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Review Article

A role for glutamate in the treatment of anxiety and depression: focus on group I metabotropic glutamate (mGlu) receptors

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Introduction

In several countries the burden of mental disorders is third after that of heart disease and cancer. Depression and anxiety are fluctuating, very chronic and disabling mental disorders, which account for half of all mental disorders (1). The prevalence of depression has increased during the last 50 years dramatically, from less then 1% in the 1950s to 10-15% of population in the 1990s (2). By the year 2020, depression may become the second most costly disease to treat (3). Taking into account that only 1 case out of 4 is diagnosed and treated and that about 15% of the patients with depression may commit suicide, the problem is difficult to overestimate (4, 5). The prevalence of anxiety is also rising and may reach half of the value for depression (6, 7). The majority of the patients with a principal diagnosis of unipolar major depressive disorder have a comorbid anxiety disorder (8). Taking into account all the abovementioned problems and the fact that the existing drugs used for the treatment of depression and anxiety are not satisfactory, it is important to look for new potential anxiolytic and/or antidepressant drugs. There are several data indicating that substances influencing the glutamatergic system may be the antidepressant and/or anxiolytic drugs of the future.

Glutamatergic system

Excitatory amino acids (EAA) are present in abundance in the brain. It has been estimated that approximately 50% of cerebral neurons may utilize glutamate as a neurotransmitter (9). Glutamate, the most abundant amino acid in the brain, acts via stimulation of ionotropic and metabotropic glutamate (mGlu) receptors (10, 11). The ionotropic glutamate receptors are coupled to ion channels and are classified into NMDA, AMPA and kainate receptors (10). The NMDA receptor complex consists of an ion channel with multiple, allosterically coupled recognition sites for glutamate, glycine$_B$, phencyclidine, polyamines, zinc and magnesium (12). mGlu receptors are members of a relatively new class of glutamate receptors linked to G proteins. Eight different subtypes of mGlu receptors have been cloned so far (mGlu 1-8). On the basis of their sequence homology, effector coupling and pharmacology, mGlu receptors have been subdivided into 3 groups: group I mGlu receptors (mGluR1 and mGluR5), positively coupled to phospholipase C; group II mGlu receptors (mGluR2 and mGluR3) and group III mGlu receptors (mGluR4, mGluR6, mGluR7 and mGluR8), negatively coupled to adenylate cyclase (13).

Glutamate seems to play a major role in both the physiology and pathophysiology of the central nervous system. Some data show that the changes in ionotropic glutamate neurotransmission may be involved in a variety of neuropsychiatric disorders (14). Converging lines of evidence indicate crucial involvement of glutamate receptors in the phenomena related to the mechanism of

action of anxiolytic (15, 16) and antidepressant drugs (17-19).

Functional NMDA receptor antagonists/agonists

Ligands interacting with different sites of NMDA receptor complex were widely investigated as potential agents for the treatment of a variety of neuropsychiatric disorders (20). In recent years, several experiments have demonstrated the anxiolytic- and/or antidepressant-like effects of uncompetitive and competitive antagonists of NMDA receptors, as well as the antagonists and partial agonists of a glycine$_B$ site.

Anxiolytic-like effects

a) Phencyclidine site

Most of the studies examining potential antianxiety-like effects of uncompetitive NMDA receptor antagonists include MK-801 (dizocilpine). MK-801 exerts antianxiety-like effects in several experimental models of anxiety including the modified versions of Vogel, Geller-Seifter and Cook-Davidson tests (21, 22), elevated plus maze test (23-25), open field test (26), social interaction test (23, 24) and other tests such as "fear-potentiated startle response" (27) or separation-induced ultrasonic vocalizations test (28, 29). However, Stephens and Andrews did not observe anxiolytic-like effects of MK-801 (30) in the four-plate test in mice. It is worth noting that intrahippocampal administration of MK-801 also exerted anxiolytic-like effects in the Vogel and open field tests (31).

