World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Neurogenesis for the treatment of Alzheimer's disease

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World Journal of Biology Pharmacy and Health Sciences, 2025, 21(02), 001–007

Publication history: Received on 17 December 2024; revised on 28 January 2025; accepted on 31 January 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.21.2.0112

Abstract

Alzheimer's disease is a complex neurodegenerative condition marked by progressive cognitive impairment, memory deficits, and loss of neurons. Current treatment options primarily alleviate symptoms without targeting the root causes of the disease. Emerging research on adult neurogenesis, the generation of new neurons from neural stem cells has introduced innovative strategies for addressing the underlying pathology of Alzheimer's disease. This review explores key aspects of neurogenesis, including its regulatory mechanisms, pharmacological interventions, and the role of natural products in enhancing neurogenesis. Additionally, it highlights the therapeutic potential of these approaches in mitigating Alzheimer's disease progression. Challenges such as delivery barriers, safety concerns, and the translational gap between preclinical and clinical research are also discussed. Future studies integrating neurogenesis-based methods with existing therapies could transform Alzheimer's disease management and improve patient outcomes.

Keywords: Alzheimer's disease; Neurogenesis; Neural stem cells; Therapeutic strategies; Stem cell therapy

1. Introduction

Alzheimer's disease affects over 55 million people globally, with the numbers projected to rise to 139 million by 2050. Alzheimer's disease is marked by pathological hallmarks, including amyloid-beta plaques, neurofibrillary tangles of hyperphosphorylated tau protein, synaptic dysfunction, and extensive neuronal loss, particularly in the hippocampus and cortex. These pathological changes culminate in progressive memory impairment, cognitive decline, and behavioural disturbances. Despite decades of research, current pharmacological treatments such as cholinesterase inhibitors (donepezil, rivastigmine) and N-methyl-D-aspartate receptor antagonists (memantine) offer only limited symptomatic relief and fail to modify the disease process.

Neurogenesis, the process of forming new neurons in the adult brain, occurs in two key regions: the subventricular zone and the dentate gyrus of the hippocampus. These regions are particularly vulnerable in Alzheimer's disease, where decreased neurogenesis has been linked to cognitive deficits. Recent research suggests that enhancing neurogenesis could potentially restore neuronal populations, improve synaptic connectivity, and counteract neurodegeneration. This review explores the potential of neurogenesis as a therapeutic strategy for Alzheimer's disease, highlighting key mechanisms, pharmacological agents, and challenges.

1.1. Pathological mechanisms of alzheimer's disease impacting neurogenesis

Neurogenesis, the process of generating new neurons, is significantly impacted by the pathological hallmarks of Alzheimer's disease, including amyloid-beta toxicity, tau pathology, and neuroinflammation. These mechanisms disrupt the microenvironment required for neural stem cell proliferation, differentiation, and survival, contributing to cognitive decline and memory impairment. 1

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Amyloid-Beta Toxicity: Amyloid-Beta peptides, derived from the cleavage of amyloid precursor protein, accumulate extracellularly to form insoluble plaques. These plaques are not only toxic to mature neurons but also detrimental to Neural stem cells. Experimental studies suggest that Amyloid-Beta interferes with critical signalling pathways, particularly the Wnt/β-catenin pathway, which regulates Neural stem cell proliferation and differentiation.

