ASL based phMRI in assessing serotonergic response in users of XTC

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Introduction

In animals, MDMA (ecstasy or XTC) has been shown to selectively damage the serotonin (5-HT) system, at doses that very similar those used by humans. Users of XTC may therefore be at risk of developing MDMA- induced neuronal injury. In line with this, we and others have observed reductions in serotonin transporter (SERT) densities using single photon emission computed tomography (SPECT). However, SPECT imaging is hampered by a poor temporal and spatial resolution. Recently, it has been shown that an amphetamine challenge combined with pharmacologic magnetic resonance imaging (phMRI) is able to detect dopamine terminal loss in dopaminergic depleted monkeys (Jenkins 2004). In this study, we investigate how the hemodynamic changes evoked by the selective serotonin reuptake inhibitor (SSRI) citalopram can be mapped with phMRI in users of XTC and use combined SPECT imaging to assess the degree of SERT loss. We hypothesized that citalopram administration would allow us to assess changes in the 5-HT system in the brain of XTC users.

Subjects & Methods

10 XTC users (mean lifetime exposition 281 tablets; [range: 50-900], average age 26.0 y) and 6 controls (average age 22.3 y) underwent SPECT imaging with the validated SERT label [^{123}I]β-CIT and 10 XTC users and 7 controls underwent phMR imaging. Subjects had to abstain from psychoactive drugs for at least 2 weeks SPECT imaging was performed 4 hours after intravenous injection of the radiotracer, using a 12 headed dedicated brain SPECT camera (SME 810). Within 2-4 weeks of the SPECT scan, subjects underwent phMR imaging with citalopram on a Philips Intera 3.0T MRI scanner. A T1 weighted anatomical scan was acquired and following this a combined ASL EPI sequence (PULSAR, Golay 2005) of 375 volumes was used with FOV 240 x 240 mm, TR of 3 s., TE 14 ms, 17 slices, thickness 7 mm. ASL slab was 80 mm with a 1200 ms label delay. Following baseline scanning, citalopram (7.5 mg, i.v.) was administered slowly over 7.5 minutes (Tab 1).

Baseline scan 7.5 min.	→	Infusion SSRI 7.5 min.	→	Post infusion I 7.5 min.	→	Post infusion II 7.5 min.	→	Post infusion III 7.5 min.

Table 1

Analysis

SPECT scans were rendered into 3D. Based on the literature, ROIs were positioned over the frontal cortex, thalamus, and hippocampus. The cerebellum was used for calculation of non-specific binding, as it is presumed free from SERT. Binding ratios of ROI over cerebellum were calculated and compared between the two groups using student t-test.
phMRI data were analyzed using FSL 4.1 software (Analysis Group, FMRIB, Oxford, UK). Perfusion weighted images were obtained using in house software and subsequently registered to standard space via corresponding 3DT1 anatomical scans. The time series for CBF (ml/100mg brain tissue) were separated into 15 sections of 2.5 minutes and for each timeslot mean CBF was calculated. Baseline CBF (3 sections of 2.5 minutes) was compared to post infusion CBF and analyzed using paired t-tests. Thus four comparisons were made: (1) baseline vs. infusion; (2) baseline vs. post infusion I; (3) baseline vs. post infusion II; (4) baseline vs. post infusion III. (table 1)

Results

A significant reduction in SERT density in the prefrontal cortex (PFC) cortex was observed (p=0.02) and a trend towards reduced SERT density (p = 0.09) in the thalamus of XTC users when compared to controls. With the phMRI, whole brain perfusion (Fig 1, grey area represents infusion period) did not change significantly over the whole scanning session for both groups, but was overall significantly lower for the XTC users compared to controls (p < 0.0001). In the hippocampus (fig 4) a significant increase in CBF was noted in control subjects following citalopram infusion. No such effect was noted in any of the ROIs of the XTC users. In fact, in the XTC users a significant *reduction* in CBF was noted in the thalamus (fig 3) and hippocampus (fig 4) following citalopram infusion (post infusion II and III, p = 0.02 and p = 0.0003, respectively for hippocampus; p = 0.0001 and p = 0.003 respectively for thalamus). In the PFC (fig 2) only a significant transient reduction in CBF was noted (post infusion II, p=0.009).

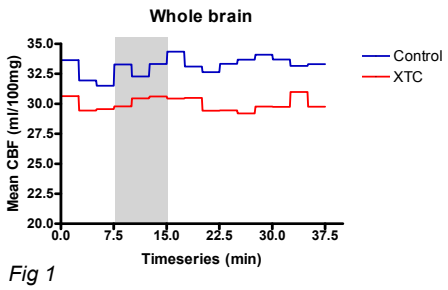

Fig 1

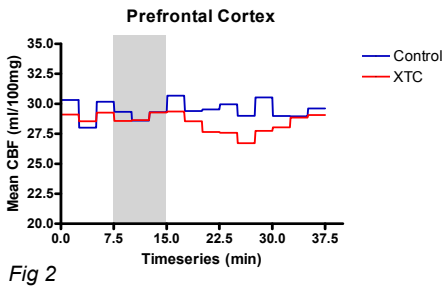

Fig 2

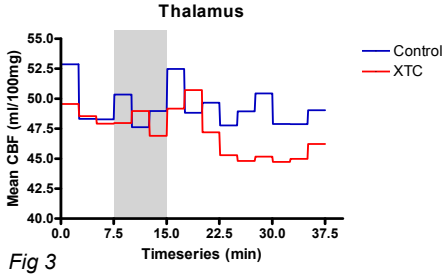

Fig 3

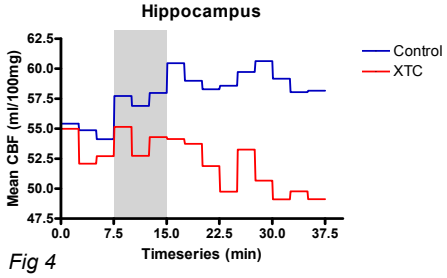

Fig 4

Discussion

Here we report markedly different citalopram-induced CBF changes, in the hippocampus in particular, in users of XTC when compared to controls using ASL based phMRI. These changes are confined to brain regions in which we also observed a reduction in SERT using SPECT (in the prefrontal cortex) or a trend towards such a reduction (thalamus). The SPECT findings are in line with previous (prospective) studies (de Win 2008), suggesting that the thalamus and prefrontal cortex are particularly sensitive to the neurotoxic effects of MDMA. ASL based phMRI may turn out to be a powerful new tool with high temporal resolution to detect changes in the 5-HT system.

Refs: Jenkins et al.J Neurosci. 2004 Oct 27;24(43):9553-60. Golay et al. MRM 2005;53:15-21. De Win et al. Brain. 2008; 131: 2936-2945