BIOCHEMICAL PHARMACOLOGY 75 (2008) 997–1006

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Mood disorders: Regulation by metabotropic glutamate receptors

Andrzej Pilc[a], *Shigeyuki Chaki*[b], *Gabriel Nowak*[a], *Jeffrey M. Witkin*[c,*]

[a] *Institute of Pharmacology, Polish Academy of Sciences and Collegium Medicum, Jagiellonian University, Krakow, Poland*
[b] *Taisho Pharmaceutical Co. Ltd., Saitama, Japan*
[c] *Psychiatric Drug Discovery, Lilly Research Labs, Eli Lilly and Company, Indianapolis, IN 46285-0510, USA*

ARTICLE INFO

Keywords:
Metabotropic glutamate
mGlu receptors
Depression
LY341495
MGS0039
MPEP
MTEP

ABSTRACT

Medicinal therapies for mood disorders neither fully serve the efficacy needs of patients nor are they free of side-effect issues. Although monoamine-based therapies are the primary current treatment approaches, both preclinical and clinical findings have implicated the excitatory neurotransmitter glutamate in the pathogenesis of major depressive disorders. The present commentary focuses on the metabotropic glutamate receptors and their relationship to mood disorders. Metabotropic glutamate (mGlu) receptors regulate glutamate transmission by altering the release of neurotransmitter and/or modulating the post-synaptic responses to glutamate. Convergent biochemical, pharmacological, behavioral, and clinical data will be reviewed that establish glutamatergic neurotransmission via mGlu receptors as a biologically relevant process in the regulation of mood and that these receptors may serve as novel targets for the discovery of small molecule modulators with unique antidepressant properties. Specifically, compounds that antagonize mGlu2, mGlu3, and/or mGlu5 receptors (e.g. LY341495, MGS0039, MPEP, MTEP) exhibit biochemical effects indicative of antidepressant effects as well as *in vivo* activity in animal models predictive of antidepressant efficacy. Both preclinical and clinical data have previously been presented to define NMDA and AMPA receptors as important targets for the modulation of major depression. In the present review, we present a model suggesting how the interplay of glutamate at the mGlu and at the ionotropic AMPA and NMDA receptors might account for the antidepressant-like effects of glutamatergic- and monoaminergic-based drugs affecting mood in patients. The current data lead to the hypothesis that mGlu-based

* *Corresponding author*. Tel.: +1 317 277 4470; fax: +1 317 276 7600.
E-mail address: jwitkin@lilly.com (J.M. Witkin).

Abbreviations: ACPD, 1-aminocyclopentane-*trans*-1,3R-dicarboxylic acid; ACPT-I, (1S,3R,4S)-1-aminocyclo-pentane-1,3,4-tricarboxylic acid; AMN082, *N*,*N*′-dibenzyhydryl-ethane-1,2-diamine dihydrochloride; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; L-CCG-I, (2S,1′S,2′S)-2-(carboxycyclopropyl)glycine; CPPG, (R,S)-alpha-cyclopropyl-4-phosphonophenyl glycine; CNS, central nervous system; DCG-IV, ((2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine); ECT, electroconvulsive treatment; EMQMCM, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate; FST, forced swim test; iGlu, ionotropic glutamate; LY341495, 9*H*-xanthene-9-propanoic acid α-amino-α-[(1S,2S)-2-carboxycyclopropyl]-(α S)-(9CI); mGlu, metabotropic glutamate; MGS0039, 2-amino-3-[(3,4-dichlorophenyl)methoxy]-6-fluoro-, (1R,2R,3R,5R,6R)-(9CI); MPEP, 2-methyl-6-(phenylethynyl)pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-ylethynyl]pyridine; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*f*)quinoxaline; PHCCC, *N*-phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-1acarboxamide; (R,S)-PPG, (R,S)-4-phosphonophenylglycine; SSRI, selective serotonin reuptake inhibitor; TST, tail suspension test.

0006-2952/$ – see front matter
doi:10.1016/j.bcp.2007.09.021

compounds and conventional antidepressants impact a network of interactive effects that converge upon a down regulation of NMDA receptor function and an enhancement in AMPA receptor signaling.

1. Introduction

Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system. Preclinical and clinical evidence have suggested that altered glutamate neurotransmission plays a role in mood disorders (see [1,2] for an overview). The exciting finding that the NMDA receptor antagonist ketamine was effective in treating antidepressant-resistant patients [3,4] has increased the promise that improved treatments for the major depressive disorders might be possible by modulation of glutamatergic neurotransmission. Current therapies for mood disorders involve medications that increase the synaptic availability of monoamine neurotransmitters. The need for improved medicines is stressed by data emphasizing the poor remission rates and high rate of relapse in depressed patients seeking treatment [5].

Regulation of excitatory neurotransmission is guided in part by the interactions of glutamate at multiple families of glutamate receptors and transporters. The present commentary will focus on the metabotropic glutamate (mGlu) receptors and their potential involvement in mood disorders. The review focuses on the preclinical data that converge to suggest that mGlu receptors are involved in the central regulation of mood and could thereby serve as molecular targets for the discovery of novel antidepressants. The suggestion of novel treatments for a disease by necessity raises the issue of the potential side effects or adverse events anticipated by such mechanisms. Since the question of safety is in itself a large one and since many types of safety issues need to be considered (renal, cardiovascular, etc.) in addition to neurological and psychological concerns (memory, sedation, abuse liability, etc.), we have left this discussion largely out scope. Moreover, clinical study and experience must ultimately be the final word in these areas as they are in the substantiation of efficacy.

mGlu receptors are in a position to alter the neurotransmission of glutamate as well as other neurotransmitters that are known to be involved in mood [6]. mGlu receptors are divided into eight subtypes (mGlu1–8 receptors) that fall within three groups based upon homology and functional biology. These G-protein-coupled receptors consist of seven transmembrane spanning domains, a relatively large N-terminus extracellular domain containing the ligand recognition site, the presence of a cysteine-rich region just prior to the TM1 domain, and an intracellular carboxy terminal region involved in receptor regulation and trafficking [7]. Two groups of mGlu receptors are Gi-coupled (group II or mGlu2 and mGlu3 receptors and group III or mGlu4–8 receptors) and are negatively coupled to adenylyl cyclase and thereby negatively modulate excitatory neurotransmitter efflux and neuronal excitability when activated [6,8]. Group I mGlu receptors (mGlu1 and mGlu5) are coupled to the activation of phospholipase C, and in general function to enhance glutamate excitations [6,9].

For prior reviews of this general area, see [10,11]; for metabotropic receptors, see [2,10]; for AMPA receptors, see [12,13]; and for NMDA receptors, see [1,14]. We will not focus greatly on the cascade of posttranslational events that are affected by the mGlu receptors but reviews in this area are also available [6,8,11,15,16].

