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Stem Cells and Lithium with Regards to Alzheimer's Therapy

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ABSTRACT

Alzheimer's Disease is a condition caused by neural plaques and tangles that affects the lives of millions of people worldwide. The average life expectancy after the initial dementia diagnosis in the United States of America is about 3-4 years. Currently, there is no complete cure for the disorder. However, recent research has been investigating the therapeutic effects of both stem cells and lithium. Stem cells are cells that have the capability to differentiate into other cells when necessary to assist in damage repair. As neurons die off in Alzheimer's patients, certain types of stem cells have been shown by several studies to be effective in increasing the proliferation of neurons, astrocytes, and oligodendrocytes. Furthermore, stem cell proliferation associated with their transplantation into the brains of rodent models has been studied, and the results demonstrated that rodents had an increased level of cognitive and motor functioning. Lithium has been more recently studied in combination with MSC transplantation therapy and provided promising results, in that it was able to increase neuronal proliferation and differentiation. Alone, lithium is the most potent inhibitor of the GSK-3β pathway that, when hyperactive, leads to the development of Alzheimer's Disease. This finding has given way to studies that have been able to show that lithium can decrease the plaques and tangles, stemming from Tau hyperphosphorylation, that characterize AD.

Keywords

Alzheimer's Disease, Neural plaques, Lithium, Stem cells.

Abbreviations

AD: Alzheimer's Disease, FDA:- Food and Drug Administration, mmol: millimole, L: Liter, MSC: Mesenchymal Stem Cell, CNS: Central Nervous System, ERK1/2: Extracellular Signal-Regulated Kinase ½, NSC: Neuronal Stem Cell, ESC: Embryonic Stem Cell, mESC: Mouse Embryonic Stem Cells, IPSC: Induced Pluripotential Stem Cell, WNT: Wingless/Integrated, APP: Amyloid Precursor Protein, PSEN1: Presenilin 1, PSEN2: Presenilin 2, APOE ε4: Apolipoprotein E4, GSK-3β: Glycogen Synthase Kinase 3 Beta, NPC: Neural Progenitor Cell.

Introduction to Lithium

Lithium is a silvery-white alkali metal with an atomic number of three. It is found non-uniformly throughout the earth's crust, within almost all igneous rocks, and combined with many other minerals in several springs. This element is not found alone in nature due to its properties of high reactivity and flammability. Johann August Arfvedson first discovered lithium in 1817 [1]. Today it serves many uses: incorporation into batteries, assistance in obtaining tritium, and the treatment of certain medical diseases and disorders in the form of a drug [1].

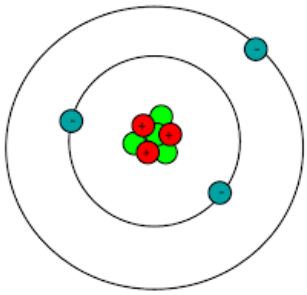

Figure 1: The atomic structure of lithium [2].

History of Lithium as Medication

Lithium was first discovered by Johann August Arfvedson in 1817 in Stockholm, Sweden [1]. Later that century, around 1847, lithium began being used to treat gout by Alfred Baring Garrod. This was due to lithium's effective ability to dissolve uric acid crystals that were found in abundance in the blood of gout patients [3].

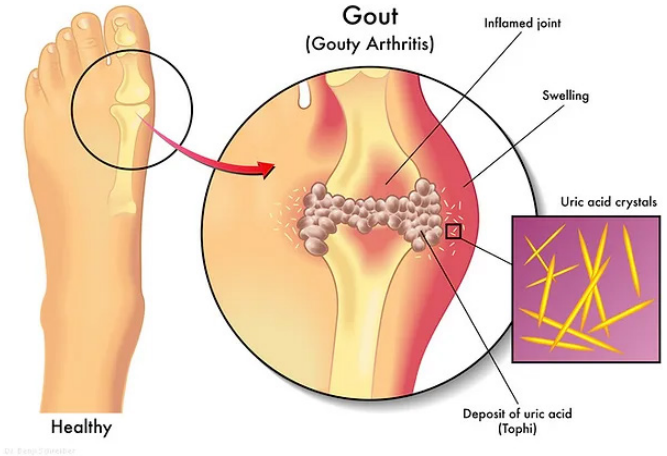

Figure 2: An example of the inflammation exacerbated in Gout reversed with lithium [4].

