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The Effect of Mutated TPH2 on Depression

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Abstract. Depression is a worldwide disease which has a great impact on people's mental health and social functioning. Finding the factor causing depression is the precondition of treatment. This area has been investigated by enormous researchers. This paper reviews the researches about depression, including the effect of depression on brain, the relationship between tryptophan hydroxylase 2 (TPH2) and depression and treatment. These references indicate that depression can affect the structure of brain, including synaptic plasticity and hippocampal volumetric changes and so on. Mutated TPH2 is a major reason of depression. This mutation will inhibit the expression of TPH2 and affect the produce of serotonin. Moreover, researchers are able to use mice to do experiments on TPH2, because TPH2 is conserved between human and mice. Medication can be used to treat depression and it's the main way to treat it. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) can also be used to treat it, but now it has some technical problems in treating human and also have some ethical problem because it will change patients' gene.

Keywords: depression, TPH2 mutation, 5-HT, treatment, brain

1. Introduction

Depression is a common disorder worldwide, affecting an estimated 3.8% of the population, and about 280 million people worldwide suffer from depression. Among them, 5.0% are adults and 5.7% are over 60 years old. Patients present with severe impairment of social functioning, including always feeling depressed, loss of interest or pleasure in normal activities, sleep disturbances, feelings of worthlessness or guilt and fixating on past failures or self-blame, recurrent suicidal thoughts or attempt to suicide, and unexplained physical problems like headaches, etc. However, it has a low cognitive among the public. What causes depression? how do depression affect our brain? what evidence was found before? how to treat depression? These questions and discussions are significantly important for education and mental health of the society.

Depression can lead to a decrease in hippocampus volume, and some studies have confirmed the hippocampus plasticity (hippocampus volume, synaptic number, synaptic plasticity, glutamate receptor changes, neurogenesis, glial cell plasticity) is changed in patients with depression. The change in volume may result in changes in neurons and glial cells. For factors that trigger depression, they can be divided into two parts. The first one is the environmental factors, including social environment, diet, experience

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in childhood and so on. The researches indicate that Vitamin D deficiency, stress from childhood can increase the risk of having depression. The second factor is genetic factors, for example mutated TPH2 plays an important role in depression. TPH2 is a gene located in chromosome 12. At most of the time, the mutation for this gene will be recognized as the main causation for major depressive disorder. Because TPH2 can affect the produce of serotonin (5-HT), a kind of neurotransmitter that is involved in the regulation of physiological and emotional function.

Traditionally, using medicine like TCAs, MAOIs and SSRIs. But if the depression is caused by mutated gene like TPH2, CRISPER may be used to treat it in the future.

This paper synthesizes previous researches on the effects of depression on the brain, factors that trigger depression and treatment approaches.

2. The effect of depression on brain

2.1. Amygdala

The frontal lobe of the brain is more active when a person is paying attention. On the MRI, the prefrontal lobe is more visible than the surrounding regions. or when a person has anxiety and fear. His amygdala, located in the center of his brain, is active and seems to be lit up on mri scans. The hippocampus receives information from the amygdalae, which interpret external stimuli including sounds and sights as potentially threatening. This procedure triggers a release of energy so that individuals can react to and defend themselves against outside threats (the flight-or-fight response). 1 Additionally, the amygdalae are in charge of imbuing situations with meaning and transforming them into memories.

The prefrontal and temporal lobes, as well as the hypothalamus, continuously receive, process, and transmit information from the amygdalae. As a result, they take on the role of a manager, associating negative emotions like fear or rage with external cues and invoking the flight or fight reaction.

The study demonstrated that those with anxiety and depressive disorders experienced reduced brain shrinking, and even experienced an increase in amygdala volume, which is the brain region responsible for emotion production, emotion recognition, and mood regulation. As a result, anxiety and sadness may impact the brain in different ways. At the same time, depression's true effects are underappreciated because it affects the amygdala in the opposite way.

