Curcumin for Traumatic Brain Injury

A study determined whether the neuroprotective role of curcumin in mouse TBI is dependent on the NF-E2-related factor (Nrf2) pathway. The Feeney weight-drop contusion model was used to mimic TBI. Curcumin was administered intraperitoneally 15 min after TBI induction, and brains were collected at 24 h after TBI. The levels of Nrf2 and its downstream genes (Hmox-1, Nqo1, Gclm, and Gclc) were detected by Western blot and qRT-PCR at 24 h after TBI. In addition, edema, oxidative damage, cell apoptosis and inflammatory reactions were evaluated in wild type (WT) and Nrf2-knockout (Nrf2-KO) mice to explore the role of Nrf2 signaling after curcumin treatment. In wild type mice, curcumin treatment resulted in reduced ipsilateral cortex injury, neutrophil infiltration, and microglia activation, improving neuron survival against TBI-induced apoptosis and degeneration. These effects were accompanied by increased expression and nuclear translocation of Nrf2, and enhanced expression of antioxidant enzymes. However, Nrf2 deletion attenuated the neuroprotective effects of curcumin in Nrf2-KO mice after TBI. These findings demonstrated that curcumin effects on TBI are associated with the activation the Nrf2 pathway, providing novel insights into the neuroprotective role of Nrf2 and the potential therapeutic use of curcumin for TBI [1)].

The protective effect of tetrahydrocurcumin (THC) after experimental traumatic brain injury (TBI) has been demonstrated, as demonstrated by the inhibition of oxidative stress, mitochondrial dysfunction, and apoptosis. However, the mechanisms underlying this effect are still not well understood.

A study was to investigate the neuroprotective effects of THC, and its potential mechanisms, in a rat model of TBI. To this end, rats were divided into 4 groups: the sham group, the TBI group, the TBI + vehicle (V) group, and the TBI + THC group. THC or V was administered via intraperitoneal injection to rats in the TBI + V and TBI + THC groups 30 min after TBI. After euthanasia (24 h after TBI), neurological scores, brain water content, and neuronal cell death in the cerebral cortex were recorded. Brain samples were collected after neurological scoring for further analysis. THC treatment alleviated brain edema, attenuated TBI-induced neuronal cell apoptosis, and improved neurobehavioral function. In addition, NFE2-related factor 2 (Nrf2) expression was upregulated following TBI. These results suggest that THC improves neurological outcome after TBI, possibly by activating the Nrf2 signaling pathway [2)].

The aim of a study was to investigate the potential neuroprotection of curcumin and the possible role of Nrf2-ARE pathway in the weight-drop model of TBI. The administration of curcumin significantly ameliorated secondary brain injury induced by TBI, such as brain water content, oxidative stress, neurological severity score, and neuronal apoptosis. Curcumin possessed anti-apoptotic character evidenced by elevating Bcl-2 content and reducing that of cleaved caspase-3. Moreover, curcumin markedly enhanced the translocation of Nrf2 from the cytoplasm to the nucleus, proved by the results of western blot and immunohistochemistry, subsequently increased the expression of downstream factors such as heme oxygenase 1 (HO1) and NAD(P)H: quinone oxidoreductase 1 (NQO1) and prevented the decline of antioxidant enzyme activities. In conclusion, curcumin could increase the activities of antioxidant enzymes and attenuate brain injury in the model of TBI, possibly via the activation of the Nrf2-ARE pathway [3)].

In a study, Huang et al., evaluated the therapeutic potential of curcumin for the treatment of DAI and investigated the mechanisms underlying the protective effects of curcumin against neural cell death and axonal injury after DAI. Rats subjected to a model of DAI by head rotational acceleration were treated with vehicle or curcumin to evaluate the effect of curcumin on neuronal and axonal injury. We observed that curcumin (20 mg/kg intraperitoneal) administered 1 h after DAI induction alleviated the aggregation of p-tau and β-APP in neurons, reduced ER-stress-related cell apoptosis, and ameliorated neurological deficits. Further investigation showed that the protective effect of curcumin in DAI was mediated by the PERK/Nrf2 pathway. Curcumin promoted PERK phosphorylation, and then Nrf2 dissociated from Keap1 and was translocated to the nucleus, which activated ATF4, an important bZIP transcription factor that maintains intracellular homeostasis, but inhibited the CHOP, a hallmark of ER stress and ER-associated programmed cell death. In summary, we demonstrate for the first time that curcumin confers protection against abnormal proteins and neuronal apoptosis after DAI, that the process is mediated by strengthening of the unfolded protein response to overcome ER stress, and that the protective effect of curcumin against DAI is dependent on the activation of Nrf2 [4)].

