Functional imaging of ketamine in the rat brain: a model for glutamate dysfunction in schizophrenia

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Introduction

Ketamine can be used in both rats and humans to model some of the symptoms of schizophrenia (Krystal et al., 2003). The schizophrenia-like effects of ketamine are possibly due to blockade of NMDA receptors located on GABAergic interneurons resulting in disinhibition of glutamate release in the prefrontal cortex (PFC). We used pharmacological-challenge magnetic resonance imaging (pMRI) to test the hypothesis that ketamine-induced glutamate release will result in an increased blood-oxygen level dependent (BOLD) response in the PFC.

Methods

pMRI was used to study the effects of ketamine in two subanaesthetic doses (10 and 30 mg/kg) and vehicle (0.9% saline) in 18 male Sprague Dawley rats (6 per group, 260±8.8g). Rats were anaesthetized with alpha-chloralose (i.v.) and placed in a small bore 7T horizontal superconducting magnet. BOLD sensitive T2*-weighted images were acquired using a gradient echo (GE) sequence. A 2.5 cm surface coil was used for excitation and detection. Eleven contiguous 1 mm thick axial slices were collected per volume. GE images were recorded at a flip angle of ~90° at the centre of the coil, TR=272 ms, TE=15 ms, matrix dimensions 128/64, acquisition time 70 seconds per volume. In total 72 volumes were collected, with 16 volumes (19 minutes) as baseline scans and 52 post-injection scans (65 minutes). Data were pre-processed (smoothing, normalization to an in-house template) and analyzed using a general linear model in SPM2. For each individual subject, a series of contrast images were generated comparing the pre-infusion baseline scan to time-binned post injection scans. The post-injection images were divided into six time bins. To detect effects of time and treatment a one-way ANOVA was used. Effectively, SPM2 treats the time bins as epochs in a pseudo-block analysis, with the pre-infusion bin acting as a baseline epoch.

Results

One-way ANOVA analysis revealed significant ketamine-induced BOLD changes in multiple brain regions. Positive BOLD changes were found in the cingulate cortex (F=7.35, Z=4.60), somatosensory cortex (F=4.99, Z=3.56), motor cortex (F=4.90, Z=3.51), and retrosplenial cortex (F=4.45, Z=3.26). Negative BOLD changes were found in the hippocampus (F=4.42, Z=3.25), colliculus (F=4.23, Z=3.14), geniculate nucleus (F=4.23, Z=3.14), and cerebellum (Z=3.74, Z=2.84). Ketamine-induced BOLD signal changes peaked around 40 minutes post-injection. Percentage BOLD changes ranged from 1.5 to 6%. The results confirm the hypothesis that ketamine produces BOLD changes in the rat prefrontal cortex and are in line with human imaging studies (Lahti et al., 1995).

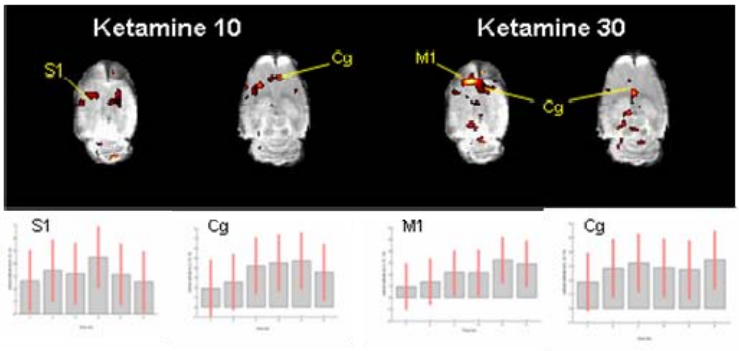

Fig 1: Axial slices of the rat neocortex with Spm_F maps superimposed, to demonstrate the effects of ketamine (compared to vehicle) at two doses, 10 and 30 mg/kg.

Fig 2: Timecourse of % BOLD signal change in identified brain regions (S1 – primary sensorimotor cortex; Cg – cingulate cortex; M1 – motor cortex)

Discussion

Our study demonstrates that ketamine produces dose- and time-dependent changes in the BOLD response in brain regions relevant to schizophrenia. Furthermore, our study confirms that drug-induced changes are detectable in α-chloralose anaesthetized rats (Ireland et al., 2005). Rat pMRI at 7T is a suitable and sensitive method to detect drug-induced changes with high anatomical and temporal resolution in a model of psychiatric disease.

References

1.Krystal et al. (2003) Psychopharmacology 169: 215-233.
2.Lahti et al. (1995) Neuroreport 6: 869-872.
3.Ireland et al. (2005). Neuroscience 133: 315-326.