



## REVIEW ARTICLE

# Advancing neuroprotection in traumatic brain injury: Maximizing the potential of the nuclear factor erythroid 2-related factor 2/nuclear factor kappa B pathway through insights from animal models

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### ABSTRACT

Traumatic brain injury (TBI) is a primary public health concern that can result in significant long-term disability and mortality. Neuroprotection strategies that can mitigate the effects of TBI are urgently needed. The nuclear factor erythroid 2-related factor 2 (Nrf-2)/nuclear factor kappa B (NF-κB) pathway has emerged as a promising TBI neuroprotection target because it regulates inflammation, oxidative stress, and mitochondrial dysfunction. This review summarizes the current preclinical evidence supporting the role of the Nrf-2/NF-κB pathway in TBI and the mechanisms underlying its regulation. Pharmacological and genetic approaches have been used to modulate the pathway in animal models of TBI, resulting in improved functional, histological, and molecular outcomes. The molecular mechanisms underlying the Nrf-2/NF-κB pathway in TBI involve regulating inflammation, oxidative stress, and mitochondrial dysfunction. The future studies should focus on identifying safe and effective agents for modulating this pathway, optimizing dosing regimens, and exploring combination therapies targeting multiple TBI pathways. While preclinical studies have shown promising results, further research is needed to determine the safety and efficacy of modulating the Nrf-2/NF-κB pathway in human TBI patients. Overall, the Nrf-2/NF-κB pathway represents a promising target for neuroprotection in TBI, and further research is needed to translate these preclinical findings into effective treatments for human patients.

**KEY WORDS:** Genetic approaches, Inflammation, Mitochondrial dysfunction, Molecular mechanisms, Neuroprotection, Nuclear factor erythroid 2-related factor 2/Nuclear factor kappa B pathway, Oxidative stress, Pharmacological approaches, Preclinical evidence, Traumatic brain injury

### INTRODUCTION

**Briefly introduce traumatic brain injury (TBI) as a major public health concern and the need for effective neuroprotective strategies**

Briefly introduce TBI as a major public health concern and the need for effective neuroprotective strategies. TBI is a significant public health concern, affecting millions of individuals worldwide. It is a leading cause of death

and disability, accounting for over 50 million new cases annually.<sup>[1]</sup> External mechanical forces that harm the brain tissue are what cause TBI, which results in physical, cognitive, and psychological impairments. The severity of TBI can range from mild to severe, depending on the extent of the injury.<sup>[2]</sup> Unfortunately, there are currently

