

Dopaminergic Neuron Regulation with and without Dopamine

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Abstract

Background and aims: Near-normal activity patterns of dopamine-depleted midbrain dopaminergic neurons observed in freely moving mice have raised the suggestion that there is a fundamental gap in our understanding of how the bursting activity of the dopaminergic neuron is regulated. Our aim is to propose a model for this activity, validate it by neurophysiological and clinical evidence, and examine its implications.

Methods: Neurophysiological observations were compressed into analytically plausible models of the midbrain information pathways and of the bursting mechanism of the dopamine neuron. Cross-examination of clinical data obtained for patients with different movement disorders, Parkinson's disease and multiple sclerosis in particular, was used to validate the proposed model.

Results: The bursting activity of the dopamine neuron is shown to be regulated by three topologically and functionally nested phase-locked inhibit-and-fire circuits. Modulated by behavior through proprioceptive and sensory feedback, the dopaminergic regulator may be viewed as a valve for timely release of dopamine reward. Yet, long-term potentiation and depression make neuronal bursting possible even without dopamine, stressing its role in sensory-motor control, and the long-term significance of sensory-motor training. A comparative analysis of clinical data obtained for healthy individuals and for PD and MS patients using artificially enhanced sensory feedback shows age and disease-related benefits, conforming with the proposed model.

Conclusions: The bursting activity of the midbrain dopamine neuron is regulated by nested phase-locked inhibit-and-fire circuits, modulated by behavior. Movement disorders are compensated by sensory feedback enhanced by memory, which makes neuronal bursting possible with and without dopamine.