Published in final edited form as:

Biol Psychiatry. 2018 July 15; 84(2): 95–105. doi:10.1016/j.biopsych.2017.08.025.

mGluR5 and Stress Disorders: Knowledge Gained from Receptor Imaging Studies

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Abstract

The metabotropic glutamatergic receptor subtype 5 (mGluR5) may represent a promising therapeutic target for stress-related psychiatric disorders. Here, we describe mGluR5 findings in stress disorders, particularly major depressive disorder (MDD), highlighting insights from positron emission tomography (PET) studies. PET studies report either no differences or lower mGluR5 in MDD; potentially reflecting MDD heterogeneity. Unlike the rapidly acting glutamatergic agent ketamine, mGluR5-specific modulation has not yet shown antidepressant efficacy in MDD and bipolar disorder (BD). Although we recently showed that ketamine may work, in part, through significant mGluR5 modulation, the specific role of mGluR5 downregulation in ketamine's antidepressant response is unclear. In contrast to MDD, there has been much less investigation of mGluR5 in BD, yet initial studies indicate mGluR5-specific treatments may aid in both depressed and manic mood states. The direction of modulation needed may be state-dependent, however, limiting clinical feasibility. There has been relatively little study of post traumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD) to date, although there is evidence for the upregulation of mGluR5 in these disorders. However, while antagonism of mGluR5 may reduce fear conditioning, it may also reduce fear extinction. Therefore, studies are needed to determine the role mGluR5 modulation might play in the treatment of these conditions. Further challenges in modulating this prevalent neurotransmitter system include potential induction of significant side effects. As such, more research is needed to identify level and type (positive/negative allosteric

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modulation or full antagonism) of mGluR5 modulation required to translate existing knowledge into improved therapies.

Keywords

metabotropic glutamate receptor subtype 5; mGluR5; major depressive disorder; bipolar disorder; anxiety; positron emission tomography

Glutamate neurotransmission is regulated by ionotropic and G-protein coupled metabotropic glutamate receptors (mGluRs), which are divided into: group I (mGluR1 and 5), group II (mGluR2 and 3) and group III (mGluR4, 6, 7, 8)(1). mGluR5 specifically is located predominantly on post-synaptic neurons(2–4) on the cellular and intracellular membranes(5–7) of glutamatergic (excitatory) and gamma-aminobutyric acid-ergic (GABA-ergic, inhibitory) neurons and on glial cells in the perisynaptic space(8–10). Highest mGluR5 density in human is in the hippocampus and putamen, followed by the caudate and cerebral cortex (~10–15% lower than highest density regions), and thalamus (~45–50% lower than highest density regions), and lowest expression in the cerebellum (~65% lower than highest density regions)(11). mGluR5s are regulated by both positive and negative allosteric modulators (PAMs and NAMs, respectively) which potentiate or inhibit endogenous glutamate(12). PAMs enhance the activation of receptors or prevent agonist-related desensitization, while NAMs can be either non-competitive receptor antagonists or inverse agonists. Drugs that target mGluR5 may bring about a therapeutic effect through secondary N-methyl-D-aspartate receptor (NMDAR) modulation. Both NMDA and mGluR5 are localized closely on the cell surface and activation of mGluR5 potentiates NMDAR activity while mGluR5 NAMs potentiate the effects of NMDA receptor antagonists(13–16).

Here, we discuss the role of mGluR5 in stress-related disorders, providing information from preclinical and clinical studies. Clinical investigations include magnetic resonance spectroscopy (MRS), and, when available, we specifically highlight positron emission tomography (PET) studies. Further, we provide results from our recent investigations and, when conflicting, equivocal, or limited findings are presented, we present potential hypotheses that might unify results.

