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Contribution of SERCA and IP3 sensitivity to calcium signaling in astrocytes: a computational study

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Modeling the mechanisms of astrocytic calcium signals is important, as astrocytes have an essential role in regulating the neuronal microenvironment of the central nervous system [1,2]. The results of the wet-lab and clinical studies can be complemented by mathematical models to gain better understanding of the complex molecular level interactions seen, for example, in the pathogenesis of Alzheimer's disease (AD). In the aging brain astrocytes are known to change their phenotype [3], also their ionic equilibrium and function can be altered by the interaction of released and accumulated transmitters and peptides, such as, amyloid-β peptides [Aβ, 4]. The authors have recently shown, experimentally and computationally, that small amounts of Aβ25-35 fragment amplify the transmitter-induced calcium signals in astrocytes [5]. The reason for the amplification may be changes in calcium release from endoplasmic reticulum (ER) via, for example, changes in the function of sarco(endo)plasmic calcium adenosine 5'-triphosphatase (SERCA) pumps and/or in intracellular inositol 1,4,5-trisphosphate (IP3) sensitivity [6]. Mutations in presenilin 1 (one of the factors in familial AD involved in the accumulation of Aβ fragments in the brain) may change the activity of the SERCA, which pumps the cytosolic calcium into the ER lumen, leading eventually to higher concentration of calcium in ER [6]. Thus, the current hypothesis is that exceptional cytosolic calcium signals via ER, overfilled with calcium, may explain the calcium changes detected in the presence of Aβ.

We here study the effect of SERCA pumps and IP3 sensitivity on calcium signals in astrocytes by further exploring the existing deterministic [7] and stochastic [5] models to explain the altered calcium regulation. The models include the six major mechanisms known to be involved in calcium signaling in astrocytes; 1) calcium leak from/to extracellular matrix (ECM), 2) capacitive calcium entry from ECM, 3) calcium entry via ionotropic receptors, 4) calcium leak from intracellular stores, such as ER, 5) storage of calcium to ER via SERCA pumps, and 6) calcium release from ER mediated by IP3. In this study, we computationally explore and verify the role of SERCA pump and IP3 sensitivity -induced changes in intracellular calcium signals experimentally shown in [8] and [9]. The understanding of calcium signals in astrocytes is essential as the changes in astrocytic calcium signaling are prone to cause widespread alterations in neuronal network function and can lead to neurological disorders.

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