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Stem Cells, Lithium and Neuropsychiatric Disorders

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Abstract

Mental health disorder prevalence is rising within the United States and worldwide. With this growing incidence, treatment for individuals suffering from such disorders is imperative. Stem cells have shown promising results for treating different disorders and/or traumas and are seen to be a potential treatment for mental health disorders. Stimulation by lithium has demonstrated beneficial outcomes as a result of promoting leukocyte production, neurogenesis, and neuroplasticity. When included in stem cell treatment, lithium can promote self-renewal along with migration. This discovery has led to research regarding whether stem cells can be utilized to treat psychiatric disorders. Current studies have shown the ability to treat neurodegenerative diseases such as Parkinson's, and further studies are being conducted in cases of depression and schizophrenia. The purpose of this paper is to analyze the potential applications of stem cells for treatment of psychological disorders and to determine the challenges of using stem cells to target areas of the brain.

Keywords

Neuronal stem cell; Psychological disorders; Lithium; Schizophrenia; Depression

Introduction

Mental disorders are disorders that affect either the thinking, mood, and/or behavior of an individual, and which interfere with daily life. The prevalence of such disorders has been increasing throughout the 21stcentury across different demographics. Mental health disorders normally arise from a combination of genetic and environmental factors, which can make treatment for these disorders rather complex. Most mental health disorders are discovered between the ages 14-24, but they are prevalent at all ages. According to recent studies, it has been estimated that 1 in 3 individuals have suffered from a mental health disorder during their lifetime and many are not receiving the necessary treatment for those disorders [1]. The most common psychiatric disorders include substance abuse disorders. This is followed by mood disorders, such as depressive disorder, and anxiety disorders. Many times, these disorders are comorbid which can make treatment difficult [2]. With mental illness becoming more common within the medical community, it is imperative to find effective methods of treatment.

Currently, the most common treatments include medication, such as SSRI, in combination with cognitive behavioral therapy. However, difficulties with treatment arise from the biological and chemical differences between individuals. That unique biological and chemical nature leads to treatment being a complex process which is different for every individual. Stem cells provide an opportunity for observing the progression of a disease at an individual level. Currently, there are several studies underway to test the effectiveness of pluripotent stem cells on different psychological disorders.

Stem cells are cells that have the potential to develop and differentiate into other cells of specialized function. These types of cells show promise in being able to treat and cure diseases because of their ability to replace damaged tissue and restore cell function. There are two types of stem cells which are embryonic stem cells and adult stem cells. Embryonic stem cells (ESC) are pluripotent which means that these cells can give rise to any cell from the three germ layers. This category of stem cell comes from the blastocyst which develops shortly after fertilization. These types of cells show the greatest promise because the cells can self-renew for the longest period, but ESC can lead to the formation of teratomas. The proliferation and spontaneity of these ESCs can lead to the formation of this tumor tissue. Adult stem cells (ASC) however are multipotent which means that these stem cells have a limited differentiation potential, based on their location. ASC are commonly isolated from the bone marrow [3]. This class of stem cell is used to replace cells of a specific organ. The purpose of stem cells is to replace damaged cells in the body. Stem cells are also used to better understand the underlying biology of the human body and to study the progression of differentiation of different types of cells. Understanding of this process can allow researchers to determine the progression of a disease and elucidates potential avenues for treatment. Stem cell treatment has been shown to assist with several different disorders [4]. For example, hematopoietic stem cells can assist in replacing healthy blood cells, and skin stem cells can be used to help patients with skin conditions or extreme burns. Clinical trials have shown great potential for the use of stem cells as a treatment but there are challenges to using stem cells, such as ethical issues or rejection.

Stem cells provide great promise in the treatment for a variety of diseases and traumas. Within this literature review, stem cell treatment for psychological disorders will be studied. This research will examine the history of the relationships between stem cells and psychological disorder treatment, human studies and animal studies, and the challenges of utilizing stem cells within this area of focus.

