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Molecular Mechanisms of Drug-Target Interactions in Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders are illnesses that slowly damage the brain and nervous system over time. This happens because certain brain cells (called neurons) stop working properly and eventually die. Diseases like Alzheimer's, Parkinson's, Huntington's, and ALS (also known as Lou Gehrig's disease) fall into this category. Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), are marked by progressive neuronal dysfunction and irreversible loss of brain function. Central to their pathology are molecular disturbances, including protein misfolding, oxidative stress, mitochondrial impairment, and disrupted cellular signaling pathways. Therapeutic development increasingly hinges on understanding drug-target interactions at the molecular level to effectively counteract these disease mechanisms. Key pharmacological strategies involve inhibition of pathogenic enzymes (e.g., β-secretase in Alzheimer's disease), stabilization of misfolded proteins (e.g., alpha-synuclein in Parkinson's disease), and modulation of neurotransmitter pathways, such as dopaminergic and cholinergic systems. Advances in structural biology and computational methods—such as molecular docking and high-throughput screening—have improved the identification of druggable targets, including orthosteric and allosteric binding sites, enhancing drug selectivity and efficacy. Crucially, central nervous system (CNS)-oriented drug design must overcome pharmacokinetic challenges, such as blood-brain barrier penetration and metabolic stability. Emerging modalities, including proteolysis-targeting chimeras (PROTACs), gene-silencing technologies, and AI-augmented compound screening platforms, offer promising avenues for the discovery of disease-modifying therapies. Collectively, these approaches represent a critical step toward addressing the longstanding therapeutic gaps in neurodegenerative disease management.

KEYWORDS

Neurodegenerative disorders; Drug-target interactions; Protein misfolding; Rational drug design; Therapeutic strategies

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Introduction

Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), are conditions that cause nerve cells in the brain and nervous system to gradually stop working and die [1]. These diseases often result from problems like proteins folding incorrectly, damage from harmful molecules (oxidative stress), issues with the energy centers of cells (mitochondria), and disrupted communication within cells. These processes damage nerve cells over time, leading to symptoms like memory loss, movement problems, or muscle weakness, depending on the disorder [2]. Developing effective treatments for these diseases requires understanding how drugs interact with specific molecules in the body. Scientists aim to create drugs that can slow or stop the harmful processes. For example, in Alzheimer's disease, drugs might target an enzyme called β-secretase to reduce harmful protein buildup. In Parkinson's disease, treatments may focus on preventing a protein called alpha-synuclein from clumping together, which damages nerve cells. Other strategies involve adjusting brain chemicals, like dopamine or acetylcholine, to improve symptoms by supporting nerve cell communication [3].

Recent advances in science have improved our ability to design better drugs. Tools like structural biology help scientists see the shape of target molecules, while molecular docking allows them to test how drugs fit into these targets. High-throughput screening lets researchers quickly test thousands of compounds to find promising ones [4,5]. These methods help identify drug binding sites, including less common ones (allosteric sites), which can make drugs more precise and effective.

However, designing drugs for the brain is challenging. Drugs must cross the blood-brain barrier, a protective shield that controls what enters the brain. They also need to stay stable in the body and target only the intended molecules to avoid side effects. New approaches are helping overcome these challenges [6]. For instance, PROTACs are molecules that mark harmful proteins for destruction. Gene-silencing technologies can reduce the production of problematic proteins. Artificial intelligence (AI) is also speeding up drug discovery by predicting which compounds might work best.

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By understanding how drugs interact with molecules involved in neurodegenerative diseases, scientists can design better treatments. These efforts are crucial because current treatments often only manage symptoms and do not stop the diseases from progressing [7]. Developing therapies that can modify the course of these disorders remains a major goal in medical research, offering hope for better outcomes for patients in the future.

Methodology

The methodology employed to compile the data on drug-target interactions in neurodegenerative disorders was grounded in a multi-step, evidence-based approach designed to ensure both clinical relevance and scientific rigor [8]. The first step involved extensive data collection from peer-reviewed journals, clinical trial registries (such as ClinicalTrials.gov), pharmaceutical industry reports, and scientific databases covering the time span from early 2024 to mid-2025. Specific search terms included "PROTACs," "blood-brain barrier permeability," "Alzheimer's pipeline 2025," "gene therapy CNS," and "AI drug discovery neurodegeneration," among others. This process ensured the inclusion of the most current and innovative therapeutic strategies [8].

