

Icariside II preconditioning evokes robust neuroprotection against ischemic stroke: Targeting Nrf2 mediated by OXPHOS/NF- κ B/ferroptosis pathway

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Abstract

Background and Purpose: Astrocytic nuclear factor erythroid-derived 2-related factor 2 (Nrf2) is a potential therapeutic target of ischemic preconditioning (IPC). Icariside II (ICS II) is a naturally occurring flavonoid derived from *Herba Epimedii* with Nrf2 induction potency. This study was designed to clarify whether ICS II simulates IPC neuroprotection and to decipher if the astrocytic-Nrf2 is contributed to ICS II preconditioning against ischemic stroke. **Experimental Approach:** Mice with transient middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia and oxygen-glucose deprivation (OGD)-injured primary astrocytes were used to explore the neuroprotective of ICS II preconditioning. Additionally, Nrf2-deficient mice were pretreated with ICS II to determine whether ICS II exerts its neuroprotection by activating Nrf2. **Key results:** ICS II pre-treatment dramatically mitigated the cerebral injury in ischemic stroke mice along with restoring long-term recovery. Furthermore, proteomics screening identified Nrf2 is a crucial gene evoked by ICS II stimulation and is required for the anti-oxidative effect and anti-inflammatory effect of ICS II. Most interestingly, ICS II directly bound with Nrf2 and reinforced the transcriptional activity of Nrf2 after MCAO. Moreover, ICS II pre-treatment exerted cytoprotective effect on astrocytes after lethal oxygen-glucose deprivation insult via promoting Nrf2 nuclear translocation and mediating OXPHOS/NF- κ B/ferroptosis axis. While, abrogated neuroprotection in Nrf2-deficient mice and astrocyte potently supports Nrf2-dependent neuroprotection of ICS II. **Conclusions and implications:** ICS II preconditioning confers robust neuroprotection against ischemic stroke via astrocytic Nrf2-mediated OXPHOS/NF- κ B/ferroptosis axis, it is concluded that ICS II will be serve as a promising Nrf2 activator to rescue ischemic stroke.

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