Biomedical Data Science
2025, VOL. 5, NO. 2, 169-173
DOI: 10.47297/wspbdsWSP2752-630532.20250502

Mechanisms of depression and drug treatment

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ABSTRACT
Depression is a complex mental illness, with its pathogenesis involving multiple factors such as social environment, genetics and genes, changes in brain structure and function, alterations in receptor function, inflammation, and immunity. The onset of depression may be related to abnormal levels of neurotransmitters like serotonin, norepinephrine, and dopamine in the brain. Major symptoms include persistent low mood, reduced interest, and loss of energy. Medications for treating depression primarily work by regulating the balance of neurotransmitters in the brain; common drugs include fluoxetine, sertraline, venlafaxine, and duloxetine.

KEYWORDS
depression; fluoxetine; sertraline; venlafaxine; duloxetine

1 Introduction

According to statistics, about 320 million people worldwide suffer from depression. Among adolescents aged 10-19 globally, the risk of developing depression is as high as 34%, with female adolescents from Asia, the Middle East, and Africa having the highest risk. In the United States, approximately 20% of teenagers develop depression by age 18. People with depression have poorer quality of life and more severe social dysfunction, placing a heavy burden on individuals, families, and society. Severe cases may involve self-harm or even suicide, making it an extremely terrifying illness. Depression is a comprehensive disorder characterized by mood depression, cognitive impairment, mental activity disorders, cognitive deficits, and physical symptoms. The diagnosis of depression is not based on objective diagnostic tests but rather on a set of highly variable signs. Therefore, depression should not be viewed as a single disease but rather as a heterogeneous syndrome composed of various etiologies and pathophysiological mechanisms. Combining medication with psychotherapy can enhance its effectiveness. In recent years, rapid development in various industries has increased peoples living and working pressures. The incidence of depression has also risen, causing harm not only to patients themselves but also negatively impacting their families, work, studies, daily life, and social interactions. As a result, depression is receiving increasing attention.[8]

2 Overview of depression mechanisms

The causes of depression include social environment, genetics and genes, brain structure and function changes, receptor function changes, inflammation and immunity.

2.1 Social environment

Environmental factors are currently recognized as one of the causes of depression. Studies have shown that adverse social experiences are associated with depressive symptoms. Azadmarzabadi et al. found that when environmental demands exceed the subjects adaptive capacity, psychological stress is generated. The biological mechanisms related to stress have not yet been fully elucidated, but research has confirmed that stressful life events are linked to mental disorders. Research indicates that major depression is associated with genetic factors, and family genetics studies and whole-genome analyses also show that genetics play a significant role in the development of major depression.[9]

2.2 Genetics and genes

Genetic factors are also widely recognized as one of the causes of depression. Studies show that major depressive disorder is associated with genetic factors, and both family genetics research and whole-genome studies indicate that genetics plays a significant role in the development of major depressive disorder. Strong epidemiological evidence suggests that genes influence the progression of depression; first-degree relatives of individuals with depression have a

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threefold higher risk of developing depression compared to those without a first-degree relative diagnosed with depression. Research by He Tangli et al. shows that the frequency of the TT genotype and T allele at locus FKPB5rs1360780 is higher in patients with depression than in healthy individuals, and logistic regression model analysis indicates that the TT genotype at locus rs1360780 is a significant factor influencing the onset of depression. The FKBP5 gene is located on human chromosome 6 (6p21.31), approximately 14kb long, containing 12 exons and 11 introns. This gene encodes FKBP5, an immune response gene with molecular chaperone activity. The FKBP5 protein is primarily expressed in the nervous system and immune system, participating in various physiological and pathological processes such as apoptosis, immune regulation, and tumor development. Keijser et al. found that the SNP srs1360780 of FKBP5 plays a crucial role in the development of depressive symptoms in young people when analyzing the triadic interaction effects between FKBP5 and early life stress and positive parenting on the development of depressive symptoms in the general population. A study included 16A meta-analysis of 5,125 patients with depression and 8,399 controls in an independent study also showed that FKBP5rs1360780, rs3800373 were associated with the risk of depression in a co-occurrence model.[2]The research results of Deng Rui et al. show that the clinical efficacy of CYP2D6*10 is inferior to that of *1/*10 and *10/*10 types. CYP2D6*10 involves a point mutation at position 188 on exon 1, where proline is converted to serine, resulting in a C188 →T mutation, and at position 486, where glycine is changed to threonine due to G4268→C. This leads to instability in the protein structure, reducing the affinity between the drug substrate and the enzyme, thereby decreasing and destabilizing the activity of metabolic enzymes. The study suggests that for the Han population, the polymorphism of the CYP2D6*10 gene is associated with the efficacy of paroxetine in treating depression. Patients with genotype *1/*1 who smoke may appropriately increase their medication dosage to improve patient outcomes.[3]

