The 472nd IMEG Seminar

Mitochondrial homeostasis is regulated by neuronal activity in developing dendrites of hippocampal neurons

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【Venue】1F Conference Room, IMEG

Dendrite development accompanies extensive cytoskeletal remodeling and intracellular transport, which consumes large amounts of ATP. To constantly meet the high energy demands, mitochondrial homeostasis needs to be maintained by dynamic fission and fusion events in response to changes in the cellular metabolic state. However, the spatiotemporal regulation of mitochondrial dynamics during dendrite development remains elusive. We demonstrate that activity-dependent calcium signaling controls mitochondrial homeostasis via AMP-activated protein kinase (AMPK) in growing dendrites of differentiating hippocampal neurons. We found that the inhibition of neuronal activity induces dendritic hypotrophy with abnormally elongated mitochondria. In growing dendrites, AMPK is activated by neuronal activity and dynamically oscillates in synchrony with calcium spikes, and this AMPK oscillation is inhibited by CaMKK2 knockdown. AMPK activation leads to phosphorylation of Mitochondrial fission factor (MFF) and Unc-51-like kinase 1 (ULK1), which initiate mitochondrial fission and autophagy, respectively. Dendritic mitochondria in AMPK-depleted neurons exhibit impaired fission and mitophagy and display multiple signs of dysfunction. Genetic inhibition of fission leads to dendritic hypoplasia reminiscent of AMPK deficient neurons. Thus, AMPK activity is finely tuned by the calcium-CaMKK2 pathway and regulates mitochondrial homeostasis by facilitating removal of damaged components of mitochondria in growing neurons during normal brain development.

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