Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst056P.pdf

An investigation of the pharmacology of vortioxetine at human 5-HT_3 receptors

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Introduction: Vortioxetine is a novel antidepressant that was approved by the FDA in September 2013 for use in Major Depressive Disorder (MDD). Some of the most common side-effects are emesis and diarrhoea, which may indicate activation of 5-HT_3 receptors at therapeutic concentrations. Indeed, vortioxetine displays affinity for a number of 5-HT receptors including the 5-HT_{1B}, 5-HT_3, and 5-HT_7 receptors, and a previous study demonstrated activation of the 5-HT_3 receptor but only upon first application of the drug[1]. The 5-HT_3 receptor is a ligand-gated ion channel expressed by neurones in the brain (e.g. chemoreceptor trigger zone) as well as in the periphery (e.g. gastrointestinal tract). Two major subtypes of the receptor have been studied in the most detail; the homomeric 5-HT_3A receptor and the heteromeric 5-HT_3AB receptor. The aim of this study was to further explore the interaction of vortioxetine with the 5-HT_3 receptor.

Methods: Using HEK293 cell lines stably expressing either the 5-HT_3A or 5-HT_3AB receptor, the agonist profile of vortioxetine was investigated using fluorescent intracellular calcium assays, as previously described[2]. Furthermore, the interaction of vortioxetine with the orthosteric site of the 5-HT_3 receptor was examined using receptor binding techniques[2].

Results: In functional assays, vortioxetine behaved as a partial agonist with intrinsic efficacy of 42±3 % at 5-HT_3A receptors and 37±4 % at the 5-HT_3AB receptors (mean±SEM, n=4). 5-Chloroindole (5-Cl; 10 µM), a 5-HT_3 receptor positive allosteric modulator, increased the efficacy of vortioxetine at both the 5-HT_3A receptor (to 80±6 % relative to 5-HT) and 5-HT_3AB receptor (77±10 % relative to 5-HT)[2] (mean±SEM, n=4). The EC_{50} of vortioxetine was similar at 5-HT_3A and 5-HT_3AB receptors (179±14 nM and 119±9 nM, respectively). Receptor binding experiments demonstrated the affinity of vortioxetine was comparable between 5-HT_3A and 5-HT_3AB receptors (9±1.4 and 19±2 nM, respectively; mean±SEM, n=3-4). In saturation binding experiments, vortioxetine (10-30 nM) increased the K_d of [^{3}H]-granisetron, but had no effect on the density of labelled receptors, indicative of a competitive interaction (n=4).

Conclusion: Our studies indicate vortioxetine is a relatively high affinity competitive partial agonist at the 5-HT_3 receptor. Such actions may be responsible for the emesis and/or diarrhoea experienced by some patients receiving vortioxetine.

References:

1. Bang-Anderson et al. (2011). *J. Med. Chem* **54:** 3206–3221.

2. Newman et al. (2013). *Br J Pharmacol* **169:** 1228–1238.