Second International Calcium Channel Conference - Placencia, Belize
March 28 – April 2, 2010

The splicing factor Fox-2 controls N-type calcium channel activity in sympathetic neurons

Summer E. Allen, Cecilia G. Phillips, Diane Lipscombe

Department of Neuroscience, Brown University, Providence, RI, USA 02912

The *CACNA1B* gene encodes the pore-forming subunit of CaV2.2 (N-type) calcium channels and contains several alternative exons. We know that different neurons express their own unique combination of CaV2.2 splice isoforms; these combinations underlie functional differences between neuron subtypes. However, we know almost nothing about the factors that control alternative splicing of calcium channel pre-mRNAs in specific neurons. Exon 18a (e18a) is a cassette exon that can be included or skipped during pre-mRNA splicing of CaV2.2. Channel mRNAs including e18a are relatively rare in tissues like the neocortex and cerebellum whereas the vast majority of channel mRNAs in adult mouse sympathetic ganglia contain e18a. E18a inclusion also depends on development. At birth, 42% of channel mRNAs from mouse superior cervical ganglia (SCG) neurons include e18a, compared to 89% at P60. We now show that the RNA-binding protein Fox-2 controls this splicing event in neurons: Fox-2 represses e18a inclusion. We can induce a concentration-dependent increase in the percentage of channel mRNAs that include e18a by transfecting siRNA against Fox-2 in a neuronal cell line. When injected into SCG neurons, Fox-2 siRNA induces a change in calcium channel function that mimics e18a-containing channels. Calcium currents in neurons injected with Fox-2 siRNA were larger and more sensitive to persistent inhibition by Gs coupled receptor activation. We conclude that Fox-2 controls G protein signaling to N-type calcium channels in neurons by repressing e18a inclusion during pre-mRNA splicing. Supported by NIH grants NS29967 (DL), NS066691 (SEA), NS066712 (CGP).