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Pathomechanisms and Neuroprotective Strategies in Traumatic Brain Injury

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Abstract
Traumatic brain injury (TBI) is a major cause of mortality and neurological disability resulting from the initial mechanical insult and a progressive secondary injury cascade involving excitotoxicity, mitochondrial dysfunction, neuroinflammation, blood–brain barrier disruption, cerebral edema, axonal degeneration, and cell death. This narrative review synthesized scientific literature published primarily between 2016 and 2026 to discuss the pathophysiology of primary and secondary injury, endogenous neuroprotective mechanisms, emerging therapeutic strategies, and the role of biomarkers in TBI. Secondary brain injury involves interconnected pathological mechanisms in which glutamate excitotoxicity promotes excessive Ca^{2+} influx, mitochondrial dysfunction, reactive oxygen species generation, and apoptosis, while neuroinflammation, BBB disruption, edema, and axonal degeneration aggravate neurological dysfunction. Potential neuroprotective strategies include modulation of excitotoxicity, antioxidant and mitochondrial protection, inflammatory modulation, neurotrophic factors, stem-cell-based therapies, and extracellular vesicles. GFAP and UCH-L1 may detect acute intracranial injury, whereas NF-L more closely reflects persistent axonal injury. Effective neuroprotection requires a multitarget, time-dependent approach that considers biological heterogeneity and biomarker profiles.

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1. INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide, with a continuously increasing disease burden, particularly among individuals of productive age and males [1]. Operationally, TBI is defined as damage to brain tissue resulting from external mechanical forces and is classified according to severity using the Glasgow Coma Scale (GCS) [2]. Its pathophysiology involves two phases: primary injury, which occurs instantaneously, and secondary injury, which develops progressively and involves excitotoxicity, oxidative stress, and neuroinflammation [3], [4].

Although various neuroprotective agents have demonstrated promising results in preclinical studies, a substantial translational gap remains in their application to human clinical practice due to the complexity of the injury cascade, patient heterogeneity, and the limited availability of sensitive biomarkers [3], [4]. Therefore, a comprehensive understanding of endogenous neuroprotective mechanisms, such as heat shock proteins (HSPs) and brain-derived neurotrophic factor (BDNF), as well as various external therapeutic interventions, is needed [5], [6].

This literature review aims to comprehensively examine the neuroprotective pathomechanisms involved in TBI. In addition, this review evaluates the role of various neuroprotective agents in inhibiting mechanisms such as excitotoxicity, oxidative stress, inflammation, and mitochondrial

dysfunction, while identifying factors that influence their effectiveness in clinical practice. The scope of this review includes a discussion of the pathophysiology of TBI, the classification and mechanisms of action of neuroprotective agents, and the available preclinical and clinical evidence. Accordingly, this review is expected to provide a deeper understanding of the scientific basis of neuroprotective therapies as a foundation for developing more effective and targeted management strategies.

2. METHODS

This article is a narrative review conducted through a literature search focusing on the pathomechanisms of traumatic brain injury (TBI), neuroprotective mechanisms, therapeutic strategies, and biomarkers. Literature published between 2016 and 2026 was prioritized. The keywords used in the search were focused on the main themes of the article and included Traumatic Brain Injury, Neuroprotection, Secondary Injury Cascade, Biomarkers, GFAP, NF-L, and UCH-L1. The literature sources included preclinical studies, clinical studies, narrative reviews, systematic reviews, meta-analyses, and other scientific publications relevant to the scope of the discussion.

The retrieved literature was initially screened based on titles and abstracts to identify publications that were relevant to the scope of the review. Relevant articles were subsequently assessed in greater depth through full-text review. At this stage, information related to pathophysiological mechanisms, neuroprotective targets, the effectiveness or potential of therapeutic strategies, as well as the characteristics and clinical utility of biomarkers, was extracted and compared across studies. Literature reporting conflicting findings was also considered to provide a more objective overview of the development of evidence in the field of TBI.