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no effective treatments for TBI, highlighting the need for novel neuroprotective strategies. Finding potential neuroprotective techniques that can lessen TBI damage and enhance patient outcomes have been the focus of recent research. One promising avenue of research is the modulation of the nuclear factor erythroid 2-related factor 2 (Nrf-2)/nuclear factor kappa B (NF-κB) pathway.<sup>[3]</sup> This pathway plays a critical role in regulating the inflammatory and oxidative stress responses to brain injury and is involved in the pathogenesis of TBI. Modulating the Nrf-2/NF-κB pathway has shown promise as a potential neuroprotective strategy in animal models of TBI,<sup>[4]</sup> and thus, it represents an attractive target for developing therapeutic interventions. In this review article, we will summarize the current preclinical evidence supporting the role of the Nrf-2/NF-κB pathway in TBI and the potential mechanisms underlying its neuroprotective effects. We will also discuss the challenges and opportunities for translating preclinical findings into clinical practice and provide recommendations for future research directions. Overall, we aim to provide an in-depth analysis of the potential of targeting the Nrf-2/NF-κB pathway as a promising neuroprotective strategy for TBI. Describe the Nrf-2/NF-κB pathway as a potential target for neuroprotection against TBI. The Nrf-2/NF-κB pathway has recently gained attention as a possible neuroprotection target in the fight against TBI. This route is essential in regulating cellular responses to oxidative stress, inflammation, and apoptosis, all necessary in TBI-induced brain injury. The Nrf-2, often known as Nrf-2, is a transcription factor that performs the role of a master regulator of the antioxidant response in cells.<sup>[5]</sup> Under normal circumstances, Kelch-like ECH-associated protein 1 (Keap1) sequesters Nrf-2 in the cytoplasm. In response to oxidative or electrophilic stress, Nrf-2 breaks away from Keap1 and moves to the nucleus, where it binds to antioxidant response elements (AREs) in the promoter regions of target genes.<sup>[6]</sup> This results in the upregulation of several antioxidant and cytoprotective genes, such as heme oxygenase-1 (HO-1), NAD(P)H: Quinone oxidoreductase 1 (NQO1), and glutamate-cysteine ligase. On the other hand, NF-κB is a transcription factor that controls the expression of genes implicated in inflammatory and immune responses. Inhibitors of kappa B (IBs) are proteins that typically lock NF-κB away in the cytoplasm.<sup>[7]</sup> When cytokines, reactive oxygen species (ROS), or pathogen-associated molecular patterns (PAMPs) cause inflammation, the IBs get phosphorylated and broken down, which makes NF-κB move into the nucleus. Once inside the nucleus, NF-κB binds to particular DNA sequences known as B sites, thereby promoting the transcription of diverse pro-inflammatory mediators. These mediators consist of cytokines (like interleukin-1 and tumor necrosis factor-), chemokines, adhesion molecules, and inducible enzymes (like cyclooxygenase-2 and inducible nitric oxide synthase).<sup>[8]</sup> The Nrf-2/NF-κB pathway exhibits a complex interplay in the context of TBI. In the aftermath of TBI, an imbalance between

oxidative stress and antioxidant defense mechanisms produce ROS and reactive nitrogen species (RNS). This oxidative stress activates NF-κB, resulting in the production of pro-inflammatory cytokines and the amplification of the brain's inflammatory response.<sup>[9]</sup> The Nrf-2 pathway is simultaneously activated as a protective response against oxidative stress. By inducing the expression of antioxidant enzymes and Phase II detoxifying enzymes, Nrf-2 activation mitigates the harmful effects of oxidative stress. The modulation of the Nrf-2/NF-κB pathway holds great promise for TBI neuroprotection. Activation of Nrf-2 can boost the endogenous antioxidant defense system, decrease oxidative damage, and promote neuronal survival. In addition, inhibiting NF-κB can reduce neuroinflammation and secondary brain injury by dampening the inflammatory response. Consequently, pharmacological interventions designed to promote Nrf-2 activation or inhibit NF-κB activation have been investigated as potential therapeutic strategies for TBI.<sup>[10]</sup>

### NEUROPROTECTIVE EFFECTS OF NRF-2/NF-κB PATHWAY MODULATION IN TBI: PRECLINICAL EVIDENCE

Briefly describe the current *in vitro* and *in vivo* data for the function of the Nrf-2/NF-κB pathway in TBI. Modulating the Nrf-2/NF-κappa B pathway may have neuroprotective benefits in TBI, as shown by an increasing body of experimental research. Various studies have investigated the effects of pharmacological agents that target either Nrf-2 or NF-κB, or both, on TBI-induced brain damage and neurological deficits in animal models.<sup>[11]</sup> One study demonstrated that treatment with sulforaphane, a natural Nrf-2 activator found in cruciferous vegetables, improved cognitive function, and reduced neuronal damage in a rat model of TBI. Sulforaphane treatment was associated with increased expression of Nrf-2 and its downstream target genes and decreased levels of pro-inflammatory cytokines and oxidative stress markers. Similar results were shown in a mouse model of TBI when treated with the synthetic Nrf-2 activator bardoxolone methyl, which enhanced cognitive performance and decreased neuronal damage.<sup>[12]</sup> A correlation was found between the neuroprotective effects of bardoxolone methyl and increased expression of Nrf-2 and the genes it targets, as well as decreased oxidative stress and inflammation levels. In contrast, it has been demonstrated that inhibiting NF-κB can also give neuroprotection in cases of TBI. In a rat model of TBI, treatment with a specific NF-κB inhibitor known as pyrrolidine dithiocarbamate (PDTC) enhanced cognitive performance and decreased the amount of neuronal damage.<sup>[13]</sup> Treatment with PDTC was linked to lower levels of pro-inflammatory cytokines and higher levels of anti-apoptotic proteins.

