Innovations in Pharmacy Planet (iP-Planet)
eISSN: 2348 – 7275

Review

Advances in Pharmacotherapy for Neurodegenerative Disorders: From Mechanisms to Clinical Trials

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Abstract

Neurodegenerative disorders (NDs), such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis, are progressive conditions with complex pathophysiology involving protein aggregation, oxidative stress, neuroinflammation, and mitochondrial dysfunction. Current pharmacotherapies primarily offer symptomatic relief, with limited success in modifying disease progression. However, recent advances have introduced promising strategies, including neuroprotective agents, immunomodulatory therapies, gene and RNA-based interventions, and small-molecule inhibitors targeting protein misfolding. AI-driven drug discovery is revolutionizing therapeutic development, while biomarker-guided precision medicine enhances patient stratification and treatment efficacy. Additionally, advancements in stem

cell-based therapies and regenerative medicine offer new hope for restoring neuronal function and slowing disease progression. Innovative clinical trial designs, such as adaptive and biomarker-based approaches, are improving the evaluation of novel therapies, increasing their likelihood of clinical success. Despite these advancements, challenges such as blood-brain barrier limitations, drug resistance, patient heterogeneity, and lengthy trial durations continue to hinder progress. Further, the high costs of drug development and regulatory complexities present additional obstacles to bringing novel therapies to market. Future research must focus on overcoming these barriers through multi-omics integration, personalized medicine, AI-driven analytics, and advanced drug delivery systems to develop effective disease-modifying treatments, enhance therapeutic accessibility, and improve long-term patient outcomes.

Keywords: Neurodegenerative disorders, Pharmacotherapy, Gene therapy, Biomarkers, Drug discovery

Introduction

Neurodegenerative disorders (NDs) are a group of progressive, debilitating conditions characterized by the gradual loss of neuronal function, ultimately leading to cognitive, motor, and autonomic dysfunction. These disorders, which include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS), pose significant challenges to global healthcare systems due to their increasing prevalence, lack of curative treatments, and high socioeconomic burden.[1]

With the rise in aging populations, the incidence of NDs has escalated, placing immense pressure on healthcare infrastructure and caregivers. Despite decades of research, effective disease-modifying therapies remain limited, and most available treatments primarily focus on symptom management rather than halting or reversing disease progression. The complexity of these disorders, involving multiple pathological mechanisms such as protein misfolding, neuroinflammation, mitochondrial dysfunction, and synaptic loss, further complicates the development of effective pharmacotherapies.[2]

Recent advancements in pharmacotherapy have focused on targeting the underlying mechanisms of neurodegeneration rather than merely alleviating symptoms. Novel therapeutic approaches, including monoclonal antibodies, gene therapies, neuroprotective agents, and small molecules, are now being explored with promising outcomes. The transition from bench to bedside, facilitated by

rigorous preclinical research and clinical trials, is paving the way for innovative treatments with potential disease-modifying effects. This review aims to provide a comprehensive overview of the latest advances in pharmacotherapy for neurodegenerative disorders, exploring the mechanisms of action and their translation into clinical applications.[3]

Pathophysiology and Mechanisms of Neurodegeneration

Neurodegenerative disorders (NDs) share several common pathological mechanisms, yet each condition has distinct molecular and cellular processes that drive disease progression. Understanding these mechanisms is crucial for developing targeted pharmacotherapies that can effectively modify disease outcomes.

One of the key mechanisms in neurodegeneration is protein aggregation and misfolding**,** where abnormal proteins accumulate and disrupt cellular homeostasis. In Alzheimer's disease (AD), amyloid-beta (Aβ) and tau aggregates form extracellular plaques and intracellular tangles, respectively, triggering neurotoxicity. In Parkinson's disease (PD), α-synuclein aggregates form Lewy bodies, contributing to dopaminergic neuron loss. Similar pathological inclusions of proteins such as SOD1, TDP-43, and mutant huntingtin (mHTT) are implicated in amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD).[4]

Oxidative stress and mitochondrial dysfunction play a crucial role in neurodegeneration. Neurons, due to their high metabolic activity, are vulnerable to oxidative damage. Excessive reactive oxygen species (ROS) impair mitochondrial function, leading to ATP depletion and neuronal apoptosis. In diseases like AD, PD, and ALS, mutations in genes such as PINK1 and PARKIN contribute to mitochondrial dysfunction, accelerating disease progression.

