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IMPORTANCE OF EXCITOTOXICITY IN STRESS: A MINI REVIEW

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Abstract
Excitotoxicity refers to the process where nerve cells are damaged or killed due to excessive stimulation by neurotransmitters, primarily glutamate. This overactivation of receptors, such as NMDA (N-methyl-D-aspartate) receptors, causes an influx of calcium ions into the neurons, leading to cell damage or death. It is a key factor in various neurodegenerative diseases and acute neurological conditions like stroke and traumatic brain injury. Many researchers suggested that chronic stress can exacerbate excitotoxicity by increasing the release of glutamate in the brain. There are numerous factors play extremely important roles in many endorsing the excitotoxicity are increased glutamate levels, vulnerability of the neurones and neuro-degeneration in the diseases like Parkinsons. Several protective measures are obtained by the review of many researches. Effective stress management, including mindfulness, exercise, and therapy, can help regulate glutamate levels and reduce the risk of excitotoxicity.Enhancing antioxidant defences through diet or supplementation may protect neurons from the oxidative stress induced by excitotoxicity.Drugs that block NMDA receptors or regulate glutamate activity are being explored as treatments for conditions associated with excitotoxicity.

Key Words: *Excitotoxicity, Parkinson, Neuro degeneration, stress, NMDA*

1. Introduction:

Excitotoxicity is a process where neurons are damaged and killed by excessive stimulation by neurotransmitters, particularly glutamate. When there's an overabundance of glutamate in the synaptic cleft, it can lead to overactivation of glutamate receptors. This excessive stimulation causes an influx of calcium ions into the neurons, triggering a cascade of events that can result in cell damage and death. Excitotoxicity is implicated in various neurological disorders, such as stroke, Alzheimer's disease, and multiple sclerosis. The phenomenon highlights the delicate balance that the brain maintains between neurotransmission and neuroprotection (1).

Excitotoxicity can arise from several factors, including (2):

1. Ischemia: Reduced blood flow (e.g., during a stroke) leads to energy failure, causing cells to release excess glutamate.
2. Trauma: Brain injuries can cause cell damage and disrupt normal neurotransmitter levels, increasing glutamate release.
3. Neurodegenerative Diseases: Conditions like Alzheimer's, Parkinson's, and Huntington's disease often involve chronic excitotoxicity due to neuronal degeneration and imbalanced neurotransmitter signalling.
4. Seizures: Epileptic activity can lead to high levels of glutamate, promoting excitotoxic effects on neurons.
5. Toxic Exposure: Certain substances, such as heavy metals and some drugs, can disrupt glutamate signalling and lead to excitotoxicity.
6. Inflammation: Neuroinflammatory responses can increase the release of glutamate and reduce its reuptake, contributing to excitotoxic conditions.
7. Metabolic Disorders: Conditions like diabetes can alter energy metabolism in neurons, increasing vulnerability to excitotoxic damage.

2. Literature Review:

Multiple researches suggested that there are many reasons well established to make remarkable evidences proving excitotoxicity amongst the individuals, which are as follows (3); overstimulation of glutamate receptors, leading to a series of physiological mechanisms for example; few evidences suggest that, overactivation of glutamate receptors lead to excess glutamate binding to its receptors (primarily NMDA and AMPA receptors), causing prolonged depolarization of the postsynaptic neuron (4). Other researches suggested that activation of calcium receptors allows excessive calcium ions (Ca^{2+}) to flow into the neuron. Calcium is a crucial signalling molecule, but too much of it can be toxic (5). Other researches, showed elevated intracellular calcium levels activate various enzymatic pathways, including: (a) **Phospholipase A2:** This can lead to the release of arachidonic acid, promoting inflammation and further damaging cell membranes. (b) **Nitric Oxide Synthase:** Excess calcium can activate this enzyme, resulting in increased production of nitric oxide, which can cause oxidative stress (6).Numerous evidences also show that, high levels of calcium can overwhelm mitochondria, impairing their ability to produce ATP and leading to energy deficits (7). Mitochondrial dysfunction also increases the production of reactive oxygen species (ROS), which can damage cellular components (8). Activation of numerous cell death pathways initiate combination of oxidative stress, inflammation, and energy failure can trigger apoptotic (programmed cell death) and necrotic pathways, leading to irreversible neuron damage (9).Under normal conditions, glial cells (like astrocytes) help recycle glutamate. In excitotoxic scenarios, the ability of these cells to uptake and clear glutamate may be compromised, exacerbating the problem (10). These mechanisms collectively contribute to neuronal injury and death, highlighting the importance of tightly regulating glutamate levels and receptor activity in the brain (11). It has been already researched and established that excitotoxicity refers to the process by which excessive activation of glutamate receptors leads to neuronal damage and cell death (12). This can occur due to a variety of factors, including:**Ischemia** (lack of blood flow), **Traumatic brain injury, Neuro-degenerative diseases** (like Alzheimer's and Parkinson's), **Chronic stress etc.** When neurons are exposed to high levels of glutamate, they can become overstimulated, leading to increased intracellular calcium levels, oxidative stress, and ultimately cell death (13). This process is often associated with inflammation and the activation of apoptotic pathways.