2.2. Hippocampus

And underneath the hippocampus is something called the Lateral Habenula, which is a kind of anti-reward center in the brain, and it's a bad institution because it's associated with all kinds of negative emotions, like fear, anxiety, and stress, and there's a good institution beneath the hippocampus. Happiness is produced in monoamine nuclei, also known as reward centers. Lateral Habenula relies on the brain's primary excitatory transmitter, NMDAR Ketamine, which works by blocking the lateral habenula's cluster discharge, assisting the reward center in dealing with the anti-reward center, and thus alleviating depression. The hippocampus's volume shrinks. Depression-induced changes in synaptic plasticity are linked to structural and functional changes in the hippocampus. The disruption and atrophy of neurons and glia in depression may also result in prefrontal cortex and hippocampus volume reduction. The severity of depression is not associated with hippocampal volumetric changes. Evidence suggests that larger hippocampal volumes in depressed people indicate faster recovery.

3. The relationship of TPH2 and depression

Environmental factors influence depression. People who experience too much stress or violence are more likely to be depressed. They show impairment in information processing and memory. Tph1 and Tph2 are affected by stress, and studies show that stress and trauma experienced as a kid increase the risk of developing depression as an adult because early stress exposure can have long-lasting consequences on the regulation of the hypothalamic-pituitary-adrenal (HPA) axis [1]. Others, on the other hand, come to conclusion that there is inadequate evidence linking certain childhood experiences with certain psychiatric diseases [2]. Other factors, like chemical exposure also increases the risk of

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depression. For example, vitamin D, a chemical causes depression when its level is too low. It is involved in the synthesis of 5-HT, effecting its metabolism and circadian rhythm maintenance, which are the main areas of depression development.

However, though external factors can also contribute to the occurrence of depression, genetic influence is more significant and dominant. Mutations in the Tph2 gene generate depression. Tph2, which whole name is tryptophan hydroxylase2, is the rate-limiting enzyme in 5-HT biosynthesis (Figure 1). 5-HT, is a normal neurotransmitter, and only 2% of it is found in the brain. It is linked to the control of breathing, temperature regulation, and a number of behavioral processes. Additionally, eating behavior, neuroendocrinology, stress, behavioral inhibition, and aggression all exhibit a strong 5-HT influence [3]. The function of 5-HT is the inhibition of the organism's response to external stimuli, which is enhanced when 5-HT is absent. For instance, lots of literature put forward that the lessening of 5-HT will result in increasing pain sensitivity, startle behavior, and aggressive and sexual behavior.

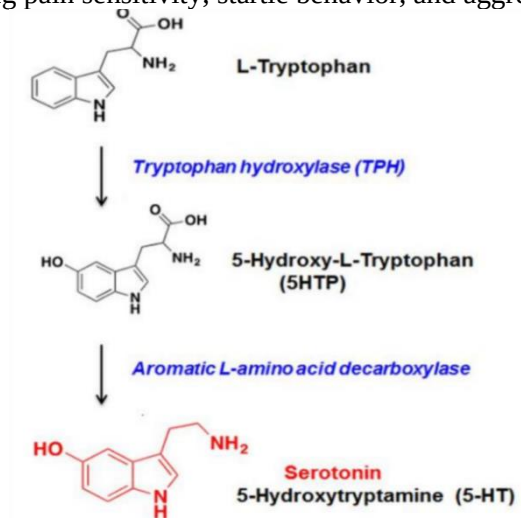


Figure 1. Tryptophan hydroxylase2, the rate-limiting enzyme in 5-HT biosynthesis.

Since 5-HT is difficult to cross the blood-brain barrier, and since the central and peripheral 5-HT systems are independent of each other, researcher assumed that there was only one Tph gene in the past. In previous studies, it was widely believed that the cause of abnormal 5-HT levels was related to TPH1, but TPH1 was not found to be expressed in the brain. It has been found that Tph1 synthesize peripheral 5-HT in vertebrates and Tph2 synthesize intracerebral 5-HT (Figure 2), as well as in humans. Stress Patients with anxiety disorders, emotional disorders, and serious depressive disorders experience a reduction in 5-HT expression in the central nervous system. Additionally, 5-HT concentration plays an important role in depression. The synthesis, transport, and reuptake of 5-HT are critical elements affecting depressed behaviors, and 5-HT also exhibits a significant impact on the inhibition of 5-HT reuptake in promoting depressive disorder. When the Tph gene is aberrant, gene expression and activity are also abnormal. This leads to 5-HT dysfunction, which has major side effects include depression, appetite loss, sleeplessness, anxiety, and endocrine disorders. According to research, normal mice and depressed mice express Tph2 differently in the brain, liver, and kidney.

