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Review Article

Astrocytes as metabolic suppliers to support neuronal activity and brain functions

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Energy metabolism is essential for brain function. In recent years, lactate shuttling between astrocytes and neurons has become a fundamental concept of neuroenergetics. However, it remains unclear to what extent this process is critical for different aspects of cognition, their underlying mechanisms, as well as for the signals used to monitor brain activation.

Introduction

The coupling between brain metabolism and blood flow on the one hand, and neuronal activity on the other hand, is well recognized in Neuroscience (Figure 1). This notion appeared very early, at the end of the 19th century, when Sherrington proposed a relationship between blood flow, energy supply, and neuronal activity by asserting '. . . the brain possess an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity' [1]. Later on, in the 1970s and 1980s, the work of Louis Sokoloff clearly demonstrated a coupling between neuronal activity and glucose metabolism, with the use of ^{14}C-2-deoxyglucose (DG) and autoradiography [2]. This notion of a close relationship between neuronal activity, blood flow, and metabolism has been the basis of functional brain-imaging techniques that are widely used today by neuroscientists and clinicians. Now, local changes in glucose use, blood flow, and therefore local changes in hemoglobin oxygenation level, for blood oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI), are the classical parameters used to detect neuronal activation [3]. Although blood glucose is the primary substrate for the central nervous system (CNS) in adults, the direct link between its consumption and neuronal activation is far from being fully understood. Indeed, if brain function is generally attributed to neuronal activity, the nervous tissue is made up of different cell types: neurons, of course, but also glial cells, which are closely associated with neurons. Traditionally, neuroscience students were taught that there is on average ten astrocytes for one neuron. This ratio has recently been challenged and is now considered to be overestimated (1:1 ratio in the cortex [4]). From a morphological point of view, astrocytes possess endfeet-ensheating blood capillaries on the one side, thus forming a privileged zone of glucose capture, and are in tight contact with neurons on the other side. As early as 1886, Golgi proposed, in view of this particular organization, that astrocytes might have a role in the delivery of substrates to neurons [5]. Indeed, their privileged location naturally predisposes them to a role in metabolic control, which was already suggested at the end of the 19th century by Andriezen [6] and Holmgren [7], in 1958 by Tschirgi [8] and in 1969 by Henri Laborit [9]. In 1994, a major breakthrough occurred with the proposal of the existence of a lactate shuttle between neurons and astrocytes, which was described by Pellerin and Magistretti [10]. Based on data obtained *in vitro* on astrocytes, this hypothesis suggested that upon brain activation, the glutamate released as a neurotransmitter is taken up by neighboring astrocytes via a sodium-dependent glutamate transporter. The entry of sodium will then activate the Na^+/K^+ ATPase, in order to restore the ionic balance. Activation of this pump consumes ATP, which will then be regenerated by activation of glycolysis, which converts glucose into pyruvate. This pyruvate is subsequently converted to lactate, exported by astrocytes, and transferred

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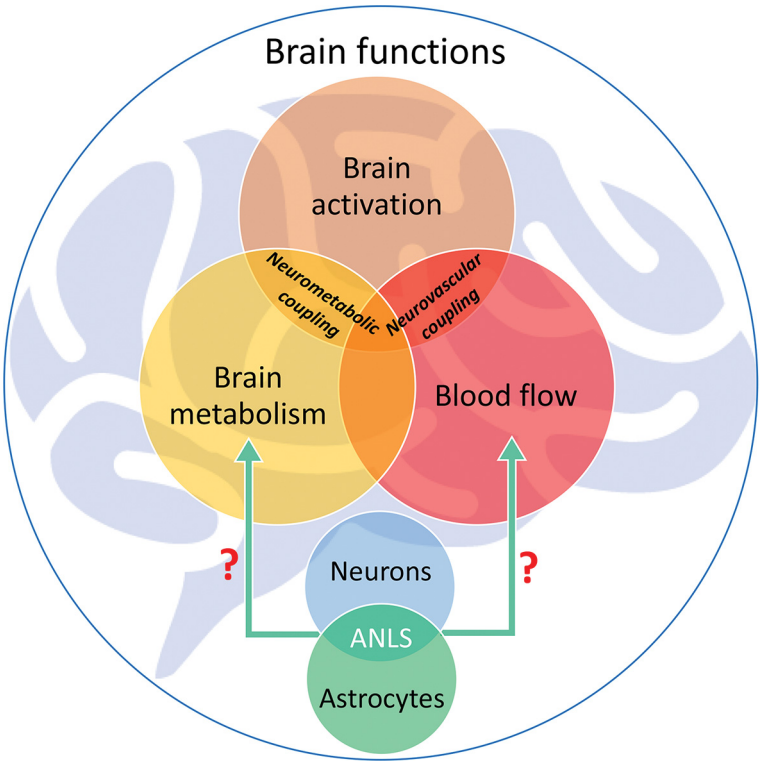

Figure 1. Schematic representation of the links between brain activation, blood flow, and brain metabolism

The impact of the astrocyte-neuron lactate shuttle (ANLS) on both neurovascular and neurometabolic coupling is still unsettled. Using *in vivo* techniques, the link between brain activity and blood flow (**neurovascular coupling**) can be visualized by BOLD fMRI, and the link between brain activation and brain metabolism (**neurometabolic coupling**) by functional magnetic resonance spectroscopy (fMRS).

