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How genetic therapy can be used to treat patients undergoing clinical depression?

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Abstract: Clinical depression can be described as a common medical disorder that negatively affects how an individual feels, thinks, and acts. Today, the chances of a person suffering from depression are much more common worldwide, and it is critical to understand depression and most importantly how to treat the disease. While it currently remains unclear exactly how depression works in the human body, research shows that a protein called P11 might play a vital role in the molecular and cellular mechanisms underlying depression in the body. According to research, as the level of P11 protein decreases, it increases an individual's risk of undergoing depression. The main problem is that the existing treatment, which includes medication and psychotherapy, is not as effective as it could be for treating such a disease. Genetic therapy treatment would be an attractive alternative treatment for depression treatment since regulating the levels and mechanisms involving protein P11 would hopefully alleviate one's symptoms of depression in the body. This paper intends to highlight the benefits of using gene therapy to treat depression and elaborate on why the treatment may be useful.

Keywords: Clinical Depression, Depression, Genetic therapy, P11 protein, Treatment for Depression, Psychiatric Disorder

1. Introduction

This paper aims to give a brief overview of major depressive disorders and highlight the benefits of using gene therapy to treat depression. It also aims to elaborate on why this genetic therapy might be useful to someone undergoing depression and if this treatment will be more effective than the current treatments for depression used nowadays.

2. Discussion

Major depressive disorder, commonly known as clinical depression, is a mental health disorder commonly associated with a drastic increase in sadness and loss of interest in the surroundings, such as leisure activities. This disorder can severely impact an individual's quality of life and cause significant problems with an individual performing basic day-to-day activities. It affects approximately 6.7% of adults annually, and within a span of their lifetime, 16.6% of people may experience depression (Dowrick & Frances, 2013). On average, this disease frequently appears during an individual's adolescent period which can be described as the period between 10 and approximately 24 years old. As for symptoms, it causes patients not only to feel sad or have a depressed mood but also to think of death or suicide in severe cases. Depression removes positive reinforcement (Fournier et al., 2010), which is a desirable or pleasant stimulus

after the performance of the behavior from an individual. As a patient can not feel any positive stimuli after the performance, it conveys that the depressed individual cannot obtain a sense of achievement from their performance.

Although it still remains unclear how clinical depression works in the human body or how someone may get this disorder, there have been many breakthroughs concerning the genetic factors behind this disorder. Scientific researchers have proposed that there is a high risk of heritability when first-degree relatives such as parents and siblings have depression (Mcleod, 2023). There are different factors that might cause depression. As for congenital factors, lack or imbalance of certain chemicals or hormones in the brain might cause depression, or a certain gene that is likely to cause depression might have been inherited. It would risk an individual from suffering from depression. For example, if an individual lacks certain hormone such as dopamine, serotonin, or oxytocin, which are hormones that cause an individual to be multifaceted, modulating mood, cognition, reward, learning, memory, and numerous other physiological processes, would not be able to be as optimistic as what other people would. For another instance, the shortage of the p11 gene in an individual also causes depression. As for acquired risk, continuous pessimistic thoughts based on low self-esteem or even exposure to traumatic violence or to poverty might cause an individual to undergo depression. These situations would cause an individual to lose positive reinforcement, which would eventually cause an individual to struggle with depression.

To understand the mechanism of depression in the body, we must know about the nervous system. The basic unit of the nervous system is a nerve cell, also known as a neuron. Different types of neurons control and perform different activities in the human brain. For example, motor neurons send messages from the brain to muscles to generate movement. Sensory neurons also sense sound, smell, light, taste, pressure, and heat, then send the information they obtain to the brain. When a neuron sends a piece of information to another neuron, it sends an electrical signal down the axon length. At the end of the axon, electrical signals are converted into chemical signals. The axon then releases chemical signals and chemical messengers called neurotransmitters into the synapse, which is the space between the axon tip and the dendrite tip of another neuron. Neurotransmitters convert chemical signals back into electrical signals by transporting them through synapses to adjacent dendrites. The electrical signal, according to National Institute of Health, then travels through the neuron and undergoes the same transformation process as it travels to the facing neuron. (NIH, 2018)

P11 is a part of the S100 EF-hand protein family, which is a helix-loop-domain. The S100 proteins demonstrate the properties of small acidic proteins, also known as 10-12 kDa, and are the largest subfamily of EF-hand proteins, with at least 25 members. This conveys a symmetrical hetero and homodimer form, with each monomer containing two EF-hand motifs. A special property that makes p11 gene unique is that it entails mutations in the calcium-binding sites, which causes it to be an incentive from calcium. p11 was identified within a heterotetrametric complex that it forms with annexin A25. Prior studies have also suggested that the p11 gene interacts with ion channels and enzymes, such as plasminogen, activator, and phospholipase A2. (Svenningsson et al., 2013)

Treatment with several antidepressants chronically, which exert therapeutic action by increasing the extra synaptic concentration of monoamine, increases p11 mRNA levels in the cortex and hippocampus of creatures (Svenningsson et al., 2013). Moreover, treatment with the dopamine precursor L-DOPA also induces p11 mRNA and protein levels. It is speculated that the underlying mechanism of increased monoamine regulation of p11 involves the upregulation of brain-derived neurotrophic factor (BDNF) signaling. Therefore, it is possible that antidepressant therapy would also modulate BDNF levels. Recent experiments incorporating neuronal cell cultures and mice with a mutation that the overexpression of BDNF conveyed evidence that signaling through the trkB receptor and the ERK-mediated signaling pathway appears to mediate the derivation of p11 through this neurotrophin (Warner-Schmidt et al., 2010).