The findings from the literature were subsequently thematically categorized according to the pathological processes and neuroprotective approaches discussed. The discussion was organized beginning with the progression from primary injury to secondary injury, followed by the mechanisms of excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, blood–brain barrier (BBB) disruption, edema, axonal injury, and apoptosis. Subsequently, literature on endogenous neuroprotective defense mechanisms, neuroprotective strategies, and TBI biomarkers was synthesized to illustrate the relationship between disease mechanisms and potential therapeutic targets. This approach was used to integrate the available evidence and identify the developments and limitations of neuroprotective strategies in TBI.

3. RESULTS AND DISCUSSION

3.1. Primary Injury and the Initiation of the Secondary Injury Cascade

Primary injury refers to the mechanical damage that occurs directly at the time of trauma. Mechanical energy can cause tissue deformation, cell membrane damage, hemorrhage, contusion, and axonal injury. These injuries may also disrupt the axonal cytoskeleton and cause alterations in membrane permeability and ionic homeostasis [7], [8]. Primary injury occurs immediately and tends to be irreversible, whereas the complex molecular processes that follow constitute secondary injury, which may be modified through medical interventions. This process results in tissue damage and structural and cellular functional alterations that occur immediately after the impact and substantially contribute to early outcomes, including skull fractures, cerebral contusions, hematomas (epidural, subdural, intraparenchymal, intraventricular, and subarachnoid), as well as diffuse axonal injury (DAI) [2], [9].

3.2.Glutamate Excitotoxicity

Excitotoxicity is one of the early mechanisms involved in secondary injury. Neuronal damage and membrane disruption following trauma can increase glutamate release and impair glutamate clearance from the extracellular space. Reduced function of glutamate transporters, such as GLT-1 and GLAST, may result in elevated extracellular glutamate concentrations. Excessive glutamate

activates ionotropic receptors, particularly N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Activation of these receptors increases the influx of Na^+ and Ca^{2+} into neurons. The subsequent increase in intracellular Ca^{2+} activates various enzymes and signaling pathways that contribute to cytoskeletal damage, reactive oxygen species (ROS) generation, mitochondrial dysfunction, and apoptosis [4].

3.3.Mitochondrial Dysfunction and Energy Crisis

Mitochondria are the primary sites of cellular energy production and play an important role in Ca^{2+} regulation. Following TBI, increased intracellular Ca^{2+} and oxidative stress can cause mitochondrial membrane depolarization, disruption of the electron transport chain, and reduced ATP production. Opening of the mitochondrial permeability transition pore can increase mitochondrial membrane permeability and promote the release of cell-death mediators, such as cytochrome c and apoptosis-inducing factor, which contribute to the activation of cell-death pathways following mitochondrial dysfunction. This condition subsequently creates a pathological cycle in which excessive Ca^{2+} triggers mitochondrial dysfunction, reduced ATP production, increased ROS generation, membrane damage, and progressively impaired Ca^{2+} regulation [4]. This relationship makes mitochondria an important target for the development of neuroprotective strategies.

3.4.Neuroinflammation

Neuroinflammation is a complex response involving microglia, astrocytes, and peripheral immune cells. Following disruption of the BBB, neutrophils, monocytes, and lymphocytes can enter the brain tissue. Activation of these cells is associated with the release of inflammatory mediators such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Neuroinflammation has a dual role. During the early phase, the inflammatory response is necessary for the clearance of damaged tissue. However, excessive or persistent inflammation may exacerbate tissue damage, increase BBB permeability, and prolong cerebral edema. Therefore, neuroprotective strategies should not simply aim to eliminate the entire inflammatory response but should instead focus on modulating pathological inflammation while preserving inflammatory processes that are necessary for tissue repair [4].

3.5.Blood–Brain Barrier Disruption and Cerebral Edema

The blood–brain barrier (BBB) plays a critical role in maintaining the brain's microenvironment. Following TBI, alterations in tight junction proteins, such as occludin, claudin-5, and zonula occludens-1 (ZO-1), can increase BBB permeability [10], [11]. Matrix metalloproteinases (MMPs), particularly MMP-9, also contribute to the degradation of BBB components and the extracellular matrix. MMP activation may exacerbate vascular damage and facilitate the development of cerebral edema [12]. Cerebral edema is an important component of secondary injury. It may include a vasogenic component resulting from increased BBB permeability and a cytotoxic component associated with impaired cellular homeostasis [13]. Regulation of aquaporins, particularly aquaporin-4 (AQP4), also plays an important role in brain fluid dynamics and the development of cerebral edema following TBI [14], [15].