Quantifying mGluR5 with PET

PET can be used to quantify mGluR5 availability *in vivo*. (Note: Receptor function may not be directly related to availability.) Current mGluR5 radioligands bind to a site in the transmembrane domain of mGluR5 and not to the N-terminal orthosteric site where glutamate binds(17, 18). These radioligands are (*E*)-3-((6-methylpyridin-2-yl)ethynyl)cyclohex-2-en-1-one-*O*-[¹¹C]methyloxime ([¹¹C]ABP688(19)) and 3-[¹⁸F]fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile ([¹⁸F]FPEB(20)), which have differing advantages relating to quantification techniques and half-life of the isotope(17, 18). Both appear to target cell surface receptors only and are not able to penetrate the cell membrane to bind to internalized receptors(21). As such, it is expected that mGluR5 availability levels measured with PET *in vivo* reflect neural and glial mGluR5 levels in the perisynaptic or extrasynaptic space (22–24)

In PET studies, the outcome measure V_T (volume of distribution, a ratio of radiotracer in the regions of interest to that in the plasma) can be used. However, it is a combination of both specific (i.e. to mGluR5) and non-specific binding. There is no evidence that non-specific binding (which is the sum of nondisplaceable and free radiotracer, e.g. tracer not bound to mGluR5) differs in disease conditions from that of healthy controls, however, this has not been fully explored. When blood sampling is not performed, the outcome measure commonly used is *DVR* (distribution volume ratio, i.e., binding in the region relative to a reference region). *DVR* calculation requires the use of a reference region, assumed to be devoid of mGluR5 receptors. As such a region does not exist, caution must be taken when evaluating this outcome measure.

MOOD DISORDERS (Major Depressive Disorder – MDD, Bipolar Disorder – BD)

A review of 16 ^1H MRS studies (281 patients and 301 healthy subjects) reported significantly lower glutamate and GLX (combination of glutamate and glutamine) levels in individuals with MDD(25), although a smaller number of studies reported higher levels of glutamate in MDD(18, 26, 27) including our recent examination(18). A study using ^{13}C MRS in the occipital cortex did not detect differences in glutamate neurotransmission (which has been far less examined than glutamate levels) between control and MDD individuals. However, given the recent rise in techniques and modeling methods(28), and our ability to collect ^{13}C MRS data in the frontal cortical regions, it is likely that future neurotransmission studies will enhance our understanding of glutamate's role in mood disorders.

The relationship between glutamate levels and mGluR5 availability is complex, and unraveling this relationship is made more complicated by the method of assessing each. While PET measures neural and glial mGluR5 levels in the perisynaptic or extrasynaptic space;(22–24) ^1H -MRS assesses the total amount of glutamate within a “box” containing neuronal tissue, non-neuronal tissue, and extracellular fluid(29, 30). Using [^{18}F]FPEB PET and MRS, we did not detect significant between-group differences (MDD: n=30, healthy subjects: n=35) in mGluR5 availability using V_T or *DVR*.(18) However, we observed a negative association between mGluR5 and tissue glutamate, providing first potential evidence *in vivo* for the hypothesized excitotoxicity of receptors under conditions of elevated glutamate levels.(31) Or, alternatively, increases in glutamate led to mGluR5 internalization, yielding lower mGluR5 availability in line with our work showing downregulation in mGluR5 upon rapid increases in glutamate (see explanation below and Fig 1)(32, 33).

Similar to the lower(25, 34) and higher glutamate(18, 26, 27) (or related marker) levels reported, directionality of mGluR5 availability in depression varies across studies. The first *in vivo* report of mGluR5 availability in MDD (using [^{11}C]ABP688 PET, MDD: n=11, healthy subjects: n=11) reported 10–20% lower mGluR5 density in several brain regions using *DVR*(35). We recently reported a similar magnitude of mGluR5 availability changes in MDD using the same tracer, a similar cohort size (MDD: n=13, healthy subjects: n=13) and

the outcome measure V_T . However, our examination of mGluR5 availability using V_T or DVR (using [^{11}C]ABP688 PET, MDD: $n=20$, healthy subjects: $n=22$) did not provide support for lower mGluR5 associated with geriatric depression(36). Given that available data does not suggest age-related changes in mGluR5 *in vivo* in humans,(37, 38) the variability in the mGluR5 findings in MDD may be a reflection of the heterogeneity of the disorder, variability in comorbidity with anxiety-related disorders, or a reflection of the smaller sample sizes in the above-mentioned studies.

