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Review Article

Neurodegenerative Alterations and GABA–Glutamate Imbalance Following Traumatic Brain Injury: Molecular Mechanisms and Therapeutic Perspectives

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ABSTRACT

Traumatic brain injury (TBI) is a major neurological condition associated with both immediate and long-term alterations in neuronal structure and function. Although the primary mechanical injury occurs at the time of trauma, secondary pathological processes including excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, blood–brain barrier disruption, synaptic dysfunction, and neuronal degeneration may continue for days to months after injury. Among these mechanisms, disruption of the physiological balance between excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABAergic) neurotransmission has emerged as an important contributor to secondary brain injury. Excessive extracellular glutamate, impaired astrocytic glutamate uptake, and overactivation of NMDA and AMPA receptors can promote calcium influx and initiate downstream pathways associated with neuronal injury. At the same time, loss or dysfunction of GABAergic interneurons, alterations in GABA receptor subunits, and changes in GABA synthesis and signaling may reduce inhibitory control and contribute to cortical hyperexcitability. These alterations may persist into the chronic phase and contribute to cognitive impairment, behavioral abnormalities and post-traumatic epilepsy. Recent research also indicates that GABA-related mechanisms interact with neuroinflammation, oxidative stress, mitochondrial dysfunction and neurodegenerative pathways. This review summarizes the molecular mechanisms underlying GABA–glutamate imbalance after TBI, its relationship with neurodegenerative `alterations, and emerging pharmacological strategies targeting excitatory–inhibitory dysfunction.

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INTRODUCTION

Traumatic brain injury is a complex neurological disorder resulting from an external mechanical force that produces structural and functional abnormalities in the brain. Falls and motor vehicle accidents are the primary causes of TBI, while sports, assaults, and gunshot wounds also contribute significantly to these types of injuries [1]. The clinical consequences range from transient neurological symptoms to persistent cognitive, behavioral and neurological deficits. The pathological response to TBI is generally divided into primary and secondary injury. The injury that occurs at the moment of impact is known as the primary injury. Primary injuries can involve a specific lobe of the brain or can involve the entire brain. Sometimes the skull may be fractured, but not always. During the impact of an accident, the brain crashes back and forth inside the skull causing bruising, bleeding, and tearing of nerve fibers [2]. whereas secondary injury develops progressively through interconnected molecular and cellular mechanisms. The etiology of TBI is multifactorial that consists of travel accidents, wounds due to gunshots, sports and fight related events [3]. When the head strikes a playing mat or field, or an arena floor. The impact can lead to coup injury (an injury on the side of the head where the impact was made) and contrecoup injury of the cerebral cortex [4].

One of the important mechanisms involved in secondary brain injury is disruption of excitatory and inhibitory neurotransmission. Glutamate is the major excitatory neurotransmitter in the central nervous system, whereas GABA is the principal inhibitory neurotransmitter [5]. Their coordinated activity is essential for maintaining neuronal homeostasis and appropriate network function. Following TBI, this balance can shift toward excessive excitation. Experimental and clinical evidence indicates that increased glutamate release, impaired glutamate clearance, altered glutamate receptor expression and dysfunction of GABAergic interneurons contribute to this disturbance.

Persistent neurotransmitter imbalance may also interact with mitochondrial dysfunction, oxidative stress, neuroinflammation and neuronal loss, thereby linking acute TBI with chronic neurodegenerative alterations [6].

Traumatic brain injury is usually caused by a blow or any other traumatic injury directly to the head or body. The degree of damage can depend on several factors, including the nature of the injury and the force of impact.

Epidemiology Of Traumatic Brain Injury:

It has been estimated that traumatic brain injury affects over 54 to 60 million people annually leading to either hospitalization or mortality. Of all types of injury, the injury to brain are among the most likely to result in death or permanent disability [7]. Traumatic brain injury (TBI) is one of the biggest challenges faced by neurosurgeons globally. The Global Burden of Disease Study 2019 showed a 11.1% increase in the adjusted incidence rate of TBI (from 499 per 100,000 in 1990 to 554 per 100,000 in 2019) and a 22.4% increase in adjusted prevalence (from 818 per 100,000 in 1990 to 1,002 per 100,000 in 2019) in India. This contrasts starkly with a 5.5% decrease in incidence and are 0% change in the prevalence of TBI at the global scale [8].

The primary causes of traumatic brain injury vary by age, socio-economic factors, and geographic region, so any planned interventions must take into account for this variability. The low- and medium-income countries (LMICs) experience nearly three times more cases of traumatic brain injury proportionally than high-income countries (HICs), with Southeast Asian and Western Pacific regions experiencing the greatest overall burden [9].

