Antibiotic minocycline suppressess the phMRI response to acute ketamine challenge

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Introduction

Minocycline is a safe, widely prescribed antibiotic which has beneficial effects against apoptotic cell death, inflammation, and microglial activation. Initial clinical evidence suggests minocycline improves negative symptoms in schizophrenia if added adjunctively to usual therapy [1]. Pre-clinically it has also been shown that minocycline can reverse the behavioural effects of NMDA antagonists in animal models [2]. However, the precise neuropharmacological mechanisms underlying this efficacy remain unclear. Here, we have tested the hypothesis that pre-treating with minocycline modifies the functional activated response to acute ketamine challenge in the rat brain.

Methods

16 male Sprague-Dawley rats (253-318g) were randomly assigned to one of four challenge arms: (veh/veh), (veh/ket), (min/veh), and (min/ket) (N=4 per arm). The pre-administration of 50mg/kg minocycline or vehicle *i.p.* was followed by 30mg/kg ketamine or vehicle *s.c.* 30min later. MRI data were acquired using a Varian 7T system with a custom-made RF transmit-receive birdcage coil. For each study, a T_2-weighted anatomical image was acquired via FSE sequence (TR=240ms, TE=60ms, FOV=32mm^2, 256x256 matrix, 24 contiguous 1mm slices), followed by a three-echo GE BOLD-sensitive time-series with the same spatial coverage but lower resolution (TR_{eff}=469ms, TE_{eff}=10ms, 64x64matrix). The resulting in-plane pixel dimensions were 0.5 mm^2, with a temporal resolution of 30s per scan. Data analysis was conducted in SPM5, and individual subjects were spatially normalised to a stereotactic rat brain MRI template set [3]. Functional data was smoothed to a FWHM 1mm (2x in-plane pixel dimensions), and multiplied by a brain parenchyma mask from the template set to remove extra-cranial and CSF contributions. Time-series analysis was performed using the *"p-block"* analysis method as described previously [4]. This method enables accurate assessment of direct drug-related changes in human [5] and animal models [6]. Statistical parametric maps were thresholded using a significance value of $p < 0.05$ FWE corrected, and volumes of interest (VOI) analysis was conducted using a 3D digital reconstruction of a rat brain atlas (Paxinos and Watson (1998)) co-registered with the MRI template [3] .

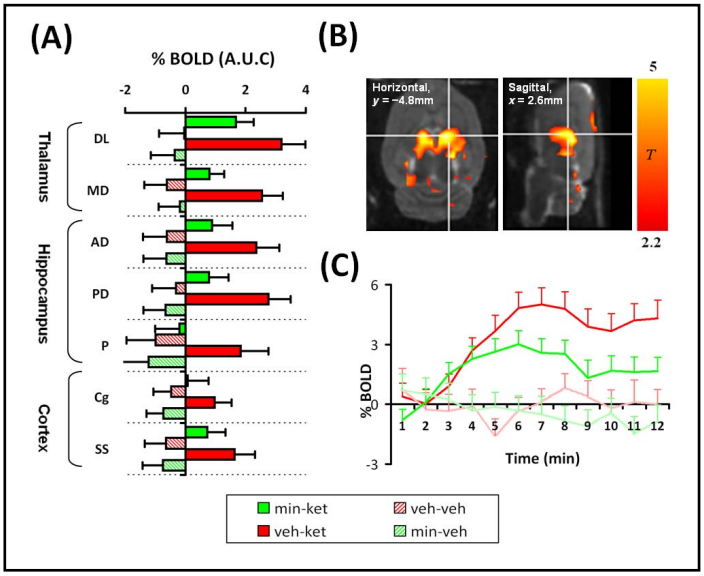

Figure 1: *Magnitude of the BOLD response in statistically significant VOI's, defined using the co-registered atlas. Histograms represent the mean area-under-curve (AUC) for each group, and error bars show 90% confidence interval* ***(A)****.Distribution of the central BOLD response induced by ketamine versus vehicle, illustrated at the level of the thalamus* ***(B)****.Example group mean time-courses from dorso-lateral thalamus (DLthalamus), with baseline data from pre-treated and challenged animals reported for comparison* ***(C)****.*

Results

Acute administration of ketamine produced robust BOLD signal increases in discrete cortico-thalamic and hippocampal structures. The time-dependent effects of ketamine typically reached maxima 6 or 7 mins after injection, and remained sustained over the examined period. Pre-administration with minocycline strongly suppressed ketamine's response in all the regions examined. The BOLD signal changes produced by pre-administration of minocycline *per se* were negligible.

Conclusions

Ketamine's response profile was similar to the pattern seen in healthy volunteers [5] and 2-DG metabolic maps in conscious rats [7]. Pre-treatment with minocycline produced widespread inhibition of ketamine-induced functional activation, indicating direct involvement of this drug in modulating glutamate neurotransmission. Minocycline represents a potential new target for preventative and therapeutic compounds in treating schizophrenia.

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References

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