Gene Focus

Concise expert focus on a gene at the heart of pharmacogenomic research

For reprint orders, please contact:
reprints@futuremedicine.com

Serotonin type 3 receptor genes: *HTR3A, B, C, D, E*

Beate Niesler[†], Johannes Kapeller,
Christian Hammer & Gudrun Rappold

[†] Author for correspondence
Department of Human Molecular Genetics,
University of Heidelberg, Im Neuenheimer Feld 366,
69120 Heidelberg, Germany
Tel.: +49 622 156 5067; +49 622 156 5058;
Fax: +49 622 156 8884;
E-mail: beate_niesler@med.uni-heidelberg.de

Highlights

There are five human serotonin type 3 receptor genes: *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D* and *HTR3E*.

Functional receptors are pentameric complexes of diverse composition.

5-HT₃ receptor antagonists are established in the therapy of chemotherapy-induced nausea and vomiting and irritable bowel syndrome.

HTR3A and *HTR3B* variants seem to be involved in psychiatric disorders and serve as predictors in the medical treatment of chemotherapy-induced nausea and vomiting and psychiatric patients.

The 5-HT₃ receptor is a ligand-gated ion channel composed of five subunits. To date, five different human subunits are known, 5-HT_{3A-E}, which are encoded by the serotonin receptor genes *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D* and *HTR3E*, respectively. Functional receptors are pentameric complexes of diverse composition. Different receptor subtypes seem to be involved in chemotherapy-induced nausea and vomiting (CINV), irritable bowel syndrome and psychiatric disorders. 5-HT₃ receptor antagonists are established in the therapy of CINV and irritable bowel syndrome. *HTR3A* and *HTR3B* polymorphisms may also contribute to the etiology of psychiatric disorders and serve as predictors in CINV and in the medical treatment of psychiatric patients.

Human 5-HT₃ receptor system

The 5-HT₃ receptor is a ligand-gated ion channel (LGIC) permeable to Na⁺, K⁺ as well as Ca²⁺ ions. To date, five different 5-HT₃ receptor subunits are known in humans: 5-HT_{3A}, B, C, D and E [1–5]. The 5-HT₃ receptor is encoded by *HTR3* genes residing in close proximity on chromosome 11q23 (*HTR3A* and *HTR3B*) and 3q27 (*HTR3C*, *HTR3D* and *HTR3E*) in the human genome (Figure 1) [4,5].

The serotonin type 3 receptor is formed by a pentameric complex. Only 5-HT_{3A} subunits are able to form functional homo-oligomeric receptors, whereas the 5-HT_{3B}, C, D and E subunits cannot build a functional homopentameric receptor on their own [1–3,5,6]. Although heteromeric 5-HT_{3A/X} receptors show individual differences compared to homomeric 5-HT_{3A} receptors, the overall pharmacological profiles are similar [3,7]. By contrast, structurally different compounds and 5-HT₃ receptors of diverse composition may very likely present distinct pharmacological properties. Consequently, investigating

the composition and stoichiometry of native 5-HT₃ receptors will help gain insight into the structural and functional diversity of the 5-HT₃ receptor system and facilitate the development of novel drugs.

HTR3A, *HTR3B* and *HTR3C* are almost ubiquitously expressed in the CNS as well as in the periphery, whereas *HTR3D* is predominantly, and *HTR3E* exclusively, expressed in the GI tract [4]. Thus, 5-HT_{3D} and 5-HT_{3E} may act as modulators of 5-HT₃ function in the GI tract [4,8]. Since the majority of 5-HT₃ receptor expression data are extrapolated from rodent studies [9,10] and the novel subunits C, D and E apparently are absent in rodents [8], detailed investigation of the nervous system in humans is required to elucidate the role of the different 5-HT₃ receptors.

Activation of the 5-HT₃ receptor regulates a variety of physiological effects, such as drug-evoked emesis and nociception, and is believed to influence behavior relevant to anxiety and cognitive disorders [11,12]. Furthermore, in the GI tract, 5-HT₃ receptors are involved in gut motility, peristalsis, visceral sensation and secretion [13].