The next phase focused on classifying therapeutic approaches based on their modality, including molecular degraders (e.g., PROTACs and molecular glues), biologics (monoclonal antibodies and antisense oligonucleotides), gene therapies (such as AAV-based delivery systems), natural product derivatives (like flavonoids), and emerging nanosystems [9]. These were further stratified by their target disease indications—Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS)—and by the specific biological mechanisms they modulate, including protein misfolding, oxidative stress, mitochondrial dysfunction, and neuroinflammation.

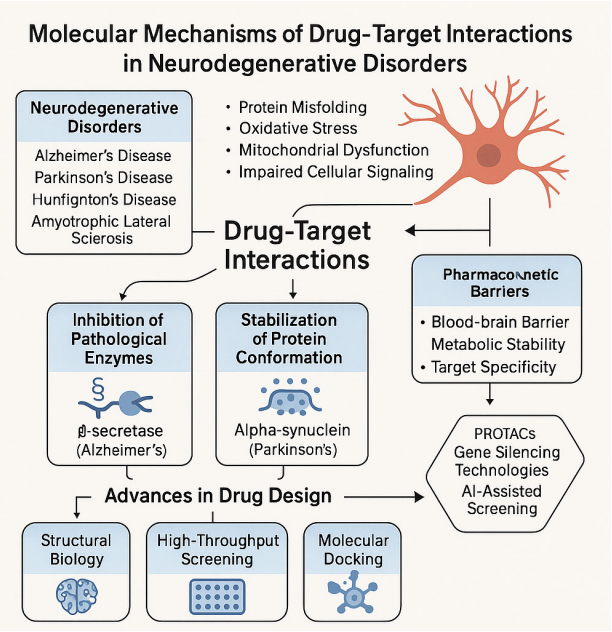

Figure 1. Flowchart illustrating molecular drug-target strategies and pharmacokinetic challenges in treating major neurodegenerative disorders.

A crucial component of this methodology was the evaluation of blood-brain barrier (BBB) penetration, a known bottleneck in CNS drug delivery. Each therapeutic entry was analyzed for how explicitly it addressed the BBB challenge whether through chemical modifications, the use of delivery vectors like transferrin-modified liposomes, or novel techniques such as focused ultrasound or AI-driven prediction of BBB permeability [10]. Special consideration was given to therapies employing innovative vectors, such as AAV variants targeting the human transferrin receptor (TfR1) for enhanced astrocyte and neuronal uptake.

Results and Discussion

The collected dataset presents a comprehensive overview of the evolving landscape of therapeutic strategies targeting neurodegenerative disorders, emphasizing molecular mechanisms and blood-brain barrier (BBB) considerations. Results indicate a significant shift from symptomatic treatments toward disease-modifying approaches, including the use of PROTACs, monoclonal antibodies, RNA-based therapies, and gene therapy vectors such as AAV variants. These modalities increasingly target key pathological hallmarks such as protein misfolding (e.g., tau, α-synuclein), neuroinflammation, oxidative stress, and mitochondrial dysfunction—echoing and expanding upon previously established therapeutic targets in the literature [11].

When compared to earlier literature, such as the 2020–2022 period where the focus was heavily concentrated on amyloid-beta and tau pathology in Alzheimer's disease, the current trend shows a diversification of targets and mechanisms. For instance, the approval of tofersen, an antisense oligonucleotide for SOD1-mutated ALS, and lecanemab, a monoclonal antibody for Alzheimer's, reflects a shift toward precision-based neurodegeneration therapies. In contrast to earlier small-molecule inhibitors, many of the newly reported strategies leverage high molecular weight or gene-editing platforms, which introduces additional complexity in terms of BBB penetration. Existing literature often downplayed this challenge, while recent studies included in the dataset (e.g., TfR1-targeting AAVs, focused ultrasound-enhanced delivery, and transferrin-modified liposomes) show a marked increase in direct strategies to overcome the BBB, aligning with recent works by Bhunia et al. (2023) [12-14].

