

Research Progress on Post Stroke Depression and 5-HTTLPR Methylation

Yiming Jiang¹, Huikai Wang^{2,*}, Jian Sun³, Xinchen Ren³

¹Yantai Affiliated Hospital of Binzhou Medical University, Yantai, China

²Binzhou Hospital of Traditional Chinese Medicine (Binzhou Medical University TCM Hospital), Binzhou, China

³Binzhou Medical University Hospital, Binzhou, Shandong, China

*Corresponding author

Abstract: The emergence of PSD can lead to adverse emotional experiences for patients and also affect rehabilitation outcomes. Due to the relatively hidden occurrence of post stroke depression and the presence of post stroke language disorders in some patients, the treatment of post stroke depression is more difficult. The lower concentration of 5-HT in the intercellular space of the brain is associated with depression. The raphe nuclei contains serotonergic neurons whose main function is to produce 5-HT. The activation of serotonin neurons has an inhibitory effect on depression. For patients with post-stroke depression, the combination of acupuncture and medical treatment can effectively reduce the incidence of post-stroke depression on the basis of traditional treatment methods. With the establishment of the "biological psychological social" medical model, the mechanism of post stroke depression has begun to be addressed through humanized thinking. Pay more attention to the quality of life of patients with post-stroke depression. It is particularly important to seek more systematic treatment for post-stroke depression. Therefore, it is necessary to study the treatment mechanism of post stroke depression (PSD).

Keywords: post stroke depression, 5-HTTLPR, methylation

1. Introduction

Post stroke depression is a common complication that occurs after a stroke. Epidemiological surveys show that approximately 40% -60% of stroke patients experience varying degrees of depression at different stages of stroke, with more than half of the population occurring between 2 months and 1 year after stroke, which is a critical period for post stroke recovery [1]. Depression in the short term after stroke is a common psychological disorder. The incidence rate of post-stroke depression is 20%~60% according to literature statistics. 45.4% of patients have depression within one month after stroke, of which 91.8% have mild and moderate depression[2]. The incidence rate varies with different ages. According to experimental statistics, the incidence rate of post-stroke depression is 47.24%, the incidence rate of the youth group is 13.33%, the incidence rate of the middle-aged group is 43.18%, and the incidence rate of the elderly group is 55.88% [3]. Older people are more likely to have post-stroke depression than young people. Due to the relatively hidden occurrence of post stroke depression and the presence of post stroke language disorders in some patients, the treatment of post stroke depression becomes more difficult. The occurrence of depression after stroke not only affects the recovery of patients, but also to a certain extent leads to unexpected events in patients. According to the 2018 World Health Organization report on the incidence rate of depression, depression is currently the fourth largest disease burden in the world. Approximately 14.28% of the population will develop depression at some stage of their lives [4]. Depression is a common psychological disorder that often manifests as emotional depression, depression, or irritability. If left untreated, the consequences can be even more severe. The risk of depression is high for patients. The causes of post stroke depression are multidimensional, and the pathogenesis is not yet clear, so there is a lack of effective treatment and nursing measures. Related studies have shown that the onset of depression is related to genetic and psychosocial factors [5]. Genetic factors mainly refer to familial genetic predispositions towards depression, which can occur in patients from young age to old age or when symptoms worsen after an emergency. Related studies have confirmed that the concentration of steroids in patients with post-stroke depression affects their psychological state [6]. Secondly, changes in the secretion of serotonin, dopamine, nor epinephrine, and sex hormones, as well as plasma levels of orphanin, HCG, DHA, and

cholesterol, also have an impact on the psychological state of patients [7]. Related surveys have shown that the serum free triiodothyronine levels in patients with post-stroke depression are significantly lower than those in normal patients.

2. DNA methylation

Methylation refers to the process of catalytic transfer of methyl groups from active methyl compounds to other compounds. It can form various methyl compounds or chemically modify certain proteins or nucleic acids to form methylation products. In biological systems, methylation is catalyzed by enzymes, which involves heavy metal modification, gene expression regulation, protein function regulation, and RNA processing. Methylation includes DNA methylation and protein methylation.

DNA methylation of vertebrates generally occurs at the CpG site (cytosine phosphate guanine site, that is, the site where cytosine is followed by guanine in the DNA sequence). The conversion of cytosine to 5-methylcytosine is catalyzed by DNA methyltransferase. About 80% - 90% of the CpG sites in human genes have been methylated, but some specific regions, such as CpG island rich in cytosine and guanine, have not been methylated. This is related to the promoter in 56% of mammalian genes, including all widely expressed genes. 1% - 2% of the human genome is a CpG group, and CpG methylation is inversely proportional to transcriptional activity.

Although DNA methylation does not change the nucleotide sequence and composition, it can inhibit gene expression at the transcriptional level. There are three ways to suppress gene expression.

