HTR4 (5-hydroxytryptamine receptor 4)

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Abstract

Being a member of the serotonin receptor family, 5-HT4 receptor ties up the neurotransmitter-serotonin (5-hydroxytryptamine/5-HT) in the central nervous system (CNS) of mammals. Commonly 5-HT4 receptors (5-HTR4) are G-protein-coupled receptors (GPCRs), in which the G proteins cause the induction of adenylate cyclase, subsequently leading to cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activations. These receptors are commonly expressed in gastrointestinal, cardiovascular, nervous, and urinary systems, as well as the adrenal cortex (Tack et al., 2012). In this review article, the genetic, cellular, and biochemical knowledge of 5-HT4 receptors is deliberated. Besides the emphasis on receptor-ligand interaction with therapeutics, the implication of these receptors in several health disturbances/diseases is considered on the basis of available literature.

Keywords
5-hydroxytryptamine receptor 4, Serotonin (5-HT), Central Nervous System (CNS), Alzheimer's Disease, Inflammatory Bowel Disease (IBD), Obesity.

Identity

Other names
5-HT4, 5-HT4R
HGNC (Hugo): HTR4
Location: 5q32

DNA/RNA

Local order: Shown in Chromosome 5 - NC_000005.10 Reference GRCh38.p13 Primary Assembly. Cytogenetic Location of 5-HTR: 5q32, which is the long (q) arm of chromosome 5 at a position 32 (UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly)

Note
The 5-HTR4 gene is 172,607 bp long (according to UCSC, GRCh38/hg38), located on the minus (-) strand and spans 12 exons (NCBI Homo sapiensAnnotation Release 109).

Transcription

The gene has 13 transcripts (Table 1)

| Name       | Transcript ID    | bp    | Protein (aa) | Biotype      |
|------------|-----------------|-------|--------------|--------------|
| HTR4-201   | ENST00000360693.7 | 3082  | 428          | Protein coding |
| HTR4-202   | ENST00000362016.6 | 2979  | 428          | Protein coding |
| HTR4-203   | ENST00000377888.7 | 2962  | 388          | Protein coding |
| HTR4-209   | ENST00000521530.5 | 1323  | 387          | Protein coding |
| HTR4-210   | ENST00000521735.5 | 1242  | 378          | Protein coding |
| HTR4-207   | ENST00000520514.5 | 1236  | 411          | Protein coding |
| HTR4-213   | ENST00000631296.1 | 1224  | 388          | Protein coding |
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| HTR4  | ENST00000517929.5 | 1201 | 360 | Protein coding |
|-------|------------------|------|-----|---------------|
| HTR4  | ENST00000520086.1| 2272 | 87  | Protein coding |
| HTR4  | ENST00000522588.5| 1326 | 378 | Nonsense mediated decay |
| HTR4  | ENST00000524063.3| 2274 | 371 | Nonsense mediated decay |
| HTR4  | ENST00000519495.1| 869  | No protein | Processed transcript |
| HTR4  | ENST00000521124.5| 1221 | No protein | Retained intron |

Table 1. Transcripts of the human 5-HTR4 gene (Ensemble, GRCh38.p12).

Protein

The product of HTR4 gene (5q32) is 5-HT4 receptor (Ohtsuki et al., 2002), weight as 43,761 Dalton with a length of 388 amino acids (Blondel et al., 1997; Claeyssen et al., 1997; Van den Wyngaert et al., 1997). The protein has 9 known isoforms produced by alternative splicing, but the potential isoforms seem to exist (https://www.uniprot.org/uniprot/Q13639). Isoform 5-HT4(B) (Q13639-1) was considered as canonical sequence and provided in Figure 1. The translated glycoprotein is a member of the serotonin receptor family which are induced in response to the presence of serotonin via G-protein coupling process. In general, the 5-HT4 receptor is a glycosylated transmembrane protein expressed in both CNS and peripheric nervous system (PNS) that acts as a modulator in the release of various neurotransmitters (NCBI). It expressed in various tissues/cells such as the brain, esophagus, ileum, colon, bladder, heart, and adrenocortical cells. In the brain, they are particularly expressed in the hypothalamus, nucleus accumbens, amygdala, Calleja islands, olfactory tubercle, fundus striatum, ventral pallidum, septum, hippocampus, and basal ganglia including substantia nigra (Bockaert et al., 2008).