Discussion

History of lithium in application of stem cells

Lithium is a monovalent cation that is commonly used in the treatment for psychiatric disorders as a mood stabilizer by facilitating GABA release. Treatment with lithium is commonly used to treat bipolar disorder by decreasing the number of manic episodes associated with that disorder. Lithium is also used to treat other psychiatric disorders. Lithium has been observed to be involved in neuroprotection against excitation, oxidative stress, and inflammation by blocking glutamate and dopamine neurotransmitter receptors as well as through the activation of neuropathic pathways. Furthermore, lithium treatment can diminish neurotrophic effects which are positively correlated with disease progression [5]. This progression can be seen as apoptosis, inflammation, or glial dysfunction. The protection of lithium has led to this monovalent cation's use in treatment of neurological diseases such as schizophrenia, Huntington's, Alzheimer's, and Parkinson's diseases. In the case of Alzheimer's, lithium reduces the production of B-amyloid accumulation, a defining feature of Alzheimer's which leads to rapid memory decline [5]. While lithium has proven to assist in the treatment of such disorders, there are some drawbacks to lithium-based treatment of psychiatric disorders. Lithium can be a toxic agent and lead to side effects during treatment. These side effects may include nausea, vomiting, trouble with vision, and other effects. The most detrimental effect of lithium however is kidney damage arising from prolonged use. After prolonged use, the kidneys may no longer be able to concentrate urine and remove lithium from the body. This long-term effect can allow lithium levels to accumulate in the body and damage other organs [6]. Because of the complexity of lithium treatment, it is essential that patients work diligently with providers to ensure that this medication is taken carefully and correctly. Lithium provides an opportunity for treatment of many neurological disorders and provides insight into stem cell treatment.

Lithium has been observed to trigger an immunological response that has provided further insight into the potential for stem cell treatment. Specifically, lithium has led to an increase in both monocytes and lymphocytes. Those immune cells are responsible for the inflammatory response, antibody production, cell-mediated killing, and many other processes that help fight against infections. Lithium can stimulate this immune defense by inhibiting the glycogen synthase kinase-3beta (*GSK3b*). *GSK3b* is responsible for turning off nuclear signals that stop cell growth and immune responses, especially the activation of T-cells which are responsible for cell-mediated killing [7]. The immune response means lithium can be used in conjunction with iPSC to proliferate and avoid the potential for tumor growth, by inducing leukocyte production. This immune response could provide protection in connection with the use of stem cells, especially ESC that may cause teratomas. Furthermore, and most importantly in relation to

stem cells, lithium is responsible for cell proliferation. The inhibition of the GSK3b pathway also enables for lithium to promote iPSC proliferation. Lithium phosphorylates serine 9 on GSK3b, which inhibits this pathway. The inhibition leads to the increase in the *B*-catenin/Wnt pathway. This pathway is responsible for proliferation/differentiation of iPSCs [8]. One study observed the ability of lithium to assist in nucleus pulpous cell differentiation of adipose derived stem cells and found that lithium assisted in cell proliferation.

Lithium can reduce cell death and increasing extracellular membrane synthesis which can help stem cells adapt to the environment or survive in a harsh environment. This reduction in cell death is due to lithium activating anti-apoptosis genes such as *Naip1*, and *Faim2* [9]. Lithium also increases neurogenesis and neural plasticity within the brain, promoting the proliferation of iPSCs and further inhibiting apoptotic factors, showing that lithium utilization with iPSC can be very beneficial, especially in neuronal derived stem cells. Lithium is also able to induce reprogramming of iPSC into different specialized cells. One study used mouse embryonic fibroblasts during early stages of stem cell treatment to determine if lithium is more involved in the proliferation or reprogramming of cells. The results showed that days 3-8 were the most critical for usage of lithium to assist with stem cell incorporation and growth. Prolonged use of lithium does not continue to assist in stem cell growth. When used on day 9, it was found that there is no assistance in cell growth and that lithium can hinder colony development. Continued use of lithium caused cytotoxic effects that can damage stem cells. The benefits of early incorporation of lithium suggests that this cation is more involved in the reprogramming of stem cells rather than proliferation [10]. In addition to cell reprogramming, lithium assists in cell migration, which can allow for stem cells to reach the needed areas of cell replacement or injury.

Lithium is shown to upregulate MMP-9 (Figure 1). The MMM‑9 proteinase works to remodel pathways by degrading the extracellular matrix and inducing cytokines involved in tissue remodeling. When lithium is used in conjunction with sodium valproate (VPA), another mood stabilizer, optimal conditions for iPSC migration are observed (Figure 2). VPA is found to upregulate *CXCR5* which is responsible for creating receptors for cells in the central nervous system [11]. VPA and lithium are commonly used together for treatment of bipolar disorders because these treatments utilize two different mechanisms. The differing mechanisms also allow for these two treatments to be used in conjunction to enhance stem cell migration.

