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Chapter

GROUP I AND GROUP II METABOTROPIC GLUTAMATE RECEPTORS: ROLE IN PATHOPHYSIOLOGY AND TREATMENT OF MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Major depressive disorder (MDD) is a chronic, recurring illness with a lifetime prevalence of 16.5% in the United States (1). For the past 50 years, drugs that increase the synaptic availability of monoamines (norepinephrine, serotonin, and dopamine) have been used to treat depression (2). However, these traditional antidepressants take at least 2 weeks for meaningful improvement in core depressive symptoms, suggesting that downstream neural adaptations as a result of monoaminergic elevation may be more responsible for therapeutic effects. Recently, the role of the glutamatergic system in the pathophysiology and treatment of depression has received increased attention. Disruptions within the glutamatergic system have been observed in individuals suffering from depression, particularly abnormalities in glutamate/glutamine cycling and glutamate receptors. Furthermore, elevated levels of mGluR2/3 and reduced levels of mGluR5 protein have been demonstrated in the prefrontal cortex of patients with MDD, and drugs targeting Group I and Group II mGluRs have shown promise in preclinical studies. This chapter will review Group I and Group II metabotropic glutamate receptors, their role in the pathophysiology of depression, and new potential avenues for treatment.

Keywords: metabotropic glutamate receptors, major depressive disorder, mGluR1, mGluR5, mGluR2/3, glutamate, antidepressant

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INTRODUCTION

Major depressive disorder (MDD) is the most commonly occurring mood disorder in both the United States and European countries with a prevalence rate of 7.1% and 6.9%, respectively (3, 4). Due to the prevalence, MDD has created a substantial economic burden for these countries as well as others worldwide. For example, the total economic burden costs was USD$83.1 billion for the United States in 2000 (5) and €105.6 billion for European countries in 2004 (6). Despite the availability of treatment, the World Health Organization has estimated that MDD will be the second leading cause of disability worldwide by 2020 (7). For more than 50 years, drugs that increase levels of monoamines (norepinephrine, serotonin, and dopamine) at the synapse, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants have been used to treat depression (2). The primary mechanism of these antidepressant drugs is increasing the presence of monoamines in the synapse, allowing for greater postsynaptic cell activation. Most the clinically available antidepressant drugs work through the same mechanisms of action. However, a major limitation with the current antidepressant drugs is the delayed onset (4-12 weeks) before symptom remission (8). This suggests that downstream neuronal adaptations, likely a result of increased synaptic monoamines, may be responsible for therapeutic effects (9). As such, efforts to develop more effective antidepressants with fewer side effects and faster onset of clinical benefits have begun to target alternative neural systems.

GLUTMATE DYSFUNCTION IN MDD

The glutamatergic system has emerged as a potential target to improve clinical efficacy and onset of remission for the treatment of MDD. Both clinical and postmortem research has provided evidence of glutamatergic dysfunction in patients diagnosed with MDD (See **Table 1**). For example, elevated levels of glutamate, glutamine, and glycine have been found patients with MDD using indirect measures such as plasma, serum, or cerebrospinal fluid (10-16). Interestingly, antidepressant treatment has been found to reduce the elevated serum glutamate levels in MDD patients (17). Hashimoto and colleagues found elevated levels of glutamate in the frontal cortex of postmortem tissue from patients with MDD (18). Additionally, the glia high affinity glutamate transporter (EAAT2), the main source the glutamate reuptake, has been shown to be down-regulated in the postmortem brain tissue in MDD patients (19, 20). In contrast, several studies have found reduced levels of excitatory amino acids (i.e. glutamate, glutamine, and glycine) using the same direct measures mentioned above (10, 21, 22). These indirect measures of glutamate in CSF, plasma, and serum are difficult to interpret, as these disruptions may be due to medication, metabolic effects, or the inability of these methods to distinguish between central and peripheral glutamate. As such, proton magnetic resonance spectroscopy (^{1}H-

MRS) has been used to more directly measure neurotransmitter concentration, specifically glutamate and glutamine, in adults with severe depression. ^{1}H-MRS studies have shown increased glutamate levels in the occipital cortex (23), but reduced Glx (glutamate and glutamine) in the anterior cingulate cortex (24, 25), amygdala (26), hippocampus (27), left dorsolateral prefrontal cortex (28), dorsomedial and ventromedial prefrontal cortex (29) of adult MDD patients. Moreover, a 19% reduction in glutamate and glutamine has been observed in adolescent patients with severe MDD (30).

Table 1. Evidence for glutamate system dysfunction in patients with MDD

Interest	Region of Analysis	Change	Reference
Glutamate/ Glutamine	Serum	Increased	(11)
		No difference	(17)
	Plasma	Increased	(10) (13) (14) (15)
	CSF	Increased	(16) (12)
		Decreased	(22)
	Occipital cortex	Increased	(23)
	Anterior cingulate cortex	Decreased	(24) (25)
	Amygdala	Decreased	(26)
	Hippocampus	Decreased	(27)
	Dorsolateral prefrontal cortex	Decreased	(28)
	Dorsomedial and ventromedial prefrontal cortex	Decreased	(29)
mGluR5	Hippocampus, frontal, temporal, and parietal cortices	Decreased	(31)
mGluR2/3	Prefrontal cortex	Increased	(32)