to neurons via monocarboxylate transporters (or MCTs) [11,12]. Such a prominent metabolic compartmentalization between astrocytes and neurons offers several advantages. For astrocytes, it allows to couple glutamate recycling (requiring two ATP), a major function of astrocytes, to a rapid cytoplasmic source of ATP (i.e. glycolysis providing two ATP) in compartments (astroglial leaflets adjacent of synapses) essentially devoid of mitochondria [13]. For neurons, it was previously shown that lactate is a preferential oxidative energy substrate over glucose [14,15]. Moreover, it was shown that neurons have a limited glycolytic capacity due to the constant degradation of PFKFB3 [16]. They preferentially use glucose for the pentose phosphate pathway (PPP) in order to regenerate NADPH and maintain their antioxidant defenses against radical oxygen species (ROS) (see Almeida et al. in this issue). The use of astrocyte-derived lactate as an oxidative substrate would allow to spare glucose for utilization in the PPP to fight against ROS. Numerous experiments conducted over the last 28 years *in vitro*, *ex vivo*, and *in vivo* have brought evidence that support this concept. However, the importance of this process for brain function is still debated [17,18] (+ comment—Supplementary of this cross-talk).

Metabolic support from astrocytes is essential for somatosensory cortex activity

In order to provide solid evidence of the existence of a lactate transfer between astrocytes and neurons during brain activation, Roumes et al. [19] developed a rat model in which the expression of specific lactate transporters has been repressed in a selective manner either in astrocytes (MCT4) or neurons (MCT2) within a specific brain region: the barrel cortex. This cortical region is involved in environmental exploration with the use of whiskers (including object recognition), but is also a brain region that allows *in vivo* exploration of the neurovascular and neurometabolic couplings. Using a MRI-compatible device, whiskers of control, MCT2- or MCT4-down-regulated rats were stimulated directly into the magnet (7T) and both fMRS (to follow metabolic changes linked to brain activation; the neurometabolic coupling) and BOLD fMRI signals (which reflect neurovascular coupling) were recorded. When

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right whiskers were stimulated, a positive BOLD fMRI signal was measured in control animals in the left barrel cortex, as well as an increase in lactate content. In contrast, when the same experiments were conducted on MCT2- or MCT4-down-regulated rats, both fMRI and fMRS signals associated with this specific neuronal activation disappeared (MCT2) or were reduced (MCT4). Interestingly, the loss of BOLD fMRI signal in MCT4-KD rats was rescued with infusion of lactate. In parallel, while the ability of animals to recognize and distinguish a new object in the classical novel object recognition task (visual task) was preserved, the ability of MCT-down-regulated rats to recognize and distinguish a new object using their whiskers (same object but with a different texture) has been abolished (MCT2) or altered (MCT4). We may notice that if both BOLD fMRI signal and function were lost in MCT2-down-regulated rats, they were abolished in only 50% of MCT4-down-regulated rats. This is consistent with the fact that both MCT4 and MCT1 are present on astrocytes, and that lactate can also be released from connexin hemichannels [20] and/or from lactate-permeable ion channels [21]. Regarding MCT1, which is expressed in most glial cells, endothelial cells and some populations of neurons [22], its role in lactate shuttling and associated brain function remains to be established. A study performed in cultured astrocytes proposed that MCT1 and MCT4 might have distinct roles, MCT1 being essential for basal lactate release while MCT4 would be involved in activity-dependent enhancement of lactate release [23].

Taken altogether, these *in vivo* data indicate that, despite glucose availability, lactate shuttling from astrocytes to neurons turned out to be essential to give rise to the BOLD fMRI signal and to sustain behavioral performance associated with whisker stimulation, highlighting the key role played by astrocytes in sustaining higher cognitive functions, at least in the somatosensory cortex. However, even if fMRI and fMRS are two powerful techniques to study brain activation *in vivo*, they are far from being at the cellular resolution. The link between neuronal-firing rate and the use of lactate as an energy substrate in the barrel cortex at the cellular scale was recently explored by Karagiannis et al. [24]. First, the authors have studied the expression of K_{ATP} channels in the different neuronal populations within the barrel cortex area (layers I–IV). Then, they evaluated their ability to modulate neuronal excitability (membrane potential, membrane resistance, and spiking activity measurements). They found that 32 out of 39 recorded neurons showed modulation of neuronal excitability using K_{ATP} channel pharmacological tools. Since K_{ATP} channels are metabolically sensitive, they also tested their ability to couple astrocytic glycolysis (via lactate provided extracellularly) with spiking activity. While decreasing extracellular glucose concentration from 10 to 2.5 mM had no effect on the firing rate, the addition of 15 mM lactate (to 2.5 mM of glucose; an isoenergetic condition compared with 10 mM glucose) strongly increased the firing rate. Using modulators of K_{ATP} channels, the authors found that lactate enhances neuronal activity via a closure of K_{ATP} channels. This enhancement was abolished with 4-CIN (α-cyano-4-hydroxycinnamic acid, a MCT blocker), indicating that the transport of lactate was required for the firing rate acceleration. Moreover, this lactate was oxidized since an increase in NADH was measured (consistent with the activity of the lactate dehydrogenase). Taken altogether, these *in vivo* and *ex vivo* data suggest that increased astrocytic lactate production induced by whisker stimulation could enhance the activity of cortical neurons, which can be detected by the enhancement of the neuronal firing rate at the cellular level, and by a BOLD fMRI signal at the regional level (Figure 2). Both signals were abolished when the neuronal lactate transporter was impaired (*ex vivo* with 4-CIN, *in vivo* using genetically modified animals), leading also to the loss of function associated with this brain area.