3.6.Axonal Degeneration and Apoptosis

Axonal injury caused by primary trauma may progress through cytoskeletal damage, impaired axonal transport, and Ca^{2+} dysregulation. These processes lead to axonal degeneration and white matter damage, which may persist longer than the initial injury and contribute to persistent neurological deficits [4]. Axonal damage also results in the release of neurofilament light chain (NF-L), making this biomarker potentially useful for reflecting ongoing axonal injury over a longer period compared with other biomarkers of acute injury [16], [17].

In addition to axonal degeneration, apoptosis plays an important role in the death of neurons and oligodendrocytes during secondary injury. This pathway can be triggered by death receptors and mitochondrial dysfunction. The release of cytochrome c activates caspases, particularly caspase-3,

while calpains and mitochondrial mediators further contribute to cellular damage [4]. Because apoptosis represents a downstream endpoint of multiple pathological processes, its inhibition should be accompanied by the control of upstream triggers, such as excitotoxicity, oxidative stress, and mitochondrial dysfunction.

3.7.Endogenous Neuroprotective Mechanisms

a. Heat Shock Proteins

Heat shock proteins are cellular defense mechanisms against various forms of stress. HSP70 acts as a molecular chaperone that helps maintain protein homeostasis and can inhibit apoptotic pathways. Gu et al. [5] demonstrated that induction of HSP70 with 17-AAG exerted neuroprotective effects in a TBI model through anti-inflammatory mechanisms. HSP27 also plays a role in maintaining cytoskeletal stability and protecting cells against cellular stress [18]. These findings suggest that HSPs may represent an attractive therapeutic target because they can modulate multiple injury mechanisms.

b. Neurotrophic Factors

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that plays an important role in neuronal survival and synaptic plasticity. Activation of the TrkB receptor can stimulate the PI3K/Akt and ERK pathways, which are associated with neuronal survival, neurite growth, and synaptic plasticity [6]. Other neurotrophic factors, such as nerve growth factor (NGF) and neurotrophin-3 (NT-3), may also support neurorestoration. However, the direct administration of neurotrophic proteins presents challenges related to pharmacokinetics and BBB penetration. Therefore, the development of small-molecule mimetics represents a promising approach [19].

c. Nrf2 Pathway and Antioxidant Defense

Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important regulator of the cellular antioxidant response. Activation of Nrf2 increases the expression of various cytoprotective genes and antioxidant enzymes. Strategies that enhance Nrf2 activity may potentially reduce the effects of oxidative stress following TBI. Studies investigating Nrf2 modulation have also demonstrated that this pathway can interact with inflammatory and apoptotic responses [9].

d. Autophagy, Mitophagy, and Neuroplasticity

Autophagy is a cellular maintenance mechanism that preserves homeostasis through the elimination of damaged proteins and organelles. In TBI, this process may exert either neuroprotective or detrimental effects depending on its intensity and biological context. Mitophagy, a form of autophagy that specifically eliminates damaged mitochondria, helps reduce the accumulation of ROS and apoptotic mediators, thereby supporting cell survival [20].

In addition to preserving injured neurons, recovery from TBI also depends on neuroplasticity, which refers to the ability of neural tissue to reorganize through changes in synaptic connectivity, dendritic remodeling, axonal sprouting, and the formation of new connections [21]. Thus, neuroprotection and neurorestoration are continuous processes: interventions during the acute phase aim to preserve viable tissue, whereas interventions during the later phase support tissue reorganization and the recovery of motor and cognitive functions.

3.8.Neuroprotective Therapeutic Strategies

Based on the mechanisms underlying secondary injury, various neuroprotective strategies have been developed to target different pathological processes. The approaches discussed in the literature include modulation of excitotoxicity, control of oxidative stress, mitochondrial protection, modulation of inflammation, neurotrophic factors, as well as cell- and extracellular vesicle-based therapies.

Modulation of excitotoxicity is one approach that is directly related to increased glutamate activity and Ca^{2+} influx. The TBI literature indicates that this mechanism represents an important target for the development of neuroprotective therapies; however, the complexity of the injury

cascade remains a major challenge in translating experimental findings into clinical treatment [4], [8].

