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Review

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The NMDA receptor and new possibilities in antidepressant therapy

Receptor NMDA i nowe możliwości leczenia depresji

Weronika Stasiuk, Monika Prendecka, Krzysztof Chara, Teresa Małecka-Massalska

Department of Human Physiology, Medical University of Lublin, Poland

Summary

Due to the inadequate effectiveness of pharmacological methods currently being utilized in the treatment of depression, there is an ongoing need to find newer and safer treatment strategies. Studies undertaken to date aimed at finding more effective methods for the treatment of affective disorders have been widened to incorporate other neurotransmission systems.

Experiments with compounds that modify the function of the glutamatergic system highlight a new direction in the study of affective disorder treatment methods. It has been shown that one of the key mechanisms in achieving an antidepressant effect is by weakening the function of the NMDA receptor. Pre-clinical as well as clinical trials have revealed that compounds that modulate the activity of the NMDA receptor are characterized by a significant antidepressant effect which identifies them as potential antidepressant medications.

In this study an attempt was made at identifying the role of the NMDA receptor in the pathogenesis and therapy of depressive disorders as well as the influence of ligands (especially antagonist) of this receptor on the function of classical antidepressant medications. Results shown in the attached studies by numerous scientists will in the future potentially add to the development of more effective and safer therapies for patients with affective disorders as well as offering a potential alternative in the treatment of drug resistant forms of depression.

Keywords: **depression • antidepressant therapy • resistant depression • NMDA receptor**

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Author's address: Weronika Stasiuk MSc Pharmacy, PhD; Department of Human PhysiologyMedical University of Lublin, Radziwiłłowska 11, 20-080 Lublin, Poland; e-mail: weronika.stasiuk@umlub.pl

Abbreviations: **ACPC** - 1-aminocyclopropanecarboxylic acid; **AMPA receptor** - **α**-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **BDNF** - brain derived neurotrophic factor; **CREB** - cAMP response element binding protein; **EAAT** - excitatory aminoacid transporter; **HPA** - hypotalamic-pituitary-adrenal axis; **KA receptor** – kainate receptor; **MAO** - monoamine oxidase; **mTOR** - mammalian target of rapamycin (kinase); **NMDA receptor** - N-methyl-D-aspartate receptor; **NR1, NR2 -** receptor NMDA subunits; **SNRI** - selective noradrenaline reuptake inhibitors; **SSRI** - selective serotonin reuptake inhibitor; **TCA** - tricyclic antidepressants.

INTRODUCTION

Depression is one of the most commonly occurring affective disorders, and its principal symptom is the long-term reduction in a patient's sense of wellbeing. It is a disorder which is not uncommonly prolonged in nature with a tendency to reoccur in a patient, leading to a reduction in the normal functioning of a person and a marked decrease in the persons quality of life. The most significant clinical problem associated with depression is suicide, attempted by 15-20% of persons with severe depression [52]. A worrying factor is also the rise in the number young people suffering from this illness, as well as the continuing rise in cases of drug resistant depression [20].

Antidepressant treatment incorporates pharmacotherapy as well as non-pharmacological forms of therapy. The aim of treatment therapy in cases of depression is to eliminate symptoms, achieve full remission as quickly as possible as well as to prevent the reoccurrence of the illness [44]. However, it needs to be noted that therapy utilizing currently available pharmacological treatment methods is not foolproof and is linked with many side effects; accordingly, there is an ongoing search for newer and more effective treatment strategies. One of the new directions of research concentrates on the glutamatergic system, with new antidepressant medications being explored among compounds that are glutamatergic receptor ligands. This study shows the role of the NMDA receptor in the pathology of depression as well as looks at various ligands that effect the expression and function of the NMDA receptor and as such brings to attention other possibilities in the therapeutic treatment of affective disorders.

