Application of Functional Magnetic Resonance Imaging to the study of 5-HT2C Neurotransmission in Rat Brain

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Introduction

We are developing pharmacological challenge fMRI (pMRI) to characterise the role of neurotransmitters in common homeostatic and reward pathways involved in appetite regulation. In this study we probed the serotonergic system by using an agonist m-Chlorophenylpiperazine (mCPP) which acts at two of the serotonin (5 hydroxytryptamine – 5-HT) receptor subtypes – the 5HT1B and 5HT2C receptors. mCPP is a powerful appetite suppressor and is a metabolite of the anti-depressant Trazodone. We combined, in a pMRI experiment, mCPP challenge with pre-infusion of specific 5-HT1B and 5-HT2C receptor antagonists to determine the brain areas involved in 1B and 2C receptor activity.

Methods

Rats were imaged in a 7T magnet for 84 minutes under alpha-chloralose anaesthesia, and injected intraperitoneally after a 15 min baseline period with 5-HT1B antagonist (SB 224289 2.5 mg/kg), 5-HT2C antagonist (SB 242084, 2 mg/kg), or vehicle; followed by a subcutaneous injection of mCPP (3 mg/kg) or saline 15 min later. A T_2*-weighted gradient echo sequence was used to record whole brain volumes every 70s (TR = 172ms, TE = 15ms, matrix 128 x 64, 4 averages). Brain volumes were realigned and normalized to an in-house rat brain template using SPM2. The effect of mCPP or saline was analyzed by comparing post infusion time-binned data (14 min blocks) to the pre-infusion period, for all of the experimental conditions. A one-way ANOVA was used to compare all experimental conditions in order to determine the effects of the antagonists. The results were masked to include only those areas which responded to mCPP in the absence of any pre-treatment. SPM2 was used for these analyses.

Results

mCPP alone induced both positive and negative BOLD responses in a number of brain regions, including areas of the limbic system and motor areas. Overall, 5-HT2C antagonist SB 242084 reversed effects measured by BOLD contrast elicited by mCPP, whereas the 5-HT1B antagonist SB 224289 had virtually no impact. SB 242084 eliminated BOLD signal in areas of the limbic system: nucleus accumbens, mediobasal hypothalamus, bed nucleus of the stria terminalis, amygdala, thalamus, and the hippocampus. The 5-HT2C antagonist also diminished activation in the pontine nuclei, motor areas such as the caudate putamen, pallidum, substantia nigra and ventral tegmental area. In addition BOLD signal was returned to baseline levels in the cortical regions, and the cerebellum. The 5-HT1B antagonist produced either no change or a partial elimination of BOLD signal in these areas.

Discussion and Conclusion

Though at this stage it is difficult to attribute regional brain activity to specific effects of the drugs, these results suggest that mCPP may reduce food intake by acting specifically on 5-HT2C receptors in the brain. This is supported by feeding studies by other groups demonstrating the dependency of satiety on 5-HT2C receptors.[1, 2, 3]

REFERENCES

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