Effect of zinc/lipid/ autophagy-mediated plasma membrane integrity signaling pathway on hippocampal regenerative mossy fiber sprouting induced by developmental seizures

Ni Hong
Soochow University, China

Developmental convulsions, especially status epilepticus, are common clinical emergency in pediatrics. In addition to causing acute short term outcome and mortality in children, it can also induce long-term neurobehavioral and cognitive dysfunctions. An important etiological feature of these adverse changes is the aberrant mossy fiber sprouting in hippocampus. The hippocampal mossy fibers (MFs) are the axons of dentate gyrus of granule cells. Excessive stimulation of epileptic activity leads to abnormal regenerative sprouting of mossy fibers, resulting in an abnormal neural circuit, which is recognized to be the pathological basis for the hyperexcitability of brain neurons. So far, the molecular mechanism of hippocampal MFs sprouting remains a hot topic in neuroscience and pediatric clinical research. It is currently believed that the most important and initial cause of MFs sprouting is the lack of innervation caused by neuronal death. Our study found that developmental seizures can rapidly activate autophagy signaling in hippocampal neurons, whereas autophagy inhibitors (3-MA, CBI, E-64d) injected i.p. immediately after the episode can restore the long-term neurobehavioral injury and sprouting. Recent studies have found that there are other factors that may affect sprouting, including zinc transporters, especially zinc transporter 3 (ZnT3), and destruction of plasma membrane integrity. We have recently shown that melatonin can modulate the integrity of neuronal plasma membrane through zinc/lipid metabolism signaling, thereby inhibiting hippocampal MFs sprouting. Ketogenic diet (KD), a low-carbohydrate, moderate-protein, high-fat diet has been used to successfully treat medically intractable epilepsy for 95 years and can inhibit the epilepsy-induced MFs sprouting. Our study shows that the inhibitory effect of KD on MFs sprouting may be through regulating the expression of zinc transporters, lipid metabolism and autophagy related genes in hippocampus. In summary, our work tentatively revealed a new epilepsy therapeutic target, that is the zinc/lipid/autophagy mediated plasma membrane integrity pathway.