William Hammond became the first physician to prescribe lithium as a mood stabilizer in 1871 [5]. He deduced that it calmed patients who were in a manic state through a reduction of blood in the cerebral vessels [5].Following this, there were very few mentions of lithium within psychiatric literature until the mid-20th century when John Cade sparked its revival. Hypothesizing that a condition involving uric acid may be the cause of his patients' manic episodes, Cade designed an experiment to test the effectiveness of lithium as a potential treatment [3]. Some of his patients experienced immense benefits from the trial and were able to finally be discharged after years of suffering [3]. Unfortunately, this experiment was published as an article in a more obscure journal, and it was released shortly after a separate lithium trial had tarnished the drug's name with its failure to treat congestive heart failure [3]. The result was that lithium, once again, did not receive the proper recognition it deserved.

In 1952, lithium finally made its resounding breakthrough within the medical field. Mogens Schou randomized a group of patients who experienced mania and gave them either a lithium or a placebo treatment [3]. This trial produced results that allowed for the conclusion that the administration of a maintenance dose of lithium can assist patients in keeping a normal state of mind [3]. The only matter in question remaining regarding the treatment was that physicians' assessments of the level of lithium in a patient's blood were no more than mere conjectures. This obstacle was quickly overcome with the introduction of the Coleman Flame Photometer in 1958, an invention that made boundless therapeutic lithium usage possible [3].

Figure 3: The first Coleman Flame Photometer in use [2].

Lithium in Recent Medicine

Despite its proven healing power, only about one percent of lithium on earth, currently, is used for medical purposes [1]. As of 1970, lithium is an FDA-approved, mood-stabilizing medication for bipolar disorder [5]. It is currently the most extensively studied, standard treatment, especially in terms of prophylaxis of the disorder [7]. Although the exact mechanism of mood stabilization is not well understood, it is known that lithium acts on the central nervous system to decrease abnormalities in brain activity [8]. Much literature contains evidence that the underlying pathway for this involves neuronal plasticity due to lithium's relief of the dysregulation of glial-neuronal interactions in patients with bipolar disorder [9]. Based upon the results produced by its large volume of studies, many physicians have found that lithium is effective in reducing depressive, schizophrenic, and impulse control symptoms of certain disorders, as well [10].

Contraindications and Complications of Lithium

Despite the drug's proven efficiency in the treatment of certain patients, it may not be the paramount choice of therapy for others. Firstly, those with decreased renal function should not use lithium because lithium is excreted by the kidneys, so reduced functioning will ultimately lead to the accumulation of lithium [11]. This accretion eventually gives rise to toxicity [12].

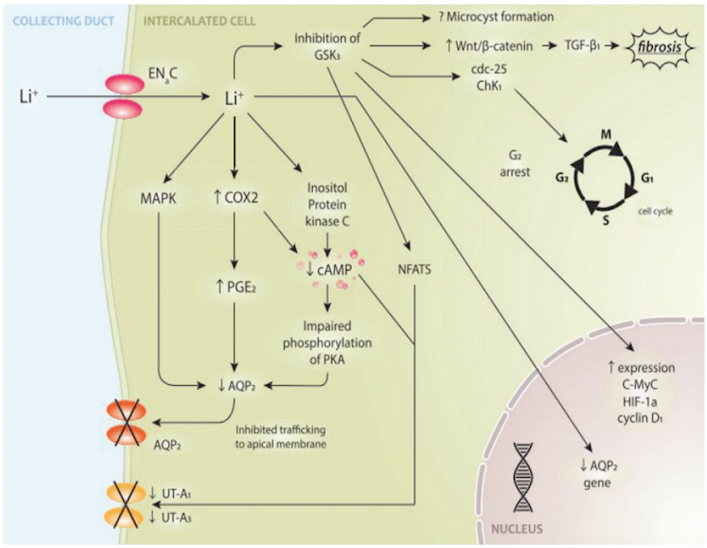

Figure 4: The effects of lithium on the kidney [13].

