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Review Article

Glutamate-Induced Excitotoxicity and Its Impact on Neurodegenerative Diseases

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A B S T R A C T

Glutamate, the predominant excitatory neurotransmitter in the central nervous system, is crucial for normal brain function, including synaptic transmission, plasticity, learning, and memory. However, excessive activation of glutamate receptors can lead to excitotoxicity, a pathological process resulting in neuronal injury and death. Excitotoxicity is implicated in the pathogenesis of several major neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS). In AD, amyloid-beta plaques and tau tangles disrupt glutamate homeostasis, leading to NMDA receptor overactivation and subsequent calcium overload. In PD, dopaminergic neuron degeneration enhances NMDA receptor sensitivity, exacerbating excitotoxic damage. ALS is characterized by impaired glutamate uptake due to EAAT2 dysfunction, leading to motor neuron death through NMDA and AMPA receptor overactivation. In HD, mutant huntingtin protein disrupts glutamate transporters and increases NMDA receptor activity, resulting in striatal neuronal loss.

Keywords: Glutamate-Induced Excitotoxicity, Neurodegenerative Diseases, Neurotransmitter, Synaptic transmission

Introduction

Glutamate, the primary excitatory neurotransmitter in the central nervous system (CNS), plays a crucial role in synaptic transmission, plasticity, and overall brain function. However, under certain pathological conditions, excessive glutamate release or impaired uptake can lead to a phenomenon known as excitotoxicity. This process is characterized by overactivation of glutamate receptors, leading to neuronal injury and death. Excitotoxicity has been implicated in a variety of acute and chronic neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, and multiple sclerosis.[1] NMDA receptor antagonists, such as memantine and ketamine, have shown promise in reducing neuronal damage and slowing disease progression. Enhancing glutamate uptake with agents like ceftriaxone, modulating intracellular signaling pathways through mGluR agonists and antagonists, and protecting against oxidative stress and mitochondrial dysfunction with antioxidants and mitochondrial protectants are discussed. Additionally, emerging therapies, including gene therapy, stem cell therapy, and CRISPR-Cas9, offer innovative approaches to counteract excitotoxicity and promote neuroprotection.[2]

Mechanisms of Glutamate-Induced Excitotoxicity

Glutamate Receptors

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system (CNS), essential for various brain functions, including learning, memory, and synaptic plasticity. The effects of glutamate are mediated through its interaction with glutamate receptors, which are classified

into two major categories: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs).

Ionotropic Glutamate Receptors (iGluRs)

Ionotropic glutamate receptors are ligand-gated ion channels that mediate fast synaptic transmission. They are further subdivided into three main types based on their pharmacological properties and the agonists that activate them: NMDA receptors, AMPA receptors, and kainate receptors.

NMDA Receptors (NMDARs)

NMDA receptors are heterotetrameric complexes composed of two NR1 subunits and two NR2 (or NR3) subunits. The NR2 subunits (NR2A-D) determine the receptor's pharmacological properties and are crucial for its function. NMDARs are highly permeable to calcium (Ca2+), sodium (Na+), and potassium (K+) ions. Their activation requires the simultaneous binding of glutamate and glycine (or D-serine) as co-agonists, as well as membrane depolarization to relieve the voltage-dependent magnesium (Mg2+) block.[3] This unique requirement for dual ligand binding and depolarization allows NMDARs to act as coincidence detectors, essential for synaptic plasticity mechanisms such as long-term potentiation (LTP) and long-term depression (LTD). NMDARs are critical for synaptic plasticity, learning, and memory. They are predominantly located postsynaptically at excitatory synapses and contribute to the slow component of excitatory postsynaptic currents (EPSCs). Dysregulation of NMDARs is implicated in several neurological disorders, including Alzheimer's disease, schizophrenia, and excitotoxicity-related neurodegeneration.[4]

AMPA Receptors (AMPARs)

AMPA receptors are also tetrameric complexes, composed of GluA1-A4 subunits. The combination of different subunits determines the receptor's properties, including ion permeability and kinetics. AMPARs mediate fast excitatory synaptic transmission by allowing the influx of Na+ and, to a lesser extent, Ca2+ ions. The permeability to Ca2+ depends on the presence of the GluA2 subunit, which generally renders the receptor impermeable to Ca2+. AMPARs are responsible for the majority of fast excitatory neurotransmission in the CNS. They rapidly respond to glutamate release and are essential for synaptic strength and plasticity. Alterations in AMPAR function are associated with various neurological conditions, including epilepsy, autism spectrum disorders, and neurodegenerative diseases.[5]