While postmortem work is in line with the *in vivo* imaging studies suggesting decreases or no differences in mGluR5 availability in MDD(35, 39, 40), preclinical studies repeatedly implicate reduced mGluR5 in the pathophysiology of depression(41). mGluR5 knockout mice exhibit depressive-like behavior(42) and rat models of depression show reductions in mGluR5 protein and density in various brain regions.(43, 44)

Glutamatergic dysfunction is also implicated in BD. In contrast to the majority of studies in MDD, higher GLX and glutamate levels are more commonly observed throughout the brain, and particularly in frontal areas (dorsolateral prefrontal cortex and ACC) in BD(45–51). This may point to differing pathophysiology between bipolar depression and MDD, or choice of regions examined. A challenge in evaluating this literature is that studies, including metaanalyses, in BD tend to group subjects across affective states, which may miss dynamic glutamate fluctuations. Such fluctuation has been reported by Xu et al.(49), with higher glutamate levels in the left thalamus during depression and lower glutamate levels in the posterior cingulate cortex during mania.

Differences in affective state and methodology further confound our understanding of the relationship between glutamate levels and mGluR5 in BD. Postmortem evaluation of mGluR5 demonstrated lower PFC (BA9) mRNA and protein expression as well as cerebellar mGluR5 protein expression in BD, as compared to MDD and controls(40). However, an autoradiography study did not observe significant differences in mGluR5 density in the ACC(39). Further, interestingly, a case report described symptoms of bipolar illness, including euphoria, impulsivity, psychomotor agitation and insomnia associated with deletion of the SHANK3 protein, a scaffold protein known to stabilize mGluR5 in the postsynaptic membrane of neurons (Fig 2)(52, 53). This provides evidence for potential mGluR5 alterations in BD; however, PET studies of mGluR5 have yet to be reported.

Treatment Trials

The most successful antidepressant glutamatergic treatment in MDD and BD to date is ketamine(54–72) including in elderly patients(73). Ketamine leads to numerous neurochemical changes including a rapid surge in glutamate immediately following administration(74–76). This glutamate surge increases AMPA receptor activation, which, coupled with ketamine's inhibition of extrasynaptic NMDA receptors, initiates and facilitates postsynaptic activation of neuroplasticity-related signaling pathways, including those involving BDNF and mTOR (for review, see (77))(56, 78).

Modulation of mGluR5, via the glutamate surge, may work synergistically with other ketamine-induced changes to elicit the antidepressant response. We therefore established a

PET paradigm to measure ketamine-induced mGluR5 changes(32). In this work, we found a downregulation of mGluR5 following ketamine (in both controls(32) and in MDD(33)), which we hypothesize to be related to the surge in glutamate (Fig 1). This downregulation contributed to the antidepressant response (individuals with the greatest improvement in mood symptoms exhibited the greatest decrease in mGluR5 availability). Interestingly, reductions in receptor availability persisted 24 hours after the ketamine infusion which may be among the persisting neuroadaptations that are associated with antidepressant effects beyond the glutamate surge(79). These sustained effects may rely on new protein synthesis and mTOR signaling pathways that lead to normalization of synaptic plasticity(80, 81) or pathways independent of mTOR(82). Although appearing counterintuitive (based on the potentially lower levels of mGluR5 in MDD), the direction of ketamine-induced modulation needed for the antidepressant effect is consistent with preclinical studies in which mGluR5 antagonism and internalization have also been associated with rapid, although not long lasting, antidepressant effects (see Supplementary Material)(83–85).