2.3 Changes in brain structure and function

In terms of brain structure, changes in the brain regions responsible for regulating stress responses (such as the hippocampus) may serve as the pathophysiological basis for the onset of depression. In patients with depression, there are alterations in both the structure and function of the brain, with the limbic system showing heightened reactivity to negative stimuli. Multiple studies have confirmed that adolescents with major depressive disorder exhibit significant reductions in gray matter volume in both hemispheres of the hippocampus, as well as thinning of the cortical layers adjacent to the hippocampus, including the limbic and insular limbic regions. Therefore, it is believed that alterations in neural areas involved in emotional perception and reward processing during development may contribute to the onset of depression. In recent years, more research has been conducted using fMRI (functional magnetic resonance imaging) on depression. Resting-state fMRI shows a weakening of functional connectivity between the left dorsal striatum and the cerebellum in depressed individuals, while the functional connection to the pre-central and middle cingulate cortices is strengthened. Under task conditions, during cognitive and overt emotion tasks, the dorsolateral and ventrolateral prefrontal cortices of depressed individuals remain persistently underactive, whereas under covert emotion tasks, activation in the ventromedial prefrontal cortex increases.[10]

2.4 Changes in receptor function

According to the monoamine hypothesis (an important theory about the pathogenesis of depression), serotonin (an important inhibitory neurotransmitter, a type of biogenic amine compound, widely present in mammalian tissues), dopamine, and norepinephrine are the primary neurotransmitters in depression. Serotonin plays a dominant role in the pathophysiology of depression, with serotonin 3 receptors ($5\text{-}HT_3R$) are also expressed in the central nervous system, regions that play a crucial role in the vomiting reflex, pain perception, reward system, cognition, depression, and anxiety control. Clinical studies have shown that $5\text{-}HT_3R$ may be a relevant target for treating mood disorders. Dopamine receptors also play key roles in various brain functions and are involved in the pathogenesis of numerous mental illnesses. Patients with major depressive disorder exhibit reduced levels of dopamine D1 and D2 receptors; blocking or reducing dopamine can trigger and exacerbate symptoms of major depression. Additionally, low activation of the dopamine system has been found to be associated with depression. On the receptor side, Sigma-1 receptor is a multifunctional protein located on the endoplasmic reticulum membrane, which plays a vital role in cellular signaling through interactions with receptors, ion channels, lipids, and kinases. Changes in their function and expression can lead to the onset of depression. In recent years, increasing evidence suggests that sigma-1 receptors directly interact with proteins on neuronal cell membranes and enhance neural transmission. Protein balance is closely related to the occurrence of depression and various diseases. The sigma-1 receptor plays an important role in protein homeostasis within the body, and its activation can also lead to alterations in N-methyl-D-aspartate receptors. These receptors are upregulated and transmitted to the plasma membrane, further regulating the intrinsic properties of neuronsExcitability, and may be important in the regulation of calcium ion-dependent antidepressant mechanisms.