MCT-based lactate shuttling is required for learning and memory involving either the hippocampus or the motor cortex

The importance of astrocytic lactate to support brain function was also demonstrated in another brain region, the hippocampus [25]. In that study, DAB (1,4-dideoxy-1,4-imino-D-arabinitol, an inhibitor of glycogen phosphorylation) was injected into the dorsal hippocampus before or immediately after training in an inhibitory avoidance task. Results indicated that DAB was able to block long-term memory but did not affect short-term memory. While short-term memory requires post-translational modifications, long-term memory, or consolidation, depends upon the activation of gene cascades, cytoskeleton and synaptic structural changes, which cause higher-energy demands. Since it has been shown that astrocytic glycogen breakdown leads to lactate release (*in vitro* [26] and *in vivo* [25]), these data support the idea that astrocytic lactate derived from glycogen is required for long-term memory formation in rats. Moreover, DAB was shown to block the maintenance but not the induction of LTP (long-term potentiation), which could explain the difference observed between short- and long-term memory. Finally, using antisense oligonucleotides to knock down (KD) the astrocytic lactate transporters MCT1 or MCT4, or the neuronal transporter, MCT2, in the hippocampus, the authors showed that lactate export through MCT1 and MCT4, and neuronal import through

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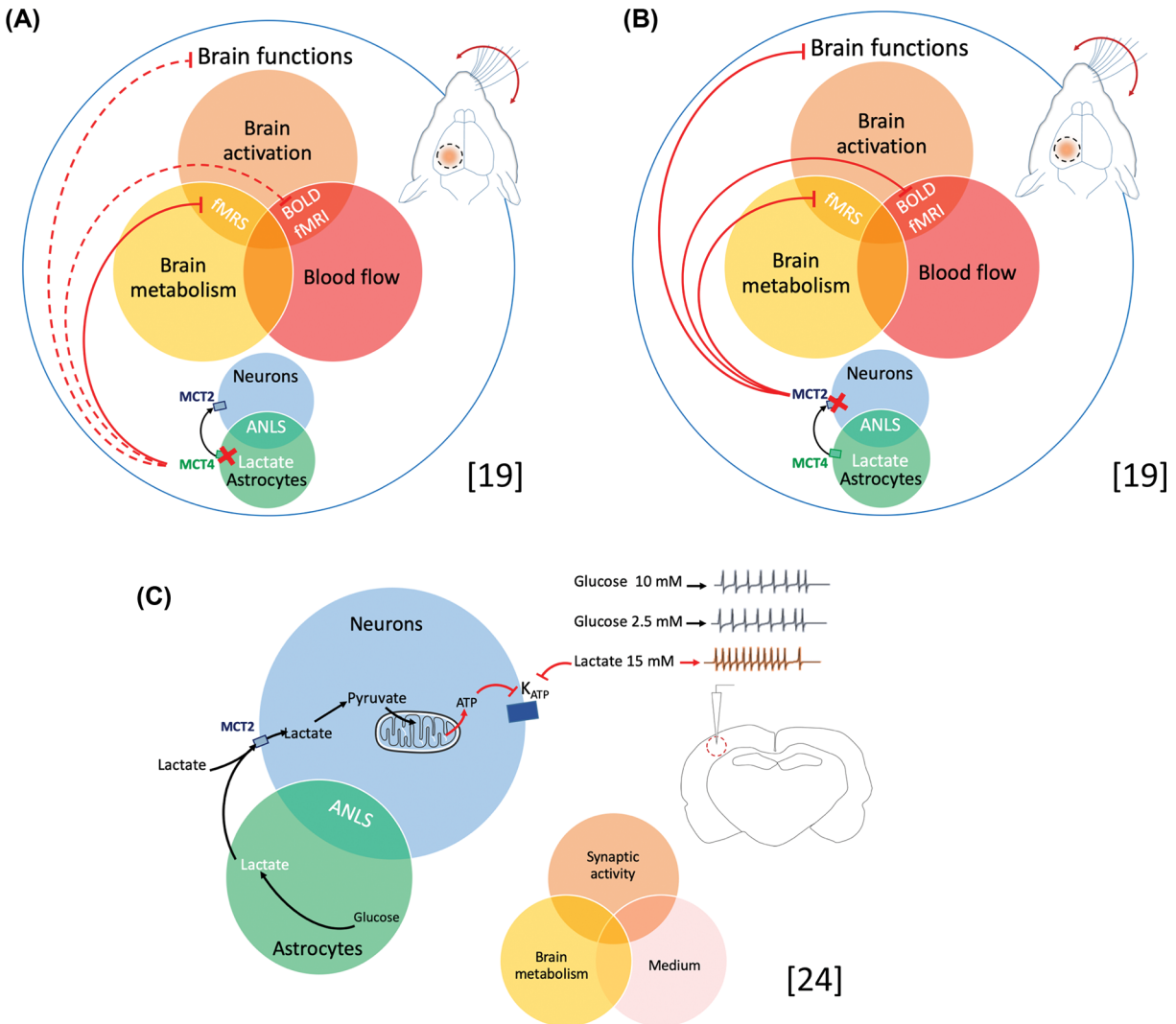

Figure 2. Schematic representation of the demonstration that the astrocytic metabolic supply to neurons through lactate is key for barrel cortex activity and the associated neuronal excitability

(**A**) When MCT4 was down-regulated, BOLD fMRI and fMRS signals as well as behavioral function were reduced (dotted lines) or disappeared (solid line) in 50% of MCT4-KD animals. (**B**) When MCT2 was down-regulated, both BOLD fMRI and fMRS signals linked to whisker stimulation disappeared (solid lines). Behavioral function was also lost. (**C**) At the cellular level, lactate provided by astrocytes to neurons via the MCTs was shown to increase neuronal excitability by allowing the closure of K_{ATP} channels via its oxidative metabolism.