Chronic neuroinflammation, driven by activated microglia and astrocytes, leads to the release of pro-inflammatory cytokines that exacerbate neuronal injury. This immune response is especially pronounced in multiple sclerosis (MS), where persistent inflammation results in demyelination and neuronal damage. Additionally, excitotoxicity, caused by excessive glutamate release and NMDA receptor overactivation, leads to calcium influx and neuronal death, particularly in ALS and HD. Synaptic dysfunction and neuronal loss further contribute to cognitive and motor impairments across various NDs, disrupting communication between neurons and impairing overall brain function.[5]

Disease-Specific Mechanisms of Neurodegeneration

While these shared mechanisms contribute to the pathology of multiple disorders, each ND has distinct molecular and cellular features that define its progression:

A. Alzheimer's Disease (AD)

Alzheimer's disease is the leading cause of dementia, characterized by progressive cognitive decline and widespread neuronal loss. One of the major pathological hallmarks of AD is the accumulation of amyloid-beta (Aβ) plaques, which result from the abnormal cleavage of amyloid precursor protein (APP). These plaques disrupt neuronal communication and trigger inflammatory responses that exacerbate neuronal damage. Another key feature is the formation of tau neurofibrillary tangles, where hyperphosphorylated tau proteins destabilize microtubules, leading to impaired axonal transport and neuronal death. Additionally, a significant loss of cholinergic neurons in the basal forebrain contributes to the cognitive deficits observed in AD. Chronic neuroinflammation and oxidative stress further accelerate disease progression, highlighting the multifaceted nature of neurodegeneration in Alzheimer's disease.[6]

B. Parkinson's Disease (PD)

Parkinson's disease is primarily a movement disorder caused by the progressive degeneration of dopaminergic neurons in the substantia nigra. The loss of these neurons leads to a deficiency in dopamine, which manifests as hallmark symptoms such as bradykinesia, rigidity, and resting tremors. A major pathological characteristic of PD is the aggregation of misfolded α-synuclein proteins, forming intracellular inclusions known as Lewy bodies. These aggregates interfere with neuronal function and contribute to cell death. Mitochondrial dysfunction plays a significant role in PD pathogenesis, as mutations in genes such as PINK1 and PARKIN impair

mitochondrial quality control, leading to increased oxidative stress and neuronal apoptosis. Chronic neuroinflammation, driven by activated microglia and astrocytes, further exacerbates neurodegeneration, making it a key target for emerging therapeutic strategies.[7]

C. Amyotrophic Lateral Sclerosis (ALS)

ALS is a rapidly progressing neurodegenerative disorder affecting upper and lower motor neurons, leading to muscle weakness, paralysis, and eventual respiratory failure. One of the primary mechanisms implicated in ALS is oxidative stress, particularly due to mutations in the SOD1 gene, which result in toxic protein misfolding and increased reactive oxygen species (ROS) production. Another key contributor to neuronal damage in ALS is glutamate excitotoxicity, where impaired clearance of glutamate by astrocytes leads to excessive excitatory neurotransmission and neuronal injury. Additionally, the accumulation of RNA-binding proteins, such as TDP-43 and FUS, in motor neurons leads to toxic protein aggregates that disrupt normal cellular processes. The combination of these factors accelerates motor neuron degeneration and contributes to the progressive loss of motor function in ALS patients.[8]