Furthermore, coupled Nrf-2 and NF-κB regulation has been demonstrated to have synergistic neuroprotective

effects in TBI. In a rat model of TBI, treatment with tert-butylhydroquinone (tBHQ), a dual Nrf-2/NF- $\kappa$ B modulator, enhanced cognitive performance and decreased neuronal damage. Treatment with tBHQ was linked to higher levels of Nrf-2 and its target genes and lower levels of pro-inflammatory cytokines and oxidative stress indicators.<sup>[14]</sup> Describe the methods used to modulate the pathway in animal models of TBI, including pharmacological and genetic approaches. In preclinical studies investigating the neuroprotective effects of modulating the Nrf-2/NF- $\kappa$ B pathway in TBI, various methods have been employed to manipulate the activity of these transcription factors in animal models. These methods include pharmacological and genetic approaches. Pharmacological approaches involve using compounds that target Nrf-2, NF- $\kappa$ B, or both, to activate or inhibit their activity.<sup>[15]</sup> For example, sulforaphane, a natural Nrf-2 activator found in cruciferous vegetables, has been used to activate Nrf-2 in animal models of TBI. Similarly, synthetic Nrf-2 activators such as bardoxolone methyl and tBHQ have also been used. These compounds are administered orally or by injection at various doses and times before or after TBI induction.<sup>[16]</sup> Conversely, pharmacological inhibition of NF- $\kappa$ B activity has been achieved using compounds such as pyrrolidine dithiocarbamate (PDTC) and SN50, which target different components of the NF- $\kappa$ B signaling pathway. These compounds are also administered orally or by injection at various doses and times before or after TBI induction. Genetic approaches involve using genetically modified animals or viral vectors to alter the expression of Nrf-2 or NF- $\kappa$ B in specific brain regions or cell types.<sup>[17]</sup> For example, transgenic mice overexpressing Nrf-2 have been used to investigate the effects of Nrf-2 activation in TBI. Similarly, viral vectors have been used to deliver Nrf-2, NF- $\kappa$ B siRNA, or shRNA to knock down their expression in specific brain regions. Other methods to modulate the Nrf-2/NF- $\kappa$ B pathway include using antioxidants, which can increase Nrf-2 activity by reducing oxidative stress, and cytokines or growth factors, activating NF- $\kappa$ B signaling.<sup>[18]</sup> These methods allow researchers to investigate the role of Nrf-2 and NF- $\kappa$ B in TBI and assess the potential neuroprotective effects of modulating these pathways. However, the efficiency of these therapies may vary depending on the animal model, the exact technique of pathway modulation utilized, and other experimental factors.<sup>[19]</sup> Discuss the observed neuroprotective effects of modulating the pathway in terms of functional, histological, and molecular outcomes. Modulating the Nrf-2/NF- $\kappa$ B pathway possesses neuroprotective properties in various preclinical models of TBI. These effects have been assessed using a range of functional, histological, and molecular outcomes. Functional outcomes refer to setting cognitive, motor, and sensory functions affected by TBI. Studies have shown that modulating the Nrf-2/NF- $\kappa$ B pathway can improve these functions in animal models of TBI.<sup>[20]</sup> For example, treating sulforaphane, a natural Nrf-2 activator, has enhanced cognitive function in rats subjected to controlled