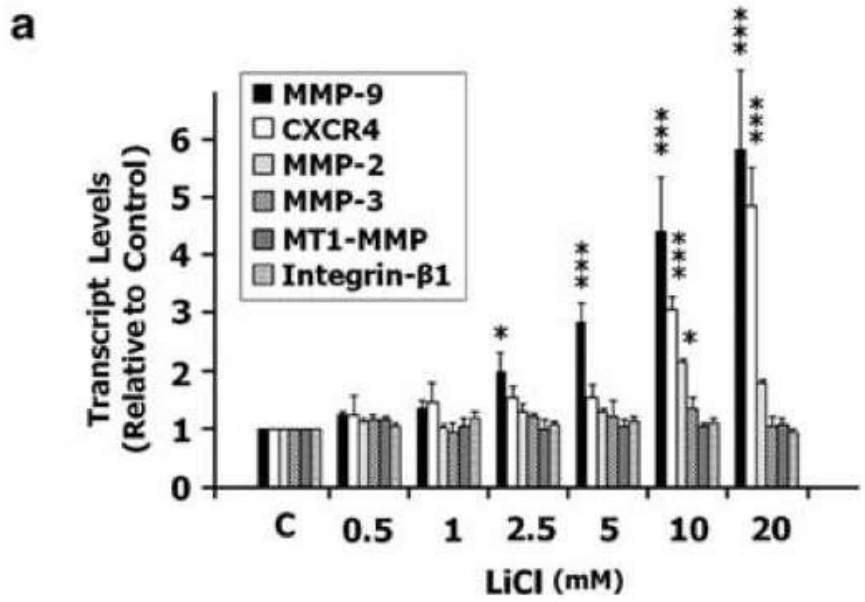

Figure 1: Lithium Increasing the Transcription of MMP-9 [11].

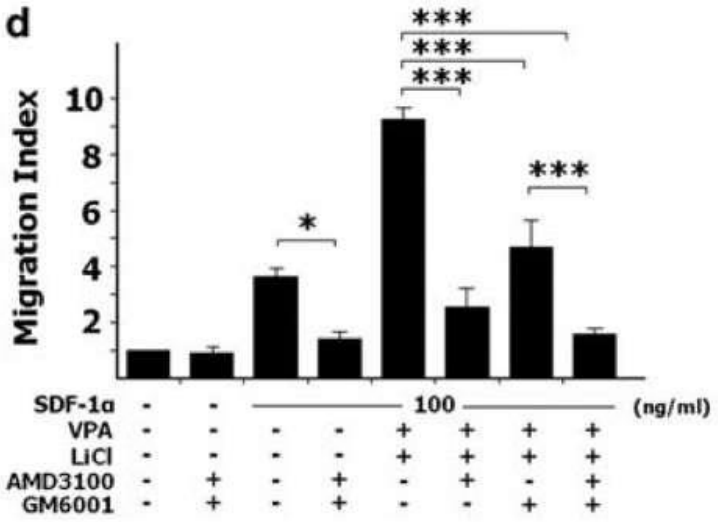

Figure 2: Cell Migration with Pre-Treatment of VDA and Lithium in SDF-1alpha Treated Cells [11].

Lithium incorporation into stem cell treatment provides a variety of advantages which can improve the potential for the successful reprogramming, proliferation, and migration of stem cells. The cation also provides protection against stem cell spontaneous proliferation which can induce tumors. While there are a multitude of benefits using lithium in conjunction with stem cell treatment, it also must be regulated. Lithium's toxicity can induce detrimental effects if used in too high of a concentration.

Furthermore, there are optimal times for utilization of lithium that must be considered. It is vital that further research is conducted to determine the parameters of lithium usage in pluripotent stem cell treatment.

