Trends in
Endocrinology & Metabolism

CellPress
OPEN ACCESS

Review

Microglial metabolic flexibility: emerging roles for lactate

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Microglia, the resident macrophages of the central nervous system (CNS), play important functions in the healthy and diseased brain. In the emerging field of immunometabolism, progress has been made in understanding how cellular metabolism can orchestrate the key responses of tissue macrophages, such as phagocytosis and inflammation. However, very little is known about the metabolic control of microglia. Lactate, now recognized as a crucial metabolite and a central substrate in metabolic flexibility, is emerging not only as a novel bioenergetic fuel for microglial metabolism but also as a potential modulator of cellular function. Parallels with macrophages will help in understanding how microglial lactate metabolism is implicated in brain physiology and pathology, and how it could be targeted for therapeutic purposes.

Highlights

Microglia, the innate immune cells of the central nervous system (CNS), are highly dynamic and rely on metabolic flexibility to sustain their cellular functions.

In addition to energy production, metabolic pathways are important in regulating immune cell function by influencing the inflammatory profile and phagocytic capacity of the cell.

Recent single cell RNA-seq datasets indicate that microglia have all the machinery for rapid metabolic reprogramming and for the utilization of different bioenergetic substrates.

Lactate is emerging as a key brain metabolite associated with synaptic plasticity and CNS pathologies, and recent studies highlight its possible role in controlling microglial function.

Targeting microglial lactate metabolism might prove to be an effective approach to modulate microglia in several CNS diseases.

Microglial metabolic control: a function of context and time

Microglia, the innate immune cells of the CNS, are key players in both physiological and pathological contexts. They actively participate in an ever-growing list of biological processes, including blood vessel sprouting, control of neural precursor cell numbers, the formation and elimination of synapses, and ceaseless monitoring of the brain parenchyma [1]. To ensure constant surveillance, microglia rapidly extend and retract their processes via continuous energy-dependent cytoskeleton rearrangement [2,3]. Their constant motility and phagocytic activities are likely to require sustained ATP levels [4–6]. This observation raises the question of how microglia are able to meet such a high energy demand that is essential for their function. Although an extensive literature covers the link between metabolic reprogramming and immune function in peripheral macrophages (reviewed in [7]), much less is currently known about microglial regulation of energy metabolism.

Most current knowledge about microglial metabolism relies on transcriptomic data, or has been extrapolated from studies on immortalized cell lines or primary cultures. In principle, microglia express all the key enzymes implicated in the major metabolic pathways, indicative of considerable plasticity [8,9]. Thus, the specific metabolic profile adopted by microglia at any given moment likely depends on the availability of the bioenergetic substrates and on the expression of the metabolic machinery in different microglial states. This is further supported by the observation that, at least in mice, genes related to metabolic pathways are differentially expressed in microglia according to the age of the animal and the CNS structure examined [9,10]. Under homeostatic conditions, microglia mostly rely on oxidative metabolism of glucose, which can be replaced by alternative metabolic pathways in the case of scarce glucose availability. In particular, in the absence of glucose, microglia can rapidly shift to other substrates, such as glutamine, to sustain ATP production and preserve homeostatic surveillance [6]. Consistent with this emerging concept of microglial metabolic flexibility, a role for lactate as an alternative metabolic fuel in microglia is highly plausible yet poorly explored.

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Lactate: from a mere waste product to a key brain metabolite

There is extensive evidence that glucose is the main substrate metabolized in adult brain [11,12]. However, during development, brain metabolism is somewhat plastic, and other metabolic fuels such as lactate and ketone bodies are also abundantly catabolized by brain cells [13,14]. For instance, lactate metabolism is believed to play a central role in the perinatal brain, but it seems to gradually decline later on – in parallel with an overall increase in glucose utilization [15]. The exact rate, timing, and triggers of the shift from lactate/ketone to glucose metabolism have been the subject of intense investigations (extensively reviewed in [16]). However, specific changes in differential substrate catabolism by individual brain cell types have not yet been fully elucidated.

