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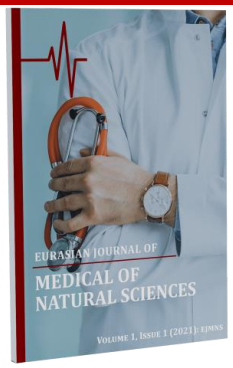

NEUROTRANSMITTER ASPECTS OF ACHIEVING REMISSION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Major Depressive Disorder (MDD) represents one of the most significant challenges in modern psychiatry, affecting approximately 280 million people globally and constituting a leading cause of disability worldwide. Despite advances in treatment approaches, achieving and maintaining remission remains a complex clinical challenge, with only about 30-40% of patients achieving full remission after initial treatment.

Introduction. Understanding the neurotransmitter mechanisms underlying successful remission in MDD has become increasingly crucial for developing more effective therapeutic strategies. Recent research has revealed that remission is not simply a reversal of depressive pathophysiology but rather involves complex neurobiological adaptations and reconfigurations of neural circuits.

The role of neurotransmitters in MDD extends far beyond the traditional monoamine hypothesis. While alterations in serotonin, norepinephrine, and dopamine systems are well-documented in the pathogenesis of depression, their involvement in remission appears to be more complex and dynamic. Recent evidence suggests that achieving remission involves not only the restoration of neurotransmitter levels but also modifications in receptor sensitivity, synaptic plasticity, and neural circuit functionality.

Neuroimaging and biochemical studies have demonstrated that successful remission is associated with specific patterns of neurotransmitter activity and receptor adaptation. These changes occur across multiple brain regions, including the prefrontal cortex, hippocampus, and limbic structures, reflecting the complex nature of emotional regulation and cognitive processing in MDD.

The temporal dynamics of neurotransmitter changes during the transition from active depression to remission are particularly noteworthy. Research indicates that this process involves sequential alterations in different neurotransmitter systems, with early changes in

monoamine availability followed by more sustained modifications in synaptic function and neural circuit reorganization.

Clinical observations have shown that patients achieving remission often display distinct patterns of neurotransmitter activity compared to both actively depressed individuals and healthy controls. These differences may represent compensatory mechanisms or restoration of normal neurobiological function, providing potential biomarkers for monitoring treatment response and predicting long-term outcomes.

The interaction between different neurotransmitter systems during remission is particularly significant. Evidence suggests that successful treatment outcomes are associated with coordinated changes across multiple neurotransmitter systems, rather than modifications in a single system. This understanding has important implications for developing more effective therapeutic approaches that target multiple neurotransmitter pathways simultaneously.

Furthermore, individual variations in neurotransmitter responses to treatment may explain why some patients achieve remission more readily than others. Genetic polymorphisms affecting neurotransmitter metabolism, receptor function, and synaptic plasticity may influence both the likelihood of achieving remission and the maintenance of improvement over time.

Understanding the neurotransmitter aspects of remission also has practical implications for treatment optimization. This knowledge can help in developing more precise therapeutic strategies, identifying early markers of treatment response, and potentially preventing relapse through targeted interventions based on individual neurotransmitter profiles.

Recent technological advances in neuroimaging and molecular biology have provided new tools for studying neurotransmitter dynamics during remission. These methodologies offer unprecedented opportunities to track changes in neurotransmitter function in real-time, potentially leading to more personalized treatment approaches based on individual neurobiological patterns.

The study of neurotransmitter mechanisms in MDD remission represents a critical frontier in psychiatric research, with implications for both understanding the nature of recovery and developing more effective therapeutic strategies. This investigation aims to elucidate the complex interplay of neurotransmitter systems during remission, potentially leading to improved treatment outcomes for patients with MDD.

A large number of studies have shown that when MDR is treated with selective serotonin reuptake blockers (SSRIs) or norepinephrine (norepinephrine), levels of serotonin or norepinephrine increase in the brain of patients, respectively. Long-term treatment with these drugs also increases the level of cyclic adenosine monophosphate (cAMP) in the brain, which stimulates a specific protein kinase A. Activation of this enzyme activates the state of the part of the cell genome responsible for the synthesis of BDNF. The production of cAMP induced by antidepressants also increases the sensitivity of GH, inhibits the negative effect of increased cytokine production and thereby restores their functional activity and regulation in the corresponding neural circuits. The effect of increased levels of monoamines (dopamine, serotonin and norepinephrine) In the treatment of antidepressants, an increase in the synthesis of BDNF and other neurotrophic factors is one of the leading mechanisms of their

