wiegers EC, de Galan BE. Effect of lactate administration on cerebral blood flow during hypoglycemia in people with type 1 diabetes. BMJ Open Diabetes Res Care 2022, 10.
100. Yamanishi S, Katsumura K, Kobayashi T, Puro DG. Extracellular lactate as a dynamic vasoactive signal in the rat retinal microvasculature. Am J Physiol Heart Circ Physiol. 2006;290:H925–934.
101. Bharadwaj S, Venkatraghavan L, Mariappan R, Ebinu J, Meng Y, Khan O, Tung T, Reyhani S, Bernstein M, Zadeh G. Serum lactate as a potential biomarker of non-glial brain tumors. J Clin Neurosci. 2015;22:1625–7.
102. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, Donnan GA. Ischaemic stroke. Nat Rev Dis Primers. 2019;5:70.
103. Qin C, Yang S, Chu YH, Zhang H, Pang XW, Chen L, Zhou LQ, Chen M, Tian DS, Wang W. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2022;7:215.
104. Henriksen O, Gideon P, Sperling B, Olsen TS, Jørgensen HS, Arlien-Søborg P. Cerebral lactate production and blood flow in acute stroke. J Magn Reson Imaging. 1992;2:511–7.
105. Cvoro V, Wardlaw JM, Marshall I, Armitage PA, Rivers CS, Bastin ME, Carpenter TK, Wartolowska K, Farrall AJ, Dennis MS. Associations between diffusion and perfusion parameters, N-acetyl aspartate, and lactate in acute ischemic stroke. Stroke. 2009;40:767–72.
106. Berthet C, Lei H, Thevenet J, Gruetter R, Magistretti PJ, Hirt L. Neuroprotective role of lactate after cerebral ischemia. J Cereb Blood Flow Metab. 2009;29:1780–9.
107. Berthet C, Castillo X, Magistretti PJ, Hirt L. New evidence of neuroprotection by lactate after transient focal cerebral ischaemia: extended benefit after intracerebroventricular injection and efficacy of intravenous administration. Cerebrovasc Dis. 2012;34:329–35.
108. Tseng MT, Chan SA, Schurr A. Ischemia-induced changes in monocarboxylate transporter 1 reactive cells in rat hippocampus. Neurol Res. 2003;25:83–6.
109. Zhang F, Vannucci SJ, Philp NJ, Simpson IA. Monocarboxylate transporter expression in the spontaneous hypertensive rat: effect of stroke. J Neurosci Res. 2005;79:139–45.
110. Moreira TJ, Pierre K, Maekawa F, Repond C, Cebere A, Liljequist S, Pellerin L. Enhanced cerebral expression of MCT1 and MCT2 in a rat ischemia model occurs in activated microglial cells. J Cereb Blood Flow Metab. 2009;29:1273–83.
111. Schurr A, Payne RS, Miller JJ, Tseng MT, Rigor BM. Blockade of lactate transport exacerbates delayed neuronal damage in a rat model of cerebral ischemia. Brain Res. 2001;895:268–72.
112. Yu X, Zhang R, Wei C, Gao Y, Yu Y, Wang L, Jiang J, Zhang X, Li J, Chen X. MCT2 overexpression promotes recovery of cognitive function by increasing mitochondrial biogenesis in a rat model of stroke. Anim Cells Syst (Seoul). 2021;25:93–101.
113. Schurr A. Lactate, glucose and energy metabolism in the ischemic brain (review). Int J Mol Med. 2002;10:131–6.
114. Pu J, Han J, Yang J, Yu L, Wan H. Anaerobic Glycolysis and ischemic stroke: from mechanisms and Signaling pathways to Natural Product Therapy. ACS Chem Neurosci. 2024;15:3090–105.
115. Shen Z, Jiang L, Yuan Y, Deng T, Zheng YR, Zhao YY, Li WL, Wu JY, Gao JQ, Hu WW, et al. Inhibition of G protein-coupled receptor 81 (GPR81) protects against ischemic brain injury. CNS Neurosci Ther. 2015;21:271–9.