DEPRESSION

Due to a relatively limited understanding within the community as well as the lack of clearly definable causative factors, depression has until quite recently been marginalized; however, in the last decade or so there has been an increase in all developed European countries in the number of cases of affective disorders reaching epidemic proportions, which has resulted in this problem being noticed. Currently, depression is considered as being one of four most important health problems in the world with the prognosis for the next decade of the 21st century indicating that it will be the second most important (after coronary heart disease) in limiting work ability and causing disability within the community [13]. Its negative health impact as well as the linked effects on the community and the economy were recognized as a priority health problem in all developed countries. Depression as understood by psychiatry is not treated as a singular form of illness but rather a heterogenic collection of disorders with various clinical pictures and various etiology [5]. It is thought that a significant role in the pathogenesis of affective disorders is played by genetic factors (40-50% of cases). The cumulative and variable nature of symptoms of depression reveals the complex nature of the pathogenesis of the illness and its linkage with various neurotransmitter systems. It is commonly thought that the onset of affective disorders is linked with changes in the metabolism of biogenic amines (noradrenaline, serotonin, dopamine) as well as weakening of the function of noradrenergic and serotonergic neurons in the central nervous system [5]. A significant role in the etiology of depression is played by the hormonal system: the hypothalamic-pituitary-adrenal axis which is responsible for the overall stress response [9]. Depression also causes neurodegenerative changes. Depression is a type of prolonged stress, leading to chronic hipercortisolemia and decreases in the production of neurotrophins, which play a significant role in the brain derived neurotrophic factor (BDNF) [28]. In patients suffering from depression there is an observed increase in the rate of various infections, which has brought to the attention of scientists the role of the immune system. The immune system theory of depression asserts that the incorrect functioning of the immune system can cause changes in the monoamine neurotransmitter, neuroendocrine changes as well as disruptions in the process of neurogenesis [27]. The above theories linked to the incidence of depression do not exhaust the subject relating to pathomechanisms responsible for its occurrence as characterized by multiple causative agents of this disorder. It also needs to be noted that these theories are not mutually exclusive but rather complementary.

ANTIDEPRESSANT THERAPIES – BASIS FOR TAKING ACTION, TREATMENT AIM

The most popular method of treatmenting affective disorders is the administration of antidepressant medications. Their application has revolutionized the treatment of depression, limited the application of electroshock therapy, significantly improved prognosis in the short term, shortened the treatment period and, most importantly, allowed for treatment without the need for patient hospitalization [43]. However, the therapeutic effectiveness of currently used medications, estimated at 60-70%, is not satisfactory and the therapy is linked with many unwanted side effects, which limits its application. A very significant limitation in the current pharmacotherapy of depression is the lag time of 2-4 weeks (following the commencement of therapy) before an observable effect can be ascertained [15]. The lack of a clearly perceivable effect over such a long period of time contributes to the cessation of therapy by patients as well as increasing the risk of suicide [52]. The aim of effective treatment of depression is to prevent the development of drug resistance, curing the illness as quickly as possible and achieving permanent remission. By obtaining only a partial and incomplete remission we are faced with an increased risk of reoccurrence of the illness, increased number and frequency of episodes, increased severity of symptoms as well as a reduction in the potential for achieving a complete and

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lasting cure. Chronic depression and drug resistance worsen the quality of life and the somatic condition of the sufferer and increases the risk of suicide [33]. Obtaining full remission in cases of drug resistant depression is a lot harder than obtaining it following the initial application of antidepressant medications [20]. Resistance to treatment increases with each following therapy and, at the same time, the chances of obtaining a full and permanent cure are reduced. Amongst the many concepts related to episodes of pharmaceutical resistant depression special attention needs to be paid to the potentiation of antidepressant therapy. This is defined as the combined application of antidepressant medication with a substance that potentiates its antidepressant effects. The most commonly used potentiating agents include: lithium, carbamazapine, lamotrygine, valproinian acid, thyroid hormones, gonadotropic hormones, buspiron, pindolol, olanzapine, risperidon [23]. Potentiating agents may in the future also include some activity modulators of the NMDA receptor.

THE GLUTAMATERGIC SYSTEM AND THE NMDA RECEPTOR

The glutamatergic system also known as the amino acid stimulating system is one of the principal neurotransmiter systems of the brain and glutamic acid is the main stimulating neurotransmiter; it is an agonist of all types of glutamatergic receptors, both iono- (AMPA, NMDA, KA) as well as metabotropic [51]. The term NMDA receptor derives from a compound that is its selective agonist N-methylo-D-asparagine acid. It is a complex protein, its four subunits comprise the ion channel permeable to potassium, sodium and calcium ions. The complex structure of NMDA receptors means that they contain many modulating sites involved in regulating the frequency of the ion channel opening, which are potential pharmaceutical action sites [53]. NMDA receptors play a significant role in brain physiology. They take part in rapid synaptic transmission, in the development and maturation of the central nervous system, and in synaptic process adaptation. They also play an important role in brain plasticity, recognition processes, formation of anxiety and associated reactions, transfer of optic signals, control of the breathing function, as well as the transmission of pain signals [38].

