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Does astrocytic L-lactate enhance cognition through myelination?

Mastura Akter, Ying Li*

Introduction: Astrocytes, the predominant glial cell in the brain, play a vital role in a plethora of central nervous system functions. They are the major storage site of glycogen in the central nervous system. They produce L-lactate by glycogenolysis and glycolysis which is then transported to neurons (Magistretti and Allaman, 2018). Multiple evidence using diverse behavioral paradigms, such as fear conditioning, conditioned place avoidance, rat gambling task (RGT), and flavor-place paired associate (PA) learning suggest that L-lactate has a beneficial effect on various aspects of cognition (Wang et al., 2017; Akter et al., 2023b). While the molecular mechanisms underlying the cognitive benefits of L-lactate are still emerging, it is well-established that astrocytic L-lactate can be used as an energy substrate by neurons and can induce N-methyl-D-aspartate receptor-dependent plasticity-driven gene expression during cognition (Magistretti and Allaman, 2018). Additionally, recent evidence has revealed more roles of L-lactate which include myelination, neuronal mitochondrial biogenesis, and antioxidant defense (Sanchez-Abarca et al., 2001; Ichihara et al., 2017; Akter et al., 2023a, b). Myelin in the central nervous system is a specialized lipid-rich membrane formed by oligodendrocytes. It ensheathes axons and facilitates the fast and synchronized transfer of information between neurons. Multiple studies, as reviewed by (Xin and Chan, 2020), have suggested that oligodendrocytes and myelin play an important role in modulating cognitive functions such as motor learning, spatial learning, and fear learning. By synthesizing recent evidence, this perspective posits that astrocytic L-lactate-mediated cognitive enhancement, particularly schema memory and decision-making, may be mediated by myelination facilitated by L-lactate.

L-lactate may promote myelination: Astrocytes are known to modulate myelination by secreting different factors. Ichihara et al. (2017) found that blocking the L-lactate production *in vivo* by 1,4-dideoxy-1,4-imino-d-arabinitol, an inhibitor of glycogen phosphorylase, inhibits remyelination of corpus callosum in a cuprizone-induced demyelination mouse model. In line with this, the recovery from cuprizone-induced reduction in the number of GSTπ-positive mature oligodendrocytes was impaired by 1,4-dideoxy-1,4-imino-d-arabinitol. By investigating mouse primary oligodendrocyte progenitor cells (OPC)-rich culture, the authors demonstrated that low glucose condition (0.4 mM) acutely (within 1 day) induced slower cell cycling of cells compared to higher glucose conditions (5.4 and 36.6 mM). L-lactate administration rescued the cell cycle progression deficit as evidenced by increased $BrdU^+$ cell ratio. L-lactate also increased *Mbp* mRNA expression and the MBP^+ cell ratio in both low and high glucose conditions. These data suggested that L-lactate promotes the cell cycling rate and differentiation of OPCs. Another study demonstrated that oligodendrocytes oxidize L-lactate at a higher rate than that observed for neurons and astrocytes (Sanchez-Abarca et al., 2001). They found that the rate of lipid synthesis from L-lactate in oligodendrocytes was at least 6-fold higher than that found in astrocytes or neurons, which is consistent with the high need for lipids for myelin synthesis. Together, these findings suggest that L-lactate is a potential contributor to oligodendrogenesis and myelination.

L-lactate and myelination in different cognition: A recent study demonstrated the role of myelination in conferring stress resilience. The study revealed axonal demyelination in the medial prefrontal cortex of mice in a chronic restraint stress model, which is associated with anxiety-like behaviors. However, exercise prevented both the anxiety-like behaviors and axonal demyelination in this model (Yan et al., 2023). Similarly, several previous studies demonstrated the crucial role of oligodendrocytes and myelin in modulating different cognitive functions (Xin and Chan, 2020). On the other hand, the advantageous effects of L-lactate on cognitive functions have been demonstrated in several behavioral paradigms (Wang et al., 2017; Akter et al., 2023b). Nonetheless, research that demonstrates the cognitive benefits of both myelination and L-lactate within a single behavioral paradigm remains limited. In this context, we discuss our recent studies that have shown the contributions of both L-lactate and myelination in enhancing schema memory and decision-making.

Astrocytic L-lactate and myelination in anterior cingulate cortex (ACC) are essential for schema memory: Schema is a framework of knowledge and is based on multiple episodes that are variable but share a common or basic structure. New learning occurs rapidly if it occurs against a pre-existing relevant schema. Tse et al. (2011) described an experimental paradigm to study PA learning and schema consolidation in rats. The experimental setup involves training rats to associate specific flavors of food pellets given in a start box with specific sand wells in an event arena. Rats are expected to learn multiple flavor-place PAs after several training sessions. Rats are then tested on their ability to retrieve this PA memory through non-rewarded probe tests. Once rats learn multiple PAs and schema is formed, they can learn new PAs in a single training session. Learning of these PAs is dependent on the hippocampus and the memory gradually becomes hippocampus-independent and is stored in the ACC (Tse et al., 2011; Hasan et al., 2019; Akter et al., 2023b).

