Sirtuin 3

NAD-dependent deacetylase sirtuin-3, mitochondrial also known as SIRT3 is a protein that in humans is encoded by the SIRT3 gene [sirtuin (silent mating type information regulation 2 homologs) 3 (S. cerevisiae)]. SIRT3 is a member of the mammalian sirtuin family of proteins, which are homologs to the yeast Sir2 protein. SIRT3 exhibits NAD+-dependent deacetylase activity.

Estrogen-related receptors (ERRs) were shown to play an important role in the regulation of free radical-mediated pathology. This study aimed to investigate the neuroprotective effect of ERRγ activation against early brain injury (EBI) after subarachnoid hemorrhage (SAH) and the potential underlying mechanisms. In a rat model of SAH, the time course of ERRs and SIRT3 and the effects of ERRγ activation were investigated. ERRγ agonist DY131, selective inhibitor GSK5182, or SIRT3 selective inhibitor 3-TYP were administered intracerebroventricularly (icv) in the rat model of SAH. The use of 3-TYP was for validating SIRT3 as the downstream signaling of ERRγ activation. Post-SAH assessments included SAH grade, neurological score, Western blot, Nissl staining, and immunofluorescence staining in rats. In an vitro study, the ERRγ agonist DY131 and ERRγ siRNA were administered to primary cortical neurons stimulated by Hb, after which cell viability and neuronal deaths were accessed. Lastly, the brain ERRγ levels and neuronal death were accessed in SAH patients. They found that brain ERRγ expressions were significantly increased, but the expression of SIRT3 dramatically decreased after SAH in rats. In the brains of SAH rats, ERRγ was expressed primarily in neurons, astrocytes, and microglia. The activation of ERRγ with DY131 significantly improved the short-term and long-term neurological deficits, accompanied by reductions in oxidative stress and neuronal apoptosis at 24 h after SAH in rats. DY131 treatment significantly increased the expressions of PGC-1α, SIRT3, and Bcl-2 while downregulating the expressions of 4-HNE and Bax. ERRγ antagonist GSK5182 and SIRT3 inhibitor 3-TYP abolished the neuroprotective effects of ERRγ activation in the SAH rats. An in vitro study showed that Hb stimulation significantly increased intracellular oxidative stress in primary cortical neurons, and DY131 reduced such elevations. Primary cortical neurons transfected with the ERRγ siRNA exhibited notable apoptosis and abolished the protective effect of DY131. The examination of SAH patients' brain samples revealed increases in ERRγ expressions and neuronal apoptosis marker CC3. We concluded that ERRγ activation with DY131 ameliorated oxidative stress and neuronal apoptosis after the experimental SAH. The effects were, at least in part, through the ERRγ/PGC-1α/SIRT3 signaling pathway. ERRγ may serve as a novel therapeutic target to ameliorate EBI after SAH [1)].

Neuronal injury following subarachnoid hemorrhage (SAH) has been shown to be associated with mitochondrial dysfunction and oxidative stress. βIIPKC, a subtype of protein kinase C (PKC), accumulates on the mitochondrial outer membrane and phosphorylates mitofusin 1 (Mfn1) at serine 86. Here, we investigated the role of Mfn1-βIIPKC interaction in brain damage and neurological function in both in vivo and in vitro experimental SAH models. The expression of βIIPKC protein and the interaction of Mfn1-βIIPKC were found to be increased after OxyHb treatment in primary cultured cortical neurons and were also observed in the brain following SAH in rats. Treatment with the βIIPKC inhibitor βIIV5-3 or SAMβA, a peptide that selectively antagonizes Mfn1-βIIPKC association, significantly attenuated the OxyHb-induced neuronal injury and apoptosis. These protective effects were accompanied by inhibited mitochondrial dysfunction and preserved mitochondrial biogenesis. The results of western blot showed that βIIV5-3 or SAMβA markedly increased the expression of Sirt3 and enhanced the activities of its downstream mitochondrial antioxidant enzymes in OxyHb-treated neurons. Knockdown of Sirt3 via specific targeted small interfering RNA (siRNA) partially prevented

the βIIV5-3- or SAMβA-induced protection and antioxidative effects. In addition, treatment with βIIV5-3 or SAMβA in vivo was found to obviously reduce brain edema, alleviate neuroinflammation, and preserve neurological function after experimental SAH in rats. In congruent with in vitro data, the protection induced by βIIV5-3 or SAMβA was reduced by Sirt3 knockdown in vivo. In summary, our present results showed that blocking Mfn1-βIIPKC interaction protects against brain damage and mitochondrial dysfunction via Sirt3 following experimental SAH [2].

1)
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2)
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