Omaveloxolone

RTA 408 (Omaveloxolone) is a traditional Asian medicine with a valid anti-inflammatory property.

Lu et al. aimed to investigate the therapeutic effect of RTA-408 on mechanical allodynia in chronic constriction injury (CCI) rats as well as the underlying mechanisms. Neuropathic pain was induced by using CCI of the rats' sciatic nerve (SN) and the behavior testing was measured by calibrated forceps testing. Activation of Nrf2, the phosphorylation of nuclear factor-κB (NF-κB), and the inflammatory response were assessed by western blots. The number of apoptotic neurons and degree of glial cell reaction were examined by immunofluorescence assay. RTA-408 exerts an analgesic effect on CCI rats. RTA-408 reduces neuronal apoptosis and glial cell activation by increasing Nrf-2 expression and decreasing the inflammatory response (TNF-α/ p-NF-κB/ TSLP/ STAT5). These data suggest that RTA-408 is a candidate with the potential to reduce nociceptive hypersensitivity after CCI by targeting TSLP/STAT5 signaling [1].

Tsai et al. randomly assigned 60 Sprague-Dawley male rats (350 to 420g) to five groups twelve rats each: one control group (no SAH), one untreated SAH only group, and three RTA-408 treatment groups (SAH+ RTA 408 0.5 mg/kg/day, SAH+RTA 408 1 mg/kg/day and a SAH+RTA 408 1.5 mg/kg/day). The treatment groups were administered RTA 408 by intraperitoneal injection thirty min following the first induction of SAH for seven days starting with the first hemorrhage. Cerebral vasospasm was determined by averaging the cross-sectional areas of the basilar artery 7 days after the first SAH. Expressions of Nrf2, NF-κB, and iNOS in the basilar artery and expressions of Nrf2, HO-1, NQO1, and Cleaved caspase-3 were evaluated. Tissue TNF-alpha was assessed by ELISA using the protein sampled from the dentate gyrus, cerebral cortex, and hippocampus.

Prior to perfusion fixation, there were no significant physiological differences among the control and treated groups. RTA 408 treatment attenuated the morphological changes caused by cerebral vasospasm. It mitigated SAH-induced suppression of Nrf2 and increased expression of NF-κB and iNOS in the basilar artery. In the dentate gyrus, it reversed SAH-decreases in Nrf2, HO-1, NQO-1, and cleaved caspase-3, and RTA 408 1.5 mg/kg/day reversed SAH increases in TNF-alpha.

It was concluded that RTA 408 reversal vasospasm was achieved via increases in Nrf2 and decreases in NF-κB and iNOS. It exerted a neuron-protection effect by decreasing the apoptosis-related protein-cleaved caspase-3 and decreasing the information cytokine TNF-alpha expression, which it achieved by increasing HO-1 and NQO-1 protein found downstream from Nrf2 and Nrf2. We believe that RTA 408 can potentially be used to manage of cerebral vasospasm and secondary brain injury following SAH [2]

1)
Lu YY, Tsai HP, Tsai TH, Miao HC, Zhang ZH, Wu CH. RTA-408 Regulates p-NF-κB/TSLP/STAT5 Signaling to Ameliorate Nociceptive Hypersensitivity in Chronic Constriction Injury Rats. Mol Neurobiol. 2023 Sep 29. doi: 10.1007/s12035-023-03660-w. Epub ahead of print. PMID: 37773082.
2)
Tsai TH, Lin SH, Wu CH, Tsai YC, Yang SF, Lin CL. Mechanisms and therapeutic implications of RTA 408, an activator of Nrf2, in subarachnoid hemorrhage-induced delayed cerebral vasospasm and secondary brain injury. PLoS One. 2020 Oct 5;15(10):e0240122. doi: 10.1371/journal.pone.0240122.

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