A recent study published in 2021defined the epidemiology of almost 15,000 head injury patients during the period of March 2016 to February 2020 treated at PGIMER, Chandigarh. Road traffic accidents accounted for the majority of neurotrauma (61%) cases and the most commonly affected group was males aged 10 to 24 years. One-third of the patients had severe head injuries and only 30% of patients reached the hospital within 6hours. This scenario has remained mostly unchanged from the epidemiological data published by NIMHANS in 2002 [7]. This study highlights the well-known facts about neurotrauma in the Indian scenario. The urgent requirement for better legislation, stronger enforcement of traffic rules, faster hospital transfers and prehospital care, reduction of the burden

on tertiary care centres, and the necessity of neurorehabilitation services are important steps forward for ensuring better neurotrauma care [10].

India has been experiencing a much higher incidence of fall related traumatic brain injury with fractured skulls and intracranial long-term injuries in comparison to other countries, with the incidence rate amongst Indian males of 50.3 per 100 000 population, in comparison with the global average of 13. 3 per 100 000 [11].

In China, traumatic brain injury is a 5th leading cause of death in younger adults. Road traffic accident account for 61% of traumatic brain injury with third of those motorcyclists, 31% pedestrians and only 14% of car users.

Middle Eastern and other Asian Regions do not have consistent data collection process, but some local studies are emerging e.g. in Yemen traumatic brain injury prevalence rate at the level of 210 per 100 000 population, with domestic violence and falls being the leading causes, followed closely by Road traffic accident [12].

Causes of Traumatic Brain Injury: Common events that lead to traumatic brain injury include the following:

Fall**• s** : Falls from beds, ladders, stairs, bathtubs, and other situations are the most frequent cause of traumatic brain injury, especially among older adults and young children.

- Vehicle-related collisions **:** Accidents involving cars, motorcycles, bicycles, and pedestrians are a common source of traumatic brain injury.
- Violence: Gunshot wounds, domestic violence, child abuse, and other types of assault are frequent causes. Shaken baby syndrome, which occurs when an infant is violently shaken, is a type of traumatic brain injury.
- Sports injuries: Traumatic brain injuries can result from participation in various sports, such as soccer, boxing, football, baseball, lacrosse, skateboarding, hockey, and other high-impact or extreme sports. These injuries are particularly common among children [13].
- Explosive blasts and other combat injuries: Explosive blasts are a common cause of traumatic brain injury among active-duty military personnel. While the exact mechanism of damage is not fully understood, many researchers believe that the pressure wave passing through the brain causes significant disruption to brain function. Traumatic brain injury can also occur from penetrating wounds, severe blows to the head with shrapnel or debris, and collisions with objects following a blast [14].

Symptoms of TBI are: The signs and symptoms of mild traumatic brain injury may include :

Physical symptoms : Headache, Nausea or vomiting, Fatigue or drowsiness, Difficulty with speech, Dizziness or loss of balance .**Sensory symptoms :** Sensory issues such as blurred vision, ringing in the ears, a bad taste in the mouth, or changes in the ability to smell , Sensitivity to light or sound [15]. **Cognitive, behavioural or mental symptoms :** Loss of consciousness for a few seconds to a few minutes , No loss of consciousness, but a feeling of being dazed, confused, or disoriented, Difficulty with memory or concentration , Mood changes or mood swings, Feeling depressed or anxious, Trouble sleeping , Sleeping more than usual [16].

Moderate to severe traumatic brain injuries : Moderate to severe traumatic brain injuries may include all the signs and symptoms of mild injuries, as well as additional symptoms that could appear within the first hours or days after a head injury.

Physical symptoms may include: Loss of consciousness for several minutes to several hours, A persistent or worsening headache , Repeated vomiting or nausea , Convulsions or seizures , Dilated pupils in one or both eyes , Clear fluid draining from the nose or ears , Inability to wake up from sleep , Weakness or numbness in the fingers and toes , Poor coordination [17].

Cognitive or mental symptoms may include: Profound confusion , Agitation, aggression, or unusual behavior , Slurred speech , Coma or other consciousness disorders , Children with brain injuries may not be able to express symptoms such as headaches, confusion, or sensory issues [18].

Signs to watch for in a child with traumatic brain injury may include: Changes in eating or nursing habits, Increased irritability or fussiness , Persistent crying that is difficult to comfort, Difficulty focusing or paying attention , Changes in sleep patterns , Seizures , Sad or depressive mood , Drowsiness , Loss of interest in favourite toys or activities [19,20].

2. Pathophysiology of Traumatic Brain Injury

2.1 Primary brain injury: Primary injury occurs as a direct result of mechanical forces.

It may involve damage to the membranes of neurons and glial cells, injury to axons, damage to blood vessels, and deformation of brain tissue. This type of injury happens immediately at the time of impact, accident or trauma.

Primary brain injury is the immediate damage to the brain that occurs at the moment of a traumatic event, such as a road traffic accident, fall, sports injury, or physical assault. It results from the direct application of mechanical forces to the head and brain. This injury may damage brain tissue, blood vessels, neurons, and nerve fibres.