Neurological function, brain water content and cytokine levels were tested in TLR4$^{-/-}$ mice subjected to weight-drop contusion injury. Wild-type (WT) mice were injected intraperitoneally with different concentrations of curcumin or vehicle 15 minutes after TBI. At 24 hours post-injury, the activation of microglia/macrophages and TLR4 was detected by immunohistochemistry; neuronal apoptosis was measured by FJB and TUNEL staining; cytokines were assayed by ELISA; and TLR4, MyD88 and NF-κB levels were measured by Western blotting. In vitro, a co-culture system comprised of microglia and neurons was treated with curcumin following lipopolysaccharide (LPS) stimulation. TLR4 expression and morphological activation in microglia and morphological damage to neurons were detected by immunohistochemistry 24 hours post-stimulation.

The protein expression of TLR4 in pericontusional tissue reached a maximum at 24 hours post-TBI. Compared with WT mice, TLR4$^{-/-}$ mice showed attenuated functional impairment, brain edema and cytokine release post-TBI. In addition to improvement in the above aspects, 100 mg/kg curcumin treatment post-TBI significantly reduced the number of TLR4-positive microglia/macrophages as well as inflammatory mediator release and neuronal apoptosis in WT mice. Furthermore, Western blot analysis indicated that the levels of TLR4 and its known downstream effectors (MyD88, and NF-κB) were also decreased after curcumin treatment. Similar outcomes were observed in the microglia and neuron co-culture following treatment with curcumin after LPS stimulation. LPS increased TLR4 immunoreactivity and morphological activation in microglia and increased neuronal apoptosis, whereas curcumin normalized this upregulation. The increased protein levels of TLR4, MyD88 and NF-κB in microglia were attenuated by curcumin treatment.

The results suggest that post-injury, curcumin administration may improve patient outcome by reducing acute activation of microglia/macrophages and neuronal apoptosis through a mechanism involving the TLR4/MyD88/NF-κB signaling pathway in microglia/macrophages in TBI [5)].

The neuroprotective effects of curcumin were evaluated in a weight drop model of cortical contusion trauma in rat. Male Wistar rats (350-400 g, n=9) were anesthetized with sodium pentobarbital (60 mg/kg i.p.) and subjected to head injury. Five days before injury, animals randomly received an i.p. bolus of either curcumin (50 and 100 mg/kg/day, n=9) or vehicle (n=9). Two weeks after the injury

and drug treatment, animals were sacrificed and a series of brain sections, stained with hematoxylin and eosin (H&E) were evaluated for quantitative brain lesion volume. Two weeks after the injury, oxidative stress parameter (malondialdehyde) was also measured in the brain. Curcumin (100 mg/kg) significantly reduced the size of brain injury-induced lesions ($P<0.05$). Neurological examinations (rotarod and inclined-plane tests) were performed on days 1, 3, 7 and 14 post-brain injury. Control injured rats had a significant neurological deficit during 2 weeks ($P<0.001$). The injury increased brain levels of the malondialdehyde by 35.6% and these increases were attenuated by curcumin (100 mg/kg). Curcumin treatment significantly improved the neurological status evaluated during 2 weeks after brain injury. The study demonstrates the protective efficacy of curcumin in rat traumatic brain injury model [6)].