D. Huntington's Disease (HD)

Huntington's disease is an inherited neurodegenerative disorder caused by an expansion of CAG repeats in the HTT gene, resulting in the production of mutant huntingtin protein (mHTT). This mutant protein forms toxic aggregates that interfere with cellular homeostasis and impair neuronal function. Excitotoxicity also plays a crucial role in HD, as disrupted glutamate uptake leads to excessive neuronal stimulation and early synaptic dysfunction. Mitochondrial dysfunction further exacerbates neurodegeneration by reducing ATP production and increasing oxidative stress, which is particularly detrimental to neurons in the striatum, the brain region most affected in HD. Over time, the cumulative effects of these pathological processes result in the progressive motor, cognitive, and psychiatric symptoms characteristic of Huntington's disease. [9]

E. Multiple Sclerosis (MS)

Multiple sclerosis is a chronic autoimmune disorder characterized by demyelination, neuroinflammation, and axonal degeneration. In MS, autoreactive T cells mistakenly target the myelin sheath surrounding neurons, leading to its destruction and impaired signal conduction. Persistent inflammation in the central nervous system results in the release of cytokines and other immune mediators that exacerbate neuronal injury. Over time, chronic demyelination leads to irreversible axonal degeneration, contributing to progressive disability in MS patients. The complex interplay between autoimmune processes, neuroinflammation, and neurodegeneration makes MS a highly heterogeneous disease, requiring multifaceted therapeutic approaches for effective management.[10]

Symptomatic vs. Disease-Modifying Treatments

Currently, pharmacological interventions for NDs fall into two broad categories: symptomatic treatments and disease-modifying treatments. Symptomatic treatments aim to alleviate clinical manifestations without significantly altering disease progression. For example, in AD, cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine temporarily enhance cholinergic function to improve cognition, but they do not prevent the underlying neurodegeneration. Similarly, Parkinson's disease (PD) treatments such as levodopa and dopamine agonists help manage motor symptoms but do not halt the progressive loss of dopaminergic neurons.

In contrast, disease-modifying treatments (DMTs) seek to slow or halt disease progression by targeting key pathological mechanisms. In AD, monoclonal antibodies such as aducanumab, lecanemab, and donanemab aim to clear amyloid-beta plaques, one of the hallmarks of the disease. In MS, immunomodulatory drugs such as interferon-β, fingolimod, natalizumab, and ocrelizumab work by suppressing autoimmune attacks on myelin, thereby reducing relapse rates and slowing disease progression. While these therapies represent important advancements, their overall effectiveness remains limited, and they often come with significant risks and side effects.[11]

FDA-Approved Drugs for Major Neurodegenerative Disorders and Their Mechanisms

For AD, the mainstay pharmacological approach has traditionally focused on enhancing cholinergic neurotransmission with cholinesterase inhibitors and reducing excitotoxicity with NMDA receptor antagonists such as memantine. More recently, the development of anti-amyloid monoclonal antibodies has shifted the therapeutic paradigm, although their clinical benefits remain a subject of debate.

In PD, levodopa remains the gold standard treatment, often used in combination with carbidopa to enhance its bioavailability. Dopamine agonists such as pramipexole and ropinirole provide additional symptom control, while MAO-B inhibitors (selegiline, rasagiline) and COMT inhibitors (entacapone, tolcapone) help extend dopamine activity. Despite these advancements, the progressive nature of PD leads to complications such as motor fluctuations and dyskinesia over time.

Amyotrophic lateral sclerosis (ALS) has very limited pharmacological options, with riluzole and edaravone being the only FDA-approved drugs. Riluzole works by reducing glutamate excitotoxicity, modestly prolonging survival, while edaravone acts as an antioxidant to combat oxidative stress. However, neither of these drugs significantly alter disease progression.

