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Investigating the function of adenosine receptors in Alzheimer's disease

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ABSTRACT

Alzheimer's disease remains a major challenge in neurodegenerative medicine, characterized by progressive cognitive decline, amyloid beta plaques, tau pathology, and neuroinflammation. Despite extensive studies, there is still no definitive treatment for this disease. Stem cells, including neural stem cells, mesenchymal stem cells, induced pluripotent stem cells, embryonic stem cells, and hematopoietic stem cells, have recently been considered as a promising approach due to their unique properties, including the ability to differentiate into cell types and regenerate damaged tissues. Preclinical studies have shown the positive effects of these cells in reducing amyloid plaques, improving synaptic function, and reducing brain inflammation. However, challenges such as safety, long-term efficacy, and ethical issues still require further investigation. This review reviews the types of stem cells, mechanisms, recent achievements, hopes, and challenges facing this path.

Introduction

Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory decline, cognitive and motor impairments, and exacerbating behavioral changes. The increasing prevalence of this disease has posed unprecedented challenges for the World Health Organization, with projections indicating that the incidence of Alzheimer's disease may triple by the year 2050 (Andrade and Martínez, 2024).

Common pathological features of Alzheimer's disease include the accumulation of beta-amyloid plaques (Aβ) outside neurons, the formation of neurofibrillary tangles composed of tau protein (NFTs), and neuronal death in critical areas of the brain, including the cerebral cortex and hippocampus (Abdul et al., 2019).

Current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, primarily aim to alleviate the symptoms associated with the disease and have not demonstrated efficacy in slowing disease progression. These limitations have prompted researchers to explore cell therapy using stem cells. Their unique ability to differentiate into various cell types, secrete protective factors, and modulate inflammation presents a potential for these cells in the treatment of damaged brain tissues (Gao et al., 2023). This review synthesizes recent findings and describes the types, mechanisms, advantages, and challenges of stem cell therapy for Alzheimer's disease.
2. Theoretical Foundations of the Research

1-2. Types of Stem Cells and Their Mechanisms

Stem cell-based therapies for Alzheimer's disease primarily include embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), neural stem cells (NSCs), and hematopoietic stem cells (HSCs) (Qin and Wang, 2022).

Embryonic Stem Cells (ESCs)

Embryonic stem cells are considered candidates for the treatment of Alzheimer's disease due to their pluripotent characteristics and ability to differentiate into various cell types, including neurons and glia. Studies have shown that these cells can improve cognitive function by replacing lost neurons. ESCs can differentiate into cholinergic neurons of the basal forebrain and gamma-aminobutyric acid (GABA) neurons, enhancing spatial learning and memory in mice with Alzheimer's disease. However, ethical concerns and the potential for tumor formation present challenges to the use of ESCs (Jin et al., 2016).

Mesenchymal Stem Cells (MSCs) Mesenchymal stem cells (MSCs) are multipotent cells capable of differentiating into skeletal system cells, including osteocytes, chondrocytes, and adipocytes. Due to their anti-inflammatory properties and the secretion of neurotrophic factors, they have been investigated for the treatment of Alzheimer's disease. Results from animal studies indicate that the use of these cells leads to a reduction in beta-amyloid plaques, decreased inflammation, and improved synaptic function; they also possess the ability to reduce apoptosis (Lyon, 2018).

Induced pluripotent stem cells (iPSCs) can serve as a substitute for embryonic stem cells (ESCs) since they are derived from mature cells and present fewer ethical challenges. These cells have the capacity to differentiate into cortical neurons and glial cells, and in animal models, they have been shown to enhance cognitive function. However, they may also be associated with issues such as the risk of genetic mutations and chromosomal instability (Cha et al., 2017).

Neural stem cells (NSCs) are found in the brains of both embryos and adults and have the ability to

differentiate into neurons and glial cells. In response to tissue stimuli, these cells can promote neurogenesis and provide therapeutic benefits for neurodegenerative diseases such as Alzheimer's. Studies indicate that these cells can improve memory function by reducing amyloid plaques (Pradhan and Uwishema, 2022).

Hematopoietic stem cells (HSCs) are multipotent cells located in the bone marrow, primarily responsible for the production of blood and immune cells, including microglia-like cells in the brain. Research has been conducted on HSC transplantation to replace defective microglia that play a role in the progression of Alzheimer's disease (Gao et al., 2023).

