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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.


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## 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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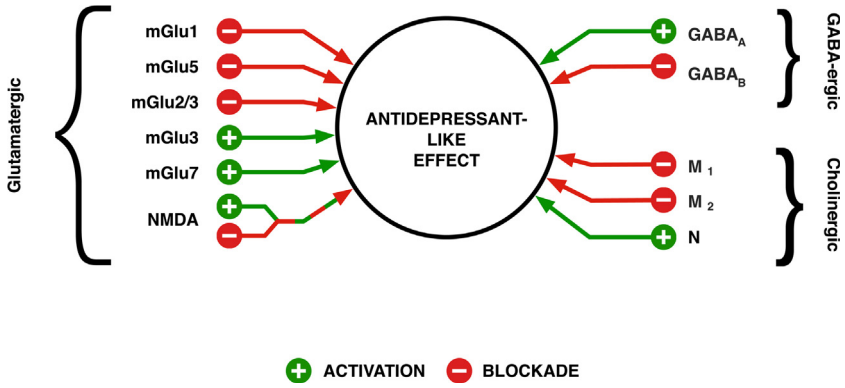


**Fig. 1.** The involvement of glutamatergic, GABA-ergic, and cholinergic receptors in antidepressant-like effect observed in animals.

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