177f Astrocyte Signaling in the Presence of Spatial Inhomogeneities

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Astrocytes, a special type of glial cells, were considered to have just supporting role in information processing in the brain. However, several recent studies have shown that they can be chemically stimulated by various neurotransmitters such as ATP, and propagate the signal over many cell lengths in the form of a wave before the wave becomes blocked. Pathological conditions, such as spreading depression and epilepsy, have been linked to abnormal range of wave propagation in astrocytic cellular networks. Nevertheless, the underlying intra- and inter-cellular signaling mechanisms responsible for wave propagation and blocking remain unclear. Specifically, it is still an open question whether the experimentally observed finite range of propagation can be attributed to the underlying biological mechanisms or the geometric arrangment of cells, which can in vivo communicate through reaction-free gap junctions. Mathematical modeling and computational experiments can contribute towards revealing the effects of various factors on the range of propagation and investigating the validity of the different hypotheses for wave blocking. Motivated by the above, we constructed a single cell model which accounts for ATP-mediated IP3 production, the subsequent Ca2+ release from the ER through IP3R channels and Ca2+-dependent ATP release into the extracellular space. To describe the coupled astrocytic network, the single cell model was incorporated in a reaction-diffusion framework. To account for spatial inhomogeneities, intracellular reactions were omitted from the part of the domain corresponding to reaction-free gap junctions. Both one-gap and multiple-gap cases were investigated. The minimum gap length that blocks the wave was computed as a function of various signal transduction parameters as well as the geometric arrangement of the cells. In addition to wave blocking, various experimentally observed nonlinear patterns, such as wave reflection and generation of sequences of echo waves, were also predicted by the model and their relationship to the geometric characteristics of the network was numerically elucidated. Such patterns have been reproduced by models describing other systems, like the heart tissue, however none of these has taken into account the salient features of intracellular signal transduction mechanisms in astrocytes. Therefore, the proposed model can provide valuable insight into understanding the relationship between single-cell signal transduction mechanisms and wave propagation and blocking in spatially inhomogeneous astrocytic networks. Furthermore it can offer possible explanations for the observed abnormal wave propagation in pathological situations.