Advances in Applied Mathematics and Mechanics
Adv. Appl. Math. Mech., Vol. **3**, No. 6, pp. 759-773

DOI: 10.4208/aamm.10-m1052
December 2011

A Simplified Neuronal Model for the Instigation and Propagation of Cortical Spreading Depression

Huaxiong Huang[1,2,*], Robert M. Miura[2,3] and Wei Yao[4]

[1] *Department of Mathematics and Statistics, York University, Toronto, Ontario M3J 1P3, Canada*
[2] *Center for Applied Mathematics and Statistics, New Jersey Institute of Technology, Newark, NJ 07102, USA*
[3] *Department of Mathematical Sciences, New Jersey Institute of Technology, Newark, NJ 07102, USA*
[4] *Department of Mechanics and Engineering Science, Fudan University, Shanghai 200433, China*

Received 27 August 2010; Accepted (in revised version) 17 May 2011

Available online 31 October 2011

Abstract. In this paper, we construct a simplified neuronal model that is capable of simulating the instigation of cortical spreading depression (CSD) and propagation of a CSD wave. Our model is a simplification and extension of a single neuron model proposed in the literature for studying the instigation of CSD. Using the simplified neuronal model, we construct a network of these simplified neurons. This network model shows that the propagation of a CSD wave occurs naturally after it is instigated electrically or chemically. Although the model is simple, the speed of the CSD wave predicted by our model is consistent with experimentally observed values. Finally, our model allows us to investigate the effects of specific ion channels on the spread of a CSD wave.

AMS subject classifications: 34A33, 34A34, 92C20, 92C42, 97M60

Key words: Cortical spreading depression, neuronal model, network, numerical simulation.

1 Introduction

Cortical spreading depression (CSD) is a slow wave phenomenon in the cortex of the brain that is associated with the spread of depression of the electroencephalogram signal. Functionally, it is associated with migraine with aura, see Hadjikhane et al. [5]. CSD was discovered in 1944 by A. A. P. Leão [11], a Brazilian neurophysiologist, during his Ph.D. studies on epilepsy at the Harvard Medical School. These waves are

*Corresponding author.
URL: www.math.yorku.ca/∼hhuang
Email: hhuang@yorku.ca (H. X. Huang), miura@njit.edu (R. M. Miura), weiyao@fudan.edu.cn (W. Yao)

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characterized by their slow speeds (on the order of 1 to 10 mm/min) and their appearance in a variety of cortex structures in the brains of many different animals, see Bures et al. [2], and in humans. Although CSD was discovered over 65 years ago, we still do not have a good understanding of how the different mechanisms conspire to form this coherent phenomenon [12].

While there are many interesting aspects of CSD, its intimate connection with migraine with aura makes it a particularly important neurophysiological phenomenon to try to understand from the clinical point of view. In particular, the fact that migraine occurs three times more often in women than in men and recent experimental findings by Brennan et al. [3] that show the threshold for CSD in female mice is lower than that for male mice make a compelling argument for further theoretical studies of CSD. An important question is whether we can identify physiological and/or anatomical indicators that would explain these important findings.

Mathematical models of CSD have been proposed almost since the time that CSD was discovered. The cellular automata method developed by Wiener and Rosenblueth [21] for the study of cardiac waves was used by Shibata and Bures [16] to study CSD. It was postulated early on by Grafstein [4] that potassium was the major ion involved in CSD and that repeated neuronal firings were responsible for the large increase in extracellular potassium. Hodgkin proposed a simple single partial differential equation model, essentially the first equation in the FitzHugh-Nagumo equations [13] for action potentials, to describe the leading edge of the CSD wave. Both the cellular automata methods and the simple single PDE model do not lend themselves easily to the incorporation of physiological mechanisms to explain the instigation and propagation of CSD waves. Furthermore, the flexibility in using mathematical models based on physiological mechanisms allows us to perform extensive studies of CSD occurrence which would be impossible to perform in the laboratory.

The first detailed mathematical model of CSD that incorporated physiological mechanisms was proposed by Tuckwell and Miura [20]. Their model was based on the neurotransmitter hypothesis. It had been shown by Sugaya et al. [18] that CSD waves initiated in untreated cortical tissue could propagate through TTX-treated tissue, so that CSD waves did not need action potentials for their propagation. Tuckwell and Miura [20] postulated that CSD waves could be initiated in TTX-treated tissue by application of KCl. They conjectured that a high concentration of extracellular potassium, $[K]_e$, would be sufficient to instigate a CSD wave. Since the space scale of a CSD wave is large compared to neuron size, Tuckwell and Miura formulated a one-dimensional continuum model of these processes by dividing the space into a connected extracellular space overlapping a disconnected intracellular space. The effect of this assumption is that ion diffusion can occur in the extracellular space, but cannot occur in the intracellular space, i.e., intracellular ions would first have to pass through the neuronal membrane and become an extracellular ion before it could diffuse. The model formulated by Tuckwell and Miura consists of a coupled system of nonlinear diffusion equations for the extra- and intracellular concentrations of potassium and calcium and accounts for ion movements across neuronal membranes.