Limited clinical proof of concept for mGlu receptor ligands in the treatment of affective disorders has been achieved. mGlu2/3 receptor agonists have shown efficacy in the treatment of generalized anxiety disorder, a stress-related disorder having marked comorbidity with the major depressive disorders [11,17]. Fenobam, an anxiolytic in humans, may produce this clinical outcome through blockade of specific metabotropic glutamate receptors (mGlu5) [18]. It was also recently disclosed that an mGlu2/3 agonist was effective in mitigating positive and negative symptoms in schizophrenic patients [19]. Nonetheless, support for the role of mGlu receptors in mood disorders presented in the present commentary rests primarily on the weight of preclinical evidence given the limited information on these ligands in humans

2. Group I mGlu receptors

2.1. *Molecular biology and anatomy*

The group I mGlu receptors include the mGlu1 and mGlu5 receptors for which splice variants exist (mGlu1α, β and mGlu5a, b) [20]. The distribution of the group I receptors overlaps with brain areas implicated in mood disorders (see [2]). mGlu1 (but not mGlu5) receptors are abundant in the cerebellum, olfactory bulb, CA3 region of hippocampus, thalamus, dentate gyrus, substantia nigra and medial central gray [20]. mGlu5 receptors are highly expressed in the telencephalic regions, CA1 and CA3 regions of the hippocampus, in the septum, basal ganglia, striatum, amygdala, and nucleus accumbens [20].

2.2. *Physiology*

Activation of group I mGlu receptors evokes excitatory synaptic effects in the brain that impinge upon the ionotropic glutamate (iGlu) receptors. Group I mGlu receptors are coupled to phospholipase C, through $G_{q/11}$ proteins and induce phosphoinositide hydrolysis [21]. Activation of adenylyl cyclase by stimulation of group I mGlu receptors has also been reported [21]. Stimulation of group I mGlu receptors can also depolarize neurons by reduction of K^+ conductance or by increasing inward currents [21,22]. Immunoreactivity for

group I mGlu receptors is observed in the postsynaptic neuronal elements including postsynaptic densities [20] and also seen in regions around iGlu receptors [23]. Group I mGlu receptors are associated with the Homer family of proteins which link them functionally with IP_3 [24] and NMDA receptors where activation of group I mGlu receptors leads to activation of NMDA receptors. mGlu5 receptors potentiate NMDA-evoked current via G proteins, while mGlu1 receptors act via activation of Src tyrosine kinase [25].

2.3. Modification by antidepressants

The group I mGlu receptors are influenced by antidepressant administration. Biochemical and electrophysiological data indicate that repeated exposure to antidepressant treatments decrease the sensitivity of group I mGlu receptors in brain. For example, subchronic antidepressant or electroconvulsant therapy (ECT) inhibited both ibotenate-induced cAMP accumulation and the interaction between ibotenate and noradrenaline [26]. Group I mGlu receptor activation by ACPD or DHPG, which caused an increase in the activity of neurons from the CA1 region of the hippocampus in rats, was inhibited by subchronic imipramine administration and by ECT sessions [27]. The immunoreactivity of mGlu1α was increased after multiple but not single ECT in the CA regions of the hippocampus, with the most pronounced effect observed in CA3 [28,29]. The expression of mGluR5a increased significantly after subchronic imipramine in CA1 and increased in CA3 after subchronic ECT [29]. The observed upregulation of these receptors may reflect a compensatory mechanism caused by receptor subsensitivity engendered by the antidepressant treatments [28,29]. Chronic mild stress in rats that displays high face and construct validity as an antidepressant screening test [30], also increased mGlu5 receptor protein in hippocampal CA1 [31] further supporting the involvement of this mGlu receptor subtype in the pathophysiology of depression.

2.4. Antidepressant-like effects

Experimental data from pharmacological studies with the selective mGlu5 receptor antagonists MPEP and MTEP have also been consistent with the antidepressant potential of these receptors. Administration of MPEP and MTEP decreased immobility in the tail-suspension test (TST) in C57BL/6J mice [32–34]. The TST detects antidepressant-like activity of a host of diverse antidepressant agents [35]. Although efficacy in the forced-swim test (FST, [36] for a review of this antidepressant screen) was initially not reported with rats given MPEP [32], efficacy was detected in this assay using mice [37]; MTEP was active in rats in a modified version of the FST [34]. Both antagonists also produced antidepressant-like effects [33,38] in the olfactory bulbectomy model. Multiple administrations of MPEP (14 days, 10 mg/kg per day) reversed the olfactory bulbectomy-induced deficits in passive avoidance learning [38] and repeated administration of MTEP (1 mg/kg) attenuated the hyperactivity of olfactory bulbectomized rats [33].

The data which demonstrated that mGlu5 receptor antagonists produced antidepressant-like effects are supported by the demonstration that mGlu5 receptor knockout mice displayed an antidepressant-like behavioral phenotype (a significant decrease in the immobility) [37]. In these mice, imipramine further decreased the immobility time, while MPEP was not effective, proving that mGlu5 receptors are necessary for the antidepressant-like effect of this compound [37]. In addition, synergy of MPEP with imipramine in the FST was observed that was not due to pharmacokinetic interactions. It was, therefore, hypothesized that the efficacy of conventional monaminergic-based antidepressants would be enhanced by concomitant administration of mGlu5 receptor antagonists [37].

The first evidence for antidepressant-like activity of an mGlu1 receptor antagonist was recently reported with the demonstration that EMQMCM was active in both the TST and in the modified FST in rats [34].

3. Group II mGlu receptors

3.1. Molecular biology and anatomy

The group II mGlu receptors (mGlu2 and mGlu3 receptors) are also well positioned both anatomically and physiologically to regulate glutamate and other neurotransmitters within the CNS in the control of mood. High levels of expression of mGlu2 mRNA have been observed in neurons of the accessory and external regions of the anterior olfactory bulb, pyramidal neurons in the enthorhinal and parasubicular cortical regions, and granule cells of the dentate gyrus [39]. mGlu3 mRNA, on the other hand, is highly expressed in neuronal cells of the cerebral cortex and the caudate-putamen and in granule cells of the dentate gyrus [40]. Unlike other mGlu receptors, mGlu3 mRNA is highly expressed in glial cells throughout the brain [40]. Immunohistochemical studies have revealed intense mGlu2-like staining that corresponds with the distribution of mRNA [41]. mGlu2 receptors are mainly localized presynaptically as an autoreceptor or heteroreceptor, and are seen in preterminal rather than terminal portions of axons [42]. mGlu3 receptors are primarily localized on postsynaptic sites in addition to their high expression on glial cells [43].

3.2. Physiology

mGlu2/3 receptors are coupled to Gi/Go proteins and negatively coupled to adenylyl cyclase [21]. Electrophysiological investigations of hippocampal slices indicated that the mGlu2/3 receptor agonists LY354740 and DCG-IV presynaptically inhibited the field excitatory postsynaptic potential (fEPSP) in the medial and lateral perforant paths [15,44]. The inhibitory effect of LY354740 on fEPSPs evoked by both the dentate gyrus mid-molecular and the CA1 stratum lacunosum molecular was reduced in mGlu2 receptor knockout mice, indicating the effect is mediated through mGlu2 receptor [45].