cortical impact injury.<sup>[21]</sup> Similarly, genetic overexpression of Nrf-2 has improved motor function in mice subjected to fluid percussion injury.<sup>[21]</sup> Histological outcomes refer to assessing brain tissue damage and repair following TBI. Modulating the Nrf-2/NF- $\kappa$ B pathway has been shown to reduce histological damage in animal models of TBI.<sup>[11]</sup> Sulforaphane, for instance, has been demonstrated to lessen TBI-induced hippocampal and cortex neuronal damage and inflammation in rats. Similarly, genetic overexpression of Nrf-2 has been shown to reduce cortical tissue loss in mice subjected to fluid percussion injury. Molecular outcomes refer to changes in gene expression and signaling pathways associated with TBI. Modulating the Nrf-2/NF- $\kappa$ B pathway has been shown to regulate these molecular outcomes in animal models of TBI. For example, treating sulforaphane has been shown to increase the expression of antioxidant genes and reduce the expression of pro-inflammatory cytokines in the brain following TBI. Similarly, genetic overexpression of Nrf-2 has been shown to increase the expression of antioxidant and anti-inflammatory genes in the brain following TBI. Modulating the Nrf-2/NF- $\kappa$ B pathway has improved functional, histological, and molecular outcomes in animal models of TBI. Targeting these pathways may be a promising strategy for developing neuroprotective therapies for TBI in humans, as suggested by these findings. Additional research is required to fully comprehend the mechanisms underlying these effects and optimize the timing and dosage of pathway modulation for maximum efficacy.<sup>[22]</sup>

### MECHANISTIC INSIGHTS INTO THE NRF-2/NF- $\kappa$ B PATHWAY AND ITS ROLE IN TBI PROVIDE AN IN-DEPTH ANALYSIS OF THE MOLECULAR MECHANISMS UNDERLYING THE NRF-2/NF- $\kappa$ B PATHWAY AND ITS REGULATION IN TBI

The Nrf-2/NF- $\kappa$ B signaling pathway is essential for controlling oxidative stress and inflammation in the brain. Two transcription factors, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and Nrf-2 work together in this pathway to control gene expression.<sup>[23]</sup> The cytosolic protein Keap1 is responsible for the sequestration of Nrf-2 in the cytoplasm when circumstances are physiologically normal. When cells are subjected to oxidative stress or electrophilic chemicals, Nrf-2 is released from Keap1 and translocates to the nucleus. Once there, it binds to AREs in the promoter regions of target genes and stimulates the expression of those genes.<sup>[6]</sup> A range of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, as well as additional cytoprotective genes, such as HO-1 and NAD(P)H quinone dehydrogenase 1 (NQO1), are included among these target genes.<sup>[24]</sup> In the cytoplasm of healthy cells, inhibitory kappa B (IB) proteins keep the transcription factor NF- $\kappa$ B inactive. In response to pro-inflammatory stimuli such

as cytokines or lipopolysaccharide (LPS), however, IB is degraded following phosphorylation, permitting NF-κB to translocate into the nucleus. Once in the nucleus, NF-κB attaches to B sites in the promoter regions of target genes and promotes their expression. These target genes include those for pro-inflammatory cytokines (such as interleukin-1 and tumor necrosis factor-) and inducible nitric oxide synthase and cyclooxygenase-2. These genes are responsible for producing reactive nitrogen and oxygen species. In TBI, the Nrf-2/NF-κB pathway becomes dysregulated, resulting in an imbalance between oxidative stress and inflammation.<sup>[25]</sup> Injured neurons and glia produce excess ROS and RNS, which can cause damage to lipids, proteins, and DNA, leading to oxidative stress. In response to injury, microglia and astrocytes become activated, releasing pro-inflammatory cytokines and chemokines that draw in more immune cells and worsen tissue damage.<sup>[26]</sup> Restoring this equilibrium and minimizing TBI damage has been demonstrated in several studies to be possible by regulating the Nrf-2/NF-κB pathway. By activating Nrf-2, for instance, the expression of antioxidant genes is upregulated while the production of pro-inflammatory cytokines is downregulated in the brain after TBI. Reducing the expression of pro-inflammatory cytokines and enhancing cognitive and motor performance have been shown in animal models of TBI when NF-κB is inhibited.<sup>[11]</sup>