In combination with significant alterations in glutamate, levels of glutamatergic receptor expression are altered in patients with MDD. In addition to differences in N-methyl-D-aspartate (NMDA) receptor levels (33-35), several studies have shown a reduction in the expression of type 5 metabotropic glutamate receptors (mGluR5) in patients diagnosed with MDD. A positron emission tomography (PET) scan study found a decrease in mGuR5 distribution volume ratio (DVR) in multiple brain regions including the frontal, temporal, and parietal cortices (31). Specifically, the study found an 8.8% decrease in DVR for the prefrontal cortex (Brodmann's area 10) in MDD patients compared to healthy controls. In a complementary study using postmortem tissue, this same research group found a reduction in mGluR5 expression in the prefrontal cortex. Together these results suggest the reductions in DVR are likely due to a reduction in mGluR5 expression. Furthermore, the PET scan study revealed that mGluR5 binding in the hippocampus negatively correlated with the depressive symptoms

(31). Disruptions have also been reported within Group II mGluRs in MDD patients. In a postmortem analysis of MDD patient brain tissue, compared to healthy controls patients with MDD had a 67% increase in type 2/3 mGluRs (mGluR2/3) expression in the prefrontal cortex (32).

Taken together, these results may suggest a bi-directional glutamatergic dysfunction in MDD, with disruptions both in glutamate/glutamine cycling and glutamatergic receptor expression.

GLUTAMATE AND mGluR PHYSIOLOGY

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS), and is present at over 60% of synapses. The fact that glutamate acts as a rapid excitatory transmitter, combined with its prevalence, suggests that it may be involved in abnormal circuitries, and may facilitate or even cause disease symptoms.

Like many neurotransmitters, glutamate acts on two types of receptors, ionotropic and metabotropic. Ionotropic glutamate receptors include α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and NMDA receptors. These receptors are ion channels that are permeable to cations, and function by allowing Na^+ and Ca^{2+} to enter the cell, thus causing depolarization and other intracellular changes. Eight subtypes of metabotropic glutamate receptors (mGluR1-8) are divided into Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) based upon their homology and function. These receptors are G-protein-coupled receptors (GPCRs), and function by either influencing intracellular second messenger formation, and/or releasing G protein subunits which influence ion channel activity (36-38). Since assessing all glutamate receptors and their implications with major depressive disorder would be outside the scope of this chapter, we will focus only on Group I and Group II metabotropic receptors.

mGluRs are densely expressed in areas of the brain necessary for cognition, such as the PFC, striatum and hippocampus (39). Group I mGluRs (mGluR1 and mGluR5) are usually found postsynaptically (40-42), and generally function to enhance glutamatergic excitation. Their intracellular signaling mechanisms stimulate phospholipase C (PLC) which forms diacylglycerol (DAG) and inositol triphosphate (IP_3). DAG activates protein kinase C (PKC), while IP_3 exerts further downstream effects by binding to receptors on the endoplasmic reticulum causing intracellular Ca^{2+} release. PKC exerts further downstream effects by phosphorylating CREB and other signaling molecules which can eventually lead to altered gene transcription (40-42).

mGluR5 receptors are physically linked to NMDA receptors through their intracellular anchors such as post synaptic density (PSD) proteins and synaptic

associated protein (SAP) 102 (43). Through its activation of PKC, mGluR5 activation also increases the phosphorylation of NMDA receptor subunits, thereby indirectly increasing the probability of NMDA receptor channel opening. This physical and biochemical connection allows the stimulation of Group I mGluRs to activate NMDA receptors without inducing desensitization or excitotoxicity (44, 45). Increased NMDA receptor functioning may benefit cognition via the upregulation of AMPA receptors which facilitate learning and memory through strengthening LTP (46).

Group II mGluRs include mGluR2 and mGluR3. Unlike Group I mGluRs, Group II mGluRs are predominantly located presynaptically (40-42). Additionally, the intracellular signaling mechanisms of Group II mGluRs involve releasing inhibitory G protein subunits (G_i/G_o), which inhibit adenylate cyclase (AC) and reduce the formation of cyclic adenosine monophosphate (cAMP), which ultimately results in reduced neurotransmitter release (40-42).

Glutamate acts as the endogenous ligand to all mGluRs, however numerous antagonist and agonist ligands have been synthesized to bind to the orthogonal binding site of mGluRs (47). Also, numerous positive (PAMs) and negative (NAMs) allosteric modulators have been synthesized to bind within the GPCR transmembrane domains, which modulate receptor functioning by either potentiating or attenuating orthogonal binding (47).

ANIMAL MODELS OF DEPRESSION

While robust animal models of depression are lacking, there are some paradigms that have proven sensitive to clinically active antidepressant drugs and may provide insight into the pathophysiology of depression. Describing in detail the various animal models of depression is beyond the scope of this chapter (see (48) for detailed review).

Some models, such as olfactory bulbectomy, do not necessarily result in a depressive or anhedonic-like phenotype, but rather are characterized by their high predictive validity in that they produce distinct symptoms that are exclusively reversed by clinically effective antidepressant drugs. Other models, such as chronic mild stress, prenatal restraint stress, and chronic corticosterone administration, induce deficits in behavioral tasks that have been linked to anhedonia. The most common of these behavioral assays to screen for antidepressant activity include the forced swim test (FST) and tail suspension test (TST). In both assays, immobility has been construed as avolition or "behavioral despair", and many clinically relevant antidepressants have been shown to reduce immobility time.

