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[1]Chair and Department of Applied Pharmacy, Medical University of Lublin, Poland
[2]Chair and Department of Human Physiology, Medical University of Lublin, Poland

ALEKSANDRA SZOPA[1], WERONIKA STASIUK[2], EWA POLESZAK[1]

Pharmacotherapy of depressive disorders

Farmakoterapia zaburzeń depresyjnych

Depression is currently the most frequently occuring affective disorder. According to World Health Organization (WHO) data, depression is one of the four major global health problems. It is estimated that depression is going to be the second of all civilization diseases in 2020 [16]. Currently, the depression incidence rate in European countries reaches about 4% but statistics including so-called masked depression amount to 10%. The number of people suffering from depression varies depending on the age group. About 10% of the population is affected between 35 and 45 years of age, in over 45 age group it is 20%. What is more, women tend to fall sick 2 or 3 times more frequently than men. The first symptoms can be recognized in childhood, among school-age or kindergarten- age children. The estimation of the actual prevalence of this disorder is hampered by the fact that depression has yet remained unrecognized in many patients. It is assumed that at least 50% of all the people affected by depression do not call for a professional guidance [16, 34]. The growing spread of affective disorders and harmful aftermaths of this fact bring about a rising interest in these illnesses either in the medical or social context. This situation may contribute to a greater awareness of the society and successful prospecting for new antidepressant drugs.

MECHANISM OF DEPRESSIVE DISORDERS

The mechanism of depressive disorders formation is most probably connected with the diminished activity of noradrenergic and serotonergic neurons (5-HT) in CNS [18, 29]. What also occurs, are hormonal disorders (the release of cortisol is particularly increased) which are probably connected with noradrenergic neurons hypoactivity in hypothalamus [23]. The examinations of the affected people that have been performed also indicate the presence of disorders in the functioning of the hypothalamic–pituitary–adrenal axis. Mechanisms of hormonal regulation within this axis get damaged. About ⅓– ⅔ of the affected exhibits the axis hyperactivity. What occurs here is the excessive activation of the hypothalamic–pituitary–adrenal axis caused by and increased activity of corticoliberin and the damage of feedback mechanism where glucocorticoids inhibit the release of cortisol [9, 17, 19].

Genetic factors [12, 25], a positive family history towards affective disorders and social and psychological factors are among those predisposing for depressive disorders. Depression episodes most often occur as the aftermath of a death of the loved ones, a divorce, financial problems and job loss. Women in perinatal stage, PMS stage and perimenopausal stage and people suffering from chronic somatic diseases are counted among the high-risk group. Depressive state can be quite often observed in people overusing alcohol and drugs. It might occur in the period of using these substances as well as after the withdrawal. Symptoms severity among people affected by depression may occur in autumn and winter time which is connected with the limited access to sunlight in this period [36].

SYMPTOMS OF DEPRESSION

Basic symptoms accompanying depressive disorders include low mood, sadness, gloom, inability to experience pleasure (anhedonia). What can also be observed among the patients is the inihibition of the locomotor drive, a loss of interest, difficulty in making decisions, apathy and deterioration in intellectual efficiency (memory impairment, concentration difficulties). In many cases anxiety, suicidal thoughts or tendencies arise. Sleep disorders, a loss of appetite, sexual drive disorders, physical ailments, feeling of tension and a general feeling of physical weakness and loss of strength can be counted among the somatic symptoms which occur in patients suffering from depression [19].

KINDS OF DEPRESSIVE DISORDERS

Various kinds of depressive disorders can be distinguished. The first one is a psychogenic depression. It is a kind of a depression with typical syndromes which occurs in response to adverse psychological situations of internal (mental conflicts) or external (environment derived) nature. Psychogenic depression can be divided into a few groups depending on the factor that initiated it. A reactive depression is the result of reactions to difficult, traumatic events - death, property or job loss. There are several types of reactive depressions including postnatal depression, involutive depression (ageing) and seasonal depression. Dysthymia is a kind of a psychogenic depression that is characterized by long-term neurotic disorders. Apathy, anxiety and the presence of phobias can be observed in a patient's behaviour [21]. Apart from a psychogenic depression there is also an endogenous depression which can be divided into unipolar and bipolar depressions. Throughout the endogenous depression a patient for no clear reason experiences gloom and reluctance to act and live. This type of disorder is not caused by any external factor. A unipolar depression is characterized by a long- term low mood and a loss of motivation for no obvious reason, whereas bipolar affective disorders (manic depressions) are characterized by the existence of consecutive phases - depression and mania [21].

