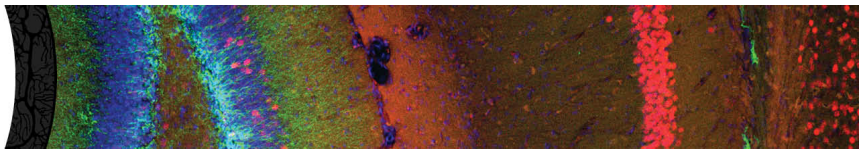
NEUROSCIENCE 2021
50TH ANNUAL MEETING



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Session P127 - Excitability Control: Ion Channel

# P127.03 - Dominant role of calcium and calcium-dependent potassium channels in regulating complex spike bursting in a heterogeneous population of CA3 pyramidal neuron models

November 11, 2021, 8:30 AM - 9:30 AM | Virtual Only

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**Abstract**
Complex spike bursting (CSB) is a characteristic neuronal signature exhibited by hippocampal CA3 pyramidal neurons. Although complex burst patterns have been implicated in place cell formation and in inducing synaptic plasticity, assessment of the heterogeneities in the ionic mechanisms underlying CSB generation in CA3 pyramidal neurons remains unexplored. In this study, we employed an unbiased stochastic search algorithm (involving 11 ion channels and 14 parameters) to generate a heterogenous population of morphologically realistic CA3 pyramidal neurons models that accounted for their ion-channel kinetics, gating properties, and associated heterogeneities. We validated 12,000 stochastically generated models against 11 signature electrophysiological intrinsic measurements, and found 236 valid models. These valid models were endowed with broad distributions of underlying parameters showing weak pair-wise correlations. We found two functional subclasses of valid models, intrinsically bursting (IB; n=67) and regular spiking (RS; n=169), which exhibited two distinct clusters in the parametric space with both linear (PCA) and non-linear (t-SNE) dimension reduction analyses. As the clustering was predominantly along the first principal component, which aligned with the parametric axes for calcium and calcium-activated conductances, we tested if those parameters were different between the two subpopulations. We found the N-type calcium (CaN) conductance to be significantly higher and the small-conductance calcium-activated potassium (SK) conductance to be significantly lower for IB neurons compared to RS neurons. We then triggered CSB in all 236 models by subjecting them to 5 different kinds of inputs, and observed considerable heterogeneity in their propensity for exhibiting CSB. Quantitatively, these models manifested heterogeneities in the 3 characteristic signatures of CSBs: (i) amplitude difference between the first and the last action potential within the CSB; (ii) sub-threshold ramp voltage; and (iii) CSB rate with 4 consecutive pulse-current inputs. Finally, we employed virtual knockout analyses involving 7 voltage- and/or calcium-dependent channels as well as NMDA receptors, and showed that synergistic interactions among several ion channels regulated CSB. Of these different ion channels and receptors, we found dominant roles for NMDA receptors as well as CaN and SK channels in regulating CSBs across models. Together, our analyses unveil the expression of ion-channel degeneracy in CA3 pyramidal neurons and emphasize the dominance of calcium and calcium activated potassium channels in the emergence of CSB.