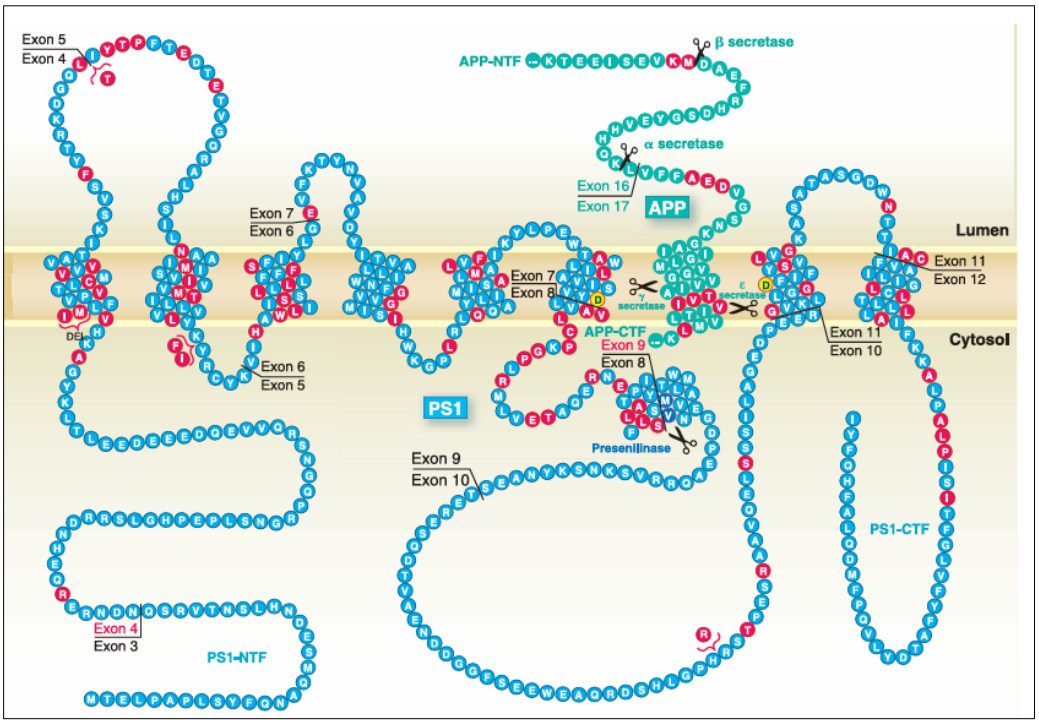

Figure 1 Diagram illustrating the processing of amyloid precursor protein (APP) and its role in Amyloid-Beta (Aβ) production. Key cleavage sites by secretases (scissors) and familial Alzheimer's disease-related mutations (red) are highlighted, emphasizing the molecular basis of Amyloid-Beta toxicity (1)

The disruption of this pathway leads to reduced expression of genes involved in cell survival and synaptic plasticity, further exacerbating neuronal loss. Additionally, Amyloid-Beta oligomers are known to induce oxidative stress and mitochondrial dysfunction, creating an environment unfavourable for neurogenesis. Animal models of Alzheimer's disease demonstrate that Amyloid-Beta accumulation in the hippocampus, a primary site of adult neurogenesis, significantly reduces the pool of Neural stem cell and immature neurons [1].

Tau Pathology: The hyperphosphorylation of tau, a microtubule-associated protein, leads to the formation of neurofibrillary tangles within neurons. These tangles impair axonal transport, which is essential for delivering nutrients and organelles to neuronal processes. This disruption of transport pathways not only affects mature neurons but also impacts Neural stem cells.

Tau toxicity inhibits the differentiation of Neural stem cells into functional neurons by altering intracellular signalling cascades such as the phosphatidylinositol 3-kinase/protein kinase B pathway. Moreover, neurofibrillary tangles interfere with cytoskeletal dynamics, which are crucial for the migration and integration of new neurons into existing neural circuits. Studies in tauopathy mouse models reveal that tau aggregation reduces hippocampal neurogenesis, correlating with deficits in spatial memory and learning [2].

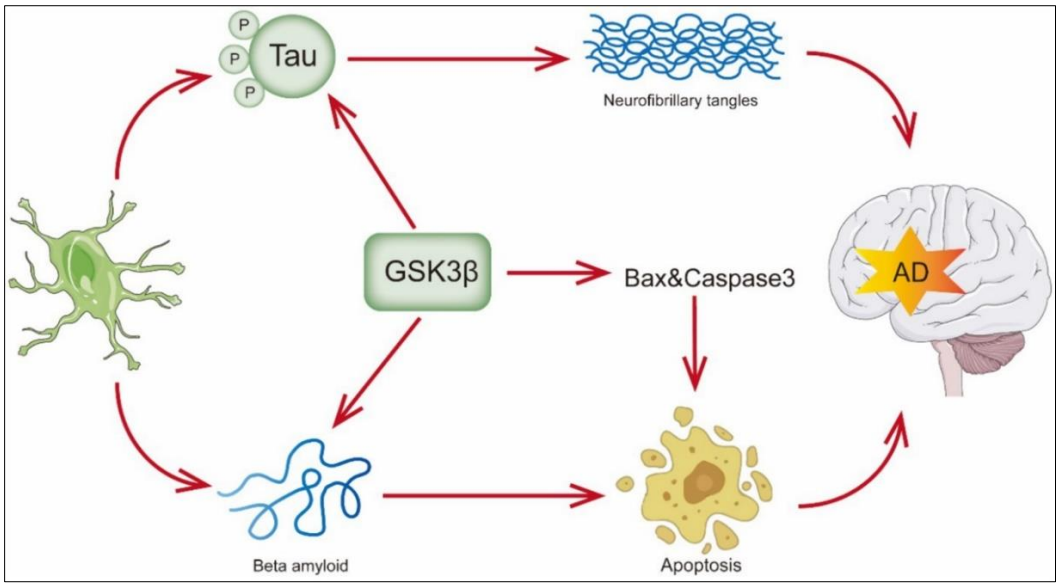

Figure 2 Tau Pathology in Alzheimer's Disease: Hyperphosphorylated Tau Leads to Neurofibrillary Tangles, Impairing Axonal Transport and Neurogenesis [3]