DISRUPTIONS IN THE MGLUR SYSTEM AS A CONSEQUENCE OF ANIMAL MODELS OF DEPRESSION

In line with clinical data indicating disruptions in mGluR levels, preclinical studies have also found disruptions within both Group I and Group II mGluRs in animal models of depression (See **Table 2**). Chronic mild stress has been shown to upregulate mGluR5 in the CA1 region of the hippocampus while mGluR5 is downregulated in the CA3 region (49). Similarly, hippocampal mGluR5 levels are also reduced after prenatal restraint stress (50) and chronic corticosterone treatment (51), while hippocampal mGluR1a is upregulated after olfactory bulbectomy (52). Flinders Sensitive Line (FSL) rats are a putative genetic animal model of depression, with these spontaneously depressed rats showing many of the distinct features of MDD. Much like the receptor changes found in behavioral models of depression, FSL rats also display decreased mGluR5 density in a variety of brain regions, including the hippocampus, ventral tegmental area, and nucleus accumbens (53).

In addition to altering Group I mGluR expression, both olfactory bulbectomy and prenatal restraint stress reduce mGluR2/3 levels in the rodent hippocampus, while FSL rats similarly express reduced mGluR2/3 levels in the hippocampus (50, 52, 54).

Table 2. mGluR disruptions in animal models of depression.

Receptor	Model	Region(s)	Change	Reference
Group I				
mGluR1	OB	CA1	Increased	(52)
mGluR5	Chronic mild stress	CA1	Increased	(49)
		CA3	Decreased	
	Prenatal restraint stress	Hippocampus	Decreased	(50)
	Chronic corticosterone	Hippocampus	Decreased	(51)
	FSL	Hippocampus, VTA, NAC	Decreased	(53)
Group II				
mGluR2/3	OB	Hippocampus	Decreased	(52)
	Prenatal restraint stress	Hippocampus	Decreased	(50)
	FSL	Hippocampus	Decreased	(54)

mGluR=metabotropic glutamate receptor; OB=olfactory bulbectomy; FSL=Flinder's Sensitive Line; VTA=ventral tegmental area; NAC=nucleus accumbens

Overall, there has been very little work detailing mGluR disruptions in the various animal models of MDD, yet the studies that have been reported show distinct alterations within Group I and Group II receptor expression, in line with postmortem tissue from MDD patients.

DISRUPTIONS IN THE MGLUR SYSTEM AS A CONSEQUENCE OF CHRONIC ANTIDEPRESSANT ADMINISTRATION

In addition to the above-mentioned alterations in receptor expression within animal models, there are a handful of studies that have demonstrated significant alterations in mGluR expression as a result of chronic antidepressant treatment in both animal models of depression and normal, otherwise unmanipulated animals (See **Table 3**). Chronic imipramine treatment upregulates both mGluR1 and mGluR5 in the rat hippocampus and reverses olfactory bulbectomy-induced upregulation of mGluR1 (52, 55-57). However, while Group I mGluRs may be upregulated within the hippocampus after chronic antidepressant treatment, Zahorodna and Bijak (58) demonstrated that 14 days of twice daily imipramine (10 mg/kg, ip), hippocampal CA1 neurons attenuated the enhancing effect of dihydroxyphenylglycine (DHPG), a Group I mGluR agonist, on population spikes, depolarization, and decreased afterhypolarization. This indicates that while there may be alterations within the Group I mGluR distribution as a result of chronic antidepressant treatment, the potential decreased function of the receptors should not be ignored.

Table 3. Effects of chronic antidepressant treatment in animals

Receptor	Region(s)	Drug	Change	Reference
Group I	CA1	Imipramine	Decreased function	(58)
mGluR1	Hippocampus	Imipramine	Increased	(56) (55)
	Hippocampus	Amitriptyline	Recovered OB-induced increase	(52)
mGluR5	Hippocampus	Imipramine	Increased	(57)
Group II				
mGluR2/3	Prefrontal cortex	Fluoxetine	None	(32)
	Hippocampus, nucleus accumbens, cortex, striatum	Imipramine	Increased	(55)
	Hippocampus	Amitriptyline	Recovered OB-induced decrease	(52)

mGluR=metabotropic glutamate receptor; OB=olfactory bulbectomy

Thus far, there have been only three reports of chronic antidepressant treatment on Group II mGluRs. In one study, rhesus monkeys were treated chronically with fluoxetine to determine if the previously mentioned mGluR2/3 increases found in human postmortem tissue were a result of antidepressant medication, but no significant changes were found between fluoxetine and placebo treated monkeys. However, others demonstrated widespread mGluR2/3 upregulation following chronic imipramine treatment, with increased expression

in the hippocampus, nucleus accumbens, cortex, and corpus striatum (55). Similarly, the decreased expression of mGluR2/3 in mice after olfactory bulbectomy has been reversed with chronic amitriptyline treatment (52). Interestingly, much like what has been observed with Group I mGluRs, chronic imipramine also inhibits the function of mGluR2/3 in cortical slices (59).

In light of these recent reports, it seems that the efficacy of SSRIs and tricyclic antidepressants may at least partially depend on alterations within the metabotropic glutamate receptor system. While there may be up or down regulation of receptor expression, it is important to note that chronic imipramine treatment has been demonstrated to inhibit both Group I and Group II mGluR receptor function. Thus, directly targeting or inhibiting these receptors may provide a novel avenue for treatment.

