1H MRS Neurochemical Predictors of Response to Intravenous Ketamine in Treatment-Resistant Depression

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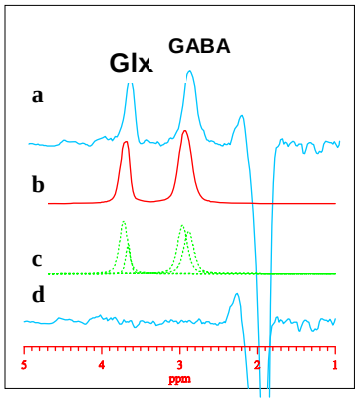
Background: Intravenous (IV) ketamine, a glutamate NMDA receptor antagonist, has been associated with rapid improvements of depressive symptoms in patients with treatment-resistant major depression (TRD) [1,2]. Previous proton magnetic resonance spectroscopy (^{1}H MRS) studies in major depressive disorder (MDD) have shown reductions in occipital lobe GABA concentrations of approximately 30-50% and glutamate elevations of approximately 10% [3]. Reductions in occipital lobe GABA normalized in depressed patients following chronic administration of electroconvulsive therapy (ECT) and selective serotonin reuptake inhibitors, but not following cognitive behavioral therapy. The objectives of this study were to test the antidepressant and anxiolytic potential of IV ketamine in TRD and to identify spectroscopic (e.g. GABA or glutamate) predictors of response.

Methods: 12 medication-free TRD patients (mean age = 45.3 ±13.2; 5 females) completed both the pre-treatment scan and the open-label IV ketamine treatment protocol (0.5 mg/kg infusion over 40 minutes). All patients were medication-free for at least two weeks prior to scan and had negative urine toxicologies on scan day. The TRD sample had moderate-to-severe depressive symptoms, with baseline Montgomery Asberg Depression Rating Scale (MADRS) scores = 36.6 ± 4.7, with significant comorbid anxiety [mean Hamilton Anxiety Rating Scale (HAM-A) = 27.2 ± 5.5], and had previous inadequate response to a mean ± SD of 4.8 ± 3.0 antidepressants in the current episode. The primary efficacy outcome measures were MADRS and HAM-A scores 24 hours following IV ketamine infusion, with response defined as > 50% reduction in baseline scores. Levels of occipital lobe and anterior cingulate cortex (ACC) GABA and Glx were recorded in 13 min from 3x3x2 cm^3 voxels with an 8-channel phased-array coil using the J-editing technique (TE/TR 68/1500ms) on a 3.0 T GE 'LX' MR system, as previously described [4]. Mean peak areas for all metabolites of interest were obtained by frequency-domain nonlinear least-squares procedures, and then expressed as ratios relative to the unsuppressed voxel tissue water signal (W). We examined the associations of MRS metabolites with clinical characteristics using the Pearson product moment correlation coefficient. All statistical tests were 2-tailed, with a level of significance of $P \leq 0.05$.

Results: **Figure 1** illustrates the quality of the occipital GABA and Glx spectra (Fig. 1a), with model fitting (Fig. 1b) and residual difference (Fig. 1c), used in the present analysis. Nine of 12 patients met MADRS criteria for response, with six of 12 patients maintaining the antidepressant response for at least 72 hours. Baseline anxiety severity, as indexed by HAM-A, was positively correlated with occipital Glx/W concentrations (r=.63, p=.029), while baseline depression severity (MADRS scores) correlated with occipital Glx/W at the trend level (r=.52, p=.08). There was a significant positive correlation between concentrations of GABA/W in occipital cortex and MADRS score 24 hours following IV ketamine infusion, controlling for age and baseline MADRS score (r=.76, p=.011), signifying that lower levels of GABA/W predicted greater improvements in depressive symptoms. No significant associations were found between GABA/W or Glx/W in ACC and baseline symptomatology or the degree of treatment response.



Discussion and Conclusion: The current findings further support the hypothesis that IV ketamine has rapid-onset antidepressant properties in TRD and provide new evidence for its anxiolytic potential. Lower occipital cortical GABA strongly predicted the antidepressant response to IV ketamine. These findings suggests that MR spectroscopy might provide a useful predictive marker of disorder severity and treatment response.

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References

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