Interaction of NMDA receptor and pacemaking mechanisms in the midbrain dopaminergic neuron

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July 04, 2013

Dopamine neurotransmission has been found to play a role in addictive behavior and is altered in psychiatric disorders. Dopaminergic (DA) neurons display two functionally distinct modes of electrophysiological activity: low- and high-frequency firing. A puzzling feature of the DA neuron is the following combination of its responses: N-methyl-D-aspartate receptor (NMDAR) activation evokes high-frequency firing, whereas other tonic excitatory stimuli (-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptor (AMPAR) activation or applied depolarization) block firing instead. We suggest a new computational model that reproduces this combination of responses and explains recent experimental data. Namely, somatic NMDAR stimulation evokes high-frequency firing and is more effective than distal dendritic stimulation. We further reduce the model to a single compartment and analyze the mechanism of the distinct high-frequency response to NMDAR activation vs. other stimuli. Standard nullcline analysis shows that the mechanism is based on a decrease in the amplitude of calcium oscillations. The analysis confirms that the nonlinear voltage dependence provided by the magnesium block of the NMDAR determine its capacity to elevate the firing frequency. We further predict that the moderate slope of the voltage dependence plays the central role in the frequency elevation. Additionally, we suggest a repolarizing current that sustains calcium-independent firing or firing in the absence of calcium-dependent repolarizing currents. We predict that the ether-a-go-go current (ERG), which has been observed in the DA neuron, is the best fit for this critical role. We show that a calcium-dependent and a calcium-independent oscillatory mechanisms form a structure of interlocked negative feedback loops in the DA neuron. The structure connects research of DA neuron firing with circadian biology and determines common minimal models for investigation of robustness of oscillations, which is critical for normal function of both systems.

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