Lactic acid was first isolated in 1780 by the Swedish chemist Carl Wilhelm Scheele from sour milk. For a long time it was considered to be a waste product of glycolysis, but it is now widely accepted to be a key metabolite [17,18]. Lactate is formed and utilized continuously not only under anaerobic but also under fully aerobic conditions [19]. This observation laid the foundation for the lactate shuttle hypothesis that describes the movement of lactate both intracellularly (within a cell) and intercellularly (between cells) [20,21]. Indeed, lactate produced by highly glycolytic cells can be shuttled to adjacent cells, where (i) it can be oxidized to pyruvate and serve as a major energy source, (ii) it can act as gluconeogenic precursor, enabling the net synthesis of glucose, (iii) it can work as a signaling molecule [20,21], and (iv) it can modulate transcriptional activity through an epigenetic modification named lactylation [22]. One of the best-studied intercellular lactate shuttles refers to the so-called astrocyte–neuron lactate shuttle (ANLS) hypothesis [23,24]. According to this model, lactate is largely produced by highly glycolytic astrocytes upon sensing synaptic activity. Lactate is then shuttled into neurons and is used to generate energy through its conversion to pyruvate, ultimately fueling oxidative phosphorylation. More recently, oligodendrocytes have also been proposed to act either as lactate providers to neurons [25], or as lactate recipients from astrocytes, to fuel fatty acid synthesis and myelin production [26]. Previous studies have shown that oligodendrocytes – and also astrocytes themselves – can utilize lactate in specific conditions and developmental phases [26,27].

Recent studies indicate that, similarly to what has been extensively described for macrophages, microglia can adapt and fine-tune their metabolic status to meet their functional requirements [28,29]. *In vitro* data indicate that microglia can utilize lactate as a key metabolite and signaling molecule to sustain energy demand and control cellular function [30,31]. This experimental evidence suggests that microglia are not only able to produce lactate through glycolysis, for instance upon lipopolysaccharide (LPS) stimulation [28,29,32], but are also capable of importing it from the extracellular space.

The toolbox for lactate metabolism: sifting through microglial credentials

For lactate to be imported and metabolized, recipient cells need to be equipped with transporters and enzymes that allow efficient oxidation. Lactate transport across cell membranes is made possible by the presence of monocarboxylate transporters (MCTs). Among these, MCT1, MCT2, and MCT4 – encoded by the genes *Slc16a1*, *Slc16a7*, and *Slc16a3*, respectively – are the most abundant in the brain and are all capable of shuttling lactate, pyruvate, and ketone bodies, although with different affinities [33]. The directionality of lactate transport depends on the concentration gradient as well as on the presence of protons because these proteins act as lactate/proton symporters. Each transporter exhibits a specific cellular distribution, and the literature reports that MCT1 is expressed mostly by endothelial cells, ependymocytes, and astrocytes, MCT4 is expressed by astrocytes, whereas MCT2 is found almost exclusively in neurons [23]. MCT expression can vary according to the developmental stage of the individual as well as in pathological states.

Do microglia express MCTs? Although not extensively investigated, it has been recently reported that microglia do express MCTs [34–37]. The expression of MCT1 peaks in these cells between postnatal day (P) 4 and P14 [38]. Transcriptomic databases also reveal that *Slc16a3,* encoding MCT4, is enriched in microglia among other brain cell types [9].

In addition to the presence of suitable transporters, lactate oxidation is tightly dependent on the expression of the enzyme lactate dehydrogenase (LDH) which catalyzes the reversible conversion of pyruvate and NADH to lactate and NAD^+ in a dynamic equilibrium [39]. This enzyme is found either as a homotetramers or a heterotetramers of two different subunits (LDHA and LDHB). LDHB is mostly responsible for catabolizing lactate into pyruvate, whereas the opposite is true for LDHA [39,40]. Therefore, the differential composition of the LDH tetramer can also contribute, together with other factors, to shifting the reaction towards lactate catabolism or production. Interestingly, the expression of *Ldhb* peaks in microglia in early postnatal brain (~2 weeks of age), a period characterized by high microglia-dependent synaptic remodeling. By contrast, the expression of *Ldha* is minimal at this timepoint [41], suggesting that lactate oxidation, rather than production, takes place in microglia during this developmental window. Consistent with a role for lactate during the perinatal period, a higher concentration of this metabolite has been reported in human neonatal brain compared with the brains of infants and children [42].