High concentrations of agonists may lead to the disruption of glutamatergic neurotransmission. This phenomenon, also termed excitotoxicity, takes place when there is long-term exposure of nerve cells to glutamine resulting in excessive activation of the NMDA receptors, causing a large increase in the intercellular concentration of calcium and in effect cell death. This is of special significance in cases of hemorrhage and brain hypoxia. Blockage of the NMDA receptor can minimize the uncontrolled rise in calcium ion concentration in the neurons and associated necrosis [22]. Excessive activation of NMDA receptors most probably is one of the factors responsible for the development of many psychological and neurological illnesses such as: depression, schizophrenia, anxiety disorders, Alzheimer's disease, Parkinsons disease, Huntington's disease, stroke, addiction to alcohol [ex. 35, 36, 56]. It also seems to be the cause of neuron degeneration as well as slowing neurogenesis in the hippocampus, resulting from hiperstimulation of the HPA axis, which can be seen in depression and reaction to stress [9]. This is why reducing the activity of NMDA receptors may be one of the options of treating illnesses resulting from excessive activation of the glutamatergic system.

THE NMDA RECEPTOR IN PATHOPHYSIOLOGY, THERAPY OF DEPRESSION AND MECHANISM OF ACTION OF ANTIDEPRESSANT MEDICATIONS

As indicated by research undertaken in the last few years, excessive activity of the glutamatergic system plays a significant role in the pathophysiology of depressive disorders [ex. 4, 10, 47, 51]. It has been shown that the glutamine levels are at a higher concentration in the blood plasma as well as cerebrospinal fluid in patients suffering from depression in comparison with healthy individuals, and a post mortem analysis has shown a higher level of glutamic acid in the prefrontal cortex of the brain in patients with affective disorders as well as a markedly reduced number of NMDA receptors in the hippocampus [11, 37]. However, in patients with uni- and bipolar affective disorders there was a confirmed reduction in the presence of the NR1 subunit of the NMDA receptor in the temporal cortex [32].

There exists a lot of data indicating that the glutamatergic system, including the NMDA receptor, may play a significant role in the pathogenesis of psychic, neurodegenerative and neurological disturbances as well as addiction. As a result of genetic-molecular research, many genes have been identified that may increase the risk of affective disorders. A correlation has been shown to exist between the polymorphism of the gene of the NMDA receptor (GRIN1 and GRIN2B) and bipolar affective disorder [25].

In recent years much evidence has been gathered with respect to the influence of the glutamatergic system on the function of antidepressant and normotimic medications. Information found in literature indicates that antidepressant medications slow the activity of the glutamatergic system via reducing the release of glutamic acid by nerve cells in the prefrontal cortex, as well as in the hippocampus [37]. It is probable that the most important mechanism of action of antidepressant medications on the glutamatergic system is through their influence on the NMDA receptors, resulting in the weakening of the function of these receptors [10].

Research shows that TCA -tricyclic antidepressants (imipramine), SSRI- selective serotonin reuptake inhibitors (fluoxetin), SNRI- selective noradrenaline reuptake inhibitors (reboxetin) and MAO inhibitors - monoamine oxidase inhibitors (moclobemid) inhibit the expression and

function of the NMDA receptors [30]. A similar effect was noted following the application of electroconvulsive therapy [26]. It was noted during research undertaken on animal subjects that the sudden cessation in the administration of imipramine results in a significant increase in glutamatergic transmission [39].

The NMDA receptor is also subject to regulation via a neurotrophic factor such as BDNF. Mechanisms linked with this activity may be significant in being a predisposing factor to the bipolar affective disorder. It has been shown that the level of BDNF in blood increases with the use of antidepressant medications. It has also been shown that BDNF has a reducing effect on the release of mRNA subunit GluN2A and 2B of the NMDA receptor, which causes a reduction in the activity of this receptor [6].

