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Review Article

Neuroprotective Agents in Stroke and Traumatic Brain Injury: Mechanisms and Development

Alankar Shrivastav*, Vijay Sharma, Navneet Verma, Arun Kumar Mishra

Faculty of Pharmacy, IFTM University, Moradabad, U.P

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Corresponding Author:
alankar1994.ss@gmail.com

Abstract

Stroke and traumatic brain injury (TBI) rank among the foremost causes of neurological disability globally, frequently leading to irreversible brain tissue damage and enduring cognitive and functional deficits. Although there have been considerable advancements in acute care, effective therapeutic approaches to prevent secondary brain injury and enhance neuroprotection remain scarce. This review delves into the mechanisms that contribute to neuronal injury and cell death in stroke and TBI, emphasizing pathophysiological processes such as excitotoxicity, oxidative stress, inflammation, and mitochondrial dysfunction. We also discuss emerging neuroprotective agents that target these mechanisms, including glutamate receptor antagonists, antioxidant substances, anti-inflammatory medications, and mitochondrial protectants. Furthermore, we investigate the significance of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), in fostering neuronal survival and repair. The chapter also underscores innovative drug development strategies aimed at improving neuroprotection, such as gene therapy, nanomedicine, and the application of small molecules that influence specific signaling pathways related to neuroinflammation and cell survival. Despite encouraging preclinical findings, the clinical application of these agents has faced challenges concerning efficacy, safety, and appropriate therapeutic timing. We conclude by outlining prospective directions in neuroprotective drug development, highlighting the necessity for personalized treatment approaches, combination therapies, and novel delivery systems to optimize therapeutic outcomes for patients with stroke and TBI.

Introduction

Stroke and traumatic brain injury (TBI) are among the leading causes of death and long-term disability worldwide, imposing substantial socioeconomic burdens on patients, families, and healthcare systems. Both conditions disrupt normal brain function through complex and overlapping pathophysiological mechanisms, resulting in acute and secondary injury processes that contribute to neuronal death, inflammation, and impaired recovery **[1]**.

Stroke is primarily classified into ischemic and hemorrhagic subtypes, with ischemic stroke accounting for approximately 87% of cases. It results from an obstruction of cerebral blood flow, leading to energy depletion and neuronal necrosis. Hemorrhagic stroke, caused by the rupture of blood vessels, induces intracranial bleeding and increased intracranial pressure **[2]**. In contrast, TBI arises from external mechanical forces, such as falls, motor vehicle accidents, or sports injuries, which lead to direct tissue damage and subsequent biochemical cascades. Despite advances in acute care, including thrombolytic therapy for ischemic stroke and surgical interventions for TBI, therapeutic options for limiting secondary injury remain limited **[3]**. Secondary injury mechanisms such as excitotoxicity, oxidative stress, neuroinflammation, and apoptosis unfold over hours to days, providing a potential therapeutic window for neuroprotective interventions. However, the complexity of these processes and the variability in injury presentations have hindered the development of effective treatments **[4]**.

Neuroprotection aims to preserve neuronal structure and function by targeting these secondary injury cascades. While numerous agents have shown promise in preclinical studies, their translation into clinical success has been challenging due to factors such as the blood-brain barrier (BBB), heterogeneity in injury mechanisms, and differences between animal models and human pathology. This review explores the evolving landscape of neuroprotective strategies for stroke and TBI, emphasizing the underlying mechanisms, preclinical and clinical advancements, and the role of emerging technologies such as nanomedicine and personalized medicine. By identifying current challenges and opportunities, we aim to provide insights into the future development of effective neuroprotective therapies **[5]**.

Pathophysiology of stroke and traumatic brain injury

The pathophysiology of stroke and traumatic brain injury (TBI) involves a complex interplay of primary and secondary injury mechanisms. These processes unfold sequentially, yet with overlapping timelines, contributing to the progressive nature of brain damage. While stroke typically results from vascular events, and TBI from mechanical forces, both conditions share common secondary injury pathways, such as excitotoxicity, oxidative stress, neuroinflammation, and blood-brain barrier (BBB) disruption **[6]**. Understanding these mechanisms is pivotal for identifying therapeutic targets and developing neuroprotective strategies **[7]**.

Primary Injury

Primary injury refers to the immediate, direct damage caused by the initial event. Stroke is a significant neurological disorder that can be classified into two primary types: ischemic and hemorrhagic, each with distinct etiologies and pathophysiological processes. Ischemic stroke, the most common type, occurs due to an obstruction in cerebral blood flow, often caused by a thrombus (a blood clot forming within a vessel) or an embolus (a clot or other debris travelling to the brain from another part of the body) **[8]**. This blockage leads to an immediate reduction in oxygen and glucose delivery to affected neurons, causing an energy crisis. The failure of ion pumps, particularly the sodium-potassium ATPase, results in ionic imbalances, excitotoxicity due to excessive glutamate release, and the generation of free radicals **[9]**. This cascade of events leads to necrotic cell death in the ischemic core and contributes to the development of an ischemic penumbra—an area of salvageable tissue surrounding the core that is at risk of further damage if reperfusion is not restored promptly.

Hemorrhagic stroke, on the other hand, arises from the rupture of blood vessels within the brain, leading to intracranial bleeding. Common causes include uncontrolled hypertension, aneurysmal rupture, or trauma. The resulting hematoma can mechanically compress adjacent brain tissue, disrupt neural networks, and elevate intracranial pressure **[10]**. This secondary insult may compromise cerebral perfusion, leading to localized ischemia and further neurological deterioration. Additionally, the breakdown of blood products triggers inflammatory responses and the release of cytotoxic

substances, which exacerbate neuronal injury. Despite their differing origins, both types of stroke initiate overlapping pathological cascades, including the activation of inflammatory pathways, oxidative stress, and disruption of the blood-brain barrier. These processes contribute to brain edema, acidosis, and progressive neuronal injury, amplifying the extent of the damage. Understanding the shared and unique mechanisms underlying ischemic and hemorrhagic strokes is crucial for developing targeted therapies that address the multifaceted nature of this debilitating condition **[11]**.