Expression

5-HTR4 is expressed in different human tissues/organisms but mostly in gastrointestinal tract, brain, and muscles in descending order. Please see the Human Protein Atlas (http://www.proteinatlas.org)

Function

5-hydroxytryptamine (5-HT or serotonin) is a crucial neurotransmitter of CNS with highly conserved monoamine structure (Hodge et al., 2013). It plays a role in different physiological events of CNS and PNS by interacting with more than one receptor subtype (Cichon et al., 1998). These countless functions are actualized by seven 5-HT subtype receptors (Kroeze et al., 2002; Hodge et al., 2013). The 5-HT4R is a G-protein-coupled receptor that arouses adenylylate cyclase as a primary mode of signal transduction. By the arousal of adenylylate cyclase, the concentration of cAMP elevates (Lalut vd., 2017). However, 5-HT4R refers to both G protein-dependent and G protein-independent pathways (Figure 2a-b). The main G protein introduced by 5-HT4 signaling is the Gs (shown in Figure 2a) that leads to the activation of the cAMP/PKA pathway (Barthet et al., 2005). The G-protein independent non-canonical pathway activates Src (shown in Figure 2b) and subsequently ERK kinases, causing pERK1/2 phosphorylation (Barthet et al., 2007).

This receptor was first described in primary cultures of mouse embryonic colliculus neurons based on 5-HT-induced cAMP production (Dumuis et al., 1988). It plays potential roles in the physiology of cardiovascular, urinary, and endocrine systems. It is also implicated in the pathophysiology of diseases occurring in adrenal glands as well as urinary and gastrointestinal systems (Ford and Clarke., 1994). 5-HTR4s are responsive in the events occurring in adrenal glands, colon, cortex (Monferini et al.,1993), and atrial appendages (Kaumann et al., 1990, 1991; Turconi et al., 1991; Quadid et al., 1992) of human tissues by encouraging cAMPs. In turn, cAMP inductions lead to steroid secretion in adrenal glands (Lefebvre et al., 1992) and circular muscle contraction in the colon (Tam et al.,1992).

Therapeutic agents interacting with 5-HT4

Advances in research on 5-HT set forward the development of therapeutics selectively interacting with 5-HT receptors. In the present day, these ligands mainly divided into 5 categories/classes. They are indoles including 5-HT analogs, indole carboxylates, and indole carboxamides, benzamides, benzoates, aryl ketones, and benzimidazoles (Bockaert et al., 2004).

First-class 5-HT4 agonists include substituted tryptamines or 5-HT agonists next to the substituted triple-carbazimidamides. 5-MeOtryptamine is an interesting vehicle due to the lack of its affinity to 5-HT3 (Craig et al., 1990). The indole carbazimamide derivative, HTF 919 (Tegaserod), has been found to be a potent partial agonist with high affinity to 5-HT4. In vivo studies show that
Tegaserod enhances gastrointestinal motor activity and adjusts impaired motility throughout the gastrointestinal tract. (Bockaert et al., 2004). Tegaserod is a benzamide derivative which was approved by the FDA and other regulatory agencies for the treatment of women with inflammatory bowel disease (IBD) in which the constipation is predominant or functional constipation (Tonini and Pace 2006; Shin et al., 2015). However, it was later withdrawn from the market due to possible cardiovascular side-effects (Chey et al., 2008; Thompson 2007).

Three novel 5-HTR4 agonists (Prucaloprid, Naronapride, and Velusetrag) have therapeutic potential for patients with IBD. These alternative drugs have a higher affinity for 5-HTR4 compared to Tegaserod (Halland and Talley, 2013). YKP10811 is a mucosal partial agonist for the 5-HTR4, induces serotonin release, initiates peristaltic reflex, and has a low cardiovascular adverse effect. Unlike traditional prokinetic drugs such as Tegaserod, YKP10811 exhibits an antinociceptive effect on inflammation as well as acute stress-associated colonic hypersensitivity, and also considered as a candidate drug for IBD (Gilet et al., 2014).