ANTIDEPRESSANT ACTIONS OF DRUGS THAT TARGET MGLURS

Due to the growing preclinical and clinical literature pointing to a key role of glutamatergic systems in the pathophysiology and treatment of MDD, and the disruptions within mGluRs in both MDD patients and preclinical models of depression, mGluRs have proven an attractive target for therapeutic intervention.

Thus far, drugs targeting mGluR1 have not received significant attention, in part due to their minimal disruption in the disorder (See **Table 4**). However, the mGluR1 antagonist 3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM) has been shown to reduce immobility and increase escape behaviors in the FST (60-62), while another mGluR1 antagonist, 1-aminoindan-1,5-dicarboxylic acid (AIDA), decreases immobility time in the TST (60, 63). mGluR5, on the other hand, is proving to be a more promising target. Tatarcsyńska and colleagues (64) first showed that the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) decreased immobility time in the TST, while having no effect in the FST. Others have shown that MPEP decreases immobility in both FST and TST, as well as reverses olfactory bulbectomy-induced passive avoidance deficits (60, 65-67). Another study reported decreased immobility in FST after acute MPEP, and decreased escape failures in a learned helplessness task after chronic MPEP administration (68). Another selective mGluR5 antagonist, 3-((2-methyl-1,3-thiazol-4-yl)ethyn yl)pyridine (MTEP), has been shown to decrease immobility in both TST and FST, and chronic MTEP administration reverses olfactory bulbectomy-induced deficits (69). Others have also found similar antidepressant effects of MTEP, including reduced immobility in FST and TST after acute treatment (60-62, 65). A later study demonstrated that these effects are dependent on mGluR5 interactions with NMDA receptors (70). Recently, a novel mGluR5 negative allosteric modulator, 4-(difluoromethoxy)-3-(pyridin-2-ylethynyl)phenyl)(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)methanone (GRN-529), has been synthesized, and it has also shown antidepressant activity in both TST and FST (71).

Table 4. Antidepressant effects of Group I mGluR compounds in preclinical models

Compound	Model/Test	Result	Reference
mGluR1 antagonists			
EMQMCM	FST	Decreased immobility	(60) (61, 62)
AIDA	TST	Decreased immobility	(63) (60)
mGluR5 antagonists			
MPEP	FST	Decreased immobility	(65) (68)
	TST	Decreased immobility	(60) (64)
	OB	Reversed passive avoidance deficits	(66) (67)
	Learned helplessness	Reduced escape failures	(68)
MTEP	FST	Decreased immobility	(60) (65) (61, 62) ´
	TST	Decreased immobility	(60) (69)
	OB	Reversed passive avoidance deficits	(69)
mGluR5 NAMs			
GRN-529	TST	Decreased immobility	(71)
	FST	Decreased immobility	(71)

mGluR=metabotropic glutamate receptor; NAM=negative allosteric modulator; FST=forced swim test; TST=tail suspension test; OB=olfactory bulbectomy

Similarly, there are limited data on the clinical efficacy of mGluR5 ligands for treating MDD. A 5-week double blind study evaluated the anxiolytic and antidepressant effects of fenobam, an mGluR5 NAM (72), in patients with severe anxiety. Fenobam produced both anxiolytic and antidepressant effects compared to vehicle by reducing anxiety and depression symptoms measured by the Hamilton Rating Scale for Anxiety and Hamilton Rating Scale for Depression, respectively (73). The AstraZeneca mGluR5 NAM AZD2066 underwent Phase II clinical trials, but AZD2066 was found to be no more effective for the treatment of MDD than controls (i.e., placebo and duloxetine). Importantly, no serious side effects were reported (see http://clinicaltrials.gov/ct2/show/study/NCT01145755). Roche also has developed an mGluR5 NAM (RO4917523) that has completed Phase II clinical trials for treatment-resistant patients with MDD (see http://clinicaltrials.gov/ct2/show/study/NCT00809562 – no data available). This same compound is currently undergoing Phase II clinical trials as an adjunctive therapy in patients with MDD and inadequate response to ongoing antidepressant treatment (see http://www.clinicaltrials.gov/ct2/show/NCT01437657).

Drugs targeting group II mGluRs are also receiving growing attention for possible MDD treatment, particularly for treatment resistant depression (TRD, see **Table 5**). Chronic corticosterone treatment has been heralded as a model for TRD, as traditional antidepressants such as fluoxetine or desipramine cannot

reverse anhedonic-like deficits (74). The mGluR2/3 antagonists MGS0039 and LY341495 have been shown to decrease the chronic corticosterone-induced increase in immobility in the FST (74, 75). These two compounds have also decreased immobility in both TST and FST in otherwise untreated rodents (76-78). Interestingly, AMPA and not serotonin receptor activation is required for these effects (76), and LY341495 induces intracellular pathways similar to those mediating the antidepressant efficacy of ketamine (79). A negative allosteric modulator of mGluR2/3 (RO4491533) has recently been developed, and both RO4491533 and LY341495 have been shown to decrease immobility time in both TST and FST in C57BL6/J and Helpless (a genetically selective strain of mice demonstrating a depression-like phenotype) mice (80).

mGluR2/3 NAMs and antagonists are also proceeding into clinical trials. The Roche mGluR2/3 NAM (RO4995819; a.k.a. RG1578) has undergone several safety and tolerability Phase I clinical trials (for full list see http://www.roche-trials.com/resultsByProductGet.action?productName=RO4995819), but no published results are currently available. Phase II clinical trials are underway to assess the effects of RO4995819 as an adjunctive treatment in patients with MDD and inadequate response to ongoing antidepressant treatment (see http://www.clinicaltrials.gov/ct2/show/NCT01457677). BrainCells Inc has developed an mGluR2/3 antagonist (BCI-632**;** a.k.a. MGS0039) and several prodrugs (BCI-838, BCI-1038, BCI-1206, BCI-1283) that have completed Phase I clinical trials (see http://clinicaltrials.gov/show/NCT01546051 or for full list see http://www.braincellsinc.com/pipeline/bci-632). These drugs have been shown to have poor gastrointestinal permeability resulting in low oral bioavailability.

