The Effects of Ketamine on Anterior Cingulate Glutamatergic Activity in Healthy Humans: A 4T 1H-MRS Study

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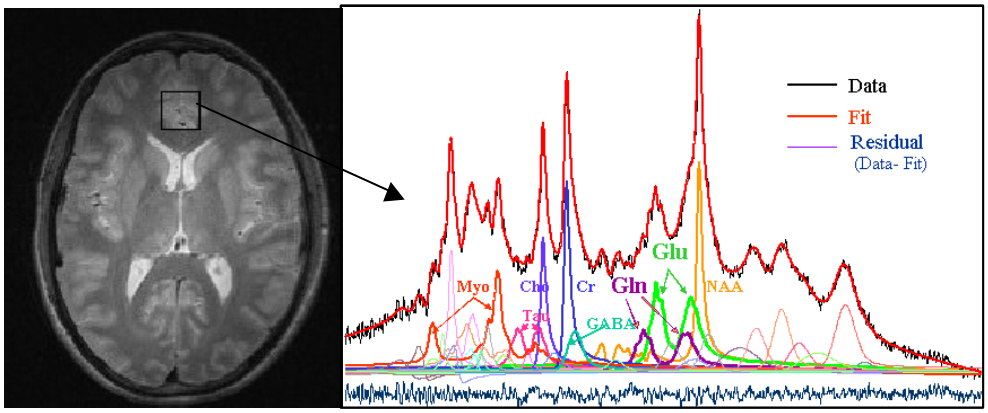
Background

Evidence suggests that glutamate dysfunction, specifically at the N-methyl-D-aspartate (NMDA) receptor site, is involved in the pathophysiology of schizophrenia. NMDA antagonists, such as PCP and ketamine, induce schizophrenia-like features in healthy humans better than other pharmacological agents. According to the NMDA receptor hypofunction hypothesis, NMDA blockade results in inhibition of GABAergic neurons, which then causes disinhibition of glutamatergic neurons that converge onto pyramidal neurons in vast cortical regions resulting in schizophrenia-like features (1). Supporting this hypothesis, extracellular glutamate (Glu) concentrations in the prefrontal cortex were found to increase in awake rats when administered ketamine. Providing some indirect evidence, PET studies in humans have shown elevations of blood flow and glucose metabolism in the anterior cingulate (AC) with ketamine administration. However, studies directly assessing the effects of ketamine on glutamatergic activity and the relation to schizophrenia-like features in humans have not been conducted. The present study investigated the effects of ketamine on AC glutamatergic activity and the relation to ketamine-induced schizophrenia-like features in healthy humans with 4T- proton magnetic resonance spectroscopy (^{1}H-MRS). Although a tight coupling between the neurotransmitter and metabolic Glu pools has been suggested, the functional relevance of total Glu assessed through spectroscopy is not clear. It has been shown that >80% of brain glutamine (Gln) takes part in the glutamatergic neurotransmission cycle (2). Hence, Gln concentrations measured with ^{1}H-MRS should be a good index of the turnover of Glu involved in neurotransmission.

Methods

Nine healthy males were scanned on two separate occasions while being infused with a subanesthetic dose of ketamine or saline, administered in a block-randomized manner. All imaging and spectroscopy were performed on a 4T whole body spectrometer (Varian Palo Alto). Fast-Spin Multislice images that allowed for the placement of spectroscopic voxels were acquired *(Echo Spacing=14ms, ETL=4, TR=7.5s, 70 slices, 2mm, no gap)*. Spectra were acquired three times (1 prior to and 2 post infusion start) from an 8 cc voxel in the bilateral AC (Figure 1) using a STEAM sequence *[TR = 2000 ms, TE = 20 ms, TM = 30 ms, 256 averages*; (3)]. Water suppression was achieved using three CHESS pulses. The spectra were analyzed using curve-fitting software developed at the University of Western Ontario (3). Each fitted spectra were normalized to the unsuppressed water, allowing concentrations to be calculated for NAA, Cho, Cre, Glu and Gln. The behavioral rating scales used to assess schizophrenia-like symptoms were the Brief Rating Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), Clinician Administered Dissociative States Scale (CADSS), and the Index of Change in Schizophrenic Symptomatology (ICISS). Performance on the Stroop, a task shown to involve the AC, was also assessed. Spectroscopic measures were analyzed between baseline and post-infusion time points (1 or 2) with paired t-tests, separate for each condition (placebo or ketamine). In addition, difference scores (i.e. time 1- baseline, time 2 -baseline) paired t-tests were performed between placebo and ketamine conditions. Difference scores were analyzed to account for the possible effects that anticipation, novelty, or nervousness may exhort on Gln levels with placebo administration. The relationship between glutamine change and behavioral ratings was analyzed with Pearson's correlations.

Figure 1. Illustration of Voxel Placement and Representative Spectrum



Results

As predicted, results revealed a significant increase in glutamine from baseline to the first time point following ketamine infusion ($t = 2.0$, $p < 0.05$). The glutamine concentration for the second time point was still elevated when compared to baseline, but not to a statistically significant degree ($p > 0.05$). Comparison of glutamine difference scores [(placebo baseline – placebo time 1) vs (ketamine baseline – ketamine time 1)] revealed a trend difference ($t = 1.8$, $p = 0.059$). All participants experienced schizophrenia-like features associated with ketamine as exhibited by an increase in behavioral rating scores, but contrary to expectations this was not related to Gln changes (all p's > 0.1). However, there was a trend for a negative correlation ($r = -0.6$, $p = 0.06$) for Stroop performance and glutamine difference values, indicating that increases in glutamine associated with ketamine were related to poorer performance.

Discussion

Consistent with hypotheses, results revealed a significant increase in AC glutamine, a putative marker of glutamate neurotransmitter release, with ketamine administration. However, glutamine increases were not significantly related to schizophrenia-like symptoms but were related to performance on a cognitive test known to involve the AC. Therefore, increased cortical glutamatergic activity may not be related to psychotic symptoms, but may be an adverse downstream effect, and could be an important catalyst in the deteriorating course (cognitive and social functioning) of schizophrenia. To our knowledge, this is the first study in humans to suggest that NMDA antagonism results in increased glutamate release in the AC. This provides important evidence for a missing component of the NMDA hypofunction model of schizophrenia. The findings of this study could have direct clinical applications. Hence, this study could potentially provide a ^{1}H-MRS paradigm to test drugs that modulate glutamate for their potential use of treating the deteriorating course of schizophrenia.

References

1. Olney et al. (1999). *Journal of Psychiatry Research, 33*, 523-33.
2. Rothman et al. (2003). *Annual Review of Physiology, 65*, 401-427
3. Bartha et al. (2000). *Magnetic Resonance in Medicine, 44*, 185-92