J-editing/MEGA-PRESS Time-course Study of the Neurochemical Effects of Ketamine Administration in Healthy Humans

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Background: The effects on the brain of acute administration of ketamine are of current interest because of its known psychotogenic [1, 2] and antidepressant [3, 4] properties. Early rodent microdialysis studies [5] showed a surge in medial prefrontal cortex (MPFC) glutamate (Glu), and recent rodent studies of molecular mechanisms have suggested that this surge is a key step in downstream synaptogenesis and antidepressant action [6]. Magnetic resonance spectroscopy (MRS) studies in humans of the effects of ketamine in the MPFC and other brain regions have been reported [7-10]. These studies have examined one or two time points and have in some but not all cases documented a ketamine-induced increase in glutamatergic compounds. Our goal was to study the time course of the response of glutamate-glutamine (Glx) and GABA levels to acute ketamine administration in healthy human subjects.

Methods: We studied 12 healthy volunteers (7 female, ages 28 ± 6 y) who were given a constant i.v. infusion of ketamine 0.5 mg/kg over 40 min during an MRS study of Glx and GABA in the MPFC **(Fig. 1)** using a 3T GE system and a J-edited PRESS sequence **(Fig. 2)**. Both neurochemicals were normalized to the internal water signal of the MPFC voxel. Six sequential acquisitions each of 15 min duration (90 min total) were obtained before, during, and following the infusion. Subjects were rated with Profile of Mood States (POMS), Clinician-Administered Dissociative States Scale (CADSS), and Brief Psychiatric Rating Scale (BPRS) before and after scanning.

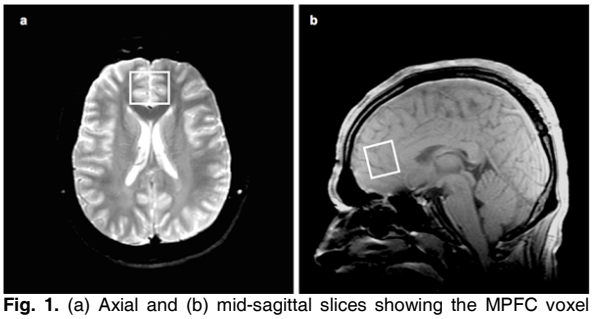

Fig. 1. (a) Axial and (b) mid-sagittal slices showing the MPFC voxel where 6 successive J-edited acquisitions were performed before, during, and following i.v. ketamine infusion.

Results: After the start of ketamine infusion, both Glx/W and GABA/W increased to a maximum in the third (15-30 min post initiation of infusion) acquisition and returned to baseline levels by the end of the study **(Fig. 3)**. Maximum increases were more marked for Glx (to 117% ± 25% of baseline) than for GABA (to 111% ± 24% of baseline), and changes were significant by repeated measures ANOVA ($p = .02$ for Glx; $p = .04$ for GABA), while a more conservative linear mixed model gave $p = .03$ for Glx and $p > .05$ for GABA. Rating scales showed significant increases in POMS ($P = .01$) and CADSS ($P < .001$) but not BPRS.

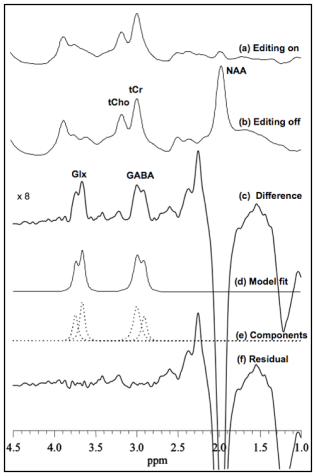

Fig. 2. J-editing acquisition showing Glx and GABA peaks obtained from difference spectrum.

Discussion: These data constitute the first dynamical study of neurochemical effects of ketamine in healthy humans. They represent the first suggestion of a GABA surge in these subjects concurrent with the Glx surge. These data 1) are consistent with the time course of the surge in extracellular glutamate seen in rodent studies [5]. However, since MRS cannot distinguish neurochemical compartments, but instead provides total tissue neurochemical levels, they suggest that ketamine induces acute surges in net Glx and GABA synthesis of the magnitudes reported here; 2) show a remarkable correspondence to baseline neurochemical abnormalities seen in unmedicated patients with schizophrenia, who show elevated Glx/W and GABA/W in the same brain region [11], consistent with the NMDA receptor hypofunction hypothesis of schizophrenia; 3) are qualitatively similar to data acquired by our group in depressed patients [12], supporting the extrapolation from rodent studies to depressed human subjects of the possible role of the glutamate surge in the antidepressant action of ketamine; and 4) by showing elevations rather than reductions in GABA/W, suggest that the idea that GABAergic interneurons disinhibit pyramidal cells as a mechanism for the acute NMDA receptor blockade-induced glutamate surge may need refinement.

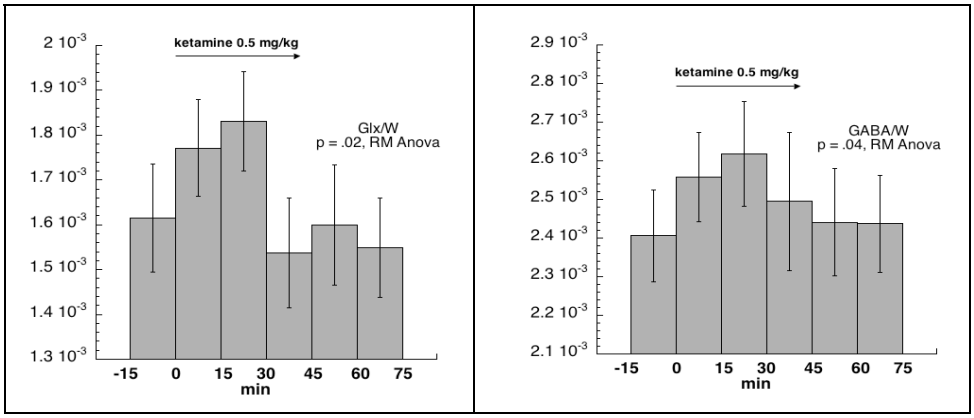

Fig. 3. Response of MPFC Glx and GABA levels in real time to acute i.v. infusion of ketamine 0.5 mg/kg over 40 min showing surges following the start of infusion and return to baseline (first frame) levels by 75 min following the start of infusion.

References: [1] Domino et al, *Clin Pharmacol Ther* 1965;**6**:279. [2] Krystal et al, *Arch Gen Psychiatry* 1994;**51**:199. [3] Berman et al, *Biol Psychiatry* 2000;**47**:351. [4] Zarate et al, *Arch Gen Psychiatry* 2006;**63**:856. [5] Moghaddam et al, *J Neurosci* 1997;**17**:2921. [6] Li et al, *Science* 2010;**329**:959. [7] Rowland et al, *Am J Psychiatry* 2005;**162**:394. [8] Valentine et al, *Psychiatry Res* 2011;**191**:122. [9] Taylor et al, *J Psychopharmacol* 2012;**26**:733. [10] Stone et al, *Mol Psychiatry* 2012;**17**:664. [11] Kegeles et al, *Arch Gen Psychiatry* 2012;**69**:449. [12] Shungu et al, *Proc Intl Soc Mag Reson Med* 2011;**19**:4346.