5-HT₃ receptors as therapeutic targets

5-HT₃ receptors are of particular interest due to their pathophysiological implications and therapeutic potential. 5-HT₃ receptor antagonists, such as ondansetron, granisetron, dolasetron, tropisetron and palonosetron are routinely used to treat emesis and radiotherapy- and chemotherapy-induced nausea and vomiting (CINV) in patients with cancer and postoperative nausea and vomiting (PONV) [14]. The 5-HT₃ receptor antagonist alosetron is the only effective treatment of diarrhea-predominant irritable bowel syndrome. Furthermore, 5-HT₃ receptor antagonists have been shown to be effective in the treatment of neuropsychiatric disorders, bulimia, fibromyalgia and rheumatic diseases [12,15,16].

Owing to the potentially different composition and tissue distribution of 5-HT₃ receptors, new drugs with a

higher selectivity for a certain, as yet undefined, 5-HT₃ receptor subtype are highly desirable.

HTR3 genes as candidates for neuropsychiatric disorders

Association analyses of *HTR3A* and *HTR3B* in case-control studies revealed polymorphisms of both genes to be associated with psychiatric disorders such as bipolar affective disorder (BPAD) and major depression (Table 1) [17,18]. The SNP c.-42 C>T residing within a regulatory region of *HTR3A* was found to be associated with BPAD and may lead to increased expression of 5-HT_{3A} receptor subunits [19]. Interestingly, this variant was reported to be associated with harm avoidance in women and increased amygdaloid activity, probably by regulation of 5-HT_{3A} subunit expression [20,21]. Furthermore, two missense mutations in *HTR3A* (c.1031G>A and c.1172C>G) were detected in schizophrenic patients and may be involved in the etiology of schizophrenia [17,22–25]. The deletion c.-100_102delAAG within the 5' UTR of *HTR3B* seems to contribute to the etiology of BPAD [26] and the SNP c.386A>C in *HTR3B* was found to be associated with major depression [18], both of which have been shown to be functional and presumably predispose to the susceptibility of the respective condition [27,28].

HTR3 genes in pharmacogenetic approaches

A pharmacogenetic study of cancer patients treated with 5-HT₃ receptor antagonists showed no association of *HTR3A* SNPs with chemotherapy-induced emesis [29], however, the *HTR3B* deletion c.-100_102delAAG was observed to be associated with CINV. Patients homozygous for the deletion had the highest score of nausea and vomiting after antiemetic treatment with 5-HT₃ receptor antagonists, whereas patients harboring the wild-type allele showed the lowest score. Identification of patients carrying the deletion by genotyping

Figure 1. Genomic localization and organization of the human *HTR3* genes.

could contribute to a different and more efficient medical treatment of these individuals [30].

The SNP c.386A>C in *HTR3B* had a significant effect on the incidence of nausea induced by paroxetine treatment in psychiatric patients; individuals with the AA genotype had a fourfold increased risk of developing nausea compared with patients with the C allele. Therefore, this *HTR3B* SNP may serve as a significant predictor of paroxetine-induced nausea [31].

The -42 C/C genotype of *HTR3A* was found to be associated with the clinical responses to paroxetine in patients with major depression [32].

In conclusion, polymorphisms in *HTR3A* and *HTR3B* may serve as pharmacogenetic predictors for efficient

antiemetic treatment with 5-HT₃ receptor antagonists in cancer patients and for paroxetine treatment of patients with psychiatric disorders.

The pharmacogenetic and candidate approaches of *HTR3* genes are still in their infancy and replication analyses are needed to define their true contribution to neurological and psychiatric disorders.

■ ■ ■ ■ ■ The 5-HT₃ receptor database

We are currently setting up the first 5-HT₃ receptor database to collect *HTR3* variant data, including SNPs, deletions and insertions, along with data concerning investigated patient groups (ethnic background and pharmacogenetic data). This central source of information will help to evaluate diagnostic findings and use the respective information for subsequent genotype–phenotype correlation studies and pharmacogenetic approaches. This database will soon be available on our institute's website [101].

■ ■ ■ ■ ■ Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Table 1. Summary of *HTR3* variants which have been reported to be associated in different case control as well as pharmacogenetic studies.

