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Metabotropic Glutamate Receptor 5 and Glutamate Involvement in Major Depressive Disorder: A Multimodal Imaging Study

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ABSTRACT

BACKGROUND: Preclinical and postmortem studies have implicated the metabotropic glutamate receptor 5 (mGluR5) in the pathophysiology of major depressive disorder (MDD). The goal of the current study was to determine the role of mGluR5 in a large group of individuals with MDD compared with healthy control subjects (HCs) in vivo with 3-[^{18}F]FPEB and positron emission tomography. Furthermore, we sought to determine the role glutamate plays in mGluR5 availability in MDD.

METHODS: A total of 65 participants (30 individuals with MDD and 35 HCs) completed 3-[^{18}F]FPEB positron emission tomography to estimate the primary outcome measure, mGluR5 volume of distribution, and the secondary outcome measure, mGluR5 distribution volume ratio. A subgroup of 39 participants (16 individuals with MDD and 23 HCs) completed proton magnetic resonance spectroscopy to estimate anterior cingulate cortex glutamate, glutamine, and glutamate + glutamine levels relative to creatine.

RESULTS: No significant between-group differences were observed in mGluR5 volume of distribution or distribution volume ratio. Compared with HCs, individuals with MDD had higher anterior cingulate cortex glutamate, glutamine, and glutamate + glutamine levels. Importantly, the anterior cingulate cortex mGluR5 distribution volume ratio negatively correlated with glutamate/creatine and glutamate + glutamine/creatine levels.

CONCLUSIONS: In this novel in vivo examination, we show an inverse relationship between mGluR5 availability and glutamate levels. These data highlight the need to further investigate the role of the glutamatergic system in depression.

Keywords: [^{18}F]FPEB, Glutamate, ^{1}H MRS, MDD, mGluR5, PET

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Major depressive disorder (MDD) is highly prevalent and disabling, with poorly understood neurobiology and with available treatment options that require weeks to months to exert full therapeutic benefit (1). Better understanding of the pathophysiology of MDD may facilitate the development of novel effective rapid-acting therapeutics. Accumulating evidence strongly implicates altered glutamate neurotransmission in the pathophysiology of MDD and suggests that glutamate modulation may induce rapid relief of depressive symptoms in treatment-refractory patients (2). The metabotropic glutamate receptor 5 (mGluR5) is a key component of the glutamatergic system and has been thought to play a critical role in the pathophysiology of depression (3,4). In this study, we used the high-affinity positron emission tomography (PET) radiotracer 3-[^{18}F]fluoro-5-[(pyridin-3-yl) ethynyl]benzonitrile ([^{18}F]FPEB) to compare in vivo mGluR5 availability in individuals with MDD and healthy control subjects (HCs). In addition, we collected proton magnetic resonance spectroscopy (^{1}H MRS) data to investigate the relationship between mGluR5 availability and cortical glutamate level.

Chronic stress and depression are associated with alterations in glutamate (the major excitatory neurotransmitter) transmission, including an increase in extracellular glutamate, which could lead to excitotoxicity and impaired synaptic integrity, contributing to the brain abnormalities observed in MDD (5). Glutamate neurotransmission is regulated by ionotropic and G protein–coupled metabotropic GluR, which are divided into three groups: group I (mGluR1 and -5), group II (mGluR2 and -3), and group III (mGluR4, -6, -7, and -8) (6). The group I mGluRs couple to phospholipase C and stimulate cyclic adenosine monophosphate formation and arachidonic acid release (7), modulating synaptic transmission, neuronal excitability, gene expression, and neuroplasticity. The mGluR5s are mostly located postsynaptically and on glial cells in the perisynaptic space (8–10) and have highest density in the hippocampus, intermediate density in the caudate/putamen, cerebral cortex, and thalamus, and lowest density in the cerebellum (11,12).

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Preclinical studies have repeatedly implicated mGluR5 impairment in the pathophysiology of depression (13). However, the relationship between mGluR5 changes and depressive-like behavior is complex and not fully understood. Animal models of depression showed reductions in mGluR5 protein and density in various brain regions (14,15). Similarly, mGluR5 knockout mice exhibited depressive-like behavior (16), and chronic—but not acute—antidepressant treatment increased mGluR5 expression (17), raising the possibility that therapeutic effects might be mediated by mGluR5 regulation.

