Komendantov et al. BMC Neuroscience 2010, 11(Suppl 1):P27
http://www.biomedcentral.com/1471-2202/11/S1/P27

BMC Neuroscience

POSTER PRESENTATION Open Access

Ion concentration homeostasis and the regulation of neuronal firing activity: the role of cation-chloride cotransporters

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From Nineteenth Annual Computational Neuroscience Meeting: CNS*2010
San Antonio, TX, USA. 24-30 July 2010

Ion concentration homeostasis is essential for normal neuronal functions and its changes can underlie different pathological conditions including seizures. However the mechanisms of these processes are poorly understood. Studying the dynamical and biophysical mechanisms of regulation of neuronal intra- and extra-cellular ion concentrations is important for the development of methods to treat neurological disorders.

We constructed a conductance-based neuron model [1], which includes dynamic variables representing the intracellular Na^+ and extracellular K^+ concentrations.

In this model, the Na^+ and K^+ concentrations are affected by sodium, potassium, and leak currents, Na^+-K^+ pump current, an uptake of potassium ions by glial current, and potassium diffusion. The leak current is represented by the sum of sodium, potassium and chloride leaks. The concentrations couple to the membrane voltage equations via the Nernst reversal potentials. The model also contains a voltage-gated calcium current and a simple model for the intracellular Ca^{2+} dynamics. The model produces slow and large-amplitude oscillations in ion concentrations similar to oscillations observable during seizures or seizure-like activity *in vitro*.

We extended this model to include Cl^- concentration dynamics. In the nervous system, the intracellular Cl^- ion concentration ($[Cl^-]_i$) determines the strength and polarity of GABAergic neurotransmission. This concentration is maintained by the activity of cation-chloride cotransporters (CCCs). We explored in a computational study the roles of two CCCs (the NA-K-2Cl cotransporter, NKCC1, and the K-Cl cotransporter, KCC2) in ion concentration homeostasis and in the generation of pathological oscillatory activity in neurons.

Our computational studies show that reciprocal changes in the expression of NKCC1 (which elevates $[Cl]_i$) and KCC2 (which decreases $[Cl^-]_i$) can change Cl^- reversal potential (E_{Cl}) and significantly alter the effects of $GABA_A$ receptor ($GABA_AR$) mediated inhibitory input. Under certain circumstances, this can evoke or prevent seizure-like activity, and we investigate dynamical and biophysical mechanisms of these phenomena. The model suggests that regulatory abilities of CCCs are increased with increasing $GABA_ARs$ activation. Both simulated elevation of concentration of extracellular potassium ion ($[K^+]_{o,\infty}$) and NA-K-2Cl cotransporter activity promote seizure-like activity. Our studies show that developmental regulation of expression of NKCC1 and KCC2, in conjunction with concentration dynamics, can alter Cl^- electrochemical gradient and strength and polarity of $GABA_A$ neurotransmission.

The computational studies corroborate that CCCs are potential targets for treatment of neurological diseases, which involve dysfunctions in intracellular ion concentration homeostasis.

Acknowledgements
This work was funded by NIH Grant 5R01MH079502 (EB)

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Published: 20 July 2010

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doi:10.1186/1471-2202-11-S1-P27
Cite this article as: Komendantov *et al.*: Ion concentration homeostasis and the regulation of neuronal firing activity: the role of cation-chloride cotransporters. *BMC Neuroscience* 2010 **11**(Suppl 1):P27.