

Neuromodulation of biochemical signaling and cellular electrophysiology: An integrated multi-scale modeling approach

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Abstract

Neuromodulators have profound effects on both individual neurons and neural circuits. Such modulation entails multi-scale control mechanisms involving gene regulation, intracellular signaling, and membrane electrophysiology that function over a range of temporal and spatial scales. Moreover, recent analyses show extensive cell-to-cell variability in the expression of ion channels and neuromodulator receptors. However, the physiological consequences of neuromodulator response to such variable expression in both channel and receptor levels still remain unclear. Here we present a novel multi-scale modeling approach which integrates biochemical pathway models with computational neurophysiology. We investigated the mechanistic basis of the neuronal response to a peptide modulator angiotensin-II (AngII), a critical regulator of autonomic homeostasis, and explored two central issues. First, we performed detailed examination of otherwise intractable interactions between signaling components and membrane ionic conductances by studying enzymatic cascades regulating calcium signaling, kinase activation, and ion channel phosphorylation. Second, we investigated the effects of variability in receptor and conductance levels to identify differential neuromodulator response phenotypes that were indicative of co-regulation. Analysis of the response to AngII showed a non-linear baseline calcium dependent regulatory mechanism, in which AngII evoked an increase in cytosolic Ca^{2+} for low calcium baseline and a decrease in cytosolic Ca^{2+} for a relatively higher calcium baseline. Additionally, frequency response analysis of AngII neuromodulation revealed a low pass filter property, where a weak and sustained stimulation showed

higher excitability over a strong and transient stimulus. Using our model, we also showed that variability in the relative levels of ionic conductances and GPCR receptors can result in similar or identical basal firing rates, whereas the neuromodulator responses can lead to divergent phenotypes. Finally, our analyses revealed that receptor levels and channel balances had distinct influences on neuromodulator response amplitude and kinetics. Our integrated model expands the ability to predict functional relations between neuromodulator signaling and membrane potential dynamics, and presents a methodology for *in silico* evaluation of hypotheses regarding potential therapeutic targets.