The regulation of the glutamatergic system through the use of antidepressant medications may also be linked with the increased release and activity of the glutamate transporter. Research has shown a weakening in the release of some transporter proteins in the brain of patients suffering from depression [58]. It needs to be noted that an increase in the release of the EAAT1 transporter in the neurons of the brain cortex may be a marker of the activity of antidepressant medications [29].

Research related to the influence of normotimic medications on the activity of the glutamatergic system has revealed that in the case of healthy individuals taking lithium there exists a double-sided reduction of glutamine acid level in the basal ganglia; however, experimental studies have shown that long-term lithium therapy has a neuroprotective effect. This prevents neurotoxicity caused by excessive glutamine and is linked with a weakening in the activity of the NMDA receptors [49].

To date, much data has been published, both preclinical as well as clinical, which indicates the role of the glutamatergic system in the development of depressive disorders as well as antidepressant characteristics of NMDA receptor antagonists. Unfortunately, the clinical application of most of the studied NMDA receptor ligands is linked with a large number of undesirable side effects (psychotomimetic effects, ataxia, increased locomotor activity, neurodegenerative changes), which handicaps their use in people; accordingly, there is a continuing effort being made to find new compounds that influence the modulation of the NMDA receptor, safe, effective and quick acting.

Preclinical studies reveal that ligands of specific sites modulating the NMDA receptor show an antidepressant activity in tests as well as models of depression in animals, e.g. MK-801 – blocker of the NMDA receptor channel, possesses both an antidepressant as well as antianxiety effect, as well as strengthening the action of antidepressant medications – imipramine, citalopram and flouxetine [34]. The significant antidepressant potential of MK-801 can be further shown through the fact that the long-term application of this compound causes β-down regulation, this being characteristic in cases of prolonged administration of the majority of currently used antidepressant medications [16].

An antidepressant effect was also noted following the administration of L-701, 324 (an antagonist of the glycine site GLY_B). This compound decreased the inactivity time of mice in the forced swim test as well as strengthening the action of imipramine, fluoxetine and tianeptine [39, 55]. Antidepressant activity was also shown in the case of other ligands of the glycine site: D-cycloserine and ACPC. Its use in people has shown its effectiveness in treating endogenic depression [12]. Glycine site antagonists show relatively few side effects; however, their clinical usefulness is handicapped by the development of tolerance as shown by the Porsolt test, following long-term application [21].

Many preclinical studies have also shown an antidepressant action by competitive NMDA receptor antagonists (CGP 37849 and CGP 39551), which was comparable to that of imipramine [34, 39]. Amongst antagonists binding polyamine sites, most studied have been: ifenprodil and eliprodil, which are characterized by their high affinity for subunit NR2B. It has been shown that these ligands possess an antidepressant action, with ifenprodil strengthening the action of some antidepressant medications (imipramine and fluoxetine) [40]. Another ligand - traxoprodil (CP-101, 606) – is an antagonist of the NMDA receptor with a selective form of action with respect to subunit NR2B. It is a derivative of ifenprodil [1].

Its action is based on reducing the activity of the NR1/NR2B channel by shortening the time and frequency of its opening. This mechanism prevents the damaging effects of calcium ions entering the neurons following the release of large amounts of glutamic acid [2]. This medication has found use in neuroprotection in cases of head trauma, damage and insufficient blood supply to the brain following stroke [17, 56]. Due to good permeability through the blood-brain barrier, it reduces oedema, reestablishes circulation in the brain and prevents neuron damage. Results obtained from treatment of patients with trauma related brain injury or stroke related hemorrhage uniformly show a positive action by the medication as well as the reduction in the rate of patient death by 7% as compared with placebo [56].

The main action site of traxoprodil is the hippocampus as well as the external layers of the brain cortex, which is why its protection effect is linked with these specific structures [1]. Recently, there have been encouraging results obtained from the assessment of traxoprodil in the treatment of depression, which showed its rapid antidepressant effect in comparison with ketamine. Traxoprodil showed a greater reduction in the

number of depression related symptoms in comparison with placebo and caused a rapid improvement in patients not responding to treatment with SSRI, and remission related characteristics lasted for up to a week following medication infusion [42]. It was also shown that it is well tolerated by patients and has a good safety profile [56]. There were only a few, mild unwanted side effects noted such as: dizziness, feeling unwell, sleepiness and dryness of the mouth. There were no observable hematologic changes or psychological disturbances [42]. Only in the case of administring large doses was there a noted increase in the level of psychomotor activity, and in tests with an EKG a lengthening of the QT interval, which normalized itself following completion of medication infusion [56]. Most recent research undertaken on mice has shown that ifenprodil and traxoprodil have an antidepressant action and allow for a reduction in the dosage of antidepressant medications from the SSRI group [40, 41].