Secondly, patients with thyroid issues must be closely monitored in response to the prevalence of hypothyroidism found in those administered lithium. The pathology for this complication is associated with lithium's influence on thyroid-stimulating hormone, thyroxine, and triiodothyronine, as well as its positive correlation with the number of thyroid autoantibodies circulating in the bloodstream and the development of thyrotoxicosis [12]. With the presence of these side effects to a lesser degree, but still worth noting, lithium may induce or worsen hyperparathyroidism and excessive weight gain [11]. Patients who suffer from these clinical obstacles prior to lithium prescription should be closely monitored if being started on lithium therapy.

In a more severe light, lithium intoxication is a potential outcome of unregulated lithium usage. This occurs when the plasma levels indicate that there is a presence of more than 1.2 mmol/L of lithium [5]. The onset of this malady often presents itself in the form of, but is not limited to, confusion, tremors, nausea, vomiting, polyuria, arrhythmia, low blood pressure, and/or respiratory distress [5]. In extreme cases, this ailment may be fatal.

What are Stem Cells?

The classification of "stem cell" is more of an overarching term that encompasses many different subcategories. Despite the differences between the specific types, there are several similarities that lead to their generalization in a grouping. Stem cells have a unique ability to renew themselves, as well as to differentiate into particular cell types that are needed throughout the body [14]. They allow for insight into the etiology of specific diseases when studied in laboratories, the generation of unimpaired cells that may replace those that are diseased in regenerative medicine, and the investigation of the effectiveness of specific-cell-targeting drugs [14].

Main Forms of Stem Cells

Pluripotent stem cells are stem cells that are found within embryos, aged three to five days old [14]. During this phase of development, the embryo is classified as a blastocyst. This type of stem cell can be subject to differentiation to become any type of cell in the body, or they may undergo division to generate new pluripotent stem cells [14]. These cells exhibit a high level of versatility and are crucial for the processes of regenerative medicine.

Mesenchymal stem cells, or adult stem cells, are less active and more limited in their differentiation capabilities [14]. These stem cells typically remain quiescent unless there is a need for them to repair tissue [14]. Furthermore, mesenchymal stem cells are typically found in definitive anatomical locations throughout the body that generally create system-specific cells. Current research involves genetically reprogramming adult stem cells to enclose the same properties as embryonic stem cells; these reprogrammed cells are referred to as induced pluripotent stem cells [14].

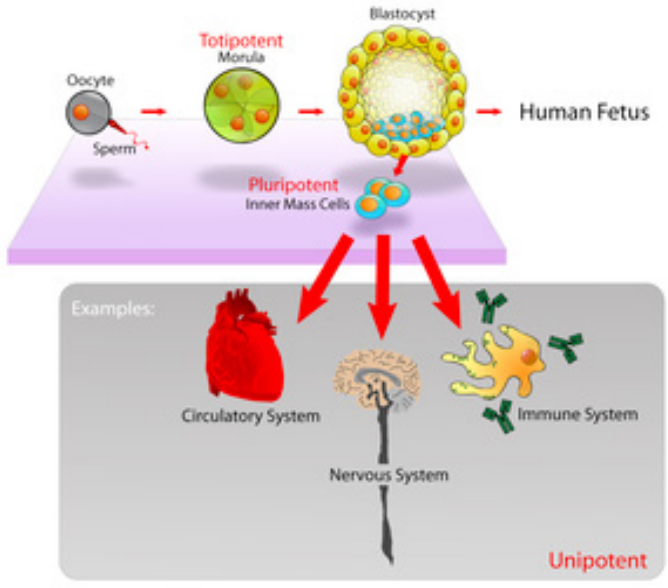

Figure 5: The formation and possible life courses for pluripotent stem cells [15].

