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TREATING ALZHEIMER'S DISEASE BY TRANSPLANTATION OF NEURAL STEM CELLS

Korina Pervan
University of Zagreb, School of Medicine
0009-0002-1927-1698

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuronal death and brain atrophy. Although its prevalence is on the rise, there is no effective cure yet, so the treatment is only symptomatic. As a result of the devastating symptoms, AD is becoming an increasing social and economic problem. Currently, there are two key indicators of the disease: tau protein tangles and beta-amyloid plaques. With that in mind, there is a need for new treatment options, and transplantation of neural stem cells (NSCs) arises as a potential candidate. NSCs are multipotent cells found in the nervous system, primarily in two parts of the hippocampus in the adult brain. With the potential to differentiate into many kinds of neural cells, they provide promising grounds for research and transplantation trials on rodents. However, there are still many obstacles to the initiation and execution of clinical trials on humans which could lead to more significant advancements in the future.

KEYWORDS: Alzheimer's disease (AD), amyloid β, neural stem cells (NSCs), rodent models, tau protein, transplantation therapy

INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disease and the leading cause of dementia. In 2018, the World Alzheimer Report estimated the global prevalence of dementia to be about 50 million people, two-thirds of which have AD.[1] According to recent studies, the prevalence of AD in Europe was 5.05% (95% CI, 4.73-5-39), with higher rates recorded in the south, in Italy, Greece and Spain.[2] The disease is characterized by progressive memory loss, executive dysfunction, aphasia, and apraxia due to neuronal death, loss of synapses, and neuroinflammation leading to brain atrophy (Figure 1.). The current hypothesis attributes these pathological effects to amyloid plaques formed by the extracellular deposition of amyloid β (Aβ) and the formation of neurofibrillary tangles, consequent to the intracellular accumulation of hyperphosphorylated tau protein. While the complete etiology is unknown, multiple risk factors are associated with the onset of the disease, including genetics, aging, infections, sociopsychological and environmental factors, toxin intake, immunity, and others.[3] The influence of these factors varies depending on the type of AD. Early onset AD is responsible for less than 10% of AD cases, manifesting in the age range from 30 to mid-60s. This type of AD is directly linked to mutations of the genes coding for amyloid precursor protein (APP) on chromosome 21, as well as presenilin 1 and presenilin 2 on chromosomes 14 and 1, respectively.[4] On the contrary, late-onset Alzheimer's is the more common type, with peak presentation in the sixth decade of life and later. Unfortunately, there are no specific mutations leading to this type of AD that would provide a starting point for research, but several risk factors have been discovered. Well-known is the increased risk for people who have one or two APOE ε4 alleles which code for apolipoprotein E4, an isoform of a molecule with a crucial role in lipid metabolism.[5] However, that specific isoform has been associated with lower Aβ clearance and increased plaque formation along with Aβ-independent effects on AD pathophysiology.[5] Furthermore, recent studies have identified at least a dozen other alleles that could have a role in AD pathogenesis.[4] Although the latest treatments aim to decrease Aβ levels in the extracellular matrix, currently none of those are approved for clinical use, which still mainly relies on NMDA receptor antagonists and acetylcholine esterase inhibitors, such as memantine and donepezil respectively.[6]

NEURAL STEM CELLS

As opposed to the developing brain, in the adult brain neural stem cells (NSCs) remain restricted to the subventricular zone and the granular layer of the dentate gyrus in the hippocampus.[3] As visualized in Figure 3, such an anatomical location, including the surrounding cells, is known as the ''stem cell niche'' due to its role in the regulation of NSCs.[7]