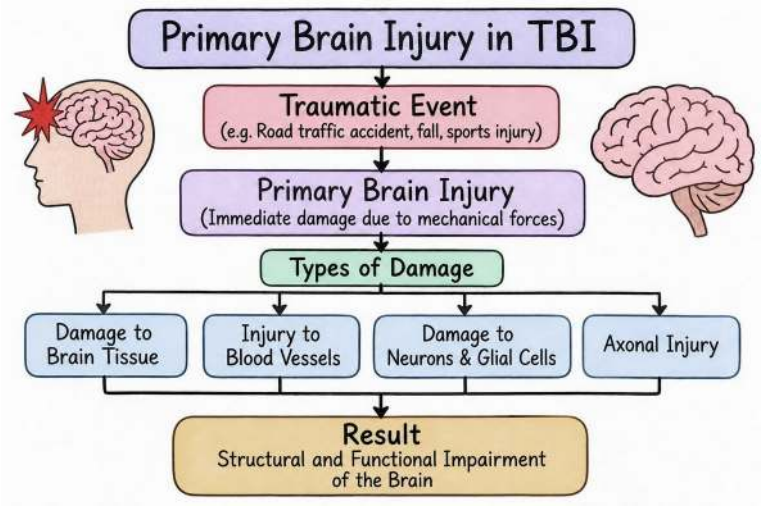


Figure None: 2.1 Pathophysiological Mechanisms of Primary Brain Injury Following Traumatic Brain Injury (TBI).

Primary brain injury occurs before secondary brain injury develops. The initial structural damage may be irreversible, and current medical treatment mainly focuses on preventing further damage and managing complications [21]. A schematic representation of the pathophysiological mechanisms involved in primary brain injury following TBI is presented in Figure 2.1.

2.2 Secondary brain injury

Secondary brain injuries refers to the additional damage that develops in brain tissue following an initial brain injury it commonly occurs after traumatic brain injury (TBI), such as injuries caused by road traffic accidents, sports injuries or physical trauma.

Secondary injury occurs after the initial trauma and involves various processes such as: Excitotoxicity, Calcium overload, Oxidative and nitrosative stress , Mitochondrial dysfunction, Neuroinflammation, Disruption of the blood–brain barrier, Brain swelling (edema), Impaired synaptic function, Cell death through apoptosis and other mechanisms , Neurodegenerative changes .These processes interact with each other rather than occurring in isolation, leading to progressive damage to brain cells and their networks [22]. A schematic representation of the pathophysiological mechanisms involved in secondary brain injury is presented in Figure 2.2.

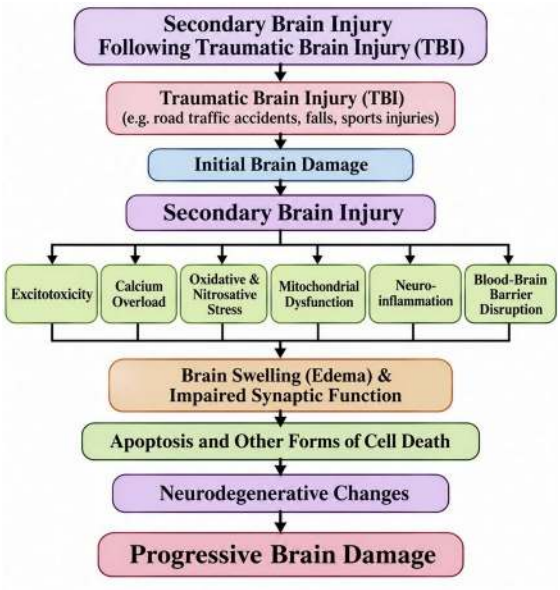


Figure None: 2.2 Pathophysiological Mechanisms of Secondary Brain Injury Following Traumatic Brain Injury (TBI).

3. Glutamatergic Neurotransmission Following TBI

Glutamate is the predominant excitatory neurotransmitter in the central nervous system (CNS). Glutamate is released from pre-synaptic terminals and diffuses across the synaptic cleft where it binds glutamate receptors. Glutamatergic transmission is terminated once excitatory amino acid transporters (EAATs) take up synaptic glutamate. Five mammalian EAAT isoforms (EAAT1-5) have been characterized (for review see: [23–27] with each having different nomenclatures, expression patterns, and uptake kinetics (Table 1). EAAT1, 2, and 3 are widely expressed in the CNS, whereas the expression of EAAT4 and 5 is predominately limited to the cerebellum and retina, respectively. The expression of EAAT2 is higher than that of EAAT1 in the forebrain while the inverse is true in the cerebellum. Under normal conditions, EAAT1 and 2 are mainly expressed in astrocytes and localized to the cellular membrane while EAAT3, 4, and 5 are mainly expressed in neurons [28-34]. EAAT2 is the most abundant EAAT and is primarily responsible for glutamate homeostasis in the forebrain [28, 35-38]. Therefore, dysfunction or dysregulation of EAAT2 can lead to excessive glutamate-mediated toxicity [38].

