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NEUROINFLAMMATION AND OXIDATIVE STRESS IN PARKINSON'S DISEASE PATHOGENESIS

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta. Increasing evidence suggests that neuroinflammation and oxidative stress play central roles in the pathogenesis and progression of the disease. Chronic activation of microglia, elevated production of pro-inflammatory cytokines, mitochondrial dysfunction, and excessive reactive oxygen species (ROS) contribute to neuronal damage and alpha-synuclein aggregation. This article reviews the molecular mechanisms linking neuroinflammation and oxidative stress in Parkinson's disease and discusses their potential as therapeutic targets. Understanding these interconnected pathways may provide new opportunities for disease-modifying strategies.

Keywords: Parkinson's disease, neuroinflammation, oxidative stress, microglia, reactive oxygen species, alpha-synuclein, mitochondrial dysfunction.

Introduction

Parkinson's disease is the second most common neurodegenerative disorder worldwide and primarily affects individuals over the age of 60. The hallmark pathological features include the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of intracellular inclusions known as Lewy bodies, mainly composed of misfolded alpha-synuclein protein.

Although the precise cause of Parkinson's disease remains unclear, accumulating research indicates that neuroinflammation and oxidative stress are critical contributors to neuronal degeneration. These processes are closely interconnected and may create a self-perpetuating cycle that accelerates disease progression. Understanding the role of these mechanisms is essential for developing targeted therapeutic interventions.

Methods

This article is based on a narrative review of peer-reviewed scientific literature focusing on molecular and cellular mechanisms underlying Parkinson's disease. Studies examining inflammatory pathways, oxidative damage, mitochondrial dysfunction, and their interaction in experimental models and clinical observations were analyzed to synthesize current knowledge on disease pathogenesis.

Results

Neuroinflammation refers to the activation of the brain's innate immune system, primarily mediated by microglia and astrocytes. In Parkinson's disease, activated microglia release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β),

and interleukin-6 (IL-6). Elevated levels of these inflammatory mediators have been detected in the brains and cerebrospinal fluid of patients with Parkinson's disease.

Chronic microglial activation contributes to neuronal injury by producing nitric oxide (NO), reactive oxygen species (ROS), and other cytotoxic factors. Furthermore, aggregated alpha-synuclein can stimulate microglial activation, amplifying inflammatory responses. This creates a feedback loop in which inflammation promotes protein aggregation and neuronal damage, which in turn enhances inflammation.

Peripheral immune cells may also contribute to neuroinflammation by infiltrating the central nervous system under conditions of blood-brain barrier dysfunction, further exacerbating neuronal injury.

Oxidative stress occurs when the production of reactive oxygen species exceeds the capacity of antioxidant defense systems. Dopaminergic neurons are particularly vulnerable to oxidative damage due to dopamine metabolism, which naturally generates reactive intermediates.

Mitochondrial dysfunction is a major source of oxidative stress in Parkinson's disease. Impairment of mitochondrial complex I has been consistently observed in patients, leading to reduced ATP production and increased ROS generation. Excessive ROS can damage cellular components, including lipids, proteins, and DNA, ultimately triggering apoptosis.

Reduced levels of endogenous antioxidants, such as glutathione, have also been reported in the substantia nigra of Parkinson's patients, further increasing vulnerability to oxidative damage.

Neuroinflammation and oxidative stress are closely interconnected processes. Activated microglia generate reactive oxygen and nitrogen species, intensifying oxidative stress. Conversely, oxidative damage can activate inflammatory signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway, promoting cytokine production.

Alpha-synuclein aggregation appears to be both a consequence and a driver of these processes. Oxidative stress enhances alpha-synuclein misfolding, while aggregated alpha-synuclein activates microglia and inflammatory cascades. This bidirectional interaction contributes to progressive neuronal degeneration.

Discussion

The evidence suggests that neuroinflammation and oxidative stress are not merely secondary events but active contributors to Parkinson's disease pathogenesis. Their interaction forms a vicious cycle that accelerates dopaminergic neuron loss.

Targeting these mechanisms represents a promising therapeutic strategy. Anti-inflammatory agents, antioxidants, mitochondrial protective compounds, and inhibitors of microglial activation have shown beneficial effects in experimental models. However, clinical trials have produced mixed results, highlighting the complexity of disease mechanisms and the need for early intervention.

Emerging therapies aim to modulate immune responses, enhance antioxidant defenses, and prevent alpha-synuclein aggregation. Gene therapy and stem cell approaches may also offer future solutions by restoring neuronal function and reducing pathological processes.

A major challenge remains identifying reliable biomarkers to detect neuroinflammation and oxidative stress at early disease stages. Early detection may improve the effectiveness of disease-modifying therapies.

Conclusion

Neuroinflammation and oxidative stress play central and interconnected roles in the pathogenesis of Parkinson's disease. Chronic microglial activation, mitochondrial dysfunction, excessive ROS production, and alpha-synuclein aggregation collectively contribute to progressive dopaminergic neuron degeneration.

Understanding these molecular pathways provides valuable insight into potential therapeutic targets. Although current treatments primarily address symptoms, future strategies focusing on reducing inflammation and oxidative damage may slow or prevent disease progression. Continued research into these mechanisms is essential for developing effective disease-modifying interventions.

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