

**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 ERR $\gamma$  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 ERR $\gamma$  activation were investigated. ERR $\gamma$  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 ERR $\gamma$  activation. Post-SAH assessments included SAH grade, neurological score, **Western blot**, **Nissl staining**, and immunofluorescence staining in rats. In an vitro study, the ERR $\gamma$  agonist DY131 and ERR $\gamma$  siRNA were administered to primary cortical neurons stimulated by Hb, after which **cell viability** and neuronal deaths were accessed. Lastly, the brain ERR $\gamma$  levels and neuronal death were accessed in SAH patients. They found that brain ERR $\gamma$  expressions were significantly increased, but the expression of SIRT3 dramatically decreased after SAH in rats. In the brains of SAH rats, ERR $\gamma$  was expressed primarily in **neurons**, **astrocytes**, and **microglia**. The activation of ERR $\gamma$  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-1 $\alpha$ , SIRT3, and **Bcl-2** while downregulating the expressions of 4-HNE and **Bax**. ERR $\gamma$  antagonist GSK5182 and SIRT3 inhibitor 3-TYP abolished the neuroprotective effects of ERR $\gamma$  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 ERR $\gamma$  siRNA exhibited notable apoptosis and abolished the protective effect of DY131. The examination of SAH patients' brain samples revealed increases in ERR $\gamma$  expressions and neuronal apoptosis marker CC3. We concluded that ERR $\gamma$  activation with DY131 ameliorated oxidative stress and neuronal apoptosis after the experimental SAH. The effects were, at least in part, through the ERR $\gamma$ /PGC-1 $\alpha$ /SIRT3 signaling pathway. ERR $\gamma$  may serve as a novel therapeutic target to ameliorate EBI after SAH <sup>1)</sup>.

<sup>1)</sup>

Guo Y, Hu Y, Huang Y, Huang L, Kanamaru H, Takemoto Y, Li H, Li D, Gu J, Zhang JH. Role of Estrogen-Related Receptor  $\gamma$  and PGC-1 $\alpha$ /SIRT3 Pathway in Early Brain Injury After Subarachnoid Hemorrhage. *Neurotherapeutics*. 2022 Dec 8. doi: 10.1007/s13311-022-01330-8. Epub ahead of print. Erratum in: *Neurotherapeutics*. 2023 Jan 13;; PMID: 36481985.

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