b) Glutamate site

The competitive NMDA receptor antagonists L-2-amino-5-phosphonopentanoic acid (AP-5), DL-2-amino-7-phosphonoheptanoic acid (AP-7) and 3-[(*R*)-2-carboxypiperazine-4-yl]-propyl-1-phosphonic acid (CPP) exert anxiolytic-like effects in several animal models of anxiety after peripheral administration (22-24, 28-30, 32). Moreover, anticonflict efficacy of AP-5 and AP-7 was also described after their central administration (Fig. 1). Following intrahippocampal administration, AP-7 produced anxiolytic-like effects in Vogel and open field tests (31) and when injected into the dorsal periaqueductal gray, that compound was effective in the elevated plus maze test (33). AP-5 and AP-7 exerted anxiolytic-like effects in the fear-potentiated startle response after injection into the amygdala (34). Moreover, intraventricular injections of L-AP-7 produced anxiolytic-like responses in the Vogel and open field tests (26). Other competitive NMDA receptor antagonists DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP-37849), as well as its carboxymethyl ester (CGP-39551) and 5,7,-di-chloro-1,4-dihydro-[4-[-(methoxycarbonyl)amino]-phenyl]-sulfonyl]imino]-2-quinoline carboxylic acid (MDL-100458) also showed potential aniolytic-like effects in the Vogel, open field and elevated plus maze tests (26, 35, 36). Another antagonist, MDL-100458, produced antianxiety-like effects in the separation-induced ultrasonic vocalization test (28). The anxiolytic effect of AP-7 (in the rat pup isolation calls test) was abolished by NMDA but not by glycine administration (29).

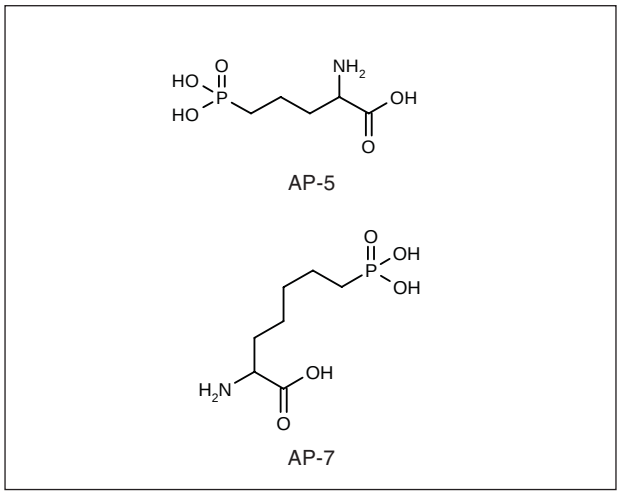

Fig. 1. Chemical structures of AP-5 and AP-7.

c) Glycine$_B$ site

Glycine is a coagonist of NMDA receptor acting at the strychnine-insensitive glycine$_B$ site. The antagonists and partial agonists of glycine$_B$ receptors inhibit the function of NMDA receptor complex and evoke anxiolytic-like and/or antidepressant-like effects similar to those exerted by competitive and uncompetitive NMDA receptor antagonists. Most of the experiments were conducted using glycine$_B$ site antagonists, such as 7-chlorokinurenic acid (7-CKA) and 5,7-dichlorokinurenic acid (5,7-DCKA) as well as its partial agonists 3-amino-1-hydroxypirrolidin-2-one (HA-966), 1-aminocyclopropanecarboxylic acid (ACPC) and D-cycloserine (Fig. 2 and 3).

In the elevated plus-maze test, all the above mentioned compounds, when injected peripherally, increased the time spent in the open arms (22, 25, 37). In the Vogel test, an anticonflict effect was observed after peripheral

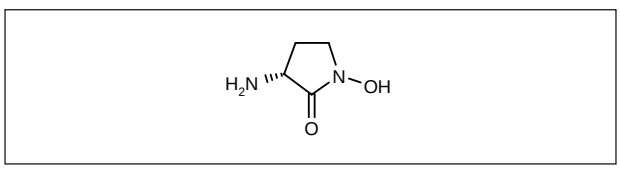

Fig. 2. Chemical structure of HA-966.