Regulation of other neurotransmitters than glutamate via mGlu2/3 receptors has been observed with biochemical and electrophysiological methods. In rat cortical primary cultures, LY354740 reduced KCl-induced [^{3}H]GABA release, which was attenuated by the mGlu2/3 antagonist LY341495 [46]. As observed with a slice patch-recording method, LY354740 (but not *N*-acetyl-aspartyl-glutamate, a selective agonist for

mGlu3 receptors) reduced IPSCs in rat superior colliculus slices, while LY341495 increased them [47]. Because the IPSCs were demonstrated to mediate GABA release, it is suggested that stimulation of mGlu2 receptor inhibits GABA release via a presynaptic mechanism.

3.3. *Modification by antidepressants*

Alterations in mGlu2/3-mediated functions following chronic treatment with a tricyclic antidepressant have been reported. Chronic imipramine treatment reduced mGlu2/3 receptor agonist-mediated inhibition of forskolin-stimulated cAMP formation, while it enhanced mGlu2/3 receptor-mediated phosphoinositol responses in hippocampal slices [48]. In this report, the authors hypothesized that chronic imipramine administration reduced the function of presynaptic mGlu2/3 receptors, whereas the same manipulation enhanced post-synaptic mGlu2/3 receptor function, actions that could contribute to increased glutamatergic synaptic transmission. Interestingly, when imipramine was combined with LY341495 or a low dose of the mGlu2/3 agonist LY379268, neuroadaptation to imipramine (change in β1 adrenoceptor expression) occurred at shorter times than with imipramine alone [49], suggesting the possibility that mGlu2/3 receptor ligands might shorten the time required to exert full antidepressant effects, which is generally delayed by several weeks [50].

3.4. *Antidepressant-like effects*

mGlu2/3 receptors regulate the release of neurotransmitters known to be involved in mood. Administration of the mGlu2/3 antagonists, MGS0039 or LY341495 (iv), increased firing rates of serotonergic dorsal raphe neurons [51]. Linked to these effects, MGS0039 increased extracellular levels of serotonin in its projection region, the medial prefrontal cortex (mPFC) [51]. Likewise, increases in serotonin, and to a lesser extent noradrenaline, were observed with LY341495 in the ventral hippocampus [2]. The increased serotonin release in the mPFC produced by MGS0039 was attenuated by NBQX, an AMPA receptor antagonist [52], indicating that stimulation of AMPA receptors is responsible for the serotonin efflux changes engendered by mGlu2/3 receptor blockade. MGS0039, injected locally into the nucleus accumbens shell, increased dopamine release in this brain area while local injection of the mGlu2/3 agonist LY354740 decreased dopamine release [53]. Emerging lines of evidence have suggested that increased hippocampal neurogenesis might be a common mechanism of antidepressant treatments across different mechanisms of action [54,55] (see [12] for discussion). Treatment with MGS0039 for 14 days increased progenitor cell proliferation in the dentate gyrus [56], showing that blockade of mGlu2/3 receptors increases hippocampal neurogenesis. Because AMPA receptor potentiators also have been reported to increase hippocampal neurogenesis [57] and since the increased glutamate produced by blockade of mGlu2/3 receptor has been shown to impact AMPA receptors, stimulation of AMPA receptors might be involved in the neurotrophic effects of mGlu2/3 receptor antagonism.

Two mGlu2/3 receptor antagonists, MGS0039 and LY341495, exhibit antidepressant-like effects in behavioral despair models such as the FST and TST [2,58]. Further, effects in the TST were observed after treatment with MGS0039 for 5 days with no indication of tolerance. In the rat FST, MGS0039 and LY341495 significantly increased swimming behavior without changing climbing behavior, as observed with fluvoxamine [58] and other selective serotonin reuptake inhibitors (SSRIs) [59]. Based upon these results and the neurochemical and electrophysiological effects summarized above, mGlu2/3 receptor antagonists might exert antidepressant effects by interacting with serotonergic transmission rather than noradrenergic transmission.

Antidepressant-like effects of mGlu2/3 receptor antagonists have been reported in other models predictive of antidepressant efficacy. LY341495 attenuated reward deficits observed in nicotine-dependent rats, as evaluated by intracranial self-stimulation [60] (see [61] for a review of this model), indicating that blockade of mGlu2/3 receptors opposes anhedonic effects. The AMPA receptor antagonist NBQX precipitated withdrawal-like elevations in stimulation thresholds in nicotine-treated rats [60], showing an involvement of AMPA receptors; recall that NBQX also prevented the antidepressant-like effects of MGS0039 in the TST [52]. MGS0039 also demonstrated antidepressant-like effects in the learned helplessness test where treatment with MGS0039 for 7 days significantly reduced the number of escape failures without changing body weight gain, while imipramine showed the effects at the dose which markedly reduced body weight gain [62].

Antidepressant-like behavior was also observed in mice lacking mGlu2 receptors. In the FST, mGlu2 receptor −/− mice were significantly more mobile compared to wild type mice on the second day, although there was no difference in immobility in the TST [63]. mGlu2 receptor −/− mice also showed an increase in locomotor sensitivity and conditioned place preference in association with repeated cocaine administration, indicating increased reinforcing effects, a finding that is consistent with an increase in dopamine efflux produced by MGS0039 in the nucleus accumbens shell, a region important for reinforcement [53].

In addition to models predictive of efficacy in mood disorders, MGS0039 showed anxiolytic-like effects in some anxiety models [64], while mGlu2/3 receptor agonists also exhibit anxiolytic effects in rodents and humans (for review, see [11]). The models in which mGlu2/3 receptor antagonists are effective are the models sensitive to agents acting on serotonergic transmission, while SSRIs do not exhibit efficacy in the models in which mGlu2/3 receptor antagonists are not effective. Given that antidepressants such as SSRIs and SNRIs are the first-line treatment for certain anxiety disorders including panic disorder and obsessive-compulsive disorder, mGlu2/3 receptor antagonists might be an effective therapeutics for some anxiety disorders.

4. Group III mGlu receptors

4.1. *Molecular biology and anatomy*

Group III mGlu receptors represent the largest family of mGlu receptors, which are classified into four receptor subtypes

(mGlu4, mGlu6, mGlu7 and mGlu8 receptors). Splice variants have also been identified (mGlu7a, b and mGlu8a, b) [20]. The localization of the group III mGlu receptors has also been mapped [20]. With the exception of the mGlu6 receptor subtype, expression of which is limited to the retina, all other group III mGlu receptor subtypes are expressed in several regions of the CNS with differential localizations. High expression of mGlu4 receptors is found in cerebellum and in the granule cells of the olfactory bulb; moreover, mGlu4 receptors are localized in several areas of cerebral cortex, basal ganglia, and in hippocampus where they are positioned both pre- and postsynaptically. Mammalian brain is abundant in mGlu7 receptors which are highly expressed in most brain areas, including neocortical regions, cingulate and piriform cortices, CA1, CA3 and DG regions of hippocampus, amygdala, locus coeruleus, hypothalamic and thalamic nuclei. Expression of mGlu8 receptors appears to be dominant in presynaptic terminals in the olfactory bulbs, piriform cortex, entorhinal cortex, hippocampus, and cerebellum [20].

