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“Computational modeling of Cav2.3 channel mediated bursting in substantia nigra dopamine neurons”

Parkinson’s disease (PD) is a neurological disorder that is primarily characterized by progressively worsening motor symptoms, stemming from the degeneration of dopaminergic (DA) neurons in the substantia nigra (SN). These substantia nigra dopaminergic (SNDA) neurons are selectively and more severely impacted compared to their counterparts, ventral tegmental area (VTA) DA neurons. This regional selectivity has been linked to the increased expression of the R-type voltage-gated calcium channel (Cav2.3) in nigral neurons with upregulation during aging. In a neurotoxin PD mouse model, Cav2.3 knockout was associated with decreased nigral somatic Ca^{2+} signals and Ca^{2+} dependent after-hyperpolarizations. Most importantly, it led to full protection against neurodegeneration. This suggests that Cav2.3 could be a potential therapeutic target for PD. However, the mechanism for how Cav2.3 may mediate degeneration in SNDA neurons is poorly understood and more robust models are required to elucidate the relationship.

As such, the objective of this study is to create a biophysically accurate Cav2.3 channel and incorporate it into working DA neuron models. This model will be used to interrogate the Cav2.3 mediated bursting in SNDA neurons.

Whole-cell voltage clamp recordings were obtained for adult C57BL/GJ mice via patch clamp. The current- voltage (I-V) step protocol had a holding voltage of -100 mV with steps of +10 mV for 150 ms, per sweep, up to +40 mV. The cell was measured in the presence and absence of a Cav2.3 channel blocker (SNX482). Leak current was collected and subtracted using a P5 protocol. The difference currents (calcium sensitive) were obtained by subtracting the before and after SNX482 traces. To obtain the time constants and steady state values, the difference currents were fit to a Hodgkin-Huxley (HH) like equation: $I(t) = A(1 - e^{-t/\tau_m})^p(e^{-t/\tau_h})^q$. The biophysical parameters for the Cav2.3 channel were compiled into a model file for the NEURON simulation environment. This NEURON environment was used to measure the channel states and action potentials for SNDA neurons following a simulated N-methyl-D-aspartate (NMDA) square pulse.

Further data analysis is required to verify and validate the compiled channel. This will continue to be done in SNDA neurons, with expansion to VTADA neurons. The bursting activity will be measured via parameter sweep of calcium conductance through the Cav2.3 channel.