4. GABAergic Dysfunction Following TBI

GABA is the primary inhibitory neurotransmitter of the central nervous system and its release from interneurons acts to modulate excitatory neurotransmission. Glutamine in astrocytes is transported to GABAergic neurons to be converted to glutamate and then immediately to GABA by glutamate decarboxylase (GAD). Glutamate, glutamine and GABA rely on intermediaries from the tricarboxylic acid (TCA) cycle; therefore deficits and inefficiencies in cellular energy metabolism, such as those that follow compromised tissue perfusion and increased neuronal metabolic demand after TBI, also lead to deficits in transmitter production [39]. GABA is stored in presynaptic vesicles and is released onto postsynaptic terminals that may be located on the dendritic projections, the cell body, axon, or another axon terminal [40]. Following release and its postsynaptic actions the majority of GABA is taken back up by its transporter, GAT-1 into the presynaptic neuron.

5. GABA–Glutamate Imbalance

Glutamate is the main excitatory neurotransmitter in the brain, while GABA is the primary inhibitory neurotransmitter. Maintaining a proper balance between glutamatergic and GABAergic activity is essential for

normal brain function. In the case of traumatic brain injury, the role of glutamate signaling has two main aspects. First, the sudden release of glutamate after injury causes excitotoxicity, which results in damage to neurons, cell death, and impaired function of the remaining neurons. Second, a later breakdown in the excitatory glutamate pathways can lead to problems with thinking, movement, and the brain's ability to adapt based on experiences [41].

The balance between glutamatergic excitation and GABAergic inhibition is essential for normal brain function which can we explain by Figures: 5.1 & 5.2

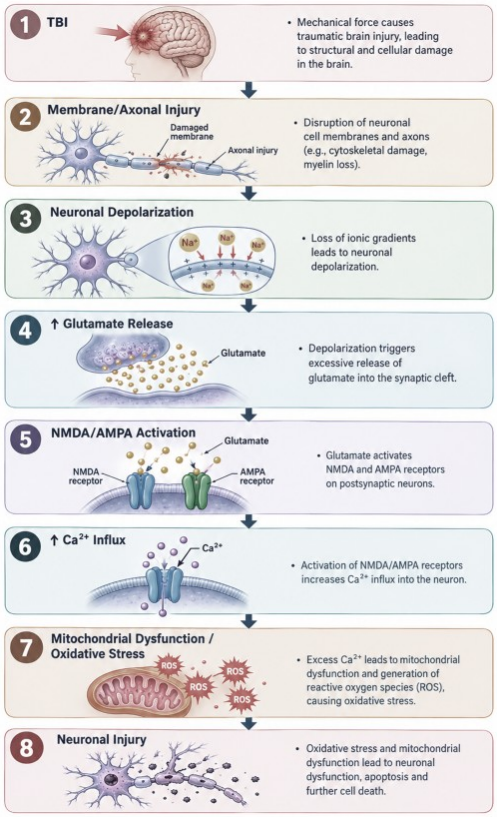


Figure None: 5.1 Pathophysiological Mechanism of Glutamate-Induced Excitotoxicity Following TBI.

Traumatic brain injury can disrupt this balance through several mechanisms:

Traumatic brain injury can cause direct harm to the membranes of neurons and their connecting fibers, which disrupts the brain's regular electrical activity. This damage results in neurons losing their normal charge balance and releasing too much of the excitatory chemical messenger glutamate into the spaces between nerve cells. Glutamate then triggers specific receptors on neighboring neurons, called NMDA and AMPA receptors, which causes an overload of calcium and sodium inside the cells. Too much calcium inside the cells activates harmful enzymes, damages the energy-producing parts of the cells, and leads to the creation of harmful substances known as reactive oxygen species.

These changes create oxidative stress, which harms important cell components like proteins, fats, and genetic material. They also reduce the cell's ability to produce energy. Over time, these effects lead to the damage and death of neurons, a process referred to as excitotoxicity caused by glutamate [42].

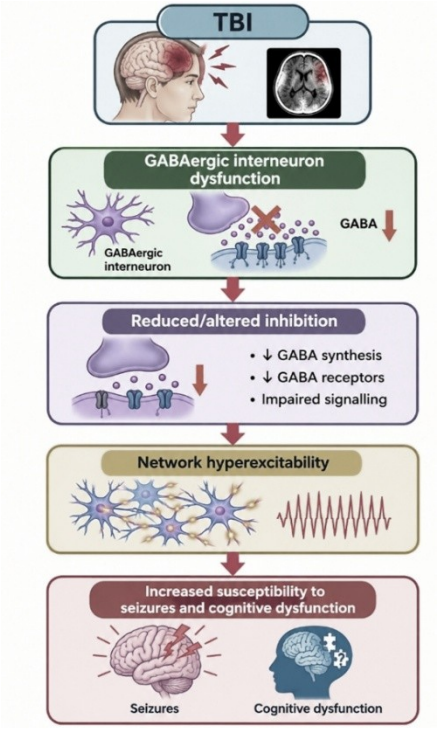


Figure None: 5.2 Mechanism of GABAergic Dysfunction Following TBI

Simultaneously:

Thus, increased excitation together with impaired or altered inhibition can create an environment favorable for neuronal dysfunction and network hyperexcitability. This excitation–inhibition disturbance has been associated with post-traumatic seizures and persistent neurological deficits.