Table 1. Summary of Types of Stem Cells, Applications, Advantages, and Disadvantages

Challenges	Benefits	Applications in Alzheimer's Disease	explanations	Stem cell type
Limited survival post-transplant, complexity of cerebral transfer.	Cognitive function restoration through the regeneration of neurons (such as cholinergic neurons). Improvement of synaptic connections, support for neuronal survival through neurotrophic factors.	Replacement of lost neurons, enhancement of neurogenesis, secretion of neurotrophic factors	Multipotent cells derived from embryonic or adult neural tissue are capable of differentiating into neurons, astrocytes, and oligodendrocytes.	Neural Stem Cells (NSCs)
Temporary effects and limited efficacy in the long term, risk of immune rejection in allogeneic transplants, variable efficacy at different stages of Alzheimer's disease.	Suppression of inflammation (via exosomes), improvement of cognitive outcomes through reduced activation of astrocytes, ease of access, and scalability of production.	Reduction of neuroinflammation, secretion of anti-inflammatory molecules, promotion of tissue repair	Multipotent cells derived from bone marrow, adipose tissue, or umbilical cord possess immunomodulatory properties.	Mesenchymal Stem Cells (MSCs)
The risk of tumorigenesis in the absence of complete differentiation, high costs, and time-consuming nature.	The potential for personalized modeling in pharmacological screening, prevention of immune rejection in autologous applications, and the high potential for differentiation..	Creation of patient-specific neuronal models, potential for autologous cell therapy.	Reprogrammed pluripotent cells from adult somatic cells are capable of differentiating into any cell type.	Induced Pluripotent Stem Cells (iPSCs)
Ethical limitations in usage. High risk of immune rejection. Risk of tumorigenesis in the absence of complete differentiation.	High differentiation potential for neural repair, enhancement of cognitive function in preclinical models.	Differentiation into neuronal cells for cell replacement therapies.	Pluripotent cells derived from early embryos are capable of differentiating into any cell type.	Embryonic Stem Cells (ESCs)

Need for pre-treatment with toxic agents (such as chemotherapy). Limited efficacy in sporadic Alzheimer's disease. Complexity of transfer and survival issues.	Reduction of beta-amyloid and neuroinflammation, Preservation of memory in Alzheimer's models, Targeting microglial dysfunction.	Replacement of dysfunctional microglia, reduction of amyloid plaques, modulation of inflammation.	Multipotent cells derived from bone marrow produce blood and immune cells, including microglia-like cells.	Hematopoietic Stem Cells (HSCs)

Each type of stem cell plays a role in therapeutic effects through distinct mechanisms that can be broadly classified as follows:

Cell Replacement and Neurogenesis

Stem cells, particularly neural stem cells (NSCs) and neurons derived from induced pluripotent stem cells (iPSCs), can differentiate into neurons and glial cells to replace damaged or lost cells in the brains of individuals with Alzheimer's disease. Transplanted NSCs have been shown to regenerate cholinergic neurons, which are critical for memory and cognitive functions and are significantly reduced in Alzheimer's. For instance, studies indicate that NSCs that overexpress choline acetyltransferase can recover spatial memory and learning deficits in Alzheimer's rodent models by enhancing cholinergic neurotransmission (Marsh and Blurton-Jones, 2022). Additionally, stem cells promote endogenous neurogenesis in the hippocampus, a region vital for memory, by upregulating pathways such as Wnt signaling that support the differentiation of neural progenitor cells (Gao et al., 2023).

Reduction of Aβ and Tau Pathology

Stem cells, particularly mesenchymal stem cells (MSCs), can modulate the pathological signs of Alzheimer's disease by reducing the burden of Aβ plaques and tau hyperphosphorylation. MSCs secrete extracellular vesicles (EVs) and microvesicles containing neurogenic and angiogenic cytokines that cross the blood-brain barrier (BBB) and decrease Aβ deposition. This approach is promising due to the ability of exosomes to non-invasively traverse the BBB, offering a scalable and minimally invasive therapeutic option. A study in 2021 demonstrated that MSC-derived exosomes reduced Aβ plaques and improved cognitive function in Alzheimer's mouse models by decreasing β-secretase (BACE1) activity and increasing anti-inflammatory cytokines (Wang et al., 2021).

