Neuron-glia metabolic coupling mediated by lactate: relevance for neuronal plasticity, memory and disease

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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).

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 and for maintenance of LTP (Suzuki et al, Cell, 2011). 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 animal models of neuropsychiatric disorders. Indeed we have shown that peripheral administration of lactate exerts antidepressant-like effects in three animal models of mood disorders (Carrard et al, Mol.Psych., 2016). Finally, we have shown that the transfer of L-Lactate from astrocytes to neurons plays a key role in an appetitive memory task involving the basolateral amygdala such as cocaine place preference in mice (Boury-Jamot et al. Mol Psy, 2016).

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