4.2. *Physiology*

Group III mGlu receptors are negatively coupled to adenylyl cyclase where activation inhibits cAMP formation [21]. Group III mGlu receptors are expressed on both neuronal and glial cells and are predominantly localized to axon terminals where they are in a position to control the synaptic availability of glutamate, as well as of GABA, dopamine, and serotonin [6,20]. As opposed to other group III mGlu receptors, which may be localized perisynaptically, mGlu7a and b receptors are restricted to the center of the presynaptic active zone of axon terminals (i.e., the site of synaptic vesicle fusion) [20]. As such, mGlu7 receptors are well positioned to play the role of the main glutamatergic autoreceptor responsible for the regulation of glutamate release under normal physiological conditions [8].

4.3. *Modification by antidepressants*

There is little neurochemical data on the modificiations of group III mGlu receptors after antidepressant treatment. Existent data suggest that mGlu7, but not mGlu4 receptors are modified by multiple administrations of the antidepressant drug citalopram in the brain regions that are considered to be involved in the clinical response to antidepressant therapy. No changes in mGlu4a-immunoreactivity in rat brain after chronic imipramine were reported [48,65], whereas, mGlu7a-immunoreactivity was decreased after prolonged citalopram, but not imipramine treatment, both in the hippocampus and in the cortex [65]. Subchronic dosing with antidepressant drugs failed to change the action of group III mGlu receptor agonist, ACPT-1, on forskolin-stimulated cAMP accumulation [65].

4.4. *Antidepressant-like effects*

Pharmacological studies of group III mGlu receptors have been limited because subtype-selective and centrally bioavailable pharmacological tools are almost completely lacking. Therefore, behavioral studies of group III mGlu receptors are currently based on central administration of compounds or on observation of the behavior of receptor knockout animals. Thus, the involvement of group III mGlu receptors in depression is poorly defined at present.

Antidepressant-like effects of the selective group III mGlu receptor agonist ACPT-I were observed after icv dosing in the FST [66,67]; this effect of ACPT-I was prevented by the group III mGlu receptor antagonist, CPPG. Moreover RS-PPG, an mGlu8 receptor agonist, induced dose-dependent antidepressant-like effect in the FST after icv administration in rats [67]. Klak et al. [68] confirmed activity of ACPT-I in the FST in rats and showed that PHCCC, a positive allosteric modulator of mGlu4a receptors, given icv in combination with a non-effective dose of ACPT-I, produced antidepressant-like effects in this assay. The specificity of the interaction was confirmed by the fact that the behavioral effects were blocked by CPPG [68]. The behavioral pharmacological data suggest that mGlu4 and mGlu8 receptor activation may engender antidepressant-like effects; however, additional data in other assays with other subtype selective ligands will be needed to confirm this suggestion. Cryan et al. [69] reported that mGlu7 receptor-deficient mice exhibited an antidepressant-like phenotype with shortened immobility times in the FST and TST. Palucha et al. [70] have confirmed this finding. However, they also demonstrated antidepressant-like effects of the mGlu7 agonist AMN082 that was absent in mGlu7 deficient mice. Although there exists an apparent disparity of results from phenotypic comparison and drug challenge; mGlu7 receptors might also be involved in antidepressant-related mechanisms. A reduction in glutamate overflow, which has been observed after activation of group III mGlu receptors in several brain areas [6], might be responsible for the antidepressant-like effects of group III mGlu receptor agonists.

5. A model of mGlu receptor involvement in mood disorders

An involvement of glutamate neurotransmission in the pathophysiology of mood disorders has been suggested by a host of convergent data that have been discussed above and in the reviews referred to earlier. As seen in the above overview, evidence is also accumulating to define mGlu receptors as integral to mood regulation and as potential targets for novel antidepressant drug discovery. mGlu receptors modulate the transmission of glutamate and of other neurotransmitters and involve multiple biochemical transduction pathways that have been previously shown to be involved in the regulation of mood. What remains much less certain are the specific transduction mechanisms responsible for the ways in which mGlu receptors impact antidepressant-like effects and are impacted by antidepressant drugs in animal models.

From the data summarized above, a model is proposed that accounts for the interactions that are known to occur between the mGlu receptors and the NMDA and AMPA subtype ionotropic glutamate receptors (Fig. 1). The model leaves out the monoaminergic synapses for simplification but the ways in which these systems interface with the glutamatergic process have been discussed [12,14,71]. The model is highly oversimplified but provides a cohesive framework for

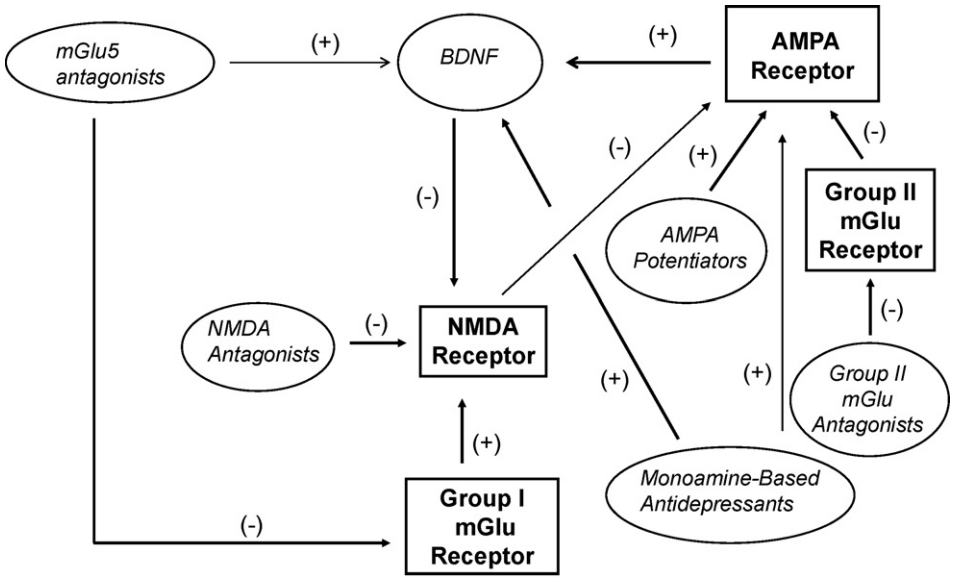

Fig. 1 – A model for the induction of antidepressant effects focusing on mGlu receptors. Ovals represent compounds, drugs, or chemical entities that can interact with receptors (squares). Plus signs represent biological interactions that are excitatory whereas minus signs represent biological interactions that are inhibitory. As with monoamine-based antidepressants, the mGlu receptors likely impact antidepressant-like biological responses through the dampening of NMDA receptor function and the amplification of AMPA receptor function. Data supporting this model are in the text and predominantly outlined in Section 5. The model is uncertain in a number of places due to limited data (non-bold arrows). There is very limited information on the specific mechanisms responsible for antidepressant-like effects of the group III mGlu receptors and therefore, this class of mGlu receptors is not represented in the model. Additional details of the mechanisms (e.g. secondary biochemical pathways) contributing to these biochemical changes are not shown for clarity at this level.