An antidepressant action is also shown by biometals, having properties which are antagonistic to the NMDA receptor (zinc and magnesium). These are important glutamatergic transfer modulators and the lack of these is linked with many symptoms typical of depressive disorders. Research to date has shown a reduced ion level of these in blood plasma of patients with depression, which normalized themselves following antidepressant therapy [7, 54]. It was also shown that ions of zinc and magnesium strengthen the antidepressant action of antidepressant medications (imipramine, fluoxetine, citolopram, tianeptine) [3, 50]. Clinical studies have shown that the addition of zinc to antidepressant medications potentiates the treatment in patients being treated with clomipramine, amitryptyline, citalopram and fluoxetine [31, 50]. Most recently, it has been stated that supplements of this element cause a potentiation of the therapeutic effect of imipramine in the treatment of drug resistant forms of depression [48].

Clinical studies have also revealed the antidepressant action of ketamine, amantadine and memantine [4, 57]. They showed that the application of ketamine causes rapid and significant improvement in the psychological condition of patients with drug resistant depression [4, 8, 24]. Ketamine is a drug registered for use in Poland and is used as a pain relief agent during short diagnostic and surgical procedures as well as an agent used to commence the process of full sedation prior to the administration of other sedative substances. Hypothesis explaining the occurrence of a rapid reaction and reduction in side effects of depression following the administration of ketamine relate to its reducing effect on the activity on the function of NMDA receptors, induction of the CREB transcription agent (c-AMP response element-binding) as well as strengthening the AMPA receptor activity [8, 24]. An increasing amount of results confirm that the administration of ketamine reduces the severity of symptoms associated with "depression syndrome" [4, 8]. Zarate et al. show that a single injection of ketamine at a dose of 0.5 mg/kg of body mass causes a rapid antidepressant effect lasting for up to a week [57]. Subsequent studies have shown a reduction in suicidal thought and suicidal tendencies following the intravenous administration of ketamine at a dose of 0.2 mg/kg [18]. Other studies involving the infusion of ketamine as an addition to normotimic medications in patients with depressive symptoms linked with the bipolar affective disorder also revealed an observable positive therapeutic effect [4]. It was also shown that patients who after 7 days from infusion with ketamine were in remission exhibited a significant increase in the level of BDNF in blood plasma [18]. In the antidepressant action of ketamine, a large role may be played by the activation of neuronal connections between the frontal cingulate cortex and amygdala [46], instead on the cellular level a significant activation of the mTOR kinase (mammalian target of rapamycin (kinase)), leading to an increase in the synaptic signal level, as well as an increase in the number and function of new synapse in the prefrontal cortex [19].

Amantadine also shows an antidepressant action in people. This compound, apart from blocking the function of the NMDA receptor, possesses an antiviral action as well as partially dopaminergic activity. In the case of patients with drug resistant depression, the addition of amantadine to the treatment regime resulted in potentiating the action of imipramine [45]. Memantine, an amantadine derivative, was shown to be effective in patients with symptoms of depression as well mania [14, 57].

CONCLUSIONS

An increase in the level of interest in the role played by glutamatergic transmission in the pathophysiology of depressive disorders is a result of the potential therapeutic applications which may form an interesting alternative to currently used antidepressant medications. The NMDA receptor has a strong position in the pathophysiology of depression and is the subject of intensive research, both preclinical as well as clinical. Results from the undertaken research indicate that the NMDA receptor antagonists show an antidepressant activity as well as influence the activity of the majority of the studied antidepressant medications. The observed synergism is probably a result of their influence on neurotransmitter systems involved in the development of depressive disorders. The application of NMDA receptor ligands allows for a reduction in the dose of conventionally utilized antidepressant medications and is much more beneficial than monotherapy, which may be of specific benefit in the case of patients with drug resistant depression. Attempts at influencing the NMDA receptor may in the future lead to the development of new types of medications as well as safer and more effective therapies for many illnesses including depressive disorders.

