

5-HT₃ receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

Nicholas M. Barnes¹, Tim G. Hales², Sarah C. R. Lummis³, Beate Niesler⁴ and John A. Peters²

1. University of Birmingham, UK
2. University of Dundee, UK
3. University of Cambridge, UK
4. University of Heidelberg, Germany

Abstract

The 5-HT₃ receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-Hydroxytryptamine (serotonin) receptors [66]**) is a ligand-gated ion channel of the Cys-loop family that includes the zinc-activated channels, nicotinic acetylcholine, GABA_A and strychnine-sensitive glycine receptors. The receptor exists as a pentamer of 4TM subunits that form an intrinsic cation selective channel [5]. Five human 5-HT₃ receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT_{3A} and hetero-oligomeric assemblies of 5-HT_{3A} and 5-HT_{3B} subunits have been characterised in detail. The 5-HT_{3C} (*HTR3C*, *Q8WXA8*), 5-HT_{3D} (*HTR3D*, *Q70Z44*) and 5-HT_{3E} (*HTR3E*, *A5X5Y0*) subunits [83, 122], like the 5-HT_{3B} subunit, do not form functional homomers, but are reported to assemble with the 5-HT_{3A} subunit to influence its functional expression rather than pharmacological profile [124, 63, 157]. 5-HT_{3A}, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT_{3A} receptor [157]. The co-expression of 5-HT_{3A} and 5-HT_{3C-E} subunits has been demonstrated in human colon [82]. A recombinant hetero-oligomeric 5-HT_{3AB} receptor has been reported to contain two copies of the 5-HT_{3A} subunit and three copies of the 5-HT_{3B} subunit in the order B-B-A-B-A [7], but this is inconsistent with recent reports which show at least one A-A interface [96, 150]. The 5-HT_{3B} subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT_{3AB} versus homo-oligomeric 5-HT_{3A} recombinant receptors [32, 41, 56, 85, 139, 129, 79], influences the potency of channel blockers, but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists ([17], but see [41, 30, 35]) which may be explained by the orthosteric binding site residing at an interface formed between 5-HT_{3A} subunits [96, 150]. However, 5-HT_{3A} and 5-HT_{3AB} receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles [138, 135, 71]. The potential diversity of 5-HT₃ receptors is increased by alternative splicing of the

from different transcriptional start sites has been reported for the *HTR3A*, *HTR3B*, *HTR3D* and *HTR3E* genes, which could result in 5-HT₃ subunits harbouring different N-termini [152, 79, 120]. To date, inclusion of the 5-HT_{3A} subunit appears imperative for 5-HT₃ receptor function.

Contents

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