The first is that DNA methylation directly interferes with the binding of transcription factors and sequential action elements: many transcription factors recognize GC enrichment sequences containing CpG. When CpG is methylated, some transcription factors cannot bind to DNA, thereby reducing the transcription efficiency of genes.

The second is the silencing of gene expression by methylated CpG binding protein (MBP) mediated DNA methylation: methylated CpG binding protein (MBP) is a class of sequence specific DNA binding proteins, including MBD protein, UHRF protein and zinc finger protein. After binding with methylated DNA, MBP can inhibit gene transcription in H ways.

Method 1: In the promoter region of a gene, MBP binds to DNA to ancestral transcription factors and their corresponding cis acting elements, thereby inhibiting gene transcription.

Method 2: In the gene, MBP combines with methylated DNA to prevent the extension of RNA polymerase during transcription.

Method 3: MBP regulates gene expression by recruiting co inhibitory complexes and changing the structure of chromatin. These co inhibitory complexes often contain histone deacetylase and (or) methylase and chromatin remodeling proteins.

The third is that DNMT mediates the inhibition of DNA methylation on gene transcription: in addition to catalyzing DNA methylation, DNMT also participates in the formation of inhibitory chromatin and directly regulator gene expression. DNMT1 and DNMT3a can bind to histone methyltransferase SUV39H1. SUV39H1 can methylate H3K9 to generate inhibitory histone H3K9m3. Because of its combination with histone modifying enzymes, DNMT can change the structure of chromatin and inhibit gene transcription.

3. 5-HT levels and depression

The lower concentration of 5-HT in the intercellular space of the brain is associated with depression. Among various depressive phenotypes, including melancholia, the transmission of 5-HT is actually enhanced; The highest quality evidence currently available shows that during depressive episodes, the release and use of 5-HT are actually higher. 5-HT can be associated with regulating brain energy and improving the body's ability to adapt to depression by reallocating resources within the patient's brain. However, 5-HT reuptake inhibitors (SSRIs) disrupt energy homeostasis and often exacerbate depressive symptoms during acute treatment. The reduction of depressive symptoms is not due to the direct pharmacological effects of 5-HT reuptake inhibitors (SSRIs), but rather to the compensatory response of the brain in attempting to rebuild energy homeostasis; This process takes several weeks and can also explain the delayed therapeutic effects of SSRIs. In fact, drugs may just interfere with the brain's own recovery process.

3.1 Dorsal raphe nucleus

The raphe nuclei refers to several nuclei located in the narrow area near the raphe of the brain stem. The divided nuclei are called raphe nuclei, which contains 5-hydroxytryptaminergic neurons. Its main function is to produce the neurotransmitter 5-HT. This neurotransmitter is associated with violence, anger, adventure, and depression. The activation of serotonin neurons has an inhibitory effect on depression.

3.2 5-HTTLPR gene

There are three variants of the 5-HTTLPR gene, of which two shorter variants increase the risk of depression and suicide. A shorter variant will exaggerate the neurochemical reactions that the human body undergoes when facing pressure, resulting in a stronger "defensive tendency". The 5-HTTLPR gene acts on the human body through hormones and is an important factor in determining the effect of serotonin on the brain. Serotonin is a hormone that transmits chemical signals between nerve cells and is closely related to emotions. Some antidepressants are treated by regulating serotonin levels.

3.3 Methylation of 5-HTTLPR gene

There is a 799 bp CpG island around the promoter region and the first exon of the 5-HTT gene, which contains 81 CpG sites. This CpG island is a candidate region for gene environment interaction, which is sensitive to epigenetic modification, but its role in mental disease is still unclear. Roth et al.'s research suggests that methylation plays an important role in the regulation of SLC6A4 expression, therefore SLC6A4 is often selected as a target gene. Miller et al. have shown that early life events may reduce 5-HTT expression, and their effects can continue into adulthood. Ansorge et al. believe that central 5-HT may have long-term effects on children's emotional development by altering the methylation status of the SLC6A4 regulatory region in infancy. Philipert et al. showed that methylation of the CpG island in the 5-HTT promoter region was associated with mRNA transcription, 5-HTT methylation was an important regulator of 5-HT function, and the degree of 5-HTT methylation was associated with the 5-HTTLPR genotype. The methylation of the L/L allele in the promoter region is less than that of the L/S and S/S alleles containing the S allele, while there is no statistically significant difference in the degree of methylation between the US and S/S alleles. Philibert et al. believe that genetics and epigenetic mechanisms jointly affect the transcription rate of 5-HTT, and there is an increasing trend of SLC6A4 methylation in patients with depression. Olsson et al. believe that depressive symptoms may not be related to the methylation status of the 5-HTT gene and 5-HTTLPR in buccal cells. However, when the 5-HTTLPR carries the S allele, depressive symptoms are usually accompanied by hypermethylation of the 5-HTT gene in buccal cells, and complete or partial methylation of the 5-HTT gene in expressing cells reduces 5-HTT activity.