Modulation of the Immune System and Reduction of Neuroinflammation

Neuroinflammation, driven by activated microglia and astrocytes, is a hallmark of Alzheimer's progression. Mesenchymal stem cells and their exosomes exert immunomodulatory effects by shifting the microglial phenotype from a pro-inflammatory (M1) to an anti-inflammatory (M2) state. This shift reduces the release of pro-inflammatory cytokines such as TNF-α and IL-1β while increasing anti-inflammatory cytokines like IL-10. A study in 2024 reported that the transplantation of human neural stem cells in transgenic mice with Alzheimer's reduced microglial inflammation and restored genetic markers associated with disease progression, leading to improved spatial memory (Feldman et al., 2024). Furthermore, mesenchymal stem cells increase neuroprotective factors such as brain-derived neurotrophic factor (BDNF), which mitigates neuronal damage caused by inflammation (Chen et al., 2021).

Paracrine Effects and Neurotrophic Support

Stem cells secrete neurotrophic factors, including BDNF, glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF), which support neuronal survival, synaptic plasticity, and angiogenesis. These paracrine effects enhance the brain's microenvironment, promote repair, and reduce neuronal apoptosis. For example, a study in 2021 showed that MSC transplantation in Alzheimer's mice increased the expression of synaptic proteins (such as synaptophysin and synapsin) and improved cognitive function through GDNF-mediated pathways (Jahed et al., 2021). MSC-derived exosomes also transfer microRNAs that regulate gene expression, further supporting neuroprotection (Zhang et al., 2024).

Enhancement of Synaptic Plasticity and Connectivity

Stem cells improve the integrity and connectivity of synapses, which are severely disrupted in Alzheimer's disease. Transplanted neural stem cells establish synaptic connections with host neurons, as evidenced by increased expression of synaptic markers such as synaptophysin and growth-associated protein 43 (GAP-43). A study in 2021 demonstrated that neural progenitor cells derived from iPSCs integrate into the brains of Alzheimer's mice, form functional synapses, and enhance cognitive performance in the Morris water maze test. This synaptic increase is crucial for the recovery of memory and learning capacities (Armijo et al., 2021).

Mitochondrial Function and Metabolic Support

Mitochondrial dysfunction plays a role in neurostress in Alzheimer's disease. Stem cells, particularly mesenchymal stem cells (MSCs), improve mitochondrial function by reducing oxidative stress and enhancing energy metabolism. A study conducted in 2024 demonstrated that extracellular vesicles derived from MSCs restored mitochondrial membrane potential and reduced reactive oxygen species in Alzheimer's cellular models, thereby supporting neuronal survival (Lin et al., 2024).

Studies Conducted and Recent Achievements

While this therapeutic approach is in its early stages, it has already yielded promising results. For instance, the differentiation of neural stem cells guided by nanotechnology and exosome-based therapies for improved targeted delivery and therapeutic outcomes is currently under investigation (Feldman et al., 2024). In experiments involving the transplantation of mesenchymal stem cells into mice, a reduction in inflammation and the safety of these cells were observed. However, the long-term efficacy and improvement of transplantation methods require further investigation (Zhang et al., 2024). A study in 2021 showed that human iPSC-derived NPCs, when transplanted into the hippocampus of 3xTg-AD mice, integrated into the host neural network and formed functional synapses. These cells increased the expression of synaptic markers (such as PSD-95, synaptophysin) and improved cognitive performance in spatial memory tasks by 25% compared to the control group. This achievement highlights the potential of iPSCs for reconstructing neural circuits and addresses a major deficit in Alzheimer's disease (Armijo et al., 2021).

A study in 2024 introduced a novel nanotechnology-based approach to enhance the survival and differentiation of neural stem cells (NSCs) in the brains of Alzheimer's patients. Researchers achieved targeted delivery to the hippocampus of APP/PS1 mice by encapsulating NSCs in a graphene oxide-based hydrogel, resulting in a 40% increase in NSC survival and enhanced differentiation into cholinergic neurons. This approach also led to a reduction in tau hyperphosphorylation and improved memory performance in behavioral assessments. This achievement represents a significant advancement in overcoming the challenge of stem cell loss (Pan et al., 2024).

Advancements in gene editing have enabled the development of stem cells with enhanced therapeutic properties. A study in 2024 utilized CRISPR/Cas9 to overexpress brain-derived neurotrophic factor (BDNF) in MSCs, which were then transplanted into the brains of 5XFAD mice. The modified MSCs increased BDNF levels by 50%, reduced neuroinflammation, and enhanced synaptic plasticity, leading to significant improvements in cognitive performance (Ahn et al., 2021). This achievement demonstrates the potential of combining gene editing with stem cell therapy to enhance neuroprotective effects.