appreciating the data relating mGlu receptors to the NMDA and AMPA receptors. Moreover, the model can be used to make specific predictions about pharmacological influences upon mood as discussed below. Highlighted in this schema are two major targets of downstream effects of antidepressant treatments: NMDA receptors and AMPA receptors. The preponderance of evidence points to antidepressant-like effects being engendered by NMDA receptor blockade and by AMPA receptor facilitation. While either alone might be sufficient for antidepressant effects, the data although scant, point to an interaction of these ionotropic glutamate receptors; NMDA receptor blockade ultimately facilitates AMPA receptors likely via glutamate efflux and AMPA receptor amplification dampens NMDA receptor function through brain-derived neurotrophic factor (BDNF). The mGlu receptors impact both NMDA and AMPA receptors such that these antidepressant-like impacts can be expressed by the appropriate ligand. Thus, mGlu5 and perhaps mGlu1 antagonists by blocking mGlu 5 and 1 receptors, respectively, produce functional blockade of NMDA receptors. These mGlu receptors also impact BDNF, which is purported to result in functional blockade of NMDA function. The group II mGlu receptor antagonists impact AMPA receptors and then through secondary activation of BDNF, NMDA receptor function can be modified. Data supporting this general thesis is presented above and discussed below.

The antidepressant-like effects of the group I mGlu receptor (mGlu1/5) antagonists might be related to the reduction of glutamatergic transmission produced by this mechanism. The mGlu5 antagonist MPEP inhibited glutamate release [72] by blocking presynaptically located mGlu5 receptors [73]. Stimulation of group I mGlu receptors potentiates ionotropic glutamate responses in various preparations including potentiation of NMDA currents [74]. Conversely, several lines of evidence suggest that mGlu5 receptor antagonists reduce NMDA receptor function in a number of brain areas [75]. Therefore, inhibition of mGlu5 receptors may lead to a decrease in NMDA receptor-mediated neurotransmission, producing a final effect functionally comparable to that evoked by NMDA receptor antagonists. NMDA receptor antagonists are known to display antidepressant-like activity as discussed below. Another mechanism by which group I antagonists might impact depression is through their action upon neurotrophic factors. Antidepressants can increase BDNF [76]. The generation of BDNF and its consequent impact upon neural cell integrity and neurogenesis has become a heuristic model of antidepressant drug action [12,77]. The group I mGlu receptors have been shown to impact this process although the molecular mechanisms of these effects remains obscure. Chronic treatment with MPEP and the tricyclic antidepressant desipramine both increased BDNF mRNA level in the rat hippocampus [78]. These data, linked with the data that increased BDNF levels decrease NMDA receptor function [71], provide an additional potential path to identifying mechanisms associated with the antidepressant-like efficacy of group I mGlu receptor antagonists.

This hypo-NMDA state hypothesis is reinforced by the finding that repeated MTEP reduced expression of the mRNA encoding the NR1 subunit of the NMDA receptor in the cingulate and piriform cortices [79].

Data also implicate the cooperation of mGlu5 antagonism with monoaminergic systems. MPEP produced several neuroendocrine responses typical of conventional monoamine-based antidepressants, including an increase in plasma corticosterone after acute injection (the effect was partially blocked with a 5-HT_{1A} antagonist) and desensitization of neuroendocrine responses stimulated by a 5-HT_{1A} agonist after repeated 5-day treatment [80]. Interactions of MPEP and MTEP with the noradrenergic system were also described; these compounds decreased basal and stress-induced norepinephrine efflux in rat cortex that suggested anxiolytic-like activity [81]. As both serotonergic and noradrenergic systems are closely related to the efficacy of monoamine-based antidepressants and anxiolytics, these monoaminergic effects of mGlu5 receptor antagonists might contribute to the antidepressant- and antianxiety-like effects of this class of compounds.

Although the specific role of mGlu2 versus mGlu3 receptors has not been defined, antagonism of group II mGlu receptors has also been shown to have antidepressant-like neurochemical and neurobehavioral effects predictive of antidepressant efficacy as summarized above [64]. Group II mGlu receptor antagonists exhibit antidepressant-like effects that might be related to BDNF induction arising through potentiation of AMPA receptors (involving serotonergic and/or dopaminergic enhancement) ([82], our unpublished data). Thus, mGlu2/3 receptor antagonism engenders antidepressant-like behavioral and neurochemical effects that are prevented by AMPA receptor antagonists as summarized above. These data fit with predictions that positive allosteric modulators of AMPA receptors (AMPA receptor potentiators) produce antidepressant-like behavioral and neurochemical effects [12]. These data also join with findings that the selective serotonin uptake inhibitor fluoxetine [83] and the tricyclic antidepressant imipramine [84] produce changes in the phosphorylation state of AMPA receptor subunit GluR1 that are conducive with increased current flow.

For the group III mGlu receptor agonists, reduced glutamate release might account for the biological effects of these agents [6]. Indeed, clinically used antidepressant drugs have been shown to reduce glutamate release in the brain. Such effects have been observed both *in vivo* and *in vitro* and after acute and/or chronic treatment with several antidepressants [85–87]. However, other mechanisms of group III mGlu receptors activation, including heterosynaptic inhibition of GABAergic neurotransmission and control of serotonin release [88,89] cannot be ruled out as mechanisms.

In addition, a number of pieces of data supporting the glutamate pathway of antidepressant mechanisms came from zinc research [90,91]. Zinc is a non-selective antagonist of the NMDA receptor complex and one of the potential mechanisms of antidepressant activity of zinc might be by direct antagonism of NMDA receptors ([91,92], our unpublished data). Additionally, zinc may act through antagonism of group I mGlu receptors or through potentiation of AMPA receptor activity, both of which could attenuate NMDA receptor function [91]. Induction of BDNF gene expression may also participate in the antidepressant-like effects of zinc [93].

The major breakthrough in the glutamate hypothesis of mood disorders has come recently with the disclosure of two clinical findings on the efficacy of the NMDA receptor antagonist ketamine in the treatment of antidepressant-refractory depression [3,4]. As noted above, group I mGlu receptor antagonists and AMPA receptor potentiators including the mGlu2/3 antagonists, impact NMDA receptor function in the direction predicted by the NMDA hypothesis of depression. Recent preclinical findings with ketamine have substantiated that a mechanism of action of the antidepressant-like effects of ketamine are through AMPA receptor facilitation [94].