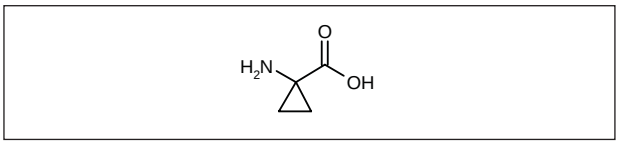

Fig. 3. Chemical structure of ACPC.

administration of D-cycloserine (38) or ACPC (36). In the Cook-Davidson test, the anticonflict activity of 5,7-ClKYN (23) and HA-966 (22, 37) were described after peripheral administration. 5,7-DCKA (23) and HA-966 (22) were effective in the social interaction test; 7-CKA, HA-966, ACPC and D-cycloserine exhibited anxiolytic-like effects in the fear-potentiated startle response test (32), while ACPC, 7-CKA and 5,7-DCKA (28, 29) were effective in the rat pup isolation test. All of these compounds were effective after single, peripheral injection.

The new selective, brain-penetrable glycine receptor antagonists, which cross the blood-brain barrier, such as MDL-100458, MDL-102288 (39), MDL-105519 (40) and ACEA-1021 (15), showed only weak antianxiety-like effects in the rat pup separation model or in the elevated plus maze test. L-701324 produced weak antianxiety-like effects in the elevated plus maze and four-plate tests (25, 41), while in the Vogel test, equivocal effects were demonstrated, such as either anticonflict action (41) or no effect (25). In the experiments of Karcz-Kubicha *et al.* (25), the new glycine antagonists MRZ 2/570, 2/571, 2/576 did not show antianxiety-like effects in the elevated plus maze test, while MRZ 2/576 was inactive also in the Vogel test. However, most of the new $glycine_B$ receptor ligands at doses only slightly higher than those showing potential antianxiety-like effects, produced changes in the motor performance of rats (25, 39-41). Although the data concerning antianxiety-like effects of antagonists of $glycine_B$ receptors are not very promising, the investigations are still in progress.

(d) Polyamine site

Antagonists of the polyamine site like ifenprodil and the more selective agent eliprodil that are inactive either in the Geller-Seifter test in rats (42, 43) or in the conflict test in pigeons (44), did show a potential anxiolytic-like activity in the rat pup isolation test (29).

Antidepressant-like effects

a) Phencyclidine site

The antidepressant-like effects of MK-801 were evaluated using the forced swim (45, 46) and tail suspension tests (47). Both procedures, because of their high predictive value for screening of clinically effective antidepressants, are used to screen for antidepressant drugs with high therapeutic potential. MK-801 was effective in the forced swim test in mice or in rats, reducing the immobility time (48-50), and in the tail suspension test in mice (51).

The chronic mild stress model of depression in rats, shows high face and construct validity as an antidepressant screening test (52). In that test, MK-801 lowered the consumption of a palatable sucrose solution (53, 54). MK-801 was also effective in shock-induced depression in mice (55), in footshock-induced fighting behavior in chronically stressed rats (56) and in olfactory bulbectomy-induced locomotor hyperactivity (57). Bilateral olfactory bulbectomy in the rat is associated with neurochemical, physiological and behavioral changes which parallel some of the symptoms observed in depressed patients (58), and that are reversed by chronic but not acute treatment with antidepressant drugs (59-62). The anxiolytic- or antidepressant-like effects of MK-801 are observed after low doses, while higher doses of the compound induce hyperlocomotion, motor disturbances and ataxia (51, 63, 64). In spite of the fact that MK-801 shows pronounced antianxiety- and/or antidepressant-like effects in animal models, it cannot be regarded as a potential anxiolytic drug, mainly due to its adverse effect profile of which the majority are psychotomimetic effects (65, 66).

b) Glutamate site

The competitive NMDA receptor antagonist AP-7 was also effective in animal tests, such as the forced swim test in mice, where it reduced immobility time (48). Other competitive NMDA receptor antagonists, CGP-37849 as well as with CGP-39551 were active in the forced swim test in rats (49, 67). CGP-39551 and CGP-37849 and its (*R*)-enantiomer CGP-40116 were also active in the chronic mild stress model of depression (53, 54).

The great hopes for the success of NMDA receptor antagonists in the therapy of depression and/or anxiety have been hampered by the adverse effect profile of these compounds. Blockers of NMDA receptor channel and its competitive antagonists produce psychotomimetic effects, leading to drug dependence, memory dysfunction, ataxia and neurodegeneration (12). Both competitive and noncompetitive NMDA receptor antagonists disturb motor performance, while higher doses can cause ataxia, myorelaxation and impaired learning and memory (20, 65). Thus, clinical application of these agents is limited.

