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Review article

The role of glutamatergic, GABA-ergic, and cholinergic receptors in depression and antidepressant-like effect

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ABSTRACT

Depression is one of the most common mental disorders and social issue worldwide. Although there are many antidepressants available, the effectiveness of the therapy is still a serious issue. Moreover, there are many limitations of currently used antidepressants, including slow onset of action, numerous side effects, or the fact that many patients do not respond adequately to the treatment. Therefore, scientists are searching for new compounds with different mechanisms of action. Numerous data indicate the important role of glutamatergic, GABA-ergic, and cholinergic receptors in the pathomechanism of major depressive disorder. This review presents the role of glutamatergic, GABA-ergic, and cholinergic receptors in depression and antidepressant-like effect.

Contents

Introduction

Depression is a destructive psychiatric illness, which affects more than 350 million people all over the world [1]. Although there are many antidepressants (ADs) available, there is still a problem with their effectiveness. About 30% of patients do not respond to pharmacotherapy, and less than 50% show full remission of the disease [2,3]. The disadvantages of currently available drugs, such as delayed onset of action and a wide range of adverse effects, are some of the reasons for searching for new treatment strategies. We previously demonstrated the involvement of serotonergic, adrenergic, and dopaminergic receptors in antidepressant-like (AD-like) effect [4]. Since many studies showed the association between glutamatergic, GABA-ergic and cholinergic receptors, and major depressive disorder (MDD), in this review we discuss their role in AD-like effect (Fig. 1).

mGluRs

Glutamate metabotropic receptors (mGluRs) play a pivotal role in the neurobiology of depression, and several preclinical data indicated that mGluR ligands are promising compounds in the

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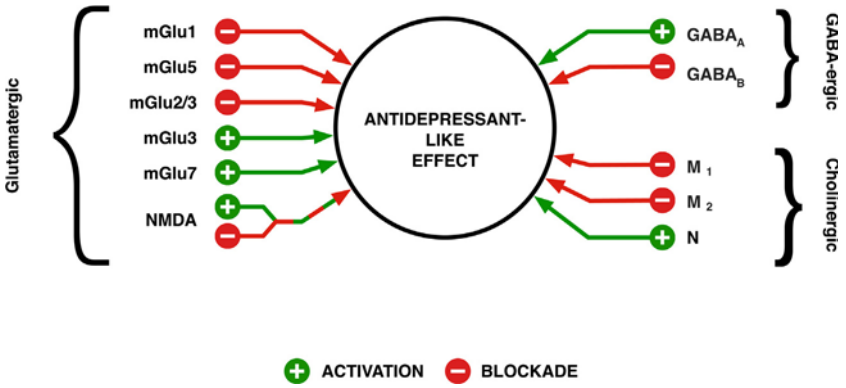

Fig. 1. The involvement of glutamatergic, GABA-ergic, and cholinergic receptors in antidepressant-like effect observed in animals.

treatment of depression [5]. Glutamate metabotropic receptors are divided into three groups based on amino acid sequence homology, which are coupled to G-proteins. Group I (mGlu1 and mGlu5 receptors) is positively coupled to phospholipase C, while group II (mGlu2 and mGlu3 receptors) and group III (mGlu4, mGlu6, mGlu7, and mGlu8 receptors) are coupled to adenylyl cyclase (AC) in an inhibitory manner. These receptors are highly expressed in the central nervous system (CNS). Group I is predominantly expressed in the postsynaptic neurons, group II is localized pre- and postsynaptically, whereas group III is situated mainly presynaptically, and is responsible for the regulation of the release of glutamate or other neurotransmitters [6]. The mGluR1 and mGluR5 are expressed throughout the animal brain, and can be found almost in every region of limbic system, including hippocampus, prefrontal cortex, amygdala, or thalamus [7]. The mGluR2 were predominantly observed in the cerebral cortex and olfactory bulb, while mGluR3 and mGluR7 are widely distributed throughout the brain. The mGluR4 and mGluR5 are restricted to the cerebellum and to the retina, respectively. mGluR8 are mainly expressed in the olfactory bulbs, olfactory nucleus, piriform cortex, entorhinal cortex, and medulla oblongata [7]. Animal models of depression showed reduced mGluR2/3 expression mainly in the hippocampus [8,9]. Many studies presented the importance of mGluRs in the mechanism of action of some antidepressants. For instance, imipramine treatment upregulated the expression of mGluR2/3 in the hippocampus, cerebral cortex, nucleus accumbens, and corpus striatum [10], while amitriptyline downregulated the mGluR4 expression, and normalized the level of mGluR2/3 in olfactory bulbectomy (OB) model of depression in mice [8].

