Human stem cell implantation in Alzheimer’s disease

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Alzheimer’s disease (AD) is a progressive debilitating neurodegenerative disease and the most common form of dementia in the older population. At present, there is no definitive effective treatment for AD. Therefore, researchers are now looking at stem cell therapy as a possible treatment for AD, but whether stem cells are safe and effective in humans is still not clear. In this narrative review, we discuss both preclinical studies and clinical trials on the therapeutic potential of human stem cells in AD. Preclinical studies have successfully differentiated stem cells into neurons in vitro, indicating the potential viability of stem cell therapy in neurodegenerative diseases. Preclinical studies have also shown that stem cell therapy is safe and effective in improving cognitive performance in animal models, as demonstrated in the Morris water maze test and novel object recognition test. Although few clinical trials have been completed and many trials are still in phase I and II, the initial results confirm the outcomes of the preclinical studies. However, limitations like rejection, tumorigenicity and ethical issues are still barriers to the advancement of stem cell therapy. In conclusion, the use of stem cells in the treatment of AD shows promise in terms of effectiveness and safety.

Keywords: stem cells ; neurogenesis ; Alzheimer’s disease ; stem cell therapy ; neural stem cells

1. Introduction

Alzheimer’s Disease (AD) is a common neurodegenerative disease, accounting for 60–70% of neurocognitive disorder-related illnesses [1]. Neurocognitive disorder is an umbrella term covering a wide range of cognitive disorders that are increasingly common in the aging population, leading to considerable economic and societal burdens [2]. In 2015, 5.1 million individuals over the age of 65 were diagnosed with clinical AD in the United States, and over 47 million people worldwide were estimated to have neurocognitive disorders [3]. The number of cases is predicted to increase to 13.8 million in the United States and to more than 130 million worldwide by 2050 [4][5]. Key characteristic symptoms of AD include various cognitive impairments such as difficulty in remembering or recalling recent events [6]. The symptoms of AD can be categorized as mild, moderate, or severe. Individuals with mild AD symptoms are more likely to get lost, have poor judgment leading to bad decisions, increased anxiety, and personality changes. Individuals with moderate AD symptoms lose the ability to learn new things, have language problems such as reading and organizing thoughts, and have difficulty in recognizing family members. Individuals with severe AD symptoms experience weight loss, skin infections, difficulty in swallowing, and lose the ability to communicate [1].

One of the major risk factors for AD is age. A study by Guerreiro et al. identified a locus on chromosome 17 associated with onset age, with a specific variant CCL11 suspected to be associated with the onset of AD [7]. Recent studies have established an association between depression and AD [8]. In 2021, Tanaka et al. demonstrated a link between AD and late-life depression by using resting-state functional magnetic resonance imaging. The dissociated functional connectivity pattern with decreased posterior default mode network (DMN) and increased anterior DMN is commonly observed in AD and late-life depression [9]. Aside from depression, gender is also a factor for AD risk, with a greater prevalence in females than males [10][11][12][13][14]. Some studies, such as Scheyer et al., have suggested a possible link between menopause and AD [15][16][17]. More recently, Sini et al. indicated several environmental factors could lead to AD. They found that cyanobacteria, present in natural water samples, can produce four classes of neurotoxins: saxitoxins, ciguatoxins, anatoxins, and β-N-methylamino-L-alanine (L-BMAA), which can all lead to an increased risk of AD [18]. Adding to the neurological disorders elicited by AD, some infections are more prone to appear in AD patients. Infections associated with AD include pneumonia, oral herpes, and spirochete bacterial infections causing Lyme disease and gum disease. These associated infectious illnesses can lead to chronic inflammation and eventually death [19]. Nonetheless, the life expectancy of AD patients following diagnosis can be up to 9 years [6].

The high rate of neuronal loss in AD patients can make treating this disorder difficult [20]. Conventional drug treatments that can restore brain tissue and improve cognitive functions can have undesirable side effects [21]. Stem cell therapy is a potential AD therapy that can overcome these undesirable outcomes. Stem cell therapy as a treatment for neurological

disorders has been gaining interest in the field. With a self-renewal property, stem cells can go through numerous cycles of division and growth [22]. Stem cells can also differentiate into various specialized cell types [23]. These properties make stem cells a possible treatment option for AD by aiding in the proliferation and repair of damaged brain tissues [21]. Recent preclinical studies on stem cell therapy for AD have been promising and clinical trials on humans are ongoing. In this review, we first provide a brief description of AD etiology. Next, we summarize the current as well as the alternative treatments for AD. We further discuss the mechanisms of stem cells and their applications in preclinical studies and clinical trials. Lastly, we explore the limitations and possible future applications of stem cell therapy in AD.