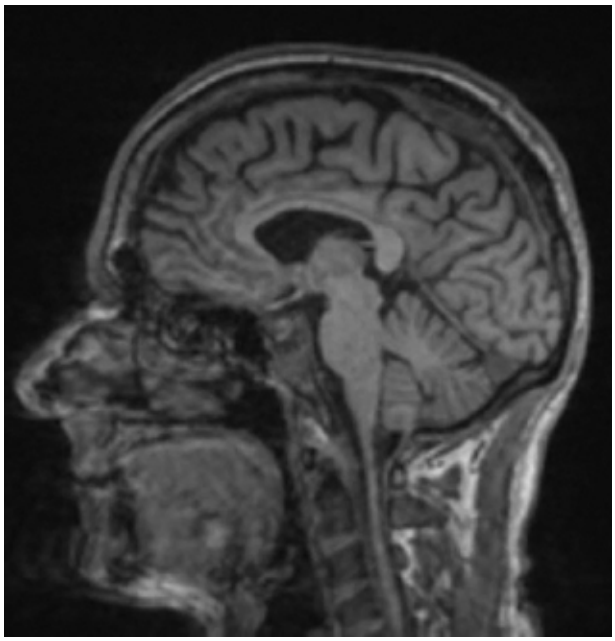


Figure 1. MRI image of the brain of a 50-year-old man with Alzheimer's disease.

The expanded sulci and narrowed gyri are visible, which are recognizable morphological characteristics of the disease.

Source: Wibawa P, Alzheimer's disease: with apraxia. Case study, Radiopaedia.org
Permalink: https://radiopaedia.org/cases/54763; DOI: https://doi.org/10.53347/rID-54763; (Accessed on 05 Dec 2023; case published on 03 Aug 2017). Available under the CC BY-NC-SA 3.0 Unported license (https://creativecommons.org/licenses/by-nc-sa/3.0/deed.en).

Their proliferative potential includes self-renewal and differentiation into new neurons, oligodendrocytes, and astrocytes. In rodent AD models, many potentially therapeutic effects have been observed, including paracrine release of neuroprotective and immunomodulatory molecules resulting in decreased neuroinflammation, as well as a decrease in tau protein and Aβ levels.[3] These phenomena are shown to stimulate neurogenesis, synapse formation, as well as cognitive deficit reversal.[3] However, probably the most important recorded mechanism by which NSCs establish their therapeutical effects is neurogenesis and increasing synaptic density without altering Aβ levels.[6] Notably, Ljila et al. (2015) transplanted human-derived NSC (hNSCs) into mice exhibiting neurodegeneration and by using an early neuronal marker showed that the neurogenesis after transplantation primarily stemmed from endogenous neurogenesis, rather than exogenous, transplanted NSCs.[8] One of the mechanisms behind that effect could be NSC-mediated secretion of brain-derived neurotrophic factor (BDNF) and higher expression of its tyrosine receptor kinase B (TrkB), with consequent activation of the BDNF/TrkB signaling pathway. In the brains of individuals with AD, the activity of this pathway is decreased and the decrease correlates positively with the degree of cognitive deterioration. The subsequent pathway activation after NSC transplantation results in upregulation of long-term potentiation (LTP) in CA1 synapses in the dentate gyrus of the hippocampus, thus enhancing the learning process and memory, not only via neurotrophic effects on the endogenous stem cells, but also by halting further neuronal deterioration and repairing damaged neurons.[9]

