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Prefrontal Connectivity and Glutamate Transmission: Relevance to Depression Pathophysiology and Ketamine Treatment

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ABSTRACT

BACKGROUND: Prefrontal global brain connectivity with global signal regression (GBCr) was proposed as a robust biomarker of depression and was associated with ketamine's mechanism of action. Here, we investigated prefrontal GBCr in treatment-resistant depression (TRD) at baseline and following treatment. Then, we conducted a set of pharmacological challenges in healthy subjects to investigate the glutamate neurotransmission correlates of GBCr.

METHODS: In the cohort A study, we used functional magnetic resonance imaging to compare GBCr between 22 patients with TRD and 29 healthy control subjects. Then, we examined the effects of ketamine and midazolam on GBCr in patients with TRD 24 hours posttreatment. In the cohort B study, we acquired repeated functional magnetic resonance imaging in 18 healthy subjects to determine the effects of lamotrigine (a glutamate release inhibitor), ketamine, and lamotrigine-by-ketamine interaction.

RESULTS: In the cohort A study, patients with TRD showed significant reduction in dorsomedial and dorsolateral prefrontal GBCr compared with healthy control subjects. In patients with TRD, GBCr in the altered clusters significantly increased 24 hours following ketamine (effect size = 1.0, confidence interval = 0.3 to 1.8) but not following midazolam (effect size = 0.5, confidence interval = −0.6 to 1.3). In the cohort B study, oral lamotrigine reduced GBCr 2 hours postadministration, while ketamine increased medial prefrontal GBCr during infusion. Lamotrigine significantly reduced the ketamine-induced GBCr surge. Exploratory analyses showed elevated ventral prefrontal GBCr in TRD and significant reduction of ventral prefrontal GBCr during ketamine infusion in healthy subjects.

CONCLUSIONS: This study provides the first replication of the ability of ketamine to normalize depression-related prefrontal dysconnectivity. It also provides indirect evidence that these effects may be triggered by the capacity of ketamine to enhance glutamate neurotransmission.

Keywords: Functional MRI, Global brain connectivity, Glutamate, Ketamine, Rapid-acting antidepressants, Treatment-resistant depression

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Major depressive disorder (MDD) is a disabling mental illness with poorly understood pathophysiology and high rates of inadequate treatment response (1,2). Accumulating evidence over the past 2 decades strongly implicated glutamate neurotransmission alterations in the pathophysiology and treatment of MDD (3,4), particularly the exciting discovery of rapid-acting antidepressant effects induced by subanesthetic doses of ketamine, a glutamate modulator (5–8). However, with the exception of ketamine, translating the glutamate findings into novel antidepressants has been difficult, with various agents showing no antidepressant effects or exiting development pipelines by the pharmaceutical industry owing to failure in reaching primary targets (9–11). A major challenge in the field is to establish robust in vivo human biomarkers that could serve as measures of target engagement and target validation in the development of rapid-acting antidepressants (12–14). These biomarkers would advance our understanding of the neurobiology of depression and could play a critical role in early phases of drug development. In this study, we used a promising biomarker of functional network connectivity, termed global brain connectivity with global signal regression (GBCr) (15,16), to establish the effects of ketamine on prefrontal connectivity in patients with MDD and healthy subjects and to demonstrate a direct link between large-scale connectivity networks and underlying glutamate neurotransmission.

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is a rapid-acting antidepressant that is believed to exert its therapeutic effect by inducing a glutamate neurotransmission surge leading to increased synaptogenesis and reversal of depression-related glutamate synaptic deficits (17,18). To date, two non–mutually exclusive models have been proposed for the mechanisms through which ketamine induces glutamate neurotransmission (19,20). The NMDA

SEE COMMENTARY ON PAGE 549

model proposes that subanesthetic doses of ketamine preferentially block NMDA receptors on a subpopulation of interneurons, precipitating disinhibition of glutamate neurotransmission (21,22). A more recent model suggests the presence of ketamine metabolites (*Z*-6-hydroxynorketamine) that activate synaptic glutamate neurotransmission independent of inhibiting NMDA receptors through a yet unidentified mechanism (20). Both models converge on the role of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid–dependent activation of glutamate neurotransmission as a common pathway to induce downstream synaptogenesis and rapid-acting antidepressant effects (23). Preclinical work showed a robust glutamate neurotransmission surge after administering ketamine or other rapid-acting antidepressants (24). In humans, proton magnetic resonance spectroscopy has been used to provide indirect evidence of the ability of ketamine to stimulate glutamate (25,26), although one study failed to support this conclusion (27). In depressed individuals, preliminary evidence in 8 subjects showed increased medial prefrontal cortex (mPFC) glutamate/glutamine mix during ketamine infusion (28). Others failed to show occipital cortical glutamate changes 3 and 24 hours after ketamine administration (29). Together, these data provided mechanistic evidence of a ketamine-induced mPFC glutamate surge during infusion in healthy subjects and subjects with depression. However, the inconsistencies affect the potential utility of these methods as a robust biomarker for drug development. These inconsistencies are potentially influenced by the limited spatial and temporal resolutions of the approach and by the fact that proton magnetic resonance spectroscopy measures total levels of glutamate (i.e., intra- and extracellular) that might not sufficiently capture glutamate activation and transmission.

