Epileptic seizure in neuron-specific AP-3B knockout mice

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There are two isoforms of the AP-3 complex, the ubiquitous AP-3A, and the neuron-specific AP-3B. AP-3A consists of δ, β3A, μ3A and σ3 subunits. AP-3B shares δ and σ3 subunits with AP-3A, while the other two subunits of AP-3B, β3B and μ3B, are neuron-specific. In human, mutations in the β3A subunit of AP-3A were identified in patients suffering from the Hermansky-Pudlak syndrome (HPS), in which function and/or biogenesis of lysosomes and lysosome-related organelles such as melanosomes and platelet dense granules were impaired. *Pearl* mice, one of the HPS model mice, also bear a mutation in the β3A gene and share the same phenotypes with HPS. Another HPS model, *mocha* mice, has mutations in the δ subunit common to AP-3A and AP-3B. In addition to the phenotypes shared with *pearl* mice and HPS patients, *mocha* mice have been reported to suffer from neurological disorders, such as abnormal EEG and inner ear disorders (deafness and balance problems).

To elucidate that these neurological disorders of *mocha* mice result from the impairment in AP-3B, we established μ3B$^{-/-}$ mice. The inner ear disorder was not observed in ourμ3B$^{-/-}$ mice, suggesting that the phenotype is only observed when both AP-3A and AP-3B are deficient in *mocha* mice. However, μ3B$^{-/-}$ mice exhibited epileptic seizures (figure). Kindling stimulation and a $GABA_A$ receptor antagonist corroborated the seizure susceptibility ofμ3B$^{-/-}$ mice. Morphologically, electron microscopy revealed that synaptic vesicles were not homogeneous in size in μ3B$^{-/-}$ mice when compared to those in wild-type mice. We also employed an *in vitr*o synaptic vesicle formation assay. Brain lysates of wild-type mice, but not ofμ3B$^{-/-}$ mice, promoted the formation of synaptic-like vesicle formation from isolated endosomal membranes of NGF-treated PC12 pheochromocytoma cells, suggested that AP-3B is required for the *de novo* formation of synaptic vesicles from endosomal membranes. These observations led us to measure the neurotransmitter release. Release of an excitatory glutamate and an inhibitory GABA from the hippocampus was measured in microdialysis experiments. The amount of basal release of the two neurotransmitters was similar betweenμ3B$^{-/-}$ mice and wild-type mice. Of note, however, was that the K^+-evoked release of GABA was significantly impaired, while that of glutamate was slightly increased, inμ3B$^{-/-}$ mice. This difference could not be attributed to the changes in the content of the neurotransmitters themselves in the hippocampus. Taken together, these results suggest that epileptic seizures observed inμ3B$^{-/-}$ mice are likely due to impairment in the GABAergic inhibitory neurons. μ3B$^{-/-}$ mice may serve as a novel animal model for epilepsy, one of the most common neurological disorders.