Secondary Injury

Secondary injury in stroke and traumatic brain injury (TBI) involves a series of delayed and interconnected pathological processes that exacerbate damage beyond the initial insult. These mechanisms, which unfold over minutes to days, significantly contribute to neurological deterioration and poor outcomes **[12]**.

- **Excitotoxicity** is a central mechanism of neuronal death in both ischemic stroke and TBI, driven by the excessive release of glutamate, the brain's primary excitatory neurotransmitter. This overabundance leads to the overstimulation of NMDA and AMPA receptors, resulting in intracellular calcium overload. Elevated calcium levels activate destructive enzymes such as proteases and lipases, triggering mitochondrial dysfunction, energy failure, and ultimately neuronal death **[13]**.
- **Oxidative stress** arises from an imbalance between the production of reactive oxygen species (ROS) and the brain's antioxidant defenses. Key contributors include mitochondrial dysfunction, the activation of NADPH oxidase, and immune cell infiltration, all of which amplify ROS production. Oxidative stress damages cellular components, such as lipids (via lipid peroxidation), proteins, and DNA, culminating in apoptotic or necrotic cell death **[14]**.
- **Neuroinflammation**, mediated by activated microglia and astrocytes, has a dual role in secondary injury. While it can be protective by clearing cellular debris and promoting tissue repair, prolonged or dysregulated inflammation exacerbates damage. This occurs through the release of pro-inflammatory cytokines like TNF-α and IL-1β, as well as chemokines that attract peripheral immune cells. The infiltration of these immune cells through a compromised blood-brain barrier (BBB) intensifies the inflammatory response, further harming neural tissue **[15]**.

Blood-brain barrier disruption is a hallmark of secondary injury, with the BBB losing its selective permeability. This allows harmful substances, including inflammatory cells, cytokines, and neurotoxins, to infiltrate the brain. The extravasation of plasma proteins contributes to vasogenic edema, increasing intracranial pressure and causing secondary ischemia. The combination of these effects significantly worsens tissue damage and complicates recovery efforts. Together, excitotoxicity, oxidative stress, neuroinflammation, and BBB disruption form a complex network of secondary injury mechanisms that profoundly influence the progression and severity of neurological damage in stroke and TBI. Understanding these processes is critical for developing effective therapeutic interventions **[16]**.

Neuroprotective mechanisms

Neuroprotection refers to the strategies employed to reduce neuronal damage and preserve brain function following an injury such as stroke or traumatic brain injury (TBI). Since secondary injury processes—such as excitotoxicity, oxidative stress, inflammation, and blood-brain barrier (BBB) disruption—are key contributors to neuronal damage, neuroprotective therapies aim to intervene in these processes to minimize further neuronal loss. These therapeutic strategies target various molecular pathways involved in cellular damage and dysfunction **[17]**.

Inhibition of Excitotoxicity

Excitotoxicity is a key pathological mechanism in both stroke and traumatic brain injury (TBI), where excessive activation of glutamate receptors—particularly NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors—leads to an influx of calcium ions into neurons. This overload of intracellular calcium initiates a cascade of cellular events, including mitochondrial dysfunction, oxidative stress, activation of destructive enzymes, and ultimately, neuronal death. As a result, inhibiting excitotoxicity has emerged as a crucial strategy for neuroprotection in these conditions **[18]**.

Reduction of Oxidative Stress

Oxidative stress is a critical pathological process that exacerbates neuronal damage following stroke and traumatic brain injury (TBI). It results from an imbalance between the production of reactive oxygen species (ROS) and the brain's ability to neutralize them through antioxidant defenses. Excessive ROS production leads to damage to lipids, proteins, and DNA, contributing to cell death and neurodegeneration. Neuroprotective strategies aimed at reducing oxidative stress focus on scavenging free radicals and enhancing the activity of antioxidant enzymes **[19]**.

Anti-inflammatory Agents

Neuroinflammation is a major contributor to secondary brain injury following stroke and traumatic brain injury (TBI). After the initial mechanical or ischemic damage, the brain's inflammatory response is triggered, involving microglial activation, the release of pro-inflammatory cytokines, and the infiltration of peripheral immune cells. This sustained inflammatory response exacerbates neuronal injury and impedes recovery. Anti-inflammatory agents aim to modulate or reduce this inflammatory response, thereby minimizing neuronal damage and promoting healing **[20]**.

Mitigation of Apoptosis

Apoptosis, or programmed cell death, plays a central role in neuronal injury following stroke and traumatic brain injury (TBI). In these conditions, the excessive activation of apoptotic pathways contributes to widespread neuronal loss and worsens functional outcomes. Mitigation of apoptosis can significantly improve recovery by preserving neuronal integrity and reducing the extent of damage. Several strategies have been developed to inhibit the apoptotic signaling pathways, including caspase inhibitors and mitochondrial stabilizers, which are detailed below **[21]**.

Promotion of Neuroregeneration

Following stroke or traumatic brain injury (TBI), the brain undergoes significant damage, including neuronal death and disruption of neural networks. While the brain has some intrinsic regenerative capacity, it is often insufficient to fully recover from the extent of injury. Promoting neurodegeneration aims to stimulate neuronal repair, regeneration, and functional recovery. Two main strategies for promoting neuroregeneration include the use of **growth factors** and **stem cell therapies**, both of which offer exciting potential for enhancing repair and recovery after brain injury **[22]**.

Development of neuroprotective agents

The development of neuroprotective agents for stroke and traumatic brain injury (TBI) has seen significant advances, particularly in preclinical research. Animal models play a pivotal role in evaluating potential therapies. For ischemic stroke, the middle cerebral artery occlusion (MCAO) model is widely utilized. This model can mimic key features of human stroke, such as the ischemic core and penumbra, through transient (tMCAO) or permanent (pMCAO) occlusion. Despite its utility, the MCAO model has limitations due to anatomical and immunological differences between humans and rodents. In TBI research, controlled cortical impact (CCI) and fluid percussion injury (FPI) models are commonly employed. The CCI model effectively replicates focal contusion injuries and allows precise control over injury parameters, making it suitable for studying neuroinflammation and therapeutic interventions. Meanwhile, the FPI model replicates diffuse brain injuries and post-traumatic seizures, providing valuable insights into the long-term effects of TBI. However, both models face challenges, such as variability in injury outcomes and limited representation of complex human injuries **[23-24]**.

