Mitochondrial fragmentation

Mitochondrial fragmentation drastically regulates mitochondrial homeostasis in brain illness. However, the role of mitochondrial fragmentation in cerebral ischemia reperfusion injury remains unclear. Nur77, a regulator of mitochondrial homeostasis, is associated with heart and liver IR injury, but its effects on mitochondrial function in cerebral IR injury has not been studied intensively. The aim of our study is to explore whether cerebral IR injury is modulated by Nur77 via modification of mitochondrial homeostasis. Our results indicated that Nur77 was upregulated in reperfused brain tissues. Genetic ablation of Nur77 reduced infarction area and promoted neuron survival under IR burden. Biochemical analysis demonstrated that Nur77 deletion protected mitochondrial function, attenuated mitochondrial oxidative stress, preserved mitochondrial potential, and blocked mitochondria-related cell apoptosis. In addition, we illustrated that Nur77 mediated mitochondrial damage via evoking mitochondrial fragmentation that occurred through increased mitochondrial fission and decreased fusion. Besides, our results also demonstrated that Nur77 controlled mitochondrial fragmentation via upregulating INF2 in a manner dependent on the Wnt/β-catenin pathway; inhibition of the Wnt pathway abrogated the protective effect of Nur77 deletion on reperfused-mediated neurons. Altogether, our study highlights that the pathogenesis of cerebral IR injury is associated with Nur77 activation followed by augmented mitochondrial fragmentation via an abnormal Wnt/β-catenin/INF2 pathway. Accordingly, Nur77-dependent mitochondrial fragmentation and the Wnt/β-catenin/INF2 axis may represent novel therapeutic targets to reduce cerebral IR injury [1)].

Hemin is a decomposition product of hemoglobin that is related to neuronal apoptosis after hemorrhage, although the molecular basis for this association remains unclear. To address this issue, at study investigated hemin-induced changes in the apoptotic index and mitochondrial ultrastructure in SH-SY5Y cells. Cell viability was evaluated using Cell Counting Kit-8 and by terminal transferase dUTP nick-end labeling, western blotting, and flow cytometry. Changes in mitochondrial ultrastructure were examined by super-resolution three-dimensional structured illumination microscopy. They found that cleaved-caspase-3 expression and the number of apoptotic cells increased in a time-dependent manner upon hemin treatment, which was associated with mitochondrial fragmentation. This data suggest that hemin induces apoptosis and mitochondrial fission in neuronal cells. Thus, therapeutic strategies that target hemin could mitigate the damage caused by hemorrhagic stroke [2)].

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2)
Dai J, Wu P, Xu S, Li Y, Zhu Y, Wang L, Wang C, Zhou P, Shi H. Changes in mitochondrial ultrastructure in SH-SY5Y cells during apoptosis induced by hemin. Neuroreport. 2017 May 5. doi: 10.1097/WNR.0000000000000790. [Epub ahead of print] PubMed PMID: 28489664.