116. Jourdain P, Allaman I, Rothenfusser K, Fiumelli H, Marquet P, Magistretti PJ. L-Lactate protects neurons against excitotoxicity: implication of an ATP-mediated signaling cascade. Sci Rep. 2016;6:21250.
117. Castillo X, Rosafio K, Wyss MT, Drandarov K, Buck A, Pellerin L, Weber B, Hirt L. A probable dual mode of action for both L- and D-lactate neuroprotection in cerebral ischemia. J Cereb Blood Flow Metab. 2015;35:1561–9.

118. Valenzuela PL, Castillo-García A, Morales JS, de la Villa P, Hampel H, Emanuele E, Lista S, Lucia A. Exercise benefits on Alzheimer's disease: state-of-the-science. Ageing Res Rev. 2020;62:101108.
119. Wang Q, Duan L, Li X, Wang Y, Guo W, Guan F, Ma S. Glucose Metabolism, Neural Cell Senescence and Alzheimer's Disease. Int J Mol Sci 2022, 23.
120. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci. 2019;20:148–60.
121. Liguori C, Stefani A, Sancesario G, Sancesario GM, Marciani MG, Pierantozzi M. CSF lactate levels, τ proteins, cognitive decline: a dynamic relationship in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015;86:655–9.
122. Liguori C, Chiaravalloti A, Sancesario G, Stefani A, Sancesario GM, Mercuri NB, Schillaci O, Pierantozzi M. Cerebrospinal fluid lactate levels and brain 18F FDG PET hypometabolism within the default mode network in Alzheimer's disease. Eur J Nucl Med Mol Imaging. 2016;43:2040–9.
123. Verri M, Aquilani R, Ricevuti G, Rondanelli M, Ghitti M, Bongiorno AI, Venturini L, Buonocore D, Boschi F, Dossena M. Plasma energy substrates at two stages of Alzheimer's disease in humans. Int J ImmunoPathol Pharmacol 2018, 32.
124. Zhang M, Cheng XF, Dang RZ, Zhang WW, Zhang J, Yao ZX. Lactate deficit in an Alzheimer Disease Mouse Model: the relationship with neuronal damage. J Neuropathol Exp Neurol. 2018;77:1163–76.
125. Zheng J, Xie Y, Ren L, Qi L, Wu L, Pan X, Zhou J, Chen Z, Liu L. GLP-1 improves the supportive ability of astrocytes to neurons by promoting aerobic glycolysis in Alzheimer's disease. Mol Metab. 2021;47:101180.
126. Zebhauser PT, Berthele A, Goldhardt O, Diehl-Schmid J, Priller J, Ortner M, Grimmer T. Cerebrospinal fluid lactate levels along the Alzheimer's disease continuum and associations with blood-brain barrier integrity, age, cognition, and biomarkers. Alzheimers Res Ther. 2022;14:61.
127. Kavanagh K, Day SM, Pait MC, Mortiz WR, Newgard CB, Ilkayeva O, McClain DA, Macauley SL. Type-2-Diabetes alters CSF but not plasma metabolomic and AD risk profiles in Vervet monkeys. Front Neurosci. 2019;13:843.
128. Redjems-Bennani N, Jeandel C, Lefebvre E, Blain H, Vidailhet M, Guéant JL. Abnormal substrate levels that depend upon mitochondrial function in cerebrospinal fluid from Alzheimer patients. Gerontology. 1998;44:300–4.
129. Parnetti L, Reboldi GP, Gallai V. Cerebrospinal fluid pyruvate levels in Alzheimer's disease and vascular dementia. Neurology. 2000;54:735–7.
130. Malm J, Kristensen B, Ekstedt J, Adolfsson R, Wester P. CSF monoamine metabolites, cholinesterases and lactate in the adult hydrocephalus syndrome (normal pressure hydrocephalus) related to CSF hydrodynamic parameters. J Neurol Neurosurg Psychiatry. 1991;54:252–9.