2.5 Inflammation and immunity

At the end of the 19th century, it was discovered that psychological stress can affect the immune system in healthy individuals. Excessive stress can overstimulate the immune system, leading to an imbalance between pro-inflammatory and anti-inflammatory functions. Stress can also activate brain and peripheral inflammatory responses. The nervous system and the immune system communicate with each other; during a state of stress, the hypothalamus secretes corticotropin-releasing hormone, activating the hypothalamic-pituitary-adrenal axis, which releases glucocorticoids from the adrenal glands to suppress immune responses. Glucocorticoids have pro-inflammatory effects on the immune system, and excessive stress promotes the expression of inflammatory cytokines, which can exacerbate depressive behaviors. Neuroinflammation can worsen depressive symptoms. Therefore, reducing primary psychological stress can inhibit patients inflammatory responses and alleviate depressive symptoms. Neuroplasticity refers to growth and adaptation at the neuronal level. Inflammatory responses caused by environmental stress and dysfunction of the hypothalamic-pituitary-adrenal axis may impact neuroplastic processes. Inflammatory responses promote the development and progression of depression through mechanisms such as affecting the production of monoaminergic neurotransmitters, causing neurodevelopmental disorders, and disrupting gut microbiota balance. Changes in gut microbiota composition can increase intestinal barrier permeability, activating systemic inflammationSymptoms and immune responses, regulating the release of monoamine neurotransmitters, altering the activity and function of the hypothalamic-pituitary-adrenal axis, all contribute to the development of depression. Catechins have excellent antioxidant and anti-inflammatory properties, being the main component of tea polyphenols, which can reduce cortisol and adrenocorticotropic hormone levels, thereby delaying the progression of depression by lowering pro-inflammatory factor levels. Network analysis using PPI (the relative number reflecting the trend and magnitude of changes in the total level of industrial product ex-factory prices over a certain period) revealed that IL-6 (interleukin-6), TNF-α (tumor necrosis factor α), IL-1β (interleukin-1β), IL-10 (interleukin-10), CASP3 (a cysteine protease), AKT1 (cell process), and others may be key targets for Danshen Shenxin Tea in improving coronary heart disease with comorbid depression, involving the regulation of neuronal apoptosis and inflammatory responses. KEGG (a database for genome interpretation) pathway enrichment analysis showed that Danshen Shenxin Tea may exert its antidepressant effects through anti-inflammatory pathways such as the TNF signaling pathway, apoptosis signaling pathway, and NF-kB signaling pathway. Studies by Zhao Di et al. indicate that the intervention effect of Danshen Shenxin Tea on mice with coronary heart disease and comorbid depression may be mediated by active components like luteolin, tanshinone, and catechins, acting on IL-6 and TNF-αKey targets such as IL-1β and IL-10 regulate the NLRP3 inflammatory pathway.[5]

3 Medication for depression

3.1 SSRIs

SSRIs are selective serotonin reuptake inhibitors, a class of antidepressants commonly used to treat mental disorders such as depression, anxiety, and obsessive-compulsive disorder. SSRIs improve mood and behavior by inhibiting the reuptake of serotonin in neurons, thereby increasing the concentration of serotonin in the brain.

3.1.1 Fluoxetine

For the treatment of first-episode depression, fluoxetine is often one of the preferred medications due to its long half-life (about 4-6 days) and relatively mild side effects. Fluoxetine demonstrates good antidepressant efficacy in most patients, especially those with anxiety symptoms accompanied by significant depressive features. Additionally, the risk of long-term use is low, and it is less likely to cause dependence, making it widely used in initial treatments.[1]In the study by He Ting et al., the incidence of adverse reactions in elderly patients with epilepsy and mild to moderate depression treated with fluoxetine was 15.22%, which showed no statistically significant difference compared to the control group ($P>0.05$). In this study, the overall incidence of adverse reactions in the observation group was 12.64%, while it was 9.09% in the control group. The comparison between the two groups showed no statistically significant difference ($P>0.05$).[6]

3.1.2 Sertraline

Citalopram is commonly used to treat depression in adolescents by regulating neurotransmitters in the brain, thereby increasing the concentration of serotonin and thus alleviating depressive moods. In a study by Tang Fangfang et al., citalopram was compared with fluoxetine to investigate its efficacy in treating depression. The results showed that there was no statistically significant difference between the experimental group and the control group in terms of HAMD scale scores (8.3 ± 2.7) after treatment ($P>0.05$). This is consistent with literature reports that citalopram has similar HAMD score