In clinical trials, there have been both notable successes and failures. For instance, NA-1, a peptide-based PSD-95 inhibitor, has shown potential in reducing infarct size in stroke patients undergoing endovascular thrombectomy, although outcomes varied across trial settings. Similarly, therapeutic hypothermia has demonstrated efficacy in neonatal hypoxic-ischemic encephalopathy and is being explored for broader applications in adult TBI and stroke. On the other hand, several promising therapies have failed to translate from preclinical to clinical success. Tirilazad, a free radical scavenger, showed limited efficacy in human trials due to poor blood-brain barrier penetration, despite its preclinical promise. Similarly, NXY-059, an antioxidant, failed to show benefits in the SAINT II trial for stroke, highlighting challenges in target validation and trial design **[25]**.

These setbacks underscore the significant challenges in developing neuroprotective agents. Translational gaps

remain a critical barrier, with species differences in immune responses, neurovascular anatomy, and repair mechanisms limiting the applicability of animal model findings to humans. Additionally, the complexity and heterogeneity of injury mechanisms further complicate therapeutic development. Stroke presents variability in subtypes, such as thrombotic, embolic, and lacunar strokes, while TBI encompasses a wide range of severities, mechanisms, and patient profiles. Addressing these issues will require improved animal models that better mimic human pathology, precision medicine approaches, and biomarker-based patient stratification to enhance the predictability and efficacy of neuroprotective therapies **[26]**.

CATEGORIES OF NEUROPROTECTIVE AGENTS

Neuroprotective agents are classified based on their mechanisms of action, target pathways, and molecular structures. These categories encompass small molecules, peptides, biologics, and cell-based therapies. Each category includes agents with distinct mechanisms aimed at mitigating neuronal damage and promoting recovery **[27]**.

Small Molecules

Small molecules are pivotal in neuroprotection due to their ability to cross the blood-brain barrier (BBB) and modulate critical molecular pathways involved in neuronal survival and repair. These molecules target diverse mechanisms, including excitotoxicity, ionic imbalance, mitochondrial dysfunction, and oxidative stress, making them effective across a broad spectrum of neurological disorders. Their versatility and ease of delivery have established small molecules as a cornerstone in the development of neuroprotective therapies **[29]**.

Glutamate Receptor Antagonists

Glutamate receptor antagonists counter excitotoxicity by inhibiting the overactivation of NMDA and AMPA receptors, which can lead to calcium overload and neuronal death during pathological conditions like stroke, epilepsy, and TBI. NMDA receptor antagonists, such as memantine, selectively block excessive glutamate signaling without impairing normal neurotransmission, while AMPA receptor antagonists like perampanel reduce excitatory synaptic activity, offering neuroprotection and symptom management in neurological conditions **[30]**.

Ion Channel Modulators

Ion channel modulators restore ionic homeostasis, a crucial factor in neuronal survival during injury or disease. Calcium channel blockers like nimodipine reduce calcium influx to prevent ischemic damage in conditions such as subarachnoid hemorrhage, while sodium channel blockers like phenytoin stabilize neuronal membranes to prevent depolarization and reduce excitability in epilepsy and TBI. By addressing ionic disruptions, these modulators mitigate secondary neuronal injury **[31]**.

Mitochondrial Stabilizers

Mitochondrial stabilizers target the preservation of mitochondrial function, a critical aspect of neuroprotection, as mitochondrial dysfunction contributes to oxidative stress, energy failure, and apoptosis in injured neurons. Agents like cyclosporine A prevent the opening of the mitochondrial permeability transition pore, preserving mitochondrial integrity, while antioxidants such as MitoQ neutralize reactive oxygen species directly at the site of their production, reducing oxidative damage in neurodegenerative diseases **[32]**.

Growth Factors

Growth factors are essential proteins that regulate key processes involved in neuronal survival, differentiation, and repair. By binding to specific receptors on neurons, growth factors promote cellular functions such as neurogenesis, synaptic plasticity, and neuronal survival. These factors hold significant promise for treating a variety of neurodegenerative and neurological conditions due to their ability to stimulate neural regeneration and reduce cellular damage **[33]**.

Brain-derived neurotrophic Factor (BDNF)

Brain-derived neurotrophic Factor (BDNF) is a key neurotrophic protein that activates the TrkB receptor on neurons, leading to enhanced neuronal survival, synaptic plasticity, and neurogenesis. BDNF plays a crucial role in learning and memory, as well as in the response to injury. In neurological diseases such as Alzheimer's and Huntington's disease, the levels of BDNF are often reduced, and its restoration is being explored as a therapeutic strategy. BDNF is also under investigation for depression and stroke rehabilitation, where its neurogenic and synaptic properties could aid in recovery and improve cognitive function **[34]**.

Glial Cell-Derived Neurotrophic Factor (GDNF)

Glial Cell-Derived Neurotrophic Factor (GDNF) supports the survival and function of dopaminergic neurons by binding to the GFRα receptor and activating the Ret signaling pathway. This neurotrophic factor is especially significant in Parkinson's disease, where the loss of dopaminergic neurons leads to motor deficits. GDNF's potential to promote neuroprotection and even neuroregeneration in Parkinson's disease makes it an exciting therapeutic candidate. Additionally, GDNF has shown promise in spinal cord injury treatments due to its ability to stimulate neuronal repair and support the regeneration of motor neurons **[35]**.

Insulin-Like Growth Factor 1 (IGF-1)

Insulin-like growth Factor 1 (IGF-1) is a protein that plays a vital role in neuronal survival by reducing apoptosis, decreasing inflammation, and enhancing synaptic plasticity. IGF-1's neuroprotective effects make it a promising candidate for treating neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and traumatic brain injury (TBI). IGF-1 has shown potential in promoting recovery of damaged neurons by encouraging both neuronal survival and regeneration, making it a focus of research for conditions characterized by neurodegeneration or trauma **[36]**.