Still there is some hope concerning the clinical application of low affinity functional NMDA receptor antagonists, the so-called uncompetitive antagonists such as memantine (68). Preclinical studies have shown that amantadine and memantine, uncompetitive NMDA receptor antagonists, evoke antidepressant-like effects (69) and are devoid of the adverse effects characteristic of higher affinity NMDA receptor blockers (70). Moreover, the clinical data demonstrate antidepressant activity of

amantadine and ketamine (71-73). However, more clinical data are necessary to confirm those observations.

c) Glycine site

The antidepressant-like effects of ACPC or D-cycloserine were evident in the forced swim test in mice and in rats (48, 67, 74, 75). The hippocampus may be one of the neuroanatomical sites involved in this effect as intrahippocampal injections of these compounds were effective in the abovementioned tests (67). ACPC was also reported to reverse the reduction in sucrose consumption in the chronic mild stress model of depression in rats (76). 7-CKA and 5,7-DCKA reduced immobility time in the rat forced swim test (77).

Severe adverse-effects characteristic of both the competitive and uncompetitive NMDA receptor antagonists do not occur after administration of antagonists and partial agonists of glycine$_B$ receptor (78). However, chronic administration of partial agonists of glycine/NMDA site induces tolerance in the Porsolt swim test (74, 79) which raises some doubts about the potential clinical application of these findings.

d) Polyamine site

Eliprodil (SL- 82.0715), a NMDA receptor antagonist acting at the polyamine site, was investigated in behavioral tests predictive of antidepressant activity. In mice, eliprodil produced a dose-dependent reduction in immobility in the forced swim test, but was inactive in the tail suspension test (80). More studies are needed to evaluate both the anxiolytic- and antidepressant-like effects of antagonists of the polyamine site of NMDA receptor.

e) Zinc and magnesium sites

Preclinical studies suggest that zinc and magnesium show antidepressant activity. Both ions exhibit antidepressant-like activity in the forced swim test in mice and rats (81-83). Zinc is also active in olfactory bulbectomy and chronic mild stress rat models of depression (Nowak, unpublished results). Clinical studies are under way to investigate if the treatment with zinc influences induction of antidepressant effects of typical antidepressant drugs.

AMPA/kainate receptor antagonists

There are not too much data on the effects of the AMPA/kainate receptor antagonists in animal models of anxiety. AMPA/kainate receptor antagonist, NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzoquioxaline-7-sulphonoamide disodium) displayed potential anxiolytic activity in the four-plate test in mice (84), but was inactive in the elevated plus maze test (85) and Vogel test in rats (86). Its analog, compound CNQX when injected into the periaqueductal gray (but not after peripheral injection) demonstrated an antianxiety-like effect in the elevated plus maze test (87). With regard to the compound LY-326325 (3RS, 4aRS, 6RS, 8aRS)-6[2-(1-(2)H-tetrazole-5-yl)ethyl]decahydro-izoquinoline-3-carboxylic acid), its potential anxiolytic-like effects in the Vogel test and in the elevated plus maze test were described in rats (88) but not in mice (85).

AMPA potentiators

Recently, antidepressant-like effects of an AMPA receptor potentiator LY-392098 were described (89). Anxiolytic effects of aniracetam were observed in 3 different mouse models of anxiety such as the social interaction test, elevated plus-maze and conditioned fear stress tests (90). Clearly more data are needed to evaluate antidepressant- or anxiolytic like effects of AMPA potentiators.