![G-protein dependent pathway](image1)

![G-protein independent pathway](image2)

**Figure 2.** A simplified pathway of G-protein dependent (a) and G-protein independent (b) signaling of 5-HTR4s (Modified from Bockaert et al., 2008)
The second class of 5-HTR4 agonists includes first-generation benzamides carrying 2-methoxy-4-amino-5-chloro' substitution (Dumuis et al., 1989). These benzamides (zacopride, renzapride, and metoclopramide) were found to be non-selective and always cause antagonistic activity at the 5-HTR3 (Bockaert et al., 2004).

The third class of agonists, so-called benzoate derivatives were deliberated with the replacement of benzamide's amide bond with an ester one, resulting in increased affinity for 5-HTR4. The first partial and selective drug of this series is ML10302, which has a high affinity for 5-HTR4 and poor affinity for other 5-HT receptor subtypes including 5-HTR3 (Langlois et al., 1994; Bockaert et al., 2004). Moser and colleagues (2002) synthesized SL65.0155, a novel compound with high affinity for 5-HTR4. Being a benzodioxane derivative, it is particularly effective for learning and memory (Moser et al., 2002).

The fourth class is consist of benzimidazoles (BIMU 8 and BIMU 1), which are potent and effective 5-HTR4 agonists entering CNS (Dumuis et al., 1991; Rizzi et al., 1992). To overcome their metabolic variability, aryl ketones were prepared with 5-HTR4 ester ligands; instead of the ester linkage of the antagonist RS 23597, a partial agonist RS 17017 was synthesized, which has a similar affinity for 5-HTR4 (Clark et al., 1994). Increasing the size of the alkyl group led to an increase in the activity of the agonists RS 67333 and RS 67506 (Eglen et al., 1995). RS 67333, a selective 5-HTR4 partial agonist, is known to easily cross the blood-brain barrier. Systemic administration of selective 5-HT4 receptor partial agonists, like RS 67333 and RS 17017, enhances rodent performance in olfactory relational learning (Marchetti et al., 2004), social-spatial memory tests (Letty et al., 1997), and also improves delayed sample matching in young/old macaques (Terry et al., 1998). RS 67333 has been shown to inhibit β-amyloid peptide formation in primary cortical neurons (Cho and Hu, 2007).

Interestingly, RS 67333 produces a rapid antidepressant effect after only three days of administration to rodents (Lucas et al., 2007). A more recent study comparing RS67333 with antidepressant drug Fluoxetine (PLX) confirmed that RS67333 causes anxiolytic-like effects after only 7 days in several behavioral tests and that 5-HTR4 agonists produce faster effects than currently used antidepressants (Mendez-David et al., 2014). Another interesting agonist is a pyridine carboxamide, a cognitive drug (VRX-03011) for Alzheimer's disease (Bockaert et al., 2008). Fifth class includes indoles such as GR 113808 with high affinity for 5-HTR4, and low affinity for 5-HTR3 (Gale et al., 1994). Further, [3H] GR 113808 is the first commercially available radioligand for 5-HTR4 affinity studies (Grossman et al., 1993). SB 203186 is an indole ester with potent and selective 5-HTR4 antagonistic properties in various physiological assays, but the short half-life limits it's in vivo application (Parker et al., 1993).

In contrast, SB 207266 is a highly potent and selective antagonist with a long duration of action after oral administration (Gaster et al., 1995). SB 207266 is a very useful vehicle in CNS studies (Wardle et al., 1996; Gaster and King 1997). Three selective and high-affinity 5-HTR4 antagonists (GR 125487, SB 207266, and ML 10375) have been reported to exhibit reverse agonistic activity (Claeysen et al., 2000; Blondel et al., 1998).