Of note, we and others reported that *ldhb* is among the most abundant genes expressed in microglia, and that its expression levels are considerably higher than in macrophages in other tissues (ArrayExpress database: E-MEXP-3347 [8,9]). Furthermore, at least in the adult hippocampus, *ldhb* is almost exclusively microglia-specific in comparison to other cell types (Figure 1) [43].

Together, this evidence indicates that lactate may be imported into microglia, promptly oxidized to pyruvate by LDHB, and thus used as a bioenergetic substrate to fuel the tricarboxylic acid (TCA) cycle, supporting a critical role for microglial lactate metabolism. Of note, a recent study conducted on the immortalized murine microglial cell line BV-2 also showed that lactate positively

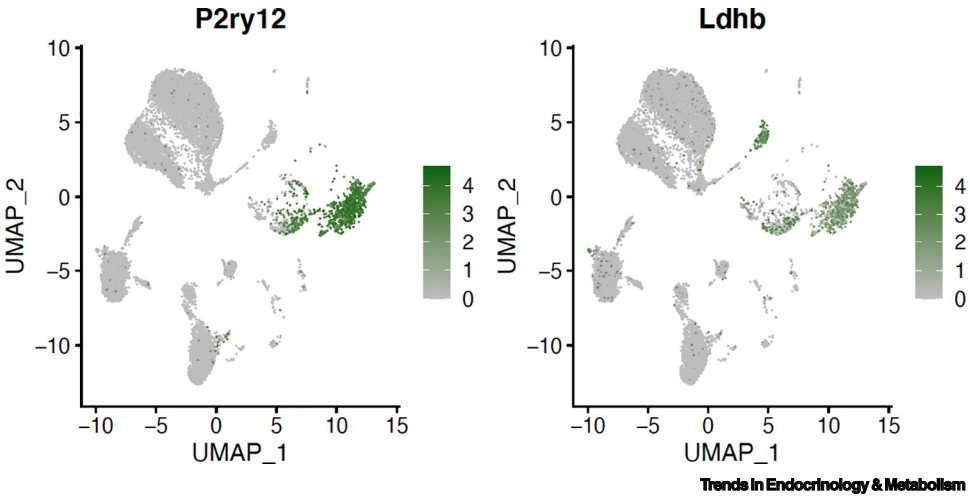

Figure 1. Lactate dehydrogenase (*Ldhb*) gene expression in mouse hippocampal cells. Uniform manifold approximation and projection (UMAP) scores showing clustering of cells isolated from adult murine hippocampus that express *Ldhb* and that are highly enriched in *P2ry12*-positive microglial cells (dataset from Mattei *et al.* [43]).

modulates several key microglia features, including proliferation, migration, and phagocytosis [31]. Although microglia appear to have all the elements required to efficiently metabolize lactate, further *in vivo* studies will be necessary to confirm a role of lactate in controlling microglial function. In addition, given the heterogeneity of microglia in the CNS, it will be important to investigate whether regional differences might influence microglial lactate metabolism.

Microglial lactate metabolism: lessons from the tumor microenvironment

The effects of lactate on microglia have been poorly investigated, and no studies are available, to the best of our knowledge, that directly address the role of lactate in modulating microglial function *in vivo*. However, more is known about the role of this metabolite in other macrophages. Tissue-resident macrophages play important roles in homeostasis and serve as sentinels for tissue damage and foreign antigens. The local environment in which macrophages reside dictates relevant differences in gene expression, and also in morphological, antigenic, and functional properties [44]. Although intrinsic and context-dependent differences emerge in microglia compared with other tissue-resident macrophages, thus limiting direct comparison, these cells share many commonalities. Therefore, some of the functions described for lactate in peripheral macrophages could be at least partially translated to microglia.

