Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU23567

Application of Biopharmaceuticals in the Treatment of Neurological Diseases

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Abstract: Neurological diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), have long posed significant health challenges due to their complex pathogenesis and the profound impact they have on patients' quality of life. Traditional treatments often fall short of providing radical cures, particularly hindered by barriers like the blood-brain barrier (BBB). In recent years, biopharmaceuticals—leveraging advanced technologies such as genetic engineering and cell engineering—have emerged as promising therapeutic alternatives. This paper summarizes biopharmaceutical strategies for treating these two neurological diseases, analyzes the advantages and disadvantages of biopharmaceutical technologies in disease treatment, and provides a detailed description of the pathogenesis and clinical manifestations of these diseases. The conclusion highlights that biopharmaceutical technology has become one of the most effective means for treating neurological diseases, but it still faces obstacles and limitations. Future advancements require technological improvements and clinical trials to enhance treatment success rates and refine preventive measures for neurological diseases.

Keywords: Biopharmaceuticals, Neurological diseases, Alzheimer's disease, Parkinson's disease

1. Introduction

Neurodegenerative diseases (NDDs), characterized by progressive neuronal damage in neurological functions, represent a critical health threat, affecting approximately 55 million individuals with Alzheimer's disease (AD) and 10 million with Parkinson's disease (PD). These conditions impose profound physical and psychological suffering on patients and create substantial economic burdens due to their chronic nature and complex care requirements. Traditional treatment approaches, such as pharmacotherapy and physical therapy, are limited to alleviating symptoms and cannot fundamentally cure the diseases. They often face challenges like severe side effects and inadequate drug delivery to central nervous system (CNS) lesions due to the blood-brain barrier (BBB) [1].

Rapid advancements in biopharmaceutical technologies offer transformative potential for treating neurological diseases. Techniques such as genetic engineering and cell engineering enable precise modification of cells to address disease mechanisms. For instance, monoclonal antibodies can target specific pathogenic proteins (e.g., amyloid-β in AD), gene therapies can deliver neurotrophic factors via viral vectors to support neuronal survival, and stem cell therapies hold promise for replacing degenerated neurons in PD [2-4]. These innovations offer new pathways to overcome the limitations of traditional therapies by achieving cellular and molecular specificity.

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This paper analyzes the advantages and disadvantages of biopharmaceutical technologies in disease treatment, discusses the pathogenesis of AD and PD, and elaborates on the clinical applications and outcomes of biopharmaceuticals. This review aims to provide a comprehensive reference for researchers, guiding future investigations and fostering breakthroughs in developing more effective and accessible treatments for neurological diseases.

2. Biopharmaceuticals

2.1. Definitions of biopharmaceuticals

Biopharmaceuticals are therapeutic products developed via biotechnologies, including genetic engineering, cell culture, and protein engineering. These encompass major categories such as monoclonal antibodies (mAbs), gene therapy, stem cell therapy, and nucleic acid drugs. Monoclonal antibodies, generated by cloned B lymphocyte populations, are highly uniform and designed to target specific antigen epitopes with precision. In neurodegenerative disease treatment, they can accurately recognize and bind pathogenic proteins—for example, Aducanumab specifically targets amyloid-β (Aβ), inhibiting its aggregation and deposition to interfere with disease progression [2].

Gene therapy involves modifying a patient's genetic material to treat diseases. In neurodegenerative contexts, viral vectors like adeno-associated viruses (AAVs) are frequently used to deliver normal or therapeutic genes into the body, correcting abnormal gene functions or supplementing missing gene products. For instance, AAV-mediated delivery of neurotrophic factors has been shown to promote neuronal survival and repair [3]. Stem cell therapy utilizes the self-renewal and multi-differentiation potential. In neurodegenerative diseases, stem cells are induced to differentiate into neurons or glial cells, replacing damaged neural cells and restoring neurological function. A prominent example is the transplantation of induced pluripotent stem cell (iPSC)-derived dopaminergic neurons, offering new therapeutic avenues for PD patients [4].