Animal Studies and Neural Stem Cells

Neuronal stem cells (NSC) show the potential to assist in the research and treatment of different psychiatric disorders. Neuronal stem cells have the potential to differentiate into different brain tissue and different parts of the central nervous system including neurons, astrocytes, and oligodendrocytes. Many animal studies are being conducted to determine the effects of application of stem cells in different neurological conditions such as Parkinson's and Alzheimer's diseases. Neuronal stem cells are typically obtained shortly after embryonic development and are undifferentiated which leads to the ability of NCS to be multipotent. The early extraction of NCS, however, has led to ethical issues surrounding the use of such stem cells. NCS can also be obtained in adults, however, which may allow for better control with differentiation.

Currently, animal studies are being conducted to determine the ability of neural stem cells to assist in treatment for trauma and neurological disease that affect the central nervous system. Using animal studies, researchers can determine the best method of insertion, location or transplantation, and potential short-term and long-term effects. Studies have shown that delivery of NSC can assist in modeling disorders such as strokes, Parkinson's, and brain tumors. It is extremely important to determine where stem cells can be inserted and if the cells can migrate to the needed area to differentiate into the damaged or missing cell. Many times, stem cells need to be inserted with specific growth factors or genes to ensure migration and proliferation. Previously, cell survival after inserting fetal brain tissue has been difficult to achieve but animals transplanted with such cells using specifically determined implantation techniques show promising results. Such results have been seen in animals induced with stroke physiology [18]. Implantation of neuronal stem cells serves as a regenerative therapy to replenish missing or damaged cells of the central nervous system in such studies, consequently diminishing the symptoms of a trauma or disease.

A major neurological disease that has been significantly studied is Huntington's disease which leads to a loss of neurons in the brain. Animal studies in preclinical trials have given great insight into the application of neural stem cells targeting the brain. Mice have been modeled to have fast and slow Huntington progression in order to discover potential treatments for both short-term and long-term effects. Studies have shown what biomarkers should be used to determine NSC differentiation such as glutamate decarboxylase for Huntington's disease, but these markers will vary for different stem cell differentiations. Many times, glutamate decarboxylase is diminished in patients with neuronal damage so surveying the concentration of this factor can show if stem cell treatment is working. The usage of stem cells in this disease has provided insight into the pathogenesis of disease which may provide a better understanding into transplantation and targets for stem cells [19].

Use of animal studies has provided the ability for researchers to deepen their understanding of certain diseases and to determine how stem cells may be applicable in treatment. The use of neural stem cells to treat neurological disorders has increased interest in the potential of stem cells for treating neuropsychiatric disorders. Animal studies have provided insight into the amount of stem cells needed, potential targets, usage of markers, and method of admission. This understanding can assist in finding the best method for stem cell implantation survival. The knowledge gained through animal studies is vital and necessary before human trials can be designed. Nonetheless, there are challenges with animal studies arising, for example, from the physiological differences between the animal models and humans. Challenges regarding neuronal stem cells will be further explored.

Stem Cells and Neuropsychiatric Disorders

Utilizing stem cells to treat psychiatric disorders is a relatively new concept but there is great potential for this upcoming treatment. The application of stem cell treatment may, for example, assist in treatment issues such as non-compliance in the case of patients who do not regularly take prescribed medication. Furthermore, stem-cell treatment may diminish the number of side-effects seen within so many medications for these disorders. Many neuropsychiatric disorders can be studied by use of neuroimaging. These imaging methods can be utilized to look for damage or dysregulation to direct stem cell treatment [12]. Stem cell research is still in the preclinical trials, which includes animal studies as described above, but there is evidence that this treatment can result in significant advancements in the field of psychiatry, especially for use in connection with neurodegenerative diseases. Stem cells have provided researchers the ability to model diseases and determine how a disease affects an individual through observing a patient's stem cells to further understand disease progression. Such studies may, for example, allow for a more personalized treatment and may assist in treatment for a specific genetic set. Stem cells provide the opportunity to replace damaged tissue and assist in neuronal plasticity that is diminished in many neuropsychiatric diseases. Two diseases that have been at the forefront of this type of treatment include depression and schizophrenia. The next part of this paper will review these two disorders in depth.

