Effect of 5-HT_4 receptor agonism on memory processing during a functional MRI hippocampal task in humans

de Cates A. N.[1,2], Wright L. C.[2], Martens M.A.[1], Gibson D.[2], Cowen P.J.[1,2], Harmer C.J. [1,2]*, Murphy S.E. [1,2]*

[1] University Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

[2] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Introduction:

The 5-HT_4 receptor is most prevalent in brain areas involved in emotion and cognition [1], and studies using animal models suggest that stimulating this postsynaptic receptor might have therapeutic potential. In particular, rodents have improved performance during learning and memory tasks after only a few doses [2,3], and 5-HT_4 receptor agonism induces the production of neurotransmitters and neurotrophic proteins required for neuroplasticity [2,4,5]. Investigating 5-HT_4 receptor agonism in humans has previously been limited due to the side-effect profile of early agents.

Aims:

Here we present results of an fMRI memory encoding task in humans following administration of 6 days of the licensed 5-HT_4 receptor partial agonist, prucalopride, as compared to placebo. We hypothesised that prucalopride would improve episodic memory and produce greater activation of hippocampal neural networks during the fMRI task.

Methods:

Right-handed healthy participants (N=44, aged 18-40) were administered either prucalopride (7 days x 1mg) or placebo, in a double-blind, randomised design. Drug allocation was stratified for gender. On day 6, participants underwent a 3T scan including an fMRI memory task designed to induce hippocampal activation. Participants were presented with 91 coloured emotionally-neutral images of animals or landscapes, and asked to identify these as animal / non-animal: 8 times for 8 randomly-selected “familiar” pictures before the scan, and again for these 8 “familiar” and 48 “novel” images during the scan. 40 minutes after the scan, participants’ ability to differentiate between novel, familiar and 27 additional “distractor” images was tested. Behavioural data were analysed using repeated-measures ANOVA. Imaging data were analysed with FSL, corrected for grey matter maps and multiple

comparisons. Brain activations showing significant group differences were identified using cluster-based thresholding ($Z>3.1$, $p<0.05$ corrected). Regions of interest analyses were pre-specified.

Results:

Administration of prucalopride led to improved memory performance. In the post-scan recall task, the prucalopride group were more accurate than participants taking placebo in distinguishing each category of image (novel/familiar/distractor) ($F(1,38)=4.806$, $p=0.035$) and selecting those seen before (novel+familiar) versus distractors ($F(1,38)=5.18$, $p=0.029$). Preliminary findings indicate that HT_4 agonism increased memory-related brain activation in the R angular gyrus (whole-brain analysis; prucalopride>placebo, $Z=4.03$, $p<0.02$, peak voxel location: $x=42$, $y=-58$, $z=52$, cluster size=134 voxels). Prucalopride also increased L and R hippocampal activation for novel images versus familiar when compared to placebo, but this did not meet significance (% signal change featquery: small volume-corrected analysis of L and R hippocampus).

Conclusions:

We found 5-HT_4 agonism in humans to be associated with superior recognition of previously-seen images and thus superior memory performance when compared to placebo. Following successful memory encoding to novel images in the hippocampus, 5-HT_4 agonism also resulted in increased activation to the R angular gyrus whilst actively undertaking memory processing. This brain region is associated with memory retrieval, as part of the default mode network, and with close connections to the hippocampus. This finding holds promise for the future use of 5-HT_4 agonists for ameliorating cognitive impairments associated with psychiatric disease. Future work could include optimising the dose to ensure maximal agonism at the receptor whilst minimising side effects.

References:

[1] Beliveau, V., Ganz, M., Feng, L., Ozenne, B., Hojgaard, L., Fisher, P. M., et al., 2017. A high-resolution in vivo atlas of the human brain’s serotonin system. Journal of Neuroscience 37(1), 120‑128.

[2] Lucas, G., Rymar, V. V., Du, J., Mnie-Filali, O., Bisgaard, C., Manta, S., et al., 2007. Serotonin(4) (5-HT(4)) receptor agonists are putative antidepressants with a rapid onset of action. Neuron 55(5), 712‑725.

[3] Lamirault, L., & Simon, H., 2001. Enhancement of place and object recognition memory in young adult and old rats by RS 67333, a partial agonist of 5-HT4 receptors. Neuropharmacology 41(7), 844‑853.

[4] Hagena, H., & Manahan-Vaughan, D., 2017. The serotonergic 5-HT4 receptor: A unique modulator of hippocampal synaptic information processing and cognition. Neurobiology of Learning and Memory 138, 145‑153.
[5] Pascual-Brazo, J., Castro, E., Díaz, A., Valdizán, E. M., Pilar-Cuéllar, F., Vidal, R., et al., 2012. Modulation of neuroplasticity pathways and antidepressant-like behavioural responses following the short-term (3 and 7 days) administration of the 5-HT$_4$ receptor agonist RS67333. International Journal of Neuropsychopharmacology 15(5), 631‑643.

Disclosures:

CJH has received consultancy fees from P1vital Ltd., Janssen Pharmaceuticals, Sage Therapeutics, Pfizer and Lundbeck.
SEM has received consultancy fees from P1vital Ltd. and Janssen Pharmaceuticals.
CJH and SEM hold grant income from UCB Pharma and Janssen Pharmaceuticals.
CJH, SEM and PJC hold grant income from a collaborative research project with Pfizer.
ANdC is funded by a Wellcome Trust Clinical Doctoral Research Fellowship.