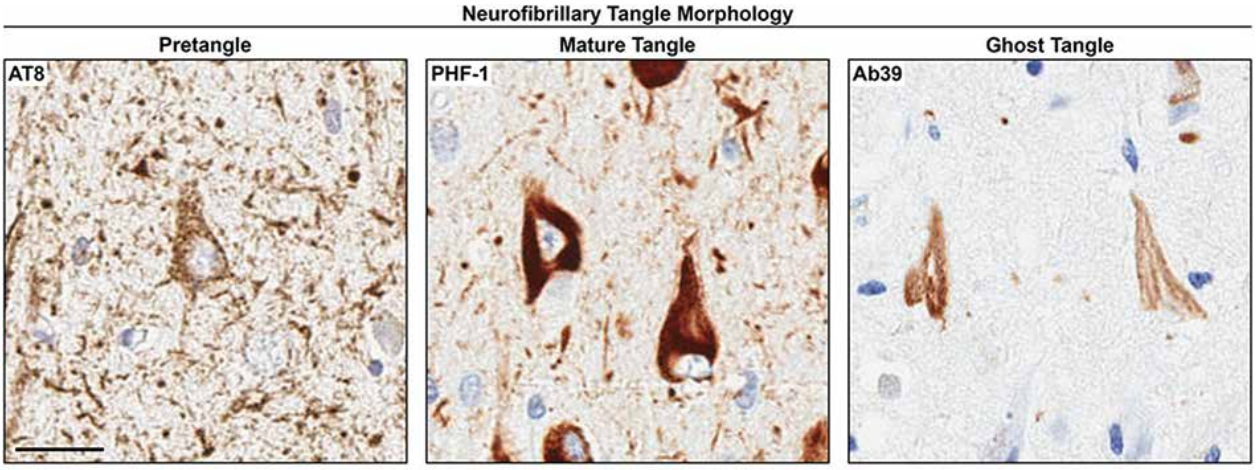


Figure 2. Formation of neurofibrillary tangles.

In the hippocampus, neurofibrillary tangles (NFTs) go through different stages of maturation. Initially, tau protein accumulates in the perinuclear space forming pretangles that show granular staining. As they mature, tangles become denser and take on the shape of the neuron, dislocating its nucleus and eventually leading to neuronal death. Ghost tangles are made of scattered remnants of fibers from mature tangles after the neuron has died.

Source: Moloney CM, Lowe VJ, Murray ME. Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. Alzheimer's Dement. 2021; 17: 1554–1574. https://doi.org/10.1002/alz.12321
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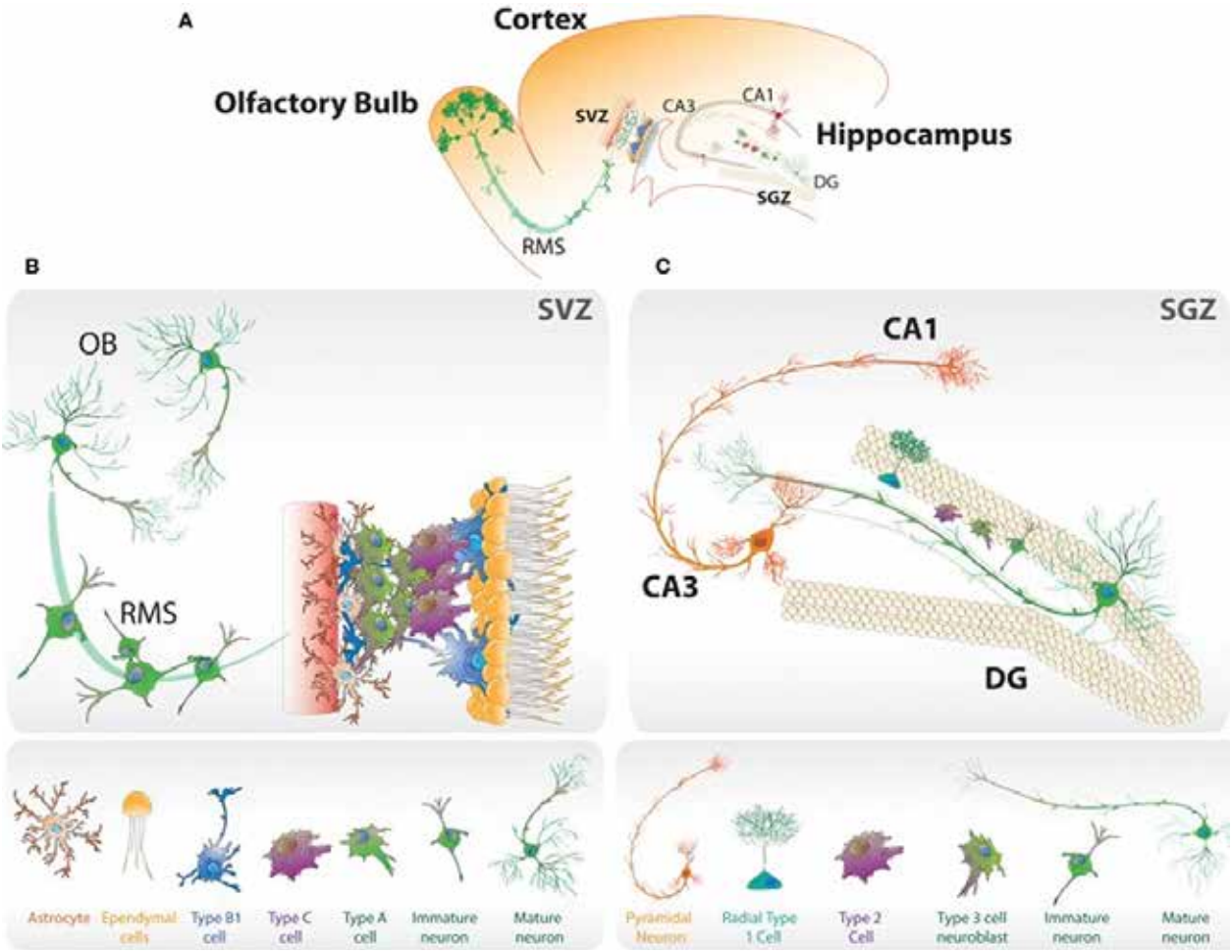


