

Cummins 2015 DSF summary

We investigated fundamental properties of three brain sodium channel (Nav1.1, Nav1.2 and Nav1.6) and examined a number of disease variants identified in these channels from patients with epilepsy. Key differences were found in the functional properties of the three channel subtypes, and these differences may help determine how different brain sodium channels regulate nerve impulse firing in cortical circuits. In particular, we found that Nav1.6, and Nav1.6 disease mutations, are especially likely to generate resurgent sodium currents. These unusual resurgent sodium currents can increase rapid and burst firing in neurons and may be a key component of hyperexcitability associated with several epilepsies. We found that low concentrations of cannabidiol could dramatically reduce these Nav1.6 resurgent currents without inhibiting Nav1.1 currents. Low concentrations of cannabidiol also reduced excitability and impulse firing in neurons with resurgent currents. These actions could explain the beneficial effect of that cannabidiol has in some patients. In the second year of the grant we will investigate other cannabinoids and small molecules to look for compounds with enhanced inhibition of resurgent currents. We will also use the Dravet syndrome mouse model to probe the potential utility of targeting Nav1.6 and resurgent currents in Dravet syndrome.