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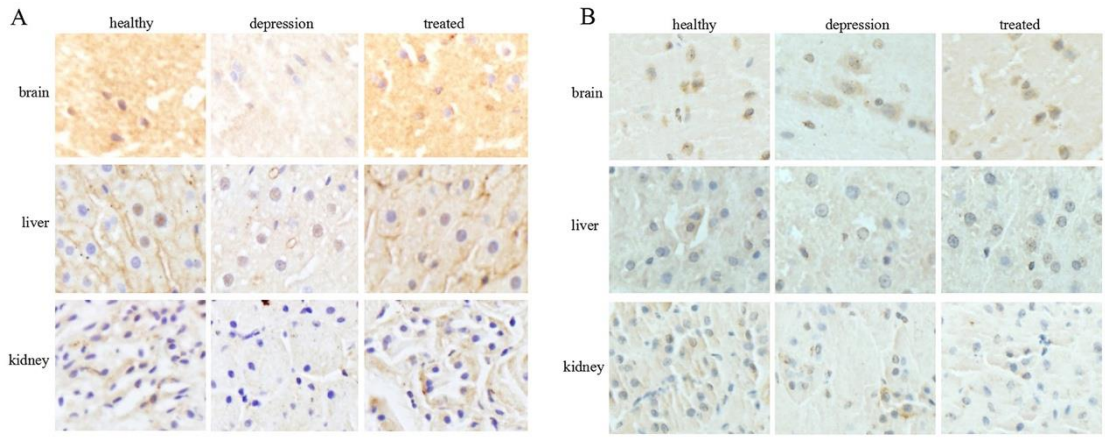


Figure 2. Tph1/2 expression and localisation in rat tissue Immunohistochemistry was used to examine the expression and localization of TPH1 (A) and TPH2 (B) in the rat brain, liver, and kidney of the control, depressed model, and treatment groups. Six separate experiments are represented by the photographs [4].

Since humans are genetically similar to mice, and they have nearly the same rates of neuronal regeneration, scientists use mice to study the human brain. Human hippocampus may have some external functions and enhance synaptic plasticity for maximum impact [5].

TPH2 expression would be significantly affected if the 264th base is mutated. Comparing the normal gene with the mutant gene, the 264th base involves a change in the coding sequence from guanine to adenine (Figure 3). Thus, the change from CTG to ATG, resulting in the amino acid change from leucine to methionine [6]. This mutation directly affects the function of TPH2 due to changes in the primary structure of the protein.

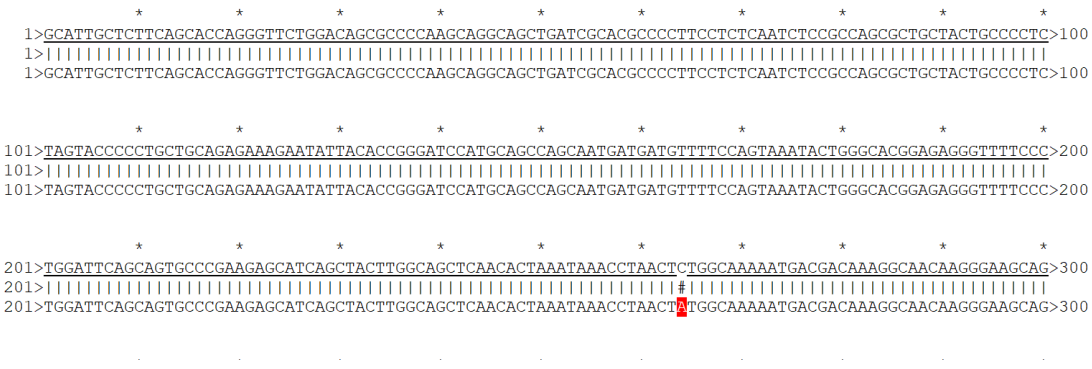


Figure 3. The 264th base involves a change in the coding sequence from guanine to adenine.