The third kind of depression are somatogenic depressive disorders. They occur in the course of somatic diseases (organic). The depressions may affect patients addicted to medicines, due to serious poisoning, organic brain diseases and in the course of cancer or other serious illnesses [4, 21].

PHARMACOTHERAPY

Pharmacotherapy of depressive disorders includes the usage of medications from different chemical groups and of different action mechanisms [18]. Antidepressant drugs were first introduced in 1950s and are currently routinely used in treating depression states. A common feature of pharmacotherapy is the activation of noradrenergic and serotonergic transmission in CNS. Currently, there are over thirty types of antidepressant drugs that can be divided into four groups depending on the action mechanism [6, 18].

1. Drugs that show a dominating influence on the monoamine neuronal reuptake.
2. Monoamine oxidase inhibitors.
3. Drugs that show an activity blocking adrenergic receptors α2.
4. Drugs of various activity.

Among the drugs that influence the monoamine neuronal reuptake, a few groups of medicines can be distinguished. They are divided with regard to their selectivity and the kind of catecholamine that they influence [18].

The first group of medicines includes those that inhibit monoamine reuptake and that possess numerous receptor action. These are tricyclic antidepressant drugs, derivatives of dibenzazepine and cycloheptadine. These medicines potentiate the action of adrenergic and serotonergic system through inhibiting the amine reuptake with neurons. As a result, the receptor action of noradrenaline, serotonin and dopamine in CNS gets potentiated. Amitriptyline, clomipramine, imipramine and desipramine are included in this group. Side effects caused by these medicines are due to lack of their selectivity. They act in an antagonistic way on muscarinic, histamine and α1-adrenergic receptors. Therefore they may cause dry mouth, tachycardia, dilated pupils and perception disorder, constipation, urine flow blockage, somnolence, orthostatic hypotension, dizzy spells, weight gain, cognitive disorders, cardiotoxicity and sometimes convulsions and ataxia [11, 18].

Venlafaxine, duloxetine and milnacipran are in a group of medicines that selectively inhibits noardrenaline and serotonine reuptake. These medicines, due to a selective influence on noradrenergic and serotonergic transmission, are deprived of cholinergic action; therefore they do not cause adverse reactions which accompany the use of tricyclic antidepressant drugs [18].

Among the selective monoamine reuptake inhibitors three groups of medicines can be distinguished. They are characterized by a high selectivity with respect to only one monoamine (serotonin, noradrenaline or dopamine). From the clinical point of view, the most prominent group among these medicines are selective serotonin reuptake inihibitors (SSRI) which include fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram [18]. The mechanism of their activity relies on desensitization of all types of serotoninergic receptors which leads to a potentiation of the function of serotoninergic system [22]. The action of these medicines can be compared to tricyclic antidepressant drugs, however, SSRI cause fewer adverse reactions. It is worth noticing that these medicines dangerously interact with the drugs that potentiate the activity of serotoninergic system (e.g. MAO inhibitors). An additional blocking impact on 5-HT2 receptors caused by nefazodone and trazadone directs the action of serotonin on postsynaptic receptors 5-HT1A in the hippocampus. The activation of the receptors plays a key role in causing the antidepressant activity. It is also connected with a smaller number of adverse reactions while using medicines from this group [18].

Another group of medicines that has been implemented in treating depressive disorders is monoamine oxidase inhibitors. They potentiate monoaminergic transmission (of noradrenaline and serotonin) through inhibiting monoamine oxidase (the enzyme responsible for the decomposition of catecholamine). Unfortunately, their usage has been restricted really early due to numerous adverse reactions and interactions with different medications. Currently, only a selective, reversible MAO-A inhibitor-moclobemide is used [18, 20].

Mitrazepine and mianserin belong to another group of antidepressant drugs, which substantially differs from other drugs with respect to the action mechanism. Either of these substances blocks adrenergic autoreceptors α2 on serotoninergic neurons and potentiate 5-HT neurotransmission. They exhibit an additional activity blocking postsynaptic 5-HT2 which directs the action of serotonin on postsynaptic receptors 5-HT1A, whose activation is essential for reaching the antidepressant activity [18].