MCT2 were critical for long-term memory formation. Interestingly, lactate, but also pyruvate or β-hydroxybutyrate (in equicaloric conditions) [27] were able to rescue consolidation in the MCT1 or MCT4-KD rats, but not glucose [27] (only a partial rescue was observed with higher concentration of glucose [25]). No rescue was observed in MCT2-KD rats. Therefore, when astrocytic hippocampal glycogen mobilization is blocked (by DAB or isofagomine) or when MCTs are down-regulated, long-term but not short-term memory is impaired, strongly suggesting that the energetic supply needed for consolidation processes is supported by astrocytic glycogen breakdown and a lactate transfer from astrocytes to neurons through the MCTs. Such results were also observed in mice [28]. In this other study, the authors went further and tried to determine to what extent lactate transporters in either neurons or astrocytes are important in learning *versus* memory. They used conditional knockout (KO) mice for either MCT2 or MCT4 (with loxP sites flanking some exons of the targeted MCT). Then, cell-specific (neuron or astrocyte) adeno-associated virus-based vectors containing the sequence encoding the Cre enzyme were injected in the hippocampus to disrupt the expression of MCT2 or MCT4, respectively. Series of behavioral tasks were performed on those mice. First, using the novel object

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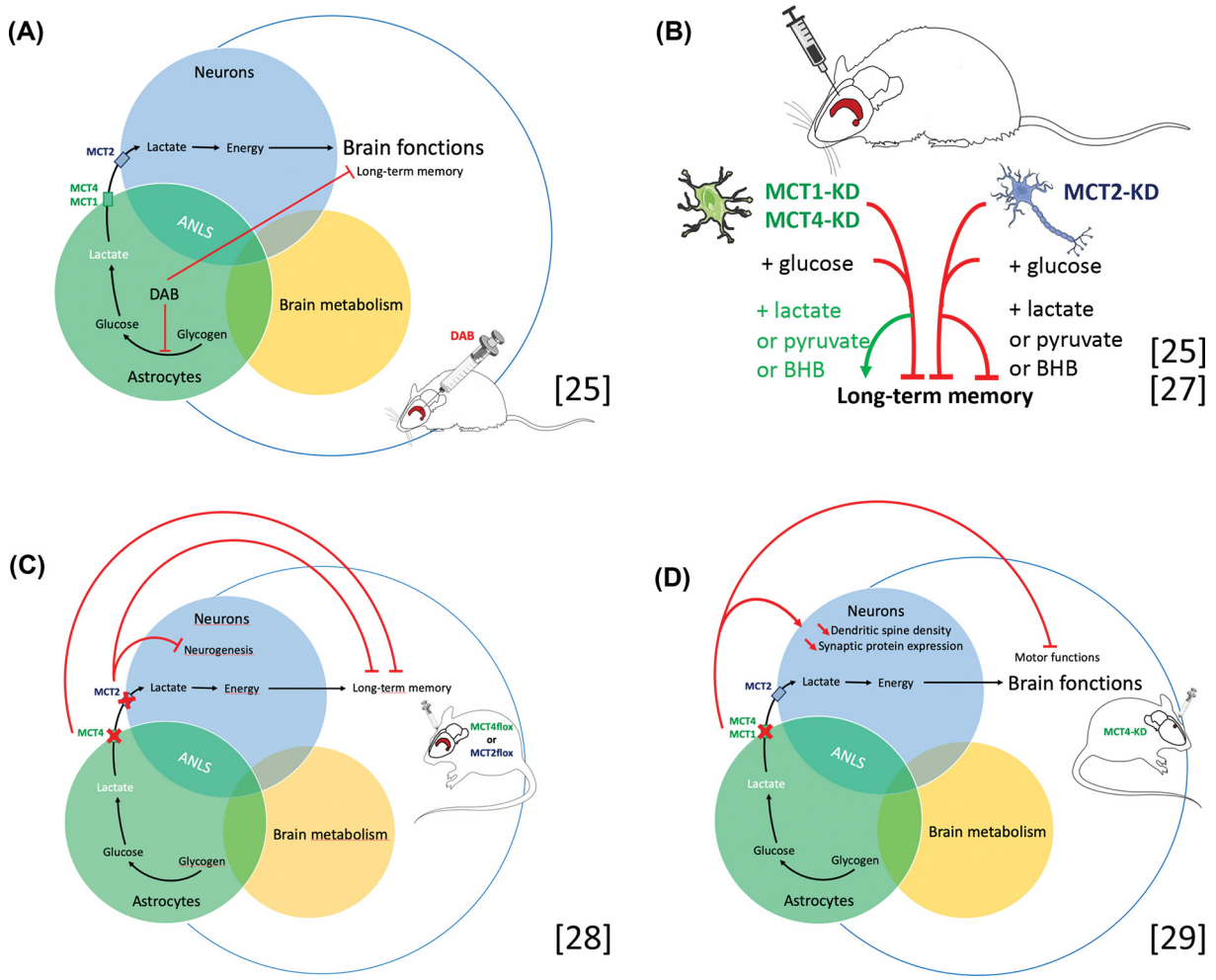