Table 5. Antidepressant effects of Group II mGluR2/3 compounds in preclinical models

Compound	Model/Test	Result	Reference
Antagonists			
MGS0039	FST after chronic cort.	Decreased the increased immobility	(74)
	FST	Decreased immobility	(76) (78)
	TST	Decreased immobility	(78) (81)
	Learned helplessness	Decreased escape failures	(82)
LY341496	FST after chronic cort.	Decreased the increased immobility	(74) (75)
	FST	Decreased immobility	(80) (78) (77)

	TST	Decreased immobility	(80) (78) (79) (83)
NAMs			
RO4491533	FST	Decreased immobility	(80)
	TST	Decreased immobility	(80)

mGluR=metabotropic glutamate receptor; NAM=negative allosteric modulator; FST=forced swim test; TST=tail suspension test; cort.=corticosterone

CONCLUSION

In conclusion, there is mounting evidence for glutamatergic dysfunction within MDD. This includes circulating glutamate levels, NMDA and AMPA dysregulation (not reviewed here), and disruption of mGluR expression and function. Ultimately, both Group I and Group II mGluRs are proving to be very promising targets for therapeutic intervention in MDD.

Group I mGluR manipulation has demonstrated marginal success with the AstraZeneca mGluR5 NAM (AZD2066), which continued to Phase II clinical trials, but ultimately was found to be no more effective for the treatment of MDD than controls. Roche mGluR5 NAM (RO4917523) has shown great promise with the completion of Phase II clinical trials for treatment-resistant patients with MDD. At the time of this chapter, it is different to interpret the clinical efficacy of Group II mGluRs in patients with MDD because there is no detailed published data on the clinical trials that have been completed. Even with the lack of published results, the mGluR2/3 NAM (RO4995819) is currently undergoing Phase II clinical trials for the treatment of MDD suggesting positive results obtained during Phase I clinical trials.

Patients diagnosed with MDD have been shown to have both elevated and reduced levels of glutamate. As Group I and Group II mGluR ligands progress in treating the symptoms of MDD, a note of caution should be reported as well. Treatment of MDD with mGluR ligands may need to be individualized for each patient. MDD patients with reduced glutamate or an underactive glutamatergic system may not respond to mGluR5 NAM; however, these mGluR5 NAMs may be a promising treatment for a patient with elevated levels of glutamate. Additionally, previous and current antidepressant treatment may influence the efficacy of mGluR ligands. For example, chronic imipramine treatment produces an upregulation of Group I mGluRs, although their function may be reduced. As a final note, many variables, such as past antidepressant treatment history, responsiveness to placebo, or bioavailability issues may interfere with any positive results. Future studies are necessary to clarify how the glutamate systems pathophysiology relates to MDD.

REFERENCES

(1) Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289:3095-3105.

(2) Belmaker RH (2008) The future of depression psychopharmacology. CNS Spectr 13:682-687.

(3) Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU (2012) Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 21:169-184.

(4) Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 21:655-679.

(5) Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK (2003) The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 64:1465-1475.

(6) Andlin-Sobocki P, Rossler W (2005) Cost of psychotic disorders in Europe. Eur J Neurol 12 Suppl 1:74-77.

(7) Murray CJ, Lopez AD (1996) Evidence-based health policy--lessons from the Global Burden of Disease Study. Science 274:740-743.

(8) Uher R, Mors O, Rietschel M, Rajewska-Rager A, Petrovic A, Zobel A, Henigsberg N, Mendlewicz J, Aitchison KJ, Farmer A, McGuffin P (2011) Early and delayed onset of response to antidepressants in individual trajectories of change during treatment of major depression: a secondary analysis of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. J Clin Psychiatry 72:1478-1484.

(9) Hashimoto K (2011) The role of glutamate on the action of antidepressants. Prog Neuropsychopharmacol Biol Psychiatry 35:1558-1568.

(10) Altamura CA, Mauri MC, Ferrara A, Moro AR, D'Andrea G, Zamberlan F (1993) Plasma and platelet excitatory amino acids in psychiatric disorders. Am J Psychiatry 150:1731-1733.

(11) Kim JS, Schmid-Burgk W, Claus D, Kornhuber HH (1982) Increased serum glutamate in depressed patients. Arch Psychiatr Nervenkr 232:299-304.

(12) Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW (2000) Increased cerebrospinal fluid glutamine levels in depressed patients. Biol Psychiatry 47:586-593.

(13) Mauri MC, Ferrara A, Boscati L, Bravin S, Zamberlan F, Alecci M, Invernizzi G (1998) Plasma and platelet amino acid concentrations in patients affected by major depression and under fluvoxamine treatment. Neuropsychobiology 37:124-129.