One of the best-characterized contexts in which the effects of lactate on immune cells have been studied is the tumor microenvironment. Lactate accumulates massively in the tumor milieu because of the preferential glycolytic metabolism adopted by cancer cells. In this environment it acts synergistically with other tumor-derived factors to reprogram surrounding immune cells to an immune-tolerant phenotype, ultimately favoring tumor growth [45]. Tumor-associated macrophages (TAMs) sense lactate through various routes, including the activation of transmembrane receptors as well as through direct lactate import. In these cells, lactate induces the expression of several genes that are linked to anti-inflammatory and tissue-repair associated phenotypes [46]. In the brain, glioblastoma microglia exhibit profound transcriptional changes, characterized by a downregulated homeostatic transforming growth factor (TGF)-β pathway and downregulation of their sensing capacity, whereas genes involved in phagocytic activity are upregulated [47]. *In vitro* experiments show that glioma cells have a rate of glucose consumption – fourfold higher than microglia [48] – and abundantly release lactate. Whether the lactate released by glioma cells instructs microglia *in vivo*, as it does for TAMs, remains to be further confirmed.

Moreover, with regard to metabolic flexibility, cancer cells themselves may also be very instructive because they are characterized by high metabolic plasticity and, depending on their availability, can rapidly adapt to diverse energetic substrates – including glucose, glutamine, lactate, and lipids (reviewed in [49]). As a convincing example, oxidative cancer cells utilize lactate provided by glycolytic cancer cells, thus sparing glucose and optimizing its bioavailability for hypoxic cells [50,51]. The term 'metabolic symbiosis' was in fact coined to describe the adaptation of some cancer cells to the preferential use of lactate as an energy substrate. Interestingly, in oxidative cancer cells, lactate is not only imported as an alternative energy source but is also utilized to promote v-ATPase-dependent lysosomal acidification and autophagy via LDHB activity [52]. This is indeed a critical process that occurs during the oxidation to pyruvate because the protons produced in the reaction are readily used by the v-ATPase pumps that are located in proximity to the LDHB complexes [52]. Microglia, the major phagocytes of the brain, heavily rely on their degradation machinery, and lysosomes are thus of utmost importance for the execution of basic microglial tasks. It is therefore tempting to speculate that – similarly to oxidative cancer cells – microglia could import extracellular lactate to enhance the acidification of their lysosomes and thus ensure their homeostatic functions in the brain.

A possible role for lactate in microglia–synapse interactions

In specific situations, local lactate metabolism can be highly relevant in the adult brain. One such example is during experience-dependent memory formation. Hippocampal lactate, released from astrocytes, is emerging as an important regulator of learning and memory, at least in hippocampus-dependent tasks [53–56]. The cell specificity of the MCTs involved in this process has been further elucidated by genetic approaches, highlighting the importance of astrocytic MCT4 and neuronal MCT2 for the transfer and import of lactate, respectively, in hippocampus-dependent learning [57]. Long-term memory storage in the brain is tightly linked to synaptic plasticity. Glutamatergic synapses can undergo molecular changes that result in either long-term increases or decreases in synaptic strength, collectively known as long-term potentiation (LTP) and long-term depression (LTD), respectively. Several studies have reported a crucial involvement of microglia in both these forms of synaptic plasticity [58,59]. Recently, Zhang and colleagues directly linked lactate to microglia-dependent induction of synaptic LTD through NADPH oxidase activation [60]. According to the proposed model, the conversion of lactate into pyruvate in microglia is required for the NADPH oxidase-dependent generation of reactive oxygen species (ROS) upon LPS exposure. ROS are thus responsible for the induction of LTD at the synapse, which depends on CR3 activation [60]. As lactate was added exogenously to hippocampal slices, it is very likely that, at least in this setting, lactate import into microglia could be the basis for the observed results. In line with this hypothesis, exogenous lactate administration and intracellular catabolism have been shown to induce ROS production *in vitro* [61].

Long-term memory formation is associated with long-term strengthening of a subset of synapses. This process is accompanied by a sustained and prolonged increase in the local concentration of lactate, which is subsequently imported into neurons where it triggers the induction of molecular changes required for memory formation [53,62]. Microglia respond to increased neuronal activity and contact synaptic terminals, where they sense and release signals that collectively participate in synaptic remodeling. In this context, lactate could itself contribute to initiating a molecular response in these cells, including the expression of soluble factors, similarly to what takes place in peripheral macrophages in a high-lactate environment. For instance, it has been shown that lactate treatment of cultured microglia results in the production of tumor necrosis factor (TNF)-α and interleukin (IL)-1β [63]. These two cytokines are classically defined as proinflammatory mediators but have been also identified as key players in synaptic scaling – a compensatory process that arises under conditions of sustained synaptic activity and that aims to re-establish the homeostatic balance [64,65]. As sustained neuronal firing is coupled with high glutamate release and increased lactate production from astrocytes, lactate might be one of the signals upstream of cytokine production by microglia, similarly to what has been shown *in vitro*. Nevertheless, these findings have not been yet translated to *in vivo* models, and whether lactate-dependent modulation of microglia plays a role in synaptic scaling remains an open question.

