Regulation of Excitability, Pacemaking, and Bursting: Insights from Dopamine Neuron Electrophysiology

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The present thesis attempts to extract the dynamical mechanisms underlying neuronal excitability and its regulation, through the use of experimental and mathematical techniques. In particular, tools of dynamical system theory are used to extract physiologically relevant key players in the firing activity of various neuron types.

The main contribution of the thesis highlights the role of voltage-gated calcium-permeable channels in neuron excitability and firing patterns. Calcium channels are shown to induce a novel type of excitability that correlates to the electrophysiological properties of many neuron types, including midbrain dopamine-releasing cells, the neurons that initially motivated our study. In particular, calcium channels play a critical role in the generation and regulation of burst firing activity, a firing pattern that is important for the signaling of many cells.

The first part of the dissertation is dedicated to the mechanisms underlying dopaminergic (DA) neuron excitability. It identifies key players in the regulation of DA neuron firing patterns both in vitro and in vivo, including voltage-gated calcium channels and calcium-activated potassium channels. In particular, it shows that these channels are key regulators of DA neuron excitability.

The second part further investigates the dynamical phenomena extracted from dopaminergic neuron electrophysiology and generalizes these concepts to other neuronal populations. It incorporates the role of voltage-gated calcium channels in the current global picture of neuronal excitability proposed by FitzHugh in 1961. The inclusion of calcium channels in reduced models leads to a revised picture that uncovers two novel types of excitability, whose electrophysiological signatures are shared by many neuronal populations. This analysis is further extended to conductance-based models of arbitrary dimension, highlighting the impact of the balance between restorative and regenerative ion channels on neuron excitability. The regulation of this balance is shown to provide a physiologically plausible route to neuronal bursting.

The last part of the thesis illustrates a potential systemic consequence of the previous insights for Parkinson's disease (PD). It spotlights the systemic role of small conductance calcium-activated potassium channels in the regulation of many neuron types, many of these neurons being affected in PD.