Variant	Alias case-control	Study type	Phenotype	Ref.
<i>HTR3A</i>				
c.-42C>T	C178T; p.P16S	Case-control	BPAD	[19]
c.-42C>T	C178T; p.P16S	Pharmacogenetic study	Paroxetine response	[32]
c.1031G>A	G1250A; p.R344H	Case-control	SZ	[17]
c.1172 C>G	C1391G; p.P391R	Case-control	SZ	[17]
<i>HTR3B</i>				
c.-104_102delAGA	-100_102delAAG; -106_104delGGA	Case-control	BPAD	[26]
c.-104_102delAGA	-100_102delAAG; -106_104delGGA	Pharmacogenetic study	CINV	[30]
c.386A>C	p.Y129S	Case-control	MD	[18]
c.386A>C	p.Y129S	Pharmacogenetic study	Paroxetine response (emesis)	[31]

BPAD: Bipolar affective disorder; CINV: Chemotherapy-induced nausea and vomiting; MD: Major depression; SZ: Schizophrenia.

■ ■ ■ ■ ■ Bibliography

- Belelli D, Balcarek JM, Hope AG, Peters JA, Lambert JJ, Blackburn TP: Cloning and functional expression of a human 5-hydroxytryptamine type 3AS receptor subunit. *Mol. Pharmacol.* 48(6), 1054–1062 (1995).
- Miyake A, Mochizuki S, Takemoto Y, Akuzawa S: Molecular cloning of human 5-hydroxytryptamine₃ receptor: heterogeneity in distribution and function among species. *Mol. Pharmacol.* 48(3), 407–416 (1995).
- Niesler B, Walstab J, Combrink S *et al.*: Characterization of the novel human serotonin receptor subunits 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E}. *Mol. Pharmacol.* 72(1), 8–17 (2007).
- Niesler B, Frank B, Kapeller J, Rappold GA: Cloning, physical mapping and expression analysis of the human 5-HT₃ serotonin receptor-like genes *HTR3C*, *HTR3D* and *HTR3E*. *Gene* 310, 101–111 (2003).
- Davies PA, Pistis M, Hanna MC *et al.*: The 5-HT_{3B} subunit is a major determinant of serotonin-receptor function. *Nature* 397(6717), 359–363 (1999).
- Dubin AE, Huvar R, D'Andrea MR *et al.*: The pharmacological and functional characteristics of the serotonin 5-HT_{3A}

