How Antidepressants Work: SSRI Treatment Induces Adaptive Changes in Brain 5-HT phMRI Responses

D. Downey[1,2], K. E. Davies[1], S. McKie[2], G. Juhasz[2], I. M. Anderson[2], M. A. Smith[3], J-F. W. Deakin[2], and S. R. Williams[1]

[1]Imaging Science and Biomedical Engineering, University of Manchester, Manchester, United Kingdom, [2]Neuroscience and Psychiatry Unit, University of Manchester, Manchester, United Kingdom, [3]Astra Zeneca R&D, Astra Zeneca U.S., Wilmington, Delaware, United States

Introduction

Serotonin specific reuptake inhibitors (SSRIs), which are used to treat depression, typically require 10-14 days of administration before clinically beneficial effects are seen. The biological mechanisms that mediate antidepressant action are not well understood. Citalopram, a standard SSRI antidepressant, can be administered intravenously and its effects on the BOLD response assessed using phMRI. Acute 5-HT challenge as detected by phMRI has highlighted several brain areas enriched with 5-HT reuptake sites, which have also been implicated in the development and treatment of depression (McKie et al., 2005; Anderson et al., 2008). The therapeutic effect of SSRIs may be the result of adaptive changes in the 5-HT system to sustained reuptake inhibition. We hypothesised that chronic SSRI usage may down regulate raphé nuclei 5-HT1a and 5-HT2c receptor expression and enhance 5-HT1 signalling in post synaptic areas mediating the delayed therapeutic effect. Using citalopram challenge phMRI we examined the BOLD response to the acute and sub-chronic effects of SSRIs in order to explore adaptive changes to the 5-HT system.

Methods

24 healthy, right handed, age and sex matched volunteers were recruited (mean age=21.1, sd=1.7 years). Participants were tested on two occasions, first with IV citalopram 7.5mg, infused over 7.5 minutes and again with the same protocol after 14 days following 11 days (+ 3 day washout) of either placebo or citalopram 20mg tablets in a randomised, balanced order, single blind design. They underwent a 25 minute fMRI sequence with 5min baseline followed by 7.5min infusion and 12.5min post infusion scanning. Whole brain images were acquired on a Philips *Intera* 1.5T scanner using single-shot echo-planar (EPI) pulse sequence. Each volume comprised 29 ascending axial slices (TR=2s, TE=40ms, 4.5mm thickness with 0.5mm slice gap, in-plane resolution of 3.5x3.5mm).
Data were analysed using SPM5. Each 25 min scan was divided into 2 min time bins in a pseudo-block design. The last 2 minutes of baseline was compared to the infusion and post infusion time bins using regression analysis. A factorial ANOVA of block x group x session was conducted.

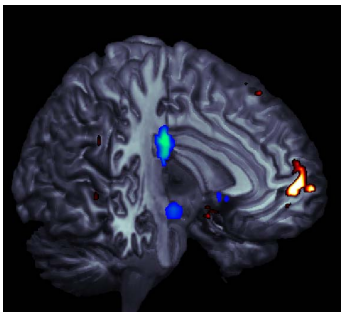

Fig. 1: Citalopram induced BOLD signal changes following chronic citalopram treatment. Attenuated response found in mid-cingulate, ventral tegmental area, and ventral striatum. Brodmann area 10 was increased after sub-chronic citalopram treatment.

Results

The second session scans were compared between placebo and citalopram treatment groups. Session 2 BOLD responses to IV citalopram were inclusively masked at $p<0.05$ uncorrected by the conjunction between the first session scans. Significant attenuation of the ventral striatum, mid cingulate, ventral tegmental area and right dorsolateral prefrontal cortex were found following sub-chronic citalopram treatment to 5-HT challenge. Significant increases in the frontal pole were also observed following SSRI treatment ($p<0.001$ uncorrected). These prior hypothesised areas survived small volume correction at $p<0.05$ (FWE).

Discussion

In a time series analysis sub-chronic citalopram modulation of an acute 5-HT challenge appears to inhibit the BOLD response in several important brain areas implicated in depression and its treatment. Desensitisation of the 5-HT system may be observed by BOLD signal changes directly at the site of reuptake inhibition or upstream on integrated 5-HT networks. The discreet changes following citalopram treatment may be indicative of decoupling of 5-HT negative feedback control mechanisms by SSRIs.

Conclusion

We observed adaptive changes to an acute pharmacological challenge following sub-chronic SSRI treatment. The results support direct phMRI as a tool to probe 5-HT function and related brain changes following exposure to SSRIs.

References

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