Figure 3. Schematic representation of the demonstration that the astrocytic metabolic supply to neurons through MCTs is important for long-term memory and neurogenesis in the hippocampus as well as for learning and synaptic plasticity in the motor cortex

(**A**) Inhibition of glycogenolysis with DAB prevents long-term but not short-term memory formation in the rat hippocampus. (**B**) Down-regulation of MCT1/4 in astrocytes or MCT2 in neurons of the rat hippocampus prevents long-term memory. This effect is rescued by lactate, pyruvate, and BHB in MCT1/4 KD. Glucose has no effect. (**C**) Invalidation of MCT4 in astrocytes or MCT2 in neurons of the mouse hippocampus prevents long-term memory in a nonspatial task while delaying spatial learning. Only neuronal MCT2 invalidation impairs very long-term memory through alteration of neurogenesis. (**D**) Invalidation of MCT4 in astrocytes of the mouse motor cortex prevents learning of a motor task and impairs synaptic plasticity.

recognition and the inhibitory avoidance tasks, data indicated no alteration in neither the acquisition of information nor short-term memory but an impairment of long-term memory. Thus, these data are in agreement with the previous study while using a different animal model (mice *versus* rats) and a different molecular strategy to reduce MCT expression (conditional KO mice *versus* antisense KD), which strengthened the idea that astrocyte-neuron lactate shuttling is essential for establishing long-term memory formation. Moreover, the Morris water maze was also used to refine the understanding of the involvement of MCTs, since this demanding task needs the more complex acquisition of spatial information. Interestingly, mice with reduced expression of neuronal MCT2 or astrocytic MCT4 exhibited a delay in learning, but were able to achieve the same latency time to reach the platform in the last training days. After having learned the task, MCT4-KD mice were able to recall such information after 7 days, while MCT2-KD animals were not. Consequently, neuronal lactate uptake via MCT2 seems crucial for very long-term memory formation, but not MCT4. Finally, it was observed in MCT2-KD mice (but not in MCT4-KD mice) an alteration of the morphology and distribution of newly differentiating neurons derived from adult neurogenesis in the dentate gyrus. Therefore,

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the present study provides evidence that both MCT2 and MCT4 are important to learn a spatial task, while only MCT2 seems to be involved in the maturation of newborn neurons in the dentate gyrus, and therefore essential for the formation of spatial memory. More recently, the role of MCT4 in learning was explored in another brain region, the motor cortex in mice [29]. The authors selectively knocked down MCT4 expression in astrocytes by injection of a Cre-inducible MCT4 shRNA construct in the M1 primary motor cortex of mice expressing the Cre-recombinase activity selectively in astrocytes. After tamoxifen injection (to allow Cre-recombinase expression), alterations in motor performances of these MCT4-KD mice were evaluated using the open field, the pole test, and the accelerating rotarod. If no difference was observed between control and MCT4-KD mice in the first two tests, these mice showed a reduced level of performance in the accelerating rotarod test, as well as a slower learning rate, indicating that MCT4 is necessary for learning. In addition, a reduction of neuronal dendritic spine density and width was observed, and a decrease in synapse-specific protein expression (cFos, PSD95, and Arc) was measured in the Cre+ (MCT4-KD) mice compared with Cre- (control) mice. Finally, a decrease in glucose uptake (used as surrogate marker for neuronal activity) in the M1 primary motor cortex was detected while performing on the accelerating rotarod when MCT4 was knocked down. However, this latter result was obtained using a near-infrared glucose analog in which size precluding its normal transport by glucose transporters may not reflect glucose utilization but rather its endocytosis, while somehow still reflecting neuronal activity. Notwithstanding, in addition to the somatosensory cortex, these studies support the idea that astrocytic lactate and its transport from astrocytes to neurons through MCTs are required for cognitive functions requiring the hippocampus and the motor cortex (Figure 3).

Adenosine monophosphate-activated protein kinase, a key astrocytic element-regulating lactate production and transfer to neurons