Metabotropic glutamate (mGlu) receptor antagonists/agonists

Group I mGlu receptor antagonists

Recently, novel, selective and systemically active compounds from this group have been described (91, 92). 2-Methyl-6-(phenylethynyl)-pyridine (MPEP) was proven to be the most potent among these substances (Fig. 4). It is a noncompetitive antagonist with an IC_{50} of 36 nM at the human mGlu5a receptor (in the PI hydrolysis assay) with no significant effect at other metabotropic or ionotropic glutamate receptors (91). MPEP exerted anxiolytic-like effects after peripheral administration, being active in unconditioned response tests, *e.g.*, social exploration test, stress-induced hyperthermia, marble burying test and elevated plus maze test (93, 94). It was also effective in the so-called conditioned response tests (Vogel test in rats and four plate test in mice) (95, 96). In the Geler-Seifter test, the effects of MPEP were inconclusive (93, 97). When applied systemically, MPEP blocked acquisition and expression of fear in the fear-potentiated startle paradigm (98). Intrahippocampal injections of other antagonists of group I mGlu receptors, namely (*S*)-4-carboxy-3-hydroxyphenylglycine

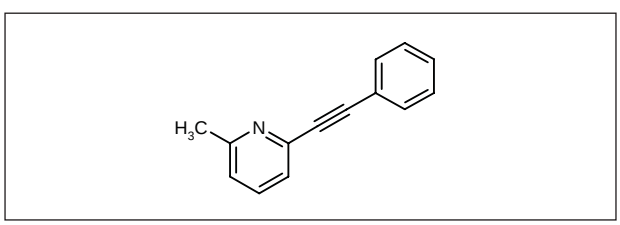

Fig. 4. Chemical structure of MPEP.

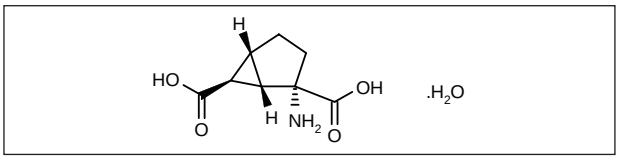

Fig. 5. Chemical structure of LY-354740.

(S-4C3HPG), (*S*)-4-carboxyphenylglycine (*S*)-4CPG, and 7-(hydroxyimino)cyclopropan[b]chromen-1α-carboxylic ethyl ester (CPCCOEt), exerted anxiolytic-like effects in rats in the Vogel test (96, 99), indicating that hippocampus may be the structure involved in the anxiolytic effects of group I mGlu receptor antagonists.

MPEP-exerted antidepressant-like effects in the tail suspension test (94, 100) but not in the Porsolt test. Moreover, MPEP reversed the bulbectomy-induced behavioral deficits similarly to the classical antidepressant drug desipramine (101). Both effects were observed only after prolonged but not acute drug administration. It is important that MPEP is remarkably free of adverse effects in animals, such as sedation, memory or motor disturbances (93, 96, 97). The nonselective group I mGlu receptor antagonist AIDA (102) produced an antidepressant-like effect in the Porsolt test (Pilc *et al*., unpublished results).

Group II mGlu receptor agonists/antagonists

Among the substances activating group II mGlu receptors, (+)1*S*,2*S*,5*R*,6*S*-2-aminobicyclo [3.1.0] hexane-2,6-dicarboxylic acid (LY-354740) (103, 104) is a selective, systemically active and high-affinity agonist. Peripheral administration of LY-354740 produced potent anxiolytic-like activity in the elevated plus maze test in mice and fear-potentiated startle models of anxiety in rats (105, 106) (Fig. 5). LY-354740 also produced anxiolytic-like effects in conflict drinking test in rats, four-plate test in mice (107) and conflict tests in pigeons (108). Both LY-354740 and another agonist of group II mGlu receptors (2*S*,1'*S*,2'*S*)-2-(carboxycyclopropyl)glycine (L-CCG-I) were also active in the conflict drinking test after intrahippocampal injection (96). On the other hand, (*RS*)-α-methylserine-*O*-phosphate monophenyl ester (MSOPPE), an antagonist of group II mGlu receptors, was inactive (99, 109, 110) after intrahippocampal injections.

As group II mGlu receptors are localized presynaptically in the brain, agonists of this receptor can inhibit glutamate release (11) and exert inhibitory effects in the central nervous system. In preclinical studies, LY-354740 caused a mild sedation in mice, did not disturb motor coordination (105, 107) and had no potential to cause dependence (107, 111, 112). Therefore, group II mGlu receptor agonists may become anxiolytics of the future, free of adverse effects characteristic of benzodiazepines.