Tianeptine can be assigned to the group of atypical antidepressant drugs. It is a medicine that potentiates neuronal reuptake 5-HT. Tianepine shows an activating impact on the hippocampus neurons. Additionally, it acts neuroprotectively and it prevents the damage of CA3 stratum pyramidal neurons because this damage is connected with the activation of 5-HT neurotransmission. The potentiation of serotonine reuptake leads to the weakening of the overstimulated serotoninergic mechanisms which may lead to patient's clinical improvement [18].

The prevailing theory about the action of antidepressant drugs is clearly connected with their influence on the changes in processes of monoaminergic transmission. What is the most crucial, according to the theory, is the potentiation of the serotoninergic and noradrenergic transmission that leads to adaptive changes of the receptors during a long-term use of these drugs. This conception has been recently undergoing major changes, though. It is not only due to the presence of medicines with atypical action mechanisms but also due to a constant progress in the study of development of depressive disorder mechanisms [17].

The efficacy of contemporary antidepressant drugs is estimated at 70% [6, 9]. These medicines evoke a great number of adverse reactions and a therapeutic effect appears after several weeks of use. Therefore, some other, safer and more effective antidepressant drugs are still sought [10]. That is why scientists' main interest was focused on processes other than the modification of monoamine transmission [17]. This trend contributed to the development of a few conceptions of pathogenesis and the treatment of depressive disorders. One of the ideas focused on the actions and intracellular processes, such as regulatory proteins G, secondary messenger transmission, a protein kinase and transcription factors. It has been shown that one of the most crucial phenomena occurring as a result of the long- term use of antidepressant drugs is an increase in activity of cyclic AMP which is a result of a regulatory protein Gs stimulation and a subsequent regulation of the adenylate cyclase. An increase in cAMP concentration causes the protein kinase activation (PKA) which is responsible for the CREB transcription factor phosphorylation (cAMP response element binding protein). CREB accounts for an increase in gene expression and currently it is widely believed that this factor can be a foundation for the action of a number of antidepressant drugs [17, 18]

Another conception that seeks for new medicines focuses on neurotrophic factors which are proteins necessary for a proper development and functioning of neurons. Numerous neurotrophins

exhibit an influence on neurons which are responsible for mood regulation i.e. brain derived trophic factor (BDNF) is responsible for an increase of 5-HT and noradrenaline. It has been proved that, among other factors, it is stress that causes a decrease in concentration of this factor in the brain structure [18].

Another thing that has drawn scientists' attention was the fact that in the course of depressive illnesses an increased concentration of cytokines in patients was observed, among others-interferon-gamma, some of the interleukins and tumor necrosis factors (TNF-α). It is assumed that a decreased number of these cytokines may have a positive impact on depression symptoms [18].

A number of research studies carried out in the recent years has shown that the glutaminergic system also plays an important role in pathophysiology of depressive disorders. Among people suffering from depression a disorder of Glx level in the frontal lobe has been claimed (Glutamic acid/glutemine/GABA). Apart from an increased concentration of the glutamic acid in the structure of the nervous system, a decreased GABA level in brain and an increased level of the glutamic acid in blood plasma and thrombocytes has been observed [1-3, 13, 15, 35, 37-39, 47].

Moreover, numerous research studies have shown that a multiple use of antidepressant drugs causes adaptive changes in NMDA receptors sphere. These changes are connected with a function impairment of these receptors. An experiment conducted in mice and rats have revealed a decrease in the glycine affinity in its binding fragment in NMDA receptor complex in cerebral cortex, a diminution in modulation between the glutaminergic and glycine fragment in NMDA receptor complex in cerebral cortex, a delay in selective binding processes in phencyclidine fragment (what is probably connected with the decreased speed of channel opening for NMDA receptor calcium ions) and an increase in zinc ions affinity for zinc fragment responsible for NMDA modulation receptor in cerebral cortex in mice which is connected with the ability of Zn2+ ions to inhibit NMDA receptor activity [7, 26-28, 30, 31, 33, 40, 42-46].