2. Etiology of Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder involving the accumulation of senile plaques and neurofibrillary tangles. Various neuropsychological, clinical, neuroimaging, and laboratory techniques are currently used to diagnose AD [24]. Individuals with AD exhibit key neuropathological changes including the deposition of extracellular beta-amyloid peptides as senile plaques [25][26][27][28] and accumulation of intracellular tau-containing neurofibrillary tangles in the brain [29][30]. All forms of AD have been found to involve senile plaques and almost all of them share increased production and decreased clearance of amyloid-beta peptides. However, certain mutations such as the "Arctic" mutation and "Osaka" mutation not only show slightly increased levels of amyloid-beta peptides, but also increased protofibrils and aggregations, respectively [31][32]. Amyloid-beta peptides are released by the cleavage of amyloid precursor protein (APP) [6] by two enzymes, beta-secretase and gamma-secretase [33]. Gamma-secretase is closely associated with presenilin (PSEN), and mutations in PSEN1 and PSEN2 can increase the synthesis of amyloid-beta [34][35]. However, the exact mechanism of how amyloid-beta proteins cause AD is not fully understood. Scientists have proposed that the aggregation and deposition amyloid-beta plaques in the brain activate neurodegeneration, leading to key symptoms such as memory loss [36][37]. Another prominent protein in the pathogenesis of AD is tau [38], which is a microtubule-associated protein that aids in the assembly and stabilization of microtubules. In AD, tau becomes hyperphosphorylated and assembles into paired helical filaments that detach from microtubules and attach to other tau molecules. They form threads that aggregate into neurofibrillary tangles, which block neuronal transport, preventing the movement of molecules and nutrients from the cell body to dendrites and the axon, leading to disrupted synaptic communication [39].

Besides the main theories, there are several other hypotheses of the pathogenesis of AD. A current theory proposes a three-part mechanism involving decreased levels of blood lactic acid, folic acid, and increased levels of blood ceramide and adipokines [40]. These three mechanisms result in age-related characteristics, such as decreased muscle mass, change in diet, and increased visceral fat, respectively.

Lactic acid is synthesized in muscle cells and blood cells due to low oxygen levels. It is vital in supplying energy to brain cells like astrocytes and pericytes [41]. Inadequate levels of lactic acid can result in damage to the endothelial cells and pericytes in the blood−brain barrier, leading to brain damage. Studies have also shown that dietary changes in the aging population may contribute to inadequate folate intake [42][43][44][45]. As folate helps maintain the blood−brain barrier in protecting endothelial cells [46], a diet that contains adequate folate could aid in delaying the onset of AD and slow the cognitive decline in older adults [46][47]. High levels of ceramide have been discovered in the brain and blood of AD patients [48], which indicates that elevated levels of ceramide could lead to a greater risk of AD [49][50][51][52]. Ceramide induces oxidative stress and increases NADPH oxidase activity outside the plasma membrane of macrophages in the brain. This can increase hydrogen peroxide production, leading to damaged neurons in the brain [52]. Inflammatory adipokines can be secreted into the blood by visceral fat, causing arthritis, type 2 diabetes, heart disease, and neurological problems [50]. Visfatin, a type of adipokine, interacts with xanthine oxidase and NADH oxidase to boost the production of oxygen radicals in the capillary lumen. This can lead to oxidative damage in the blood−brain barrier, eventually damaging neurons [40]. In 2020, Tanaka et al. discovered increased levels of pro-inflammatory cytokines and neurotoxic kynurenines in neurodegenerative diseases including AD, which can damage the neuronal structure in the brain [53].

3. Current Treatments for Alzheimer's Disease

Although some treatments for AD are available, their effectiveness is questionable due to the nature of AD [54]. Alzheimer's disease is a multifactorial disease and is diagnosed through its clinical manifestation and underlying brain pathology. Typically, a disease should contain the following three basic factors: 1. An established biological cause, 2. A specific set of symptoms, and 3. Consistent anatomy changes. However, AD does not have an established cause and the symptoms are not well-defined. Moreover, the exact biological cause is not known, and the differential symptoms can vary from person to person, making it challenging to find a cure for AD. A study conducted by Salomone et al. noted challenges in treating AD due to the ineffectiveness of drug therapies [55]. Another review by Rijpma et al. also concluded that no

single drug and nutrient-based therapy was clinically effective against AD [56]. Nevertheless, there are currently several drugs under clinical trial, and some have even been approved as treatments for AD. Possible interventions targeting metabolites and enzymes in the kynurenine pathway of tryptophan metabolism are also under investigation [57].

