Review

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Metabotropic Glutamatergic Receptor 5 and Stress Disorders: Knowledge Gained From Receptor Imaging Studies

Irina Esterlis, Sophie E. Holmes, Priya Sharma, John H. Krystal, and Christine DeLorenzo

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 studies. Positron emission tomography 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. 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 bipolar disorder, yet initial studies indicate that 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 posttraumatic stress disorder or obsessive-compulsive disorder 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 modulation or full antagonism) of mGluR5 modulation required to translate existing knowledge into improved therapies.

Keywords: Anxiety, Bipolar disorder, Major depressive disorder, Metabotrobic glutamatergic receptor subtype 5, mGluR5, Positron emission tomography

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Glutamate neurotransmission is regulated by ionotropic and G protein–coupled metabotropic glutamatergic receptors (mGluRs), which are divided into group I (mGluR1 and 5), group II (mGluR2 and 3), and group III (mGluR4, 6, 7, and 8) (1). mGluR5 specifically is located predominantly on postsynaptic neurons (2–4) on the cellular and intracellular membranes (5–7) of glutamatergic (excitatory) and gamma-aminobutyric acidergic (inhibitory) neurons and on glial cells in the perisynaptic space (8–10). The highest mGluR5 density in humans is in the hippocampus and putamen, followed by the caudate and cerebral cortex (~10–15% lower than the highest density regions) and thalamus (~45–50% lower than the highest density regions), and the lowest expression is in the cerebellum (~65% lower than the highest density regions) (11). mGluR5s are regulated by both positive allosteric modulators (PAMS) and negative allosteric modulators (NAMs) which potentiate or inhibit endogenous glutamate (12). PAMs enhance the activation of receptors or prevent agonist-related desensitization, while NAMs can be either noncompetitive 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 NMDAR and mGluR5 are localized closely on the cell surface, and activation of mGluR5 potentiates NMDAR activity while mGluR5 NAMs potentiate the effects of NMDAR 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. Furthermore, we provide results from our recent investigations, and when conflicting, equivocal, or limited findings are presented, we present potential hypotheses that might unify results.

PET can be used to quantify mGluR5 availability in vivo, but it is important to note that 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)

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cyclohex-2-en-1-one-*O*-[^{11}C]methyloxime {[^{11}C]ABP688 (19)} and 3-[^{18}F]fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile {[^{18}F]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 (8–10).

In PET studies, the outcome measure volume of distribution (V_T), 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 nonspecific binding. There is no evidence that nonspecific 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 control subjects; however, this has not been fully explored. When blood sampling is not performed, the outcome measure commonly used is distribution volume ratio (DVR), i.e., binding in the region relative to a reference region. DVR calculation requires the use of a reference region that is assumed to be devoid of mGluR5. Such a region does not exist, and therefore caution must be taken when evaluating this outcome measure.

MOOD DISORDERS

A review of 16 ^{1}H MRS studies (281 patients and 301 healthy subjects) reported significantly lower glutamate and a combination of glutamate plus glutamine levels in individuals with major depressive disorder (MDD) (22), although a smaller number of studies reported higher levels of glutamate in MDD (18,23,24), 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 (25) 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 (8–10), ^{1}H MRS assesses the total amount of glutamate within a "box" containing neuronal tissue, nonneuronal tissue, and extracellular fluid (26,27). 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 the first potential evidence in vivo for the hypothesized excitotoxicity of receptors under conditions of elevated glutamate levels (28). 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 Figure 1) (29,30).

Similar to the lower (22,31) and higher glutamate (18,23,24) (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% to 20% lower mGluR5 availability in several brain regions using DVR (32). 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 (33). Given that the available data do not suggest age-related changes in mGluR5 in vivo in humans (34,35), 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 (32,36,37), preclinical studies repeatedly implicate reduced mGluR5 in the pathophysiology of depression (38). mGluR5 knockout mice exhibit depressive-like behavior (39), and rat models of depression show reductions in mGluR5 protein and density in various brain regions (40,41).

Glutamatergic dysfunction is also implicated in bipolar disorder (BD). In contrast to the majority of studies in MDD, higher glutamate plus glutamine levels and glutamate levels are more commonly observed throughout the brain, and particularly in frontal areas (dorsolateral prefrontal cortex and anterior cingulate cortex) in BD (42–48). This may point to differing pathophysiology between bipolar depression and MDD or a 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.* (46), 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

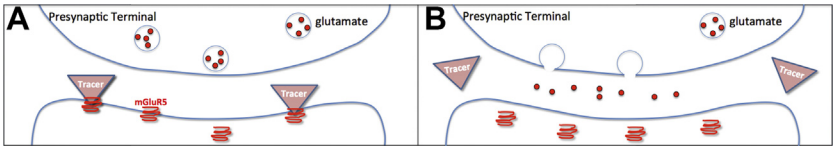

Figure 1. Metabotropic glutamatergic receptor 5 (mGluR5) expression is modulated with glutamate release in the synapse. **(A)** mGluR5 expressed on the cell surface with low levels of endogenous glutamate. The positron emission tomography tracer binds to the surface receptors. **(B)** Although glutamate and the positron emission tomography tracer do not bind to the same location on the mGluR5, when glutamate is released into the synapse, mGluR5 is downregulated/internalized with fewer receptors being available on the cell surface. Because the positron emission tomography tracer can bind only to the surface receptors, the binding decreases.