improvements (8.2±1.9) for adolescents compared to fluoxetine, indicating comparable effectiveness of both drugs in treating depression. However, citalopram has a higher treatment index than fluoxetine, which may be related to fewer adverse reactions. Animal studies have not shown any stimulating effects or potential barbiturate-like abuse in citalopram, and no reports of adverse reactions associated with severe mental disorders such as mania have been found. The drug has low side effects and high safety. Additionally, citalopram has anti-anxiety properties and improves sleep, while short-term use of fluoxetine can activate the nervous system and potentially disrupt sleep. From this perspective, citalopram also holds clinical advantages. In the study, the PSQI scale score (5.0±1.7) for the experimental group was lower than that of the control group, consistent with literature reports showing a PSQI score improvement (5.1±2.0). Furthermore, CRP is associated with depression, and individuals with high blood CRP levels are more likely to experience itProne to depression. The study found that sertraline treatment for adolescent depression can better reduce the level of CRP in patients blood, and play a role in regulating immune system balance. It suggests that sertraline may improve depressive symptoms through cytokines, but the specific mechanism remains to be further explored.[11]

3.2 SNRIs

SNRIs are selective serotonin reuptake inhibitors, a new class of antidepressants. SNRIs primarily work by inhibiting the reuptake of serotonin and norepinephrine from neurons, increasing their concentrations in the synaptic cleft, thereby improving symptoms of depression and anxiety. They are mainly used to treat major depressive disorder and generalized anxiety disorder, but can also be applied to the treatment of obsessive-compulsive disorder, panic attacks, and chronic pain. Compared with traditional antidepressants, SNRIs offer advantages such as rapid onset, broad spectrum of action, and fewer side effects.

3.2.1 Venlafaxine

Venlafaxine is a commonly used antidepressant that alleviates symptoms by blocking the reuptake of 5-HT or NE. Based on the research of Lu Heng et al., the study group used venlafaxine combined with agomelatine (a new type of antidepressant) to treat elderly patients with depression. The control group received only agomelatine for the treatment of elderly patients with depression. After treatment, the efficacy of the study group was better than that of the control group, with lower depression scores ($P<0.05$). This indicates that combined therapy can significantly improve treatment outcomes and enhance patients depressive symptoms. The study also observed a decrease in neurofunctional-related factor levels and an increase in cognitive function scores in the study group ($P<0.05$), indicating that combined therapy can effectively improve both neurological and cognitive functions.[4]

3.2.2 Duloxetine

Doxepin inhibits the reuptake of norepinephrine and 5-HT, effectively alleviating depression and generalized anxiety disorder, as well as relieving musculoskeletal pain. According to the study by Wen Youlu et al., the observation group received doxepin for elderly patients with depression, while the control group received sertraline. The results showed that after 1 week, 4 weeks, and 6 weeks of treatment, the HAMD scores in the observation group were significantly lower than those in the control group, and the PSQI scores were notably lower after treatment compared to the control group. The reason is that sertraline reaches steady blood concentration levels 4-7 days after administration, while doxepin achieves its maximum blood concentration about 6 hours after oral administration and reaches steady blood concentration levels around 3 days later. Compared to sertraline, doxepin has a faster onset of action, effectively improving depressive symptoms. Additionally, doxepin is a dual inhibitor of NE and 5-HT reuptake, which can improve mood and affect in elderly patients with depression and enhance sleep quality by influencing neurotransmitter transport and secretion. The drug has a weaker inhibitory effect on dopamine reuptake and shows no significant affinity for adrenergic receptors, dopaminergic receptors, histamine receptors, glutamate receptors, or opioid receptors, nor does it significantly inhibit the monoamine oxidase system. It can rapidly achieve antidepressant efficacy without adverse reactions. The study data also showed that the serum levels of NE, 5-HT, and DA in the observation group were all higher than those in the control groupThe dosage is high. It indicates that duloxetine can more significantly improve the condition and neurotransmitter levels of patients with depression. Duloxetine can inhibit both NE and 5-HT reuptake, increasing the extracellular levels of NE and 5-HT in the prefrontal cortex cells. By blocking monoamine reuptake transporters in the human body, it enhances DA levels outside the prefrontal cortex, thereby exciting neurons and enhancing feelings of pleasure, better improving depressive symptoms, making the therapeutic effect more pronounced.[7]

4 Summary and outlook

Some progress has been made in the study of depression mechanism and drug treatment, but due to the complexity of depression mechanism and side effects brought by drug treatment, the research needs to be further developed.

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