Kainate Receptors (KARs)

Kainate receptors are composed of GluK1-5 subunits. Similar to other iGluRs, their subunit composition affects their functional properties. KARs have dual roles, acting both postsynaptically to mediate excitatory transmission and presynaptically to modulate neurotransmitter release. They allow the influx of Na+ and K+ ions, and some subtypes are also permeable to Ca2+. KARs contribute to synaptic transmission and plasticity, although their role is less well understood compared to NMDARs and AMPARs. They are involved in regulating neuronal excitability and network dynamics. KAR dysfunction has been linked to epilepsy, pain syndromes, and neurodevelopmental disorders.

Metabotropic Glutamate Receptors (mGluRs)

Metabotropic glutamate receptors are G-protein-coupled receptors (GPCRs) that modulate synaptic transmission and neuronal excitability through slower, longer-lasting signaling pathways. They are divided into three groups based on sequence homology, signal transduction mechanisms, and pharmacology.[6]

Group I mGluRs (mGluR1 and mGluR5)

Group I mGluRs are coupled to Gq proteins, which activate phospholipase C (PLC) and result in the production of inositol trisphosphate (IP3) and diacylglycerol (DAG). Activation of Group I mGluRs leads to the release of Ca2+ from intracellular stores and activation of protein kinase C (PKC), modulating various cellular processes. Group I mGluRs are primarily located postsynaptically and play key roles in modulating synaptic plasticity, excitability, and intracellular signaling pathways. Dysregulation of Group I mGluRs is associated with several neurological and psychiatric disorders, including fragile X syndrome, schizophrenia, and chronic pain.

Group II mGluRs (mGluR2 and mGluR3)

Group II mGluRs are coupled to Gi/o proteins, which inhibit adenylyl cyclase, reducing cyclic AMP (cAMP) levels. These receptors primarily act to inhibit neurotransmitter release and reduce neuronal excitability. Group II mGluRs are located presynaptically and postsynaptically, modulating synaptic transmission and plasticity. They play a protective role against excitotoxicity. Alterations in Group II mGluR function are linked to anxiety, depression, and neurodegenerative diseases..[3,4]

Group III mGluRs (mGluR4, mGluR6, mGluR7, and mGluR8)

Group III mGluRs are also coupled to Gi/o proteins, inhibiting adenylyl cyclase activity. These receptors generally serve to inhibit neurotransmitter release and modulate synaptic transmission. Group III mGluRs are predominantly located presynaptically and play roles in modulating synaptic plasticity and protecting against excessive neuronal activity. Dysfunction in Group III mGluRs is implicated in various conditions, including Parkinson's disease, anxiety disorders, and epilepsy.

Calcium Overload and Cellular Damage

Calcium ions (Ca2+) play a pivotal role in a variety of cellular processes, including neurotransmitter release, muscle contraction, gene expression, and cell survival. Under physiological conditions, intracellular Ca2+ levels are tightly regulated by a complex network of channels, pumps, and buffers. However, in pathological conditions, such as excitotoxicity, excessive Ca2+ influx can occur, leading to a phenomenon known as calcium overload. This condition triggers a cascade of detrimental intracellular events, ultimately resulting in cellular damage and death. This section delves into the mechanisms by which calcium overload causes cellular damage and its implications for neurodegenerative diseases.[7]

Mechanisms of Calcium Overload

Overactivation of Glutamate Receptors

The primary cause of calcium overload in neurons is the overactivation of ionotropic glutamate receptors, particularly NMDA receptors. NMDA receptors are highly permeable to Ca2+ and their prolonged activation leads to significant Ca2+ influx. AMPA and kainate receptors can also contribute to this process, especially if they lack the GluA2 subunit, which renders them permeable to Ca2+.