131. Leen WG, Willemsen MA, Wevers RA, Verbeek MM. Cerebrospinal fluid glucose and lactate: age-specific reference values and implications for clinical practice. PLoS ONE. 2012;7:e42745.
132. Lu WT, Sun SQ, Li Y, Xu SY, Gan SW, Xu J, Qiu GP, Zhuo F, Huang SQ, Jiang XL, Huang J. Curcumin ameliorates memory deficits by enhancing Lactate Content and MCT2 expression in APP/PS1 transgenic mouse model of Alzheimer's Disease. Anat Rec (Hoboken). 2019;302:332–8.
133. Hypoxia-sensing VGLL4 promotes LDHA-driven lactate production to ameliorate neuronal dysfunction in a cellular model relevant to Alzheimer's disease. *Faseb Journal* 2023, 37.
134. Ravera S, Torazza C, Bonifacino T, Provenzano F, Rebosio C, Milanese M, Usai C, Panfoli I, Bonanno G. Altered glucose catabolism in the presynaptic and perisynaptic compartments of SOD1(G93A) mouse spinal cord and motor cortex indicates that mitochondria are the site of bioenergetic imbalance in ALS. J Neurochem. 2019;151:336–50.
135. Liu FT, Ge JJ, Wu JJ, Wu P, Ma Y, Zuo CT, Wang J. Clinical, dopaminergic, and metabolic correlations in Parkinson Disease: a dual-Tracer PET Study. Clin Nucl Med. 2018;43:562–71.
136. Schirinzi T, Di Lazzaro G, Sancesario GM, Summa S, Petrucci S, Colona VL, Bernardini S, Pierantozzi M, Stefani A, Mercuri NB, Pisani A. Young-onset and late-onset Parkinson's disease exhibit a different profile of fluid biomarkers and clinical features. Neurobiol Aging. 2020;90:119–24.
137. Fedotova EI, Dolgacheva LP, Abramov AY, Berezhnov AV. Lactate and pyruvate activate autophagy and Mitophagy that protect cells in toxic model of Parkinson's Disease. Mol Neurobiol. 2022;59:177–90.
138. Komilova NR, Angelova PR, Berezhnov AV, Stelmashchuk OA, Mirkhodjaev UZ, Houlden H, Gourine AV, Esteras N, Abramov AY. Metabolically induced intracellular pH changes activate mitophagy, autophagy, and cell protection in familial forms of Parkinson's disease. FEBS J. 2022;289:699–711.
139. Li J, Chen L, Qin Q, Wang D, Zhao J, Gao H, Yuan X, Zhang J, Zou Y, Mao Z, et al. Upregulated hexokinase 2 expression induces the apoptosis of dopaminergic neurons by promoting lactate production in Parkinson's disease. Neurobiol Dis. 2022;163:105605.
140. Xu Y, Liu C, Chen S, Ye Y, Guo M, Ren Q, Liu L, Zhang H, Xu C, Zhou Q, et al. Activation of AMPK and inactivation of akt result in suppression of mTOR-mediated S6K1 and 4E-BP1 pathways leading to neuronal cell death in in vitro models of Parkinson's disease. Cell Signal. 2014;26:1680–9.
141. Rahman MH, Bhusal A, Kim JH, Jha MK, Song GJ, Go Y, Jang IS, Lee IK, Suk K. Astrocytic pyruvate dehydrogenase kinase-2 is involved in hypothalamic inflammation in mouse models of diabetes. Nat Commun. 2020;11:5906.
142. Tsai SF, Chen YW, Kuo YM. High-fat diet reduces the hippocampal content level of lactate which is correlated with the expression of glial glutamate transporters. Neurosci Lett. 2018;662:142–6.
143. Timofeev I, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, Smielewski P, Pickard JD, Menon DK, Kirkpatrick PJ, et al. Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. Brain. 2011;134:484–94.
