Human Proteins

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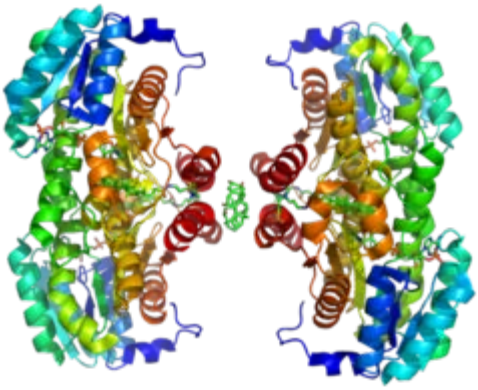
11β-Hydroxysteroid Dehydrogenase Type 1 and 21-Hydroxylase

11β-hydroxysteroid dehydrogenase type 1

Hydroxysteroid (11-beta) dehydrogenase 1



PDB rendering based on 1xu7.

Identifiers	
Symbols	HSD11B1; 11-DH; 11-beta-HSD1; HDL; HSD11; HSD11B; HSD11L; MGC13539
External IDs	OMIM: 600713 MGI: 103562 HomoloGene: 68471 GeneCards: HSD11B1 Gene
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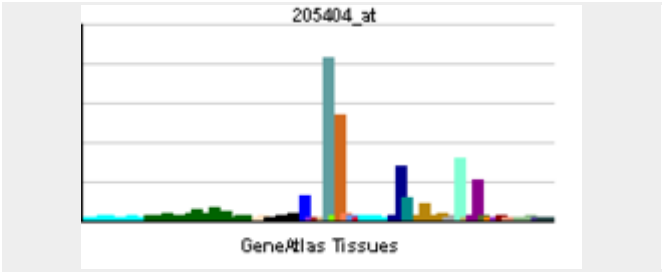

Orthologs

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Entrez	3290	15483
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UniProt	P28845	Q3TJI8
RefSeq (mRNA)	NM_005525	NM_001044751
RefSeq (protein)	NP_005516	NP_001038216
Location (UCSC)	Chr 1: 207.93 - 207.97 Mb	Chr 1: 194.92 - 194.96 Mb

11β-hydroxysteroid dehydrogenase type 1 is an NADPH-dependent enzyme highly expressed in key metabolic tissues including liver, adipose tissue, and the central nervous system.

In these tissues, **HSD11B1** reduces cortisone to the active hormone cortisol that activates glucocorticoid receptors.

It is inhibited by carbenoxolone, a drug typically used in the treatment of peptic ulcers.

The protein encoded by this gene is a microsomal enzyme that catalyzes the conversion of the stress hormone cortisol to the inactive metabolite cortisone. In addition, the encoded protein can catalyze the reverse reaction, the conversion of cortisone to cortisol. Too much cortisol can lead to central obesity, and a particular variation in this gene has been associated with obesity and insulin resistance in children. Two transcript variants encoding the same protein have been found for this gene.

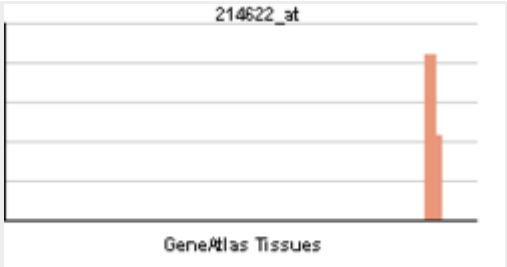
21-Hydroxylase

Steroid 21-monooxygenase

Identifiers	
EC number	1.14.99.10
CAS number	9029-68-9
Databases	
IntEnz	IntEnz view
BRENDA	BRENDA entry
ExPASy	NiceZyme view
KEGG	KEGG entry
MetaCyc	metabolic pathway
PRIAM	profile
PDB	structures
Gene Ontology	AmiGO / EGO

Cytochrome P450, family 21, subfamily A, polypeptide 2

Identifiers	
Symbols	CYP21A2; CPS1; CA21H; CAH1; CYP21; CYP21B; MGC150536; MGC150537; P450c21B
External IDs	OMIM: 201910 MGI: 88591 HomoloGene: 68063 GeneCards: CYP21A2 Gene
RNA expression pattern	



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Ensembl	ENSG00000168482	ENSMUSG00000024365
UniProt	P08686	A0JP50
RefSeq (mRNA)	NM_000500	NM_009995
RefSeq (protein)	NP_000491	NP_034125
Location (UCSC)	Chr c6_COX: 32.1 - 32.1 Mb	Chr 17: 34.41 - 34.41 Mb

Steroid 21-hydroxylase is a cytochrome P450 enzyme that is involved with the biosynthesis of the steroid hormones aldosterone and cortisol.

