Brain Serotonin neurotransmission and Affect regulation in Humans: A Positron Emission Tomography study

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Background

Serotonin (5-HT) neurotransmission is thought to be critical for affect regulation in the brain and many antidepressants are thought to primarily work by altering 5-HT levels. [1]. However it has not been possible to directly measure 5-HT brain levels in vivo in humans.

The aims of the study are

1) To assess the sensitivity of a highly selective 5-HT_{1A} agonist radioligand [^{11}C]CUMI-101 to changes in endogenous 5-HT levels induced by an intravenous challenge with the citalopram, a selective serotonin re-uptake inhibitor (SSRI), in healthy human participants.

2) To determine the relationship between brain serotonin neurotransmission and affect regulation in vivo.

Methods

We studied 15 healthy volunteers, of which 13 (12 Men; mean age 50.9yrs) underwent two PET scans

Subjects received either citalopram 10mg or saline before PET scan on each day in a randomized design.

[11C]-CUMI binding potential (BP) were obtained for dorsal raphe and cortical regions

All 15 (13 Men) subjects underwent a functional MRI based Faces-emotion processing task known to activate the amygdala on a separate day

Results - 1

Relative to placebo, citalopram infusion significantly increased [^{11}C]-CUMI-101 binding potential at postsynaptic regions (t= -3.72; df=1; 12; p=0.003) but there was no change in binding at 5-HT_{1A} autoreceptors in the DRN (t= 0.57; df=1, 12; p=0.58).

Repeated measures analysis of postsynaptic regions revealed a significant treatment effect (F=6.31; df=1, 12; p=0.03).

Across the cortical brain regions citalopram treatment induced a mean 7% increase in [^{11}C]CUMI-101 binding potential (placebo 1.3 (0.2); citalopram 1.4 (0.2); paired t-test p=0.003) (Fig 1, 2 & 3).

Fig 1

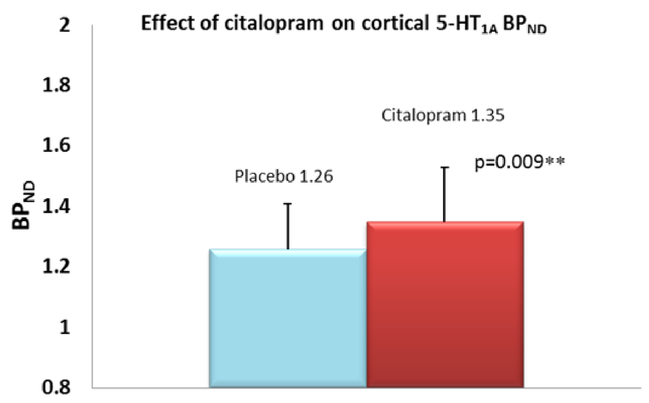


Figure 2: Serotonin (5-HT_{1A}) receptor availability binding potential (BP_{ND}) in the postsynaptic region and presynaptic raphe in 13 subjects who received placebo or citalopram.

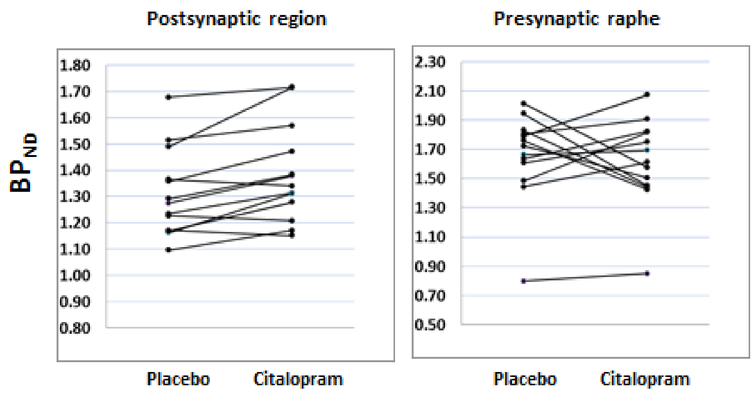
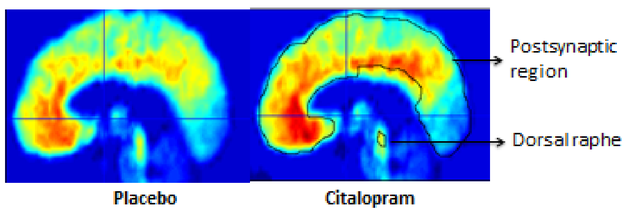


Figure 3: The [^{11}C]CUMI-101 summated BP_{ND} parametric PET image of a representative subject showing citalopram-induced increases in 5-HT_{1A} receptor availability in the postsynaptic brain region

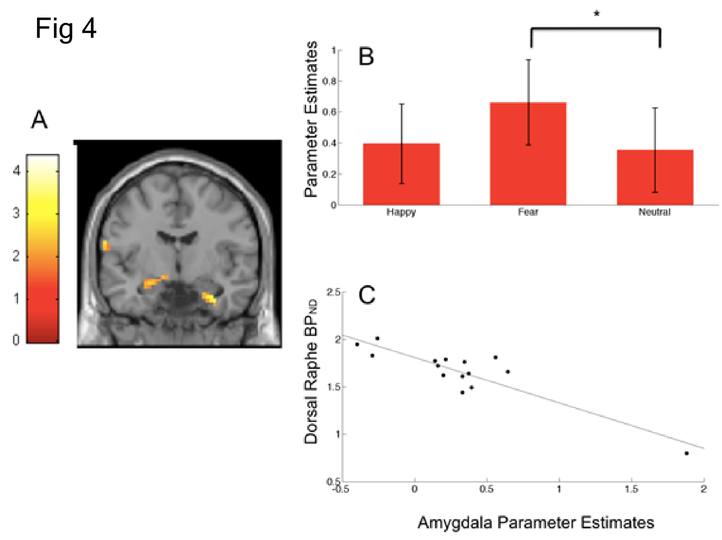


Results - 2

Blood-oxygen-level-dependent (BOLD) response to fearful vs neutral faces in the left amygdala inversely correlated with baseline (placebo) 5-HT_{1A} dorsal raphe BP (Pearson r2=-0.87, p<0.001) (Fig 4)

No significant correlation observed between BOLD signal and regional BP changes observed after citalopram challenge.

Fig 4



Discussion

Study 1:

- Increase in postsynaptic [^{11}C]CUMI-101 availability could be attributable to a decrease in endogenous 5-HT availability in cortical terminal regions due to SSRI activation of 5-HT1A autoreceptors and resultant decrease in DRN cell firing (1-3).
- [^{11}C]CUMI-101 may be sensitive to changes in endogenous 5-HT release in humans.

Study 2:
The relationship between amygdala responsivity during emotion processing task and baseline dorsal raphe [^{11}C]CUMI-101 binding suggests presynaptic 5-HT_{1A} autoreceptors exerts possibly a tonic serotonergic control and plays important role in the regulation of affect. Presynaptic 5-HT_{1A} could be a potential treatment target for affective disorders.

References

1. Gartside SE et al. Br J Pharmacol 1995; 115(6): 106
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3. Giovacchini G et al. Neuroimage 2005; 28(1): 238-248.

Fig 1,2 & 3 has been published at S. Selvaraj et al., Measuring endogenous changes in serotonergic neurotransmission in humans: a [11C]CUMI-101 PET Challenge Study. Mol Psychiatry (2012)

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