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Spatio-temporal dynamics of dopamine activated 2nd messenger pathways

(NIAAA R01-AA016012 FY 05)

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The long term objective of the proposed research is to delineate the mechanisms underlying reinforcement learning in the striatum: specifically, the essential second messenger pathways and neuromodulatory interactions mediating plasticity of synaptic and voltage dependent channels in striatal neurons. As a first step, the proposed research evaluates the sensitivity of synaptic plasticity and calcium dynamics to the temporal interval between cortical and dopaminergic inputs to striatal spiny projection neurons, using a combination of experiments and computational modeling.

To evaluate the hypothesis that long term potentiation occurs only when supra-threshold cortical stimulation is followed by nigral (dopamine) stimulation, we developed a computer model of the biochemical reaction pathways involved in the phosphorylation of AMPA channels. Simulations using a single compartment, deterministic model show that paired calcium and dopamine stimuli produce a synergist activation of PKA and Thr34 phosphorylated DARPP.

Since most of the biochemical reactions leading to activation of kinases and phosphatases are localized to dendritic spines, stochastic equations describe more accurately the molecular interactions in these small structures. In addition, the electrical activity of the neuron controls calcium influx and is modulated by kinase activity. Thus, computationally efficient computer algorithms for stochastic diffusion are required to model second messenger pathways in a multitude of spines on the dendritic tree of an entire neuron. We have developed such an algorithm which may be used to develop a spiny projection neuron model that includes not only *in vivo* like synaptic inputs, but also the spatio-temporal dynamics of calcium and second messengers activated by dopamine.

Project (or PI) Website

http://www.gmu.edu/departments/krasnow/CENlab/CENlab.html

Publications

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2. Blackwell K.T. (2006) An efficient stochastic diffusion algorithm for modeling calcium in dendrites and spines. J. Neuroscience Methods, In Press.

3. Gustafson N, Gireesh-Dharmaraj E, Czubayko U, Blackwell KT, Plenz D. (2006) A comparative voltage and current-clamp analysis of feedback and feedforward synaptic transmission in the striatal microcircuit in vitro. J Neurophysiol. Feb;95(2):737-52.

4. Hellgren Kotaleski J, Plenz D, Blackwell K.T. (2006) Using potassium currents to solve signal noise problems in inhibitory feedforward networks of the striatum. J. Neurophysiology, 95(1):331-41.

5. Blackwell K.T. (2005). Modeling Calcium Concentration and Biochemical Reactions. Brains, Minds, and Media, Vol.1, bmm224.