(14) Mitani H, Shirayama Y, Yamada T, Maeda K, Ashby CR, Jr., Kawahara R (2006) Correlation between plasma levels of glutamate, alanine and serine

with severity of depression. Prog Neuropsychopharmacol Biol Psychiatry 30:1155-1158.

(15) Kucukibrahimoglu E, Saygin MZ, Caliskan M, Kaplan OK, Unsal C, Goren MZ (2009) The change in plasma GABA, glutamine and glutamate levels in fluoxetine- or S-citalopram-treated female patients with major depression. Eur J Clin Pharmacol 65:571-577.

(16) Garakani A, Martinez JM, Yehuda R, Gorman JM (2013) Cerebrospinal fluid levels of glutamate and corticotropin releasing hormone in major depression before and after treatment. J Affect Disord 146:262-265.

(17) Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpe S (1998) Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. Acta Psychiatr Scand 97:302-308.

(18) Hashimoto K, Sawa A, Iyo M (2007) Increased levels of glutamate in brains from patients with mood disorders. Biol Psychiatry 62:1310-1316.

(19) Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP, Myers RM, Bunney WE, Jr., Akil H, Watson SJ, Jones EG (2005) Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. Proc Natl Acad Sci U S A 102:15653-15658.

(20) Bernard R, Kerman IA, Thompson RC, Jones EG, Bunney WE, Barchas JD, Schatzberg AF, Myers RM, Akil H, Watson SJ (2011) Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. Mol Psychiatry 16:634-646.

(21) Altamura C, Maes M, Dai J, Meltzer HY (1995) Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. Eur Neuropsychopharmacol 5 Suppl:71-75.

(22) Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM (2007) Low cerebrospinal fluid glutamate and glycine in refractory affective disorder. Biol Psychiatry 61:162-166.

(23) Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL, Krystal JH, Mason GF (2004) Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. Arch Gen Psychiatry 61:705-713.

(24) Auer DP, Putz B, Kraft E, Lipinski B, Schill J, Holsboer F (2000) Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. Biol Psychiatry 47:305-313.

(25) Pfleiderer B, Michael N, Erfurth A, Ohrmann P, Hohmann U, Wolgast M, Fiebich M, Arolt V, Heindel W (2003) Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. Psychiatry Res 122:185-192.

(26) Michael N, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B (2003) Neurotrophic effects of electroconvulsive therapy: a proton magnetic resonance study of the left amygdalar region in patients with treatment-resistant depression. Neuropsychopharmacology 28:720-725.

(27) Block W, Traber F, von Widdern O, Metten M, Schild H, Maier W, Zobel A, Jessen F (2009) Proton MR spectroscopy of the hippocampus at 3 T in patients with unipolar major depressive disorder: correlates and predictors of treatment response. Int J Neuropsychopharmacol 12:415-422.

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

(29) Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC (2007) Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry 64:193-200.

(30) Mirza Y, Tang J, Russell A, Banerjee SP, Bhandari R, Ivey J, Rose M, Moore GJ, Rosenberg DR (2004) Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. J Am Acad Child Adolesc Psychiatry 43:341-348.

(31) Deschwanden A, Karolewicz B, Feyissa AM, Treyer V, Ametamey SM, Johayem A, Burger C, Auberson YP, Sovago J, Stockmeier CA, Buck A, Hasler G (2011) Reduced metabotropic glutamate receptor 5 density in major depression determined by [(11)C]ABP688 PET and postmortem study. Am J Psychiatry 168:727-734.

(32) Feyissa AM, Woolverton WL, Miguel-Hidalgo JJ, Wang Z, Kyle PB, Hasler G, Stockmeier CA, Iyo AH, Karolewicz B (2010) Elevated level of metabotropic glutamate receptor 2/3 in the prefrontal cortex in major depression. Prog Neuropsychopharmacol Biol Psychiatry 34:279-283.

(33) Beneyto M, Kristiansen LV, Oni-Orisan A, McCullumsmith RE, Meador-Woodruff JH (2007) Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. Neuropsychopharmacology 32:1888-1902.

(34) Feyissa AM, Chandran A, Stockmeier CA, Karolewicz B (2009) Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. Prog Neuropsychopharmacol Biol Psychiatry 33:70-75.

(35) Nudmamud-Thanoi S, Reynolds GP (2004) The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. Neurosci Lett 372:173-177.

(36) Pin JP, Duvoisin R (1995) The metabotropic glutamate receptors: structure and functions. Neuropharmacology 34:1-26.

(37) Schoepp DD, Conn PJ (2002) Metabotropic glutamate receptors. Pharmacol Biochem Behav 74:255-256.

(38) Schoepp DD, Conn PJ (1993) Metabotropic glutamate receptors in brain function and pathology. Trends Pharmacol Sci 14:13-20.

(39) Stefani MR, Moghaddam B (2010) Activation of type 5 metabotropic glutamate receptors attenuates deficits in cognitive flexibility induced by NMDA receptor blockade. Eur J Pharmacol 639:26-32.