Roche Bioscience generated three potent 5-HTR4 reverse agonists, RO 116-2617, RO 116-0086, and RO 116-1148 (Joubert et al., 2002). 5-HTR4 ligands that may be of interest in CNS studies are listed in Table 2.
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Homology

| Pairwise Alignment Scores |
|---------------------------|
| Gene          | Symbol | Protein | DNA |
| H. sapiens    | HTR4   |         |     |
| vs. P. troglodytes | HTR4   | 99.8    | 99.6 |
| vs. M. mulatta | HTR4   | 98.6    | 98.1 |
| vs. C. lupus  | HTR4   | 96.6    | 93.6 |
| vs. B. taurus | HTR4   | 94.8    | 93.7 |
| vs. M. musculus | Htr4 | 93.3    | 90.9 |
| vs. R. norvegicus | Htr4 | 92.7    | 90.6 |
| vs. G. gallus | HTR4   | 88.5    | 82.6 |
| vs. X. tropicalis | LOC100493952 | 83.4 | 74.5 |
| vs. D. rerio  | LOC556843 | 75.3 | 71.9 |
| vs. D. melanogaster | Oa2 | 47.5    | 54.3 |

Table 2. 5-HTR4 ligands used in CNS studies (Adopted from Bockaert et al., 2004).

Inflammatory bowel disease (IBD)

5-HTR4s which are widely expressed in the human intestine can also be expressed in inhibitory nitrergic neurons to induce smooth muscle relaxation and cholinergic neurons to control muscle contraction (Bockaert et al., 2011; Hoffman et al., 2012). In addition to their neuronal localization, they are found in enterocytes and enteroendocrine cells of the intestinal mucosa that regulate fluid, mucus and 5-HT secretion (Hofmann et al., 2012; Tonini, 2005). Accordingly, 5-HTR4s are attractive targets for the treatment of IBD. The receptor agonists increase motility and accelerate transit from the gut, thereby help in the alleviation of IBD and functional constipation (Halland and Talley, 2013). More selective 5-HTR4 agonists, including Naronapride (ATI-7505), Prucaloprid and Velusetrag (TD-5108), effectively target this receptor to support the intestinal motility. However, the full mechanism of action of these compounds is not clearly resolved. One possibility is that 5-HTR4 agonists increase motility by stimulating receptors on the enteric nerve terminals and increasing neurotransmitter release (Hoffman et al., 2012). A single nucleotide polymorphism (SNP) (rs201253747) c.* 61T>C in HTR4 were identified in diarrhea-IBD patients (Wohlfarth et al., 2017). miRNAs can adjust HTR4 expression, and this regulation can be influenced either by the SNP c.*61 T>C or by lessened amounts of miR-16 and miR-103 proposing the role HTR4 in the pathogenesis of IBD (Wohlfarth et al., 2017). Colonic biopsy specimens from patients with Crohn’s disease also showed greatly increased mucosal 5-HTR4 expression (Shajib et al., 2018).

Mutations

Somatic

A list of 5-HTR4 mutations in cancer can be found in COSMIC, the Catalogue Of Somatic Mutations In Cancer, https://cancer.sanger.ac.uk/cosmic/gene/ analysis?ln=HTR4. According to the Human Protein Atlas, HTR4 has been found strongly expressed in prostate and endometrial cancers.