Adenosine monophosphate-activated protein kinase (AMPK) is an evolutionary conserved kinase that couples cellular activity with energy consumption. Therefore, the role of AMPK in the regulation of glycolysis and lactate production in the rodent brain was recently studied [30]. First, the authors performed *in vitro* studies on AMPK-KO (AMPK*null*) astrocytes or neurons. While AMPK*null* astrocytes were deficient in lactate production (lactate concentration measurements in the medium), the invalidation of AMPK in neurons had no effect (to allow lactate detection in the neuronal medium, three times more neurons had to be plated compared with astrocytes). When glucose in the medium was replaced by [U-^{13}C]glucose, AMPK*null* astrocytes showed a 50%-reduction in [U-^{13}C]lactate production. Using a fluorescent glucose analog (2NBDG), glucose import was shown to be significantly reduced in AMPK*null* astrocytes and the membrane translocation of the glucose transporter GLUT1 was markedly reduced. Concerning AMPK*null* neurons, when their culture medium was switched to 0.75 mM glucose, an important cell death was measured, which was completely rescued: (1) by addition of lactate in the medium, (2) by conditioned medium or cocultured condition using wild-type astrocytes. No rescue was observed using conditioned medium or cocultures using AMPK*null* astrocytes. Therefore, AMPK modulates astrocyte-derived lactate production and this lactate plays a specific role in neuronal viability. In a second step, *in vivo* experiments were conducted. ^{1}H-magnetic resonance spectroscopy (MRS) was performed in mice KO for AMPK in both astrocytes and neurons, in the dorsal hippocampus (a brain region enriched in astrocytes) and in the midbrain. *In vivo* quantification of lactate clearly indicated a 40% reduction in these AMPK-KO mice compared with controls. These data were obtained on postnatal day 28, when development of the multilayered murine cerebral cortex is completed. Moreover, neuronal excitability was measured by cortical electroencephalography (wireless-recording system) and found to increase in AMPK-KO mice, which were found to be seizure prone, compared with control mice. Then, cell-specific AMPK-KO mice were produced, in order to suppress AMPK either in astrocytes or in neurons. A reduction in cortical thickness was observed in astrocyte-specific AMPK-KO mice as well as a neuronal loss, indicating that AMPK-regulated metabolic support by astrocytes seems to be essential for postnatal neuronal survival. On the contrary, the neuron-specific AMPK loss was insufficient to reduce cortical thickness. These data were confirmed by silencing AMPK in the fly, in which a hole (indicative of neuronal loss) was observed in the cortex region of the glia-specific AMPK-RNAi fly but not in the neuron-specific AMPK-RNAi fly. Taken altogether, these data indicate that AMPK regulates astrocytic glucose uptake, glycolysis and lactate production and that its activity is required to support neuronal energy metabolism and neuronal survival (Figure 4).

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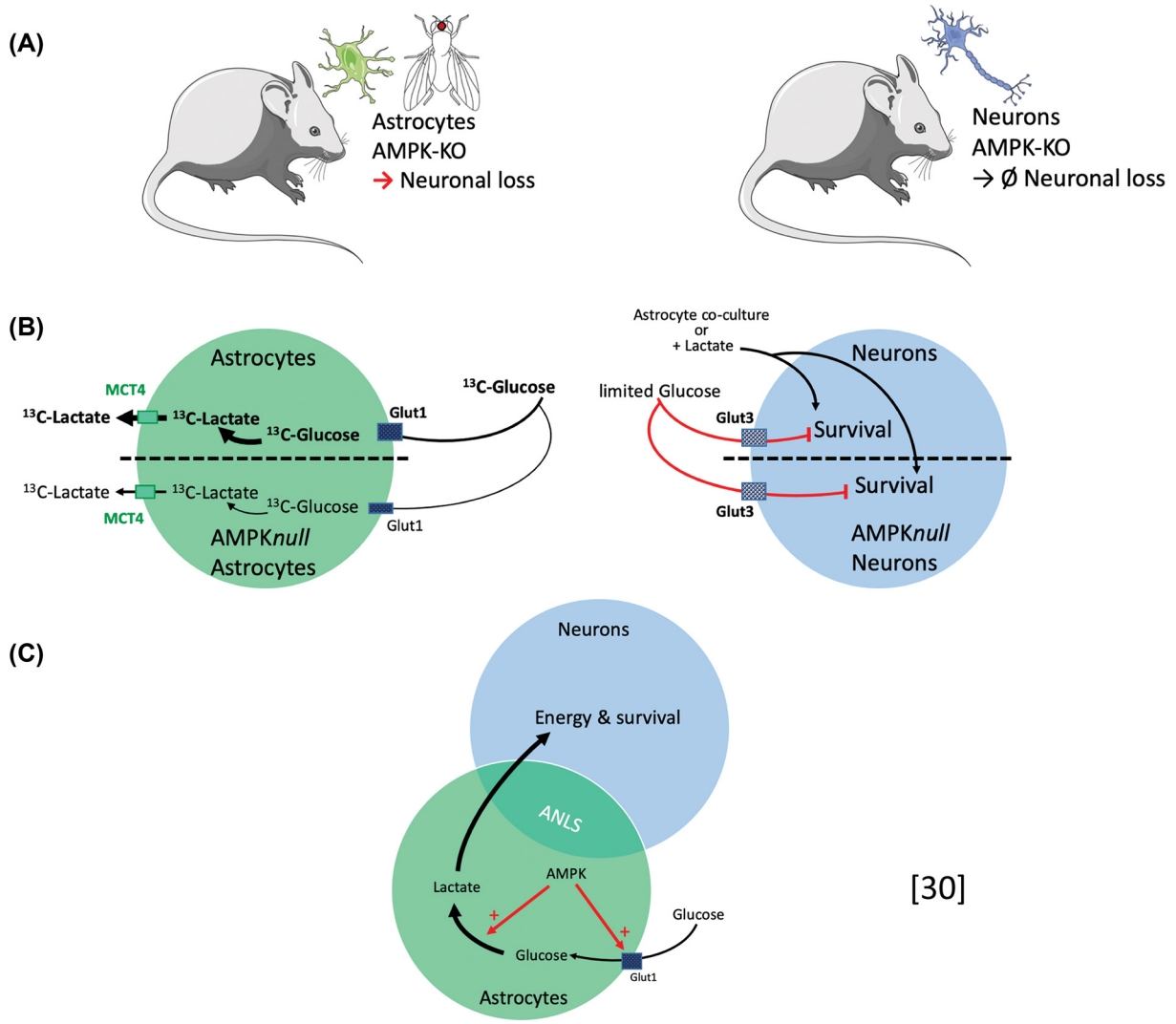