Figure 3. Neural stem cell niches.

The image shows the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus (DG) in an adult rodent brain. (B) In the SVZ niche, B1 cells represent neural stem cells. (C) Neurogenesis in the SGZ. Radial type 1 cells give rise to type 2 cells that differentiate into type 3 neuroblasts that become immature neurons and then mature into granule neurons that migrate into the granule cell layer.

Source: Varela-Nallar L, Inestrosa NC. Wnt signaling in the regulation of adult hippocampal neurogenesis. Front Cell Neurosci. 2013 Jun 26. DOI: 10.3389/fncel.2013.00100. PMID: 23805076
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THE ROLES OF AMYLOID B AND TAU PROTEIN IN AD PATHOGENESIS

Aβ is widely recognized as one of the most important causes of AD because of its accumulation in the extracellular matrix. Its synthesis starts by cleavage of amyloid precursor protein into soluble amylase precursor protein, which is then released outside the cell, and C99, which is further cleaved intracellularly into APP intracellular domain and Aβ. Amyloid β is usually cleared from the brain because of its tendency to form insoluble, toxic plaques, but in AD this process is impaired leading to neuronal damage and death. On the other hand, tau protein activity is diminished in AD because of the hyperphosphorylation caused by an imbalance in kinase activity. In a healthy brain, it has a role in stabilizing axonal microtubules using its microtubule-binding region. Consequently, in AD, there is accumulation of the inactive tau protein form into neurofibrillary tangles (NFT) inside of the cell, inducing further neuronal deterioration (Figure 2).[3]

NEURAL STEM CELLS IN AD RODENT TRIALS

Numerous transgenic rodent models play a crucial role in research; nonetheless, their significance remains uncertain given the intricate nature of the human brain compared to rodents as well as the complexity of AD pathophysiology.[6] To replicate AD brain pathology in rodents, it is necessary to introduce mutations to genes coding for amyloid precursor

protein, which causes Aβ plaques to form, and presenilin 1, which in physiological conditions elevates the production of Aβ. These mice are known as APP/PS1 and are the most widely used, followed by the 3xTg and Tg2576 models.[10] The 3xTg model is triple transgenic, carrying mutations for APP Swedish, MAPT P301L, and PSEN1 M146 V, making it the first transgenic model able to express both formation of neurofibrillary tangles and amyloid β plaques. Tg2576 model mice carry only the human APP Swedish mutation resulting in a dramatic increase in Aβ production. However, with a lack of cognitive deficits it is considered as a partially satisfactory model.[6] Recently, there has been a meta-analysis by Zhou et al. including 30 rodent trials using NSC transplantation.[10] The models used were mostly APP/PS1. In most of the trials, the Morris water maze experiment was used for the cognitive assessment of the animals. The NSC treatment group consistently showed lower escape latency compared to the control group, suggesting an improvement in learning and memory. Additionally, increased synaptic density has been confirmed by using the expression of the SYP protein which is likely associated with the formation of synaptic vesicles. Furthermore, it was shown that both allogenic and xenogeneic transplantations lead to an improvement in cognitive function.[10]