Some postmortem studies connect the dysregulation of glutamatergic neurotransmission with MDD. Clinical positron emission tomography and postmortem studies of depressed victims showed decreased mGluR5 binding in the cortical regions, thalamus, and hippocampus [11]. Another postmortem analysis reported the elevated level of mGluR2 and mGluR3 in prefrontal cortex in depressed subjects [12]. These findings suggest that basal or compensatory changes in the excitatory neurotransmission are involved in the pathomechanism of MDD, but this issue definitely needs further studies.

Group I mGluRs antagonists exhibit AD-like effects in rodents. EMQMCM, which is the mGluR1 antagonist, showed antidepressant-like activity in the forced swim test (FST) and tail suspension test (TST) in mice and rats [13]. The observed effect was comparable to that of imipramine [13]. Similarly, MTEP [14–16] and MPEP, selective mGluR5 antagonists, showed AD-like effect in various animal models of depression [13,17,18]. Administration of MTEP and MPEP decreased immobility time in the TST and FST in mice, and produced AD-like effect in OB model [19].

Analogously, the blockade of group II mGluRs induced AD-like effect in animals [5]. LY341495, a highly potent selective mGlu2/3 receptors antagonist, reduced immobility in the mouse FST, and in the marble burying test [20]. MG0039, which is also selective mGluR2/3 antagonist with low affinity for mGluR7, produced the dose-dependent AD-like effects in the rat FST, the mouse TST [21], and in the learned helplessness (LH) model in rats [22].

Conversely to previous groups, to observe AD-like effect in rodents, group III of mGluRs has to be activated. ACPT-I and RS-PPG, group III mGluRs agonists, administered in the brain ventricles, showed AD-like activity in the FST in rats [23,24]. Interestingly, ACPT-I was not active after peripheral injection [25]. Similarly, AMN082 a selective mGluR7 agonist, displayed AD-like activity in both TST and FST in mice [26].

Taken together, many studies confirm the important role of glutamatergic system in AD-like response, and suggest it as a new target for novel antidepressants.

NMDA receptor

The N-methyl-D-aspartate (NMDA) receptor belongs to the specific type of ionotropic channel receptors. It is present at many excitatory glutamate synapses in the CNS, where it plays a pivotal role in excitatory synaptic transmission, plasticity, and excitotoxicity [27]. The receptor is essential in the fast synaptic glutamate neurotransmission, and therefore is involved in memory processes. Moreover, it plays an important role in the pathogenesis of the CNS diseases such as stroke, epilepsy, Huntington's disease, Alzheimer's disease, and depression.

NMDA receptors are located mainly in the CNS, and particularly in the hippocampus (CA1), cerebral cortex, basal ganglia, septum, and amygdala [28]. They are localized postsynaptically in glutaminergic synapses or situated presynaptically on the terminals of neurons, where they modulate the release of various neurotransmitters. Some of them act as autoreceptors controlling the release of glutamate. Functional NMDA receptors are hetero-tetramers consisting of three different subunits termed GluN1-3. Each receptor contains common GluN1 subunits in combination with one of four GluN2 subunits (GluN2A-2D) and/or GluN3 subunits [27]. This composition determines the physiological and pharmacological properties of NMDA receptors.