In humans, postmortem examination of mGluR5 density in MDD has revealed regional variability in findings. One study showed lower mGluR5 protein levels in the cerebellum of 14 patients with MDD as compared with 14 control subjects (18). More recently, a postmortem study of tissue from ventral anterior cingulate (Brodmann area 24) failed to demonstrate significant alterations in mGluR5 density in 12 individuals with MDD as compared with 12 control subjects (19), suggesting that mGluR5 alterations might not be present in MDD. However, a different study examining mGluR5 levels postmortem and in vivo showed lower monomer mGluR5 protein levels in 15 individuals with MDD as compared with 15 comparison individuals in parts of the prefrontal cortex (Brodmann area 9) (20). The same group used (E)-3-((6-methylpyridin-2-yl)ethynyl)cyclohex-2-en-1-one-O-[^{11}C]methyloxime ([^{11}C]ABP688) PET to provide the first in vivo evidence of lower mGluR5 availability in 11 individuals with MDD in a current depressive episode as compared with 11 control subjects (20). Distribution volume ratio (DVR) with cerebellar activity as the reference region was used as the outcome measure. The authors reported 10% to 20% lower mGluR5 availability in several brain regions, including the thalamus, anterior cingulate cortex (ACC), anterior insula, lateral prefrontal cortex, and temporal and parietal lobes, as well as precentral, inferior prefrontal, and lateral prefrontal gyri (20). However, an evaluation of mGluR5 availability in elderly depression (n = 16) as compared with elderly control subjects using [^{11}C]ABP688 PET did not detect significant between-group differences in any of the regions assessed via distribution volume (V_T) or DVR outcome measures (21). Thus, the extent of mGluR5 involvement in living individuals with MDD remains inconclusive. Of note, a similar pattern was observed in postmortem studies showing decreased astrocytes in younger patients with MDD but not in older patients (22).

This study was designed to conclusively determine whether there is a difference in mGluR5 density in MDD with an adequately powered sample of medication-free individuals with MDD. Considering that there is no human brain region devoid of mGluR5 in humans (23–26), we studied V_T (an absolute measure) as our main outcome measure. Given previous study examining changes in mGluR5 availability using DVR, we also examined DVR (a relative measure) as an outcome measure for quantification of mGluR5 availability. The radiotracer we used was [^{18}F]FPEB [K_D = 0.11 ± 0.04 to 0.15 ± 0.02 nM (25)]. Test–retest for the outcome measure V_T during bolus plus infusion administration was −2% to −6% when using arterial blood and 0% to 4% when using venous blood. Furthermore, both mean arterial and mean venous radiotracer concentrations reach equilibrium by 90 minutes (time of data collection), and our work shows a 1% difference between arterial and venous quantifications, suggesting that the arterial line is not required for outcome measure calculation. Therefore, this tracer is excellent for use in psychiatric populations (27). To assess whether increased cortical levels of glutamate are associated with decreased mGluR5 density, we measured glutamate levels in the ACC of a subgroup of subjects using ^{1}H MRS. A postmortem study reported that elevated tissue glutamate levels in depression in the ACC (28) and occipital cortex detected elevated glutamate levels in individuals with MDD (29). There is, however, also MRS literature showing lower ACC glutamate and glutamate + glutamine (Glx) levels in individuals with depression (30,31), whereas other studies found reduced ACC glutamine, but not glutamate, in MDD (32). We hypothesized that individuals with MDD would have lower mGluR5 availability based on the previous report. We also hypothesized a negative correlation between ACC mGluR5 availability and ACC glutamate levels, consistent with the hypothesis that increased glutamate leads to excitotoxicity.

METHODS AND MATERIALS

Subjects

The institutional review board and safety committees approved all study procedures. All subjects provided written informed consent prior to participation. In total, 30 medication-free individuals with MDD and 35 HCs completed the PET study, and of those, 16 individuals with MDD and 23 HCs successfully completed ^{1}H MRS scans within 1 or 2 days of PET. Participants underwent physical, neurological, and psychological examination to rule out any major medical or neurological illness and to confirm diagnosis. Electrocardiography, complete blood counts, serum chemistries, thyroid function test, liver function test, urinalysis and urine toxicology screening, and plasma pregnancy tests (for women) were performed during screening. Urine toxicology and pregnancy tests were repeated prior to each scan. Study criteria included age 18 to 65 years, MDD diagnosis with current major depressive episode (MDD group) or no psychiatric disorder (HC group) as confirmed by a Structured Clinical Interview for DSM-IV (33), no active suicidal ideation, no lifetime history of bipolar disorder or schizophrenia, no diagnosis of alcohol or substance abuse (past 6 months) or dependence (past 12 months) except for nicotine, no positive urine toxicology, medication free for at least 2 weeks, and no history of loss of consciousness > 5 minutes.

Considering previous reports of lower mGluR5 binding in smokers (34), tobacco smokers and nonsmokers were matched across groups. Tobacco smokers were defined as those who had smoked at least 10 cigarettes daily for a minimum of 1 year and who had urine cotinine levels > 100 ng/mL and carbon monoxide levels > 11 parts per million. Nonsmokers were defined as having smoked < 40 cigarettes in their lifetime and having negligible urine cotinine (< 100 ng/mL) and carbon monoxide (< 8 parts per million) levels. Plasma cotinine levels of > 150 ng/mL for smokers and plasma of < 15 ng/mL for nonsmokers were preferred but were not available to collect for some subjects due to technical issues (e.g., clotting).