Figure 4. Schematic representation of the key role of AMPK in the modulation of the astrocytic metabolic supply to neurons in both mice and flies

(**A**) AMPK KD in astrocytes of both mouse and fly causes neuronal loss. In contrast, AMPK KD in mouse neurons causes no harm. (**B**) In cultured astrocytes, AMPK KO reduces lactate production. In cultured neurons, AMPK KO leads to cell death when glucose concentration is reduced but a rescue occurs with added lactate or coculture with wild-type astrocytes but not with AMPK KO astrocytes. (**C**) Overall, regulation of astrocytic glycolysis in astrocytes by AMPK is essential for neuronal survival through lactate supply, demonstrating the importance of ANLS.

Pathological implications of a deficit in the astrocytic metabolic support to neurons and possible therapeutic strategies

The link between brain energy metabolism, astrocytic lactate production, and neuronal death is now getting increased attention. Indeed, both AMPK and MCT2 were previously shown to be essential for neuronal survival in a glucose-oxygen deprivation condition (*in vitro* model of ischemia [31]). The authors demonstrated that the activation of AMPK (by tissue-plasminogen activator) leads to the recruitment of GLUT1 on the astrocytic plasma membrane, as well as an increase in astrocytic glucose uptake, followed by the synthesis and the release of lactate. Its neuronal uptake via MCT2 was necessary for neuronal survival in this OGD condition. Considering the link between AMPK and lactate production by astrocytes highlighted above, it is interesting to note that age-related reduction in AMPK activity has been reported [32]. Such an observation might be highly relevant in the context of neurodegenerative

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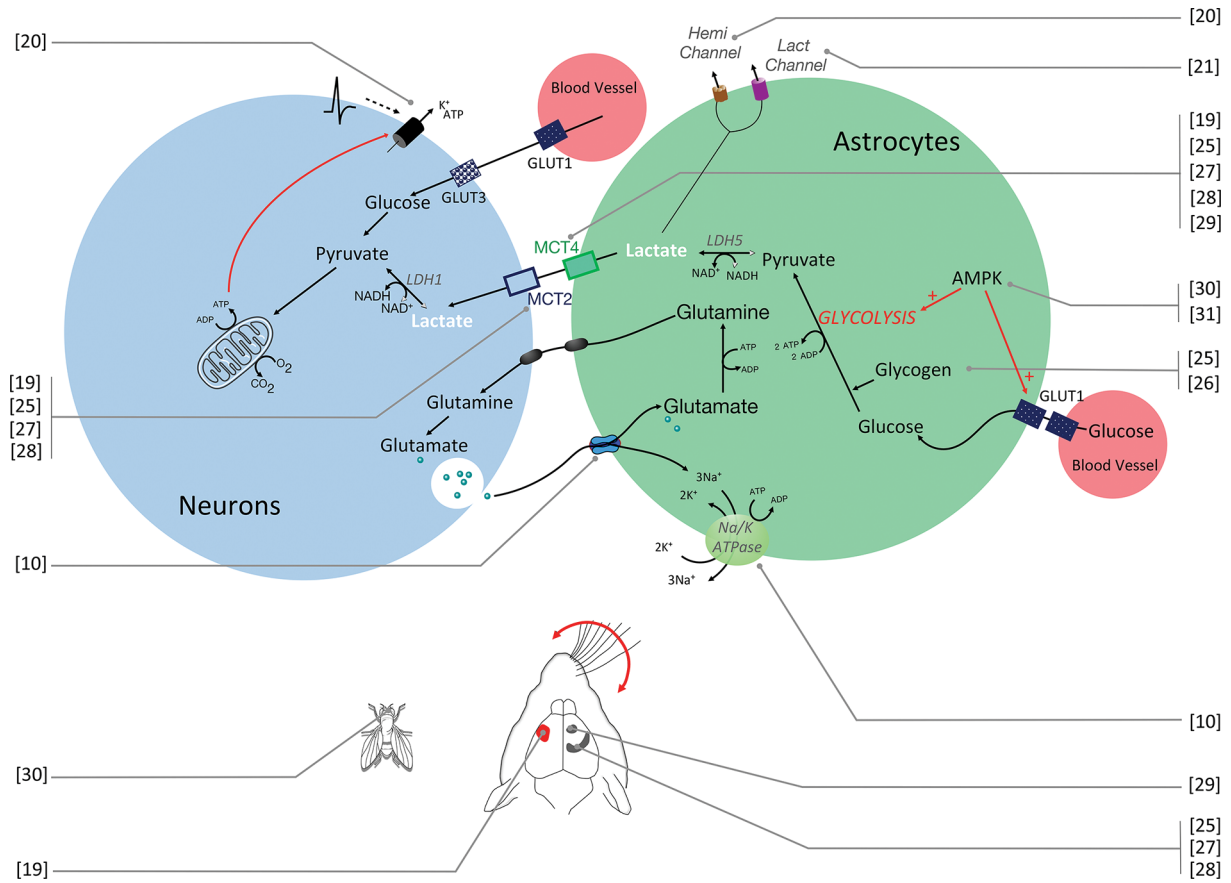

Figure 5. Schematic representation of some recent data supporting an essential role of the ANLS for cognition, based on experiments conducted in different species (fly, rodents) and different brain areas

diseases such as Alzheimer's disease for which hypometabolism has been reported at an early phase in asymptomatic patients [33]. AMPK would thus represent an interesting therapeutic target. Indeed, several interventions are known to enhance AMPK activity, including exercise [34], calorie restriction [35], or even drugs such as metformin [36]. Indeed, these interventions or drugs are known to exert beneficial effects in several conditions, although the mechanism remains poorly defined. Enhancement of astrocytic-derived lactate production via an effect on AMPK might be one explanation.