In humans, 21-Hydroxylase is encoded by the gene *CYP21B*.

Names and classification

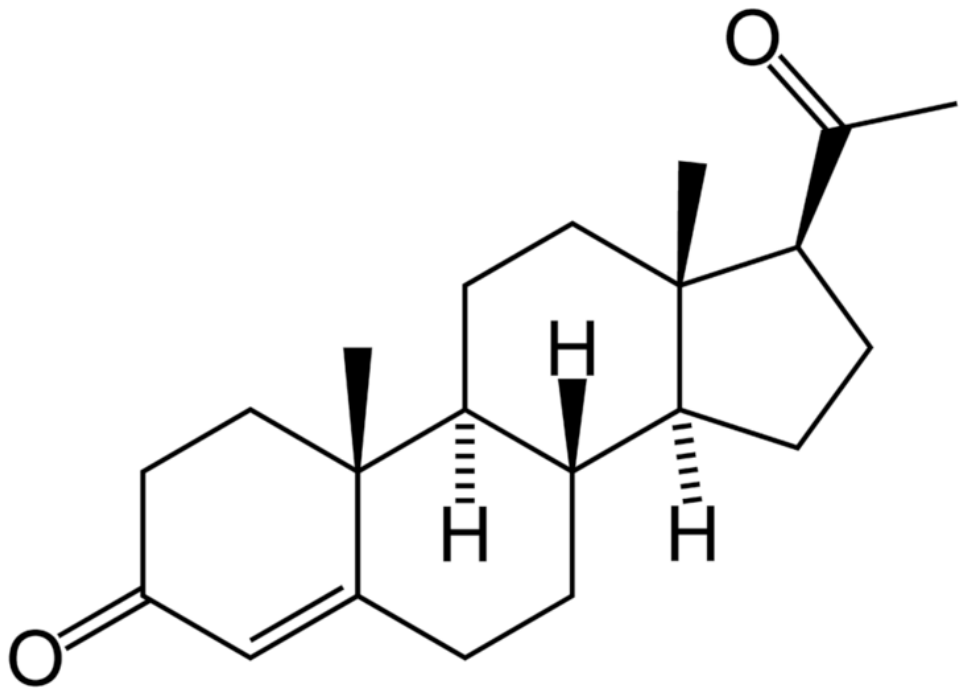
21-Hydroxylase is also called **steroid 21-monooxygenase**, **21α-Hydroxylase**, and, less commonly **21β-Hydroxylase**.