Group III mGlu receptor agonists/antagonists

This is the most heterogenous group of mGlu receptors, consisting of four receptor types. L-serine-*O*-phosphate (L-SOP) is a selective agonist of group III mGlu receptors (see (113), which are also found in the CA1 region of the hippocampus (114), representing mainly the mGlu7 receptor subtype. L-SOP with affinity for that receptor subtype in high micromolar range (115, 116) produced anxiolytic-like effects after intrahippocampal injection (96). However, anxiolytic-like effects of (*RS*)-α-methylserine-*O*-phosphate (MSOP), an antagonist of group III mGlu receptors, were also demonstrated after intrahippocaampal injection in the Vogel test in rats (99). Further development of more potent and more subtype-specific group III mGlu receptor ligands is necessary to investigate this issue.

Antidepressant-induced adaptive changes in glutamate receptors

NMDA receptor complex

Chronic treatment with antidepressant drugs and electroconvulsive shock (ECS) induce alterations in NMDA receptor reactivity and function. The first evidence came from radioligand receptor binding studies which demonstrated a reduction of glycine/NMDA receptor reactivity (117-121) (19). Next, electrophysiological (122), biochemical (123) and behavioral (124) studies indicated the reduced function of this receptor complex following chronic treatment with AD or ECS. These alterations might be connected with the reduced level of mRNA and/or protein of some receptor subunits (17).

Duman (125) has shown that antidepressant drugs cause an increase in brain-derived neurotrophic factor (BDNF) and proposed that it may be responsible for the therapeutic effect of these agents. Since NMDA receptor antagonists exert antidepressant-like effects (see above), Skolnick (17) further hypothesized that the attenuation of function of the NMDA receptor complex (evoked by BDNF and NMDA antagonists) is crucial for antidepressant treatment (Fig 7).

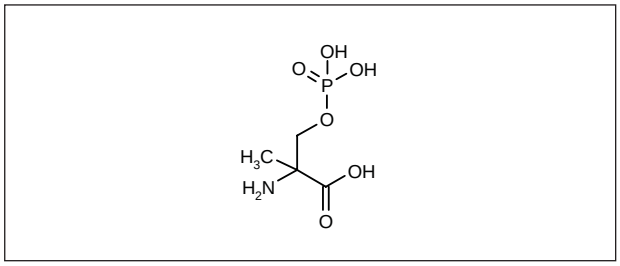

Fig. 6. Chemical structure of MSOP.