Examine the role of inflammation, oxidative stress, and mitochondrial dysfunction in TBI and how the Nrf-2/NF-κB pathway modulates these processes. Several processes characterize TBI, including inflammation, oxidative stress, and mitochondrial dysfunction. These processes are linked and can contribute to each other, ultimately causing cell death and damage. Activating microglia and astrocytes in response to damage is the first step in the inflammatory process characteristic of TBI.<sup>[27]</sup> In addition to recruiting immune cells to the site of injury and exacerbating tissue damage, these cells also release a wide range of pro-inflammatory cytokines and chemokines. ROS and RNS are byproducts of inflammation signaling that further contribute to oxidative stress. When ROS and RNS are produced at a rate faster than antioxidant defense systems can eliminate them, oxidative stress results. Cellular macromolecules, including lipids, proteins, and DNA, are vulnerable to ROS and RNS, which can cause damage and ultimately lead to cell death.<sup>[28]</sup> Since mitochondria both produce and are damaged by ROS, they are especially susceptible to oxidative stress. Mitochondrial dysfunction is characteristic of TBI and contributes to inflammation and oxidative stress development. Impaired mitochondrial biosynthesis and dynamics, as well as direct damage to mitochondrial membranes or proteins, can both lead to mitochondrial dysfunction. The inability to generate enough ATP due to problems with mitochondrial respiration and energy generation can devastate cell function and even contribute to cell death.<sup>[29]</sup> When regulating inflammation,

oxidative stress, and mitochondrial dysfunction after TBI, the Nrf-2/NF-κB pathway is crucial. By turning on Nrf-2, the expression of antioxidant enzymes can go up and the production of pro-inflammatory cytokines can go down. Turning off NF-κB, on the other hand, can reduce oxidative stress.<sup>[30]</sup> Reducing oxidative stress and increasing energy generation are only two ways modulating the Nrf-2/NF-κB pathway may boost mitochondrial function. Several studies *in vitro* and animal research have examined how TBI affects the Nrf-2/NF-κB pathway. The activation of Nrf-2, for instance, has been demonstrated to alleviate mitochondrial function and reduce neuronal mortality in animal models of TBI. Reducing inflammation and oxidative stress and enhancing cognitive and motor performance are additional benefits of NF-κB inhibition.<sup>[31]</sup>

## CONCLUSION

TBI is a major public health concern and effective neuroprotective strategies are urgently needed to improve patient outcomes. The Nrf-2/NF-κB pathway is a promising TBI neuroprotection target, as it plays a critical role in modulating inflammation, oxidative stress, and mitochondrial dysfunction. Preclinical studies have demonstrated that pharmacological or genetic approaches to modulate this pathway can improve functional, histological, and molecular outcomes following TBI. These studies have also shed light on the molecular mechanisms underlying the Nrf-2/NF-κB pathway and its regulation in TBI, including its role in modulating inflammation, oxidative stress, and mitochondrial dysfunction. While preclinical studies have shown promising results, further research is needed to determine the safety and efficacy of modulating the Nrf-2/NF-κB pathway in human TBI patients. Future studies should focus on identifying safe and effective agents for modulating this pathway, optimizing dosing regimens, and exploring combination therapies targeting multiple TBI pathways.

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## AUTHOR'S CONTRIBUTION

Mayank Kumar wrote the manuscript, manuscript reading, data collection, and data contribution. Shamsher Singh contributed as designed review paper, data analysis, manuscript reading, and final approval.



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## DECLARATIONS

### Conflicts of interest

The authors declare that they have no conflicts of interest.

### Ethics approval and consent to participate

Not applicable because this is a review paper.

### Consent for publication

All the authors are agreed for the publication of current review paper.

### Availability of data and material

All the data and material are already provided with the manuscript.

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