The NMDA receptors have some unique features like high affinity for glutamate, high unitary conductance, high permeability to calcium (Ca^{2+}), and a voltage-dependent block by magnesium ions (Mg^{2+}) [27]. NMDA receptors are activated right after binding of the agonist—glutamate to the NR2 subunit with a co-agonist, either L-glycine or D-serine, to the GluN1 subunit. At resting membrane potential, the magnesium ions block the channel and prevent Ca^{2+} influx. The channel is opened only after an initial

depolarization of the cell membrane with the cooperation of AMPA receptors. Besides Mg^{2+}, noncompetitive antagonists, such as ketamine, memantine, amantadine, phencyclidine, and dizocilpine (MK-801) may block the channel receptor. Other element responsible for the inhibition of NMDA receptor is zinc (Zn^{2+}), which seems to play an important role in depression [29]. NMDA receptor activity can be modulated both positively and negatively. Positive modulators, increase the maximal response or the affinity for the agonist, but have a binding site that is different from the agonist binding site.

Chronic antidepressant treatment causes adaptive changes in NMDA receptors [30–32]. This mechanism has been clearly explained by Skolnick [33]. For instance, antidepressants may induce a region-specific change in NMDA receptor subunit composition, and reduce the affinity of glycine-binding sites. Consequently, it leads to a decreased NMDA receptor function [34]. The differential expression of the subunits in various regions of the brain may determine the functional properties of NMDA receptor in the CNS.

There are some postmortem studies demonstrating the abnormalities in glutamatergic transmission in MDD [35]. First of all, a decreased level of NMDA receptors in the hippocampus has been reported [36]. Moreover, a significant reduction in GluN2A and GluN2B subunit expression in the prefrontal cortex of patients with MDD was found, with no changes in NR1 subunit [37]. In contrast, another study indicated a deficit in NR1 subunit expression in depression and other affective disorders [38]. Elevated levels of GluN2A in the lateral amygdala, and GluN2C in the locus coeruleus of depressed subjects were also discovered [39,40]. Furthermore, the attention was drawn to the postsynaptic density protein (PSD-95), which is one of the NMDA receptor-associated proteins. The studies showed highly elevated level of PSD-95 in lateral amygdala of depressed subjects [39]. Additional research is necessary to better understand the role of glutamate and the changes in glutamatergic neurotransmission in the pathology of depression.

Antidepressant-like properties of partial NMDA agonists and selective NMDA receptor GluN2B subtype antagonists were demonstrated in many animal models of depression [41,42]. D-cycloserine, a partial agonist at the glycine co-agonist site of NMDA receptors subunits (composed of GluN2A and GluN2B), and a full agonist of NMDA receptors containing the GluN2C and GluN2D subunits, exhibits AD-like properties [43,44]. Furthermore, parenterally and orally administered ACPC, a partial agonist with a high affinity for the glycine B site of the NMDA receptor, reduced immobility time in the FST [45]. GLYX 13, another glycine site functional partial agonist [46], and D-serine [28] induced AD-like effects in the FST and LH model. Interestingly, ACPC, dizocilpine, and memantine (antagonists of NMDA receptor) were active in a chronic mild stress (CMS) model of depression in rats [47–50]. Furthermore, memantine showed activity in chronic unpredictable stress model of depression [51]. Moreover, amantadine and MK-801 displayed AD-like activity in OB model [52–54]. Similarly, acute and chronic administration of ketamine also produced AD-like effect in animal models of MDD [55–58]. Moreover, blockade of NMDA receptor with synaptic events near resting membrane potential in physiological levels of Mg^{2+} is essential for ketamine's rapid AD-like effect in behavioral models [59]. These results highlight the importance of the glutamatergic system, and its modulation as a new potential target for novel antidepressants.