REFERENCES

[1] Chazot P.L., Lawrence S., Thompson C.L.: Studies on the subtype selectivity of CP-101,606: evidence for two classes of NR2B-selective NMDA receptor antagonists. Neuropharmacology, 2002; 42: 319-324

[2] Chenard B.L., Bordner J., Butler T.W., Chambers L.K., Collins M.A., De Costa D.L., Ducat M.F., Dumont M.L., Fox C.B., Mena E.E.: (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol: a potent new neuroprotectant which blocks N-methyl-D-aspartate responses. J. Med. Chem., 1995; 38: 3138-3145

[3] Cunha M.P., Machado D.G., Bettio L.E.B., Capra J.C., Rodrigues A.L.S.: Interaction of zinc with antidepressants in the tail suspension test. Prog Neuropsychopharmacol Biol. Psychiatry, 2008; 32: 1913-1920

[4] Diazgranados N., Ibrahim L., Brutsche N.E., Newberg A., Kronstein P., Khalife S., Kammerer W.A., Quezado Z., Luckenbaugh D.A., Salvadore G., Machado-Vieira R., Manji H.K., Zarate C.A.Jr.: A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch. Gen. Psychiatry, 2010; 67: 793-802

[5] Duman R.S.: Teorie patofizjologiczne depresji – od monoamin do neuroplastyczności. Red.: Olie J.P., Costa de Silva J.P., Macher J.P. Neuroplastyczność. Patofizjologia depresji w nowym ujęciu. Via Medica, Gdańsk 2004, 9-20

[6] Duman R.S., Monteggia L.M.: A neurotrophic model for stress-related mood disorders. Biol. Psychiatry, 2006; 59: 1116-1127

[7] Eby G.A., Eby K.L.: Magnesium for treatment-resistant depression: a review and hypothesis. Med. Hypotheses, 2010; 74: 649-660

[8] Gosek P., Chojnacka M., Bieńkowski P., Święcicki L.: Antidepressant effect of ketamine, a N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, in the therapy of treatment-resistant depression. Psychiatr. Pol., 2012; 46:283-294

[9] Gupta D., Radhakrishnan M., Bhatt S., Kurhe Y.: Role of hypothalamic-pituitary-adrenal-axis in affective disorders: anti-depressant and anxiolytic activity of partial 5-HT1A agonist in adrenalectomised rats. Indian. J. Psychol. Med., 2013; 35: 290-298

[10] Hashimoto K.: The role of glutamate on the action of antidepressants. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2011; 35: 1558-1568

[11] Hashimoto K., Sawa A., Iyo M.: Increased levels of glutamate in brains from patients with mood disorders. Biol. Psychiatry, 2007; 62: 1310-1316

[12] Heresco-Levy U., Javitt D.C., Gelfin Y., Gorelik E., Bar M., Blanaru M., Kremer I.: Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. J. Affect. Disord., 2006; 93: 239-243

[13] Jaeschke R., Siwek M., Grabski B., Dudek D.: Współwystępowanie zaburzeń depresyjnych i lękowych. Comorbidity of depressive and anxiety disorders. Psychiatria. Via Medica , Gdańsk 2010, 189-197

[14] Keck P.E. Jr., Hsu H.A., Papadakis K., Russo J. Jr.: Memantine efficacy and safety in patients with acute mania associated with bipolar I disorder: a pilot evaluation. Clin. Neuropharmacol., 2009; 32: 199-204

[15] Kennedy S.H., Giacobbe P.: Treatment resistant depression-advances in somatic therapies. Ann. Clin. Psychiatry, 2007; 19: 279-287

[16] Klimek V., Papp M.: The effect of MK-801 and imipramine on beta-adrenergic and 5-HT2 receptors in the chronic mild stress model of depression in rats. Pol. J. Pharmacol., 1994; 46: 67-69

[17] Kundrotiene J., Cebers G., Wagner A., Liljequist S.: The NMDA NR2B subunit-selective receptor antagonist, CP-101,606, enhances the functional recovery the NMDA NR2B subunit-selective receptor and reduces brain damage after cortical compression-induced brain ischemia. J. Neurotrauma, 2004; 21: 83-93

[18] Larkin G.L., Beautrais A.L.: A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int. J. Neuropsychopharmacol., 2011; 14: 1127-1131

