5-HT$_3$ (5-hydroxytryptamine$_3$)

Overview: The 5-HT$_3$ receptor [nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-hydroxytryptamine (serotonin) receptors (Hoyer *et al*., 1994; see also Peters *et al*., 2009)] is a ligand-gated ion channel of the Cys-loop family that includes the 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 (Barnes *et al*., 2009). Five human 5-HT$_3$ receptor subunits have been cloned, and homo-oligomeric assemblies of 5-HT3A and hetero-oligomeric assemblies of 5-HT3A and 5-HT3B subunits have been characterized in detail. The 5-HT3C (ENSG00000178084), 5-HT3D (ENSG00000186090) and 5-HT3E (ENSG00000186038) subunits (Karnovsky *et al*., 2003; Niesler *et al*., 2003), like the 5-HT3B subunit, do not form functional homomers, but are reported to assemble with the 5-HT3A subunit to influence its functional expression rather than pharmacological profile (Niesler *et al*., 2007; Holbrook *et al*., 2009). A recombinant hetero-oligomeric 5-HT3AB receptor has been reported to contain two copies of the 5-HT3A subunit and three copies of the 5-HT3B subunit in the order B-B-A-B-A (Barrera *et al*., 2005). The 5-HT3B subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT3AB versus homo-oligomeric 5-HT$_3$A recombinant receptors (Davies *et al*., 1999; Dubin *et al*., 1999; Hanna *et al*., 2000; Kelley *et al*., 2003; Stewart *et al*., 2003; Peters *et al*., 2005; Jensen *et al*., 2008), but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists (Brady *et al*., 2001; but see Dubin *et al*., 1999; Das and Dillon, 2003; Deeb *et al*., 2009). However, 5-HT$_3$A and 5-HT$_3$AB receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles (Solt *et al*., 2005; Rüsch *et al*., 2007; Hu and Peoples, 2008). The potential diversity of 5-HT$_3$ receptors is increased by alternatively spliced variants of the 5-HT3A and 5-HT3E subunits (Hope *et al*., 1993; Bruss *et al*., 2000; Niesler *et al*., 2007; 2008), and tissue-specific preferences for different transcription start sites in the *HTR3B* gene, which could result in three different 5-HT3B subunit N-termini (Tzvetkov *et al*., 2007; Jensen *et al*., 2008). To date, inclusion of the 5-HT3A subunit appears imperative for 5-HT$_3$ receptor function.

Nomenclature	5-HT$_3$
Former names	M
Ensembl ID	5-HT3A ENSG00000166736, 5-HT3B ENSG00000149305
Selective agonists (pEC$_{50}$)	3-Chlorophenyl-biguanide (5.4–5.8), 2-methyl-5-HT (5.5–5.6), 1-phenylbiguanide (4.1)
Selective antagonists (pK_i)	(*S*)-Zacopride (9.0), granisetron (8.6–8.8), tropisetron (8.5–8.8), ondansetron (7.8–8.3)
Channel blockers	Diltiazem, TMB-8, picrotoxin (+5-HT3B potency reduced, Das and Dillon (2003))
Radioligands (K_D)	[^{3}H]Ramosetron (0.15 nM), [^{3}H]granisetron (1.2 nM), [^{3}H]-(*S*)-zacopride (2.0 nM), [^{3}H]GR65630 (2.6 nM), [^{3}H]LY278584 (3 nM)
Functional characteristics	γ = 0.4–0.8 pS (+5-HT3B, γ = 16 pS); inwardly rectifying current (+5-HT3B, rectification reduced); n_H 2-3 (+5-HT3B 1-2); relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit

Quantitative data in the table refer to homo-oligomeric assemblies of the human 5-HT3A subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT3B subunit are indicated in parenthesis. Methadone, although not a selective antagonist, displays multimodal and subunit-dependent antagonism of 5-HT$_3$ receptors (Deeb *et al*., 2009). Human (Belelli *et al*., 1995; Miyake *et al*., 1995), rat (Isenberg *et al*., 1993), mouse (Maricq *et al*., 1991), guinea-pig (Lankiewicz *et al*., 1998), ferret (Mochizuki *et al*., 2000) and canine (Jensen *et al*., 2006) orthologues of the 5-HT3A receptor subunit have been cloned that exhibit intraspecies variations in receptor pharmacology. Notably, most ligands display significantly reduced affinities at the guinea-pig 5-HT$_3$ receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT$_3$ receptors are subject to allosteric modulation by extracellular divalent cations, alcohols, several general anaesthetics and 5-hydroxy- and halide-substituted indoles (see reviews by Parker *et al*., 1996; Davies *et al*., 2006; Thompson and Lummis, 2006; 2007).

Abbreviations: **GR65630**, 3-(5-methyl-1*H*-imidazol-4-yl)-1-(1-methyl-1*H*-indol-3-yl)-1-propanone; **LY278584**, 1-methyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-indazole- 3-carboxamide; **TMB-8**, 8-(diethylamine)octyl-3,4,5-trimethoxybenzoate

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