Over the last two decades it has been shown that there are some elements, such as zinc and magnesium, that play an important role in depression [29,60]. Both are included in the glutamatergic theory of that illness. Zinc is an antagonist of the glutamatergic NMDA receptor and shows antidepressant properties in both preclinical and clinical studies [61]. Patients suffering from depression have lower serum zinc than healthy controls [62–64]. Moreover, depressed patients receiving commonly used antidepressants supplemented with zinc showed a better response than those receiving a placebo in addition to the antidepressants. In preclinical studies to investigate whether low zinc levels lead to the development of depressive symptoms, a special diet that was low in zinc was prepared. Administration of the zinc-deficient diet for several weeks caused depressive-like behavior as measured by the forced swim test and the tail suspension test in mice and rats [65–71]. Moreover, zinc deficiency altered the antidepressant response [67]. In the past decade it has been discovered that zinc may act in the central nervous system via the metabotropic GPR39 receptor [72], which was found to play an important role in the pathomechanism of depression and the antidepressant response [73]. GPR39-down regulation was found in the hippocampus and frontal cortex in a zinc-deficient animal model of depression as well as in suicide victims [68]. Selective antidepressant administration caused a significant increase in the expression of GPR39 in the frontal cortex. A study using GPR39 knockout mice showed depressive- and anxiety-like behavior [75]. Moreover, these mice were found to be resistant to monoamine-based antidepressants, such as imipramine, escitalopram, or reboxetine, compared with a wild-type control [76], suggesting that GPR39 is required for a therapeutic effect from conventionally used antidepressants. Only NMDA inhibitors—namely, ketamine and MK-801—were active in GPR39 KO mice. The results of this study indicate that the GPR39 receptor is a possible target in the antidepressant response.

Magnesium is another element with antidepressant properties that is involved in the glutamatergic theory of depression. Magnesium blocks the NMDA receptor in a dose- and voltage-dependent manner and therefore, impairs glutamatergic neurotransmission. As with zinc, magnesium exhibits antidepressant properties and its deficiency causes depressive- and anxiety-like behavior. Patients suffering from depression showed reduced serum magnesium concentrations, and rapid recovery was observed following magnesium supplementation [77]. Magnesium also showed antidepressant effects in preclinical studies. Joint administration of magnesium in low doses and imipramine in low doses decreased immobility time in the forced swim test, suggesting that magnesium is able to enhance the effect of the antidepressant [78]. Additionally, when doses of magnesium that were ineffective alone were administered together with NMDA antagonists in low doses, they were able to produce an antidepressant response [79]. Antidepressant properties of magnesium have also been found in preclinical models of depression, such as those involving chronic CMS or OB. Chronic magnesium administration caused a significant increase in sucrose intake in the CMS model [80] and, in the OB model, a significant reduction in OB-induced hyperactivity and number of trials required to learn passive avoidance [81]. According to the authors, the AD-like activity of magnesium is probably associated with the AMPA/BDNF pathway. The BDNF level, which had previously been decreased by OB, significantly increased following chronic magnesium treatment. Similarly, levels of GluN2B, P-S831 and P-S845 protein, and mRNA were significantly increased after magnesium administration in the frontal cortex and hippocampus of OB rats [81].

Preclinical studies involving mice fed with a diet that was low in magnesium showed depressive- and anxiety-like behavior, as measured by the forced swim test, the light/dark test, and the open field test [82]. It was found that magnesium is able to modulate the hypothalamic–pituitary–adrenal axis. Increased transcription of the corticotrophin releasing hormone (CRH) and elevated levels of the adrenocorticotrophine hormone (ACTH) under magnesium-deficient conditions were observed [83], suggesting dysregulation of the HPA axis in magnesium deficiency. All these research clearly

indicate the important role of zinc and magnesium in the treatment of depression.

GABA receptors

The γ-amino-butyric acid (GABA) is the major inhibitory neurotransmitter in the CNS, and therefore plays a dominant role in inhibitory processes [84]. GABA-ergic transmission occurs in interneurons, which modulate local neurotransmission, including noradrenergic, dopaminergic, and serotonergic neurons. There is an evidence suggesting that patients with MDD exhibit a decreased level of GABA in the CNS, which is also confirmed by recent data from magnetic resonance spectroscopy [85]. The results of these research suggested that the reduced inhibitory neurotransmission caused by GABA is involved in the pathogenesis of MDD [85].

