

Role of Astrocyte in Cortical Spreading Depression: A Quantitative Model of Neuron-Astrocyte Network

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Abstract. Cortical spreading depression (CSD) involves depolarization of neurons and astrocytes due principally to a large increase in extracellular potassium. CSD is also accompanied by large increases in extracellular ATP and is blocked by glutamate N-methyl-D-aspartate (NMDA) receptor antagonists. In a previous study, we used a neuronal model to investigate the instigation of CSD and propagation of CSD wave by increasing extracellular potassium. In this paper, we extend that model by constructing a neuron-astrocyte network and incorporating the effects of ATP via the coupled biochemical pathways involving glutamate and NMDA currents. We show that both the electrical current stimuli and the local elevation in the extracellular ATP or glutamate concentration can lead to CSD in the coupled neuron-astrocyte model, while ATP or glutamate increase fails to induce CSD when the glutamate NMDA channels are blocked. These results can explain both the potassium theory postulated by Grafstein and glutamate theory by Van Harreveld. Our model showed extracellular potassium plays the key role in CSD instigation and propagation, and glutamate is a key compound mediating CSD by activating NMDA channels through neuron-astrocyte interactive.

AMS subject classifications: 35K57, 65M06, 92C05, 92C20

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1 Introduction

Since cortical spreading depression (CSD) was first discovered by Leao [1], a growing number of experimental evidence and theoretical work have linked this phenomenon to a number of pathological conditions [2–4]. However, there is still controversy to what signaling pathways mediate the propagation of a CSD wave. For example, Grafstein first raised the potassium theory as the interpretation of CSD propagation: the intense neuronal activity preceding depression results in the liberation of potassium into the extracellular space (ECS) in sufficient quantity to depolarize adjacent cells [2]. On the other hand, Van Harreveld had proposed an alternative hypothesis that CSD was triggered by glutamate [3]. Evidence seems to favor the potassium hypothesis [5], although neither of the hypotheses can fully explain the experimental observations, and propagation is probably realized by a combination of these mechanisms [6].

After the first model of CSD based on Grafstein's potassium theory [4], the regenerative release and diffusion of potassium ions were included in a number of simulations. Some of them incorporate voltage-gated potassium channels, and thus associate CSD with neuronal spiking [7]. An alternative approach is based on the experimental evidence that blocking neuronal spiking by tetrodotoxin (TTX) does not prevent propagation of the CSD wave [8]. We have presented a continuum neuronal model to show that there are CSD waves when applying KCl in the ECS either in blocking the fast sodium channels (i.e. effectively treating the cortex with TTX) or not [9], and TTX block the neuronal spiking. It was demonstrated that treating the cortex with TTX does not prevent the instigation and spreading of CSD, but slows the spreading speed.

Bennet et al. [10] proposed an astrocyte network model to study CSD wave based on the assumption that glutamate is released due to an ATP wave that acts on NMDA receptors of the neurons to trigger membrane depolarization. Further releases of ATP and glutamate occur in neighboring cells and this leads a CSD wave. However, ion diffusion in the ECS is not included in their model, therefore, blocking NMDA currents prevents CSD. Shapiro had proposed a detailed and comprehensive model [11], both potassium and glutamate-based mechanisms are implemented. This model includes more detailed ionic current and incorporates cell swelling. However, this model relies heavily on neuronal gap junctions, which is controversial to other works [10, 12].

The object of this paper is to extend our previous continuum neuron model to the coupled neuron-astrocyte model and incorporate the effects of NMDA currents and ATP. The coupled neuron-astrocyte system is surrounded by interstitial space, as a continuous compartment. To enable this study we added three features. First, the neurons are accompanied by astrocytes [10] which provide a potassium buffering mechanism and maintain ECS potassium concentration at a physiological level [14]. The second feature is the ATP effect on propagation of CSD by neuron-astrocyte interactions, and the effect of glutamate channels is also studied. The last feature is studying the calcium dynamics in astrocyte and its effect on CSD. Using numerical simulations, we show that CSD can potentially be triggered by both electrical current and increasing ATP or glutamate in ECS. Our model