Huntington's disease (HD) treatments focus on managing symptoms rather than modifying the disease itself. Tetrabenazine and deutetrabenazine, which inhibit vesicular monoamine transporter 2 (VMAT2), help reduce involuntary movements, while antipsychotic drugs such as risperidone and olanzapine manage psychiatric symptoms. However, no currently available drugs can slow or stop the progression of neurodegeneration in HD**.**

In MS, a wide range of immunomodulatory therapies are available, including interferon-β, glatiramer acetate, fingolimod, and monoclonal antibodies such as natalizumab and ocrelizumab. These drugs help suppress immune-mediated demyelination, reducing relapse rates and delaying disability progression. Corticosteroids such as methylprednisolone are also used to manage acute exacerbations. While these treatments have significantly improved patient outcomes, they are often associated with immunosuppressive risks and other adverse effects.[12]

Recent Breakthroughs in Drug Discovery for Neurodegenerative Disorders

The past decade has witnessed substantial progress in drug discovery for NDs, driven by a deeper understanding of disease mechanisms and the development of innovative therapeutic strategies. Advances in high-throughput screening, artificial intelligence-driven drug design, and biomarker-guided approaches have facilitated the identification of novel drug candidates. Precision medicine approaches, which tailor treatments based on genetic and biomarker profiles, are increasingly being explored to enhance treatment efficacy and patient outcomes.

Targeting disease-specific molecular pathways has been a central focus in recent drug development efforts. For example, in Alzheimer's disease (AD), novel anti-amyloid therapies such as lecanemab and donanemab have demonstrated promising results in reducing amyloid burden, while tau-targeting therapies are also undergoing rigorous evaluation. In Parkinson's disease (PD), new dopamine replacement strategies, α-synuclein-targeting agents, and neurotrophic factor-based therapies are being explored. Similarly, in amyotrophic lateral sclerosis (ALS), emerging treatments aim to modify disease progression by targeting genetic mutations, excitotoxicity, and oxidative stress.[13]

Ongoing and Completed Clinical Trials for Novel Pharmacotherapies

The transition from preclinical research to clinical trials represents a critical step in drug development. Several novel pharmacotherapies for NDs are currently being evaluated in human studies, ranging from early-phase safety trials to large-scale efficacy trials.

In AD, monoclonal antibodies such as lecanemab and donanemab have shown significant amyloid clearance in phase III trials, although their clinical benefits remain a topic of debate. Other investigational agents targeting tau, neuroinflammation, and synaptic dysfunction are in various stages of clinical development.

PD drug trials have focused on both symptomatic and disease-modifying therapies. Ongoing studies are evaluating α-synuclein-targeting immunotherapies, gene therapy approaches, and dopamine neuron

regeneration strategies. Additionally, repurposed drugs, such as GLP-1 receptor agonists, are being tested for their potential neuroprotective effects.

In ALS, the FDA's approval of AMX0035 (a combination of sodium phenylbutyrate and taurursodiol) and the ongoing evaluation of gene-silencing therapies like tofersen represent major milestones in treatment development. Other experimental therapies, including neuroinflammatory modulators and mitochondrial protectants, are being assessed in clinical trials.

For Huntington's disease (HD), gene therapy approaches have gained momentum, with ASO-based therapies aiming to reduce the expression of the mutant huntingtin protein. While early trials yielded mixed results, efforts continue to optimize drug delivery and dosing strategies.

In multiple sclerosis (MS), novel immunomodulatory agents and remyelination-promoting drugs are in advanced stages of clinical testing. Siponimod and ocrelizumab have demonstrated significant benefits in slowing disease progression, while stem cell-based therapies are being explored for their potential regenerative effects.[14]

Conclusion

Recent advances in neurodegenerative disorder pharmacotherapy have led to promising breakthroughs in disease-modifying treatments, gene-based interventions, and precision medicine approaches. These developments have the potential to significantly improve patient care by slowing disease progression and enhancing quality of life. Future research will focus on overcoming challenges in drug development, optimizing personalized treatment strategies, and harnessing emerging technologies to revolutionize the landscape of ND therapeutics.

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