6. Neurodegenerative Alterations Following TBI

Traumatic brain injury can lead to several neurodegenerative changes through interconnected pathological mechanisms, including excitotoxic neuronal injury, mitochondrial dysfunction, oxidative stress, neuroinflammation, synaptic dysfunction, and chronic neuronal network alterations.

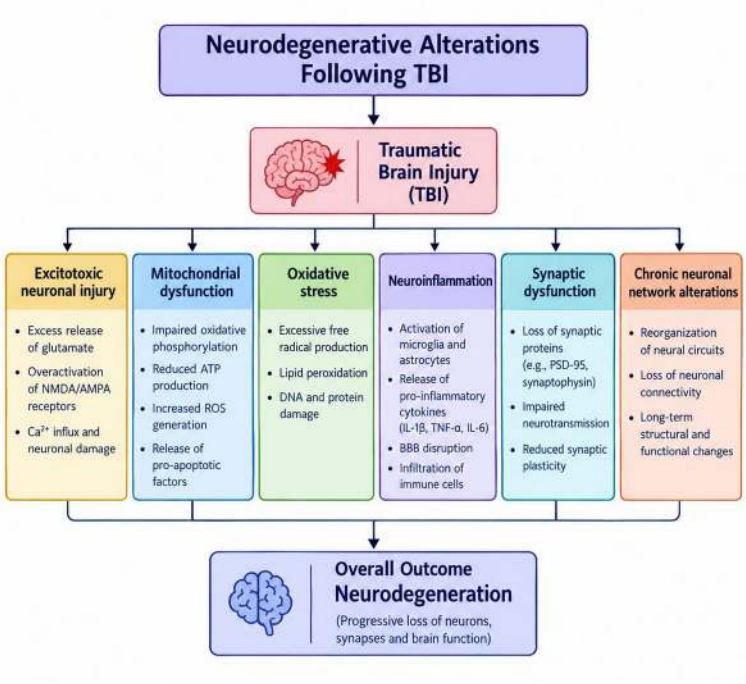


Figure None: 6 Mechanism of Neurodegeneration Following TBI

A schematic representation of the major mechanisms involved in neurodegenerative alterations following TBI is presented in Figure 6.

6.1 Excitotoxic neuronal injury

Glutamate excitotoxicity refers to the pathological process whereby excessive or sustained activation of glutamate receptors leads to toxic cellular outcomes. This phenomenon is characterized by an overwhelming influx of ions, particularly calcium, into neurons, which activates a cascade of deleterious enzymatic processes. Key enzymes, such as proteases, phospholipases, and endonucleases, are triggered, resulting in the degradation of cellular structures, disruption of normal neuronal function, and eventual cell death [43].

Persistent glutamate elevation and excessive receptor activation can initiate excitotoxic pathways leading to neuronal dysfunction and degeneration.

6.2 Mitochondrial dysfunction

mitochondrial dysfunction represents one of the core pathological mechanisms underlying secondary brain injury. This dysfunction manifests primarily as impaired oxidative phosphorylation, reduced ATP synthesis, and inadequate neuronal energy supply. As the cellular powerhouse, mitochondria are critical for sustaining the high metabolic demands of neurons. TBI triggers extensive pathological responses in brain tissue, including apoptosis, inflammatory cascades [44]. Calcium overload and oxidative stress can impair mitochondrial function, reduce ATP production and increase reactive oxygen species generation.

6.3 Oxidative stress

Oxidative stress is a product of the orchestration of multiple cellular processes including the activation of oxidative enzymes, nitric oxides, and lipid peroxidation, as well as enhanced excitotoxic activation of glutamatergic neurons. The resultant oxidative process would ultimately lead to the chronic sequelae of neuroinflammation and synaptopathy [45].

Excessive production of reactive oxygen and nitrogen species can damage proteins, membrane lipids and nucleic acids, contributing to progressive neuronal dysfunction.

6.4 Neuroinflammation

Neuroinflammation is the inflammatory response that occurs in the brain following traumatic brain injury. When brain tissue is damaged, immune cells such as microglia become activated, and astrocytes respond to

the injury. These cells release inflammatory substances called cytokines and chemokines.

Initially, inflammation helps remove damaged cells and supports tissue repair. However, if the inflammatory response becomes excessive or continues for a long time, it can damage healthy neurons, increase oxidative stress, and contribute to progressive neurodegeneration. Persistent neuroinflammation has also been associated with long-term cognitive problems following TBI [46].

Microglia and astrocytes become activated following TBI. Persistent inflammatory signaling can amplify neuronal injury and interact with excitotoxic mechanisms.