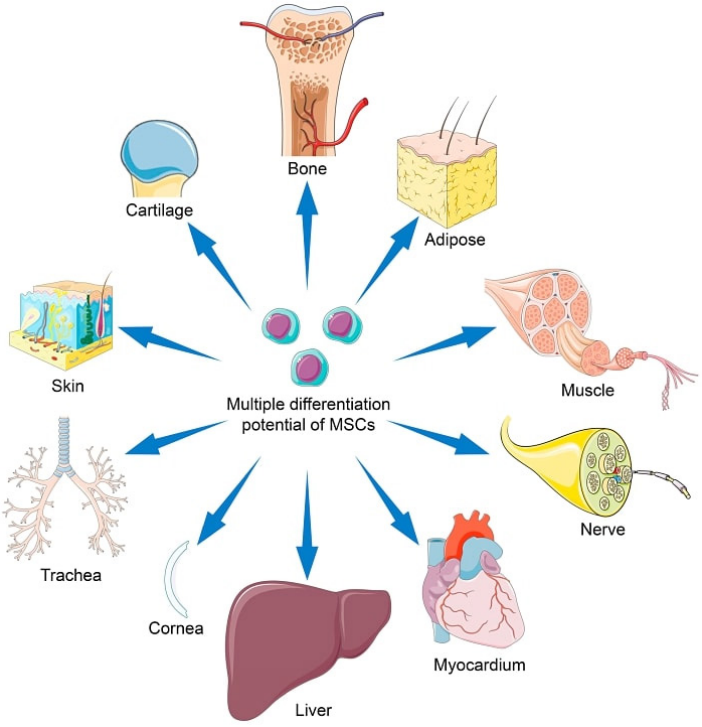

Figure 6: The differentiation possibilities of MSCs[16].

Mesenchymal Stem Cells and Lithium

Lithium has been found to positively influence the preservation and proliferation of adult stem cells. A 2015 study involving the transplantation of mesenchymal stem cells into the spinal cords of

rats provided evidence for the claim that the addition of lithium into an environment containing adult stem cells enhanced the vitality and neural differentiation of these transplanted cells [17]. The data collected suggested that lithium could prove to be an effective therapeutic measure for central nervous system disorders when used in combination with stem cell transplantation therapy. A similar study conducted in 2021 resulted in comparable outcomes. Additionally, this more recent study found that preconditioning of lithium induced the upregulation of the cellular reactive oxidative species levels and the activity of ERK1/2 in cells, which was discovered to be closely aligned with cell endurance [18]. The lithium-treated, transplanted stem cells in this study had a strengthened adaptability to hostile environments in comparison to transplanted stem cells that were not treated with lithium [18]. Thus, allowing for lithium to be a variable worth considering in future reparative and regenerative medicine therapies that involve stem cell transplantations. Yet another study found that lithium increased both the expression of cyclin D1 (a transcription factor) and the magnitude of MSCs in the replication phase of the cell cycle [20]. This provides direct evidence for the claim that lithium assists in stimulating MSC proliferation.

Neural Stem Cells

The stem cells that give rise to the nervous system during an organism's development are referred to as neural stem cells. The central nervous system is derived from a group of neural stem cells that are found along the neural tube during early embryonic development. These neural stem cells go on to differentiate into neurons, astrocytes, and oligodendrocytes- the three main cell types in the CNS.

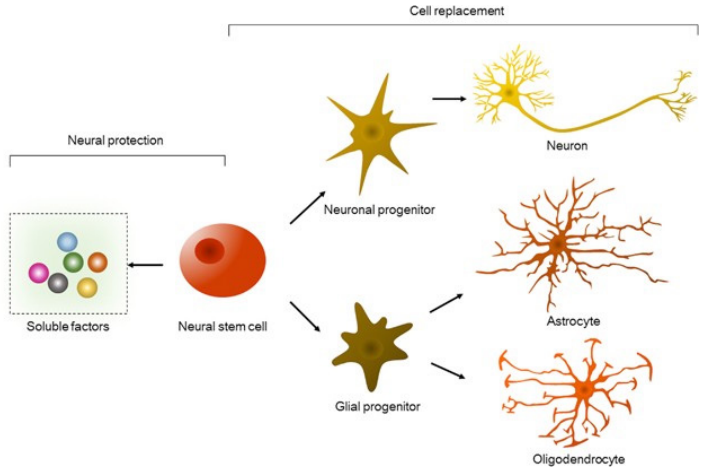

Figure 7: The differentiation process of an NSC [21].

With the aging process, neural stem cells often become confined to certain areas of the brain. It has been discovered that this limited NSC availability in the adult brain occurs due to both intrinsic and extrinsic factors involving the cell, such as transcriptional regulation and cell contact-dependent signals, respectively [22].

