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5-HT_3 receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

The 5-HT_3 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-HT_3 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-HT_3 receptors is increased by alternative splicing of the genes HTR3A and E [64, 19, 124, 123, 120]. In addition, the use of tissue-specific promoters driving expression from different transcriptional start sites has been reported for the *HTR3A, HTR3B, HTR3D* and *HTR3E* genes, which could result in 5-HT_3 subunits harbouring different N-termini [152, 79, 120]. To date, inclusion of the 5-HT_3A subunit appears imperative for 5-HT_3 receptor function.

Contents

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