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A CLINICAL PHARMACOLOGICAL APPROACH TO THE RATIONAL USE OF DRUGS IN DEPRESSIVE SYNDROME

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ABSTRACT

A review of the literature on the neurobiological mechanisms of depressive disorders, which presents the role of biochemical changes in the cholinergic, serotonergic, dopaminergic and other neurohumoral systems in the development of depression. Modern approaches to the pharmacocorrection of depressive disorders are discussed in detail, and the question of the prospects of treating depression with anticholinergic drugs is also raised.

Keywords: depression, biochemical changes, antidepressant effect, emotions, monoamines, anticholinergic drugs.

INTRODUCTION

Emotions play an important role in the life of humans and animals, participating in the organization of expedient adaptive behavior. Various types of disturbances in the normal functioning of the brain mechanisms of emotions—emotional or affective disorders and, above all, depression—disorganize adaptive behavior and are a serious illness that affects more than 12% of the population of economically developed countries [1]. In recent years, the term “social stress disorder” has even appeared, reflecting profound socio-economic changes [2].

MATERIALS AND METHODS

Depression is a mental disorder characterized by a pathologically low mood with a negative, pessimistic assessment of oneself, one’s position in the surrounding reality, one’s past and future [3]. There are three main components of the affective component of the depressive syndrome: melancholy, anxious and apathetic [3]. Each of the components is in a dynamic connection with the others, and together they make up the “alarming triad” [4]. Depressive mood changes, along with distortion of cognitive processes, are accompanied by motor inhibition, decreased motivation for activity, and somatovegetative dysfunctions [5]. The clinical picture of depressive disorder is expanding due to comorbid conditions (hypochondriacal, anxiety-phobic) [2]. Considering the difficulties of primary diagnosis of these disorders, their masking as other mental and somatic pathologies, as well as their tendency to have a long, chronic course with a parallel increasing risk of relapse of depression, serious problems arise in the process of their psychopharmacological treatment [4]. Therefore, when treating patients with depressive disorder, it is possible to achieve remission only in 30% of cases [4].

RESULTS AND DISCUSSION

Neurobiological studies of the mechanisms of depressive disorders have long focused primarily on monoamines [5]. According to the monoamine theory, one of the leading factors in the

development of depression is a deficiency of serotonin (5-HT) and norepinephrine (NA) in the synaptic cleft [2]. There is information about a sharp decrease in the content of all monoamines and an increase in the level of their metabolites in the brain of rats after modeling depression [3]. Literature data indicate that depression is caused by a functional deficiency of serotonin in the brain [28, 58, 66, 67] since the level of its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid of such patients decreases [2] . However, some researchers have observed normal or even increased levels of 5-HIAA in depression [5].

In addition to the serotonergic and noradrenergic systems, the dopaminergic system has recently attracted significant interest in connection with the development of depression.

Based on the fact that blockade of dopamine receptors by antipsychotics caused symptoms of depression, and dopamine agonists and precursors had a therapeutic effect, depression was associated with a decrease in dopaminergic activity in the brain. At the same time, it has been shown that depression can also develop against the background of increased DA activity, for example, in schizophrenia. The results obtained by various authors with direct measurements of the precursors of dopamine synthesis and its metabolites in postmortem brain samples of depressed patients are very contradictory.

It is known that disorders of dopamine metabolism are accompanied by significant changes in the balance of neurotransmitters, including acetylcholine and glutamate, which play an important role in the regulation of motor activity. Dopamine influences the striatal cholinergic system in at least two ways: it reduces the release of acetylcholine, activating D2 receptors, and at the same time increasing the release of the transmitter, activating D1 receptors. On the other hand, there is evidence confirming that a decrease in the functional activity of the nigrostriatal and mesolimbic DA-ergic systems and an increase in the activity of the NA-ergic system play an important role in the formation and maintenance of a mixed anxious-depressive state in animals. When modeling a state similar to depression in rats (raised in conditions of partial or complete isolation), a significant decrease in the content of DA and 5-HT was revealed, with a constant level of NA in the brain structures that control motor activity and emotional behavior [1]. However, some researchers note that the level of all monoamines increases in the brain during depressive disorders [2].

A great contribution to the understanding of the pathogenesis of depressive disorder was made by the development of the neuroplastic theory, which included the theory of biogenic amines. Its main postulate is that the formation of the emotional background is not determined by the level of individual neurotransmitters, but is formed as a result of the combined activity of various parts of the brain [3].

There is a hypothesis of dynamic changes in neurochemical activity during the development of experimental depression, according to which the activity of monoaminergic systems changes depending on the duration of psycho-emotional impact, the depth of development of psychopathology, and brain structure [1].

Moreover, it should certainly be taken into account that a depressive state can arise not only as a result of a violation of monoaminergic neurotransmission, but also when the function of the hypothalamic-pituitary-adrenocortical system, neurotrophins and interleukins is impaired in hereditarily predisposed individuals who are influenced by factors risk of a stressful or infectious nature [3].

Alterations in a number of serotonin receptor subtypes, which are closely associated with depression, have been reported to be heritable [2], and the suggestion that neuroinflammation plays an important role in some cases of severe depression is increasingly supported [4]. Suppression of neuroinflammation is considered as one of the mechanisms of action of antidepressants [5]. All these systems (neurotransmitter, hormonal, immune, genetic factors) are closely interconnected, therefore only an integrated approach will allow the development of effective and safe methods of treating depressive disorders. This is why the use of drugs whose mechanism of action is based solely on the monoamine hypothesis leads to a long delay in the manifestation of the therapeutic effect, as well as to the appearance of depressed patients who do not respond to these drugs at all. In addition, most of the previously developed groups of drugs cause serious or unpleasant side effects [2].

The use of psychotropic drugs is determined by the nature and severity of affective disorders [3]. Pharmacotherapy of depressive-like disorders uses antidepressants (with a stimulating effect, a balanced effect and a sedative effect), anxiolytics (most often benzodiazepine tranquilizers - BT), as well as antioxidants and antihypoxants.

Typical antidepressants are divided into three pharmacological classes. These are monoamine oxidase inhibitors (MAOIs), an enzyme that destroys biological amines; tricyclic antidepressants (TCAs), the action of which is realized through blocking the mechanism of reuptake of amines from the synaptic cleft, which leads to an increase in the concentration of neurotransmitters, as well as the third class, which consists of drugs that affect neurotransmission through blockade of receptors (α2-adrenergic receptors and serotonin - 5 HT1 A, 5 HT2 C, 5 HT2, 5 HT3) [5].

CONCLUSION

In addition to their effect on nicotinic receptors, M-anticholinergics affect the immune system, as well as hormonal status [4]. Since the neuro- and immunotransmitter systems of the body are involved in the implementation of the effects of central M-anticholinergics, it is reasonable to assume that drugs of this type of action may be promising in the pharmacotherapy of diseases such as Parkinson's disease, schizophrenia and depression.

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