Recent preclinical evidence suggests that a metabolite of ketamine, (2S,6S;2R,6R)-hydroxynorketamine (HNK) may be necessary and sufficient for ketamine's antidepressant response.(86) The metabolite pathway is independent of NMDA receptors, acting through AMPA receptors to activate BDNF and mTOR pathways. Interestingly, even this independent pathway could affect mGluR5 downstream. Evidence from other studies suggests that AMPA receptor activation leads to changes in the mGluR5 signaling and facilitation of downstream effects(87). The eukaryotic elongation factor 2 (eEF2), part of the mGluR-eEF2-AMPA pathway,(88) also effects plasticity independent of mTOR and has been implicated in the antidepressant actions of ketamine(89). Thus, it appears that the mGluR5 might be common to several mechanisms by which ketamine leads to rapid antidepressant effects.

Based on the above evidence, we propose that the downstream effects of ketamine may be enhanced by mGluR5 to produce the antidepressant response. Specifically, the activation of mGluR5 activates the inositol phosphate signaling cascade, raising levels of IP3. mGluR5 effects are linked to the endoplasmic reticulum via Homer and Shank (see Figure 2), where IP3 causes the release of intracellular calcium stores, producing a variety of downstream effects(90) including activation of mTOR(78).

Metaanalyses have also shown ketamine to be effective in bipolar depression, though as an augmentation therapy(91). A randomized, placebo-controlled, double-blind, crossover, add-on study demonstrated that individuals with BD who were maintained on lithium or valproate and received an intravenous infusion of ketamine hydrochloride (0.5 mg/kg) showed an improvement in depressive symptoms as compared to those administered placebo(92). That finding was recently replicated in cohort of treatment-resistant BD patients(91).

In MDD, clinical trials of mGluR5-specific modulators have been undertaken. A phase II trial of AZD2066 (mGluR5 antagonist, 18 mg daily for 6 weeks) in patients with MDD (including treatment-resistant depression) reported that this drug was not superior to placebo(93). Similarly, a phase 2b double blind randomized clinical trial of Basimglurant

(mGluR5 NAM; modified release, at 0.5 or 1.5 mg) in 333 adult patients with MDD in combination with ongoing antidepressant treatment showed no difference from placebo in the primary outcome measure (change in Montgomery-Åsberg Depression Rating Scale, MADRS, score from baseline, assessed by the clinician). However, the higher dose did induce greater improvements in patient-rated end points(94).

The basimglurant trial highlights the importance of dose and a link currently missing in the evaluation of these medications. So far, mGluR5-specific antidepressants have failed to achieve the same efficacy as ketamine. This may be due to the synergistic effects of ketamine at other targets and/or due to the level of downregulation of mGluR5 induced by other treatments. We estimated a $14 \pm 10\%$ decrease in surface expression of mGluR5 following ketamine in a depressed cohort(32). Though multiple trials of mGluR5 specific drugs have been undertaken, none to date have evaluated the level of mGluR5 occupancy needed for clinical efficacy (as can be done with PET). Thus, important questions regarding the occupancy-response curve are left unknown. For example, a recent review suggested a dose-response relationship between mGluR5 occupancy and reductions in substance consumption in animal models(95). Further, [^{11}C]ABP688 PET was used to determine the AZD2066 plasma concentration estimated to achieve 50% occupancy in humans (1170 nM). (96) However, this PET study occurred after the reported clinical trial. Moreover, another important factor relating to the dose-occupancy relationship is the timing of doses. Studies on intermittent versus daily dosing are needed for glutamatergic agents, which will depend on route of delivery.(97, 98)

ANXIETY, OBSESSIVE COMPULSIVE DISORDER (OCD), and POST TRAUMATIC STRESS DISORDERS (PTSD)

There is a paucity of human studies involving mGluR5 and obsessive-compulsive disorder or post-traumatic stress disorder, which were formerly categorized as anxiety disorders before the introduction of the DSM-5. Two mGluR5 PET studies have evaluated MDD with comorbid anxiety. Consistent with preclinical work (see Supplementary Material), our recent examination(33) suggests that mGluR5 downregulation (decrease in V_T) is associated with reductions in anxiety symptoms in MDD. However, baseline anxiety symptoms in MDD(35) were previously found to be negatively correlated with [^{11}C]ABP688 *DVR*.