NMDA receptors likely play a key role in the control of mood. Functional antagonists of NMDA receptors exhibit antidepressant-like effects in rodents, and the clinical efficacy of ketamine (an NMDA channel antagonist) was also demonstrated [3,4,14]. Chronic treatment with antidepressants (from a variety of classes including ECT) induced a reduction of NMDA receptor function; however, the mechanism of this effect is not quite clear [71,95–97]. Antidepressants might inhibit the function of NMDA receptors by increasing BDNF activity as proposed by Skolnick [71]. AMPA receptor potentiators also increase BDNF activity [12] and might thereby negatively impact NMDA receptor function. Group I mGlu receptor antagonists (particularly mGlu5) exhibit antidepressant-like activity that might be related to BDNF increases (through serotonergic enhancement) and/or through an indirect inhibition of NMDA receptor function ([2,78], our unpublished data).

Taken as a whole, these observations suggest a primitive system-based model that accounts for the antidepressant-like behavioral and biochemical data involving mGlu receptors, NMDA receptors, AMPA receptors, and monoamine-based antidepressant targets. The model points to the ways in which these sites interact to transduce these biological effects (Fig. 1). Other approaches to modeling such as neuroanatomical circuit views and more molecular views (secondary and tertiary biochemical/biophysical events) are also possible and have been attempted [12]. The present approach is meant to provide a wholistic view at the level of the receptor for making predictions of mood regulation. For example, the central impact of AMPA receptors on mood implicated by the model suggested the possibility that AMPA receptor activation by the antidepressant ketamine might have been the mechanism driving antidepressant response as recently reported in rodent models [94].

6. Summary and conclusions

The present commentary provides anatomical, physiological, behavioral, and neurochemical evidence supporting the hypothesis that mGlu receptors might be involved in the regulation of mood. The data also suggest that mGlu receptors might serve as molecular targets for the identification of novel antidepressants. In this regard, the present review focused on the evidence that is predictive of efficacy in humans. Neglected almost completely here has been the question of

adverse events. Although predictive data exist to suggest a number of potential safety issues (e.g. seizures, memory, etc.), the overall question of safety lies outside the scope of the current commentary and must ultimately, like efficacy, be demonstrated by clinical investigation. A simplified systems model suggesting how mGlu receptors might act in concert with other glutamate targets to affect mood is proposed. Overall, the model suggests that a dynamic interplay of NMDA receptor and AMPA receptor function might be critical pieces to both understanding and controlling mood disorders. Indeed, it is suggested that the dynamic interactive processes of NMDA receptor blockade and AMPA receptor amplification might be the key glutamatergic influence on mood.

REFERENCES

[1] Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive disorder. CNS Neurol Disord Drug Targets 2007;6:101–15.
[2] Witkin JM, Marek GJ, Johnson BG, Schoepp DD. Metabotropic glutamate receptors in the control of mood disorders. CNS Neurol Disord Drug Targets 2007;6:87–100.
[3] Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351–4.
[4] Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63:856–64.
[5] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–17.
[6] Cartmell J, Schoepp DD. Regulation of neurotransmitter release by metabotropic glutamate receptors. J Neurochem 2000;75:889–907.
[7] Pin JP, Duvoisin R. The metabotropic glutamate receptors: structure and functions. Neuropharmacology 1995;34:1–26.
[8] Schoepp DD. Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. J Pharmacol Exp Ther 2001;299:12–20.
[9] Bordi F, Ugolini A. Group I metabotropic glutamate receptors: implications for brain diseases. Prog Neurobiol 1999;59:55–79.
[10] Palucha A, Pilc A. Metabotropic receptor ligands as possible anxiolytic and antidepressant agents. Pharmacol Ther 2007;115:116–47.
[11] Swanson CJ, Bures M, Johnson MP, Linden AM, Monn JA, Schoepp DD. Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. Nat Rev Drug Discov 2005;4:131–44.
[12] Alt A, Nisenbaum ES, Bleakman D, Witkin JM. A role for AMPA receptors in mood disorders. Biochem Pharmacol 2006;71:1273–88.
[13] Bleakman D, Alt A, Witkin JM. AMPA receptors in the therapeutic management of depression. CNS Neurol Disord Drug Targets 2007;6:117–26.
[14] Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. Ann NY Acad Sci 2003;1003:250–72.
[15] Kew JN, Ducarre JM, Pflimlin MC, Mutel V, Kemp JA. Activity-dependent presynaptic autoinhibition by group II metabotropic glutamate receptors at the perforant path inputs to the dentate gyrus and CA1. Neuropharmacology 2001;40:20–7.
[16] Marino MJ, Conn PJ. Glutamate-based therapeutic approaches: allosteric modulators of metabotropic glutamate receptors. Curr Opin Pharmacol 2006;6:98–102.
[17] Schoepp DD, Wright R, Levine LR, Gaydos B, Potter WZ. LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress. Stress 2003;6:189–97.
[18] Porter RH, Jaeschke G, Spooren W, Ballard TM, Buttelmann B, Kolczewski S, et al. Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity. J Pharmacol Exp Ther 2005;315:711–21.
[19] Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat Med 2007;13:1102–7.
[20] Ferraguti F, Shigemoto R. Metabotropic glutamate receptors. Cell Tissue Res 2006;326:483–504.
[21] Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol 1997;37:205–37.
[22] Ikeda SR, Lovinger DM, Mccool BA, Lewis DL. Heterologous expression of metabotropic glutamate receptors in adult rat sympathetic neurons: subtype-specific coupling to ion channels. Neuron 1995;14:1029–38.
[23] Lujan R, Nusser Z, Roberts JDB, Shigemoto R, Somogyi P. Perisynaptic location of metabotropic glutamate receptors mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus. Eur J Neurosci 1996;8:1488–500.
[24] Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, et al. Coupling of mGluR/Homer and PSD-95 complexes by the shank family of postsynaptic density proteins. Neuron 1999;3:583–92.
[25] Benquet P, Gee CE, Gerber U. Two distinct signaling pathways upregulate NMDA receptor responses via two distinct metabotropic glutamate receptor subtypes. J Neurosci 2002;22:9679–86.
[26] Pilc A, Legutko B. The influence of prolonged antidepressant treatment on the changes in cyclic AMP accumulation induced by excitatory amino acids in rat cerebral cortical slices. Neuroreport 1995;7:85–8.
[27] Pilc A, Branski P, Palucha A, Tokarski K, Bijak M. Antidepressant treatment influences group I of glutamate metabotropic receptors in slices from hippocampal CA1 region. Eur J Pharmacol 1998;349:83–7.
[28] Bajkowska M, Branski P, Smialowska M, Pilc A. Effect of chronic antidepressant or electroconvulsive shock treatment on mGLuR1a immunoreactivity expression in the rat hippocampus. Pol J Pharmacol 1999;51: 539–41.
[29] Smialowska M, Szewczyk B, Branski P, Wieronska JM, Palucha A, Bajkowska M, et al. Effect of chronic imipramine or electroconvulsive shock on the expression of mGluR1a and mGluR5a immunoreactivity in rat brain hippocampus. Neuropharmacology 2002;42:1016–23.
[30] Papp M, Moryl E, Willner P. Pharmacological validation of the chronic mild stress model of depression. Eur J Pharmacol 1996;296:129–36.
[31] Wieronska JM, Branski P, Szewczyk B, Palucha A, Papp M, Gruca P, et al. Changes in the expression of metabotropic glutamate receptor 5 (mGluR5) in the rat hippocampus in an animal model of depression. Pol J Pharmacol 2001;3: 659–62.
[32] Tatarczynska E, Klodzinska A, Chojnacka-Wojcik E, Palucha A, Gasparini F, Kuhn R, et al. Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. Br J Pharmacol 2001;132:1423–30.
[33] Palucha A, Branski P, Szewczyk B, Wieronska JM, Klak K, Pilc A. Potential antidepressant-like effect of MTEP, a

