Neuronal effects of acute citalopram detected by pharmacoMRI (pMRI)

S. McKie[1], C. Del-Ben[2], R. Elliott[1], S. Williams[3], I. Anderson[1], B. Deakin[1]

[1]Neuroscience and Psychiatry Unit, University of Manchester, Manchester, Manchester, United Kingdom, [2]Neurology, Psychiatry and Medical Psychology, University of Sao Paulo, Sao Paulo, Sao Paulo, Brazil, [3]Imaging Science and Biomedical Engineering, University of Manchester, Manchester, Manchester, United Kingdom

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is implicated in the aetiology and treatment of a variety of psychiatric disorders including depression, anxiety and impulsive-control disorders. Attempts to demonstrate abnormal 5-HT function in patients are limited by the necessity to use indirect measures of 5-HT function. Advances in brain imaging techniques and analysis mean that a more direct investigation of neurotransmitter function within the brain is possible. The combination of pharmacological challenges and fMRI (pMRI) has the potential to detect 5-HT effects on brain function, recently demonstrated using the infusion of the 5-HT2C receptor agonist methyl-chlorophenylpiperazine (mCPP)(Anderson et al. 2002). To extend this investigation we examined the effects of intravenous administration of the selective 5-HT reuptake inhibitor, citalopram. Citalopram is an effective antidepressant and anxiolytic (Bakker et al. 2000; Keller 2000). We hypothesised that citalopram would affect the BOLD response in brain areas known to be implicated in depression and its response to antidepressants such as the ventral cingulate, medial prefrontal cortex, amygdala, hippocampus, the striatum and the thalamus.

Methods

12 healthy volunteers aged between 18 and 35 years (mean 24.7(5.8)) were tested on 2 occasions receiving saline (placebo) or citalopram (7.5mg over 7.5 minutes) in a randomised, balanced order, single-blind fashion. Each subject underwent a 22.5 minute fMRI scan during which they received the drug infusion.

Images were acquired on a 1.5T Philips *Intera* scanner with a multi-slice, single shot EPI sequence to achieve whole brain coverage. Each volume comprised of 40 contiguous axial slices (TR = 5 secs, TE = 40 secs, 3.5mm slice thickness with in-plane resolution 3x3 mm).

Data were analysed using SPM2 (Friston, The Welcome Department of Cognitive Neurology, London, UK). The 22.5 minute (270 volume) infusion scan was divided into 7 time-bins. The first time-bin (T0) consisted of 90 pre-infusion scans (7.5 minutes). The next six time-bins were each 30 scans in length (2.5 minutes), 3 during the infusion (T1, T2, T3) and 3 post-infusion (T4, T5, T6). The average of each of the six time-bins were separately compared to the baseline average using regression analysis. Six random effects paired t-tests were used to compare images after placebo and citalopram at each time-bin (Tn).

Results

Significant differences between citalopram and placebo were observed in the superior frontal gyrus, left middle frontal gyrus and superior temporal gyrus in time-bins T5 and T6. There were significant bilateral responses in the inferior frontal gyrus, however left was significant at T3 whereas right was significant later at T5. Occipital and parietal areas responded significantly at T2 and T3. The subgenual cingulate responded significantly from T3 until T6 as did the left caudate (see figure). The right caudate responded significantly during T5 and T6. The right anterior cingulate and the left cingulate gyrus were significant at T6. From T3 to T5 the right amygdaloid complex was significant whereas the left amygdaloid complex was significant in T5 and T6. There was a significant difference in the response of the left thalamus and right brainstem at T6.

There were no areas that remained significant for longer than one time-bin when investigating the placebo minus citalopram difference.

Discussion

We have developed a method of detecting the central effects of acute citalopram administration to normal volunteers. BOLD responses emerging over 15 minutes after the onset of citalopram infusion were observed in regions implicated in the mechanisms of action of antidepressants. We hypothesise that the significant changes observed in the caudate, cingulate and amygdala are mediated by 5HT2C receptors. Citalopram pMRI offers a potential new tool for investigating 5-HT mechanisms in depression and its treatment.

References

1.Anderson et al. 2002, Neuroreport, 13, 1547-51.
2.Bakker et al. 2000, Int Clin Psychopharm, 15, S25-S30.
3.Keller 2000, J Clin Psych, 61, 896-908.

Fig 1 Time series plot in a single subject for the left caudate