Using [^{18}F]FPEB PET, our group observed 20% higher mGluR5 availability (measured by V_T) in sixteen individuals with PTSD compared to controls, and the extent of mGluR5 dysregulation was related to increased avoidance symptoms, suggesting that targeting mGluR5 in PTSD might be particularly beneficial to treating this symptom domain.(99) In postmortem samples of 19 individuals with PTSD and 19 matched controls, we found no differences in mGluR5 availability; however, we observed a 3.8 fold upregulation of Shank1 in the PTSD group. Shank1 anchors mGluR5 to the cell surface, thus the observed PET finding of increased mGluR5 availability could reflect an upregulation of Shank1 (Figure 2). This change in mGluR5 localization might have an impact on psychological functioning.

In the one [^{11}C]ABP688PET study investigating the mGluR5 in OCD *in vivo* in humans no differences in mGluR5 availability (*DVR*) between 10 individuals with OCD and 10

matched controls were reported.(100) However, there was a positive correlation between mGluR5 and obsessive symptoms measured using Yale Brown Obsessive Compulsive Scale (Y-BOCS). These findings suggest that obsessions in particular may have an underlying glutamatergic pathology related to mGluR5, but further work is required. Interestingly, a recent study showed that chronic but not acute quinpirole administration, used to induce the quinpirole (QP) sensitization rat model for OCD, is associated with significant occupancy of mGluR5 (as measured by [¹¹C]ABP688).(101) Similarly, rodent studies indicate promising anxiolytic effects of mGluR5 modulation (see Supplementary Material).

Treatment Trials

In a double-blind, placebo-controlled clinical trial, fenobam was comparable to diazepam with respect to its efficacy and onset of action and was also shown to be useful in outpatients with severe anxiety symptoms(102). Although fenobam was considered promising agent in the treatment of anxiety with a good safety profile, as early as 1980, it was associated with troublesome side effects of a psychostimulant nature(103). Similarly, mGluR5 NAMs have not been successful thus far as clinical therapeutics, in part because of the induction of side effects, including psychotomimetic activity(102, 104).

To our knowledge, there have been no treatment trials in humans using potential mGluR5 targets in the treatment of PTSD. However, mGluR5 activation has been shown to contribute to stress-induced fear conditioning(105), antagonism of mGluR5 using MPEP blocks the acquisition and expression of conditioned fear(106), and ketamine (at 10 mg/kg but not 20 mg/kg) impaired fear memory reconsolidation;(107) all suggesting that mGluR5 may play some role in trauma-related memories in PTSD. (Although ketamine has many effects in addition to the recently implicated mGluR5 downregulation, which likely contribute to its efficacy.) Alternatively, MPEP has also been shown to prevent the extinction of contextual fear memory in mice(108, 109) and rats(110). Another study found that fear extinction was completely abolished in mGluR5 KO mice(111), suggesting that mGluR5 is required for adaptive learning in the context of fear extinction. Furthermore, administration of ADX47273 (a selective and potent mGluR5 PAM) enhanced extinction learning and improved reversal learning(112). Similarly, rodents identified as high novelty seekers (which is associated with higher mGluR5 V_T in humans(113)) required fewer sessions to achieve fear extinction(107) although equivocal evidence exists, as preclinical study related reduced mGluR5 in cortical neurons (due to ablation) with novelty seeking(114).

The above indicates differing roles for mGluR5 in fear-related processing relevant to PTSD. On the one hand, mGluR5 activity might underlie fear conditioning, and blocking mGluR5 disrupts the acquisition and expression of conditioned fear. However, blockade or knockout of mGluR5 also seems to interfere with fear extinction. Therefore, targeting the mGluR5 with an antagonist or NAM might reduce distress associated with PTSD, but might prolong the disorder through interference with fear extinction. A recent trial in mice partially validated this hypothesis by showing ketamine, administered prophylactically, reduced fear expression following fear conditioning; however, it was ineffective when administered following the conditioning or during extinction(115). This may be similar to what is seen with benzodiazepines in treating PTSD, where these medications can have initial anxiolytic

effects but are generally ineffective long-term(116). Further, this suggests that more study of mGluR5 is warranted, as the upregulation of surface mGluR5 we report in PTSD may exist prior to onset of the disorder, enhancing the potential for fear conditioning, as suggested by the rodent literature (consistent with an mGluR5 NAM or antagonist being effective in prevention of fear learning).