Neuroinflammation: Chronic neuroinflammation is a hallmark of Alzheimer's disease, driven by the activation of glial cells, including microglia and astrocytes. In their activated state, these cells release a variety of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). While these cytokines play protective roles in acute injury, their chronic elevation in Alzheimer's disease creates a hostile microenvironment that suppresses neurogenesis.

Activated microglia engulf neural stem cells and secrete reactive oxygen species, leading to oxidative stress that damages the neurogenic niche. Similarly, astrocytes release inhibitory molecules like nitric oxide and glutamate, further impairing Neural stem cell survival and differentiation. In the hippocampal dentate gyrus, where neurogenesis predominantly occurs, this inflammatory milieu reduces the pool of progenitor cells and hinders the maturation of newly generated neurons.

Emerging evidence also highlights the role of systemic inflammation in exacerbating neuroinflammation in Alzheimer's disease. For instance, peripheral infections and metabolic disorders like diabetes can amplify glial activation and cytokine production, indirectly contributing to the decline in neurogenesis [4].

2. Mechanisms of neurogenesis in Alzheimer's disease

Adult neurogenesis is a complex, multistep process that plays a vital role in maintaining cognitive function, especially in the hippocampus, which is responsible for learning and memory. The process of neurogenesis can be categorized into three major stages:

- Proliferation**:** Neural stem cells located in the sub granular zone of the hippocampal dentate gyrus proliferate to form neural progenitor cells. This phase is tightly regulated by signalling pathways, including the Wnt/β-catenin and Notch pathways, which ensure proper cell division and the maintenance of the Neural stem cell pool. However, in Alzheimer's disease, this proliferation is significantly compromised due to the toxic effects of amyloid-beta oligomers, which disrupt key regulatory pathways and induce oxidative stress, thereby reducing the pool of Neural stem cells.

- Differentiation**:** During differentiation, neural progenitor cells mature into neurons, astrocytes, or oligodendrocytes, depending on the environmental cues and signalling molecules present. In a healthy brain, this process ensures a balance between neurogenesis and gliogenesis. However, in Alzheimer's disease, the accumulation of Amyloid-Beta and hyperphosphorylated tau impairs this process. Studies suggest that Amyloid-Beta directly inhibits the expression of neurogenic transcription factors like NeuroD1, while tau pathology disrupts cytoskeletal integrity, further hindering neural progenitor cell differentiation.

- Integration**:** Once differentiated, newly formed neurons must migrate and integrate into existing neural circuits within the hippocampus. This integration is essential for synaptic plasticity, which underpins learning and memory. In Alzheimer's disease, hyperphosphorylated tau aggregates interfere with this integration by disrupting axonal transport and synaptic connectivity. Additionally, the pro-inflammatory environment caused by activated microglia and astrocytes releases cytokines like interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α), which impair synaptic integration [4].

Table 1 Mechanisms of Neurogenesis in Alzheimer's Disease

Mechanism	Key Factors	Impact on Neurogenesis
Stem Cell Activation	brain-derived neurotrophic factor, vascular endothelial growth factor	Promotes neuronal proliferation
Wnt Signalling	Wnt, β-catenin	Regulates differentiation and survival
Neuroinflammation	tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β)	Impairs Neural stem cell proliferation

3. Impairment in neurogenesis in alzheimer's disease

Neurogenesis is impaired in Alzheimer's Disease due to:

- Amyloid-Beta Toxicity**:** The accumulation of amyloid-beta peptides, especially in the form of oligomers, is a central feature of Alzheimer's Disease. These oligomers have been shown to significantly impair the proliferation and differentiation of neural stem cells in the hippocampus. By interfering with key cellular pathways such as N-methyl-D-aspartate receptor signalling, Amyloid-Beta oligomers lead to cellular excitotoxicity, hindering the proper development of new neurons. As a result, neurogenesis is reduced, leading to memory deficits and cognitive decline, which are characteristic of Alzheimer's disease.
- Tau Pathology**:** In Alzheimer's disease, tau proteins undergo pathological changes, including hyperphosphorylation, which results in the formation of neurofibrillary tangles. These tangles disrupt the stability of microtubules and hinder cellular transport mechanisms. In addition, the presence of hyperphosphorylated tau impairs the integration of new neurons by affecting neuronal structure and dendritic growth. This disruption in tau function decreases the ability of the hippocampus to generate new neurons, contributing to the cognitive impairments seen in Alzheimer's disease, particularly in areas related to memory and learning.
- Neuroinflammation**:** Alzheimer's Disease is characterized by chronic activation of microglia, the brain's immune cells, which respond to the accumulation of Amyloid-Beta and tau pathology. This activation leads to the release of pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α). These cytokines create an environment that is detrimental to neurogenesis, particularly by disrupting neurogenic niches within the hippocampus. The heightened inflammatory response further impairs the regenerative capacity of neural stem cells, exacerbating cognitive decline and accelerating the neurodegenerative process in Alzheimer's disease.

3.1. Role of key signalling pathways

Neurogenesis, the process of generating new neurons from neural stem cells, is tightly regulated by several signalling pathways. These pathways orchestrate critical steps such as Neural stem cell proliferation, differentiation, and integration into neural circuits. In Alzheimer's Disease, dysregulation of these pathways disrupts neurogenic processes, contributing to cognitive decline and memory deficits. Understanding the roles of these pathways provides insights into potential therapeutic targets to mitigate the effects of Alzheimer's disease. Key pathways implicated in neurogenesis and their alterations in Alzheimer's disease include:

- **Wnt/β-Catenin Pathway:** The Wnt/β-catenin pathway plays a crucial role in promoting the proliferation and differentiation of neural stem cells. It facilitates the regulation of cellular fate and supports synaptic plasticity, which are vital for cognitive functions(5).
- **Notch Signalling**: Notch signalling is essential for determining stem cell fate and maintaining a reservoir of adult Neural stem cells. It ensures the balance between proliferation and differentiation within the neurogenic niche(6).

- **Brain-derived neurotrophic factor-Tropomyosin-related kinase receptor B Pathway**: The brain-derived neurotrophic factor is a key molecule that enhances neurogenesis and synaptic plasticity by binding to its receptor, Tropomyosin-related kinase receptor B. brain-derived neurotrophic factor is crucial for hippocampal function, including memory consolidation and learning(7).

3.2. Pharmacological strategies to enhance neurogenesis:

Several therapeutic approaches aim to restore neurogenesis and improve cognitive function in Alzheimer's Disease. These strategies include small molecules, stem cell-based therapies, and epigenetic modulators, each targeting different aspects of the neurogenic process to counteract Alzheimer's disease -related deficits.

Small Molecules: Compounds like P7C3 and Isoxazole-9 enhance neurogenesis by protecting Neural stem cells from apoptosis.

- P7C3: This compound has been identified as a neuroprotective agent that safeguards newborn neurons from apoptosis. It has demonstrated the ability to improve cognitive functions in preclinical models of Alzheimer's disease by promoting the survival of newly formed neurons, particularly in the hippocampus.
- Isoxazole-9: A synthetic small molecule, ISX-9, is known to stimulate the differentiation of neural progenitor cells into mature neurons. Studies have highlighted its role in enhancing hippocampal neurogenesis and its promise for mitigating memory impairments in neurodegenerative conditions, including Alzheimer's disease.
- While drugs like donepezil and memantine, primarily prescribed to alleviate Alzheimer's disease symptoms, are not directly aimed at neurogenesis, studies suggest they may have secondary effects on hippocampal neurogenesis. These effects are thought to arise from cholinergic modulation and their influence on the brain's neurogenic niches(8).
- **Stem Cell Therapies**: Neural stem cell transplantation has emerged as a promising approach to restore neurogenic activity in the hippocampus. Experimental studies in rodent models of Alzheimer's disease have shown that transplanted Neural stem cells can integrate into existing neural networks, improve synaptic connectivity, and reverse cognitive impairments. These therapies aim to replenish the depleted Neural stem cell pool and reestablish neurogenesis, offering a potential pathway to halt or reverse disease progression(9).
- **Epigenetic Modulators**: Epigenetic regulation has garnered attention for its ability to modulate neurogenesis. Histone deacetylase (HDAC) inhibitors, such as vorinostat, function by altering chromatin structure to promote the expression of neurogenic genes. These compounds enhance the survival and differentiation of Neural stem cells and are being explored for their therapeutic potential in Alzheimer's disease. By targeting epigenetic mechanisms, HDAC inhibitors may address the underlying deficits in neurogenesis and improve cognitive outcomes(10).