Microglial lactate metabolism in infections and brain injuries

Macrophages and microglia easily tailor their metabolic signature to fulfill the energy needs of responding to perturbations in tissue homeostasis, such as in the case of infection or disease [66]. When stimulated with LPS, macrophages increase their glucose uptake, enhance aerobic glycolysis, and attenuate oxidative phosphorylation. Indeed, the macrophage proinflammatory phenotype is preferentially associated with glycolysis and with the pentose phosphate pathway (PPP) at the expense of oxidative phosphorylation and fatty acid oxidation [67–71]. The increased reduction of NADP to NADPH that is associated with the PPP is essential for increased ROS production and sustains the proinflammatory profile (reviewed in [72]).

There is an interesting dichotomy between lactate production and lactate utilization during fine-tuning of immunometabolism. LPS-treated BV-2 cells rely on glycolysis for ATP production that is associated with increased lactate release [28,29,32]. This may imply that microglia could be responsible for lactate shuttling to neurons in the context of a proinflammatory response. Furthermore, extracellular lactate, upon LPS challenge, attenuates induced proinflammatory signaling in macrophages in a dose-dependent manner [73,74]. A similar effect has been described in microglia, where lactate decreased the LPS-induced expression of inducible nitric oxide synthase (iNOS), IL-1β, IL-6, and hypoxia inducible factor (HIF)-1α [36]. This might appear to be in contradiction with previous *in vitro* evidence showing upregulation of TNF-α and IL-1β in microglia exposed to lactate [63]; however, it should be noted that in the latter case no LPS challenge was present, and this might explain the discrepancy. Consistent with lactate import, MCT1 expression was increased in BV-2 cells and primary microglia, and was necessary for the LPS-induced inflammatory response. In mice, intracerebral lactate administration reduced LPS-induced sickness behavior and was also associated with an attenuation of the LPS-induced increase in Iba1-positive cells and proinflammatory cytokine expression in substantia nigra and hippocampus [36]. An increase in MCT1 and MCT2 protein expression was also observed in perilesional macrophages/microglia in the corpus callosum of rats with focal ischemia, and *in vitro* evidence points to TNF-α as a possible trigger for MCT1 upregulation [37].

In pediatric tuberculosis, cerebrospinal fluid (CSF) lactate is increased concomitantly with a decrease in glucose [75]. The authors hypothesize that astrocytes augment the secretion of lactate which can be utilized by microglia as an energy source for the production of ROS to destroy the invading *Mycobacterium tuberculosis* [76].

Lactate is increasingly being considered a neuroprotective energy substrate in a variety of preclinical models for neurological disorders, and there is evidence for protection against excitotoxicity [77,78]. Exogenous administration of lactate was also shown to improve neurological outcome in traumatic brain injury and cerebral ischemia [79–82]. Microglia are important early responders to such insults because they rapidly migrate into ischemic areas where they play crucial roles in tissue repair and remodeling [83,84]. They highly express ROS, TNF-α, and IL-1β, and the extent of TNF-α expression correlated positively with their phagocytic activity in an ischemia mouse model [83]. Together, these data support the compelling hypothesis that the increased cytokine production and phagocytic activity may result from elevated lactate levels, where microglia couple lactate utilization with functions essential for tissue repair, such as clearing debris. In an *in vivo* stroke model characterized by progressive lactate accumulation, Arg1 expression by microglia was recently shown to mediate efficient phagocytosis and tissue repair [85]. Notably, interfering with this pathway results in exacerbated brain damage [85]. The *Arg1* gene, encoding the enzyme arginase, is involved in arginine metabolism and was shown to be upregulated in macrophages upon lactate exposure [46]. Whether lactate induces *Arg1* expression in microglia in ischemic contexts, and thus contributes to the microglia-mediated beneficial outcomes after stroke, is an interesting possibility. In macrophages, Arg1 has been shown to affect phagocytosis at multiple levels, in particular 'efferocytosis' – the process of engulfing and digesting apoptotic cells [86]. During the engulfment phase, Arg1 regulates phagolysosome formation by metabolizing L-arginine released from apoptotic bodies to polyamines, as well as by promoting Rac1 activation, thus resulting in actin polymerization necessary for phagosome formation [87]. Arg1 also regulates the digestion phase by reducing the levels of the Ragulator-Rag complex, an essential regulator of microglial lysosomal activity, leading to an impairment of microglial intracellular degradation [88]. Altogether, lactate-induced Arg1 expression might modulate microglial phagocytosis of dead cells in the ischemic area and thus accelerate tissue recovery and injury resolution.

