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The cellular basis of epilepsy in mice with partial endophilin function

The study of synaptic vesicle recycling has seen a lot of advances in the past decades, leading to an improved understanding of the pathways as well as of the molecular components of this machinery. A running thread in these studies was the observation of epileptic seizures in mutant models of many of the involved proteins. This project aims at understanding the cellular and molecular basis of epilepsy in mutants of endophilin, a key endocytic and synaptic vesicle recycling protein. The objective was to identify global or network level differences as well as the more cellular and molecular differences in these animals. Using calcium imaging, in cultures and brain slices it was observed that endophilin $1^{-/-}2^{+/-}3^{-/-}$ (endophilin KOHtKO) animals showed a tendency towards higher excitatory activity in the cortex, while complete lack of endophilin (endophilin TKO) decreases overall cortical activity. Further, inhibitory interneuron proteins like parvalbumin, were found to be significantly decreased in the hippocampus and cortex of endophilin mutants. This may point to a loss of activity of inhibitory interneurons because of a higher cost exerted on their fast spiking activity due to the loss of endophilin. The above two conclusions found support in the dentate gating hypothesis of epilepsy, which postulates that the dentate gyrus acts as a gate to prevent too much excitation from passing through to the cortex and the breakdown of this gating would lead to a hyper-excitation in the cortex. Another interesting finding was that neuropeptide Y (NPY) expression was decreased in endophilin TKO mice, but was increased in the endophilin DKO mice, which experienced seizures, verifying the idea that NPY may act as a compensatory mechanism to counter the epileptic activity (i.e. an endogenous anticonvulsant). In order to better understand the situation in-vivo, the effects of the known anti-epileptic drugs levetiracetam and gabapentin were tested, on the mutant animals, through a pilot drug study. It was found that the levels of NPY were significantly reduced in the animals treated with levetiracetam. This observation also supports the aforementioned role NPY as an endogenous anti-convulsant. Further, the reversal of the phenotype by levetiracetam and its recently discovered binding partner, synaptic vesicle protein, SV2A, may point to a synaptic mechanism of action for levetiracetam. Based on the data presented here, the synaptic vesicle recycling pathway could be an interesting model to understand the mechanisms of epileptogenesis in greater detail and also a potential target for newer antiepileptic drugs similar to levetiracetam.