potent and highly selective mGluR5 antagonist. Pharmacol Biochem Behav 2005;81:901–6.
[34] Belozertseva IV, Kos T, Popik P, Danysz W, Bespalov AY. Antidepressant-like effects of mGluR1 and mGluR5 antagonists in the rat forced swim and the mouse tail suspension tests. Eur Neuropsychopharmacol 2007;17: 172–9.
[35] Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 2005;29:571–625.
[36] Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci Biobehav Rev 2005;29:547–69.
[37] Li X, Need AB, Baez M, Witkin JM. Metabotropic glutamate 5 receptor antagonism is associated with antidepressant-like effects in mice. J Pharmacol Exp Ther 2006;319:254–9.
[38] Pilc A, Klodzinska A, Branski P, Nowak G, Palucha A, Szewczyk B, et al. Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. Neuropharmacology 2002;43:181–7.
[39] Ohishi H, Shigemoto R, Nakanishi S, Mizuno N. Distribution of the messenger RNA for a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat. Neuroscience 1993;53:1009–18.
[40] Tanabe Y, Nomura A, Masu M, Shigemoto R, Mizuno N, Nakanishi S. Signal transduction, pharmacological properties, and expression patterns of two rat metabotropic glutamate receptors, mGluR3 and mGluR4. J Neurosci 1993;13:1372–8.
[41] Ohishi H, Neki A, Mizuno N. Distribution of a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat and mouse: an immunohistochemical study with a monoclonal antibody. Neurosci Res 1998;30: 65–82.
[42] Shigemoto R, Kinoshita A, Wada E, Nomura S, Ohishi H, Takada M, et al. Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. J Neurosci 1997;17:7503–22.
[43] Ohishi H, Shigemoto R, Nakanishi S, Mizuno N. Distribution of the mRNA for a metabotropic glutamate receptor (mGluR3) in the rat brain: an in situ hybridization study. J Comp Neurol 1993;335:252–66.
[44] Kilbride J, Huang LQ, Rowan MJ, Anwyl R. Presynaptic inhibitory action of the group II metabotropic glutamate receptor agonists, LY354740 and DCG-IV. Eur J Pharmacol 1998;356:149–57.
[45] Higgins GA, Ballard TM, Kew JN, Richards JG, Kemp JA, Adam G, et al. Pharmacological manipulation of mGlu2 receptors influences cognitive performance in the rodent. Neuropharmacology 2004;46:907–17.
[46] Schaffhauser H, Knoflach F, Pink JR, Bleuel Z, Cartmell J, Goepfert F, et al. Multiple pathways for regulation of the KCl-induced [3H]-GABA release by metabotropic glutamate receptors, in primary rat cortical cultures. Brain Res 1998;782:91–104.
[47] Neale SA, Salt TE. Modulation of GABAergic inhibition in the rat superior colliculus by a presynaptic group II metabotropic glutamate receptor. J Physiol 2006;577:659–69.
[48] Matrisciano F, Storto M, Ngomba RT, Cappuccio I, Caricasole A, Scaccianoce S, et al. Imipramine treatment up-regulates the expression and function of mGlu2/3 metabotropic glutamate receptors in the rat hippocampus. Neuropharmacology 2002;42:1008–15.
[49] Matrisciano F, Scaccianoce S, Del Bianco P, Panaccione I, Canudas AM, Battaglia G, et al. Metabotropic glutamate receptors and neuroadaptation to antidepressants: imipramine-induced down-regulation of beta-adrenergic receptors in mice treated with metabotropic glutamate 2/3 receptor ligands. J Neurochem 2005;93:1345–52.
[50] Katz MM, Tekell JL, Bowden CL, Brannan S, Houston JP, Berman N, et al. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. Neuropsychopharmacology 2004;29:566–79.
[51] Kawashima N, Karasawa J, Shimazaki T, Chaki S, Okuyama S, Yasuhara A, et al. Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors. Neurosci Lett 2005;378:131–4.
[52] Karasawa J, Shimazaki T, Kawashima N, Chaki S. AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist. Brain Res 2005;1042:92–8.
[53] Karasawa J, Yoshimizu T, Chaki S. A metabotropic glutamate 2/3 receptor antagonist, MGS0039, increases extracellular dopamine levels in the nucleus accumbens shell. Neurosci Lett 2006;393:127–30.
[54] Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301:805–9.
[55] Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology 2001;25:836–44.
[56] Yoshimizu T, Chaki S. Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039. Biochem Biophys Res Commun 2004;315:493–6.
[57] Bai F, Bergeron M, Nelson DL. Chronic AMPA receptor potentiator (LY451646) treatment increases cell proliferation in adult rat hippocampus. Neuropharmacology 2003;44:1013–21.
[58] Chaki S, Yoshikawa R, Hirota S, Shimazaki T, Maeda M, Kawashima N, et al. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. Neuropharmacology 2004;46:457–67.
[59] Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology 1995;121:66–72.
[60] Kenny PJ, Gasparini F, Markou A. Group II metabotropic and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate glutamate receptors regulate the deficit in brain reward function associated with nicotine withdrawal in rats. J Pharmacol Exp Ther 2003;306:1068–76.
[61] Barr AM, Markou A. Psychostimulant withdrawal as an inducing condition in animal models of depression. Neurosci Biobehav Rev 2005;29:675–706.
[62] Yoshimizu T, Shimazaki T, Ito A, Chaki S. An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats. Psychopharmacology 2006;186:587–93.
[63] Morishima Y, Miyakawa T, Furuyashiki T, Tanaka Y, Mizuma H, Nakanishi S. Enhanced cocaine responsiveness and impaired motor coordination in metabotropic glutamate receptor subtype 2 knockout mice. Proc Natl Acad Sci 2005;102:4170–5.
[64] Witkin JM, Eiler WJA. Antagonism of metabotropic glutamate group II receptors in the potential treatment of neurological and neuropsychiatric disorders. Drug Dev Res 2006;67:757–69.
[65] Wieronska JM, Klak K, Palucha A, Branski P, Pilc A. Citalopram influences mGlu7, but not mGlu4 receptors expression in the rat brain hippocampus and cortex.. Brain Res 2007;1184:88–95.