Lastly, nucleic acid drugs, such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs), operate by binding to specific mRNAs, inhibiting the expression of pathogenic genes. In neurodegenerative disease treatment, these drugs enable targeted intervention at the genetic level, directly addressing disease-related genes [2]. This multifaceted approach highlights biopharmaceuticals' potential to advance precision medicine for complex neurological disorders.

2.2. Advantages of biopharmaceuticals

One prominent advantages of biopharmaceuticals lies in their high target specificity. Monoclonal antibodies (mAbs) can precisely bind to pathogenic proteins, minimizing effects on normal cells and tissues and reducing off-target effects [5]. In the treatment of Alzheimer's disease (AD), Aβ-targeted mAbs specifically recognize and bind to amyloid-β (Aβ), preventing its aggregation into amyloid plaques while causing minimal interference with other normal proteins and cells. This precise targeting enhances therapeutic efficacy and reduces the occurrence of adverse reactions.

Gene therapies and certain biopharmaceuticals also exhibit long-term efficacy. For example, delivering therapeutic genes into the body in a single administration can potentially achieve long-term or even permanent therapeutic effects [3]. Gene therapies utilizing adeno-associated virus (AAV) vectors can provide sustained expression of therapeutic proteins, offering patients lasting benefits while minimizing the inconvenience and potential risks associated with frequent dosing.

Furthermore, biopharmaceuticals enable personalized treatment. Patient-derived induced pluripotent stem cells (iPSCs) can be differentiated into specific neural cells in vitro and then transplanted back into the patient to achieve customized neural repair [4]. This personalized strategy better accommodates individual differences among patients, enhances treatment efficacy, and minimizes the risk of immune rejection.

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2.3. Disadvantages of biopharmaceuticals

The blood-brain barrier (BBB), a vital physiological barrier protecting the brain from harmful substances, has become a major obstacle in using biopharmaceuticals for neurodegenerative diseases. Most biopharmaceutical products are large molecules that cannot penetrate the BBB effectively, limiting their ability to reach brain lesions [6]. Researchers are exploring various strategies to overcome this challenge, such as encapsulating drugs in nanocarriers for receptor-mediated endocytosis across the BBB or using focused ultrasound (FUS) to transiently disrupt the BBB and enhance drug delivery.

Immunogenicity is another critical issue: approximately 30% of patients develop neutralizing antibodies after biopharmaceutical treatment, which can bind to the drugs, reduce efficacy, and even cause severe adverse reactions [7]. The immunogenicity of biopharmaceuticals is influenced by factors such as their origin, structure, and patient-specific differences, making the reduction of immunogenicity a key research priority.

Additionally, the high costs of developing, manufacturing, and clinically applying biopharmaceuticals pose significant barriers. For example, the annual cost of monoclonal antibody therapy exceeds $50,000 [8]. This is primarily due to the complex technology, lengthy R&D cycles, and substantial financial investments required for biopharmaceuticals. Strict requirements for production equipment, environmental control, and quality management further increase costs, while the scale and complexity of clinical trials add to the financial burden. These high costs limit the widespread accessibility of biopharmaceuticals, depriving many patients of potential benefits.

3. Applications of biopharmaceuticals in Alzheimer's disease

3.1. Pathogenesis of Alzheimer's disease

AD, a common neurodegenerative disorder, is characterized by three primary pathological hallmarks: amyloid-β (Aβ) plaque deposition, tau protein tangles and neuroinflammation [9]. Aβ is generated through the cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase. Under normal conditions, Aβ1-40 is the predominant form, but in AD patients, the proportion of Aβ1-42 increases, promoting its aggregation into amyloid plaques. These plaques trigger inflammatory responses and neuronal damage when deposited in the brain [5].

Tau, a microtubule-associated protein, normally binds to microtubules to maintain cytoskeletal stability. In AD, tau undergoes abnormal hyperphosphorylation, causing it to aggregate into double-helical filaments that form neurofibrillary tangles. These tangles disrupt critical neuronal functions such as synaptic transmission, axonal transport, and signal transduction, leading to gradual neuronal degeneration [5]. The loss of neuronal connections ultimately results in neuronal death and brain tissue atrophy. The hyperphosphorylation of tau is linked to the abnormal activity of three kinases: glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and mitogen-activated protein kinase (MAPK), including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK [10]. Additionally, tau phosphorylation correlates with Aβ plaque deposition, suggesting an interplay between these pathological processes.