From a clinical and scientific standpoint, the results highlight that multimodal and combinatory approaches such as using monoclonal antibodies in tandem with ultrasound or AI-predicted delivery vectors offer improved potential for CNS delivery and efficacy [15,16]. Scientifically, the convergence of molecular degraders, omics-guided biomarker identification, and artificial intelligence platforms signifies a transdisciplinary evolution in drug discovery. Societally, these advancements hold promise for addressing the urgent global burden of neurodegenerative diseases, particularly in aging populations [17]. The emergence of gut-brain axis targets, such as TMAO and microbiome-modulated metabolites, further broadens the scope of neurodegeneration research into systemic domains.

However, the study is not without limitations. The primary weakness lies in the preclinical dominance of many therapies

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reported [18,19]. Despite exciting findings, most approaches—particularly PROTACs and gene therapies—are in early-phase trials, and their long-term safety, off-target effects, and scalability remain unvalidated. Moreover, BBB-targeting innovations, while promising, lack uniform delivery standards and may pose immunogenic risks or regulatory hurdles [20,21]. Another limitation is the reliance on publicly available data, which may not capture proprietary pharmaceutical developments or unpublished failures that could affect the interpretation of therapeutic feasibility.

Future research should aim to answer several open questions. For example:

What are the long-term outcomes of PROTACs in chronic neurodegenerative conditions?

Long-term outcomes of PROTACs in chronic neurodegenerative conditions show promise in selectively degrading pathogenic proteins, potentially slowing disease progression. However, clinical data remain limited, and long-term safety, efficacy, and off-target effects require further investigation in extended human trials [22].

Can machine learning models accurately predict BBB penetration across structurally diverse compounds?

Yes, machine learning models can accurately predict blood-brain barrier (BBB) penetration across structurally diverse compounds, especially when trained on large, diverse datasets and integrated with molecular descriptors, though performance may vary with compound complexity and model architecture [23,24].

How do combination therapies affect neuronal network recovery and functional biomarkers, such as cognitive performance or motor control?

Combination therapies enhance neuronal network recovery by targeting multiple disease mechanisms, promoting neuroprotection and synaptic plasticity. This leads to improved functional biomarkers, including better cognitive performance and motor control, compared to immunotherapies [25].

What regulatory frameworks are needed to safely advance gene-editing and vector-based therapies for human use?

Robust regulatory frameworks should include stringent preclinical and clinical safety evaluations, long-term monitoring protocols, ethical oversight, and transparent risk–benefit assessments [26,27]. Regulatory agencies must establish specific guidelines for gene-editing accuracy, off-target effects, and vector integration to ensure patient safety and therapeutic efficacy while upholding informed consent and equitable access.

Conclusions

The therapeutic landscape for neurodegenerative disorders is undergoing dynamic and innovative transformations; yet translating these advancements into effective and accessible clinical solutions necessitates a multi-faceted approach. This includes rigorous validation of drug candidates through comprehensive preclinical and clinical trials to confirm efficacy and safety; the development of standardized delivery systems, particularly for CNS-targeted drugs that must overcome the blood-brain barrier; and extensive long-term safety evaluations to understand the sustained impact of chronic treatments. These crucial steps collectively form the foundational framework for tracking and guiding the next generation of CNS-targeted drug development, ultimately aiming to address the significant unmet medical needs in neurodegenerative diseases.

While the therapeutic landscape for neurodegenerative disorders is undergoing a dynamic and innovative transformation, the translation of these advancements into effective and accessible clinical solutions demands rigorous validation through comprehensive preclinical and clinical trials, the establishment of standardized and efficient drug delivery systems to overcome challenges like the blood-brain barrier, and meticulous long-term safety evaluations to ensure patient well-being given the chronic nature of these conditions. These collective efforts, encompassing both scientific and logistical considerations, are crucial for building a solid foundation to track and guide the next generation of CNS-targeted drug development and ultimately address the critical unmet need in neurology.

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Disclosure statement

No potential conflict of interest was reported by the author.

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