6.5 Synaptic dysfunction

Synaptic dysfunction and loss in traumatic brain injury may be incurred either acutely or chronically. In an acute trauma, the shearing impact of mechanical injury can lead to disintegration of both presynaptic and postsynaptic neuronal terminals. Moreover, studies have indicated that when an axon is transected, the presynaptic region is disintegrated almost immediately, while the postsynaptic spine later undergoes retraction. The structural synaptopathy of TBI significantly evolves over time. Indeed, weeks or months following an acute injury, additional synaptic degeneration may occur via activation of proinflammaory pathways[47].

TBI can produce loss of dendritic spines, altered receptor expression and impaired synaptic plasticity. Chronic synaptic remodeling may contribute to cognitive and behavioral abnormalities.

6.6 Chronic neuronal network alterations

Traumatic brain injury can cause long-lasting changes in the way neurons communicate with one another. Damage to axons, synapses, and white-matter pathways can interrupt communication between different brain regions [48]. These changes may affect important brain networks involved in memory, attention, learning, and decision-making.

Over time, some neural connections may weaken, while other connections may change as the brain attempts to compensate for the injury. Although this reorganization can support recovery, persistent network dysfunction may contribute to long-term cognitive difficulties and may coexist with progressive neurodegenerative changes .[49]

Persistent changes in glutamatergic and GABAergic signaling can alter neuronal network activity. Such changes may contribute to cognitive dysfunction and post-traumatic epilepsy.

7. Relationship Between GABA–Glutamate Imbalance and Neurodegeneration

GABA–glutamate imbalance should not be considered an isolated neurotransmitter abnormality. It interacts with multiple secondary injury mechanisms.

Excessive glutamatergic activity increases intracellular calcium, which can promote mitochondrial dysfunction and oxidative stress. Neuroinflammatory processes may further enhance excitotoxic signaling [50]. Conversely, dysfunction of inhibitory GABAergic circuits can reduce the ability of neuronal networks to control excessive excitation.

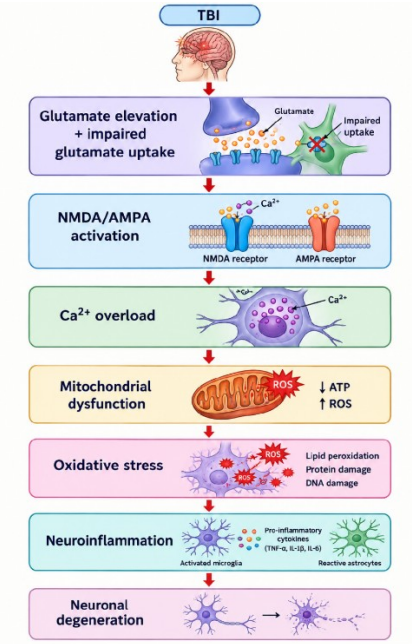


Figure None: 7.1 Major Pathophysiological Mechanisms Involved in Neurodegenerative Alterations Following Traumatic Brain Injury.

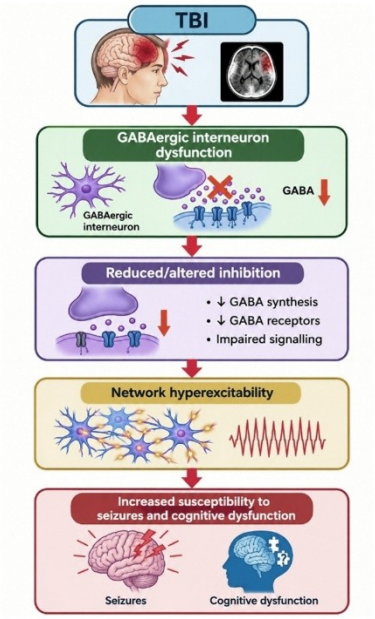


Figure None: 7.2 Molecular Pathways Linking GABA–Glutamate Imbalance to Neuronal Damage Following Traumatic Brain Injury.

The imbalance between gamma-aminobutyric acid (GABA) and Glutamate plays an important role in the progression of neurodegenerative changes following brain injury. Disruption of inhibitory and excitatory neurotransmission may impair synaptic plasticity, neuronal communication, and the normal functioning of neural circuits. Alterations in GABA and glutamate receptor expression, neurotransmitter transport, and synaptic regulation may contribute to persistent neuronal dysfunction and reduce neuronal survival. Furthermore , impaired neuro transmitter homeostasis can interfere with neuronal repair mechanisms and promote

maladaptive changes in neuronal connectivity. These alterations may contribute to long-term neurological deficits and may be relevant to the progression of neurodegenerative conditions, although the underlying mechanisms vary according to the type and severity of brain injury [51,52]. Therefore, a possible integrated pathway is shown in figure 7.1. Simultaneously in Figure:7.2

8. Temporal Changes After TBI

The GABA–glutamate system undergoes dynamic changes rather than a single permanent alteration. Temporal changes after Traumatic Brain Injury (TBI) refer to the changes that occur in the brain and in a patient's physical, cognitive, and emotional functions over time following a traumatic injury [53]. These changes may occur immediately after injury or develop over hours, days, months, or years.