[66] Tatarczynska E, Palucha A, Szewczyk B, Chojnacka-Wojcik E, Wieronska J, Pilc A. Anxiolytic- and antidepressant-like effects of group III metabotropic glutamate agonist (1S, 3R, 4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I) in rats. Pol J Pharmacol 2002;54:707–10.
[67] Palucha A, Tatarczynska E, Branski P, Szewczyk B, Wieronska JM, Klodzinska A, et al. Group III mGlu receptor agonists produce anxiolytic- and antidepressant-like effects after central administration in rats. Neuropharmacology 2004;46:151–9.
[68] Klak K, Palucha A, Branski P, Sowa M, Pilc A. Combined administration of PHCCC, a positive allosteric modulator of mGlu4 receptors and ACPT-I, mGlu III receptor agonist evokes antidepressant-like effects in rats. Amino Acids 2007;32:169–72.
[69] Cryan JF, Kelly PH, Neijt HC, Sansig G, Flor PJ, van der PH. Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. Eur J Neurosci 2003;17:2409–17.
[70] Palucha A, Klak K, Branski P, Putten H, Flor P, Pilc A. Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. Psychopharmacology 2007;194:555–62.
[71] Skolnick P. Antidepressants for the new millennium. Eur J Pharmacol 1999;375:31–40.
[72] Thomas LS, Jane DE, Gasparini F, Croucher MJ. Glutamate release inhibiting properties of the novel mGlu(5) receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP): complementary in vitro and in vivo evidence. Neuropharmacology 2001;41:523–7.
[73] Thomas LS, Jane DE, Harris JR, Croucher MJ. Metabotropic glutamate autoreceptors of the mGlu(5) subtype positively modulate neuronal glutamate release in the rat forebrain in vitro. Neuropharmacology 2000;39:1554–66.
[74] Ugolini A, Corsi M, Bordi F. Potentiation of NMDA and AMPA responses by the specific mGluR5 agonist CHPG in spinal cord motoneurons. Neuropharmacology 1999;38:1569–76.
[75] Attucci S, Carla V, Mannaioni G, Moroni F. Activation of type 5 metabotropic glutamate receptors enhances NMDA responses in mice cortical wedges. Br J Pharmacol 2001;132:799–806.
[76] Vaidya VA, Duman RS. Depression-emerging insights from neurobiology. Br Med Bull 2001;57:61–79.
[77] Tanis KQ, Newton SS, Duman RS. Targeting neurotrophic/growth factor expression and signaling for antidepressant drug development. CNS Neurol Disord Drug Targets 2007;6:151–60.
[78] Legutko B, Szewczyk B, Pomierny-Chamioło L, Nowak G, Pilc A. Effect of MPEP treatment on brain-derived neurotrophic factor gene expression. Pharmacol Rep 2006;58:427–30.
[79] Cowen MS, Djouma E, Lawrence AJ. The metabotropic glutamate 5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine reduces ethanol self-administration in multiple strains of alcohol-preferring rats and regulates olfactory glutamatergic systems. J Pharmacol Exp Ther 2005;315:590–600.
[80] Bradbury MJ, Giracello DR, Chapman DF, Holtz G, Schaffhauser H, Rao SP, et al. Metabotropic glutamate receptor 5 antagonist-induced stimulation of hypothalamic–pituitary–adrenal axis activity: interaction with serotonergic systems. Neuropharmacology 2003;44:562–72.
[81] Page ME, Szeliga P, Gasparini F, Cryan JF. Blockade of the mGlu5 receptor decreases basal and stress-induced cortical norepinephrine in rodents. Psychopharmacology 2005;179:240–6.
[82] Gewirtz JC, Chen AC, Terwilliger R, Duman RC, Marek GJ. Modulation of DOI-induced increases in cortical BDNF expression by group II mGlu receptors. Pharmacol Biochem Behav 2002;73:317–26.
[83] Svenningsson P, Tzavara ET, Witkin JM, Fienberg AA, Nomikos GG, Greengard P. Involvement of striatal and extrastriatal DARPP-32 in biochemical and behavioral effects of fluoxetine (Prozac). Proc Natl Acad Sci 2002;99:3182–7.
[84] Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, et al. The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. Neuropsychopharmacology 2007;32:793–802.
[85] Prikhozhan AV, Kovalev GI, Raevskii KS. Effects of antidepressive agents on glutamatergic autoregulatory presynaptic mechanism in the rat cerebral cortex. Biull Eksp Biol Med 1990;110:624–6.
[86] Golembiowska K, Dziubina A. Effect of acute and chronic administration of citalopram on glutamate and aspartate release in the rat prefrontal cortex. Pol J Pharmacol 2000;52:441–8.
[87] Bonanno G, Giambelli R, Raiteri L, Tiraboschi E, Zappettini S, Musazzi L, et al. Chronic antidepressants reduce depolarization-evoked glutamate release and protein interactions favoring formation of SNARE complex in hippocampus. J Neurosci 2005;25:3270–9.
[88] Gereau RW, Conn PJ. Multiple presynaptic metabotropic glutamate receptors modulate excitatory and inhibitory synaptic transmission in hippocampal area CA1. J Neurosci 1995;15:6879–89.
[89] Marek GJ, Wright RA, Schoepp DD, Monn JA, Aghajanian GK. Physiological antagonism between 5-hydroxytryptamine(2A) and group II metabotropic glutamate receptors in prefrontal cortex. J Pharmacol Exp Ther 2000;292:76–87.
[90] 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;55:1143–7.
[91] Nowak G, Szewczyk B, Pilc A. Zinc and depression. An update. Pharmacol Rep 2005;57:713–8.
[92] Nowak G, Szewczyk B, Wieronska JM, Branski P, Palucha A, Pilc A, et al. Antidepressant-like effects of acute and chronic treatment with zinc in forced swim test and olfactory bulbectomy model in rats. Brain Res Bull 2003;61:159–64.
[93] Nowak G, Legutko B, Szewczyk B, Papp M, Sanak M, Pilc A. Zinc treatment induces cortical brain-derived neurotrophic factor gene expression. Eur J Pharmacol 2004;492:57–9.
[94] Maeng S, Zarate Jr CA, Du J, Schloesser RJ, McCammon J, Chen G, et al. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol Psychiatry 2007. epub.
[95] Harkin A, Nowak G, Paul IA. Noradrenergic lesion antagonizes desipramine-induced adaptation of NMDA receptors. Eur J Pharmacol 2000;389:187–92.
[96] Paul IA, Nowak G, Layer RT, Popik P, Skolnick P. Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. J Pharmacol Exp Ther 1994;269:95–102.
[97] Popik P, Wróbel M, Nowak G. Chronic treatment with antidepressants affects glycine/NMDA receptor function: behavioral evidence. Neuropharmacology 2000;39:2278–87.