There are three major classes of GABA receptors (A, B, and C). $GABA_A$ receptors and $GABA_C$ belong to the family of ligand-gated ionotropic receptors, while $GABA_B$ are metabotropic transmembrane receptors, which are type of G-protein-coupled receptors [86]. The $GABA_A$ and $GABA_C$ receptors are located mainly postsynaptically, and induce fast synaptic inhibition [87].

$GABA_A$ receptors form a heteromeric chloride (Cl^-) channels, and have a modulatory sites for benzodiazepines and other compounds. After binding two molecules of GABA, the receptor is activated and permeable to Cl^-. The influx of Cl^- into the postsynaptic cell causes hyperpolarization in the local nerve cell membrane, which leads to an increase in the threshold depolarization potential for excitatory neurotransmitters and consequently, the neuron is unable to generate action potentials. Most $GABA_A$ receptors are comprised of two α, one β, and two γ subunits (belonging to different classes), which are necessary for the formation of binding sites for benzodiazepines [88,89].

In the CNS, $GABA_B$ receptors occur as presynaptic receptors (auto- and heteroreceptors), inhibiting the release of neurotransmitters from nerve terminals, as well as postsynaptic receptors, which stimulated by GABA cause hyperpolarization. Activation of $GABA_B$ receptor causes downstream changes in K^+ and Ca^{2+} channels, mainly through an inhibition of the cAMP synthesis [90]. $GABA_B$ receptors are widely distributed throughout the mammalian brain. The highest expression may be found in the thalamus, cortex, and cerebellum [90]. The high density of $GABA_B$ receptor in the limbic system suggests the contribution of this receptor in mood regulation [91].

One of the first observation was low GABA level in the cerebrospinal fluid in patients with MDD in comparison with the healthy controls [92]. Subsequent research confirmed that certain regions of the brain in patients suffering from depression, showed a decreased number of GABA-ergic neurons, as well as $GABA_A$ receptors in the hippocampus and prefrontal cortex [93]. Several studies also suggested that the occurrence of depression may be associated with GABA-ergic transmission disorders, as a result of GAD1 (glutamate decarboxylase 1) gene mutations [94]. The postmortem brain studies of MDD patients showed a significant reduction of the GAD67 expression in the frontal cortex in medication-free group compared with the healthy control subjects [95]. Moreover, they did not find any difference in the expression of GAD67 in the treated *versus* control group. The potential explanation of low GABA concentration MDD patients is the examination of interneuron's density, on the basis of somatostatin presence and calcium binding proteins, such as parvalbumin, calbindin, and calretinin [96]. Recent research showed a significant reduction of calbindin-IR interneurons density in the CNS areas, including the dorsolateral prefrontal cortex [97] and occipital cortex [95]. Many studies demonstrated a reduced expression of somatostatin, which is commonly associated with GABA-ergic interneurons, in postmortem brains of patients with MDD in the amygdala and subgenual cingulate [98,99].

Behavioral studies using gene-targeted mice, partially explained the role of specific $GABA_A$ receptors in depression. Mainly, heterozygous knockout γ_2 subunits (which are included in 90% of $GABA_A$ receptors) and homozygous knockout α_2 subunits induced depression-like behavior [100,101]. Behavioral deficit was reversed by chronic antidepressant treatment [102,103]. The expression of the $GABA_A$ receptors was also altered in the cortex of mice exposed to stress, as well as in MDD patients after suicide [101]. As mentioned above, behavioral studies on rodents suggest the physiological protective role of α_2 subunits of $GABA_A$ receptors in preventing depression. Interestingly, a preferential α_2/α_3 and α_1 subtype $GABA_A$ receptor modulator—eszopiclone—significantly increased antidepressant effectiveness in MDD, when administered in combination with SSRI (selective serotonin reuptake inhibitor) [93,104–106]. Therefore, selective α_2/α_3 subtypes of $GABA_A$ receptor modulators, such as TPA023, are proposed as novel antidepressants [93,101,103]. Recent research showed that L-655,708 (a moderate inverse agonist of α_5-containing $GABA_A$ receptors) significantly decreased immobility time in the FST in rats after a single and chronic administration [107]. These data suggest that negative modulation at $GABA_A$ receptors with α_5 subunit may exhibit AD-like activity in rats [107].