Implicated in

Animal Experiments

5-HTR4 was initially identified in cultured mouse colliculus cells and guinea pig brain using a functional cAMP stimulation assay (Dumuis et al., 1988). One of the oldest functions attributed to 5-HTR4 in rodents is related to its role in increasing the release of acetylcholine in the frontal cortex (Siniscalchi et al., 1999) and a stimulating effect on the hippocampus to enhance memory and cognition (Bijak et al., 1997; Mohler et al., 2007). The absence of this receptor has been found to impair stress-induced hypophagia and novelty-induced discovery efficiency in mice (Coman et al., 2004a). The 5-HTR4 expression is also associated with the development of certain behavioral characteristics of depression, like deletion or pharmacological blockade of 5-HTR4s results in increased depressive and anxiety-like behaviors in rodents (Carr and Lucki, 2011; Coman et al., 2004a; Conductier et al., 2006). Serotonin affects cardiac contraction by interacting with 5-HTR4 expressed in the human and porcine atrium and ventricle, interestingly, expressed only in the atrium in the rat. 5-HTR4 activation causes cardiac spasm as well as tachycardia and arrhythmia (Qvigstad et al., 2005). This cardiac effect of 5-HTR4 is limited to human and porcine atria and are not declared in other laboratory animals such as rats, guinea pigs, rabbits, and frogs. Moreover, 5-HTR4 activation triggers the release of acetylcholine in the ileum of guinea pig and causes esophageal and colonic strictures (Hoyer et al., 2002).
Cardiac Disorders
5-HTR4 is expressed in the atria and ventricles in humans; just like other serotonergic receptors, its expression level is quite low under physiological state but may increase significantly in the case of ventricular dysfunction. 5-HTR4 activation is known to cause heart spasms, as well as tachycardia and arrhythmia (Qvigstad et al., 2005). Even at low expression levels, 5-HTR4 increases contraction strength (inotropic effect), accelerates early stage of muscle relaxation (lusitropic effect) or enhances pulse rate (chronotropic effect) (De Maeyer et al., 2008). Since 5-HT is a neurotransmitter responsible for blood pressure regulation, peristaltic movements, heart rate, and coagulation system, it acts on 5-HTR4 in the human heart, producing a positive inotropic effect on the stimulation of the atrium (Dorszewska et al., 2017).

Cushing’s Syndrome
5-HTR4 has been shown to be overexpressed in the cortex of the adrenal gland in Cushing’s syndrome, a disease that is caused by cortisone overproduction (Cartier et al., 2003). In one study, cortisol secretion was encouraged with chorionic gonadotropin, luteinizing hormone, and 5-HTR4 stimulating drugs in patients with Cushing’s syndrome (Lacroix et al., 1999). Long-term suppression of luteinizing hormone secretion by administering leuprolide acetate every four weeks led to a complete reversal of Cushing’s syndrome (Lacroix et al., 1999). The administration of 5-HTR4 agonists such as metoclopramide, cisapride, and tegaserod stimulated aldosterone levels (Zwermann et al., 2009; Lefebvre et al., 2002; Cartier et al., 2005). Specific 5-HTR4 antagonists such as GR 113808 are potent inhibitors of basal and/or cisapride-induced aldosterone secretion (Lefebvre et al., 2002).

Asthma
The 5-HTR4 gene is located in an area previously associated with an increased risk of Asthma and Atopy (allergic diseases). Previously, 32 genetic variants in HTRA consisting of 22 intronic SNPs, 2 SNPs in the 3'-untranslated region (exon 7) and 8 SNPs in the 3'-downstream region were examined (Kim et al., 2011). Logistic regression analysis demonstrated the relationship between the 2 intronic polymorphisms with the risk of Asthma. Two minor HTRA alleles, +142828G>A and +122769G>A, appeared at higher frequencies in the Asthma patients compared to healthy individuals. Therefore, SNP and haplotypes of the HTRA gene have been reported to be associated with the Asthma phenotype (Kim et al., 2011).

Obesity
Obesity has been associated with chronic elevation of brain serotonin levels in humans (Lambert et al., 1999). Animal studies showed that 5-HTR4 is involved in food intake. The genetic or pharmacological modifications of the receptor in pleasure-associated brain segments modulate food intake as well (Haahr et al., 2012). It has been also reported that there is a strong positive correlation between body mass index (BMI) and 5-HTR4 concentrations in pleasure circuits (nucleus accumbens and ventral pallidum) controlling food intake, as well as in the left hippocampal region and orbitofrontal cortex. Therefore, stimulation of brain 5-HTR4s may be considered in the reduction of human hedonic overeating (Haahr et al., 2012). The direct stimulation of 5-HTR4s in the nucleus accumbens reduces the physiological drive to eat and increases cocaine- and amphetamine-regulated transcript (CART) mRNA levels in fed and food-deprived mice (Jean et al., 2007). The 5-HTR4 was shown to regulate CART mRNA expression through cAMP/PKA signaling pathway. This receptor-mediated upregulation of CART in the nucleus accumbens triggers the appetite-suppressant effects of ecstasy (Jean et al., 2007). The mechanisms underlying feeding disorders in 5-HT4 receptor knockout mice are related to a lesser efficacy of 5-HT (hypothalamus, nucleus accumbens), leptin and the cocaine-amphetamine related transcript to reduce food intake following stress (Compan et al., 2004b). These results show that 5-HTR4 plays an important role in nutritional behavior.

