Systemic infection alters 5-HT function in the rodent brain as demonstrated by phMRI

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Introduction

It is well established that the neurotransmitter 5-hydroxytryptamine (5-HT) is important in key brain functions such as mood regulation, cognition, sleep and pain processing. Furthermore, dysfunction of the 5-HT system has been implicated in the pathophysiology and treatment of a range of psychiatric disorders including major depression. However, animal studies of 5-HT function rely on invasive techniques and thus are non-transferable to human studies. Functional MRI offers the potential to investigate the effect of pharmacological manipulations in brain function in a non-invasive manner. We have previously described the use of pharmacological MRI (phMRI) for determining the site of action of fenfluramine upon 5-HT release in rat brain[1]. Based on those finding, we have now addressed two further questions: (i) are the effects of 5-HT releasing agent d-fenfluramine on the BOLD signal mediated by the $5HT_{2A}$ receptor subtype? and (ii) what are the effects of systemic infection, modelled by systemic injection of the bacterial endotoxin LPS, on 5-HT function in the rat brain?

Methods

Male Sprague-Dawley rats (250-300g) were anaesthetised with 2% halothane in N_2O:O_2 (60:40; 1l/min). Following anaesthesia induction animals were tracheotomised and one femoral artery and vein were cannulated for i.v. administration, measurements of MABP and withdrawal of blood samples. Animals were positioned in a quadrature birdcage resonator with in-built stereotaxic frame. fMRI was performed using a 7T horizontal-bore magnet with a Varian Inova spectrometer. Sets of 5 coronal images (1.5mm thick) spanning the forebrain were acquired using a T2*-weighted FLASH sequence (TE=25ms, TR=500ms, 40° flip angle, FOV 8cm x 4cm, matrix 256 x 128, acquisition time= 2min). Baseline images were acquired for 15min, followed by a bolus administration of fenfluramine (10mg/kg i.v.) and a further 85min acquisition. Data analysis was carried out using FEAT (http://www.fmrib.ox.ac.uk) software packages. Activation maps were thresholded at a significance level of P=0.05. ROI's were manually defined from the anatomical scans. For the $5HT_{2A}$ study animals were pre-treated with the specific $5HT_{2A}$ antagonist MDL-100907 10 minutes prior to fenfluramine administration. For the LPS study animals were injected intraperitoneally with 0.5mg/kg LPS 6h before the start of the fMRI study. At 6h animals injected with LPS display clear symptoms of systemic infection, including fever, reduced activity and piloerection.

Results

Compared to vehicle controls, d-fenfluramine significantly altered the BOLD signal across a number of brain regions as reported previously[1]. Increases in the BOLD signal intensity could be seen in the motor cortex and hippocampus, whilst a decrease in BOLD signal intensity was observed in the dorsal raphe nucleus and nucleus accumbens. Administration of the $5HT_{2A}$ antagonist MDL-100907 eliminated the response to fenfluramine in the motor cortex, hippocampus and DRN, but not the nucleus accumbens (Fig. 1). Pre-treatment with LPS reversed the fenfluramine-induced changes in BOLD signal in the dorsal raphe nucleus, motor cortex, and nucleus accumbens, but not the hippocampus (Fig. 2).

Figure 1

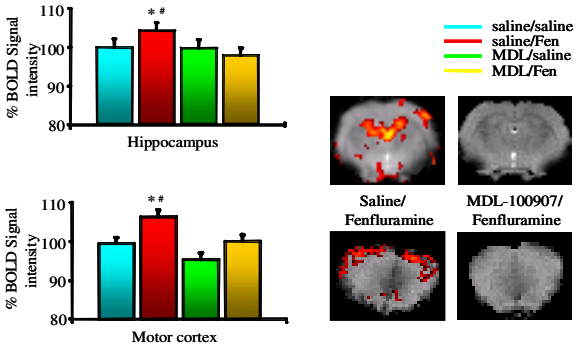

***Fig.1**, Histograms show average BOLD signal intensity in the 85 minutes following fenfluramine administration, in hippocampus and motor cortex. Images show z-score activation maps of the same regions.*

Figure 2

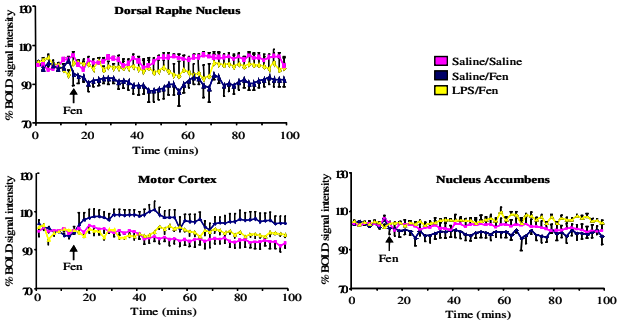

***Fig.2**, Graphs show the timecourse of BOLD signal intensity in the dorsal raphe, motor cortex and nucleus accumbens, as affected by administration of fenfluramine/LPS.*

Discussion

These findings suggest that the fenfluramine-induced BOLD responses observed in the motor cortex, hippocampus and DRN are mediated by activation of $5\text{-}HT_{2A}$ receptors, either locally within these regions or as a downstream consequence of receptor activation in other regions. The LPS findings indicate that a systemic inflammatory response can markedly alter 5HT function in the brain. Previously, pro-inflammatory cytokines have been shown to exert depression-inducing effects and 5-HT inhibitory action[2]. These studies have suggested that infection may be a key vulnerability factor for mood disorder and antidepressant treatment-resistance. Our findings strongly support a role for peripheral infection in the pathogenesis of mood disorders associated with the 5-HT system.

References

1. Preece *et al*., 2006, *ISMRM Proceedings* p.3274

2. Wichers & Maes, 2004, *J Psychiatry Neurosci* **29**, 11-7.