According to Warner-Schmidt's team, P11 mRNA and protein levels are decreased in the striatum and cortex of BDNF knockout mice (2010). Serotonin induces p11 more potently in wild-type neuronal cultures than in mice with BDNF. These findings imply that changes in BDNF might mediate the effects of neurotransmitters on p11 levels. Growth factors appear to regulate p11 levels in neurons as well. For example, nerve growth factor (NGF) has been shown to potently stimulate p11 expression in the dorsal root ganglion in vivo and in PC12 cells in vitro (Svenningsson et al., 2013).

There are a variety of different methods used to treat depression which will be summarized below.

Treatment Type	**Advantage**	**Disadvantage**
Antidepressant	Control the severity of symptom effectively	Can not completely treat depression and remains a risk of relapse
Psychotherapy	Control the severity of depression by sophisticated treatment method	Can not completely treat depression and is not free from reoccurrence
P11 Therapy treatment	Control the depression itself in the gene level	It is not yet well-developed

Table 1. The advantages and disadvantages of the different types of treatments for depression

For most research papers, it is highly recommended to clearly state the hypotheses to be tested and the corresponding research questions to be answers. The final paragraph of the introduction should usually summarize in clear terms the research questions to be addressed. Usually, if there are more than one research questions, the methods and results sections should also include discussions specific for each of the research questions.

A variety of chemicals are utilized for communicating signals by nerve cells in the brain. Most experts believe that the main reason for which people undergo depression is the lack of releasing certain chemicals, which causes an imbalance of neurotransmitters such as dopamine. Scientists aimed to use antidepressants to increase the number of lacking chemicals, which relieves an imbalance of it (Sanders, 2019). Due to this reason, numerous drugs are used in depression treatment.

Antidepressants are frequently taken for people who have already had several relapses, absolutely want to avoid a relapse, or have chronic depression. Doing so prevents them from struggling with depression again. Experiments incorporating adults have conveyed that taking antidepressants such as TCAs, SSRIs, or SNRIs can lower the risk of relapses. the experiment using a placebo and antidepressants to compare the relapse rate has shown the result that Without medication, approximately 50 out of 100 people had a relapse within one to two years (Sanders, 2019). On the other hand, with preventive treatment, about 23 out of 100 people had a relapse within one to two years (Weintraub, 2020). In other words, taking an antidepressant over a long period of time successfully prevented a relapse in an average of 27 out of 100 people.

While antidepressants supply the lacking chemical in the brain and relieve the severity of depression, it does not completely prevent or treat depression. Since supplying chemicals to the brain through taking antidepressants is quantitatively limited. Due to this reason, patients must continue taking the medication while they are struggling with depression. Even if symptoms have been relieved by taking pills, patients must rely on antidepressants as they are trying to prevent relapse. This implies that antidepressants are more meant to aid in symptom relief and prevention of recurrence than in the radical treatment of disease. Also, as other medication includes potential side effects, antidepressants might cause side effects. Some of these side effects are believed to be a direct result of the drug's effect on the brain and are relatively similar between different drugs within the same group. Examples include dry mouth, headaches, dizziness, restlessness, and sexual problems (Fournier et al., 2010b). As the presence or severity of side effects varies from person to person and is unpredictable, caution in drug use is a factor to be considered. As for the side effects of the two most common antidepressants, SSRIs are more likely to cause diarrhea, headache, sleep disturbance, and nausea than tricyclic antidepressants (Fournier et al., 2010b). On the other hand, tricyclic antidepressants, compared to SSRIs, cause vision problems, constipation, dizziness, dry mouth, tremors, and difficulty urinating (Fournier et al., 2010b). This prevents the patient from taking the drug. In fact, the study has shown that approximately 10 to 15% of patients quit taking antidepressants after suffering from side effects (Dowrick & Frances, 2013). It is, furthermore, concerned since heart problems, epileptic seizures, or liver damage might also be a side effect of antidepressants in severe cases.

Various forms of psychotherapies and interventions are effective for designated disorders. Therapists may use one primary approach or incorporate other elements depending on their professional training, the condition being treated on top of the needs of the person receiving treatment. For example, a therapist might use a type of psychotherapy called cognitive behavioral therapy (CBT). Based on this method, they would help their patients by allowing him or them to be aware of their ways of thinking that may be automatic but are inaccurate and harmful, which is also a main symptom of depression. They, furthermore, find ways to question these thoughts and understand how those ways of thinking would harmfully affect emotions and behavior. This eventually provides them an opportunity to perfect self-defeating patterns.

For many therapies, several pieces of research involving large numbers of patients have provided evidence that treatment is effective for specific disorders. These "evidence-based therapies" have been shown in research to reduce symptoms of depression, anxiety, and other disorders as the treatment are focused on treating those patients psychologically and letting them know the significance of knowing their situation.

As Psychotherapy for depression was psychologically treating the patient and letting them realize how harmful their behavior is, which would relieve the severity of depression, it does not prevent depression itself. Since the treatment is focused on treating the severe depression symptoms that patients indicate, it does not eliminate the risk of an individual having depression. In other words, psychotherapy is a good option for patients who want to relieve their severe depression symptoms.

3. Conclusion

Depression is notoriously difficult to treat. This paper investigates why such depression is difficult to treat by correlating current treatment methods and what alternatives exist. Based on this, it is concluded that treatment at the genetic level can be effective. Furthermore, if gene therapy treatment is legitimized, it can be hoped that this treatment will be able to treat not only depression but also other psychiatric diseases.

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