- receptor are specifically modified by a 5-HT(3B) receptor subunit. *J. Biol. Chem.* 274(43), 30799–30810 (1999).
7. Brady CA, Stanford IM, Ali I *et al.*: Pharmacological comparison of human homomeric 5-HT_{3A} receptors versus heteromeric 5-HT_{3A/3B} receptors. *Neuropharmacology* 41(2), 282–284 (2001).
 8. Karnovsky AM, Gotow LE, McKinley DD *et al.*: A cluster of novel serotonin receptor 3-like genes on human chromosome 3. *Gene* 319, 137–148 (2003).
 9. Gershon MD: Review article: serotonin receptors and transporters – roles in normal and abnormal gastrointestinal motility. *Aliment. Pharmacol. Ther.* 20(Suppl. 7) 3–14 (2004).
 10. Chameau P, van Hooft JA: Serotonin 5-HT(3) receptors in the central nervous system. *Cell Tissue Res.* 326(2), 573–581 (2006).
 11. Bloom FE, Morales M: The central 5-HT₃ receptor in CNS disorders. *Neurochem. Res.* 23(5), 653–659 (1998).
 12. Thompson AJ, Lummis SC: The 5-HT₃ receptor as a therapeutic target. *Expert Opin. Ther. Targets* 11(4), 527–540 (2007).
 13. Galligan JJ: Ligand-gated ion channels in the enteric nervous system. *Neurogastroenterol. Motil.* 14(6), 611–623 (2002).
 14. Aapro M: 5-HT(3)-receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. *Oncology* 69(2), 97–109 (2005).
 15. Gershon MD: Nerves, reflexes, and the enteric nervous system: pathogenesis of the irritable bowel syndrome. *J. Clin. Gastroenterol.* 39(Suppl. 5), S184–S193 (2005).
 16. Mawe GM, Coates MD, Moses PL: Review article: intestinal serotonin signalling in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 23(8), 1067–1076 (2006).
 17. Niesler B, Weiss B, Fischer C *et al.*: Serotonin receptor gene *HTR3A* variants in schizophrenic and bipolar affective patients. *Pharmacogenetics* 11(1), 21–27 (2001).
 18. Yamada K, Hattori E, Iwayama Y *et al.*: Distinguishable haplotype blocks in the *HTR3A* and *HTR3B* region in the Japanese reveal evidence of association of *HTR3B* with female major depression. *Biol. Psychiat.* 60(2), 192–201 (2006).
 19. Niesler B, Flohr T, Nöthen MM *et al.*: Association between the 5' UTR variant C178T of the serotonin receptor gene *HTR3A* and bipolar affective disorder. *Pharmacogenetics* 11(6), 471–475 (2001).
 20. Melke J, Westberg L, Nilsson S *et al.*: A polymorphism in the serotonin receptor 3A (*HTR3A*) gene and its association with harm avoidance in women. *Arch. Gen. Psychiat.* 60(10), 1017–1023 (2003).
 21. Iidaka T, Ozaki N, Matsumoto A *et al.*: A variant C178T in the regulatory region of the serotonin receptor gene *HTR3A* modulates neural activation in the human amygdala. *J. Neurosci.* 25(27), 6460–6466 (2005).
 22. Krzykowski K: Do polymorphisms in the human 5-HT₃ genes contribute to pathological phenotypes? *Biochem. Soc. Trans.* 34(Pt 5), 872–876 (2006).
 23. Thompson AJ, Sullivan NL, Lummis SC *et al.*: Naturally occurring variations in the human 5-HT_{3A} gene profoundly impact 5-HT₃ receptor function and expression. *Pharmacogenet. Genomics* 17(4), 255–266 (2007).
 24. Thompson AJ, Sullivan NL, Lummis SC: Characterization of 5-HT₃ receptor mutations identified in schizophrenic patients. *J. Mol. Neurosci.* 30(3), 273–281 (2006).
 25. Kurzwelly D, Barann M, Kostanian A *et al.*: Pharmacological and electrophysiological properties of the naturally occurring Pro391Arg variant of the human 5-HT_{3A} receptor. *Pharmacogenetics* 14(3), 165–172 (2004).
 26. Frank B, Niesler B, Nöthen MM *et al.*: Investigation of the human serotonin receptor gene *HTR3B* in bipolar affective and schizophrenic patients. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 131(1), 1–5 (2004).
 27. Krzykowski K, Davies PA, Feinberg-Zadek PL, Bräuner-Osborne H, Jensen AA: High-frequency *HTR3B* variant associated with major depression dramatically augments the signaling of the human 5-HT_{3AB} receptor. *Proc. Natl Acad. Sci. USA* 105(2), 722–727 (2008).
 28. Meineke C, Tzvetkov MV, Bokelmann K *et al.*: Functional characterization of a -100–102delAAG deletion–insertion polymorphism in the promoter region of the *HTR3B* gene. *Pharmacogenet. Genomics* 18(3), 219–230 (2008).
 29. Kaiser R, Tremblay PB, Sezer O, Possinger K, Roots I, Brockmöller J: Investigation of the association between 5HT_{3A} receptor gene polymorphisms and efficiency of antiemetic treatment with 5-HT₃ receptor antagonists. *Pharmacogenetics* 14(5), 271–278 (2004).
 30. Tremblay PB, Kaiser R, Sezer O *et al.*: Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients. *J. Clin. Oncol.* 21(11), 2147–2155 (2003).
 31. Sugai T, Suzuki Y, Sawamura K, Fukui N, Inoue Y, Someya T: The effect of 5-hydroxytryptamine 3A and 3B receptor genes on nausea induced by paroxetine. *Pharmacogenomics J.* 6(5), 351–356 (2006).
 32. Kato M, Fukuda T, Wakeno M *et al.*: Effects of the serotonin type 2A, 3A and 3B receptor and the serotonin transporter genes on paroxetine and fluvoxamine efficacy and adverse drug reactions in depressed Japanese patients. *Neuropsychobiology* 53(4), 186–195 (2006).

Website

101. 5-HT₃ receptor database
www.klinikum.uni-heidelberg.de/HTR3.6646.0.html?&L=0