In a previous study (Hasan et al., 2019), we observed an increased expression of MBP, a biomarker for myelin fibers, in the ACC of PA-trained rats. Ultrastructural analysis using electron microscopy demonstrated increased myelin sheath thickness in the ACC of PA-trained rats. Analysis of MBP in rats that were euthanized at early, middle, and late stages of PA training (after sessions 1, 9, and 18, respectively) demonstrated a progressive enhancement of myelination during PA training. The study also investigated the dynamics of oligodendrogenesis in relation to PA training and schema formation. An increased number of $NG2^+$ cells (a marker of OPCs) was observed after prolonged PA training (after sessions 9 and 18) in the ACC compared to control rats. Colabeling of EdU and CC1 (a marker of mature oligodendrocytes) revealed that a large proportion of OPCs differentiated into mature oligodendrocytes (after sessions 9 and 18), increasing the density of newly produced (i.e., EdU^+ $CC1^+$) oligodendrocytes in the ACC by nearly 50% by session 18. Colabeling of NG2 with Olig2 (a transcription factor that activates the expression of myelin-associated genes in the oligodendrocyte-lineage cells) revealed a significant increase in the Olig2-expressing $NG2^+$ cells in the ACC of PA-trained rats compared to controls. Furthermore, colabeling of Olig2 and CC1 demonstrated that PA-trained rats had a higher number of Olig2-expressing $CC1^+$ cells. Focal demyelination in the ACC by 1% lysolecithin (a demyelinating agent) before PA training resulted in impaired PA learning and schema formation. Demyelination induced after PA learning resulted in impaired memory retrieval, and impaired new PA learning. Together, these results indicate that prolonged PA learning facilitates OPC proliferation, differentiation, and maturation, together with enhanced myelination in the ACC, and that myelination is necessary for schema memory formation.

In a recent study (Akter et al., 2023b), using the same behavioral paradigm, we have shown that astrocytic Gi (hM4Di) pathway activation in the ACC impairs PA learning and schema formation. Gi activation after PA learning revealed impaired memory retrieval of learned PAs, as well as impairment of new PA learning. Astrocytic Gi activation leads to a decrease in the concentration of L-lactate in the extracellular fluid of the ACC. A reduction in the astrocytic cAMP (Akter et al., 2023b) and Ca^{2+} activity (Kol et al., 2020) was demonstrated upon Gi activation which explains the reduction of L-lactate in the ACC as both cAMP and Ca^{2+} are known to promote L-lactate production in astrocytes (Choi et al., 2012; Horvat et al., 2021). Exogenous L-lactate administration directly into the ACC rescued the impairment of PA learning and memory retrieval (Akter et al., 2023b). Given the evidence supporting L-lactate-mediated myelination as described before, one may hypothesize that astrocytic or exogenous L-lactate might facilitate OPC proliferation, differentiation, and myelination associated with PA learning and schema memory formation. Interestingly, the study (Akter et al., 2023b) also found decreased neuronal mitochondrial biogenesis in the ACC of the astrocytic Gi-activated rats, which was rescued and even enhanced by the exogenous L-lactate administration that was correlated with enhanced PA-learning ability in the exogenous L-lactate-treated rats compared to controls. Further studies could be aimed at confirming whether L-lactate's beneficial effect on schema memory is mediated by L-lactate-induced enhancement of myelination and/or neuronal mitochondrial biogenesis, as well as the relationship between myelination and neuronal mitochondrial biogenesis.

Astrocytic L-lactate and myelination in ACC enhance decision-making in visceral hypersensitive rats: Rat visceral hypersensitivity (VH) model is well-established to study visceral pain (e.g., in irritable bowel syndrome) (Wang et al., 2017) which has long been associated with cognitive impairment (Arévalo-Martínez et al., 2022). The model can be prepared through colonic anaphylaxis in adult rats, which involves sensitizing rats to egg albumin by injecting it intraperitoneally for three consecutive days, followed by colorectal perfusion with egg albumin solution and colorectal distension for three more days. VH rats demonstrate ACC astrogliosis together with decreased astrocytic L-lactate production and impaired long-term potentiation and spike-field coherence in the basolateral amygdala-ACC neuronal network which provides a compelling explanation for cognitive deficits observed in chronic visceral pain (Wang et al., 2017). We used RGT, which is a paradigm used to measure decision-making ability in rats, similar to the widely used Iowa gambling task for humans, to study the cognitive deficit in the VH model. RGT involves a conditioning chamber with four circular holes on one side and a food dispenser on the other. During the test, rats are given the freedom to choose any of the four holes, each of which has varying outcomes of food pellet

rewards and penalty times. Rats with strong decision-making ability collect a higher number of food pellets over the long term by selecting the advantageous positions that offer fewer food pellet rewards per nose poke but are associated with significantly shorter penalty times. Our study (Wang et al., 2017) showed that VH rats show decision-making deficits which could be rescued by exogenous L-lactate administration into the ACC or optogenetic activation of ACC astrocytes to enhance L-lactate production. Furthermore, the electrophysiological abnormalities in the VH rats were rescued by L-lactate. These findings provided evidence that astrocytic L-lactate exerts a beneficial effect on decision-making.