Table 2 Comparison of Neurogenesis-Promoting Agents

Category	Agent	Mechanism	Potential Benefits	Limitations
Small Molecules	P7C3	Protects newborn neurons from apoptosis and promotes their survival.	Improves cognitive deficits in Alzheimer's disease models.	Limited to preclinical studies; efficacy in humans unconfirmed.
	Isoxazole-9	Stimulates neural progenitor cell differentiation into mature neurons.	Enhances hippocampal neurogenesis and memory.	Limited data on long-term effects and safety.
	Donepezil & Memantine	Indirectly modulates hippocampal neurogenesis via cholinergic pathways.	Secondary effects on neurogenic niches; symptom relief.	Primarily symptom-focused; neurogenesis effects are not primary or robust.
Stem Cell Therapies	Neural stem cell Transplants	Restores Neural stem cell pools and integrates into neural circuits.	Improves synaptic connectivity and reverses impairments in rodent models.	Limited to experimental settings; immune rejection and ethical concerns may pose challenges.

Epigenetic Modulators	HDAC Inhibitors	Modifies chromatin structure to upregulate neurogenic genes.	Promotes Neural stem cell survival and differentiation; gene activation.	Risk of off-target effects; long-term safety and specificity remain uncertain.

4. Role of natural products

Natural products derived from plants and dietary sources are increasingly recognized for their neurogenic potential. These compounds exhibit multifaceted effects, including antioxidant, anti-inflammatory, and neuroprotective properties, making them promising candidates for countering neurodegenerative diseases like Alzheimer's Disease.

- Curcumin**:** Derived from turmeric, curcumin mitigates oxidative stress and inflammation, both of which are key contributors to neurodegenerative processes in Alzheimer's disease. Additionally, curcumin enhances brain-derived neurotrophic factor (BDNF) expression, which is crucial for hippocampal neurogenesis and synaptic plasticity. Studies have demonstrated its ability to reverse amyloid-beta-induced cognitive deficits and neuropathology in experimental models. (11).
- Resveratrol: This polyphenol, abundant in grapes and red wine, is a potent activator of sirtuin-1 (SIRT1), a pathway associated with neuroprotection and longevity. Resveratrol has been shown to enhance hippocampal neurogenesis, protect against oxidative damage, and modulate neuroinflammation, making it a promising therapeutic candidate for Alzheimer's disease (12).
- Ginsenosides: Extracted from ginseng, ginsenosides possess neuroprotective and neurogenic properties. These compounds promote the survival and differentiation of neural stem cells and have been shown to improve cognitive performance in preclinical models of Alzheimer's disease. Their multifaceted effects position ginsenosides as promising agents for neurogenesis enhancement(13).
- Epigallocatechin gallate (EGCG): Found in green tea, EGCG supports hippocampal neurogenesis and protects against oxidative stress, contributing to enhanced cognitive functions(14).
- Bacopa monnieri: Known for its cognitive-enhancing effects, Bacopa monnieri improves synaptic plasticity and promotes neurogenesis, as evidenced by clinical and preclinical studies(15).

5. Challenges in Translational Research

Despite promising results in preclinical studies, translating neurogenesis-based therapies to clinical applications is fraught with challenges:

- Ethical Concerns: Stem cell therapies, particularly those involving embryonic sources, face ethical scrutiny. Clear regulatory guidelines and public acceptance are vital for progress.
- Delivery Mechanisms: Delivering neural stem cells or drugs across the blood-brain barrier (BBB) remains a key obstacle. Innovations like nanoparticle carriers and intranasal delivery systems are being developed to improve brain targeting (16).
- Patient Variability: Individual differences in genetics, lifestyle, and comorbidities significantly impact therapy outcomes. Personalizing treatment protocols is essential to maximize effectiveness.
- Long-Term Safety: Risks like tumorigenesis and ectopic differentiation of transplanted cells raise concerns. Pre-differentiation of cells and strict monitoring are strategies under investigation to mitigate these risks (17).

6. Conclusion

Neurogenesis holds significant potential as a therapeutic strategy for Alzheimer's Disease, offering hope for reversing neuronal loss and enhancing cognitive function. While progress in understanding molecular pathways and developing treatments is encouraging, challenges like safety concerns and effective delivery remain. Moving forward, a collaborative effort is essential to refine these therapies. Integrating neurogenesis-focused strategies with existing treatments could pave the way for a more effective and holistic approach to Alzheimer's management.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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