144. Dienel GA. Lactate shuttling and lactate use as fuel after traumatic brain injury: metabolic considerations. J Cereb Blood Flow Metab. 2014;34:1736–48.
145. Wettervik TS, Engquist H, Howells T, Rostami E, Hillered L, Enblad P, Lewén A. Arterial lactate in traumatic brain injury - relation to intracranial pressure dynamics, cerebral energy metabolism and clinical outcome. J Crit Care. 2020;60:218–25.
146. Carpenter KL, Jalloh I, Hutchinson PJ. Glycolysis and the significance of lactate in traumatic brain injury. Front Neurosci. 2015;9:112.
147. Bajamal AH, Apriawan T, Ranuh I, Servadei F, Faris M, Al Fauzi A. Comparison of half-molar sodium lactate and mannitol to treat brain edema in severe traumatic brain injury: a systematic review. Chin J Traumatol. 2021;24:344–9.
148. Holloway R, Zhou Z, Harvey HB, Levasseur JE, Rice AC, Sun D, Hamm RJ, Bullock MR. Effect of lactate therapy upon cognitive deficits after traumatic brain injury in the rat. Acta Neurochir (Wien). 2007;149:919–27. discussion 927.
149. Ichai C, Payen JF, Orban JC, Quintard H, Roth H, Legrand R, Francony G, Leverve XM. Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive Care Med. 2013;39:1413–22.
150. Chen T, Qian YZ, Rice A, Zhu JP, Di X, Bullock R. Brain lactate uptake increases at the site of impact after traumatic brain injury. Brain Res. 2000;861:281–7.
151. Glenn TC, Kelly DF, Boscardin WJ, McArthur DL, Vespa P, Oertel M, Hovda DA, Bergsneider M, Hillered L, Martin NA. Energy dysfunction as a predictor of outcome after moderate or severe head injury: indices of oxygen, glucose, and lactate metabolism. J Cereb Blood Flow Metab. 2003;23:1239–50.
152. Zhai X, Li J, Li L, Sun Y, Zhang X, Xue Y, Lv J, Gao Y, Li S, Yan W, et al. L-lactate preconditioning promotes plasticity-related proteins expression and reduces neurological deficits by potentiating GPR81 signaling in rat traumatic brain injury model. Brain Res. 2020;1746:146945.
153. Millet A, Cuisinier A, Bouzat P, Batandier C, Lemasson B, Stupar V, Pernet-Gallay K, Crespy T, Barbier EL, Payen JF. Hypertonic sodium lactate reverses brain oxygenation and metabolism dysfunction after traumatic brain injury. Br J Anaesth. 2018;120:1295–303.
154. Baxter LR Jr., Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry. 1989;46:243–50.
155. Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. BMC Psychiatry. 2014;14:321.
156. Kennedy SH, Evans KR, Krüger S, Mayberg HS, Meyer JH, McCann S, Arifuzzman AI, Houle S, Vaccarino FJ. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. Am J Psychiatry. 2001;158:899–905.
157. Pan SM, Zhou YF, Zuo N, Jiao RQ, Kong LD, Pan Y. Fluoxetine increases astrocytic glucose uptake and glycolysis in corticosterone-induced depression through restricting GR-TXNIP-GLUT1 pathway. Front Pharmacol. 2022;13:872375.
158. Allaman I, Fiumelli H, Magistretti PJ, Martin JL. Fluoxetine regulates the expression of neurotrophic/growth factors and glucose metabolism in astrocytes. Psychopharmacology. 2011;216:75–84.
159. Shaif NA, Chang DH, Cho D, Kim S, Seo DB, Shim I. The antidepressant-like Effect of Lactate in an animal model of Menopausal Depression. Biomedicines 2018, 6.