In the only randomized controlled trial to date, ketamine and midazolam were associated with rapid reductions in PTSD symptoms, but ketamine outperformed midazolam(117). Although mGluR5 was likely downregulated upon ketamine administration, the cascade of other downstream effects associated with ketamine administration may have rescued the blockade of fear extinction. Further studies with mGluR5-specific medications are warranted.

In OCD, a small crossover double-blind study of one ketamine dose was performed(118). Significant decreases in OCD symptoms (in individuals meeting diagnostic criteria for OCD but not for comorbid MDD), were observed, with 50% of individuals showing treatment response 1-week post dose. This suggests that ketamine may have an anti-OCD effect regardless of potential improvements in depressive symptoms. However, a recent study of mavoglurant (an mGluR5 antagonist) as an add-on treatment to SSRIs in patients with primary OCD was terminated due to lack of efficacy compared to placebo(119). Further study is therefore warranted as potential benefits of mGluR5 modulation in OCD are seen in rodents (see Supplementary Material).

SUMMARY AND COMMENTARY

The last decade or so has seen an increased interest in the glutamatergic system, and mGluR5 in particular, as targets for psychiatric conditions including stress related disorders (see Table 1). For this reason, the current review focused on studies of mGluR5, using PET when available. However, previous reviews have explored the structure, pharmacology and treatment target implications of all three metabotropic glutamate receptor groups.(41, 120–124) Focusing on mGluR5, the largest exploration has been performed with respect to MDD, where rodent models of MDD (and some *in vivo* MDD investigations) are associated with decreased mGluR5 expression. Yet, mGluR5 antagonists and NAMs appear to bring about an antidepressant response in these rodent models, likely via modulation of glutamatergic neurotransmission. Our work shows that mGluR5 availability is related to glutamate levels in depression, as well as following a drug challenge, suggesting normalization of glutamate neurotransmission via modulation at mGluR5 may be a needed component in treating some psychiatric disorders or symptoms.

Our *in vivo* investigations in MDD have been mixed (finding both lower or the same mGluR5 V_T in depressed subjects compared to controls), reflecting post mortem studies. This may be one reason mGluR5 NAMs (and PAMs) have yet to show widespread clinical efficacy. Further complicating the therapeutic potential, the direction of glutamatergic variation may vary, for example, through mood cycling in BD, where it is hypothesized that during bipolar depression, there is lower mGluR5 availability and, during mania, there is higher mGluR5 availability. Normalizing mGluR5 in this disorder could thus require a NAM

or PAM, and may require adjuvant therapy. And, finally, it is important to consider potential side effects of these drugs such as NAM-induced psychosis(102–104) or PAM-induced toxicity(125).

One treatment that has continually exhibited clinical antidepressant efficacy is ketamine, which in addition to its multiple effects on multitudes of targets, also produces mGluR5 changes that persist beyond the initial glutamate surge. Furthermore, our work shows that rapid internalization of mGluR5 with ketamine may contribute to antidepressant and anxiolytic behavior in MDD. In our studies, the magnitude of ketamine-induced mGluR5 decrease was $14 \pm 10\%$ on average throughout the brain. This level of glutamate modulation and normalization of mGluR5 may therefore be part of glutamatergic agent efficacy, and may be one reason other glutamatergic agents such as memantine, lanicemine and nitrous oxide in MDD(126) as well as riluzole in OCD(127, 128) have not consistently demonstrated efficacy. Related to this, there are open questions regarding optimal dosing, route of administration, and even efficacy of NAMs versus full antagonists. Future PET studies are needed to evaluate the mGluR5 receptor occupancy of these treatments at relevant doses, to determine whether there is a minimum threshold for efficacy. These studies should also be undertaken for antidepressant or mood stabilizers that do not target glutamate primarily, but have been shown to affect mGluR5(129–131).