Animal experiments have confirmed that pharmacological blockade of 5-HTT in postnatal rats can lead to depression and reduced 5-HTT expression in adulthood, suggesting that a brief decrease in 5-HT uptake during important periods can have long-term effects on brain and emotional development. The decline in 5-HTT gene function during important developmental stages can lead to emotional and behavioral abnormalities, while long-term use of SSRIs in mature individuals also reduces 5-HTT function, but improves anxiety and depression symptoms. Ansorge et al. conducted research on the above issues, and the results showed that the brain development status of rats from 4 to 21 days after birth is equivalent to the development status of humans from 9 months of pregnancy to early childhood. The use of SSRIs during this period may lead to an unexpected risk of emotional disorders. However, its mechanism is still unclear and further research is needed to elucidate. Kinnally et al. have shown that CpG methylation of the 5-HTT gene in macaques may mediate or selectively regulate the effects of genotype and early life events on 5-HTT expression and behavior. The above research suggests that early life stress may alter the expression of 5-HTT or the methylation state of the SLC6A4 regulatory region, and have a lasting impact on emotional and behavioral development. DNA methylation may be an important epigenetic mechanism regulating depression like behavior, and 5-HTT gene methylation may affect the occurrence of depression by regulating the expression of 5-HTT mRNA, but its exact mechanism remains to be further explored.

4. The association between post stroke depression and 5-HTTLPR methylation

The activation of serotonin neurons has an inhibitory effect on depression. The lower concentration

of 5-HT in the intercellular space of the brain is associated with depression. Among various depressive phenotypes, including melancholia, the transmission of 5-HT is actually enhanced; The highest quality evidence currently available shows that during depressive episodes, the release and use of 5-HT are actually higher. 5-HT can be associated with regulating brain energy and improving the body's ability to adapt to depression by reallocating resources within the patient's brain [8]. Methylation refers to the process of catalytic transfer of methyl groups from active methyl compounds to other compounds. It can form various methyl compounds or chemically modify certain proteins or nucleic acids to form methylation products. Although DNA methylation does not change the nucleotide sequence and composition, it can inhibit gene expression at the transcriptional level. According to a 2003 study by the University of California and San Diego in the United States, patients with familial genetic predispositions to depression are more than three times more likely to develop post stroke depression than general patients [9]. This indicates that familial genetic tendencies can directly affect patients' susceptibility to depression [10]. In terms of social factors. Firstly, a quiet, elegant, and harmonious living environment can make people feel comfortable and full of vitality. On the contrary, an awkward, messy, and disorderly living environment often makes people feel frustrated, boring, and even tired and irritable [11]. Pathological factors can cause visceral dysfunction in patients with post-stroke depression, and pathological changes in the internal organs and blood can also cause abnormal changes in patients with post-stroke depression [12]. In addition, there are individual factors such as physical constitution, personality, age, gender, etc., which can cause different emotional changes in the same post stroke depression patient. Secondly, the patient's economic status, payment form of medical expenses, illness, ability to take care of themselves in daily life, cognitive function, social support, etc. can all affect their emotions [13].

At present, there are no research reports on the methylation of the 5-HTT promoter region and depression in China, but researchers have conducted preliminary exploration on the correlation between the methylation of the 5-HTT gene promoter region and schizophrenia. Dong Yan and other researchers suggested that there was no statistically significant difference in the methylation level of CpG island in the 5-HTT promoter region between the schizophrenia group and the control group. After stratification by sex, it was found that there was a difference in the methylation level between men and women in the patient group, but there was no difference in the control group; Zhang Haisheng et al. used methylation specific polymerase chain reaction and direct sequencing to detect the methylation status of the CpG island in the promoter region of the 5-HTT gene in 62 patients with schizophrenia type I, 38 patients with schizophrenia type II and 50 healthy people. The results suggest that the hypermethylation of the CpG island in the promoter region of the 5-HTT gene may be one of the pathogenesis of schizophrenia type I [14].

5. Conclusion

In summary, methylation of the 5-HT promoter region may affect the concentration of 5-HT in synaptic gaps by regulating its gene expression, and play an important role in the pathogenesis of depression. Further research is needed to confirm this. Although mental diseases have tissue specificity, only epigenetic analysis of cells in specific brain regions can directly explain the role of epigenetic changes in these brain regions in mental diseases, and there are difficulties such as difficult access to brain tissue and immature epigenetic research technology, but epigenetics, especially DNA methylation, provides a new direction for the study of depression etiology, Provide new potential targets for the diagnosis and treatment of depression.

The study of gene methylation modification to improve certain hormone levels in order to treat diseases and improve behavior has become a hot topic. Methylation gene modification of the promoter region genes related to 5-HT, which affects post stroke depression (PSD), may be an important direction for the treatment of PSD.

Acknowledgement

This work was supported by the Binzhou Medical University "Clinical + X" Project (No.BY2021KYC+X47) and Shandong Traditional Chinese Medicine Science and Technology Development Plan Project (No.2021Q017).

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