160. Carrard A, Cassé F, Carron C, Burlet-Godinot S, Toni N, Magistretti PJ, Martin JL. Role of adult hippocampal neurogenesis in the antidepressant actions of lactate. Mol Psychiatry. 2021;26:6723–35.
161. Karnib N, El-Ghandour R, El Hayek L, Nasrallah P, Khalifeh M, Barmo N, Jabre V, Ibrahim P, Bilen M, Stephan JS, et al. Lactate is an antidepressant

that mediates resilience to stress by modulating the hippocampal levels and activity of histone deacetylases. Neuropsychopharmacology. 2019;44:1152–62.
162. Liberti MV, Locasale JW. Histone lactylation: a New Role for glucose metabolism. Trends Biochem Sci. 2020;45:179–82.
163. Varner EL, Trefely S, Bartee D, von Krusenstiern E, Izzo L, Bekeova C, O'Connor RS, Seifert EL, Wellen KE, Meier JL, Snyder NW. Quantification of lactoyl-CoA (lactyl-CoA) by liquid chromatography mass spectrometry in mammalian cells and tissues. Open Biol. 2020;10:200187.
164. Dai X, Lv X, Thompson EW, Ostrikov KK. Histone lactylation: epigenetic mark of glycolytic switch. Trends Genet. 2022;38:124–7.
165. Dancy BM, Cole PA. Protein lysine acetylation by p300/CBP. Chem Rev. 2015;115:2419–52.
166. Moreno-Yruela C, Zhang D, Wei W, Bæk M, Liu W, Gao J, Danková D, Nielsen AL, Bolding JE, Yang L, et al. Class I histone deacetylases (HDAC1-3) are histone lysine delactylases. Sci Adv. 2022;8:eabi6696.
167. Jin J, Bai L, Wang D, Ding W, Cao Z, Yan P, Li Y, Xi L, Wang Y, Zheng X, et al. SIRT3-dependent delactylation of cyclin E2 prevents hepatocellular carcinoma growth. EMBO Rep. 2023;24:e56052.
168. Dai SK, Liu PP, Li X, Jiao LF, Teng ZQ, Liu CM. Dynamic profiling and functional interpretation of histone lysine crotonylation and lactylation during neural development. Development 2022, 149.
169. Gaffney DO, Jennings EQ, Anderson CC, Marentette JO, Shi T, Schou Oxvig AM, Streeter MD, Johannsen M, Spiegel DA, Chapman E, et al. Non-enzymatic lysine lactoylation of glycolytic enzymes. Cell Chem Biol. 2020;27:206–e213206.
170. Chen L, Huang L, Gu Y, Cang W, Sun P, Xiang Y. Lactate-lactylation hands between metabolic reprogramming and immunosuppression. Int J Mol Sci 2022, 23.
171. Yu J, Chai P, Xie M, Ge S, Ruan J, Fan X, Jia R. Histone lactylation drives oncogenesis by facilitating m(6)a reader protein YTHDF2 expression in ocular melanoma. Genome Biol. 2021;22:85.
172. Wang N, Wang W, Wang X, Mang G, Chen J, Yan X, Tong Z, Yang Q, Wang M, Chen L, et al. Histone lactylation boosts reparative gene activation post-myocardial infarction. Circ Res. 2022;131:893–908.
173. Hu X, Huang J, Li Z, Li J, Ouyang F, Chen Z, Li Y, Zhao Y, Wang J, Yu S, et al. Lactate promotes microglial scar formation and facilitates locomotor function recovery by enhancing histone H4 lysine 12 lactylation after spinal cord injury. J Neuroinflammation. 2024;21:193.
174. An YJ, Jo S, Kim JM, Kim HS, Kim HY, Jeon SM, Han D, Yook JI, Kang KW, Park S. Lactate as a major epigenetic carbon source for histone acetylation via nuclear LDH metabolism. Exp Mol Med. 2023;55:2238–47.
