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A neural-glial network for modeling spreading depression in cortex

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Background and model

Spreading depression (SD) is a propagating wave of transient neuronal hyperexcitability followed by complete electrical silence that moves slowly (15–50 μm s^{-1}) across grey matter in the central nervous system; it has been implicated in a number of brain disorders [1]. SD involves a massive redistribution of ions (K^+, Na^+, Ca^{2+}, Cl^-) between intracellular and extracellular compartments. Although first described over 60 years ago, it is still not well understood [1]. SD is accompanied by large increases in extracellular ATP, which is a principal means of transmission between astrocytes; also, ATP waves in astrocyte networks move at speeds comparable to SD [2,3]. These facts, and other evidence [4], strongly suggest that astrocytes play an important role in SD.

We have constructed a mathematical model in which SD is driven by the effects of astrocyte waves interacting with waves of glutamate released from neurons and astrocytes (Figure 1). The detailed equations and computational methods were based on our previous work on glial and neural-glial systems [2,3,5]. All major ion channels, exchangers and pumps were included in both neurons and astrocytes (cf. [6]).

Results and conclusion

The model accounts for the main experimental properties of SD; in particular, the speed of the wave and the accompanying changes in ion concentrations and potentials in the cells and in the extracellular medium (Figure 1 shows one example) and are in broad agreement with those

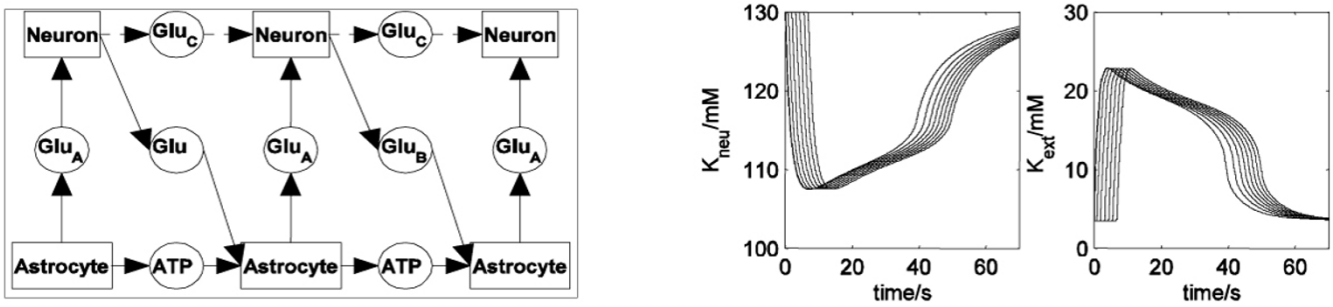

Figure 1

Left panel Model neuron-astrocyte network in which astrocytic transmission is effected by ATP and neuronal transmission by glutamate: from astrocyte to neuron by glutamate (Glu_A) acting on NMDA receptors; from neuron to astrocyte by glutamate (Glu_B) acting on metabotropic receptors; from neuron to neuron by glutamate (Glu_C) acting on AMPA receptors; from astrocyte to astrocyte by ATP acting on P2Y receptors. **Right panel** Time course of K^+ concentration in neurons, extracellular space and astrocytes, respectively; traces are for the first seven cells in the network.

observed [1,4]. This work supports the hypothesis that SD is a result of neuron-astrocyte interactions involving the neurotransmitters glutamate and ATP. Further experimental work is now needed to justify the detailed interactions proposed by the model.

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