However, the Aβ hypothesis has faced challenges in recent years. Although Aβ plaque clearance is a key therapeutic target for AD, clinical trials have shown that even when drugs effectively remove Aβ plaques, cognitive improvement remains limited [4]. For example, Lecanemab, a humanized IgG1 monoclonal antibody targeting soluble Aβ protofibrils to inhibit plaque formation and enhance microglia-mediated clearance, reduces Aβ plaques but fails to significantly improve cognitive function in clinical trials [2, 11]. This implies that AD pathogenesis is more complex than previously thought, involving multiple factors beyond Aβ deposition.

DOI: 10.54254/2753-8818/2025.AU23567

3.2. Therapeutic strategy and clinical presentation for Alzheimer's disease

Clinicians currently aim to alleviate Alzheimer's disease (AD) symptoms by balancing neurotransmitter disorders. Monoclonal antibody therapies, such as Aducanumab (Aduhelm) and Donanemab, represent key treatment strategies. Aducanumab, the first Aβ-targeted mAb approved for AD, has sparked debate due to its inconsistent efficacy [12]. While Aducanumab reduces brain Aβ plaques, cognitive improvements vary widely among patients. This variability is likely due to individual differences, disease stage, and dosing protocols. Donanemab targets pGlu-Aβ, a highly aggregated Aβ isoform in AD brains. Phase III trials demonstrate Donanemab delays cognitive decline by approximately 35%, offering new hope for AD treatment [13]. However, it carries side effects such as amyloid-related imaging abnormalities (ARIA), requiring close clinical monitoring.

Gene therapy has also advanced AD treatment. Adeno-associated virus (AAV)-mediated delivery of brain-derived neurotrophic factor (BDNF) is a promising strategy, as BDNF promotes neuronal survival, growth and connectivity. Ongoing clinical trials (NCT05040217) for AAV-BDNF show preliminary safety and feasibility, suggesting potential as a novel treatment option for AD patients [3].

Nanotechnology has emerged as a critical area of focus. For instance, gold nanoparticles loaded with siRNA enhance Aβ clearance by inhibiting Aβ production through RNA interference [14]. These nanoparticles exhibit excellent biocompatibility and stability, enabling efficient intracellular delivery of siRNA. Surface modification of nanoparticles further allows targeted delivery to pathological sites, improving therapeutic efficacy.

In the field of AD treatment, biopharmaceuticals face both opportunities and challenges. The complex pathogenesis—while involving Aβ and tau—remains incompletely understood, hindering the development of precise targeted drugs. Individual variability in treatment response also complicates the establishment of universal protocols. Nevertheless, multi-target combination therapies and breakthroughs in drug delivery technologies hold promise to overcome barriers like the blood-brain barrier, ultimately benefiting AD patients worldwide.

4. Applications of biopharmaceuticals in Parkinson's disease

4.1. Pathogenesis of Parkinson's disease

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, involving multiple interrelated mechanisms. Firstly, α-synuclein aggregation plays a central role. Abnormal accumulation forms Lewy bodies, which induce neuronal toxicity, functional impairment and cell death [15]. Lewy body formation disrupts normal neuronal metabolism, intracellular transport and signal transduction, accelerating neurodegeneration. Secondly, neuroinflammation significantly contributes to PD. Activated microglia in the PD brain release pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [16]. These cytokines initiate inflammatory cascades that damage surrounding neurons and disrupt the neural microenvironment, creating a vicious cycle of disease progression. Thirdly, mitochondrial dysfunction is a key factor. Reduced activity of mitochondrial complex I in PD patients impairs oxidative phosphorylation, decreases energy production and generates excessive reactive oxygen species (ROS), exacerbating oxidative stress [17]. Oxidative stress damages neuronal membranes, proteins, and DNA, further compromising neuronal function. Lastly, genetic factors influence about 10% of PD cases, with notable mutations in genes such as LRRK2 and GBA [18]. LRRK2 mutations disrupt intracellular signaling pathways, while GBA mutations impair lysosomal function, leading to defective α-synuclein clearance and enhanced aggregation.