Depression

Depression is a mood disorder in which one experiences a loss of enjoyment in activity, and which can lead to impairment of daily functioning. A major cause of depression is repeated stress which can lead to neuronal damage, especially to reduction in neuronal plasticity which controls communication between neurons. Reduction in neuronal plasticity results from cortisol release during stress. Stem-cell therapy aims to enhance neuronal plasticity through the targeting of the hippocampus. In patients diagnosed with depression, the hippocampal gray matter is severely diminished. This diminution leads to less neurons in depressed individuals and less communication within the brain. The loss of interneurons in the anterior cingulate cortex of the hippocampus leads to many of the symptoms experienced in depressive episodes [13]. However, this aspect of the disease offers a potential target for stem cell treatment in individuals suffering from depression by stimulating neurogenesis, leading to the

production of new neurons that have been destroyed by cortisol release. Neuronal stem cells work to replace this lost tissue of the hippocampus. Such newly discovered stem cells have the ability to differentiate into neuronal tissue. The usage of neuronal stem cell therapy may potentially return the original morphology of the damaged brain. However, there are several difficult complications in achieving such treatment. For example, it can be difficult to properly place stem cells as well as to provide the correct differentiation factors. Adult neural stem cells can be induced to differentiate into the desired lineage through the correct growth factors, gene expression, and hormones. Neurogenesis of the brain can be difficult to mimic, however.

Lithium continues to be one of the best candidates to promote neurogenesis through increasing *bcl-2* overexpression, which encoded for an apoptotic protein. Increasing *bcl-2* leads to the increase of cAMP response element binding protein (CREB). CREB has been shown to improve the plasticity of neurons which is vital for depressive treatment. CREB upregulates the brain derived neuronal factor (BDNF) which acts in the hippocampus to depolarize neurons and activate calcium voltage gates. BDNF also plays a pivotal role in lineage differentiation in the hippocampus and neurogenesis. Such activity makes BDNF a potential target for upregulation when working with neuronal stem cells to treat depression. Another factor that promotes neurogenesis is 5-hydroxytryptamine (5-HT), a monoamine neurotransmitter [14]. In rat studies, it has been observed that depletion of that factor leads to decreased neurogenesis, leading to diminished cell proliferation in the hippocampus and gyrus (Figure 3).

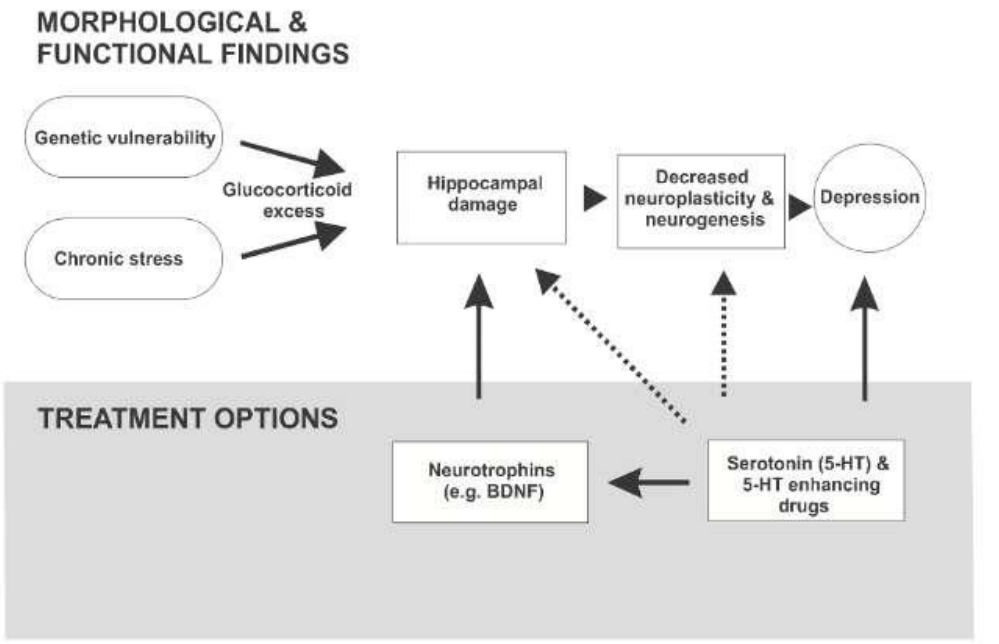

Figure 3: Causes of Depression and Options for Neurogenesis [13].