Research in anxiety models of the glutamatergic system have been guided by the principle that, as anxiolytics, benzodiazepines act to increase inhibitory GABAergic transmission, and therefore an alternative treatment strategy may lie in reducing excitatory glutamatergic transmission. In disorders such as PTSD, there appears to be an upregulation of mGluR5. While blocking mGluR5 could disrupt acquisition and expression of conditioned fear during the trauma, this same blockade may interfere with fear extinction. Consideration should also be given to non-mGluR5 treatments that may normalize mGluR5 availability and function, and which do not cause rapid down or up regulation in mGluR5 as may NAMs and PAMs. For example, our data in PTSD provide support for the association between mGluR5 and glucocorticoid system, consistent with the animal literature(132), and thus lead to relief of PTSD related symptoms. Indeed, a small trial with hydrocortisone augmentation therapy showed positive outcomes in individuals with PTSD without significant side effects or exacerbation of PTSD symptoms(133), potentially due to the slower regulation of mGluR5 induced by glucocorticoid administration. Overall, it is not clear whether mGluR5 NAMs or PAMs will prove to be treatments for the above disorders, or whether indirect modulators of mGluR5 that also have effects on other systems (e.g., AMPA) will prove to be more beneficial to individuals with mood and anxiety-related disorders.

It is important to note that mood and anxiety disorders are heterogeneous disorders and present in high comorbidity with other psychiatric disorders including substance use disorders. Although literature is still preliminary, conflicting in some cases, and beyond the scope of the current review, drugs of abuse such as tobacco and cocaine may contribute to the mGluR5 dysregulation(18, 134–138), affecting optimal treatment selection. However, if dysregulation in mGluR5 either predisposes a person to, or contributes to the persistence of, a substance use disorder then targeting mGluR5 for the treatment of substance disorders may also aid with the treatment of the (typically) comorbid mood or anxiety disorders.

Interestingly, in smokers with no other psychiatric comorbidities, quitting smoking appears to normalize mGluR5 availability as a function of time(139). Given that nicotine addiction is highly comorbid with mood and anxiety disorders, and does not appear to have anti-depressive or anxiolytic qualities as previously thought(140), smoking reduction treatments via modulation of mGluR5 might prove to not only aid with tobacco addiction, but alleviate some of the associated mood and anxiety symptoms.

PET remains an important tool to investigate mGluR5 in disease conditions and in response to therapy. However, the choice of outcome measure in these studies is an important consideration. Further, we(17) and others(141) have recently shown that mGluR5 expression may be sensitive to diurnal variation *in vivo* more significantly than other neurotransmitter systems evaluated, and this was more pronounced in female and compared to male subjects(17). Therefore, it may be imperative to control the time of day of mGluR5 quantification and drug administration. This is an important consideration for future studies, and may have affected estimation studies to date. Such considerations indicate the challenges associated with probing this system, but also the opportunities and uniqueness of this valuable target.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Anamaria and Michael Manu for their diligent and thorough work in examining references of this paper. Esterlis K01, R01, Nancy Taylor, VANCPTSD. DeLorenzo K01MH091354. Krystal VANCPTSD.

Financial Disclosures

CD, PS, SH and IE report no biomedical financial interests or potential conflicts of interest.

John H. Krystal reports having received research funding from VA NCPTSD; Dr. Krystal is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance, Inc., FORUM Pharmaceuticals, Janssen Research & Development, Lundbeck Research USA, Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Medical Sciences; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued Sep 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued Jul 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression. U.S. Application No. 14/197,767 (filed on Mar 5, 2014); U.S. application or Patent Cooperation Treaty international application No. 14/306,382 (filed on Jun 17, 2014).