In stroke (*in vivo* ischemia condition), lactate was shown to be neuroprotective [37]. In a mouse model of stroke (MCAO), after an intravenous injection of 1 µmol/g of lactate, 1 h after the insult, a reduction in brain lesion size was measured, as well as better functional outcome, measured by a neuroscore. Such neuroprotection was also observed in a rat pup model of neonatal hypoxia-ischemia [38]. Interestingly, nutritional supplementation with resveratrol or its derivatives was shown to be neuroprotective, by modulating gene expression linked to the ANLS [39–42]. Among the genes sensitive to polyphenol treatment, the glutamate transporter GLAST, the lactate dehydrogenase b isoform, and the neuronal monocarboxylate transporter MCT2 were up-regulated both at the mRNA and protein levels in the cortex of the ipsilateral hemisphere [30]. The modulation of ANLS, or increasing astrocytic glucose intake and lactate production could therefore have neuroprotective applications. Interestingly, hypometabolism in some brain regions is a hallmark of several neurodegenerative diseases but more specifically of Alzheimer's disease [43]. These metabolic deficits can be present several years prior to the first signs of neurodegeneration [33]. Demonstration that the signal recorded using fluorodeoxyglucose-positron emission tomography (FDG-PET; used to highlight the presence of hypometabolism in patients at-risk of dementia) arises in large part from astrocytes suggests a possible deficit in astrocyte-derived energy supply to neurons [44]. Thus, two recent studies have shown in animal models for Alzheimer's disease that key elements of the ANLS are reduced [45,46]. Quite importantly, both demonstrated that it is possible to reverse not only these metabolic alterations but also the associated cognitive deficits by treating the animals with the hepatokine fibroblast growth factor 21 (FGF21). This hormone has been shown previously to play

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critical roles in the maintenance of whole-body metabolic homeostasis and its actions in the CNS are numerous but remains to be explored [47]. The possibility to use it as a treatment to prevent neurodegeneration, through its action on components of the ANLS, represents a novel and promising therapeutic perspective.

Conclusion

Demonstration of a critical role for the ANLS to support cognitive functions has been provided for three brain regions: hippocampus, somatosensory, and motor cortices (Figure 5). Evidence are emerging that production of astrocyte-derived lactate, under the control of the energy-sensor AMPK, is essential for neuronal activity and survival. Lactate administration is now tested in clinic after traumatic brain injury [48]. In addition to this direct therapeutic approach, finding new ways to target deficits in metabolic supply from astrocytes as occurring in neonatal hypoxia-ischemia, stroke, or Alzheimer's disease might become a valuable therapeutical strategy.

Summary

- Recent data obtained *in vitro*, *ex vivo*, and *in vivo* in different brain regions (somatosensory and motor cortex, hippocampus) and in different species (mouse, rat, fly) support the existence of an ANLS and its importance for neuronal survival and activity, and therefore for cognition.
- Both astrocytic lactate export through the monocarboxylate transporter MCT4 and neuronal lactate import through MCT2 are essential for long-term memory and spatial learning in the hippocampus.
- Import of lactate in neurons through the monocarboxylate transporter MCT2 is essential to observe a BOLD fMRI signal and the associated behavior, in the barrel cortex, and for neurogenesis in the hippocampus.
- MCT4 is essential (but to a lesser extent compared with MCT2) for the BOLD fMRI signal and for the associated behavior in the barrel cortex and the altered signals can be rescued by lactate. MCT4 is also necessary to maintain neuronal spine density in the motor cortex.
- In the barrel cortex, lactate provided by astrocytes to neurons via the MCTs increases neuronal excitability by allowing the closure of K_{ATP} channels via its oxidative metabolism.
- Regulation of astrocytic glycolysis by AMPK is essential to limit neuronal death in the fly brain, and in the mouse hippocampus, through an increase in Glut1 and glycolysis, which leads to an increase in lactate supply, demonstrating the importance of ANLS for neuronal survival.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

H.R., L.P., and A.K.B.S. contributed to the same extent to the writing of the present review.

Abbreviations

4-CIN, α-cyano-4-hydroxycinnamic acid; ANLS, astrocyte-neuron lactate shuttle; BHB, β-hydroxy-butyrate; BOLD, blood oxygen-level dependent; CNS, central nervous system; DAB, 1,4-dideoxy-1,4-imino-D-arabinitol; DG, 2-deoxyglucose; FDG-PET, fluorodeoxyglucose-positron emission tomography; FGF21, fibroblast growth factor 21; fMRI, functional magnetic

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resonance imaging; fMRS, functional magnetic resonance spectroscopy; KD, knock down; KO, knockout; LTP, long-term potentiation; MCAO, middle cerebral artery occlusion; MCT, monocarboxylate transporter; MRS, magnetic resonance spectroscopy; OGD, oxygen-glucose deprivation; PPP, pentose phosphate pathway; ROS, radical oxygen species.

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