Role of glutamate release in ketamine-induced blood-oxygenation level dependent (BOLD) responses: an fMRI study in rats.

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Introduction

The glutamate hypothesis of schizophrenia proposes an important role for glutamate in the disease symptoms, which can be mimicked experimentally by ketamine (KET) (Krystal, 2003). Preliminary clinical evidence already suggested a therapeutic effect of the putative glutamate release inhibitor lamotrigine (LTG) in the treatment of schizophrenia (Dursun and Deakin, 2001). We previously established localized changes in blood-oxygenation level dependent (BOLD) contrast in the rat brain in regions relevant to schizophrenia using direct pharmacoMRI. To investigate the role of glutamate release in KET induced BOLD changes, we pretreated with LTG and the metabolic glutamate agonist Glu2/3 LY379268 (LY).

Methods

Young adult male rats were anaesthetized with alpha-chloralose and placed in a small bore 7T horizontal superconducting magnet. BOLD sensitive T2*-weighted images were acquired using a gradient echo sequence. A 2.5 cm surface coil was used for excitation and detection. Ten minutes before the start of functional imaging, either vehicle (VEH), LTG (10 mg/kg) or LY (3 mg/kg) were injected (i.p.). Eleven contiguous 1 mm thick axial slices were collected per volume. In total 72 volumes of 70 seconds were collected, with 18 volumes (20 minutes) of baseline scans and 52 post-injection scans (63 minutes). KET (30 mg/kg s.c.) was injected at the start of volume 19. Data were preprocessed and analyzed using a general linear model in SPM2. For each individual subject, averaged baseline values were subtracted from post-injection time which was divided into six time bins of 9 volumes each (p<0.01). Drug and time interactions were investigated using a one way ANOVA (FWE corrected, p<0.05) (McKie, 2005).

Results

KET alone produced activations in the frontal cortex and deactivations in the hippocampus. LTG pretreatment did not block ketamine activations in the frontal cortex, but reduced ketamine effects in the anterior thalamus. LY pretreatment reduced cortical activation, but enhanced subcortical activations in the thalamus and colliculus.
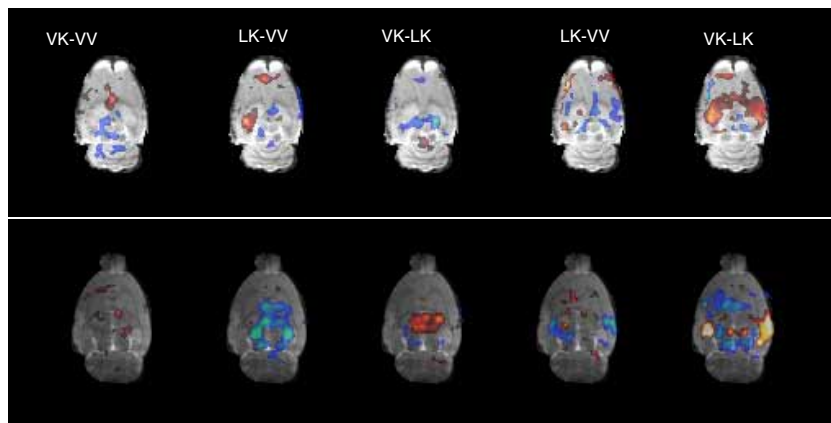
PRETREATMENT:

Figure 1a. Group T maps overlaid onto axial structural scans. Activations are shown in red and deactivations in blue. T value range is set from 1.78 to 8.00. (p<0.01, n=6-8). The upper panel shows slices -3.10 mm below Bregma, the lower panel shows slices -5.10 mm below Bregma.
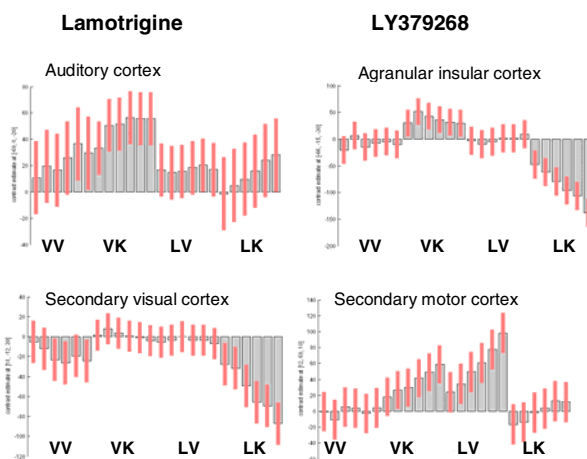
Figure 1b. Time course of selected voxels (n=6-8 each group).

Discussion

Our study demonstrates that pretreatment with the glutamate release inhibiting drugs LTG and LY modulates KET-induced BOLD changes in the rat brain. In contrast to our hypothesis, LTG and LY did not block KET activations in the prefrontal cortex, but enhanced ketamine effects in several other regions. In conclusion, rat pharmacoMRI at 7T is a sensitive method to detect pharmacologically-induced BOLD changes and may help to understand drug interactions in the brain.

References

1. Krystal et al. (2003) Psychopharmacology 169: 215-233.
2. Dursun and Deakin (2001) J Psychopharmacology 15(4):297-301.
3. Mckie et al. (2005) Psychopharmacology 180(4):680-686.