Disruption of Calcium Homeostasis

Under normal conditions, intracellular Ca2+ levels are maintained at low micromolar concentrations, while extracellular Ca2+ concentrations are in the millimolar range. This gradient is maintained by:

- **Calcium Channels:** Voltage-gated calcium channels (VGCCs) and receptor-operated channels (such as NMDA receptors) facilitate Ca2+ entry into the cell.
- **Calcium Pumps and Exchangers:** The plasma membrane Ca2+-ATPase (PMCA) and the Na+/Ca2+ exchanger (NCX) extrude Ca2+ from the cell, while the sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) pumps Ca2+ into the endoplasmic reticulum (ER).
- **Calcium Buffers:** Proteins such as calbindin, parvalbumin, and calmodulin bind free Ca2+, reducing its cytosolic concentration.

During excitotoxicity, the balance between Ca2+ entry and removal is disrupted, leading to sustained high levels of intracellular Ca2+.[8]

Pathways of Cellular Damage

Mitochondrial Dysfunction

Excessive Ca2+ uptake by mitochondria disrupts their function in several ways:

- **Impaired ATP Production:** High Ca2+ levels interfere with oxidative phosphorylation, reducing ATP synthesis.
- **Reactive Oxygen Species (ROS) Production:** Overloaded mitochondria produce excessive ROS, leading to oxidative stress.
- **Mitochondrial Permeability Transition Pore (mPTP) Opening:** Prolonged Ca2+ overload triggers the opening of the mPTP, leading to the loss of mitochondrial membrane potential, release of pro-apoptotic factors, and ultimately cell death.

Activation of Destructive Enzymes

High intracellular Ca2+ levels activate a variety of Ca2+-dependent enzymes:

- **Proteases (Calpains):** These enzymes degrade cytoskeletal and membrane proteins, leading to cellular structural damage.
- **Phospholipases:** They break down membrane phospholipids, resulting in membrane destabilization and the production of harmful lipid metabolites.
- **Endonucleases:** These enzymes cause DNA fragmentation, contributing to cell death through apoptosis.[9]

Oxidative Stress

Oxidative stress is a significant consequence of calcium overload. Elevated Ca2+ levels enhance the production of ROS and reactive nitrogen species (RNS), which damage cellular components, including lipids, proteins, and nucleic acids. This oxidative damage exacerbates mitochondrial dysfunction and promotes the activation of cell death pathways.

Neuroinflammation

Calcium overload can also trigger inflammatory responses. Damaged neurons release signaling molecules, such as cytokines and chemokines, which activate glial cells (microglia and astrocytes). While initially protective, chronic neuroinflammation can lead to further neuronal damage and exacerbate the pathological process.[10]

Impact on Neurodegenerative Diseases

Glutamate-induced excitotoxicity plays a critical role in the pathogenesis of several neurodegenerative diseases. The overactivation of glutamate receptors, particularly NMDA receptors, leads to excessive calcium influx, triggering a cascade of deleterious events that culminate in neuronal damage and death. This section examines the impact of excitotoxicity on major neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, and multiple sclerosis.

Alzheimer's Disease (AD)

In Alzheimer's disease, excitotoxicity is a key contributor to neuronal loss and cognitive decline. The accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau

tangles disrupt normal neuronal function and exacerbate excitotoxic processes:

1. **Amyloid-Beta and Glutamate Release:** Aβ plaques increase the release of glutamate from presynaptic terminals and reduce its uptake by astrocytes, leading to elevated extracellular glutamate levels.
2. **NMDA Receptor Overactivation:** Aβ interacts with NMDA receptors, enhancing their activity and leading to increased Ca2+ influx.
3. **Synaptic Dysfunction and Neurotoxicity:** The resulting Ca2+ overload contributes to synaptic dysfunction, oxidative stress, and mitochondrial impairment, promoting neuronal death.[11]

The excitotoxic damage in AD manifests as progressive memory loss, cognitive impairment, and behavioral changes. Therapeutic strategies targeting excitotoxicity, such as NMDA receptor antagonists (e.g., memantine), aim to mitigate neuronal damage and slow disease progression.

1. **Parkinson's Disease (PD):** In Parkinson's disease, the degeneration of dopaminergic neurons in the substantia nigra is a hallmark feature. Excitotoxicity contributes to this neurodegenerative process through several mechanisms:
2. **Glutamate and Dopamine Interaction:** Reduced dopamine levels lead to compensatory changes in glutamate transmission, increasing excitatory input to the striatum.
3. **NMDA Receptor Sensitization:** Dopaminergic degeneration sensitizes NMDA receptors, exacerbating Ca2+ influx and excitotoxic damage.
4. **Mitochondrial Dysfunction:** Impaired mitochondrial function in PD neurons makes them more susceptible to excitotoxicity-induced damage.