(40) Cunningham MD, Ferkany JW, Enna SJ (1994) Excitatory amino acid receptors: a gallery of new targets for pharmacological intervention. Life Sci 54:135-148.
(41) Hollmann M, Heinemann S (1994) Cloned glutamate receptors. Annu Rev Neurosci 17:31-108.
(42) Ozawa S, Kamiya H, Tsuzuki K (1998) Glutamate receptors in the mammalian central nervous system. Prog Neurobiol 54:581-618.
(43) Lau CG, Zukin RS (2007) NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. Nat Rev Neurosci 8:413-426.
(44) Albensi BC (2007) The NMDA receptor/ion channel complex: a drug target for modulating synaptic plasticity and excitotoxicity. Curr Pharm Des 13:3185-3194.
(45) Hardingham GE, Bading H (2003) The Yin and Yang of NMDA receptor signalling. Trends Neurosci 26:81-89.
(46) Lu W, Man H, Ju W, Trimble WS, MacDonald JF, Wang YT (2001) Activation of synaptic NMDA receptors induces membrane insertion of new AMPA receptors and LTP in cultured hippocampal neurons. Neuron 29:243-254.
(47) Niswender CM, Conn PJ (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol 50:295-322.
(48) Cryan JF, Slattery DA (2007) Animal models of mood disorders: Recent developments. Curr Opin Psychiatry 20:1-7.
(49) Wieronska JM, Branski P, Szewczyk B, Palucha A, Papp M, Gruca P, Moryl E, Pilc A (2001) Changes in the expression of metabotropic glutamate receptor 5 (mGluR5) in the rat hippocampus in an animal model of depression. Pol J Pharmacol 53:659-662.
(50) Morley-Fletcher S, Mairesse J, Soumier A, Banasr M, Fagioli F, Gabriel C, Mocaer E, Daszuta A, McEwen B, Nicoletti F, Maccari S (2011) Chronic agomelatine treatment corrects behavioral, cellular, and biochemical abnormalities induced by prenatal stress in rats. Psychopharmacology (Berl) 217:301-313.
(51) Iyo AH, Feyissa AM, Chandran A, Austin MC, Regunathan S, Karolewicz B (2010) Chronic corticosterone administration down-regulates metabotropic glutamate receptor 5 protein expression in the rat hippocampus. Neuroscience 169:1567-1574.
(52) Wieronska JM, Legutko B, Dudys D, Pilc A (2008) Olfactory bulbectomy and amitriptyline treatment influences mGlu receptors expression in the mouse brain hippocampus. Pharmacol Rep 60:844-855.
(53) Kovacevic T, Skelin I, Minuzzi L, Rosa-Neto P, Diksic M (2012) Reduced metabotropic glutamate receptor 5 in the Flinders Sensitive Line of rats, an animal model of depression: an autoradiographic study. Brain Res Bull 87:406-412.
(54) Matrisciano F, Caruso A, Orlando R, Marchiafava M, Bruno V, Battaglia G, Gruber SH, Melchiorri D, Tatarelli R, Girardi P, Mathe AA, Nicoletti F (2008)

Defective group-II metaboropic glutamate receptors in the hippocampus of spontaneously depressed rats. Neuropharmacology 55:525-531.

(55) Matrisciano F, Storto M, Ngomba RT, Cappuccio I, Caricasole A, Scaccianoce S, Riozzi B, Melchiorri D, Nicoletti F (2002) Imipramine treatment up-regulates the expression and function of mGlu2/3 metabotropic glutamate receptors in the rat hippocampus. Neuropharmacology 42:1008-1015.

(56) Bajkowska M, Branski P, Smialowska M, Pilc A (1999) Effect of chronic antidepressant or electroconvulsive shock treatment on mGLuR1a immunoreactivity expression in the rat hippocampus. Pol J Pharmacol 51:539-541.

(57) Smialowska M, Szewczyk B, Branski P, Wieronska JM, Palucha A, Bajkowska M, Pilc A (2002) Effect of chronic imipramine or electroconvulsive shock on the expression of mGluR1a and mGluR5a immunoreactivity in rat brain hippocampus. Neuropharmacology 42:1016-1023.

(58) Zahorodna A, Bijak M (1999) An antidepressant-induced decrease in the responsiveness of hippocampal neurons to group I metabotropic glutamate receptor activation. Eur J Pharmacol 386:173-179.

(59) Palucha A, Branski P, Klak K, Sowa M (2007) Chronic imipramine treatment reduces inhibitory properties of group II mGlu receptors without affecting their density or affinity. Pharmacol Rep 59:525-530.

(60) Belozertseva IV, Kos T, Popik P, Danysz W, Bespalov AY (2007) Antidepressant-like effects of mGluR1 and mGluR5 antagonists in the rat forced swim and the mouse tail suspension tests. Eur Neuropsychopharmacol 17:172-179.

(61) Molina-Hernandez M, Tellez-Alcantara NP, Perez-Garcia J, Olivera-Lopez JI, Jaramillo-Jaimes MT (2008) Desipramine or glutamate antagonists synergized the antidepressant-like actions of intra-nucleus accumbens infusions of minocycline in male Wistar rats. Prog Neuropsychopharmacol Biol Psychiatry 32:1660-1666.

(62) Molina-Hernandez M, Tellez-Alcantara NP, Perez-Garcia J, Olivera-Lopez JI, Jaramillo-Jaimes MT (2008) Antidepressant-like actions of minocycline combined with several glutamate antagonists. Prog Neuropsychopharmacol Biol Psychiatry 32:380-386.

(63) Smolders I, Clinckers R, Meurs A, De Bundel D, Portelli J, Ebinger G, Michotte Y (2008) Direct enhancement of hippocampal dopamine or serotonin levels as a pharmacodynamic measure of combined antidepressant-anticonvulsant action. Neuropharmacology 54:1017-1028.