Microglial metabolic flexibility in neurodegeneration and aging

Microglia are constantly engaged in sensing and interacting with the environment to ensure maintenance of CNS homeostasis. They continuously scan the brain parenchyma and sense abnormal or misfolded protein deposits for removal [89,90]. However, these basic housekeeping functions often appear to be defective in neurodegenerative diseases, where microglia seem to easily cross the line from exerting neuroprotection to contributing to neurotoxicity (reviewed by Hickman *et al.* [91]). The involvement of microglial pathways in the pathogenesis of neurodegeneration is strongly supported by emerging data from genome-wide association studies (GWAS), which reveal that hundreds of genetic variants associated with the risk of developing neurodegenerative disorders are highly expressed in microglia [92]. Despite this evidence, which highlights the role of microglia as key disease modifiers, little is known about the functional consequences of these risk variants for basic cellular properties such as metabolic flexibility. It is thus likely that risk variants affecting the metabolic fitness of microglia could underlie vulnerability to neurodegeneration, in particular in combination with other risk factors that typically contribute to the emergence of sporadic diseases.

Acute exposure to amyloid β (Aβ), the major peptide of Alzheimer's disease (AD) plaques, induces a shift from oxidative phosphorylation to glycolysis in microglia that is associated with a phagocytic phenotype [93]. However, upon prolonged exposure to Aβ, as in a mouse model of AD, microglia seem to undergo defective metabolic reprogramming via the mTOR-AKT-HIF-1α pathway, also involving TREM2 signaling, which can be restored by different approaches such as dietary cyclocreatine, interferon-γ treatment, or TRPV1 pharmacological activation [93–95]. It remains to be elucidated whether increasing extracellular lactate could mimic this metabolic boost and induce the same beneficial effects. Expression of the MCT transporter decreases in AD [96], suggestive of impaired lactate metabolism. Thus, it remains not entirely clear whether exogenously administered lactate would be efficiently imported and oxidized in AD brain. Whether microglia would positively respond to exogenous lactate by increasing their phagocytic capacity remains an interesting hypothesis that awaits further investigation.

The altered expression of MCT subtypes is not only restricted to AD but also occurs in aging. MCT1 expression decreases in aged mice, whereas MCT4 expression increases [34]. In aging *Drosophila*, LDH expression/activity and lactate levels were recently shown to be increased, and were associated with increased conversion of pyruvate into lactate. Moreover, overexpression of LDH in all adult glial cells decreased *Drosophila* lifespan, whereas LDH inhibition was effective in promoting longevity [97]. In addition, several studies report an age-related increase in CNS lactate levels [98,99]. However, the available data are currently limited and the possible link between microglial metabolic flexibility and lactate in aging remains poorly understood.

Concluding remarks and future perspectives

Microglia are key players in a range of biological processes in the CNS, and they harbor the cellular machinery that supports metabolic flexibility for rapid adaptation to changes in cellular needs. The metabolite lactate is central in both physiological and pathological contexts. Thus, it may be an important regulator of microglial metabolic flexibility and could exert modulatory roles on key cellular functions (Figure 2).

In line with this, modulating microglial metabolism to induce a specific functional outcome, such as improved phagocytic capacity and increased neuroprotective profile, is emerging as a promising therapeutic strategy for the treatment of a variety of CNS diseases. In the case of ischemia, for instance, lactate-induced modulation of clearance capacity in microglia may accelerate the removal of cellular debris and promote tissue repair, while attenuating the inflammatory response.