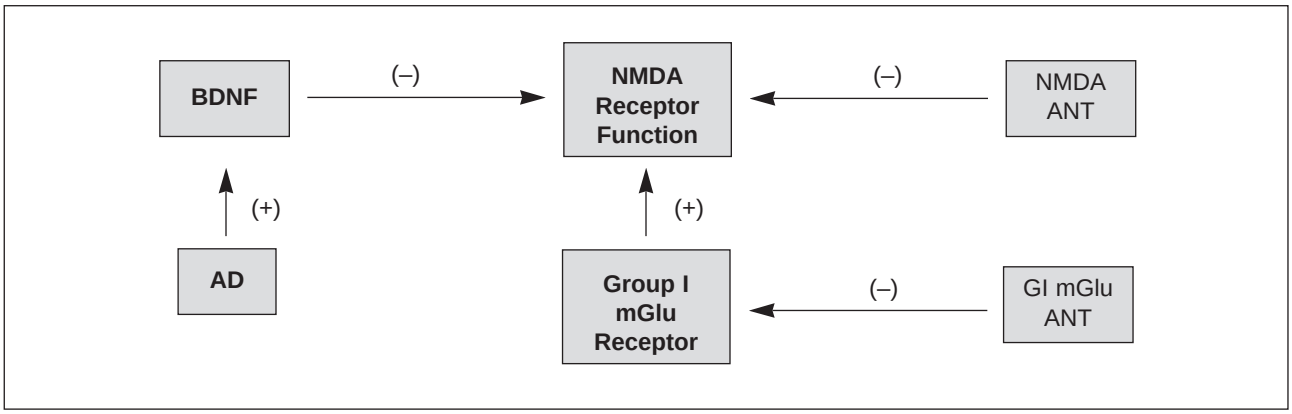

Fig. 7. Antidepressants (monoamine based) and glutamate receptor antagonists lead to the inhibiton of the NMDA receptor complex. According to Duman, classic antidepressant drugs (AD) induce cascade of biochemical events resulting in the increased activity of brain-derived neuroptrophic factor (BDNF) (125). Based on the antidepressant activity of NMDA receptor antagonists (NMDA ANT), Skolnick (17) modified this hypothesis by focusing on the NMDA receptor complex. Since stimulation of group I mGlu receptors potentiates the activity of NMDA receptors, their antagonists (GI mGlu ANT) may exhibit antidepressant activity via reduction of NMDA function.

Group I mGlu receptors

It has been shown (126-128) that multiple antidepressant drugs or ECS treatment leads to a decrease in ibotenic acid-induced cAMP accumulation and to the inhibition of synergistic interaction of ibotenate and noradrenaline upon cAMP accumulation. Both the effect of ibotenic acid on cAMP accumulation and the interaction between ibotenate and noradrenaline is due to the stimulation of group I mGlu receptors (129, 130). Therefore, group I mGlu receptors coupled (indirectly) to adenylate cyclase are influenced by antidepressant drugs. The results of electrophysiological studies led to similar conclusions. The activation of group I mGlu receptors by ACPD or DHPG which causes an increase in the activity of neurons from CA1 region of the hippocampus in rats, is markedly inhibited by both multiple imipramine or ECS treatment (131, 132). Imipramine-induced decrease in the sensitivity of hippocampal CA1 cells to agonists of group I mGlu receptors appeared after 7 days of treatment, reaching a maximum after 14 days of treatment which correlates with the delayed efficacy of antidepressants observed in human depression. A decrease in the reactivity of the cells was seen 7 days after the cessation of imipramine treatment (132).The results suggest that the changes in group I mGlu receptors may have a role in the clinical efficacy of antidepressant drugs. Group I mGlu receptors are divided into 2 types: mGlu1 and mGluR5, as well as several subtypes (*e.g.*, mGluR1a). It was found that the expression of mGluR1a-immunoreactivity significantly increased in CA regions after chronic ECS (133). The most prominent increase was observed in the CA3 region (134). The expression of mGluR5 immunoreactivity increased significantly after chronic imipramine administration in the CA1 layer, and in the CA3 region after chronic ECS treatment (134). This increase in the receptor protein level may be a compensatory mechanism developing after chronic treatment.

Preclinical data indicate that the compounds which reduce transmission at NMDA receptors behave like antidepressants (17). Glutamatergic transmission, mediated by the stimulation of group I mGlu receptors, has also been shown to potentiate responses of ionotropic glutamate receptors in various brain structures (135) including potentiation of NMDA currents (136, 137). Therefore, the inhibition of group I mGlu receptors by MPEP may lead to a decrease in NMDA-receptor-mediated neurotransmission (Fig. 7), thus contributing to the antidepressant-like effect of MPEP. It can be speculated that MPEP, which did not cause sedation or disturb the rota-rod performance, might be free of side effects produced by NMDA receptors antagonists.

Conclusions

Glutamate is a major excitatory transmitter in the brain. The antagonists of ionotropic glutamate receptors produce anxiolytic- and antidepressant-like effects in animals; however, attempts to develop drugs that are antagonists of ionotropic glutamate receptors have been undermined by the adverse effect profiles of these compounds. Whether functional antagonists of ionotropic glutamate receptors could be used as anxiolytic or antidepressant drugs in the future depends on the discovery of new selective compounds which penetrate well to the brain, are free of side effects and are unlikely to cause either development of drug dependence or drug tolerance. Stimulation/blockade of metabotropic glutamate receptors produces modulatory, less pronounced effects as compared to ionotropic glutamate receptor agonists/antagonists. Recent data indicate that both antagonists of group I metabotropic glutamate receptors or agonists of

group II mGlu receptors exert profound anxiolytic or antidepressant-like effects in animal models and are remarkably free of undesired effects characteristic of either benzodiazepines or ionotropic glutamate receptor antagonists. It is therefore possible that prospective anxiolytic drugs would belong to this group of compounds.

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