(64) Tatarczynska E, Klodzinska A, Chojnacka-Wojcik E, Palucha A, Gasparini F, Kuhn R, Pilc A (2001) Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. Br J Pharmacol 132:1423-1430.

(65) Li X, Need AB, Baez M, Witkin JM (2006) Metabotropic glutamate 5 receptor antagonism is associated with antidepressant-like effects in mice. J Pharmacol Exp Ther 319:254-259.

(66) Pilc A, Klodzinska A, Branski P, Nowak G, Palucha A, Szewczyk B, Tatarczynska E, Chojnacka-Wojcik E, Wieronska JM (2002) Multiple MPEP

administrations evoke anxiolytic- and antidepressant-like effects in rats. Neuropharmacology 43:181-187.

(67) Wieronska JM, Szewczyk B, Branski P, Palucha A, Pilc A (2002) Antidepressant-like effect of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist in the olfactory bulbectomized rats. Amino Acids 23:213-216.

(68) Liu CY, Jiang XX, Zhu YH, Wei DN (2012) Metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine produces antidepressant effects in rats: role of brain-derived neurotrophic factor. Neuroscience 223:219-224.

(69) Palucha A, Branski P, Szewczyk B, Wieronska JM, Klak K, Pilc A (2005) Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist. Pharmacol Biochem Behav 81:901-906.

(70) Palucha-Poniewiera A, Pilc A (2012) Involvement of mGlu5 and NMDA receptors in the antidepressant-like effect of acamprosate in the tail suspension test. Prog Neuropsychopharmacol Biol Psychiatry 39:102-106.

(71) Hughes ZA, Neal SJ, Smith DL, Sukoff Rizzo SJ, Pulicicchio CM, Lotarski S, Lu S, Dwyer JM, Brennan J, Olsen M, Bender CN, Kouranova E, Andree TH, Harrison JE, Whiteside GT, Springer D, O'Neil SV, Leonard SK, Schechter LE, Dunlop J, Rosenzweig-Lipson S, Ring RH (2013) Negative allosteric modulation of metabotropic glutamate receptor 5 results in broad spectrum activity relevant to treatment resistant depression. Neuropharmacology 66:202-214.

(72) Porter RH, Jaeschke G, Spooren W, Ballard TM, Buttelmann B, Kolczewski S, Peters JU, Prinssen E, Wichmann J, Vieira E, Muhlemann A, Gatti S, Mutel V, Malherbe P (2005) Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity. J Pharmacol Exp Ther 315:711-721.

(73) Pecknold JC, McClure DJ, Appeltauer L, Wrzesinski L, Allan T (1982) Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study. J Clin Psychopharmacol 2:129-133.

(74) Ago Y, Yano K, Araki R, Hiramatsu N, Kita Y, Kawasaki T, Onoe H, Chaki S, Nakazato A, Hashimoto H, Baba A, Takuma K, Matsuda T (2013) Metabotropic glutamate 2/3 receptor antagonists improve behavioral and prefrontal dopaminergic alterations in the chronic corticosterone-induced depression model in mice. Neuropharmacology 65:29-38.

(75) Koike H, Iijima M, Chaki S (2013) Effects of ketamine and LY341495 on the depressive-like behavior of repeated corticosterone-injected rats. Pharmacol Biochem Behav 107:20-23.

(76) Palucha-Poniewiera A, Wieronska JM, Branski P, Stachowicz K, Chaki S, Pilc A (2010) On the mechanism of the antidepressant-like action of group II mGlu receptor antagonist, MGS0039. Psychopharmacology (Berl) 212:523-535.

(77) Bespalov AY, van Gaalen MM, Sukhotina IA, Wicke K, Mezler M, Schoemaker H, Gross G (2008) Behavioral characterization of the mGlu group II/III receptor antagonist, LY-341495, in animal models of anxiety and depression. Eur J Pharmacol 592:96-102.

(78) Chaki S, Yoshikawa R, Hirota S, Shimazaki T, Maeda M, Kawashima N, Yoshimizu T, Yasuhara A, Sakagami K, Okuyama S, Nakanishi S, Nakazato A (2004) MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. Neuropharmacology 46:457-467.

(79) Koike H, Fukumoto K, Iijima M, Chaki S (2013) Role of BDNF/TrkB signaling in antidepressant-like effects of a group II metabotropic glutamate receptor antagonist in animal models of depression. Behav Brain Res 238:48-52.

(80) Campo B, Kalinichev M, Lambeng N, El Yacoubi M, Royer-Urios I, Schneider M, Legrand C, Parron D, Girard F, Bessif A, Poli S, Vaugeois JM, Le Poul E, Celanire S (2011) Characterization of an mGluR2/3 negative allosteric modulator in rodent models of depression. J Neurogenet 25:152-166.

(81) Karasawa J, Shimazaki T, Kawashima N, Chaki S (2005) AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist. Brain Res 1042:92-98.

(82) Yoshimizu T, Shimazaki T, Ito A, Chaki S (2006) An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats. Psychopharmacology (Berl) 186:587-593.

(83) Koike H, Iijima M, Chaki S (2011) Involvement of the mammalian target of rapamycin signaling in the antidepressant-like effect of group II metabotropic glutamate receptor antagonists. Neuropharmacology 61:1419-1423.