The Astrocyte Neuron Lactate Shuttle (ANLS): relevance for neuronal plasticity, memory and disease, with a particular focus on Glut1 deficiency syndrome

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A tight metabolic coupling between astrocytes and neurons is a key feature of brain energy metabolism (Magistretti and Allaman, Neuron, 2015). Over the years we have described two basic mechanisms of neurometabolic coupling. First the glycogenolytic effect of VIP and of noradrenaline indicating a regulation of brain homeostasis by neurotransmitters acting on astrocytes, as glycogen is exclusively localized in these cells. Second, the glutamate-stimulated aerobic glycolysis in astrocytes. Both the VIP-and noradrenaline-induced glycogenolysis and the glutamate-stimulated aerobic glycolysis result in the release of lactate from astrocytes as an energy substrate for neurons (Magistretti and Allaman, Neuron, 2015; Magistretti and Allaman, Nat Neurosci Rev, 2018). This form of neuron-glia metabolic coupling is now known as the Astrocyte Neuron Lactate Shuttle (ANLS), (Pellerin and Magistretti, PNAS, 1994).

We have subsequently shown that lactate is necessary not only as an energy substrate but also as a signaling molecule for long-term memory consolidation (Suzuki et al, Cell, 2011; Vezzoli et al, Cerebral Cortex, 2020). At the molecular level we have found that L-lactate stimulates the expression of synaptic plasticity-related genes such as *Arc*, *Zif268* and BDNF through a mechanism involving NMDA receptor activity and its downstream signaling cascade Erk1/2 (Yang et al, PNAS, 2014). A transcriptome analysis in cortical neurons has shown that the expression of a total of 20 genes is modulated by L-Lactate; of these, 16 involved in plasticity and neuroprotection are upregulated and 4 involved in cell death are downregulated

(Margineanu et al. Front. Mol Neurosci, 2018). This set of results reveal a novel action of L-lactate as a signaling molecule in addition to its role as an energy substrate (Magistretti and Allaman, Nat Neurosci Rev, 2018).

These actions of L-Lactate are also relevant for neuropsychiatric disorders. Indeed we have shown that peripheral administration of lactate exerts antidepressant-like effects in three animal models of depression (Carrard et al ., Mol Psy, 2016). These behavioral effects of L-Lactate administration are accompanied by changes in the expression of genes that have been associated with mood disorders and involve neurogenesis (Carrard et al, Mol.Psy., 2016, 2021).

A disease in which glucose and lactate metabolism are altered is transporter type 1 deficiency syndrome (Glut1DS), also called De Vivo disease (De Vivo et al, NEJM, 1991). The disease is caused by mutations in *SLC2A1* gene that encodes for glucose transporter type 1 (Glut1). In human, this mutation results in deficient glucose transport to the brain and generates early onset epilepsy, complex movement disorders and cognitive impairment (Klepper et al, Epilepsia Open, 2020).

In order to assess the impact of Glut1 deficiency on brain energy metabolism, we measured glycogen, lactate, and glucose levels in the cerebral cortex and hippocampus of a male and female mouse model for Glut1DS (GLUT1 +/-).

A significant decrease in glucose levels was already observed at 2 weeks both in the hippocampus and cerebral cortex of GLUT1 +/- mice compared to wild type (WT) animals (-29% and -42%, respectively) together with a significant reduction in glycogen (-30%) and lactate (-36.9% and -24.7%) levels. In 10-week old mice, similar decreases in hippocampal and cortical glucose, glycogen and lactate level were observed in GLUT1 +/- compared to WT mice (Burlet et al, Society for Neuroscience Abstract, 2022).

These data show that Glut1 deficiency has an early and marked impact on brain energy metabolism not limited to glucose levels but extending to other important energy substrates including lactate and glycogen.

As astrocytes are, along with capillaries, the major site of glucose uptake into the brain through Glut1, glycogen storage and release of lactate, these data suggest that Glut1DS may affect the metabolic cooperation between astrocytes and neurons as operated by the full function of the ANLS. Further elucidation of the mechanisms underlying alterations in the astrocyte-neuron metabolic cooperation in GLUT1+/- mice should help to develop therapeutic targets for the treatment of De Vivo disease. In this context work carried out at GliaPharm has identified a series of molecules that boost the activity of the ANLS and improve motor coordination in an animal model of Glut1 DS.

Conflict of interest declared: PJM is co-founder of GliaPharm.