Acute phase (minutes to hours)

Mechanical injury, membrane disruption, depolarization, glutamate release, ionic imbalance and early calcium loading may occur rapidly. Mitochondrial stress, vascular changes and early inflammatory signaling can begin during this period. Clinical priorities are stabilization, prevention of secondary insults and management of intracranial complications [54].

Loss of consciousness, confusion, headache, bleeding, and brain swelling may occur.

- Rapid glutamate release
- Ion imbalance
- Calcium influx
- Energy failure
- Initial GABAergic alterations [55,56].

Subacute phase (hours to days or weeks)

Ongoing inflammation, oxidative stress, altered transporter function, receptor remodeling, BBB changes, oedema and synaptic reorganization may contribute to evolving dysfunction. The timing and magnitude of these changes vary by injury severity and region [57].

Changes in glutamate transporters, Receptor remodeling, GABA receptor alterations, Neuroinflammation, Oxidative stress, Synaptic remodeling [55,56].

Chronic phase (weeks to years)

Some individuals experience persistent cognitive, emotional, behavioural or physical symptoms. Chronic changes may include altered network connectivity, maladaptive plasticity, persistent inflammation in selected contexts, and increased seizure susceptibility. These outcomes are variable and should not be presented as inevitable. The acute–subacute–chronic framework is a useful simplification rather than a strict biological timetable [58].

Persistent network hyperexcitability, GABAergic interneuron dysfunction, Altered glutamate receptor composition, Chronic neuroinflammation, Synaptic loss/remodeling, Cognitive and behavioral abnormalities, Risk of post-traumatic epilepsy.

This temporal perspective is important because a pharmacological strategy effective during the acute phase may not necessarily be appropriate during the chronic phase[55,56].

9. Pharmacological and Therapeutic Perspectives

Potential therapeutic approaches can be broadly divided into strategies targeting excitatory signaling, inhibitory signaling and secondary injury mechanisms.

9.1 Modulation of glutamatergic signaling

Potential approaches include modulation of NMDA/AMPA receptor activity and enhancement of glutamate clearance. Experimental evidence suggests that improving glutamate transporter function may reduce excitotoxicity and post-traumatic seizures. Glutamate acts on either ionotropic receptors enabling ion passage into the cell or metabotropic G-protein coupled receptors, both of which prompt an intracellular signaling cascade. The ionotropic receptors include N-methyl-d-aspartate (NMDA), alpha-amino-3 hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainite . The NMDA receptor (NMDAR) has been the most extensively studied due to its role in use-dependent synaptic plasticity, particularly long-term potentiation [59], and its potential contribution to diseases such as schizophrenia and Alzheimer's Disease [60,61,62]

9.2 Modulation of GABAergic signaling

GABAergic drugs have been investigated for controlling neuronal hyperexcitability and seizures following TBI. However, the complexity of GABA receptor subtypes and temporal changes in GABA signaling makes nonspecific modulation challenging. Recent research emphasizes receptor- and circuit-specific approaches. GABA is the primary inhibitory neurotransmitter of the central nervous system and its release from interneurons acts to modulate excitatory neurotransmission. Glutamine in astrocytes is transported to GABAergic neurons to be converted to glutamate and then immediately to GABA by glutamate decarboxylase (GAD). Glutamate, glutamine and GABA rely on intermediaries from the tricarboxylic acid (TCA) cycle [63]. GABA is stored in presynaptic vesicles and is released onto postsynaptic terminals that may be located on the dendritic projections, the cell body, axon, or another axon terminal . Following release and its post-synaptic actions the majority of GABA is taken back up by its transporter, GAT-1 into the presynaptic neuron [64].

9.3 Antioxidant approaches

Because oxidative stress is an important component of secondary injury, antioxidant and mitochondrial-protective strategies represent potential therapeutic areas.

9.3.1 Ascorbic acid (vitamin C)

Ascorbic acid (AA) is one of the most abundant water-soluble antioxidants within mammalian tissues, that acts as a free-radical scavenger. It helps protect cells against oxidative damage and supports intracellular antioxidant defence systems [65]. Being a powerful reducing agent, it quickly reacts, through one or two electron reactions, with a wide range of ROS and RNS, including peroxynitrite and hydroxyl radicals. AA is involved in the recycling of oxidized α-tocopherol (Vitamin E) contributing to the maintenance of it's antioxidant activity within biological membranes [66].

9.3.2Flavonoids

Flavonoids are a class of more than 5000 naturally occurring compounds, largely present in plants and fungi [67]. They possess a very negative oxido-reductive potential, therefore acting as powerful antioxidants towards any type of ROS and RNS [68].

9.3.3 Resveratrol

Resveratrol is an antioxidant with modest, but significant, solubility in water and good solubility in organic solvents, thus indicating its prevalent hydrophobic nature [69]. Resveratrol seems to modulate several cell functions, including defense mechanisms, mitochondrial functions, and inflammatory processes [70].