The above-described factors provide pathways for promoting neurogenesis which is a difficulty in the application of neural stem cells. However, significantly more research is required before such prospects can be studied in human trials. Further research is, for example, required to differentiate neural stem cells into the correct lineage for a specific disease. Appropriate location of stem cells is also of concern in applying stem cells to treat mental health disorders. Transplantation requirements are different depending on the disease. Moreover, long-term proliferation requires further consideration. In studies of Parkinson's disease, for example, it has been discovered that generated neurons are not able to survive long after being transplanted into animals [15]. While great progress has been made in the study of neuronal stem cells, it is critical to continue looking for alternative approaches so that this novel treatment can be used to assist patients who suffer daily from depression.

Schizophrenia

Schizophrenia is a disorder that manifests in symptoms including hallucinations, confusion, trouble with organized speech, and delusions. Schizophrenia is characterized by both positive and negative symptoms which can make this disorder extremely difficult for treatment. This disorder can be extremely debilitating, so methods for more effective treatment are continuously being researched. Stem cells are one avenue being researched for the treatment of schizophrenia. iPSC may provide a better option for mimicking schizophrenia than animal models. Through study of patient-derived cells, one can study schizophrenia at the cellular level for an individual patient. Such studies may provide for treatment to be personalized and account for individual differences at the synaptic level [16]. In several studies, embryonic stem cells are being used to create interneurons, which are impaired in schizophrenia, to model the disease. Furthermore, interneurons from stem cells may have the potential for transplant into schizophrenia patients to treat the disease. Schizophrenia patients show reduced GABAergic cells in the prefrontal cortex. Interneurons may potentially be transplanted in the area of the prefrontal cortex to increase connectivity. This approach may provide an avenue to reduce the amount and/or severity of negative symptoms associated with schizophrenia, such as lack of emotion, speech, and/or motivation. While there is great potential for this treatment option, significant obstacles remain. For example, there is a lack of biological markers to determine if a patient will develop schizophrenia. One of the greatest challenges is determining where interneurons should be transplanted to deliver the most beneficial effects on schizophrenic patients. A study of two models of schizophrenia in the brains of rodents, MAM, which models positive symptoms, and PCP, which generally models schizophrenia, to discover which locations of interneuron transplants produced the most promising results [17]. The results showed that there is a possibility to relieve schizophrenia symptoms through interneuron transplantation. (Table 1) summarizes the results of studies of interneuron transplants in preclinical models.

Table 1

Efficacy of interneuron transplants in preclinical models of schizophrenia

Cell Source	Target Region	Rodent Model	Behavioral and Physiological Effects	Reference
MGE	mPFC	Acute PCP	Improved novel object recognition and normalized prepulse inhibition	Tanaka 2011
MGE	mPFC	MAM	Improved reversal learning and increased social interaction time	Perez 2015
MGE	vHipp	MAM	Reduced amphetamine-induced locomotor activity, normalized dopamine population activity, reduced hippocampal hyperactivity	Perez 2013
MGE	vHipp	Cyclin D2 knock-out	Reduced amphetamine-induced locomotor activity, improved contextual fear conditioning normalized dopamine population activity, and reduced hippocampal hyperactivity	Giliani 2014
ESC	vHipp	MAM	Normalized latent inhibition (PV, SST), increased social interaction time (PV), improved reversal learning (PV, SST) and extradimensional set shifting (PV), normalized dopamine population activity (PV, SST), reduced hippocampal hyperactivity (PV, SST)	Donegan 2015

Table 1: Results from Interneuron Transplantation in MAM and PCP Modeled Rodents [17].

While positive results have been demonstrated implanting stem cells for various disorders there is still much more research to be done. Utilizing stem cells to model and further understand the complexity of neuropsychiatric disorders is critical to understanding the targets and physiological responses for stem cell treatment. Further considerations based on this treatment option must also be considered. For example, rodent brains are physiologically different from human brains and growing personalized interneurons from human cells may take a greater amount of time. A variety of challenges in stem cell research, especially in regard to neuropsychiatric diseases will be discussed below.