In the absence of TPH2, which catalyzes the first step in 5-HT production, the release of 5-HT as a neurotransmitter associated with mood coordination is reduced, especially in patients with major depression. Reduced 5-HT has been linked to different types of neurodegenerative and psychological disorders, including autism spectrum disorder, Parkinson's and Alzheimer's disease. Recently, scientists have found that there is a strong link between gastrointestinal motility and the release of 5-HT, which is involved in smooth muscle coordination in the gut, so a reduction in 5-HT can contribute to constipation in part [7].

TPH2 and depression may be related through several processes. Elevated glucocorticoids make people more susceptible to emotional disturbances, and elevated corticosteroids are linked to higher TPH2 expression. Leptin and interleukin-6 (IL-6) present a significant impact in the pathophysiology of emotional disturbance, and increased TPH2 expression was linked to increases in these two molecules while decreasing GABA.

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By comparing the amino acid of human and mouse, TPH2 is conserved between human and mouse. This means that people can do experiment about TPH2 on mouse. Some data was found on the Internet. Here are four species' amino acid sequence of TPH. Put these data in a software called seaview, the image indicate that mouse has the same amino acid in position 41th, which is the key cause of depression (Figure 4). So mouse may have depression if they have a same mutated gene in TPH2.

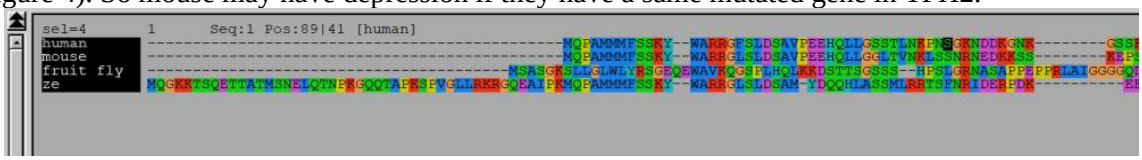


Figure 4. A mutant gene in TPH2 in mice.

While one can do some experiments on mice, not all experiments are done on mice, as middle-aged people and mice have nearly the same rate of neuronal regeneration and adults have markedly different patterns of hippocampal neurogenesis. In humans, about a third of hippocampal neurons exchange. That compares with 10 percent for mice [8].The relative rate of decline was lower in adult than in mice. Moreover, hippocampal neurogenesis in mice is cumulative, with new neurons compensating for cell loss. And human new neurons can't quite keep up with this loss.

Thus, the human hippocampus may have additional functions in the circuit and enhance synaptic plasticity for maximum impact.

4. Treatment

4.1. Medical treatment

Drugs for depression focus on blocking 5-HT reuptake or degradation. Tph2 is involved in the biosynthesis of 5-HT, and people are trying to develop new drugs by understanding Tph2.

4.2. SSRI

Fluoxetine is a selective 5-HT reabsorption inhibitor. It increases extracellular 5-HT levels by inhibiting the reabsorption of the neurotransmitter 5-HT by synaptic cells, thereby binding to postsynaptic receptors. Although it can solve the depression, there are some adverse effects like strange dreams, and may cause other illness include 5-HT syndrome, mania, seizures, an increased risk of bleeding, and even increase the possibility of suicide in people younger than 25.

4.3. TeCA

An atypical antipsychotic is Asenapine. It can also be used to treat bipolar disorder's acute mania and schizophrenia. Asenapine, the active ingredient, has a high affinity (pKi<5) for many receptors, including the 5-HT 5-HT. For the muscarinic acetylcholine receptors, it has much lower affinity (pKi 5). It also has some negative consequences. As an illustration, drowsiness, weight gain, increased hunger, and extrapyramidal adverse effects (EPS; such as dystonia, akathisia, dyskinesia, muscle rigidity, parkinsonism).

4.4. TAC

The drug Nortriptyline is used to treat depression. A active byproduct of the liver's demethylation of amitriptyline is nortriptyline. It is a first-generation antidepressant and a secondary amine diphenyl cycloheptene in terms of chemistry. In addition, the most typical side effects are tinnitus, drowsiness, diarrhea, increased hunger, and dry mouth [9]. A quick or erratic heartbeat might also occur occasionally. When taking medication, alcohol should be avoided as it may exacerbate negative effects.