A study in 2012 examined the synergistic effects of combining MSC therapy with donepezil, a cholinesterase inhibitor commonly used in Alzheimer's treatment. In B6C3-Tg mice, the combination therapy resulted in a 35% reduction in Aβ plaques and a 20% increase in hippocampal neurogenesis compared to either treatment alone. This study also reported increased expression of neurotrophic factors such as GDNF and VEGF, along with improved cognitive outcomes in maze tests (Neumeister and Riepe, 2012). This achievement highlights the potential of integrated approaches to maximize therapeutic outcomes.

Clinical Trials

Although cell therapy for Alzheimer's treatment is still in its early stages, some clinical trials have provided promising results. For example, in 2015, early-phase trials using MSCs derived from human umbilical cord blood, administered via stereotactic surgery and injected into the hippocampus of nine individuals with mild Alzheimer's, demonstrated that these cells were safe and could reduce brain inflammation. However, the clinical impact of this method on the pathogenesis of Alzheimer's requires further validation (Kim et al., 2015). Another Phase I trial using umbilical cord-derived MSCs reported stable cognitive function and a reduction in Aβ42 levels in cerebrospinal fluid (CSF) in 60% of participants after six months (Kim et al., 2021). These trials represent a significant step toward demonstrating the clinical feasibility of stem cell-based therapies. Several clinical trials involving patients with Alzheimer's are currently underway.

2-5(Challenges and Limitations)

Despite promising preclinical results, several challenges remain for clinical application:

Heterogeneity and Viability: Transplanted stem cells face issues with viability, migration, and differentiation in the microenvironment of the Alzheimer-affected brain, characterized by inflammation and oxidative stress. Embryonic stem cells may lead to teratoma formation due to uncontrolled proliferation. Mesenchymal stem cells are considered a more suitable option due to their higher safety profile; however, their efficacy is comparatively limited when juxtaposed with embryonic types. (Chen, 2023)

Tumorigenesis Risk: Embryonic stem cells and induced pluripotent stem cells carry a risk of teratoma formation due to uncontrolled proliferation, necessitating stringent immunological protocols. Mesenchymal stem cells are a more suitable option due to their higher safety profile; however, their efficacy is comparatively limited when juxtaposed with embryonic types. (Marsh et al., 2017)

Immunosuppression: Stem cell transplantation often requires immunosuppression, which increases the risk of adverse effects. (Feldman et al., 2024)

Complexity of Alzheimer’s Pathology: Alzheimer’s disease affects various brain regions and cell types, making comprehensive repair with a single type of stem cell challenging. (Ifediora et al., 2024)

Technical Challenges

Limitations such as appropriate dosing, injection routes, timing of transplantation, selection of the suitable cell type, and cell stability in the brain environment continue to pose challenges for cell therapy. Delivering stem cells to the brain is complicated by the presence of the blood-brain barrier. Additionally, direct injection or intravenous methods may have limited efficacy. (Gao et al., 2023)

Ethical Issues

The use of embryonic stem cells is associated with ethical considerations due to their origin; in contrast, mesenchymal and induced types present fewer ethical issues, although attention must be paid to standardizing their production methods and ensuring their safety. (Lyon, 2018)

2-6 Future Perspectives

Recent advancements in tissue engineering and gene therapy may enhance the efficacy of cell therapy. For instance, the use of three-dimensional scaffolds and genetic modification of stem cells to increase the production of neurotrophic factors represents promising approaches. Furthermore, combining cell therapy with pharmacological treatments, such as monoclonal antibodies against beta-amyloid, may yield synergistic effects. It is anticipated that with the completion of clinical trials and the resolution of existing challenges, cell therapy will become part of the standard treatment for Alzheimer’s disease.

3. Conclusion

Stem cells possess significant potential for treating Alzheimer’s disease due to their ability to regenerate brain tissues and modulate the pathologies associated with the condition. Preclinical and clinical evidence indicates positive effects of these cells in reducing amyloid plaques, improving synaptic function, and decreasing inflammation. Innovations in nanotechnology and gene editing have further enhanced the efficacy of stem cell therapies, and combined approaches with existing medications demonstrate synergistic benefits. Stem cells not only provide a new avenue for investigating the pathological basis of the disease but also offer a novel pathway for drug research and development.

Thus, they present a new method for drug screening, testing the efficacy of potential new drugs, and screening patient populations for clinical trials. However, challenges such as safety, technical issues, and ethical considerations require further attention. Future research should focus on optimizing transplantation methods, standardizing protocols, and evaluating long-term efficacy. Ongoing clinical trials and advancements in stem cell technology hold promise for translating these findings into effective treatments for Alzheimer’s patients.

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