Other approaches target oxidative stress and mitochondrial dysfunction. These strategies are based on the role of ROS and impaired energy metabolism in amplifying cellular damage. Activation of antioxidant defense pathways, such as Nrf2, is one of the mechanisms currently being investigated in this context [9].

Stem cell- and extracellular vesicle-based therapies represent approaches that are oriented toward both neuroprotection and neurorestoration. Mesenchymal stem cell-derived extracellular vesicles have been investigated as cell-free therapies for TBI, with the potential to exert both neuroprotective and neurorestorative effects [22]. Similarly, neural stem cell-derived exosomes have been studied as a cell-free approach to support regeneration following TBI [23].

However, based on the sources included in this manuscript, most of these innovative approaches still require further clinical validation in humans. Therefore, preclinical findings should not be equated with therapies that have already been demonstrated to be clinically effective.

3.9.Biomarkers in TBI

Table 1. Characteristics and Clinical Significance of Biomarkers in TBI

Biomarker	Primary Cellular Source	Clinical Significance
GFAP	Astrocytes (Central Nervous System)	High diagnostic accuracy; early assessment of glial injury
S100B	Astroglial cells and neurons	Marker of blood–brain barrier (BBB) permeability
NSE	Neuronal and neuroendocrine cells	Marker of neuronal injury; affected by hemolysis
NF-L	Axons (white matter)	Reflects persistent axonal injury; may remain elevated for several months
UCH-L1	Neuronal cell bodies	Detection of acute intracranial lesions during the very early phase

Blood-based biomarkers are increasingly being developed as adjunctive tools for detecting brain injury and stratifying patients. An advantage of this approach is the ability to obtain biological information through a minimally invasive method; however, biomarker interpretation remains dependent on the characteristics of each molecule and the timing of sample collection [24]. GFAP is a biomarker associated with astrocytes and glial injury. Papa et al. [25] evaluated the performance of GFAP and UCH-L1 during the very early phase following TBI and supported their potential for detecting acute intracranial injury. UCH-L1 is a biomarker associated with neuronal tissue and has also demonstrated potential for detecting intracranial injury during the acute phase. A prospective study by Spaziani et al. [26] specifically evaluated GFAP and UCH-L1 in patients with high-risk mild TBI, as well as their short- and long-term outcomes.

In contrast to these two biomarkers, NF-L is associated with axonal injury. Arena et al. [16] linked elevated NF-L levels to the neuropathological basis of axonal injury, whereas Tuure [17] reported an association between NF-L levels during the later phase and outcomes in patients with TBI. Thus, NF-L may provide information that differs from biomarkers primarily used to detect acute injury.

S100B has also been investigated as a biomarker of TBI. However, its interpretation is limited because S100B is not exclusively derived from brain tissue; therefore, extracranial trauma may influence its levels. A meta-analysis by Zarei et al. [27] compared the diagnostic and prognostic value of S100B and NSE in TBI. NSE is a biomarker associated with neuronal injury, but its interpretation

also has limitations. Sierakowska et al. [28] reviewed the use of NSE as a biomarker in various neurological disorders, whereas Behforouz et al. [29] discussed its potential application in TBI.

4. CONCLUSION

TBI is a pathological process consisting of primary injury and a secondary injury cascade involving excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, BBB disruption, cerebral edema, axonal degeneration, and apoptosis. These mechanisms are interconnected and may contribute to the progressive extension of tissue damage following the initial trauma [4].

Various therapeutic approaches have been developed, including modulation of excitotoxicity, control of oxidative stress and inflammation, and cell- and extracellular vesicle-based therapies. However, several innovative approaches still require further clinical validation. Blood-based biomarkers can provide additional information for the diagnosis and stratification of TBI. GFAP and UCH-L1 have particular potential for detecting acute intracranial injury, whereas NF-L provides information regarding persistent axonal injury. S100B and NSE may be used as supportive biomarkers, with their respective limitations taken into consideration.

In the future, the development of neuroprotective strategies for TBI should take into account the predominant pathological mechanisms, the temporal phase of injury, and the biological heterogeneity among patients. Integrating biomarkers with clinical assessment and neuroimaging may support a more individualized approach to patient management. However, prospective clinical studies are still needed to determine their optimal implementation and clinical utility.

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