antidepressant action. Animal studies have shown that increased levels of monoamines (serotonin and norepinephrine) With chronic administration of antidepressants, it causes an increase in BDNF levels in brain astrocytes. In clinical studies, it has been shown that with successful treatment of patients with BDD with antidepressants, the serum level of BDNF normalizes. It is believed that the serum level of BDNF reflects its synthesis in the brain. This is supported by animal experiments, as well as the fact that BDNF freely passes through the blood-brain barrier. It has been shown that the degree of improvement in patients' condition during treatment with antidepressants with simultaneous inhibition of serotonin and norepinephrine reuptake (dual reuptake inhibitors) significantly correlates with an increase in serum BDNF levels. Studies of postmortem brain samples showed that in cases of death of patients during treatment with double reuptake inhibitors, a higher content of BDNF was detected in its tissue than in brain samples taken from untreated patients. In one study, it was noted that a positive response to treatment with antidepressants was accompanied by normalization of cortical activity. After 1 week of treatment, the activity of the hippocampus increased in patients and the activity of the posterior cingulate and prefrontal cortex decreased. After 6 weeks of treatment, the responding patients showed signs of normalization of limbic system activity and an increase in prefrontal cortex activity, whereas the resistant patients showed no changes after the first week. It also turned out that normalization of the functioning of the amygdala and anterior cingulate cortex is associated with a positive response to treatment. In addition, it was found that antidepressant-resistant patients with BDD have increased levels of pro-inflammatory cytokines compared to controls or euthymic patients with BDD. A study of the reduction of symptoms of BDD during treatment has shown its connection with regional changes in the metabolism of the brain of patients. Thus, a decrease in the severity of cognitive impairment correlated with an increase in the activity of the dorsal part of the anterior cingulate cortex, and a decrease in the manifestations of fatigue syndrome and psychomotor retardation was associated with a decrease in the activity of the ventromedial zone of the prefrontal cortex. Interestingly, these correlations were observed regardless of whether psychopharmaceutical or psychotherapy was performed. There is a point of view that the restoration of neurobiological regulation in MDD through increased synthesis of neurotrophic factors and, as a result, neurogenesis is probably a common radical determining the effectiveness of treatment, regardless of whether it is psychopharmacological, psychotherapeutic or somatic (in the latter case, the use of diet and special physical exercises is meant). The presence of the "rocking" effect and the chronification of BDR during its long course makes it urgent to find the most effective therapy already at the first attack of the disease. Long-term studies have shown that the best predictor of the course of the disease is the patient's response to treatment already at the first attack, i.e. during the first 6 weeks after the onset of the attack. This is of particular importance for elderly patients, in whom previous inadequate treatment with antidepressants may lead to pharmacoresistance. The patient's positive response to treatment with antidepressants at an early stage of the disease gives a chance that further improvement in the quality of psychopharmacotherapy will lead to a complete or partial recovery of the patient. One of the ways to improve the quality of treatment for patients with BDD is considered to be the use of antidepressants with a broader spectrum of action or an appropriate complex of drugs with

different mechanisms of action. However, the results of a large meta-analysis. Which included 92 studies (17,036 patients), showed the same efficacy of serotonin- and noradrenergic antidepressants. However, a new generation of antidepressants that are dual selective reuptake inhibitors (both serotonin and norepinephrine) – dual antidepressants have proven to be more effective than SSRIs and SSRIs. Dual antidepressants proved to be especially effective if there were pain symptoms in the structure of depression, which is known to be characteristic of masked depression. This is due to the fact that when treated with dual antidepressants, the serotonin and norepinephrine systems are synergistically activated. The neurocirculatory and neurotrophic hypotheses of depression show that the factors that initiate an episode in MDD and the factors that support the development of the disease are different. At the initial stage, vulnerability to stress and a genetic predisposition to the disease interact with each other and initiate a cascade of neurobiological disorders that disrupt normal dynamic connections in areas of the brain associated with the regulation of mood, cognition, physical and mental activity, pain, etc. With the chronification of the disease, further structural and functional disorders begin to potentiate as BDD progresses. The main goal of treatment in the presence of the consequences of chronic BDD is to restore normal functioning and prevent further structural and functional neurobiological disorders in the brain of patients. An increase in serotonin and noradrenergic neurotransmission with antidepressants initiates the restoration of the synthesis of neurotrophic factors (especially BDNF), which normalizes glucocorticoid activity and neuroendocrine regulation. The use of dual antidepressants (serotonin and norepinephrine reuptake inhibitors) increases the likelihood of achieving remission due to the complex reduction of emotional and somatic symptoms (including pain) in depression. Conclusions: Thus, according to the neurocirculatory and neurotrophic hypotheses, the results of treatment in the early stages of the disease determine the prognosis and recurrence of the course of MDR. The presence of residual symptoms during treatment also affects the further course of the disease. When remission is achieved, patients should be informed about the greater benefits of continuing long-term, continuous treatment than episodic or incomplete treatment. Treatment, which includes individual or group cognitive therapy along with active psychopharmacotherapy, helps to correct the molecular factors of the disease pathogenesis, which reduces the subsequent risk of exacerbation of MDR. When remission is achieved, maintaining brain metabolism at a normal level is a more important task than preventing a developing exacerbation. This requires coordinated actions by the patient and the doctor in order to maintain fully or partially normalized neurobiological homeostasis.

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