110d A Multicellular Dynamic Model of Neuron-Astrocyte Metabolic Interactions in the Brain

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Understanding the cellular and molecular aspects of neurometabolic activity and neurovascular coupling is one of the challenging areas of research in clinical neuroscience and neurology. Until recently, it has not been clear as to which metabolic pathways are active in neurons as compared to the astrocytes and competing models have been proposed to explain the functional neuroimaging data. Recent findings by Kasischke et al. (2004) on the complementary separation of metabolic activity in the astrocytes and neurons have thrown new light on the energetics of the working brain. These results demonstrate that under focal neural activity the oxidative phosphorylation is increasingly active to meet the ATP demand in the neuronal dendrites. Also, the glycolysis processes in the astrocytes are enhanced only after a substantial delay and produce lactate that is shuttled to the dendrites. The expectation is that the extracellular lactate acts as a buffer in the initial period to maintain the availability of the substrate, lactate in this case, for the increased metabolic activity in the dendrites.

We have developed a novel multicellular dynamic model that accounts for the differential and complementary localization of metabolic processes between the astrocytes and neurons. In this model, the stimulation of excitatory neurons eventually activates voltage-gated sodium channels and Na+/K+ ATPase pumps in the dendrites leading to an increased demand of ATP. Oxidative phosphorylation is increased to meet this demand causing a decrease in mitochondrial NADH content. The mitochondrial NADH is recovered through stimulation of TCA cycle mostly using lactate as a substrate available from the extracellular pool. Simultaneously, a slower process occurs in the astrocytes responding to the same excitatory signal creating ATP demand through activation of the glial Na+/K+ ATPase pumps. This increase in the energy demand is met by enhanced glycolysis in the astrocyte cytoplasm and can be observed in the increased cytosolic NADH content. This enhances the activity of lactate dehydrogenase to convert pyruvate to lactate and regenerate NAD+, thus maintaining high glycolytic flux. The lactate is released in to the extracellular pool and helps maintain the late phase of neuronal activity.

The present model contains 13 states and several of the parameters are obtained from literature on metabolic processes in brain. The model captures several features observed in-vivo suggesting that the proposed mechanism of astrocyte-neuron metabolic interactions could account for the observed brain energetics. In addition, temporal profiles of several metabolic intermediates are correlated with the NADH levels suggesting additional measures for validation of the underlying mechanisms. This dynamic model of the astrocyte-neuron metabolic interactions forms the basis of future studies to analyze the effect of various physiological parameters and help identify disease-related factors that adversely affect the balance of energetics leading to defects in the brain function.

Kasischke KA, Vishwasrao HD, Fisher PJ, Zipfel WR, Webb WW. Neural activity triggers neuronal oxidative metabolism followed by astrocytic glcolysis. Science, v304, pp99-103, 2005.