The central role of astrocytes in neuroenergetics

Pierre J. Magistretti, MD, PhD

Brain Mind Institute, EPFL, Lausanne, Switzerland

Division of Biological and Environmental Sciences and Engineering, KAUST, Thuwal, KSA

A tight metabolic coupling between astrocytes and neurons is a key feature of brain energy metabolism (Magistretti and Allaman, 2015). Over the years we have described two basic mechanisms of neurometabolic coupling. First the glycogenolytic effect of VIP - restricted to cortical columns - and of noradrenaline - spanning across functionally distinct cortical areas - 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. This metabolic response is mediated by the sodium-coupled reuptake of glutamate by astrocytes and the ensuing activation of the Na-K-ATPase. 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, 2015).

We have recently revealed a second function of lactate, as a signaling molecule for plasticity. Indeed we have shown that lactate is necessary for long-term memory consolidation and for maintenance of LTP (Suzuki et al, 2011). The role of astrocyte-neuron lactate transfer is not restricted to the hippocampus nor to formation of aversive memories. Indeed in the basolateral amygdala lactate is necessary for the formation of an appetitive memory such as conditioned place preference for cocaine (Boury-Jamot etal, 2015).

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, 2014). L-lactate potentiates NMDA receptor-mediated currents and the ensuing increases in intracellular calcium. These results reveal a novel action of L-lactate as a signaling molecule for neuronal plasticity.