175. Li H, Chawla G, Hurlburt AJ, Sterrett MC, Zaslaver O, Cox J, Karty JA, Rosebrock AP, Caudy AA, Tennessen JM. Drosophila larvae synthesize the putative oncometabolite L-2-hydroxyglutarate during normal developmental growth. Proc Natl Acad Sci U S A. 2017;114:1353–8.
176. Pan RY, He L, Zhang J, Liu X, Liao Y, Gao J, Liao Y, Yan Y, Li Q, Zhou X, et al. Positive feedback regulation of microglial glucose metabolism by histone H4 lysine 12 lactylation in Alzheimer's disease. Cell Metab. 2022;34:634–e648636.
177. Yang W, Wang P, Cao P, Wang S, Yang Y, Su H, Nashun B. Hypoxic in vitro culture reduces histone lactylation and impairs pre-implantation embryonic development in mice. Epigenetics Chromatin. 2021;14:57.
178. Tian Q, Zhou LQ. Lactate activates germline and cleavage embryo genes in mouse embryonic stem cells. Cells 2022, 11.
179. Xiong J, He J, Zhu J, Pan J, Liao W, Ye H, Wang H, Song Y, Du Y, Cui B, et al. Lactylation-driven METTL3-mediated RNA m(6)a modification promotes immunosuppression of tumor-infiltrating myeloid cells. Mol Cell. 2022;82:1660–e16771610.
180. Yang Q, Liu J, Wang Y, Zhao W, Wang W, Cui J, Yang J, Yue Y, Zhang S, Chu M, et al. A proteomic atlas of ligand-receptor interactions at the ovine maternal-fetal interface reveals the role of histone lactylation in uterine remodeling. J Biol Chem. 2022;298:101456.
181. Li L, Chen K, Wang T, Wu Y, Xing G, Chen M, Hao Z, Zhang C, Zhang J, Ma B, et al. Glis1 facilitates induction of pluripotency via an epigenome-metabolome-epigenome signalling cascade. Nat Metab. 2020;2:882–92.
182. Irizarry-Caro RA, McDaniel MM, Overcast GR, Jain VG, Troutman TD, Pasare C. TLR signaling adapter BCAP regulates inflammatory to reparatory macrophage transition by promoting histone lactylation. Proc Natl Acad Sci U S A. 2020;117:30628–38.
183. Chu X, Di C, Chang P, Li L, Feng Z, Xiao S, Yan X, Xu X, Li H, Qi R, et al. Lactylated histone H3K18 as a potential biomarker for the diagnosis and Predicting the severity of septic shock. Front Immunol. 2021;12:786666.
184. Wang L, Wang Y, Meng M, Ma N, Wei G, Huo R, Chang G, Shen X. High-concentrate diet elevates histone lactylation mediated by p300/CBP through the upregulation of lactic acid and induces an inflammatory response in mammary gland of dairy cows. Microb Pathog. 2023;180:106135.
185. Yao X, Li C. Lactate dehydrogenase A mediated histone lactylation induced the pyroptosis through targeting HMGB1. Metab Brain Dis. 2023;38:1543–53.
186. Zhou Y, Yang L, Liu X, Wang H. Lactylation may be a Novel Posttranslational modification in inflammation in neonatal hypoxic-ischemic Encephalopathy. Front Pharmacol. 2022;13:926802.
187. Su J, Zheng Z, Bian C, Chang S, Bao J, Yu H, Xin Y, Jiang X. Functions and mechanisms of lactylation in carcinogenesis and immunosuppression. Front Immunol. 2023;14:1253064.
188. Yang Z, Zheng Y, Gao Q. Lysine lactylation in the regulation of tumor biology. Trends Endocrinol Metab 2024.
189. Zhang Y, Song H, Li M, Lu P. Histone lactylation bridges metabolic reprogramming and epigenetic rewiring in driving carcinogenesis: oncometabolite fuels oncogenic transcription. Clin Transl Med. 2024;14:e1614.
