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Hydrogen exerts neuroprotective effects on OGD/R damaged neurons in rat hippocampal by protecting mitochondrial function via regulating mitophagy mediated by PINK1/Parkin signaling pathway

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Abstract

Cerebral ischemia/reperfusion injury (IRI) is a serious complication during the treatment of stroke patients with very few effective clinical treatment. Hydrogen (H2) can protect mitochondria function and have favorable therapeutic effects on cerebral IRI. Mitophagy plays an important role in eliminating damaged or dysfunctional mitochondria and maintaining mitochondria homeostasis. However, whether the protection of H2 on cerebral IRI is via regulating mitophagy is still unknown. In this study, OGD/R damaged hippocampal neurons were used to mimic cerebral IRI in vivo and we detected the effect of H2, Rap (autophagy activator) and 3-MA (autophagy inhibitor) on OGD/R neurons. The results of MTT indicated that H2 and RAP could increase cell viability after OGD/R treatment, while 3-MA further aggravated injury and inhibited the protection of H2 and RAP. Furthermore, the intracellular ROS and apoptosis ratio were determined, the results showed that ROS and apoptosis level significantly increased after OGD/R, H2 and RAP effectively restrained the increment of ROS level and apoptosis ratio but their protective effect can be weakened by 3-MA. Mitochondrial membrane potential (MMP) and mitophagy level were also determined, the data showed that H2 and RAP protected against the loss of MPP and increased the co-localization of mitochondria with GFP-LC3 while 3-MA exerted antagonistic effect. At last, the mitophagy-related factors LC3, PINK1 and Parkin expression were detected and analyzed. We found that the expression of LC3 was increased after OGD/R which can be further enhanced by H2 and RAP treatment, but treatment with 3-MA was opposite. The result revealed H2 and RAP could activate mitophagy while 3-MA inhibit mitophagy. In addition, the study found H2 and RAP could significantly induce the expression of PINK1 and Parkin in OGD/R neurons which was inhibited by 3-MA. Taken together, our findings demonstrated H2 had a neuroprotective effect on OGD/R damaged neurons by protecting mitochondrial function and the potential protection mechanism may closely related to enhancement of mitophagy mediated by PINK1/Parkin signaling pathway.

Keywords: Hydrogen; LC3; Mitophagy; OGD/R; PINK1; Parkin.

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