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Determination of the Phosphate Activated Glutaminase Localization in the Astrocyte Mitochondria Using Kinetic Approach

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Abstract : Phosphate activated glutaminase (GA, E.C. 3.5.1.2) plays a key role in glutamine/glutamate homeostasis in mammalian brain, catalyzing the hydrolytic deamidation of glutamine to glutamate and ammonium ions. GA is mainly localized in mitochondria, where it has the catalytically active form on the inner mitochondrial membrane (IMM) and the other soluble form, which is supposed to be dormant. At present time, the exact localization of the membrane glutaminase active site remains a controversial and an unresolved issue. The first hypothesis called c-side localization suggests that the catalytic site of GA faces the inter-membrane space and products of the deamidation reaction have immediate access to cytosolic metabolism. According to the alternative m-side localization hypothesis, GA orients to the matrix, making glutamate and ammonium available for the tricarboxylic acid cycle metabolism in mitochondria directly. In our study, we used a multi-compartment kinetic approach to simulate metabolism of glutamate and glutamine in the astrocytic cytosol and mitochondria. We used physiologically important ratio between the concentrations of glutamine inside the matrix of mitochondria [Gln_{mit}] and glutamine in the cytosol [Glncyt] as a marker for precise functioning of the system. Since this ratio directly depends on the mitochondrial glutamine carrier (MGC) flow parameters, key observation was to investigate the dependence of the [Glnmit]/[Glncyt] ratio on the maximal velocity of MGC at different initial concentrations of mitochondrial glutamate. Another important task was to observe the similar dependence at different inhibition constants of the soluble GA. The simulation results confirmed the experimental c-side localization hypothesis, in which the glutaminase active site faces the outer surface of the IMM. Moreover, in the case of such localization of the enzyme, a 3-fold decrease in ammonium production was predicted.

Keywords : glutamate metabolism, glutaminase, kinetic approach, mitochondrial membrane, multi-compartment modeling
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