9.3.4 α-Tocopherol (Vitamin E)

Tocopherols are a family of fat-soluble compounds, found in high concentrations in various vegetal oils, having a remarkable antioxidant capacity [71]. Tocopherol may reduce ROS-mediated tissue damage and promote cerebral tissue regeneration following TBI [72]. In a model of focal moderate TBI, the effects of administration of tocopheryl-succinate (100 mg/kg) + polyethylene glycol (PEG) (2 mL/kg), injected 30 min before or 5 min after injury, were evaluated in rats subjected to fluid percussion. Although PEG alone improved the parameters under evaluation, the combination tocopheryl-succinate (100 mg/kg) + PEG (2mL/kg) showed the best increase in the survival rates and the best improvement of neurocognitive tasks and motor function, suggesting that this type of infusion might be effective in the clinical setting to decrease TBI-associated damage [73].

9.4 Anti-inflammatory approaches

Targeting persistent microglial and astrocytic activation may provide another strategy for limiting secondary neuronal damage. Anti-inflammatory drugs limit motor deficits in multiple TBI models . Most models, however, produce transient deficits reflexes and motor skills that recover spontaneously within one week. Thus, the assessment of drug efficacy using reflexes or motor deficits has the caveat that the anti-inflammatory drug is, at best, improving recovery rate. In contrast to reflex and motor deficits, deficits in cognition and memory can be permanent [74].

9.5 Combination approaches

Because TBI involves multiple interacting mechanisms, future therapies may require combinations

targeting excitotoxicity, neuroinflammation, mitochondrial dysfunction and synaptic dysfunction rather than a single molecular pathway. Combination therapy for traumatic brain injury (TBI) uses multi-mechanistic treatments—such as pairing neuroprotective drugs, stem cells, or metabolic agents with physical or cognitive rehabilitation—to target complex secondary injury cascades like inflammation, oxidative stress, and excitotoxicity that single-agent trials have historically failed to stop [75].

10. Research Gaps and Future Perspectives

Several important research questions remain:

1. How does the GABA–glutamate ratio change at different stages of TBI?
2. Which GABA-A receptor subtypes are most important during acute and chronic TBI?
3. Can restoration of glutamate transporter activity prevent chronic neurodegeneration?
4. Can GABAergic modulation reduce post-traumatic epilepsy without impairing cognitive recovery?
5. What is the relationship between GABA–glutamate imbalance and neuroinflammation?
6. Can biomarkers of neurotransmitter imbalance predict long-term neurological outcomes?
7. Can combination therapy targeting excitotoxicity, oxidative stress and GABAergic dysfunction provide better neuroprotection?

Future studies should integrate neurochemical, molecular, electrophysiological and behavioral approaches to understand the time-dependent nature of excitation–inhibition imbalance. Further research should distinguish mild, moderate and severe TBI; single from repeated injury; and focal from diffuse injury. Human studies need validated biomarkers, longitudinal follow-up and harmonised outcome measures. Preclinical studies should use clinically relevant models, both sexes, appropriate age ranges and transparent reporting. Clinical trials should account for treatment timing, drug penetration, injury heterogeneity and rehabilitation exposure. Mechanistic endpoints are useful, but they must be linked to patient-centered outcomes [76].

Emerging directions include cell-specific modulation of glutamate transport, selective targeting of GABA receptor subtypes, restoration of KCC2-dependent chloride extrusion, mitochondrial quality-control pathways, and immunomodulation through NLRP3, P2X7, TLR4 or cGAS–STING. These are promising research areas, not established clinical treatments [77].

CONCLUSION

Traumatic brain injury (TBI) causes several molecular and cellular changes that may continue even after the initial injury. Among these changes, disruption of GABA–glutamate balance plays an important role in secondary brain injury and long-term neurological problems. Increased glutamate activity can cause excitotoxicity, calcium overload, mitochondrial dysfunction and oxidative stress. On the other hand, reduced or altered GABAergic activity may decrease the normal inhibitory control of neurons, leading to neuronal hyperexcitability. These changes are closely related to neuroinflammation, synaptic dysfunction and alterations in neuronal networks. Together, they may contribute to long-term problems such as memory impairment, cognitive and behavioural changes, and an increased risk of post-traumatic epilepsy. The changes in GABAergic and glutamatergic signalling may also vary during the acute, subacute and chronic stages of TBI, making the timing of treatment an important factor.

Different pharmacological approaches, including glutamate and GABA modulation, antioxidant treatment, anti-inflammatory agents and combination therapies, have shown potential for reducing secondary brain damage. However, more research is needed to understand the long-term effects of these treatments and establish their safety and effectiveness in clinical practice. Overall, understanding the interaction between GABA and glutamate, along with other mechanisms of secondary brain injury, may help in developing better treatment strategies and improving long-term outcomes in patients with traumatic brain injury.

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