Excitotoxicity in PD results in motor symptoms, such as tremors, rigidity, bradykinesia, and postural instability. Neuroprotective approaches targeting excitotoxicity and mitochondrial dysfunction are being explored to preserve dopaminergic neurons and improve motor function.[12]

1. **Amyotrophic Lateral Sclerosis (ALS):** ALS is characterized by the selective degeneration of motor neurons. Excitotoxicity is a significant contributor to motor neuron death in ALS:
2. **Glutamate Transporter Dysfunction:** Mutations in the EAAT2 (excitatory amino acid transporter 2) gene reduce glutamate uptake, leading to elevated extracellular glutamate levels.
3. **NMDA and AMPA Receptor Overactivation:** Excessive activation of these receptors results in Ca2+ overload, mitochondrial dysfunction, and oxidative stress in motor neurons.
4. **Genetic Factors:** Mutations in the SOD1 (superoxide dismutase 1) gene and other ALS-associated genes exacerbate excitotoxic stress.

The excitotoxic damage in ALS leads to progressive muscle weakness, atrophy, and eventual paralysis. Riluzole, a drug that modulates glutamate release, is one of the few approved treatments that can modestly extend survival by mitigating excitotoxic damage.

1. **Huntington's Disease (HD):** Huntington's disease is caused by a mutation in the huntingtin gene, leading to the production of a toxic protein that disrupts cellular function:
2. **Impaired Glutamate Uptake:** The mutant huntingtin protein impairs glutamate transporters, leading to increased extracellular glutamate levels.
3. **Enhanced NMDA Receptor Sensitivity:** The mutant protein also enhances NMDA receptor activity, increasing Ca2+ influx and excitotoxic damage.
4. **Striatal Vulnerability:** The striatum, particularly vulnerable to excitotoxicity, shows significant neuronal loss in HD.

Excitotoxicity in HD results in motor dysfunction, cognitive decline, and psychiatric symptoms. Therapeutic strategies targeting NMDA receptors and glutamate transporters aim to reduce excitotoxic damage and improve quality of life.[13]

1. **Multiple Sclerosis (MS):** Multiple sclerosis is an autoimmune disorder characterized by demyelination and neurodegeneration in the CNS. Excitotoxicity plays a role in both white and gray matter damage:
2. **Inflammation and Glutamate Release:** Inflammatory cytokines released by activated immune cells increase glutamate release and impair its uptake.
3. **Oligodendrocyte and Neuronal Damage:** Elevated glutamate levels lead to excitotoxic damage of oligodendrocytes (myelin-producing cells) and neurons.
4. **Mitochondrial Dysfunction:** Chronic inflammation and excitotoxicity contribute to mitochondrial dysfunction and further neuronal injury.

Excitotoxicity in MS contributes to a range of symptoms, including motor deficits, sensory disturbances, and cognitive impairment. Neuroprotective treatments aimed at reducing excitotoxicity and inflammation are being investigated to prevent disease progression and promote remyelination.[14]

Therapeutic Approaches

1. Glutamate Receptor Antagonists

NMDA Receptor Antagonists

- **Memantine:** Memantine is an NMDA receptor antagonist approved for the treatment of moderate to severe Alzheimer's disease. It binds to NMDA receptors with moderate affinity, blocking excessive Ca2+ influx while preserving normal synaptic transmission.

Memantine has shown benefits in slowing cognitive decline and improving behavioral symptoms in AD patients.

- **Ketamine:** Although primarily used as an anesthetic and for depression, ketamine's NMDA receptor antagonism has neuroprotective effects. Research is ongoing to explore its potential in treating neurodegenerative diseases, focusing on optimizing dosing and minimizing side effects.
- **Riluzole:** Riluzole is an approved treatment for ALS that modulates glutamate release and inhibits NMDA receptor activation. It prolongs survival in ALS patients and is being studied for potential benefits in other neurodegenerative conditions.