Neural Stem Cells and Lithium

In previous studies, lithium has been shown to increase both neurogenesis and the production and differentiation of neural progenitor cells in the hippocampus of rodents. Lithium appears to be a promising candidate for the promotion of the proliferation of neural stem cells because it induces endogenous stem cell production, which is the only route possible for NSC synthesis [23]. Moreover, lithium stimulates the neurogenesis process through its assistance in the self-renewal mechanism of neural progenitor cells [23]. Yet another well-studied, beneficial outcome of lithium is that it has been shown to enhance the mitotic activity of Schwann Cells, which is most likely a key factor in the neuroprotective and neurotrophic effects exhibited by the drug [23]. These effects allow for an increased cell survival rate and a decreased amount of apoptosis- both aspects of the cell's lifespan that are dysregulated in neurodegenerative diseases.

Introduction to Alzheimer's Disease

The most common form of dementia among the elderly population, Alzheimer's Disease affects over 6 million Americans as of the year 2023 [10]. Recent studies have shown that its prevalence is expected to triple by the year 2050 with the most affected areas being low- and middle-income communities [10].

Alzheimer's Disease is known to initially damage the hippocampus and the entorhinal cortex, both areas that assist in memory formation [24]. Over the course of the disease's onset, normally functioning neurons begin to lose their functionality, surrender their connections with surrounding neurons, and eventually die off. As the illness progresses, neuronal death spreads to several different areas of the brain, causing the brain to shrink significantly [24].

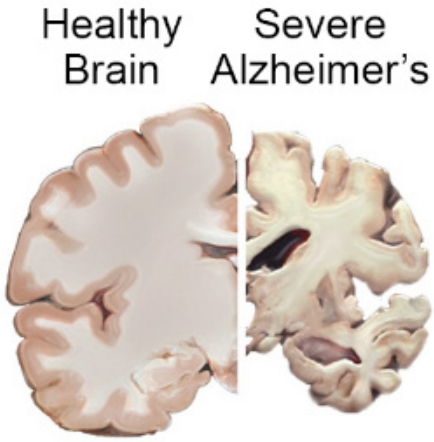

Figure 8: A comparison of the brains of a healthy person vs. a patient with Alzheimer's [24].

Causes of Alzheimer's Diseases

The exact etiology of Alzheimer's Disease is not currently entirely understood. However, there are several factors that are typically associated with its cause, such as age, genetics, and toxic changes in the brain (plaques and tangles) [25]. The aging process naturally involves atrophy, blood vessel damage, the increased production

of free radicals in the brain, and a larger presence of mitochondrial dysfunction- all of which are being studied as potential contributors to the onset of Alzheimer's Disease [19]. There are also several genes that have been linked to the inheritance of Alzheimer's Disease: *APP, PSEN1, PSEN2*, and most strongly, *APOE ε4* [23]. According to twin studies, the risk of Alzheimer's has been shown to be 60-80% heredity-dependent [23]. The fundamental characteristics of Alzheimer's Disease are changes in the brain in the form of amyloid plaques, tau phosphorylation and tangles, and microglia-mediated inflammation [25].

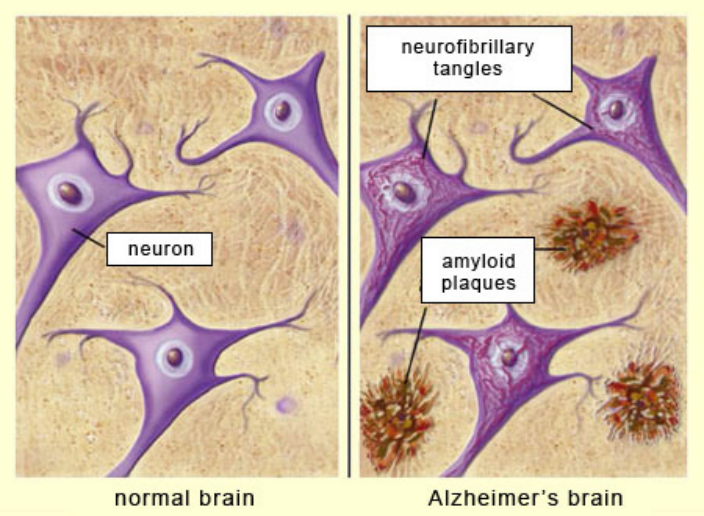

Figure 9: A comparison of the neurons of a healthy person versus those of an Alzheimer's patient [26].

