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Deciphering Neurodegeneration: Biochemical Pathways and Investigative Approaches in Neurological Disorders

Dhalvinder Raj

Research Scholar, Department of Bio-Chemistry, P.K University, Shivpuri, M.P., India.

ABSTRACT

Neurodegenerative disorders encompass a heterogeneous group of conditions characterized by the progressive loss of neuronal structure and function, leading to cognitive, behavioral, and motor deficits. Despite extensive research, the etiologies of these disorders remain incompletely understood, reflecting the complexity of their biochemical and cellular underpinnings. This review aims to decipher the biochemical pathways involved in neurodegeneration and explore contemporary investigative approaches that enhance our understanding of neurological disorders.

The biochemical basis of neurodegeneration involves a convergence of pathogenic mechanisms, including oxidative stress, mitochondrial dysfunction, excitotoxicity, protein misfolding, and impaired neuronal signaling. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) generation and antioxidant defenses, leading to lipid peroxidation, DNA damage, and protein oxidation. Mitochondrial defects exacerbate these effects by diminishing ATP availability and promoting apoptotic signaling. Excitotoxicity, driven by excessive glutamate receptor activation, further compounds neuronal vulnerability, particularly in regions critical for cognition and motor control.

Protein aggregation remains a central feature of many neurological disorders. Misfolded proteins, including amyloid-beta, tau, alpha-synuclein, and mutant huntingtin, form insoluble aggregates that disrupt synaptic connectivity and impair intracellular transport. These aggregates also trigger inflammatory responses mediated by activated microglia and astrocytes, establishing a feedback loop that accelerates neuronal degeneration. Dysregulated signaling networks, including PI3K/Akt, mTOR, and MAPK pathways, integrate metabolic stress, protein homeostasis, and inflammatory cues, influencing the trajectory of neurodegenerative processes.

Investigative approaches leveraging biochemical, molecular, and imaging techniques have advanced our understanding of these pathways. Proteomics and metabolomics provide comprehensive maps of protein and metabolite alterations associated with disease states, while advanced imaging modalities, such as PET and MRI spectroscopy, enable in vivo assessment of neuronal integrity and metabolic dysfunction. Genetic and transcriptomic analyses identify disease-linked mutations and expression patterns, elucidating the interplay between genetic predisposition and biochemical dysregulation. Furthermore, in vitro and in vivo models, including induced pluripotent stem cells (iPSCs) and transgenic animals, facilitate the study of mechanistic pathways and therapeutic interventions in a controlled setting.

Therapeutic development increasingly targets these biochemical pathways. Approaches include small molecules and biologics that inhibit protein aggregation, antioxidants that neutralize ROS, modulators of mitochondrial function, and anti-inflammatory agents that reduce neurotoxic glial activation. Personalized medicine strategies, informed by molecular profiling, offer the potential for more effective and tailored interventions.