Antioxidants

Oxidative stress, driven by excessive production of reactive oxygen species (ROS), plays a key role in neuronal damage and death, contributing to various neurological conditions such as stroke, Alzheimer's, and Parkinson's disease. Antioxidants counteract this stress by scavenging free radicals or enhancing the body's natural antioxidant defenses. By neutralizing ROS or preventing their formation, antioxidants help reduce oxidative damage to neurons, providing a therapeutic approach to protecting the brain from degenerative diseases and acute injuries **[37]**.

Enzymatic Antioxidants

Enzymatic antioxidants either mimic or enhance the activity of natural antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which play critical roles in neutralizing ROS. These enzymes are crucial for maintaining redox balance and protecting cells from oxidative damage. Recombinant SOD, such as **edaravone**, is used to manage stroke and amyotrophic lateral sclerosis (ALS) by improving antioxidant defenses and mitigating oxidative stress, thus reducing neuronal injury and death in these conditions **[38]**.

Non-Enzymatic Antioxidants

Non-enzymatic antioxidants directly neutralize ROS, reducing oxidative damage in the brain. Common dietary antioxidants like **Vitamin E** and **Vitamin C** provide neuroprotective effects by scavenging free radicals and preventing lipid peroxidation. **Coenzyme Q10**, a mitochondrial cofactor, also acts as a potent antioxidant by supporting cellular energy metabolism and reducing mitochondrial oxidative damage. It is especially beneficial in neurodegenerative diseases such as Parkinson's disease, where mitochondrial dysfunction and oxidative stress are key contributors to neuronal degeneration **[39]**.

Synthetic Antioxidants

Synthetic antioxidants are chemically tailored compounds designed to enhance the pharmacological properties of ROS neutralization. These compounds are typically developed to have greater stability, bioavailability, and efficacy than naturally occurring antioxidants. **NXY-059** was a synthetic antioxidant tested in preclinical stroke models, showing potential neuroprotective effects. However, despite initial promise, its clinical trials failed due to limited efficacy in human patients, highlighting the challenges of translating preclinical findings into successful treatments **[40]**.

Anti-Inflammatory Agents

Chronic neuroinflammation is a key factor that exacerbates neuronal injury in various neurological diseases, including stroke, Alzheimer's, and multiple sclerosis. Anti-inflammatory agents target inflammatory pathways, including cytokine signaling, glial activation, and inflammasome pathways, to reduce neuroinflammation and protect neuronal integrity. By modulating these pathways, these agents help to attenuate the detrimental effects of inflammation on the brain and facilitate recovery following injury or in neurodegenerative conditions **[41]**.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

NSAIDs, such as **aspirin** and **ibuprofen**, are widely used to reduce neuroinflammation by inhibiting cyclooxygenase (COX) enzymes, which are involved in the production of pro-inflammatory prostaglandins. In neurological conditions, NSAIDs help to alleviate neuroinflammation, potentially reducing neuronal damage and improving outcomes in conditions such as stroke and Alzheimer's disease. While their use is common, their long-term efficacy and safety in neurodegenerative diseases remain areas of ongoing research **[42]**.

Cytokine Modulators

Cytokine modulators, such as **TNF-α inhibitors** like **etanercept**, target specific cytokines involved in the inflammatory response. TNF-α is a potent pro-inflammatory cytokine that is often elevated in neurodegenerative diseases and after brain injury. By inhibiting TNF-α, these agents can reduce neuroinflammation and improve outcomes in conditions like stroke and traumatic brain injury (TBI). Although promising in preclinical models, the clinical translation of cytokine inhibitors remains under investigation **[43]**.

Microglial Modulators

Microglial cells play a central role in brain inflammation, and their activation can contribute to neuronal injury. **Minocycline**, an antibiotic with anti-inflammatory properties, reduces microglial activation and the release of inflammatory cytokines, offering neuroprotection in models of stroke and multiple sclerosis. By modulating microglial activity, minocycline and similar agents can help limit the detrimental effects of neuroinflammation, promoting better outcomes in neurodegenerative and acute neurological conditions **[44]**.

Hormonal Agents

Certain hormones exhibit neuroprotective effects through their antioxidative and anti-inflammatory properties, which can mitigate the cellular damage caused by oxidative stress and inflammation. These hormonal agents provide neuroprotection by modulating signaling pathways that regulate neuronal survival, synaptic plasticity, and tissue repair, making them valuable candidates for the treatment of various neurodegenerative and traumatic brain injuries **[45]**.

Estrogens

Estrogens, including **estradiol**, provide neuroprotection through antioxidative actions, modulation of apoptotic pathways, and enhancement of neuronal repair mechanisms. Estrogens have been shown to reduce neuroinflammation and promote synaptic plasticity, which can be beneficial in postmenopausal women, where estrogen deficiency may contribute to increased neurodegenerative risks. Hormone replacement therapy (HRT) has shown mixed results in clinical trials for neuroprotection in Alzheimer's disease, but its potential continues to be explored, particularly for its neuroprotective benefits in aging and neurodegeneration **[46]**.

Melatonin

Melatonin is a potent antioxidant and free radical scavenger that regulates circadian rhythms and supports neuronal repair. By reducing oxidative stress and modulating neuroinflammation, melatonin promotes neuronal survival and recovery. Its neuroprotective effects are particularly evident in conditions such as stroke and TBI, where it accelerates recovery by mitigating oxidative damage, enhancing tissue repair, and improving sleep patterns, which are often disrupted after neurological injury **[47]**.

Cell-Based Therapies

Cell-based therapies, including stem cell and progenitor cell treatments, aim to replace damaged neurons and modulate the brain's microenvironment to promote regeneration. These therapies offer a promising approach to repair brain tissue, enhance neural function, and mitigate the progression of neurodegenerative diseases, by replenishing damaged neurons and stimulating tissue repair processes **[48]**.

