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Toxic Synapses: Mechanisms of Neurotoxicity and Disrupted Neuromodulation in CNS Disorders

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ABSTRACT

Synapses are the fundamental units of neuronal communication, supporting cognitive, motor, and behavioral functions. However, in the context of central nervous system (CNS) disorders, synapses can become pathological entities—referred to as "toxic synapses"—that actively contribute to disease initiation and progression. Toxic synapses are characterized by disrupted neurotransmission, altered receptor activity, impaired synaptic plasticity, and pathological signaling, ultimately leading to neuronal dysfunction and death. Mechanisms driving synaptic toxicity include excitotoxicity, oxidative stress, mitochondrial dysfunction, aberrant protein aggregation, and chronic neuroinflammation. These pathological processes converge to compromise synaptic integrity and disrupt neuromodulatory systems involving acetylcholine, dopamine, serotonin, and other critical neurotransmitters. Disrupted neuromodulation exacerbates cognitive decline, emotional dysregulation, and motor impairments, hallmarks of diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis. Importantly, synaptic dysfunction often precedes overt neuronal loss, highlighting toxic synapses as early therapeutic targets. This review synthesizes current understanding of the mechanisms underlying toxic synapse formation and explores how impaired neuromodulation contributes to CNS pathology. Emerging therapeutic strategies aiming to restore synaptic health through antioxidative, anti-inflammatory, and neurotrophic interventions are also discussed. A deeper understanding of toxic synapse biology offers promising avenues for novel interventions that could halt or even reverse neurodegenerative and neuroinflammatory disease progression.

Keywords: Toxic synapses; Neurotoxicity; Neuromodulation; CNS disorders; Synaptic dysfunction

INTRODUCTION

The synapse is the fundamental unit of neural connectivity, allowing information transfer across neurons and maintaining the functional integrity of brain circuits [1]. In healthy brains, synapses adapt to experiences through synaptic plasticity, which underlies learning, memory, and behavior [2]. However, accumulating evidence shows that in numerous CNS disorders, synapses do not merely become dysfunctional but actively contribute to disease pathology [3]. These dysfunctional synapses, often termed "toxic synapses," represent a critical early event that precedes overt neuronal death. Toxic synapses are characterized by aberrant neurotransmitter release, impaired receptor activity, disrupted synaptic architecture, and pathological intracellular signaling [4]. They foster a vicious cycle of excitotoxicity, oxidative stress, and neuroinflammation, ultimately leading to neuronal damage and network collapse. Importantly, synaptic dysfunction disrupts neuromodulatory systems, impairing the brain's ability to regulate cognitive, motor, and emotional processes [5] Understanding the mechanisms behind synaptic toxicity and its effect on neuromodulation is crucial for developing targeted therapeutic strategies. This review delves into the biological underpinnings of toxic synapses, their contribution to CNS disorders, and potential interventions to restore synaptic health.

Mechanisms of Synaptic Neurotoxicity

Synaptic integrity is crucial for healthy brain function. When this integrity is compromised by pathological processes, synapses become dysfunctional and contribute directly to neuronal injury, a phenomenon increasingly recognized as "synaptic neurotoxicity [6]." Multiple overlapping mechanisms drive this pathological transformation.

Excitotoxicity

Excitotoxicity remains one of the most studied drivers of synaptic damage. Excessive stimulation of glutamate receptors, especially N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leads to a harmful influx of calcium ions into neurons [7]. High intracellular calcium triggers activation of proteases, lipases, and endonucleases, promoting oxidative stress, mitochondrial dysfunction, and cytoskeletal degradation [8]. At the synapse, excitotoxicity disrupts vesicle release mechanisms, impairs receptor recycling, and eventually dismantles the synaptic structure [9].

Oxidative Stress and Mitochondrial Dysfunction

Synapses are highly energy-dependent, requiring constant mitochondrial ATP production for vesicle cycling, ion homeostasis, and receptor function [10]. Reactive oxygen species (ROS) generated during mitochondrial respiration are normally balanced by antioxidant defenses. However, under pathological conditions, excessive ROS production overwhelms these defenses, damaging lipids, proteins, and nucleic acids within the synapse [11]. Mitochondrial damage exacerbates calcium dysregulation and amplifies excitotoxicity, setting a vicious cycle that culminates in synaptic collapse [12].

Proteinopathies and Synaptic Collapse

In neurodegenerative diseases, toxic protein aggregates accumulate at synaptic terminals, disrupting normal function. Amyloid-β oligomers in Alzheimer's disease bind preferentially to synaptic membranes, impairing NMDA receptor signaling and promoting internalization of postsynaptic density proteins [13]. Similarly, tau pathology interferes with microtubule-dependent transport of synaptic vesicles and mitochondria [14]. In Parkinson's disease, α-synuclein aggregates at presynaptic terminals disrupt dopamine release and vesicle recycling, contributing to early synaptic deficits [15].

Neuroinflammation and Synaptic Stripping

Microglial and astrocytic activation in response to CNS injury or disease leads to synaptic elimination. Activated microglia secrete complement proteins (e.g., C1q, C3) that tag synapses for phagocytosis [16]. Astrocytes contribute by releasing inflammatory cytokines that destabilize synaptic structures [17]. Although synaptic pruning is normal during development, excessive stripping during disease results in widespread loss of functional synapses, contributing to cognitive and motor impairments.