4.5. MAOI

deprenyl is also known as elegiline, which is marketed as Eldepryl and Emsam, among others. It is a medication used to treat severe depressive disorder and Parkinson's disease. It is based on selegiline, a

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covalently bound selective MAO-B inhibitor that inhibits it irreversibly. Dopamine's activity is thought to be increased by stopping its breakdown, which is how it is thought to function. Levodopa and tablet side effects included, in order of severity: nausea, hallucinations, disorientation, sadness, loss of balance, insomnia, increased involuntary movements, agitation, slow or irregular heartbeat, delusions, hypertension, new or worsening angina pectoris, and syncope [10]. Reduced levodopa dosage can help with the majority of the negative effects, which are brought on by excessive dopamine signaling.

4.6. NaSSAs

As an atypical antidepressant, mirtazapine, which is marketed under the trade names Remeron and others, is primarily used to treat depression. It is based on the fact that mirtazapine is occasionally categorized as a norepinephrine and specific serotonergic antidepressant (NaSSA), notwithstanding the questionable nature of the evidence used to make this determination. Norepinephrine, histamine, and 5-HT receptors are all affected by mirtazapine. Mirtazapine has little to no impact on anticholinergic, sodium channel blocking, or calcium channel blocking, similar to the majority of antidepressants [11].When taken in excess, mirtazapine is less harmful and better tolerated. However, it also causes weight gain (>7% rise in 50% of children), constipation, dry mouth, drowsiness, and increased hunger (17%).

The researchers thoroughly searched the databases Ovid MEDLINE PsycINFO and others. The literature comparing the effects of SSRIs and other antidepressants on preventing depression relapse included sixteen research published between 1987 and August 2017 in English. Ten of these studies compared the effectiveness of SSRIs with placebo or the effectiveness of SSRIs versus other antidepressants like TCAs and SNRIs for relapse prevention.

To sum up, the tests showed that SSRIs performed similarly to TCAs when compared to other kinds of antidepressants, and that the relative efficacy of SNRIs remained unclear. In terms of effectiveness and cure rates, SSRIs were comparable to atypical antidepressants like mirtazapine and St. John's wort. Escitalopram appeared to be more effective than other SSRIs at preventing recurrence and to cause fewer side effects when SSRIs were compared. Additionally, relapse rates were lower when SSRIs and cognitive behavioral therapy (CBT) were used together. The authors point out that while SSRIs do not appear to have a significant benefit over other classes of antidepressants, maintenance treatment with antidepressants is beneficial in preventing return of depression [12]. Escitalopram might be a better option for treating depression than other SSRIs and SNRIs, although this finding has to be confirmed in other research. Additionally, patients may have extra advantages from CBT in addition to antidepressant therapy [13].

People believe that the genome editing technology known as Crispr can be used to treat depression more effectively than current pharmaceuticals. It combines the two portions known as Cas and brief fragments of repetitive DNA sequences. With the aid of an enzyme, a tiny PIECE of RNA serves as a guide tool for cutting or otherwise altering DNA in this designed editing system.

5. Conclusion

Depression is a popular disease, and multiple symptoms are caused by it, including feelings of sadness, tiredness, lack of energy, anxiety and so on. On one hand, it caused by some environmental factors like excessive pressure and violence, the lack of vitamin D, and so on. On another hand, some intrinsic factors such as mutation on Tph2 are the major reasons. The effect of depression on neuroplasticity is a complex process, including synaptic plasticity and hippocampal volumetric changes, the volume of prefrontal cortex reduces, and the volume of amygdala augmented. In addition, because the Tph2 gene is conserved in humans and mice, it is possible to use mice to study the mechanism of Tph2 mutation on depression though there are some differences between the gene of humans and mice. The main treatment for depression is medication, consisting of SSRI, TeCA, TAC, MAOI, and NaSSAs. It is worth mentioning that a new method for the treatment of depression is gene editing named CRISPR. Though it has not been used in clinical treatment, scientists have tested it in mice which seem available. However, there is still another problem for this method is ethical problem since it changes people’s gene and may cause more uneven in social.

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