The currently approved drugs mainly alleviate symptoms and slow down the disease progression [57][58][59][60][61]. The N-methyl-D-aspartic acid (NMDA) receptor inhibitor and acetylcholinesterase inhibitor (AChEI) are two classes of approved medications for clinical use [62]. Acetylcholinesterase inhibitors (AChEIs) act by inhibiting synaptic cleft cholinesterase from breaking down acetylcholine, thereby increasing cholinergic transmission in the cerebral cortex and basal forebrain [63][64]. Donepezil, rivastigmine, and galantamine are some examples of AChEI [65]. Another drug class effective against AD is NMDA receptor inhibitors. These drugs reduce the excitotoxicity generated by NMDA receptors excitation and protect the neuronal cells in the brain [66]. Memantines, a commonly used NMDA receptor antagonist, is also useful in relieving some symptoms [67]. Drugs with mechanisms of action relating to NMDA receptors are also under clinical trials [68][69]. AVP786 is a weak NMDA receptor antagonist and is currently under phase 3 trials; however, many trials have revealed it is ineffective for treating AD [70]. Another drug, BI425809, is a co-agonist of NMDA receptors and is currently being tested in phase 2 clinical trials [71]. Besides the above two drugs, gavestinel and AXS-05 are also undergoing clinical trials [72][73]. In recent years, novel drug targets have also been established. Drugs such as Solanezumab, Aducanumab, and Crenezumab are monoclonal antibodies targeting Aβ peptide [74]. These antibodies can bind to Aβ peptides and help to clear excess amyloid plaque and reduce sunaptotoxicity, eventually leading to improved cognition in AD patients [75][76][77]. Other drugs like Anavex 2–73 and GV-971 work by blocking tau hyperphosphorylation to reduce AD pathology [78].

Another way to develop drugs against AD is to repurpose existing drugs for dementia. Moreover, other drugs can be repurposed, including diabetes agents and vitamins, as well as drugs for a wide range of diseases from cardiovascular to psychiatric disorders [79]. For example, there is evidence that antioxidants (e.g., vitamin E at a dose of 2000 IU/day) can delay functional impairments [67][80]. Masitinib, a tyrosine kinase inhibitor which was originally used as a treatment for mast cell tumors, is also suggested to have anti-dementia effects [81]. Zolpidem, a sedative−hypnotic medicine prescribed for insomnia, is also a promising drug for treating AD [57][82]. Besides drug treatments, exercise programs have been shown to help AD patients physically, but they do not improve cognitive functioning [83].

Scientists are also looking at novel targets and approaches against AD. Current research includes genetic instability, post-translational modification, and lipid metabolism related to long interspersed nuclear element-1, micro RNAs, and apolipoprotein E4, respectively [84][85][86][87][88][89][90][91]. Calmodulin-binding proteins associated with calcium homeostasis [92] have also been shown to have therapeutic potential against AD. Additionally, kynurenine analogues, which are NMDA receptor antagonists and antioxidants, can reduce neurotoxicity in AD patients [53][93][94][95][96][97][98]. In 2021, Ibos et al. suggested the presence of a sex-dependent hemodynamic compensatory mechanism could also be a potential therapeutic direction in AD [99]. Diet-wise, the use of nutraceutical compounds can also possibly play a prophylactic role in AD. Supplemental use of nutraceutical inositol was suggested to prevent the onset and progression of the cognitive impairment in AD [100].

4. Alternative Strategies for the Treatment of Alzheimer’s Disease

Currently, there is no effective treatment that can cure AD. Recent clinical studies suggest that electrical stimulation might improve memory functions when specific brain regions are stimulated. Of particular interest is a single-case report in which electrical stimulation was used to treat a patient with morbid obesity, in which the electrical brain stimulation unexpectedly evoked autobiographical memory episodes in the patient [101]. In animal studies, experimental data showed that memory functions could be enhanced by stimulating the medial prefrontal cortex [102][103][104][105], entorhinal cortex, and perifornical region [106][107][108]. It has also been shown to induce antidepressant-like effects in animal studies [109][110]. Nevertheless, without in-depth mechanisms of preclinical studies, it is still a very premature phase to draw any conclusion on whether electrical stimulation will be suitable as a treatment for patients with dementia.

Drug therapies for AD, mainly given on an individual basis, can only temporarily improve some symptoms, but cannot stop or slow down the neurodegenerative process [111]. The low efficacy of these drugs is exemplified in the high risk/benefit ratio of AChEIs, where symptoms are only slightly improved when compared with a placebo [112]. Due to the low efficacy of current treatments, pharmaceutical companies and medical institutes have been actively seeking alternative therapies for AD, including stem cells transplantation.

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