[19] Li N., Lee B., Liu R.J., Banasr M., Dwyer J.M., Iwata M., Li X.Y., Aghajanian G, Duman R.S.: mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science, 2010; 329: 959-964

[20] Little A.: Treatment-resistant depression. Am. Farm. Physician, 2009; 80: 167-172

[21] Liu Y., Zhang J.: Recent development in NMDA receptors. Chin. Med. J. (Engl), 2000; 113: 948-956

[22] Lynch D.R., Guttmann R.P.: Excitotoxicity: perspectives based on N-methyl-D-aspartate receptor subtypes. J. Pharmacol. Exp. Ther., 2002; 300: 717-723

[23] Łoza B., Czernikiewicz A., Patejuk-Mazurek I.: Politerapia zaburzeń depresyjnych. Preferencje polskich psychiatrów. Psychiatria, 2007; 4: 97-104

[24] Maeng S., Zarate C.A. Jr.: The role of glutamate in mood disorders: results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. Curr. Psychiatry Rep., 2007; 9: 467-474

[25] Martucci L., Wong A.H., De L.V., Likhodi O., Wong G.W., King N., Kennedy J.L.: N-methyl-D-aspartate receptor NR2B subunit gene GRIN2B in schizophrenia and bipolar disorder: Polymorphisms and mRNA Levels. Schizophr. Res., 2006; 84: 214-221

[26] Michael N., Erfurth A., Ohrmann P., Arolt V., Heindel W., Pfleiderer B.: Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. Psychol. Med., 2003; 33: 1277-1284

[27] Miller A.H.: Depression and immunity: a role for T cells? Brain Behav. Immun., 2010; 24: 1-8

[28] Monteggia L.M., Luikart B., Barrot M., Theobold D., Malkovska I., Nef S., Parada L.F., Nestler E.J.: Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. Biol. Psychiatry, 2007; 61: 187-197

[29] Moutsimilli L., Farley S., Dumas S., El M.S., Giros B., Tzavara E.T.: Selective cortical vGLUT1 increase as a marker for antidepressant activity. Neuropharmacology, 2005; 49: 890-900

[30] Nowak G., Legutko B., Skolnick P., Popik P.: Adaptation of cortical NMDA receptors by chronic treatment with specific serotonin reuptake inhibitors. Eur. J. Pharmacol., 1998; 342: 367-370

[31] Nowak G., Siwek M., Dudek D., Zięba A., Pilc A.: Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. Pol. J. Pharmacol., 2003; 55:1143-1147

[32] Nudmamud-Thanoi S., Reynolds G.P.: The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. Neurosci. Lett., 2004; 372: 173-177

[33] Otte C.: Incomplete remission in depression: role of psychiatric and somatic comorbidity. Dialogues Clin. Neurosci., 2008; 10: 453-460

[34] Papp M., Moryl E.: Similar effect of chronic treatment with imipramine and the NMDA antagonists CGP 37849 and MK-801 in a chronic mild stress model of depression in rats. Eur. J. Neuropsychopharmacol., 1993; 3: 348-349

[35] Permoda-Osip A., Rybakowski J.: Glutamatergic Conception of Mood Disorders. Psychiatr. Pol., 2011; 45: 875-888

[36] Phelps L.E., Brutsche N., Moral J.R., Luckenbaugh D.A., Manji H.K., Zarate C.A.Jr.: Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. Biol. Psychiatry, 2009; 65: 181-184

[37] Pittaluga A., Raiteri L., Longordo F., Luccini E., Barbiero V.S., Racagni G., Popoli M., Raiteri M.: Antidepressant treatments and function of glutamate ionotropic receptors mediating amine release in hippocampus. Neuropharmacology, 2007; 53: 27-36

[38] Pittenger C., Duman R.S.: Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology, 2008; 33: 88-109

[39] Poleszak E., Wlaź., Wróbel A., Dybała M., Sowa M., Fidecka S., Pilc A., Nowak G.: Activation of the NMDA/glutamate receptor complex antagonizes the NMDA antagonist-induced antidepressant-like effects in the forced swim test. Pharmacol. Rep., 2007; 59: 595-600