Disruption of Neuromodulation in Toxic Synapses

Neuromodulators such as acetylcholine, dopamine, serotonin, and noradrenaline fine-tune synaptic plasticity, network excitability, and behavioral outputs [18]. Toxic synapses severely disrupt these neuromodulatory systems, creating cascading deficits across cognitive, emotional, and motor domains.

Cholinergic Dysfunction

The cholinergic system, crucial for attention, memory, and learning, is severely impacted by toxic synapse formation [19]. In Alzheimer's disease, basal forebrain cholinergic neurons degenerate, leading to reduced cortical and hippocampal acetylcholine levels [19]. Amyloid-β and tau pathology at cholinergic synapses diminish receptor expression and impairs postsynaptic signaling, further compounding cognitive decline [20].

Dopaminergic Disruption

In Parkinson's disease, toxic α-synuclein aggregates interfere with dopamine storage and release at nigrostriatal synapses [21]. Reduced dopamine availability at synapses impairs motor coordination and induces non-motor symptoms such as mood disturbances and cognitive impairment [22]. Toxic synapses also affect dopaminergic neuromodulation in cortical and limbic areas, broadening the symptom profile of PD [23].

Serotonergic and Noradrenergic Alterations

Neuroinflammation-driven changes in serotonergic and noradrenergic systems are increasingly recognized in multiple CNS disorders [24]. Cytokines such as IL-1β and TNF-α alter serotonin synthesis, release, and reuptake, contributing to depression-like symptoms often seen in AD and MS. Noradrenergic dysfunction exacerbates attention deficits and emotional instability [25]. Overall, the disruption of neuromodulation by toxic synapses results not only in loss of precise neuronal communication but also in network-wide dysregulation, amplifying disease pathology across multiple functional domains.

Toxic Synapses in CNS Disorders

Synaptic toxicity is now recognized as a central event in the pathology of many CNS diseases, often preceding and predicting neuronal death and clinical symptom onset.

Alzheimer's Disease (AD)

In AD, synaptic dysfunction correlates more strongly with cognitive decline than amyloid plaque burden or neuronal loss [26]. Soluble amyloid-β oligomers localize preferentially to synapses, impairing synaptic transmission by altering NMDA receptor activity and triggering calcium dysregulation [27]. Tau pathology exacerbates this process by disrupting microtubule stability necessary for synaptic transport [28]. Early synaptic loss, especially in the hippocampus and cortex, is a key driver of memory deficits [29].

Parkinson's Disease (PD)

Parkinson's disease is marked by early synaptic deficits in dopaminergic neurons projecting to the striatum [30]. Before the appearance of motor symptoms, synaptic dysfunction, driven by α-synuclein aggregation, impairs dopamine release and receptor responsiveness [31]. Synaptic pathology also extends to cortical and limbic circuits, contributing to cognitive impairment, depression, and executive dysfunction [32].

Multiple Sclerosis (MS)

In MS, synaptic damage results from chronic neuroinflammation even in the absence of active demyelination [33]. Activated microglia and astrocytes release glutamate excessively, causing excitotoxic synaptic injury [34]. Complement-mediated synaptic pruning leads to synapse loss in gray matter regions, contributing to cognitive decline, fatigue, and depression seen in MS patients [33].

In each of these conditions, toxic synapses are not merely a consequence but a key pathogenic driver, underscoring the urgent need to develop therapies that preserve synaptic health and restore normal neuromodulation.

Therapeutic Strategies Targeting Toxic Synapses

Targeting toxic synapses offers a promising avenue for mitigating neurodegeneration and restoring neuronal network function. Several therapeutic strategies are currently under investigation. NMDA receptor modulators, such as memantine, aim to prevent excitotoxic damage without impairing physiological synaptic activity [35]. Antioxidants, including edaravone and coenzyme Q10, help reduce oxidative stress and preserve mitochondrial function at synaptic sites [36]. Anti-inflammatory agents like minocycline and complement inhibitors target microglia-mediated synaptic stripping, preserving synaptic connectivity [37]. Synaptic repair therapies, such as brain-derived neurotrophic factor (BDNF) enhancers, aim to promote synaptic plasticity and resilience [38]. Additionally, neuromodulator-based therapies, including cholinesterase inhibitors and dopamine agonists, work to restore disrupted neurotransmission in affected networks [39]. Emerging approaches like gene therapy, nanocarrier-mediated drug delivery, and personalized medicine based on synaptic biomarkers are poised to revolutionize the treatment landscape. Together, these strategies highlight the critical need to prioritize synaptic health in the management of central nervous system disorders.

CONCLUSION

Toxic synapses represent a central hub linking various pathological processes in CNS disorders. Understanding the mechanisms of synaptic toxicity and its impact on neuromodulation opens new avenues for therapeutic interventions. Targeting synaptic resilience and restoring normal neuromodulatory signaling offer promising strategies to halt or reverse the progression of neurodegenerative and neuroinflammatory diseases.

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