Outstanding questions

Current knowledge about microglial metabolic control mostly relies on *in vitro* studies. Does lactate represent a central metabolite for microglia *in vivo*?

Lactate is emerging as a key metabolite in synaptic plasticity, where microglia are established cellular players. Could lactate instruct microglial metabolic reprogramming and promote specific microglial functions, for example, synaptic pruning, in the context of high levels of synaptic remodeling?

Alterations in lactate levels are associated with several neurodegenerative diseases. What are the functional consequences of lactate-induced metabolic adaptations in microglia in the diseased brain? Could genetic risk variants that affect microglial metabolic flexibility underlie susceptibility to disease development?

Could we harness lactate metabolism to design novel targeted therapeutic approaches in neurodegeneration that aim to modulate microglial cellular properties such as phagocytic capacity and the inflammatory profile?

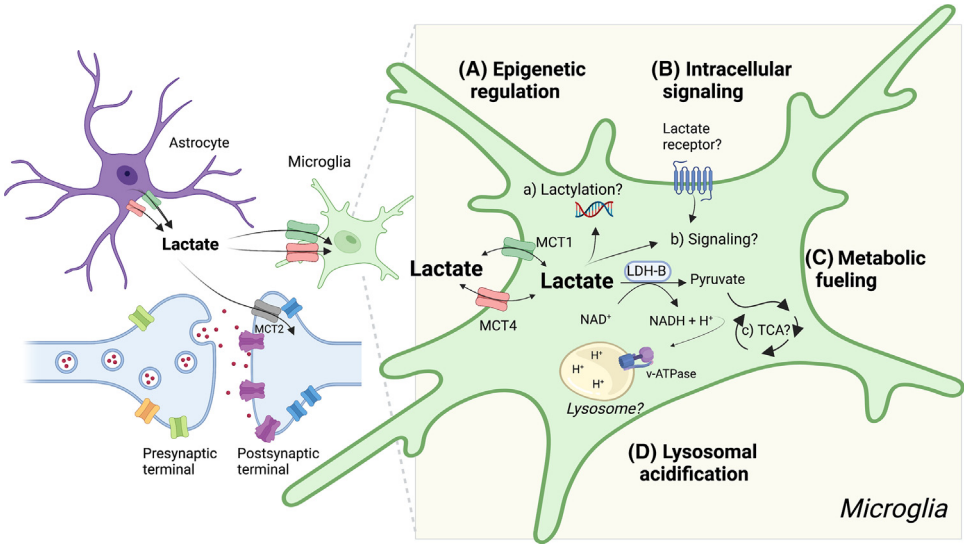

Figure 2. Proposed working model for lactate-mediated effects on microglia. Once imported into microglia via monocarboxylate transporters (MCTs), lactate could serve several distinct purposes: (A) modulation of transcriptional activity through lactylation, a recently described epigenetic modification; (B) activation of intracellular signaling pathways; (C) fueling the tricarboxylic acid (TCA) cycle upon conversion to pyruvate by LDHB; and (D) supporting lysosomal acidification by providing H^+ to lysosomes during the oxidation process. Figure created with BioRender.com.

It is becoming increasingly clear that, on a large scale, the metabolic and functional states of microglial cells are strictly interconnected. Thus, deeper understanding of how metabolic processes can influence and control microglial function will help in devising targeted therapies to restore or boost key microglial processes such as phagocytosis, brain surveillance, and the inflammatory response. Indeed, several preclinical studies have already investigated the potential for metabolic reprogramming of microglia in several CNS pathologies by targeting glucose, amino acids, or fatty acids [66]. In the light of these findings, lactate may represent a promising candidate to modulate microglial metabolism, in particular in contexts characterized by lactate abundance such as brain development, ischemic events, and traumatic brain injuries. Overall, increasing our understanding of the metabolic control of microglial function in brain development and pathology (see Outstanding questions) is imperative for advancing current knowledge in the field, as well as for potential translation to the clinic.

Acknowledgments

Work in the laboratory of the authors is supported by the Swiss National Science Foundation (SNSF 310030_197940), by a European Research Council (ERC) Starting Grant (804949), and by the Synapsis Foundation Alzheimer's Research Switzerland ARS.

Declaration of interests

None are declared.

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