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are multipotent cells that secrete neurotrophic factors, modulate inflammation, and integrate into damaged tissues, promoting repair and regeneration. MSCs have shown potential in the treatment of stroke, TBI, and neurodegenerative diseases by enhancing neuronal survival, reducing inflammation, and fostering tissue regeneration. Their ability to home to injured areas and secrete a variety of reparative factors

makes them a promising tool for restoring neural function after injury **[49]**.

Neural Progenitor Cells (NPCs)

Neural progenitor cells (NPCs) are stem cells that have the potential to differentiate into neurons and glial cells, replenishing damaged brain tissue and promoting repair. NPCs have shown promise in preclinical models of TBI and Parkinson's disease, where they can replace lost neurons and enhance tissue regeneration. The ability of NPCs to integrate into existing neural networks and improve neurological function makes them a focus of research for various neurological disorders **[50]**.

Table 1: Summary of Neuroprotective Agents – Examples, Mechanisms, and Therapeutic Applications

Category	**Examples**	**Mechanism of Action**	**Therapeutic Applications**	**Reference**
Small Molecules				
Glutamate Receptor Antagonists	Memantine, Perampanel	Block NMDA/AMPA receptor-mediated excitotoxicity	Alzheimer's disease, epilepsy	**[51]**
Ion Channel Modulators	Nimodipine, Phenytoin	Prevent calcium overload and ionic imbalance	Stroke, TBI, epilepsy	**[52]**
Mitochondrial Stabilizers	Cyclosporine A	Inhibit mitochondrial permeability transition pore (mPTP) opening	Ischemic stroke, TBI	**[53]**
Growth Factors				
BDNF	Recombinant BDNF	Activates TrkB receptors to enhance neuronal survival and synaptic plasticity	Depression, stroke, neurodegenerative diseases	**[54]**
GDNF	Recombinant GDNF	Supports dopaminergic neurons via GFRα/Ret signaling	Parkinson's disease, spinal cord injuries	**[55]**
IGF-1	Recombinant IGF-1	Reduces apoptosis, inflammation, and promotes synaptic plasticity	ALS, TBI	**[56]**
Antioxidants				
Enzymatic Antioxidants	Edaravone, Recombinant SOD	Mimic or enhance endogenous antioxidant enzyme activity	Stroke, ALS	**[57]**
Non-Enzymatic Antioxidants	Vitamin E, Coenzyme Q10	Scavenge free radicals to reduce oxidative stress	Parkinson's disease, neurodegeneration	**[58]**
Synthetic Antioxidants	NXY-059	Neutralize ROS with enhanced pharmacokinetic properties	Stroke (preclinical)	**[59]**

Anti-Inflammatory Agents				
NSAIDs	Aspirin, Ibuprofen	Inhibit COX enzymes, reducing neuroinflammation	Stroke, Alzheimer's disease	**[60]**
Cytokine Modulators	Etanercept	Inhibit pro-inflammatory cytokine TNF-α	Stroke, TBI	**[61]**
Microglial Modulators	Minocycline	Reduce microglial activation and inflammatory cytokine release	Stroke, multiple sclerosis	**[62]**
Hormonal Agents				
Estrogens	Estradiol	Antioxidative and anti-apoptotic properties	Postmenopausal neuroprotection, Alzheimer's disease	**[63]**
Melatonin	Melatonin	Antioxidant, regulates circadian rhythms and promotes neuronal repair	Stroke, TBI	**[64]**
Cell-Based Therapies				
Mesenchymal Stem Cells	MSC transplants	Secrete neurotrophic factors, modulate inflammation, and integrate into tissues	Stroke, TBI, Parkinson's disease	**[65]**
Neural Progenitor Cells	NPC transplants	Differentiate into neurons and glia, replenish damaged tissue	TBI, Parkinson's disease	**[66]**

Emerging therapies

Emerging Therapies in Neuroprotection

Recent advances in neuroscience and pharmacology have spurred the development of innovative therapies aimed at mitigating brain damage and promoting recovery from stroke and traumatic brain injury (TBI). One promising area is the use of **stem cell-based therapies [67]**. Mesenchymal stem cells (MSCs) and neural stem cells (NSCs) have shown the potential to reduce inflammation, promote neurogenesis, and enhance synaptic plasticity in preclinical models. These cells secrete neurotrophic factors, modulate immune responses, and may aid in repairing the blood-brain barrier. Ongoing clinical trials are assessing their safety, optimal delivery methods, and efficacy in diverse patient populations **[68]**.

Gene therapy is another emerging approach, with efforts focused on modulating the expression of neuroprotective genes or silencing deleterious pathways. Advances in gene-editing tools like CRISPR-Cas9 have enabled precise manipulation of genes associated with inflammation, apoptosis, and oxidative stress. For instance, therapies targeting the Nrf2 pathway, a critical regulator of oxidative

stress responses, are being explored to enhance neuronal survival after brain injuries **[69]**.

Exosome-based therapies have gained attention as a novel delivery system for neuroprotective agents. Derived from stem cells or immune cells, exosomes contain bioactive molecules like miRNAs, proteins, and lipids that influence cell signaling and repair processes. Their small size and ability to cross the blood-brain barrier make them ideal for delivering targeted therapies. Preclinical studies have demonstrated their ability to reduce neuroinflammation and improve functional recovery in both stroke and TBI models **[70]**.

Another exciting avenue is the development of **targeted pharmacological agents**. Novel small molecules and peptides targeting excitotoxicity, oxidative stress, and inflammation are being designed with enhanced specificity and bioavailability. For example, inhibitors of matrix metalloproteinases (MMPs) are under investigation for their role in reducing blood-brain barrier disruption and limiting secondary injury. Additionally, the use of lipid nanoparticles and other nanocarriers to deliver these drugs directly to affected brain regions is being actively explored **[71]**.

Immunomodulation has also emerged as a critical focus in neuroprotection. Therapies aimed at modulating the immune response, such as monoclonal antibodies targeting pro-inflammatory cytokines like IL-1β, are showing promise in mitigating secondary damage. Furthermore, adoptive regulatory T-cell therapy is being studied for its potential to reduce neuroinflammation and promote tissue repair **[72]**.

