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

Calcium-dependent modulation of P/Q-type calcium channels is altered by Familial Hemiplegic Migraine Type-1 mutations and in a $Ca_v2.1$ splice-dependent manner

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Neurotransmission is a highly dynamic process requiring the coordination of multiple pre- and post-synaptic proteins. The modulation of presynaptic P/Q-type calcium channel activity via a calmodulin-mediated calcium-dependent pathway is postulated to affect synaptic plasticity. It has been shown that disruption of calcium sensor binding to the P/Q-type channel $Ca_v2.1$ subunit can prevent calcium dependent modulation and result in a marked reduction in synaptic plasticity in a model system. We hypothesized that naturally occurring mutations in the P/Q-type channel might alter two forms of calcium-dependent modulation: calcium dependent facilitation (CDF) and calcium-dependent inactivation (CDI). In the present study we investigated how mutations implicated in Familial Hemiplegic Migraine Type-1 (FHM-1) affect $Ca_v2.1$ CDF and CDI. We find that both FHM-1 mutations significantly reduce the ability of P/Q-type channels to undergo CDF, while only one mutation affects CDI. The changes on CDF and CDI were found to have profound effects on P/Q-type calcium currents during action potential waveforms. We also find that the effects on CDF are highly $Ca_v2.1$ splice-variant dependent. Both FHM-1 mutations nearly completely abolished CDF in the Aga IVA sensitive P-type splice-variant (-NP) while they had little effect when expressed in the less sensitive Q-type variant (+NP). We hypothesize that the selective gain-of-function effects of FHM-1 mutations on a subset of $Ca_v2.1$ splice variants may underlie the increased glutamate release at central synapses relevant to the disease pathophysiology. Further, the differential affects of FHM-1 mutations in the context of $Ca_v2.1$ splice variation may contribute to the temporal and spatial aspects of FHM-1.