HUMAN AND MURINE-DERIVED NSCS

There are different approaches in terms of the origin of NSCs for transplantation. Li et al. (2016) bilaterally transplanted hNSCs into the murine hippocampus which resulted in the restoration of recognition and memory deficits. Although Aβ levels did not decrease, synaptic and neuronal density improved which suggests that neural connectivity was enhanced. Notably, there have been additional studies that did manage to decrease Aβ levels, yet this success was limited to specific subtypes of Aβ. Studies that used murine-derived NSCs (mNSCs) showed diverse effects, including differentiation into new neurons, which enhanced memory, behavioral improvement, and synaptic density. However, the majority of the studies were also unable to solve the problem of Aβ plaques despite the beneficial effects.[11] Even though these effects have not yet been fully understood, trials suggest many similarities in outcomes using hNSCs and mNSCs with both yielding promising results which can serve as another step towards further research and clinical trials.[6]

HETEROLOGOUS AND AUTOLOGOUS NSC TRANSPLANTATION

Heterologous transplantation using NSCs differentiated from embryonal stem cells (ESCs) has shown promising results in terms of improving cognitive function in rodent models.[12] Although ESCs have undergone extensive preclinical research, ethical concerns, along with uncontrolled cell growth and immunogenic effects, limit their potential therapeutical use.[12] Transplantation of autologous NSCs solves the ethical and immunogenic problems, however, tumorigenesis has still been recorded in many experiments, as has the poor survival of the cells ex vivo and differentiation into non-neuronal glia.[12] Furthermore, since NSCs are limited to inaccessible parts of the adult brain, their collection is a highly invasive procedure.[12] The solution could be in vitro reprogramming of human somatic cells from the peripheral blood.[13] Reprogrammed cells, called human induced neural stem/progenitor cells (human iNPCs), can show properties of brain NSCs without the stated risks.[13] However, further research is needed for the evaluation of their therapeutic effect.[13]

CONCLUSION

Although NSC transplantation therapy shows great promise and is one of the best new options today, further research is still necessary to implement it into medical practice. The main obstacle is our lack of understanding of the precise mechanisms of AD pathophysiology and late diagnosis when symptoms are already developed. Solutions could be to find new biomarkers that could be used to diagnose patients in asymptomatic stages to minimize further disease progression, while further research on the disease itself is imperative. The transplantation itself also faces many challenges, but focusing on the development of new equipment, improving research methods, and adjusting genetic engineering could provide more efficient and feasible solutions in the future.

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LIJEČENJE ALZHEIMEROVE BOLESTI TRANSPLATACIJOM NEURALNIH MATIČNIH STANICA

Sažetak

Alzheimerova bolest je neurodegenerativna bolest koju karakterizira smrt neurona i atrofija mozga. Iako njezina učestalost raste, još uvijek nema učinkovitog lijeka, zbog čega pacijentima preostaje samo simptomatsko liječenje. Kao rezultat razornih simptoma, Alzheimerova bolest postaje sve veći društveni i ekonomski problem. Trenutno postoje dva ključna indikatora bolesti: neurofibrilarne petlje tau proteina i plakovi beta-amiloida. Na temelju izrazite potrebe za razvojem novih vrsta liječenja, transplantacija neuralnih matičnih stanica je razmatrana kao potencijalni kandidat. Neuralne su matične stanice multipotentne stanice koje se nalaze u živčanom sustavu, na dva posebna mjesta u hipokampusu odraslog čovjeka Zbog potencijala da se diferenciraju u razne vrste neuralnih i glija stanica, neuralne matične stanice temelji su istraživanja i transplantacijskih pokusa na glodavcima. Ipak, još uvijek postoje mnoge prepreke za početak kliničkih ispitivanja na ljudima koja bi u budućnosti mogla donijeti značajnije promjene.

KLJUČNE RIJEČI: Alzheimerova bolest, amiloid β, glodavci, neuralne stem stanice, tau protein, transplantacijska terapija