DOI: 10.54254/2753-8818/2025.AU23567

4.2. Therapeutic strategy and clinical presentation for Parkinson's disease

Current biopharmaceutical strategies for PD focus on multiple mechanisms. α-synuclein-targeted monoclonal antibodies, such as Prasinezumab, have shown trends in improving motor symptoms in phase II clinical trials, despite not achieving primary endpoints [19]. This suggests potential for α-synuclein-targeted therapies, with optimization of dosing regimens and patient selection likely needed to enhance efficacy.

Gene therapy approaches include AAV-GAD and AAV-AADC. AAV-GAD delivers the GAD gene to enhance GABAergic inhibition, thereby reducing motor fluctuations in PD patients (NCT05603312) [20]. As an inhibitory neurotransmitter, GABA regulates neuronal excitability, offering promise for motor symptom improvement. AAV-AADC enhances the expression of aromatic L-amino acid decarboxylase (AADC), promoting the conversion of levodopa to dopamine and improving levodopa efficacy while reducing dosage and side effects [20]. This strategy aims to restore dopaminergic neuron function and optimize symptomatic treatment.

Anti-inflammatory therapies using NLRP3 inflammasome inhibitors (e.g., MCC950) have demonstrated neuroprotective effects in preclinical studies by suppressing pro-inflammatory cytokine release and mitigating neuroinflammation [16]. These agents hold potential to protect dopaminergic neurons and may advance to clinical trials for PD.

The application of biopharmaceuticals in PD is marked by both opportunities and challenges. While key pathogenic mechanisms are understood, individual variability and disease heterogeneity complicate precision treatment. Barriers such as the blood-brain barrier and immunogenicity limit drug delivery and efficacy, while high development costs restrict accessibility. Multi-modal combination therapies, precision medicine guided by genetic testing, and innovative delivery technologies represent critical pathways for overcoming these hurdles. As research progresses, biopharmaceuticals are poised to revolutionize PD treatment by addressing its complex biology and improving patient outcomes.

5. Conclusion

This paper systematically summarizes the applications of biopharmaceutical technologies in treating two neurological disorders: Alzheimer’s disease and Parkinson’s disease. Through clinical observations, biopharmaceuticals have demonstrated significant potential and value in the field of neurological disease treatment, yet they also face numerous challenges requiring urgent resolution. The paper provides a detailed overview of the advantages and disadvantages of biopharmaceutical technologies, as well as the main pathological mechanisms of these two diseases. For example, it discusses the high targeting specificity of monoclonal antibodies, the long-acting effects of gene therapies, and the regenerative potential of stem cell treatments, while addressing key limitations such as the blood-brain barrier, immunogenicity issues, and high development costs.

However, this paper acknowledges several shortcomings. Notably, the claim that biopharmaceuticals have become "one of the most effective means" for treating neurological diseases lacks sufficient empirical support. Although the conclusion highlights biopharmaceuticals as a leading therapeutic approach, this paper does not provide detailed data comparisons with traditional treatments or comprehensive analyses of their relative efficacy.

Looking to the future, advancing biopharmaceuticals in neurological disease treatment requires sustained research investment, technological optimization, and cost reduction to enhance safety and efficacy. Closer integration of basic research with clinical applications is essential to accelerate the translation of biopharmaceutical innovations into clinical practice. Interdisciplinary collaboration across medicine, biology, chemistry, and engineering will also be critical to driving innovation.

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Despite current challenges, biopharmaceuticals are positioned to play an increasingly important role in neurological healthcare. As technology advances, these therapies may shift the focus from symptom management to disease modification, offering new hope for patients with Alzheimer's, Parkinson's, and other neurological disorders. While substantial hurdles remain, continued scientific and technological progress will likely unlock the full potential of biopharmaceuticals, contributing significantly to the fight against neurological diseases and improving global public health outcomes.

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