GBCr is a robust, well-validated graph theory measure of large-scale functional connectivity networks. Using functional magnetic resonance imaging (fMRI), GBCr is measured as the average correlation between each voxel and all other voxels in the brain gray matter. These global brain connectivity values, also known as functional connectivity strength, have been used to identify major brain networks (30), were found to predict cognitive functioning and intelligence (31), and were shown to significantly correlate with regional cerebral blood flow (32,33). Accumulating evidence has consistently shown reduced PFC GBCr across various psychiatric disorders marked by chronic stress (15,34–39). Thus, it was proposed that these PFC GBCr abnormalities may reflect depression and stress-induced glutamate alterations (16,17,34). Depressive features and chronic stress in animal models reduce prefrontal glutamate synaptic density and strength, abnormalities that are reversed by ketamine treatment (40). Consistent with this model, we recently demonstrated widespread GBCr reduction in the dorsomedial, frontolateral, and ventral PFC (vPFC) in patients with MDD (35). In treatment-resistant depression (TRD), we found comparable GBCr reduction in dorsomedial and frontolateral PFC, but not vPFC (limbic network), in patients at baseline (16). These GBCr abnormalities were primarily located in the ventral attention and frontoparietal networks within the PFC (41). At 24 hours following ketamine administration, we found a pattern of normalization of pretreatment PFC GBCr alterations and a significant increase in frontolateral GBCr that positively correlated with improvement of depression (16).

Considering preclinical evidence of glutamate synaptic transmission normalization 24 hours after ketamine administration in models of depression (40), our previous ketamine findings in TRD suggested a crucial role for PFC connectivity in TRD and raised an essential translational question—whether the ketamine-induced increases in synaptic glutamate neurotransmission are causally related to the fMRI measure of GBCr. In the current study, we first replicated, in a new independent cohort of patients with TRD, the presence of PFC GBCr abnormalities in TRD and the ability of ketamine to reverse these GBCr alterations 24 hours posttreatment. Then, we employed experimental pharmacoimaging challenges in healthy subjects to demonstrate a correlational relationship, as well as to probe for a putative causal link, between glutamate neurotransmission and functional connectivity as measured by GBCr. The demonstration of a direct link between synaptic transmission and GBCr would provide insight into the neurobiology of depression and the mechanism of action of rapid-acting antidepressants. It would also present GBCr as a potential biomarker of target validation. Moreover, considering the robust ketamine induction of glutamate neurotransmission during infusion, GBCr could serve as a biomarker of target engagement if a direct link between GBCr and underlying synaptic transmission was demonstrated.

To accomplish the study aims, we first compared PFC GBCr between patients with TRD and healthy control subjects (HCs), predicting reduced GBCr in prefrontal regions within the ventral attention and frontoparietal networks but not within the limbic network. We hypothesized that ketamine would reverse these PFC GBCr alterations 24 hours following treatment. Then, to investigate the relationship between glutamate neurotransmission and GBCr, we examined whether lamotrigine, an inhibitor of glutamate neurotransmission, would induce a reduction in PFC GBCr. We also examined the effects of ketamine on PFC GBCr during infusion, hypothesizing that ketamine would increase dorsomedial and frontolateral GBCr but would reduce vPFC GBCr—comparable to a previous report of reduced vPFC activity during ketamine infusion (42). Finally, to provide experimental evidence of a direct link between ketamine induction of glutamate neurotransmission and GBCr, we hypothesized that lamotrigine would significantly reduce the ketamine-induced PFC GBCr changes.

METHODS AND MATERIALS

Participants

The studies were approved by institutional review boards. All subjects completed an informed consent process prior to participation (ClinicalTrials.gov identifier: NCT00768430). All imaging data presented in this article are new and have not been previously published. The cohort A study was conducted at one site (Houston, TX) as an add-on to a ketamine clinical trial that was previously published (6). The cohort B study was conducted at one site (New Haven, CT) aimed to investigate the modulation of ketamine effects by lamotrigine.

Cohort A consisted of 22 patients with TRD (54% men, mean age ± SEM = 44 ± 2.3 years) and 29 HCs (55% men, mean age = 44 ± 1.8 years). All participants completed fMRI scans at baseline. Of the 22 subjects with TRD, 20 were randomized to ketamine (n = 13; 0.5 mg/kg over 40 minutes) or to