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EDITORIAL

Unmasking Excitotoxicity—A Double-Edged Sword in Neuro-degeneration

Excitotoxicity, a term first coined in the 1960s by Dr. John Olney, represents one of the most paradoxical mechanisms in neuroscience: the same excitatory neurotransmission that sustains life and cognition can, when dysregulated, lead to neuronal death. This phenomenon, marked by excessive stimulation of glutamate receptors—especially NMDA and AMPA receptors—has been implicated in a variety of neurological disorders, ranging from acute insults like stroke and traumatic brain injury to chronic conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (1,2).

At the heart of excitotoxicity lies glutamate, the principal excitatory neurotransmitter in the central nervous system (CNS). Under physiological conditions, glutamate binds to ionotropic and metabotropic receptors, modulating synaptic transmission and plasticity. However, during pathological states—such as ischemia or energy failure—extracellular glutamate accumulates due to impaired uptake by astrocytes or uncontrolled release from neurons. This surplus leads to prolonged receptor activation, excessive Ca^{2+} influx, mitochondrial dysfunction, oxidative stress, and ultimately, apoptosis or necrosis (3).

One of the most well-characterized excitotoxic cascades is observed in ischemic stroke. When cerebral blood flow is compromised, ATP depletion impairs ion pumps, leading to neuronal depolarization and massive glutamate release. This uncontrolled excitation results in neuronal swelling, free radical generation, and activation of degradative enzymes—all hallmarks of excitotoxic injury (4).

Despite the well-established role of excitotoxicity in disease pathophysiology, translating this knowledge into effective clinical interventions has proven difficult. Numerous glutamate receptor antagonists have failed in clinical trials due to issues of toxicity or limited efficacy. For instance, NMDA antagonists like memantine have shown modest benefits in Alzheimer's disease, but broader application has been constrained by neuropsychiatric side effects (5).

Nevertheless, recent advances offer renewed hope. Targeting downstream signaling pathways, enhancing glutamate uptake through astrocytic transporters, and modulating receptor subtypes more selectively are emerging strategies. Furthermore, the role of glial cells and neuroinflammation in modulating excitotoxicity has gained attention, suggesting that a more holistic view of the neurovascular unit may be necessary to devise successful therapies (6).

Excitotoxicity remains a compelling illustration of how a fundamental physiological process, when misregulated, becomes pathogenic. Continued research is essential to unravel its complexity and to design targeted interventions that preserve neuronal integrity without compromising essential synaptic function.

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Dr. Mahadi Abdur Rouf; MBBS, MD
Associate Professor, Department of Physiology
Ad-din Akij Medical College, Khulna
Bangladesh.
email: ma_rouf@addinmedical.org

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