Thalamocortical Circits in Absence Epilepsy

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Absence seizures are generalized non-convulsive seizures characterized by the appearance of spike-and-wave discharges (SWDs) on the bilateral cortical EEG. The common model proposes that synchronized oscillations of the thalamocortical network by T-type Ca^{2+} channels in the thalamus play a key role in the generation of SWDs. Using the mouse models deficient for the channels, we have been studying the thalamic mechanism for absence seizures. We have previously shown that the *CaV3.1* gene encoding the α1G T-type channels which are primarily expressed in TC neurons is essential for the generation of absence seizures. These findings indicate that T-type channel-driven burst firings of TC neurons are critical for absence. Next, we examined the role of TRN neurons by studying the null mutant mice for the *CaV3.3* gene encoding the α1G T-type calcium channels that are abundantly expressed in TRN but not in the TC nucleus. In the TRN neurons of $CaV3.3^{-/-}$ burst firing was severely suppressed and rhythmic burst discharges were completely abolished, which is expected considering *CaV3.3* being the predominant T-channels in TRN. On the other hand tonic firing was significantly increased. In contrast to the general prediction based on these findings $CaV3.3^{-/-}$ showed an enhanced SWD response to drug-induced absence seizures. A TRN-specific knockdown of *CaV3.3* reproduced this phenotype. To test the possibility that the other T-type channel, *CaV3.2*, took over the role of *CaV3.3* in the TRN, a double KO for the two T-type channels were generated and examined. The SWD absence seizures were even further enhanced in this double KO, confirming the dispensability of TRN bursts in SWD absence seizures. These results call for a revision of the conventional model for SWD generation.

Key Words: Absence seizure; Thalamus; Calcium channels; T-type; Burst firing

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