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Differential effect of hemiplegic migraine mutations in the P/Q-type Ca^{2+} channel on cortical excitatory and inhibitory synaptic transmission

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Mutations in the $Ca_V2.1alpha_1$ gene cause familial hemiplegic migraine type 1 (FHM1), a rare subtype of migraine with aura. We have shown enhanced excitatory neurotransmission due to increased action-potential (AP)-evoked Ca^{2+} influx and increased probability of glutamate release at cortical pyramidal cell synapses of FHM1 knockin mice; in contrast, inhibitory neurotransmission at connected pairs of fast-spiking interneurons and pyramidal cells in thalamocortical slices of knockin mice was unaltered, despite being initiated by P/Q-type Ca^{2+} channels. We recently confirmed and extended these findings by measuring spontaneous excitatory and inhibitory postsynaptic currents in pyramidal cells in cortical slices in the presence of ongoing network activity; in FHM1 knockin mice, the total excitatory drive was enhanced whereas the total inhibitory drive on pyramidal cells was unaltered. Investigation of neurotransmission at inhibitory autapses of single cortical interneurons grown on glial microislands confirmed similar amplitudes of AP-evoked IPSCs in multipolar fast-spiking inteneurons of wild-type and knockin mice, despite a dominant role of P/Q-type channels in controlling GABA release at the autapses. Measurement of neurotransmission at different external [Ca^{2+}] revealed the same Ca^{2+} dependence of the IPSC in wild-type and knockin mice. This finding shows that AP-evoked Ca^{2+} influx through presynaptic P/Q channels is not affected by the FHM1 mutation at fast-spiking interneuron synapses. We are currently investigating whether this is due to the very short AP of these interneurons or to a particular $Ca_V2.1$ splice isoform little affected by the mutation.