AMPA and Kainate Receptor Antagonists

- **Perampanel:** Perampanel, an AMPA receptor antagonist, is approved for the treatment of epilepsy. Its potential for neuroprotection in neurodegenerative diseases is being investigated, given its ability to reduce excitotoxic neuronal damage.

2. Glutamate Uptake Enhancers

- **Ceftriaxone:** Ceftriaxone is an antibiotic that upregulates the expression of EAAT2 (excitatory amino acid transporter 2), enhancing glutamate uptake and reducing extracellular glutamate levels. Clinical trials are exploring its efficacy in ALS and other neurodegenerative diseases.
- **Beta-lactam Antibiotics:** Similar to ceftriaxone, other beta-lactam antibiotics have shown promise in increasing EAAT2 expression and are being investigated for their neuroprotective potential.

3. Modulation of Intracellular Signaling Pathways

mGluR Modulators:

- **Group II and III mGluR Agonists:** Agonists of Group II and III metabotropic glutamate receptors (mGluRs) can reduce glutamate release and neuronal excitability. These compounds are being studied for their neuroprotective effects in conditions like PD and HD.
- **mGluR5 Antagonists:** Antagonists of mGluR5, a Group I mGluR, can mitigate excitotoxicity and have shown potential in preclinical models of neurodegenerative diseases. Clinical trials are underway to evaluate their safety and efficacy in humans.[7]

4. Antioxidants and Mitochondrial Protectants

- **Coenzyme Q10:** Coenzyme Q10 is an antioxidant that supports mitochondrial function and reduces oxidative stress. It has been tested in clinical trials for PD, HD, and ALS, with mixed results. Further research aims to optimize dosing and patient selection.
- **Edaravone:** Edaravone is an antioxidant approved for ALS treatment in some countries. It scavenges free radicals and reduces oxidative damage, offering neuroprotective benefits.
- **Creatine:** Creatine supports cellular energy metabolism and has antioxidant properties. It has been studied in clinical trials for PD, HD, and ALS, with some evidence suggesting potential benefits in slowing disease progression.[13]

Anti-inflammatory Agents

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs): NSAIDs reduce neuroinflammation and have been studied for their potential to slow the progression of AD, PD, and other neurodegenerative diseases. However, results have been inconsistent, and concerns about long-term side effects remain.
- Minocycline: Minocycline is an antibiotic with anti-inflammatory and neuroprotective properties. It has shown promise in preclinical studies and early-phase clinical trials for ALS, HD, and MS, though larger studies are needed to confirm its efficacy.

Neurotrophic Factors

- **Brain-derived Neurotrophic Factor (BDNF):** BDNF supports neuronal survival, growth, and plasticity. Strategies to enhance BDNF signaling, including gene therapy and small-molecule agonists, are being explored for their potential to counteract excitotoxicity and promote neuroprotection.
- **GDNF and Neurturin:** Glial cell line-derived neurotrophic factor (GDNF) and neurturin are neurotrophic factors with potential therapeutic benefits in PD. Clinical trials are investigating their ability to support dopaminergic neurons and improve motor function.[12]

Emerging Therapies

- **Gene Therapy:** Gene therapy approaches aim to deliver protective genes, such as those encoding for glutamate transporters or neurotrophic factors, directly to affected neurons. Early-phase clinical trials are underway to assess the feasibility and safety of these approaches in neurodegenerative diseases.
- **Stem Cell Therapy:** Stem cell-based therapies seek to replace lost neurons and support the regeneration of damaged neural circuits. Preclinical studies have shown promise, and clinical trials are ongoing to evaluate their therapeutic potential in conditions like PD, ALS, and MS.
- **CRISPR-Cas9:** CRISPR-Cas9 gene editing technology offers the potential to correct genetic mutations underlying neurodegenerative diseases. Research is still in the early stages, focusing on developing safe and effective delivery methods.[6,7]

Conclusion

Glutamate-induced excitotoxicity is a common pathological mechanism in several neurodegenerative diseases. Understanding the precise molecular events that drive excitotoxicity and its role in disease progression is crucial for developing effective therapies. Current research is focused on targeting various aspects of excitotoxicity, from receptor modulation to oxidative stress reduction, to mitigate neuronal damage and slow disease progression. Continued advancements in this field hold promise for improving outcomes for individuals affected by these debilitating conditions.

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