In a study, pre-treatment with curcumin (75, 150 mg/kg) or 30 min post-treatment with 300 mg/kg significantly reduced brain water content and improved neurological outcome following a moderate controlled cortical impact in mice. The protective effect of curcumin was associated with a significant attenuation in the acute pericontusional expression of interleukin-1beta, a pro-inflammatory cytokine, after injury. Curcumin also reversed the induction of aquaporin-4, an astrocytic water channel implicated in the development of cellular edema following head trauma. Notably, curcumin blocked IL-1beta-induced aquaporin-4 expression in cultured astrocytes, an effect mediated, at least in part, by reduced activation of the p50 and p65 subunits of nuclear factor kappaB. Consistent with this notion, curcumin preferentially attenuated phosphorylated p65 immunoreactivity in pericontusional astrocytes and decreased the expression of glial fibrillary acidic protein, a reactive astrocyte marker. As a whole, these data suggest clinically achievable concentrations of curcumin reduce glial activation and cerebral edema following neurotrauma, a finding which warrants further investigation [7)].

In a study Rats were exposed to a regular diet or a diet high in saturated fat, with or without 500 ppm curcumin for 4 weeks (n = 8/group), before a mild fluid percussion injury (FPI) was performed. The high-fat diet has been shown to exacerbate the effects of TBI on synaptic plasticity and cognitive function. Supplementation of curcumin in the diet dramatically reduced oxidative damage and normalized levels of BDNF, synapsin I, and CREB that had been altered after TBI. Furthermore, curcumin supplementation counteracted the cognitive impairment caused by TBI. These results are in agreement with previous evidence, showing that oxidative stress can affect the injured brain by acting through the BDNF system to affect synaptic plasticity and cognition. The fact that oxidative stress is an intrinsic component of the neurological sequel of TBI and other insults indicates that dietary antioxidant therapy is a realistic approach to promote protective mechanisms in the injured brain [8)].

1)
Dong W, Yang B, Wang L, Li B, Guo X, Zhang M, Jiang Z, Fu J, Pi J, Guan D, Zhao R. Curcumin plays neuroprotective roles against traumatic brain injury partly via Nrf2 signaling. Toxicol Appl Pharmacol. 2018 May 1;346:28-36. doi: 10.1016/j.taap.2018.03.020. Epub 2018 Mar 21. PubMed PMID: 29571711.
2)
Wei G, Chen B, Lin Q, Li Y, Luo L, He H, Fu H. Tetrahydrocurcumin Provides Neuroprotection in Experimental Traumatic Brain Injury and the Nrf2 Signaling Pathway as a Potential Mechanism. Neuroimmunomodulation. 2018 Apr 18. doi: 10.1159/000487998. [Epub ahead of print] PubMed PMID: 29669346.
3)
Dai W, Wang H, Fang J, Zhu Y, Zhou J, Wang X, Zhou Y, Zhou M. Curcumin provides neuroprotection in models of traumatic brain injury via the Nrf2-ARE signaling pathway. Brain Res Bull. 2018 Apr 4. pii:

S0361-9230(17)30417-3. doi: 10.1016/j.brainresbull.2018.03.020. [Epub ahead of print] PubMed PMID: 29626606.

4)

Huang T, Zhao J, Guo D, Pang H, Zhao Y, Song J. Curcumin mitigates axonal injury and neuronal cell apoptosis through the PERK/Nrf2 signaling pathway following diffuse axonal injury. Neuroreport. 2018 Mar 22. doi: 10.1097/WNR.0000000000001015. [Epub ahead of print] PubMed PMID: 29570500.

5)

Zhu HT, Bian C, Yuan JC, Chu WH, Xiang X, Chen F, Wang CS, Feng H, Lin JK. Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway in experimental traumatic brain injury. J Neuroinflammation. 2014 Mar 27;11:59. doi: 10.1186/1742-2094-11-59. PubMed PMID: 24669820; PubMed Central PMCID: PMC3986937.

6)

Samini F, Samarghandian S, Borji A, Mohammadi G, bakaian M. Curcumin pretreatment attenuates brain lesion size and improves neurological function following traumatic brain injury in the rat. Pharmacol Biochem Behav. 2013 Sep;110:238-44. doi: 10.1016/j.pbb.2013.07.019. Epub 2013 Aug 7. PubMed PMID: 23932920.

7)

Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? J Neurochem. 2010 May;113(3):637-48. doi: 10.1111/j.1471-4159.2010.06630.x. Epub 2010 Jan 20. PubMed PMID: 20132469; PubMed Central PMCID: PMC2911034.

8)

Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol. 2006 Feb;197(2):309-17. Epub 2005 Dec 20. PubMed PMID: 16364299.