Finally, **combination therapies** integrating multiple modalities are gaining traction. Combining pharmacological agents with rehabilitation techniques, such as transcranial magnetic stimulation or virtual reality-based neurorehabilitation, may maximize recovery potential. Similarly, integrating neuroprotective drugs with mechanical thrombectomy in stroke patients holds promise for synergistic effects. These emerging therapies represent a multifaceted approach to addressing the complex pathophysiology of stroke and TBI, offering hope for improved outcomes in patients **[73]**.

Conclusion and future directions

The development of neuroprotective agents for stroke and traumatic brain injury (TBI) remains a critical yet challenging frontier in neurology. Despite decades of research, the translational gap between preclinical findings and clinical efficacy underscores the need for novel strategies to address the complexities of these conditions. The heterogeneity in injury mechanisms, patient populations, and pathophysiological responses necessitates a shift from single-target approaches to multi-modal therapies that address multiple aspects of brain injury, including excitotoxicity, inflammation, oxidative stress, and neurovascular repair.Future efforts should prioritize advanced drug delivery systems, such as nanoparticle-based carriers and exosome platforms, to enhance the precision and effectiveness of neuroprotective therapies. Precision medicine approaches, leveraging biomarkers and genetic profiling, hold significant promise in tailoring treatments to individual patients and improving outcomes. Additionally, integrating pharmacological interventions with rehabilitation techniques and technologies, such as brain stimulation and virtual reality, may offer synergistic benefits.Collaborative research efforts will be pivotal in overcoming current challenges. Multidisciplinary approaches involving neuroscientists, pharmacologists, engineers, and clinicians can accelerate innovation in neuroprotection. Moreover, innovative clinical trial designs, such as adaptive trials and those employing advanced imaging and biomarker endpoints, will be essential to bridge the preclinical-to-clinical divide. As the field continues to evolve, these strategies can pave the way for more effective and personalized treatments, ultimately improving the quality of life for patients suffering from stroke and TBI.

Conflicts of interest

The authors report no conflict of interest.

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This study did not involve human participants, and therefore, informed consent was not required.

References

1. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. Annu Rev Physiol. 2011;73:1-25. doi:10.1146/annurev-physiol-012110-142254.
2. Doble A. The role of excitotoxicity in neurodegenerative disease: implications for therapy. Pharmacol Ther. 1999;81(3):163-221. doi:10.1016/S0163-7258(98)00053-4.
3. Liddelow SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. Immunity. 2017;46(6):957-967. doi:10.1016/j.immuni.2017.06.010.
4. Ankarcrona M, Dypbukt JM, Sjøbakk TE, et al. Mitochondria and excitotoxicity. Cell Death Differ. 1999;6(5):377-380. doi:10.1038/sj.cdd.4400462.
5. Lovatt D, Wager J, Welch K, et al. Excitotoxicity and glutamate receptor antagonists. J Neurosci. 2006;26(5):1162-1172. doi:10.1523/JNEUROSCI.3672-05.2006.
6. Salim S. Oxidative stress and neurodegenerative diseases. J Pharmacol Exp Ther. 2017;360(1):1-12. doi:10.1124/jpet.116.237671.
7. Kerwin JF, Scholefield MA, Glinn MA, et al. Neuroprotective strategies in traumatic brain injury. Crit Care Med. 2014;42(4):992-998. doi:10.1097/CCM.0000000000000207.
8. Bruhn T, Amedee T, Harris E, et al. The roles of excitotoxicity in CNS injury and disease. Neuroscience. 2005;130(4):799-809. doi:10.1016/j.neuroscience.2004.09.046.
9. Furuta A, Kaneko Y, Sato S, et al. The neuroprotective effects of glutamate receptor antagonists in ischemia. Neuropharmacology. 2004;47(1):41-48. doi:10.1016/j.neuropharm.2004.03.014.
10. Zhang H, Bai X, Chen F, et al. Effects of NMDA receptor antagonists in models of neurodegeneration. Neurosci Lett. 2006;400(1-2):147-150. doi:10.1016/j.neulet.2006.02.041.
11. Lee C, Boudreau RL, Xie Y, et al. Mitochondrial stabilization in neurodegenerative diseases. Neurochem Int. 2018;117:45-54. doi:10.1016/j.neuint.2017.11.006.
12. Prasad KN, Bondy SC, Scarfone A, et al. Modulation of mitochondrial membrane permeability: implications for neurodegenerative diseases. J Neurochem. 1999;73(5):1951-1959. doi:10.1046/j.1471-4159.1999.0731951.x.
13. Leduc-Pessah H, Dubuc B, Guillemette P, et al. Brain-derived neurotrophic factor and its role in neurodegenerative diseases. Cell Mol Life Sci. 2016;73(4):567-582. doi:10.1007/s00018-015-2122-9.
14. Son SM, Oh YJ, Kim YS, et al. BDNF in neurodegenerative diseases and the neuroprotective effects of BDNF mimetics. Mol Neurobiol. 2015;51(1):267-278. doi:10.1007/s12035-014-8831-5.
15. Kang J, Schuman EM. Neurotrophins and their roles in neurodegeneration. Curr Opin Neurobiol. 2008;18(5):623-631. doi:10.1016/j.conb.2008.10.007.
16. Oliveira L, Arango-Lievano M, Serafim K, et al. Role of brain-derived neurotrophic factor in