Huntington’s Disease
Post-mortem brain samples of Huntington’s disease patients revealed a 50% loss of 5-HTR4 in putamens (Reynolds et al., 1995).

Alzheimer’s Disease
Studies focused on neurodegenerative disorders such as Alzheimer’s disease associated with decreased expression of 5-HTR4 in the hippocampus and prefrontal cortex (Reynolds et al., 1995). Activation of 5-HTR4s stimulates acetylcholine release in the prefrontal cortex and hippocampus and improves learning and memory in various acquisition and memory paradigms (Cachard-Chastel et al., 2008; Bockaert et al., 2011). These findings suggest that 5-HTR4 agonists can be used to improve cholinergic function and cognition in Alzheimer’s disease. The impact of 5-HTR4s on the non-amyloidogenic metabolic pathway of the amyloid precursor protein by stimulation of α-secretase has been described (Lezoualc’h and Robert, 2003; Cachard-Chastel et al., 2007). Stimulation of 5-HTR4 triggers soluble amyloid precursor protein α (sAPPα) release and reduces amyloid-beta (aβ) peptide formation in neuronal cell cultures (Maillet et al., 2003; Cho and Yu, 2007). A significant loss of 5-HTR4 was observed in the hippocampus and frontal cortex of patients suffering from Alzheimer’s disease. This
reduction in certain cerebral concentrations of 5-HT4 has demonstrated its effects on cognitive learning and memory processes and has been recently described as a valuable target against Alzheimer’s. (Lalut et al., 2017). 5-HT4 receptor agonists are known to improve memory deficits by increasing acetylcholine neurotransmission (Consolo et al., 1994; Bockaert et al., 2011; Johnson et al., 2012). In a transgenic Alzheimer’s mouse model, stimulation of 5-HT4 by agonists led to cognitive effects resulting in increased learning at elevated levels of acetylcholine (Consolo et al., 1994; Baranger et al., 2017; Bockaert et al., 2011; Brodney et al., 2012). In other words, 5-HT4 stimulation improves performance in memory tasks in rodents, while receptor antagonists cause performance deterioration in these tasks. In view of all this, 5-HT4 activation may have beneficial effects on Alzheimer’s disease, both by preventing disease formation and by improving memory performance (Rebholz et al., 2018).

Schizophrenia

Limited evidence suggests that 5-HT4 polymorphisms may be associated with susceptibility to Schizophrenia (Suzuki et al., 2003), attention deficit, and hyperactivity disorder (Li et al., 2006). 5-HT4 plays a role in cognitive function; that is assumed to be one of the main disorders of Schizophrenia. HTR4 coding regions were examined in 96 Japanese Schizophrenia patients. Within the coding region, a silent SNP and six intronic SNPs were detected and a significant relationship was reported between Schizophrenia and haplotype A-T (Suzuki et al., 2003).

Suicidal behavior

In a study evaluating the role of HTR4 on suicidal behavior, significantly high levels of 5-HT4 and cAMP were found in the frontal cortex and caudate nucleus of the depressed suicide victims (Rosel et al., 2004). Another secondary messenger 5-HT4, 1,4,5-inositol triphosphate (IP3) were elevated in the caudate nucleus and hippocampus, whereas no changes were observed in these parameters in the amygdala region. The caudate nucleus appears as the most affected brain site on account of the significant changes in the serotonergic system and thereby is important in terms of diagnostic sensitivity (Rosel et al., 2004).

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