Challenges

While stem cells provide a potential treatment for many diseases, there are obstacles that need to be overcome for stem cell sustainability. The ethical issues surrounding the use of stem cells, especially embryonic derived stem cells, continue to be a strongly debated topic. Further challenges include determining how many stem cells are optimal for insertion. Using fewer stem cells may provide an opportunity to avoid tissue damage, but enough stem cells are still needed for an efficient dosage. Determining the route of transmission/transplant is also very important. The stem cells need to reach a targeted location but certain routes of admission, such as injections, can be overly invasive [19]. Immune rejection must also be considered when utilizing stem cells. Using the derived stem cells derived from the patient, where possible, is one way to avoid an immune reaction from a foreign cell. In addition to these general difficulties, difficulties in determining markers for stem cells remain. Stem cells

are pluripotent and can differentiate into various lineages which can make later discovery of these cells difficult. Such difficulties can, in turn, hinder the understanding of the differentiation process of stem cells which is necessary for application of stem cell therapy. There are also problems associated with controlling differentiation which can restrict the usage of stem cells [20]. Stem cell therapy is particularly difficult for neuropsychiatric diseases because the target is in one of the most complex and least understood organs. The brain is significantly different for every individual. Brain anatomy varies as a result of, for example, differing genetic and environmental factors. This variation can affect the way that differentiation of stem cells occurs on an individual basis. Furthermore, psychiatric disorders themself are still not well understood. Such disorders can show differing symptoms in everyone [21]. This individuality in disease manifestation can make a uniform stem cell treatment difficult for a single disease. Stem cell treatment would likely require personalization to each patient.

Furthermore, in the case of neuronal stem cells, there is an absence of antibody identification that must be considered [13]. Because of the ability of embryonic stem cells to form tumors as a result of rapid and spontaneous proliferation, it is essential that a defense against potential tumor formation be implemented.

If stem cells are not able to differentiate and proliferate in a controlled manner, then utilization of such cells for treatment will be limited. Further animal studies in preclinical trials are required to overcome those obstacles. However, as set forth above, there are limitations in animal studies arising from the physiological difference between animals and humans as well as the variation between different animals (for example, weight etc.) which may lead to differing results in subsequent human trials. In psychiatric diseases particularly, animals cannot model the disease perfectly which may create issues in extending results of animal model stem cell studies to human trials [21]. Many times, a variety of animal models must be utilized in order to obtain a more accurate model of disease progression in the human brain. Animal studies are clearly not a perfect solution, but such studies do provide a basic framework for potential progress in stem cell treatments.

Conclusion

Mental disorders affect individuals globally, and it is believed that the rates of mental illness are highly underestimated. Mental illness leads to a variety of strains in society generally (particularly economically), as well in the affected individuals and their loved ones. Many individuals experience overwhelming struggles with these illnesses. With mental health disorders on the rise, many researchers are looking for improved treatment options that can help individuals manage psychiatric problems. Stem cells offer a potential treatment for those suffering from a variety of disorders, including neuropsychiatric disorders.

The use of iPCS and neuronal stem cells provide an opportunity to replace damaged cells that are observed in many individuals suffering from these debilitating disorders. While the potential for stem cell treatment is great, a variety of challenges need to be overcome in order to progress with stem cell

treatment in psychiatric disorders. Research is continuing to determine solutions to limitations associated with stem cell treatment so that stem cells can progress past the preclinical trials. Much of the research focuses upon the differentiation process of stem cells, especially into neurons [21]. The correct induction signals and suitable methods of transplantation must be determined to help with that differentiation.

Stem cell research, while still limited, has provided insight into the progression and physiology of psychiatric disorders. Even with relatively limited research regarding psychiatric disorders, studies of stem cells have enabled researchers to better understand which cells or pathways are damaged for certain diseases. Such improved understanding has allowed for improvements in pharmacological interventions, especially in the case of schizophrenia. By understanding the nature of a disease, drug therapies can be targeted more specifically which provides better treatment for patients. Potentially of even more importance, stem cells provide the opportunity to better understand the effect of a disease in connection with a specific genetic makeup. This focus provides the potential for patient-specific treatment which is very important because of variations in the brain arising from different neuronal connections and genetic and environmental influences.

The continuation of stem cell research may be an essential pathway to providing relief for neuropsychiatric disorders. Lack of understanding of underlying mechanisms in such diseases has significantly hindered treatment. However, stem cells provide a new opportunity for advancement. Research utilizing stem cells is ongoing for diseases such as anxiety, bipolar, personality, ADHD, and OCD disorders. Many of those diseases have a high prevalence around the world. Stem cells provide a novel way to both further understand and to treat such diseases. Hopefully, current research will result in the emergence of stem cell treatments soon to help the significant percentage of the world population suffering from mental illness.

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