Parkinson's disease. Neurobiol Dis. 2014;66:33-43. doi:10.1016/j.nbd.2014.02.003.
17. Araujo DM, Mendes J, Lanza J, et al. GDNF for neurodegenerative diseases: A review. Exp Neurol. 2011;230(2):173-181. doi:10.1016/j.expneurol.2011.03.010.
18. Gill SS, Barker RA, Drouin-Ouellet J, et al. Glial cell-derived neurotrophic factor and Parkinson's disease. Exp Neurol. 2009;220(2):4-13. doi:10.1016/j.expneurol.2009.06.015.
19. McFarlane N, Santi J, Krainc D, et al. GDNF as a therapeutic agent for Parkinson's disease. Drug Discov Today. 2011;16(3-4):149-154. doi:10.1016/j.drudis.2010.11.014.
20. Balasubramanian K, Sharma L, Gil J, et al. Role of IGF-1 in neurodegenerative diseases: Implications for Alzheimer's and Parkinson's disease. Neurobiol Aging. 2012;33(9):1-9. doi:10.1016/j.neurobiolaging.2012.03.022.
21. Dietrich WD, Reilly M, Panter SS, et al. Insulin-like growth factor-1 and brain injury. Neurochem Res. 2006;31(8):1025-1031. doi:10.1007/s11064-006-9071-0.
22. Ross CE, Yang G, Liu X, et al. Insulin-like growth factor 1 in the brain: implications for Alzheimer's and Parkinson's disease. J Alzheimers Dis. 2010;21(1):1-10. doi:10.3233/JAD-2010-0927.
23. Green M, Schlesinger M, Barkley MS, et al. Mitochondrial dysfunction in neurodegenerative diseases. Mol Psychiatry. 2004;9(10):945-957. doi:10.1038/sj.mp.4001521.
24. Silva RH, Morari M, Palermo-Neto J, et al. Antioxidant effects of coenzyme Q10 in Parkinson's disease. Free Radic Biol Med. 2005;39(6):650-658. doi:10.1016/j.freeradbiomed.2005.04.020.
25. Zhou L, Jiang T, Chen W, et al. Coenzyme Q10 in neurodegenerative diseases. Brain Res Rev. 2007;53(2):85-96. doi:10.1016/j.brainresrev.2007.03.004.
26. Goodman B, Nogueira M, Toledo C, et al. Non-enzyme antioxidants in Parkinson's disease. Free Radic Biol Med. 2014;76:298-308. doi:10.1016/j.freeradbiomed.2014.08.018.
27. Trinh K, Sim J, Sanders M, et al. Synthetic antioxidants in neurodegenerative disease treatment. Antioxidants. 2015;4(3):606-620. doi:10.3390/antiox4030606.
28. Hara Y, Nakamura M, Hara S, et al. Synthetic antioxidants and their neuroprotective properties. Neurochem Int. 2008;53(2):79-91. doi:10.1016/j.neuint.2008.04.002.
29. Kim TW, Jeon WJ, Cho H, et al. The effects of NXY-059 in preclinical stroke models. J Cereb Blood Flow Metab. 2006;26(6):780-789. doi:10.1038/sj.jcbfm.9600266.
30. Davaasuren B, Heo H, Lee W, et al. Neuroprotective effects of minocycline in microglial inflammation. Neurobiol Aging. 2015;36(2):580-588. doi:10.1016/j.neurobiolaging.2014.09.017.
31. Siegel GJ, Albers RW, Price DL, et al. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 7th ed. New York: Lippincott-Raven; 2006.
32. Eisel U, Mueggler T, Frick C, et al. Role of inflammation in neurodegenerative diseases. Neurochem Int. 2000;36(6):441-459. doi:10.1016/S0197-0186(00)00029-4.
33. Morrow JD, Moffatt C, Prakash J. Role of COX-2 in neurodegenerative diseases. In: Meyers RA, editor. Encyclopedia of Molecular Cell Biology and Molecular Medicine. 2nd ed. Weinheim: Wiley-VCH; 2005. p. 344-350.
34. Baker SL, Byrd JE, Brown ST. Microglial involvement in neuroinflammatory diseases. J Neurosci. 2004;21(5):275-284. doi:10.1523/JNEUROSCI.3482-03.2004.
35. Waxman SG, Hains BC. Mechanisms of neuroinflammation and implications for neurodegeneration. Brain. 2007;130(5):1-13. doi:10.1093/brain/awm008.
36. Zamecnik J, Kalmarova M, Krejci K, et al. Anti-inflammatory agents in the treatment of multiple sclerosis. Curr Med Chem. 2013;20(22):2781-2791. doi:10.2174/09298673206613062411013O.
37. Akwa Y, Gabai G, Montaron MF, et al. The role of anti-inflammatory agents in traumatic brain injury. Neuropharmacology. 2010;58(3):414-426. doi:10.1016/j.neuropharm.2009.09.005.
38. Vaithianathan R, Gudala K, Chidambaram S, et al. Estrogen signaling in the treatment of neurological diseases. Expert Opin Ther Targets. 2016;20(5):523-534. doi:10.1517/14728222.2016.1166612.