[40] Poleszak E., Wośko S., Serefko A., Szopa A., Wlaź A., Szewczyk B., Nowak G., Wlaź P.: Effects of ifenprodil on the antidepressant-like activity of NMDA ligands in the forced swim test in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2013; 46: 29-35

[41] Poleszak E., Wośko S., Serefko A., Wlaź A., Kasperek R., Dudka J., Wróbel A., Nowak G., Wlaź P.: The effects of ifenprodil on the activity of antidepressant drugs in the forced swim test in mice. Pharmacol. Rep., 2014; 66: 1031-1036

[42] Preskorn S.H., Baker B., Kolluri S., Menniti F.S., Krams M., Landen J.W.: An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. J. Clin. Psychopharmacol., 2008; 28: 631-637

[43] Pużyński S.: Leki przeciwdepresyjne. Instytut Psychiatrii i Neurologii, Warszawa 2005; 16-52

[44] Pużyński S.: Depresja w praktyce ogólnolekarskiej. Terapia, 2011; 19: 60-64

[45] Rogóż Z., Skuza G., Daniel W.A., Wójcikowski J., Dudek D., Wróbel A.: Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression. Pharmacol. Rep., 2007; 59: 778-784

[46] Salvadore G., Cornwell B.R., Sambataro F., Latov D., Colon-Rosario V., Carver F., Holroyd T., Diazgranados N., Machado-Vieira R., Grillon C., Drevets W.C., Zarate C.A.Jr.: Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology, 2010; 35: 1415-1422

[47] Sanacora G., Treccani G., Popoli M.: Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology, 2012; 62: 63-77

[48] Siwek M., Dudek D., Paul I.A., Sowa-Kućma M., Zięba A., Popik P., Pilc A., Nowak G.: Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. J. Affect. Disord., 2009; 118:187-195

[49] Shibuya-Tayoshi S., Tayoshi S., Sumitani S., Ueno S., Harada M., Ohmori T.: Lithium effects on brain glutamatergic and GABAergic systems of healthy volunteers as measured by proton magnetic resonance spectroscopy. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2008; 32: 249-256

[50] Szewczyk B., Poleszak E., Wlaź P., Wróbel A., Blicharska E., Cichy A., Dybała M., Siwek A., Pomierny-Chamioło L., Piotrowska A., Brański P., Pilc A., Nowak G.: The involvement of serotonergic system in the antidepressant effect of zinc in the forced swim test. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2009; 33: 323-329

[51] Tokita K., Yamaji T., Hashimoto K.: Roles of glutamate signaling in preclinical and/or mechanistic models of depression. Pharmacol. Biochem. Behav., 2012; 100: 688-704

[52] Tondo L., Isacsson G., Baldessarini R.: Suicidal behaviour in bipolar disorder: risk and prevention. CNS Drugs, 2003; 17: 491-511

[53] Traynelis S.F., Wollmuth L.P., McBain C.J., Menniti F.S., Vance K.M., Ogden K.K., Hansen K.B., Yuan H., Myers S.J., Dingledine R.: Glutamate receptor ion channels: structure, regulation, and function. Pharmacol. Rev., 2010; 62: 405-496

[54] Whittle N., Lubec G., Singewald N.: Zinc deficiency induces enhanced depression-like behavior and altered limbic activation reversed by antidepressant treatment in mice. Amino Acids , 2009; 36: 147-158

[55] Wlaź P., Kasperek R., Wlaź A., Szumilo M., Wróbel A., Nowak G., Poleszak E.: NMDA and AMPA receptors are involved in the antidepressant-like activity of tianeptine in the forced swim test in mice. Pharmacol. Rep., 2011; 63: 1526-1532

[56] Yurkewicz L., Weaver J., Bullock M.R., Marshall L.F.: The effect of the selective NMDA receptor antagonist traxoprodil in the treatment of traumatic brain injury. J. Neurotrauma, 2005; 22: 1428-1443

[57] Zarate C.A.Jr., Singh J.B., Carlson P.J., Brutsche N.E., Ameli R., Luckenbaugh D.A., Charney D.S., Manji H.K.: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry, 2006; 63: 856-64

[58] Zink M., Vollmayr B., Gebicke-Haerter P.J., Henn F.A.: Reduced expression of glutamate transporters vGluT1, EAAT2 and EAAT4 in learned helpless rats, an animal model of depression. Neuropharmacology, 2010; 58: 465-473

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