Stages of Alzheimer's Disease

There are three classificatory stages of Alzheimer's Disease: mild, moderate, and severe. Mild Alzheimer's is characterized by cognitive slowing and difficulties [23]. Examples would include difficulty handling financials and repetitive language. This is typically the stage where patients are diagnosed with the disease. Moderate Alzheimer's is associated with widespread damage to many of the brain's control centers, including those that maintain language, reasoning, and sensory processing [23]. Patients in this stage usually deteriorate to the degree that they are no longer able to recognize once-familiar people. Impulsive behavior due to paranoia and hallucinations is a major element of this phase. Severe Alzheimer's patients are unable to communicate or take care of their own basic needs [23]. Their bodies begin to shut down and they are typically bedridden. This stage involves the fatality aspect of the illness.

Diagnosis and Treatment of Alzheimer's

Diagnosis of Alzheimer's ordinarily involves skill-specific testing, the measurement of proteins related to the disease through the collection of cerebrospinal fluid from the patients, and brain scans that rule out other possible explanations for the symptoms being demonstrated. Most of the diagnostic tests for Alzheimer's take place after screening for other disorders and diseases that could be related to the presenting symptoms, such as depression, medication use, stroke, tumors, and/or fluid buildup in the brain [27].

Due to its complexity, there is not currently a singular drug that is capable of entirely curing the disease [27]. Most therapies work to target the underlying causes and symptoms to slow the progression. For mild Alzheimer's patients may experience improved symptom management from Cholinesterase inhibitors [27]. These drugs work to prevent the breakdown of acetylcholine- a chemical involved with memory and cognition [27]. Acetylcholine is known to be produced less in the brain as the disease progresses, so eventually, these drugs become essentially ineffective [27]. Another group of drugs used during the mild stage of Alzheimer's works to reduce amyloid plaques; these drugs, lecanemab and aducanumab, have effectively shown the reduction of amyloid plaques, but have not been overly successful in slowing the cognitive decline associated with the disease [27]. Finally, the drug, memantine, is sometimes given to patients who are in the moderate and severe stages of Alzheimer's Disease [27]. Memantine works to regulate the levels of glutamate in the brain; glutamate is a neurotransmitter that when produced in excess amounts, causes brain cell death [27]. This drug helps to decrease symptoms and enables patients to maintain the autonomy of their daily functions for longer than they would be able to without the medication.

Stem Cells and Alzheimer's Disease

Choline-rich NSCs were transplanted into rats with brain damage that recreated Alzheimer's effects, and the results of the study included a significant reduction in Alzheimer's-like symptoms [28]. Another impactful study run by Wu et al. entailed transplanting human fetal brain derived NSCs into the brains of adult rats; this led to the production of cholinergic neurons in certain brain regions [28]. Furthermore, a study performed by Wu et al. where ESC-derived neurospheres were transplanted into the prefrontal cortex of mice showed high survival and differentiation rates [28]. The results of this study were characterized by a reduction in the rate of working memory errors; the control mice that received no cell transplantation showed significant declines in the efficiency of their working memory [28].

MSCs have been more widely studied for their therapeutic effects on Alzheimer's Disease due to their increased accessibility [28]. One study, where human MSCs were transplanted into rats, showed that the stem cells were able to migrate to the brain and restore cognitive and motor functioning through their differentiation into neurons [28]. Another study involved the transplantation of bone marrow MSCs into the hippocampus of rats, and the results demonstrated that they were effective in improving memory deficit, minimizing the amount of aggregated amyloid proteins, and lessening the expression of certain genes related to Alzheimer's Disease, such as *APP* [28].