In a later study (Hasan et al., 2023), we observed a significant decrease in the fraction of EdU-labeled $CC1^+$ oligodendrocytes (despite having an increased fraction of $NG2^+$ OPCs), reduced MyRF expression (a transcription factor necessary for oligodendrocyte differentiation), decreased level of MBP, and compromised myelin sheath thickness in the ACC of VH rats compared to controls. These results suggested impaired oligodendrogenesis and hypomyelination in the ACC of VH rats. Inducing hypomyelination in the ACC by 1% lysolecithin impaired decision-making in RGT - mimicking the result of VH state. Astrocytic Gq (hM3Dq) pathway activation in the ACC induced OPC proliferation, differentiation, and myelination rescuing decision-making deficits and electrophysiological abnormalities of VH rats. Although the study did not investigate the mediator that could underlie this beneficial effect, we recently discovered that ACC astrocytic Gq pathway activation increases L-lactate levels in the ACC (unpublished data). Given the evidence supporting L-lactate-mediated OPC proliferation, differentiation, and myelination as described before, it is reasonable to hypothesize that the astrocytic Gq activation-mediated enhancement of myelination and decision-making observed in the study was mediated by the increased L-lactate level in the ACC. Future studies could be conducted to confirm this compelling hypothesis.

Conclusion: In addition to the well-established role of astrocytic L-lactate as an energy substrate and synaptic plasticity enhancer to facilitate cognitive functions, evidence suggesting its role in facilitating myelination (**Figure 1**) to enhance cognitive functions is emerging. Robust studies are needed to broaden our understanding of this yet-poorly-understood niche, as this might unravel novel therapeutic strategies for promoting myelination and ameliorating deficits associated with the loss of myelin.

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Mastura Akter, Ying Li*
Department of Neuroscience, City University of Hong Kong, Hong Kong Special Administrative Region, China (Akter M, Li Y)
Department of Biomedical Sciences, City University of Hong Kong, Hong Kong Special Administrative Region, China (Akter M, Li Y)
Centre for Regenerative Medicine and Health, Hong Kong Institute of Science & Innovation, Chinese Academy of Sciences, Hong Kong Special Administrative Region, China (Li Y)
Centre for Biosystems, Neuroscience, and Nanotechnology, City University of Hong Kong, Hong Kong Special Administrative Region, China (Li Y)
***Correspondence to:** Ying Li, MD, yingli@cityu.edu.hk.
https://orcid.org/0000-0003-3683-9695 (Ying Li)

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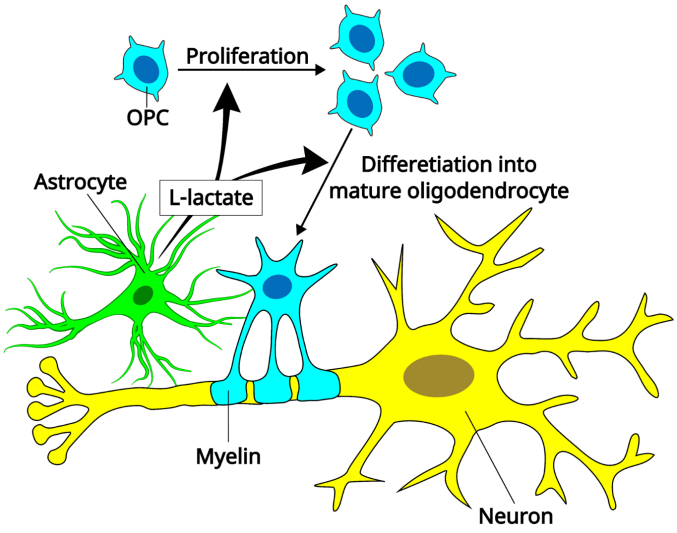

Figure 1 | **Schematic representation of L-lactate promoting myelination.**
Astrocytes may promote the proliferation and differentiation of oligodendrocyte precursor cells (OPCs) into mature myelinating oligodendrocytes through L-lactate. Enhanced myelination could facilitate cognitive functions that rely on myelination. Created with Inkscape. SVG files of astrocyte, oligodendrocyte, and neuron were downloaded from Wikimedia Commons (CC-BY-SA-3.0 or CC-BY-SA-4.0) and further modified to create this figure.

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