Involvement of Enhanced Mossy Fiber Exocytosis in Seizure Susceptibility in Zinc Deficiency.

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Alteration of zinc homeostasis in the brain is associated with the etiology and manifestation of epileptic seizures. In the brain, the hippocampus seems to be vulnerable to zinc deficiency. In temporal lobe epilepsy, seizures frequently originate in the hippocampus and then spread to other brain regions. The increase in extracellular glutamate in the hippocampus may trigger spontaneous seizures in patients with complex partial epilepsy. The hippocampus possesses zinc-containing glutamatergic neurons that sequester zinc in the presynaptic vesicles and release it in a calcium- and impulse-dependent manner. Zinc concentration in the synaptic vesicles, in addition to that in the extracellular fluid, is decreased in zinc deficiency. It is possible that the decrease in vesicular zinc elicits imbalance of inhibition-excitation in the synapses.

On the basis of the evidence of the enhanced susceptibility to kainate-induced seizures in zinc deficiency, susceptibility to NMDA-induced seizures was examined in mice fed a zinc-deficient diet for 4 weeks. Seizure susceptibility was significantly enhanced by zinc deficiency. To examine the mechanism of the enhanced seizure susceptibility, brain slices were prepared after 4-week zinc deprivation. The basal fluo-4 FF (calcium) signals were significantly more in the hippocampal CA3 of zinc-deficient group. Furthermore, calcium orange signal in mossy fiber boutons was significantly more increased after delivery of tetanic stimuli (100 Hz, 5 s) to the dentate granule cell layer in the presence of CNQX, a blocker of AMPA/kainite receptors, suggesting that Ca^{2+} levels in the mossy fiber boutons after depolarization are more increased by zinc deficiency. The decrease in FM4-64 signal (vesicular exocytosis) in mossy fiber boutons was significantly enhanced in zinc deficiency during tetanic stimulation (10 Hz, 180 s). The present study demonstrates that the increase in exocytosis at mossy fiber boutons is a possible mechanism of the enhanced seizure susceptibility in zinc deficiency. It is likely that calcium mobilization is affected by dietary zinc deficiency, followed by the increase in exocytosis.