Repeated administration of antidepressants induces adaptive changes in the $GABA_B$ receptor [108]. The GABA concentration in the cerebrospinal fluid and plasma was lower in patients suffering from depression than in the control subjects [89]. Additionally, there was reduced GABA concentration measured in the occipital cortex of MDD patients compared with patients treated with SSRI or electroconvulsive therapy [109]. Initially, it was believed that compounds enhancing GABA-ergic transmission exhibit AD-like activity. This hypothesis was based on the discovery that baclofen (a selective $GABA_B$ agonist) showed AD-like activity in OB model in rats [89]. Since further research (using other tests and animal models) did not confirm its AD-like activity [86], it is now hypothesized that the long-term reduction of GABA-ergic transmission may be associated with AD-like activity. Therefore, the $GABA_B$ antagonists were considered as a new potential antidepressants [90,108]. The $GABA_{B1}$ knockout mice showed AD-like activity in the FST [86]. Similarly, $GABA_B$ modulators, CGP 7930, SKF 97541, and SCH 50911, showed decreased immobility time in FST in rats [86]. Additionally, $GABA_B$ receptor antagonist—CGP56433A—increased BDNF level in hippocampus and cerebral cortex in rats and improved cognitive processes [93]. AD-like activity may also be related to serotonergic interaction of $GABA_B$ receptors [110]. All of these studies confirm the importance of GABA-ergic neurotransmission modulators in AD-like effect.

Cholinergic receptors

Increasing number of information suggests the role of the cholinergic system in mood disorders. The physiological evidence indicates overactivity or hypersensitivity of cholinergic system in MDD [111]. The cholinergic system is subdivided into nicotinic and muscarinic receptors with acetylcholine (ACh) as its neurotransmitter. There are five subtypes of muscarinic receptors (mAChR) M_1–M_5, which belong to the superfamily of G-coupled proteins consisting of seven hydrophobic transmembrane domains. The M_1, M_3, and M_5 receptors are selectively linked to G_q proteins and stimulate the hydrolysis of phosphoinositol, whereas the M_2 and M_4 receptors by linking to G_i class inhibit AC [112]. Nicotinic receptors (nAChR) belong to the family of ligand-gated channels [113–115]. Due to their pharmacological and physiological properties they are divided into three general classes: muscle subunits (α_1, β_1, δ, ϵ, and γ), neuronal subunits (α_2–α_6, β_2–β_4),

and subunits α_7–α_9. In the third group only α_7 subunits are identified in the human CNS [115–120].

The muscarinic receptors (mAChRs) are located in different parts of the body including the CNS. The muscarinic M_1 receptors are highly expressed in forebrain regions of the brain, especially in hippocampus, cortex, and striatum. They are mainly postsynaptic receptors responsible for cognitive function, synaptic plasticity, and pilocarpine-induced convulsant activity [114]. The muscarinic M_2 receptors are highly expressed in the heart [121] and also in the brain as the main presynaptic autoreceptors [122]. They participate in the modulation of neurotransmitters and corticosterone release, analgesia, and temperature regulation [123,124].

The muscarinic M_3 receptors have low expression level in the brain; they are located especially in smooth muscles and in many glands stimulating secretion [122]. The muscarinic M_4 receptors are situated mainly in the hippocampus, cortex, striatum, thalamus, and cerebellum. The muscarinic M_5 receptors are highly localized in the dopamine cell body regions of the substantia nigra and ventral tegmental areas in the brain, which indicate their role in dopamine function control [125].