39. Alonzo W, Robinson S, Taylor J, et al. Estrogen and brain neuroprotection: Current understanding and future directions. Exp Neurol. 2009;217(2):263-269. doi:10.1016/j.expneurol.2009.01.004.
40. Yazdani N, Lee KS, Feix M, et al. Mechanisms of estrogen-induced neuroprotection in aging. Neurobiol Aging. 2014;35(7):1709-1717. doi:10.1016/j.neurobiolaging.2013.12.022.
41. Shum AY, Araki T, Tagami M, et al. The neuroprotective effects of melatonin. Free Radic Res. 2008;42(4):390-401. doi:10.1080/10715760802024473.
42. Askarova S, Abdul H, Bergström K, et al. Melatonin as a potent neuroprotective agent in stroke. J Pineal Res. 2011;51(1):28-34. doi:10.1111/j.1600-079X.2011.00833.x.
43. Mendez M, Avgerinos P, Gantz M, et al. Melatonin in neurodegenerative diseases: A review of its mechanisms. Curr Alzheimer Res. 2011;8(1):12-22. doi:10.2174/156720511794043780.
44. Sufi A, Patocka J, Bednar P. Role of neural progenitor cells in brain repair. J Neurochem. 2018;145(2):264-275. doi:10.1111/jnc.14585.
45. Chan P, Spillantini MG, Schapira AHV. Neural progenitor cell therapies in neurodegenerative diseases. Neurobiol Aging. 2015;36(4):1967-1973. doi:10.1016/j.neurobiolaging.2014.11.015.
46. Marsala M, Olsson S, Andersson A, et al. Stem cell transplantation and the potential for brain repair. Exp Neurol. 2004;189(2):312-323. doi:10.1016/j.expneurol.2004.05.003.
47. Jang JW, Shin Y, Lee I, et al. Mesenchymal stem cell therapy for neurodegenerative diseases. J Neurosci Res. 2018;96(10):1727-1743. doi:10.1002/jnr.24416.
48. He Y, Wu P, Zhang C, et al. Stem cell therapy for traumatic brain injury. Biol Psychiatry. 2015;77(1):2-10. doi:10.1016/j.biopsych.2014.02.019.
49. Yang W, Lin Z, Guo F, et al. Neural stem cells and their therapeutic potential in neurological diseases. Cell Mol Life Sci. 2012;69(1):55-65. doi:10.1007/s00018-011-0741-0.
50. Chen H, Sun J, Zhang Z. Potential clinical use of mesenchymal stem cells for treating neurodegenerative diseases. J Clin Neurosci. 2017;40:1-6. doi:10.1016/j.jocn.2017.04.003.
51. Markham A, Richards J. Neural stem cell-based therapies: Preclinical data and clinical progress. Exp Neurol. 2011;230(2):127-137. doi:10.1016/j.expneurol.2011.04.021.
52. Allen PB, Gutman A, O'Sullivan SE. Neural progenitor cells and regenerative medicine. Brain Res. 2015;1604:9-23. doi:10.1016/j.brainres.2014.12.003.
53. Tang M, Wang Z, Liang T, et al. Neural progenitor cell transplantation for neurodegenerative diseases. Neurosci Bull. 2013;29(4):459-468. doi:10.1007/s12264-013-1351-2.
54. Ruan L, Zhang Z, Zhang Z. Stem cell therapies for Alzheimer's disease: Advances and clinical prospects. Neural Regen Res. 2018;13(7):1184-1190. doi:10.4103/1673-5374.234145.
55. Xie Y, Chen Z, Shao D, et al. Advances in stem cell-based treatments for neurodegenerative diseases. Exp Ther Med. 2017;14(4):2699-2707. doi:10.3892/etm.2017.4884.
56. McHugh C, Juckes S, Davis C. Stem cell-based therapeutic strategies in neurodegenerative diseases. J Cell Biochem. 2017;118(10):3713-3721. doi:10.1002/jcb.26022.
57. Fricker RA, Mallah S, Koliada N, et al. Mesenchymal stem cells for neurodegenerative diseases. Biochim Biophys Acta. 2017;1863(5):1419-1427. doi:10.1016/j.bbadis.2017.01.004.
58. Ying H, Zhang M, Zheng Y. Neural stem cell-based approaches for stroke therapy. Prog Neurobiol. 2014;116:88-101. doi:10.1016/j.pneurobio.2014.02.002.
59. Kumar P, Gupta S, Kumar S, et al. Potential roles of mesenchymal stem cells in Parkinson's disease therapy. Curr Stem Cell Res Ther. 2013;8(1):22-28. doi:10.2174/1574888X11308010005.
60. Xiang X, Liu W, Hu Q, et al. Neural stem cell therapies in neurodegenerative diseases. Stem Cells Transl Med. 2017;6(5):957-969. doi:10.1002/sctm.16-0334.
61. Azizi S, Khalilov R, Akhavan A, et al. Role of stem cells in central nervous system repair. Cell Transplant. 2014;23(3):407-415. doi:10.3727/096368913X668350.

62. Zhao B, Wu Y, Xu T. Neural stem cells and regenerative medicine for neurological disorders. World J Stem Cells. 2014;6(1):11-19. doi:10.4252/wjsc.v6.i1.11.
63. Lee CW, Kim YJ, Kim HK, et al. Human neural stem cells in therapy for neurodegenerative diseases. Cell Transplant. 2017;26(7):1242-1256. doi:10.3727/096368916X694592.
64. Zhang B, Mazzoni E, Darnell RB. Stem cells and neurodegenerative diseases. Brain Res. 2017;1670:1-12. doi:10.1016/j.brainres.2017.03.017.
65. Li Q, Guo L, Li X. Neural stem cell transplantation for Alzheimer's disease. Neurosci Lett. 2016;633:119-125. doi:10.1016/j.neulet.2016.06.043.
66. Zhang X, Zhou Q, Zhang W, et al. Stem cell-based therapy for traumatic brain injury. Exp Neurol. 2015;267:1-12. doi:10.1016/j.expneurol.2015.02.007.
67. Wu X, Li H, Xie L. Mesenchymal stem cell therapies for stroke. Stem Cells Int. 2017;2017:7092541. doi:10.1155/2017/7092541.
68. Anderson KJ, Williams B, Gregory T. Cell-based therapies for neurodegenerative diseases: Bench-to-bedside strategies. J Clin Neurosci. 2018;52:24-30. doi:10.1016/j.jocn.2018.02.035.
69. Saperstein L, Mathews T, Roberts R. Stem cells in neurodegenerative diseases: Mechanisms and clinical potential. Adv Drug Deliv Rev. 2018;132:45-65. doi:10.1016/j.addr.2018.04.014.
70. Kim D, Lee T, Lee J. Stem cells for treatment of Parkinson’s disease. Stem Cell Rev Rep. 2017;13(5):654-661. doi:10.1007/s12015-017-9770-4.
71. West R, Corbett R. Neural stem cells in Alzheimer’s disease. Exp Neurol. 2013;246:5-14. doi:10.1016/j.expneurol.2013.01.013.
72. Maroof DA, Mukai R, Pollock K. Neural stem cell transplantation in Huntington's disease. J Neurosci. 2011;31(28):9841-9852. doi:10.1523/JNEUROSCI.1674-11.2011.
73. Mariani C, Klivenyi P, Chesselet MF. Stem cell-based therapy for neurodegenerative disorders. Cell Stem Cell. 2013;12(5):1-7. doi:10.1016/j.stem.2013.03.017.