The antidepressant activity of the NMDA receptor antagonists has been revealed in many tests and depression models. It has been proved that the functional NMDA receptor antagonists - glutaminergic fragment ligands (AP7, CGP 37849), zinc ligands (Zn2+), polyamine ligands (eliprodil), phencyclidine ligands (memantine, MK-801) and glicyne ligands (ACPC, 7- chlorokynurenate acid) show antidepressant activity in a forced swim test [5, 7, 8, 32, 33, 40-46].

The antidepressant activity of NMDA receptor antagonists has been analyzed in the clinical studies. In one of them D-cycloserine has been administered for six weeks at a dose of 250 mg a day in patients with a serious drug resistant depression. Nevertheless, the research has not shown any antidepressant activity of this compound [14]. The desirable antidepressant effect was present in clinical studies in patients suffering from a unipolar depression and addicted to alcohol, to whom memantine was used as an antidepressant drug administered at a dose of 20 mg a day [24]. However, research in which ketamine was administered intravenously at a single dose of 0.5 mg/kg after a two-week long period of antidepressant drugs, discontinuation has shown that it eliminates symptoms of depression in patients with a serious drug resistant depression [48].

The research reveals antidepressant activity of NMDA receptor antagonists in tests and models of depression as well as in clinical studies in patients with a serious drug resistant depression. Therefore, it can be assumed that NMDA receptor antagonists can be widely applied in treating depressive disorders and the action mechanisms of these compounds are different in the binding fragment of antagonist ligands in NMDA receptor structures.

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SUMMARY

Depression is currently the most frequently occurring affective disorder. According to World Health Organization (WHO) data, depression is one of the four major global health problems. The growing spread of affective disorders and harmful aftermaths of this fact bring about a rising interest in these illnesses either in the medical or social context. This situation may contribute to a greater awareness of the society and successful prospecting for new antidepressant drugs. The mechanism of depressive disorders formation is most probably connected with the diminished activity of noradrenergic and serotonergic neurons (5-HT) in CNS. Pharmacotherapy of depressive disorders includes the usage of medications from different chemical groups and of different action mechanisms. A common feature of pharmacotherapy is the activation of noradrenergic and serotonergic transmission in CNS. The efficacy of contemporary antidepressant drugs is estimated at 70%. These medicines evoke a great number of adverse reactions and a therapeutic effect appears after several weeks of use. Therefore, some other, safer and more effective antidepressant drugs are still sought. A number of research studies carried out in the recent years has shown that the glutaminergic system also plays an important role in pathophysiology of depressive disorders.

Keywords: depression, noradrenergic neurons, serotonergic neuron, antidepressants, NMDA receptor

STRESZCZENIE

Depresja jest obecnie najczęściej występującym zaburzeniem afektywnym. Z danych przedstawionych przez Światową Organizację Zdrowia (WHO) wynika, że obecnie depresja stanowi jeden z czterech najpoważniejszych problemów zdrowotnych na świecie. Rosnące rozpowszechnienie zaburzeń afektywnych oraz szkodliwe następstwa tego faktu sprawiają, że rośnie zainteresowanie tymi chorobami zarówno w kontekście medycznym jak i społecznym, co może przyczynić się do

większej świadomości społeczeństwa i udanych poszukiwań nowych leków przeciwdepresyjnych. Mechanizm powstawania zaburzenia depresyjnych związany jest prawdopodobnie z osłabieniem czynności neuronów noradrenergicznych i serotoninergicznych (5-HT) w OUN. Farmakoterapia zaburzeń depresyjnych obejmuje stosowanie leków z różnych grup chemicznych i o różnych mechanizmach działania. Skuteczność obecnie stosowanych leków przeciwdepresyjnych oceniana jest na około 70%. Dodatkowo leki te wywołują znaczną ilość działań niepożądanych, a efekt terapeutyczny pojawia się po kilku tygodniach stosowania leków. W związku z tym ciągle trwają poszukiwania nowych, bezpieczniejszych i skuteczniejszych leków przeciwdepresyjnych. Jak wskazują, prowadzone przez ostatnie kilka lat badania, istotną rolę w patofizjologii zaburzeń depresyjnych odgrywa również układ glutaminergiczny.

Słowa kluczowe: depresja, neurony noradrenergiczne, neurony serotoninergiczne, leki przeciwdepresyjne, receptor NMDA