The nicotinic acetylcholine receptors (nAChRs) are also widely distributed in brain regions, such as habenula, locus coeruleus, hippocampus, thalamus, or cortical areas [113,117]. Nicotinic receptors increase permeability for Na^+ and Ca^{2+}, stimulating secretion of other neurotransmitters. Despite the effects on memory and consciousness they are involved in sleep and mood regulation, as well as the activity of motor neurons [126].

Neuroimaging studies have shown an increased level of choline—ACh precursor—in the brains of patients suffering from depression, and its reversal after recovery from this disease [127]. These findings confirm the hypothesis of cholinergic system overactivity in depression suggested by Janowsky et al. [111], and point at the alterations in orbitofrontal metabolism in depressed patients. Postmortem studies reported a higher number of acetylcholine muscarinic receptor-binding sites in the frontal cortex of suicide victims [128]. Another postmortem studies reported a decrease in M_2 and/or M_4 receptors in dorsolateral prefrontal cortex [129].

There are some studies, which confirm the role of muscarinic receptors in AD-like effect. The muscarinic agonists like physostigmine increase the immobility time in the FST in mice, while muscarinic antagonists produce AD-like effect in this test [114]. Chau and coworkers reported that the blockade of M_1 receptors in nucleus accumbens causes antidepressant-like effect observed in the FST in rats [130]. Interestingly, SCH226206 which is a M_2 receptor antagonist (40-fold selectivity for M_2 over M_1 receptor), was also active in the FST in wild type mice, and the effect was completely prevented in M_2 KO mice [131]. Moreover, in the same study Witkin and colleagues demonstrated that M_1 and M_2 receptors are involved in the antidepressant-like effect of scopolamine. This clearly shows that the blockade of both receptors plays a role in the AD-like effect.

It was reported that a novel compound (ZSET1446), which is a cognitive enhancer stimulating ACh release, can lead to enhanced neurogenesis in OB mice, through the interaction with nAChRs [132]. The nAChR stimulation can activate numerous signaling pathways. The tested compound reduced immobility time in the TST and in OB mice, and ameliorated depressive-like symptoms. Other studies showed that cytisine, a partial agonist of β_4/β_2 nAChRs, and a full agonist of α_3/β_4 and β_7 nAChRs, as well as its two derivatives, possess AD-like properties in several rodent models of depression. The cytisine and two novel nicotinic partial agonists were active in the TST, FST, and the novelty-suppressed feeding tests [133]. In all cases the AD-like effect was dose-dependent. These results showed that nicotinic partial agonists may be a new path for development of drugs to treat mood disorders [133].

Interestingly, the next promising compound examined for AD-like effect was sazetidine-A, which is the newest substance targeting the $\alpha_4\beta_2$ nAChR. Sazetidine-A presents different mechanism of action, involving binding and desensitization of $\alpha_4\beta_2$ nAChRs without activation, and acting mainly on the β_2 subunit [134,135]. Sazetidine-A improved performance during the FST. The administration of other $\alpha_4\beta_2$ nAChR agonist, A-85380 [136] or $\alpha_4\beta_2$ nAChR, partial agonists such as, varenicline [137] or TC-1734 [138] showed AD-like activity in FST in mice. Moreover, another $\alpha_4\beta_2$ nAChR agonist, SIB-1508Y, was effective in the LH model [139]. All this leads to conclusion that nAChRs can be an interesting new holder point for antidepressant drugs, especially with β_2 component, which is probably necessary for AD-like activity.

Conclusions

This review shows data on some important findings concerning the involvement of glutamatergic, GABA-ergic, and cholinergic receptors in AD-like effect. We demonstrate that many changes in glutamatergic, GABA-ergic, and cholinergic receptors in depressed individuals were found. The above receptors' modulators showed significant AD-like effect in many preclinical studies. Available data clearly indicate that the main monoaminergic theory of depression is incomplete, and the pathogenesis of the disease is definitely more complex, but it still needs further studies. Unquestionably, the modulation of glutamatergic, GABA-ergic, and cholinergic receptors should be considered as potential alternative for current pharmacotherapy.

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Conflict of interest statement

All the authors declare no conflict of interest.

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