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Gain of function in FHM-1 Ca_v2.1 knock-in mice is related to the shape of the action potential

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Familial hemiplegic migraine type-1 (FHM1) is caused by missense mutations in the *CACNA1A* gene that encodes the α_{1A} pore-forming subunit of Ca_v2.1 Ca²⁺ channels. We have used knock-in (KI) transgenic mice harbouring the pathogenic FHM-1 mutation R192Q to study the physiology of neurotransmission at the calyx of Held synapses and cortical layer 2/3 pyramids. Using whole cell patch clamp recordings in brainstem slices we confirmed that KI Ca_v2.1 Ca²⁺ channels activated at more hyperpolarizing potentials. However, calyceal presynaptic calcium currents (I_{pCa}) evoked by presynaptic action potentials (APs) in these neurons are similar in their amplitudes, kinetic parameters and neurotransmitter release.

Ca_v2.1 Ca²⁺ channels in cortical layer 2/3 pyramids from KI mice also showed a shift in their activation voltage. Pyramidal cells (PCs) have APs with longer durations and smaller amplitudes than those at the calyx of Held. In contrast to the calyx of Held synapse, Ca²⁺ currents (I_{Ca}) from PCs evoked by their own APs showed an increase in amplitude in KI mice compared to WT mice. Instead, when I_{Ca} were evoked in PCs by calyx of Held AP waveforms, we observed no amplitude differences between WT and KI mice. These results suggest that the longer time course of pyramidal APs is an important factor for the expression of a synaptic gain of function in the KI mice. Thus, our results show that the outcome of FHM1 mutations may vary in different neurons according to the shape of their action potentials.