3. Discussions and Observations

3.1 Stress exacerbating excitotoxicity

Whereas, stress can be defined as, particularly chronic stress, can exacerbate excitotoxicity through several mechanisms (14, 15):

- **Hormonal Changes**: Stress increases levels of cortisol and other stress hormones, which can affect neuronal health and synaptic plasticity.
- **Inflammation**: Chronic stress can lead to increased inflammatory markers, which can further promote excitotoxicity.
- **Glutamate Release**: Stress can alter glutamate dynamics, potentially leading to heightened levels of this neurotransmitter in synaptic clefts.
- **Energy Metabolism**: Stress impacts the brain's energy metabolism, which can compromise neuronal survival during excitotoxic events.

Stress can have complex effects on the body, and while the parasympathetic nervous system (PNS) is generally responsible for promoting relaxation and recovery, chronic stress can lead to dysfunction in this system (16). Here are some research-based evidences present in which it has been showed that chronic stress as well as acute stress both give extreme effects upon the central nervous system in all sensory and motor paths (17). In many researches it has been showed that,the body's stress response activates the sympathetic nervous system (SNS), which can overshadow the PNS.Prolonged activation of the SNS can lead to decreased PNS activity, making it harder to relax and recover (16). It has a potential role creating Impact on Heart Rate Variability (HRV). A healthy PNS contributes to high HRV, indicating good adaptability and resilience to stress.Chronic stress can lower HRV, suggesting reduced parasympathetic activity and poorer recovery (17). Many stresses induced abnormalities are evident in many researches that can be manifest as digestive issues (e.g., IBS), sleep disturbances, and chronic pain, often linked to impaired parasympathetic function. Even the body may struggle to maintain homeostasis due to this imbalance (18, 19). Even the mental health can be compromised due to elevated levels of stress with holding reduced parasympathetic activity which can contribute to anxiety and depression, further perpetuating the cycle of stress and dysfunction.A weakened PNS might hinder emotional regulation and resilience (20). The lifestyle factors like- poor sleep, unhealthy eating, and lack of physical activity can exacerbate the effects of stress on the Peripheral Nervous System (PNS).Techniques like mindfulness, deep breathing, and regular exercise can help restore balance (21). Drug & therapy induced evidences are very prominent on this note with multiple approaches like, stress management techniques, such as yoga, meditation, and biofeedback, can enhance PNS function.Professional support from therapists or counsellors can also be beneficial for managing chronic stress (22, 23).If you're experiencing significant stress, consider exploring relaxation techniques or speaking with a healthcare professional for tailored advice. Excitotoxicity and neurodegeneration are closely related concepts, particularly in the context of neurodegenerative diseases (24). Here's an overview of each and their interplay: under normal conditions, glutamate is crucial for synaptic transmission and plasticity.Excessive glutamate release or impaired reuptake can lead to overactivation of glutamate receptors [(e.g., *N*-methyl-*D*-aspartic acid (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)] (25).This overactivation causes a cascade of intracellular events, including excessive calcium influx, oxidative stress (26).

3.2 Excitotoxicity and neurodegenerative disorders

Neurodegenerative disorders are considered to be the heterogenous set of disorders amongst all the population. The distinct disorders show variety of clinical phenotypes and genotypes (26). The excitotoxicity based neurological disorders are basically based upon the elderly population rather the geriatric subjects. The cases which give emphasis upon the roles of excitatory neurotransmitters within the cerebral cortex and the hippocampal region relating many diseases by induced forgetfulness (27). The regulatory releases of excitatory amino acids lead to contribute to variety of clinical aspects like schizophrenia, progressive dementia and many other neuropsychiatric syndromes etc. (28). The excitotoxicity mainly effects upon glutaminergic neurons. Under the basic physiological conditions, the glutamate effects upon altering the activity of the cationic channels regulating the excitatory response. The hypothesis derived from various researches show that the classical or traditional pathways of glutamic acid eccentric activities include *N*-methyl-*D*-aspartic acid (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and kainic acid (KA) receptors (29). At first the NMDA receptors induce calcium ion activities, in excess of it leads to nerve injuries. Many researches showed that Huntington's disease is a clinical condition elevate the expressions of NMDA receptor followed by voltage calcium ion channels (30). Even the same cascade-based alterations are observed within the non-human rodents. The increased catabolic activities of calcium ions lead to activate apoptosis followed by necrosis (31). On the other hand, the AMPA receptor alteration in exhibiting calcium ion activity leads to arise hypoxic-ischemic conditions amongst the individuals. Though the scientific evaluations can be also seen for the Parkinson's and Alzheimer's disease (32, 33).

4. Conclusion

Many researches based upon stress induced by excitotoxicity have shown many evidences which found instrumental in increasing oxidative stress. Whereas, extensive experimentation may open newer findings in importance of excitotoxicity induced by stress.

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