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Figure 1.

mGluR5 expression is modulated with glutamate release in the synapse. **A:** mGluR5 expressed on the cell surface with low levels of endogenous glutamate. The PET tracer binds to the surface receptors. **B:** Although glutamate and the PET tracer do not bind to the same location on the mGluR5, when glutamate is released into the synapse, mGluR5 is downregulated/internalized with less receptors being available on the cell surface. Because the PET tracer can bind only to the surface receptors, the binding decreases.

Figure 2. mGluR5 radioligands bind to receptors at the cell surface only. Images adapted from (147). **A.** In a healthy individual, there is a balance in protein expression and mGluR5 number at the cell surface on the post-synaptic dendrite. **B.** In PTSD, there is a hypothesized increase in scaffolding protein Shank1, which anchors extra mGluR5s to the cell surface. Thus, although the number of mGluR5s may be the same in the healthy and PTSD brain, due the upregulation in Shank1, and thus increase in mGluR5 on the cell surface, quantification of mGluR5 shows higher receptor density.

Table 1

Summary of preclinical and clinical studies utilizing mGluR5 treatments. See text and Supplementary Material for details.

Major Depressive Disorder Animal Studies		
<i>Agent</i>	<i>Mechanism of Action on mGluR5</i>	<i>Finding</i>
GRN-529 (Wyeth Pharmaceuticals)	NAM	Dose-dependent efficacy demonstrated in mice models (decreased immobility time in tail suspension and FST)(85)
MPEP 2-Methyl-6-(phenylethynyl)pyridine	Antagonist	Decreased mobility in the FST Reduced immobility in wild-type mice(83)
MTEP 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP)	Antagonist	Decreased mobility in the in the FST(83)
Human Studies		
Basimglurant (code: RG 7090, RO4917523, Roche and Chugai Pharmaceutical)	NAM	No difference in MADRS scores between adjunctive Basimglurant MR and placebo. Improvements in patient-rated end points at a dose of 1.5 mg of adjunctive treatment ⁽⁹⁴⁾
AZD2066 (Astra-Zeneca)	Antagonist	Not been found to be superior to placebo on the MADRS(93)
Bipolar Disorder Animal Studies		
<i>Agent</i>	<i>Mechanism of Action</i>	<i>Finding</i>
3-cyano-N-(1,3-diphenyl-1Hpyrazol-5-yl)b enamide	Positive Allosteric Modulator (PAM)	Reversed an increase in locomotor activity and impulsivity in rats induced with amphetamines(142)
DSR-98776 (Sumitomo Dainippon Pharma Co.)	NAM	Between 1–3 mg/kg reduced rat's immobility time for 7 days consecutively Mania induced by methamphetamine/chlordiazepoxide was reduced(143)
Human Studies		
Acamprosate	Weak antagonist	Trials with this agent have shown it to be a weak antagonist, having poor affinity for glutamate receptors. Low efficacy.(144)
PTSD Animal Studies		
<i>Agent</i>	<i>Mechanism of Action</i>	<i>Finding</i>
ADX47273 (Addex Therapeutics)	PAM	Enhanced extinction learning when given in the retrieval-reconsolidation phase and improved reversal learning in the MWM(112)
MPEP 2-Methyl-6-(phenylethynyl)pyridine	Antagonist	Blocks the autonomic response to stress-induced hyperthermia(145)
OCD Animal Studies		
<i>Agent</i>	<i>Mechanism of Action</i>	<i>Finding</i>
MTEP 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP)	Antagonist	Rapidly reduced elevated <i>Sapap3</i> KO grooming activity(146)
Human Studies		
Mavoglurant (Novartis Pharma AG)	Antagonist	Phase 2 study as an add-on treatment was terminated due to lack of efficacy compared to placebo(119)

NAM: Negative Allosteric Modulator, PAM: Positive Allosteric Modulator, FST: Forced Swim Test, MADRS: Montgomery-Åsberg Depression Rating Scale, MWM: Morris Water Maze YBOCS: Yale-Brown Obsessive Compulsive Scale

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