Slow neuronal dynamics from fast activating kinetics in conductance-based models

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1 Introduction

Neurons exhibit various patterns of electrical activity depending on their functional role. One important pattern is slow pacemaking—regular spontaneous firing at 1–5 Hz. Examples include dopamine neurons in the substantia nigra, which maintain steady dopamine release in the brain, and sinoatrial cells in the heart, which regulate the heartbeat. Generating such slow activity requires a small, steady depolarizing current on the order of tens of picoamperes during the interspike interval. However, the electrophysiological mechanism responsible for this behavior remains highly debated.

For dopamine neurons, hypotheses include sodium leakage channels (unlikely due to their high conductances) or a balanced interplay of larger ion channels (unlikely since blocking individual components does not disrupt pacemaking). For sinoatrial cells, an interaction between two calcium clocks has been proposed (also unlikely, as blocking calcium entry does not eliminate pacemaking).

Recently, a chemical compound, 1-(2,4-xylyl)guanidinium (XG), was found to completely block pacemaking in both cell types [1], suggesting a shared mechanism. XG specifically blocks gating pore currents—tiny currents in the picoampere range that flow within the voltage sensor structure of ion channels rather than through the main pore [2]. While these currents are typically associated with pathological mutations, our findings suggest that distributed non-pathological gating pore currents may be responsible for slow pacemaking. The molecular identity of this ion channel remains unknown, but a complete steady-state current-voltage characteristic has been measured.

2 Results

Using a conductance-based model of dopamine neurons [3], we incorporated this newly characterized current to study its dynamical properties and ability to generate slow pacemaking. The voltage-current relationship of any conductance-based neuron model is expressed as:

$$C\frac{\mathrm{d}V}{\mathrm{d}t} + g_{\text{leak}}(V - E_{\text{leak}}) = -\sum_{\text{ion}\in\mathscr{I}} g_{\text{ion}}(V,t)(V - E_{\text{ion}}) + I_{\text{ext}},$$

where C represents the membrane capacitance, g_{ion} denotes the ion channel conductance (non-negative, gated between 0 for all channels closed and $\bar{g}_{\text{ion}}$ for all channels open), E_{ion} and E_{leak} are the reversal potentials, $\mathscr{I}$ is the index set of intrinsic ionic currents, and I_{ext} is the externally applied current *in vitro* or the combination of synaptic currents. Each ion channel conductance is nonlinear and dynamic, represented by $g_{\text{ion}}(V,t) = \bar{g}_{\text{ion}} m_{\text{ion}}^a(V,t) h_{\text{ion}}^b(V,t)$, where m_{ion} and h_{ion} are gating variables between 0 and 1, modeling the activation and inactivation gates of ion channels, respectively.

Prior models used unphysiological values for sodium and calcium currents to achieve pacemaking. Restoring physiological parameters caused the model to lose pacemaking activity. However, incorporating the new XG-sensitive current recovered pacemaking over a wide parameter range. Importantly, fast activation kinetics (fast opening and closing) are necessary to produce slow pacemaking—a counterintuitive finding confirmed *in vitro* using dynamic clamp experiments.

This work demonstrates how experiments and modeling can work synergistically to reveal novel mechanisms underlying fundamental neurophysiological processes.

References

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