190. Wang Y, Wang W, Su L, Ji F, Zhang M, Xie Y, Zhang T, Jiao J. BACH1 changes microglial metabolism and affects astrogenesis during mouse brain development. Dev Cell. 2024;59:108–e124107.
191. Hagihara H, Shoji H, Otabi H, Toyoda A, Katoh K, Namihira M, Miyakawa T. Protein lactylation induced by neural excitation. Cell Rep. 2021;37:109820.
192. Lu J, Fu S, Dai J, Hu J, Li S, Ji H, Wang Z, Yu J, Bao J, Xu B, et al. Integrated metabolism and epigenetic modifications in the macrophages of mice in responses to cold stress. J Zhejiang Univ Sci B. 2022;23:461–80.
193. Perry VH, Holmes C. Microglial priming in neurodegenerative disease. Nat Rev Neurol. 2014;10:217–24.
194. Krasemann S, Madore C, Cialic R, Baufeld C, Calcagno N, El Fatimy R, Beckers L, O'Loughlin E, Xu Y, Fanek Z, et al. The TREM2-APOE pathway drives the Transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity. 2017;47:566–e581569.
195. Wei L, Yang X, Wang J, Wang Z, Wang Q, Ding Y, Yu A. H3K18 lactylation of senescent microglia potentiates brain aging and Alzheimer's disease through the NFκB signaling pathway. J Neuroinflammation. 2023;20:208.
196. Han H, Zhao Y, Du J, Wang S, Yang X, Li W, Song J, Zhang S, Zhang Z, Tan Y, et al. Exercise improves cognitive dysfunction and neuroinflammation in mice through histone H3 lactylation in microglia. Immun Ageing. 2023;20:63.
197. Fatemi A, Wilson MA, Johnston MV. Hypoxic-ischemic encephalopathy in the term infant. *Clin Perinatol* 2009, 36:835–858, vii.
198. Liu F, McCullough LD. Inflammatory responses in hypoxic ischemic encephalopathy. Acta Pharmacol Sin. 2013;34:1121–30.
199. Zhang F, Zhou J, Lu P, Zhang X, Yang L, Wu J, Zhang L, Zhang L, Pang J, Xie H, et al. Lactylation of histone by BRD4 regulates astrocyte polarization after experimental subarachnoid hemorrhage. J Neuroinflammation. 2024;21:186.
200. Brouns R, Sheorajpanday R, Wauters A, De Surgeloose D, Mariën P, De Deyn PP. Evaluation of lactate as a marker of metabolic stress and cause of secondary damage in acute ischemic stroke or TIA. Clin Chim Acta. 2008;397:27–31.
201. Banerjee A, Ghatak S, Sikdar SK. l-Lactate mediates neuroprotection against ischaemia by increasing TREK1 channel expression in rat hippocampal astrocytes in vitro. J Neurochem. 2016;138:265–81.
202. Kalinichenko SG, Matveeva NY, Korobtsov AV. Brain-derived neurotrophic factor (BDNF) as a Regulator of apoptosis under conditions of focal experimental stroke. Bull Exp Biol Med. 2020;169:701–6.
203. Hertz L, Peng L, Dienel GA. Energy metabolism in astrocytes: high rate of oxidative metabolism and spatiotemporal dependence on glycolysis/glycogenolysis. J Cereb Blood Flow Metab. 2007;27:219–49.
204. Semenza GL. Hypoxia-inducible factor 1: Control of Oxygen Homeostasis in Health and Disease. Pediatr Res. 2001;49:614–7.
205. Ullah MS, Davies AJ, Halestrap AP. The plasma membrane Lactate Transporter MCT4, but not MCT1, is Up-regulated by Hypoxia through a HIF-1α-dependent Mechanism*. J Biol Chem. 2006;281:9030–7.
206. Wu A, Lee D, Xiong WC. Lactate Metabolism, Signaling, and function in Brain Development, synaptic plasticity, angiogenesis, and neurodegenerative diseases. Int J Mol Sci 2023, 24.

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