Embryonic and induced pluripotent stem cells are still undergoing research to investigate their overall effectiveness in assisting with the treatment of Alzheimer's. A few studies have shown that they do have potential, but they have not been as efficient as NSCs and MSCs up to this point [28]. ESCs can create neural progenitor

cells; in one study, researchers transferred the NPCs to unilateral meynert basal nucleus and found that they were able to increase memory and learning [28]. Another recent study showed that protein-induced IPSCs and ferritin can be released by mESCs to promote the differentiation of oligodendrocytes. This inherently reduced plaque build-up in the brains of the model mice [28].

Lithium and Alzheimer's

In the brains of Alzheimer's patients, amyloid plaques build up at the synapses of neurons [20]. This directly hinders regular signal transmission. The amyloid-beta protein is known for activating the GSK-3β pathway, which leads to the hyperphosphorylation of the Tau proteins in neurons [20]. The hyperphosphorylation of Tau is the definitive cause of the neurofibrillary tangles exhibited in the brains of patients with AD [20]. The tangles created give way to cell death because they are unable to transport nutrients the way that normal neurons do [20]. Lithium has been proven to be the most potent inhibitor of the GSK-3β signaling pathway [20]. Because of this, lithium can reduce, and even prevent, the hyperphosphorylation of Tau. This means that lithium has the capability to stop plaque and tangle formation, which characterizes AD, in the brain.

Lithium is the first line of treatment for bipolar disorder. Studies have found that untreated bipolar disorder is directly related to an increased risk of Alzheimer's Disease [29]. However, additional research has discovered that patients being treated for bipolar disorder with long-term lithium usage had 20 times lower of a risk of dementia than those who had only taken lithium once [29]. Furthermore, a separate study entailed comparing the Mini-Mental State Examination scores of patients with bipolar disorder being treated with lithium against those who were untreated [30]. The results of this research concluded that the patients being treated with lithium had significantly better Mini-Mental State Examination scores [30]. Both studies discussed previously resulted in the demonstration of lithium's neuroprotective effects and show that it is directly involved in preventing Alzheimer's Disease.

Conclusive Summary

Alzheimer's Disease constantly hinders the lives of millions across the globe. Although many drugs and therapies have been studied, almost all of them only succeeded in targeting the symptoms of the disease rather than the underlying causes. Without a clear-cut cure or treatment in place, several people gradually suffer from the increased loss of cognitive and motor functioning until the disease becomes fatal.

However, recent studies have demonstrated that both lithium and stem cells have therapeutic benefits in pertinence to Alzheimer's Disease. Additionally, these therapies have been studied in usage together to promote an even more favorable result for the patients. Currently, the studies of the effects of the combination of these therapies exist mainly in labs with rodents being the primary subject of research. Although, the brain defects that are exemplified and treated within the studies are typically transplanted from the brain of a human to that of a rodent. This further assists in the hopeful reciprocity of the trials in real Alzheimer's patients in the future.

Studies have shown that lithium is able to stimulate the production of MSCs in rodent brains via the suppression of the β-catenin/WNT pathway through the phosphorylation of Ser9 [20]. The result of this pathway's suppression is that the GSK-3β pathway becomes inactivated, which is necessary for the reduction of the characterizing factors of Alzheimer's Disease, as discussed previously. This increased division of MSCs influenced by lithium demonstrates that it has the potential to improve the effectiveness of MSC transplantation therapy. In one study, green fluorescent protein-MSCs were transplanted into the spinal cords of rats after being co-cultured in a neural induction medium; lithium at 0.1mM was shown to promote both neural cell differentiation and enhance cell survival rates [20]. Both benefits are keys to the reduction and treatment of AD.

The combined treatments of MSC transplantation and lithium usage seems to be a potential therapeutic measure for patients who suffer from Alzheimer's Disease. The MSC transplantation allows for the regeneration of neural tissue through the differentiation of the MSCs into astrocytes, neurons, and oligodendrocytes. The usage of lithium has been shown to increase the proliferation of these MSCs, which leads to the hope that the continued MSC proliferation after transplantation in the brain of Alzheimer's patients would eventually reverse the tangles and plaques that characterize their declined cognitive abilities. Future research should serve to investigate the possibility of the usage of lithium and MSC transplantation therapies in combination to reduce, prevent, and reverse the neurodegenerative effects of Alzheimer's Disease.

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