Function

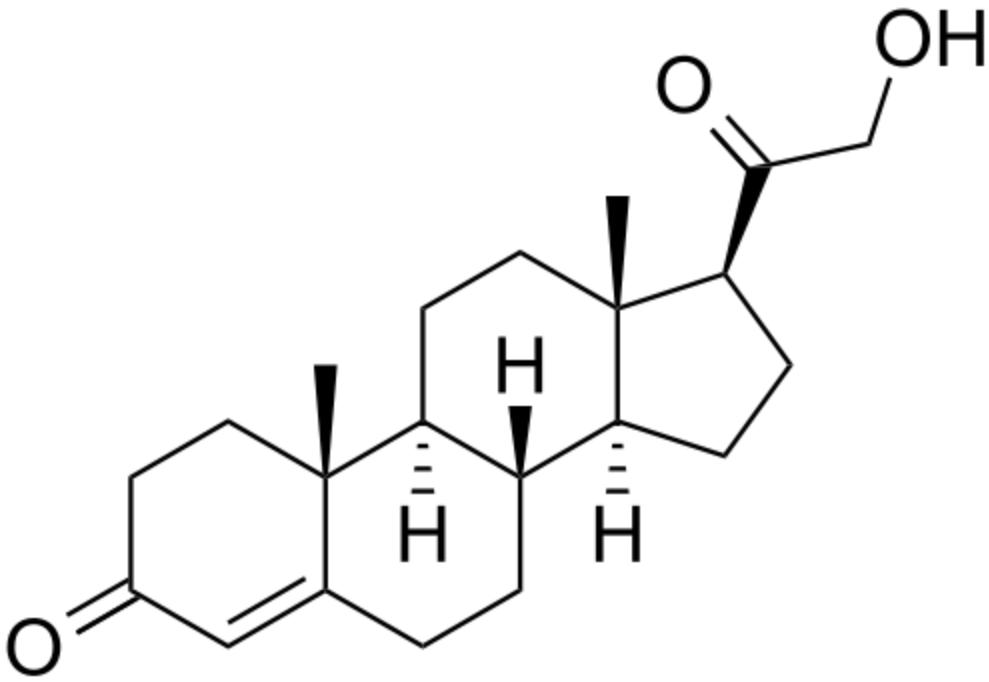
This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This protein localizes to the endoplasmic reticulum and hydroxylates steroids at the 21 position. Its activity is required for the synthesis of steroid hormones including cortisol and aldosterone.

Reaction

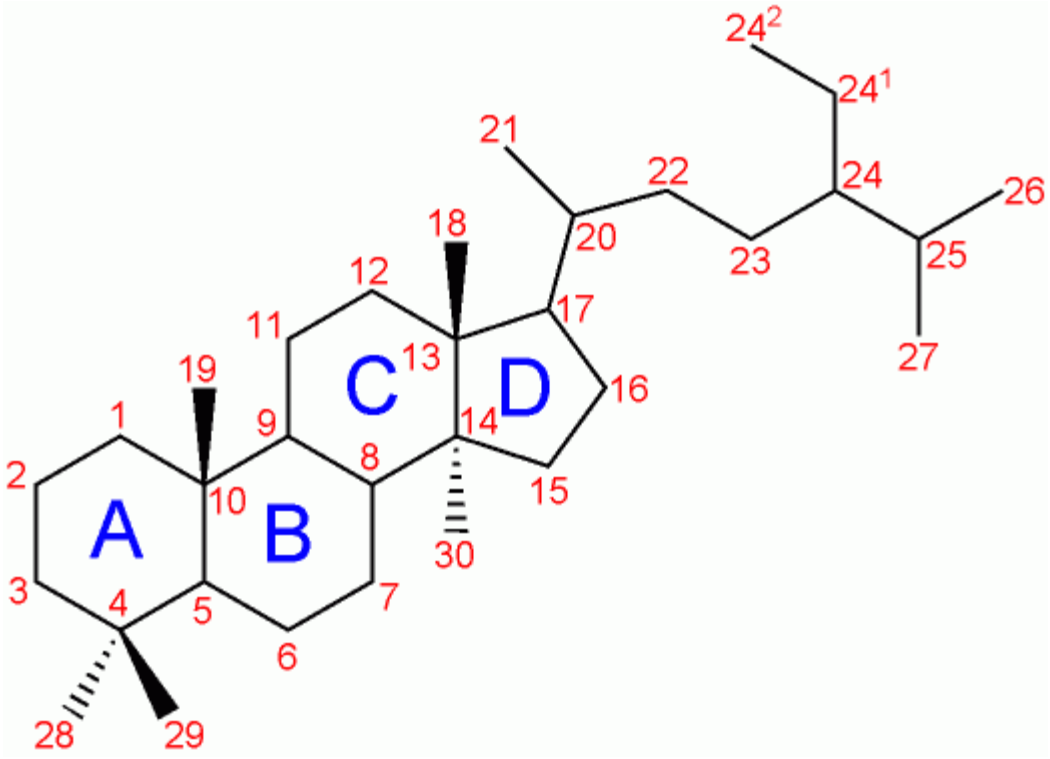
21-Hydroxylase catalyses the hydroxylation of the carbon atom 21 in steroids (adding an "–OH"), which is necessary with the formation of these hormones.



Progesterone

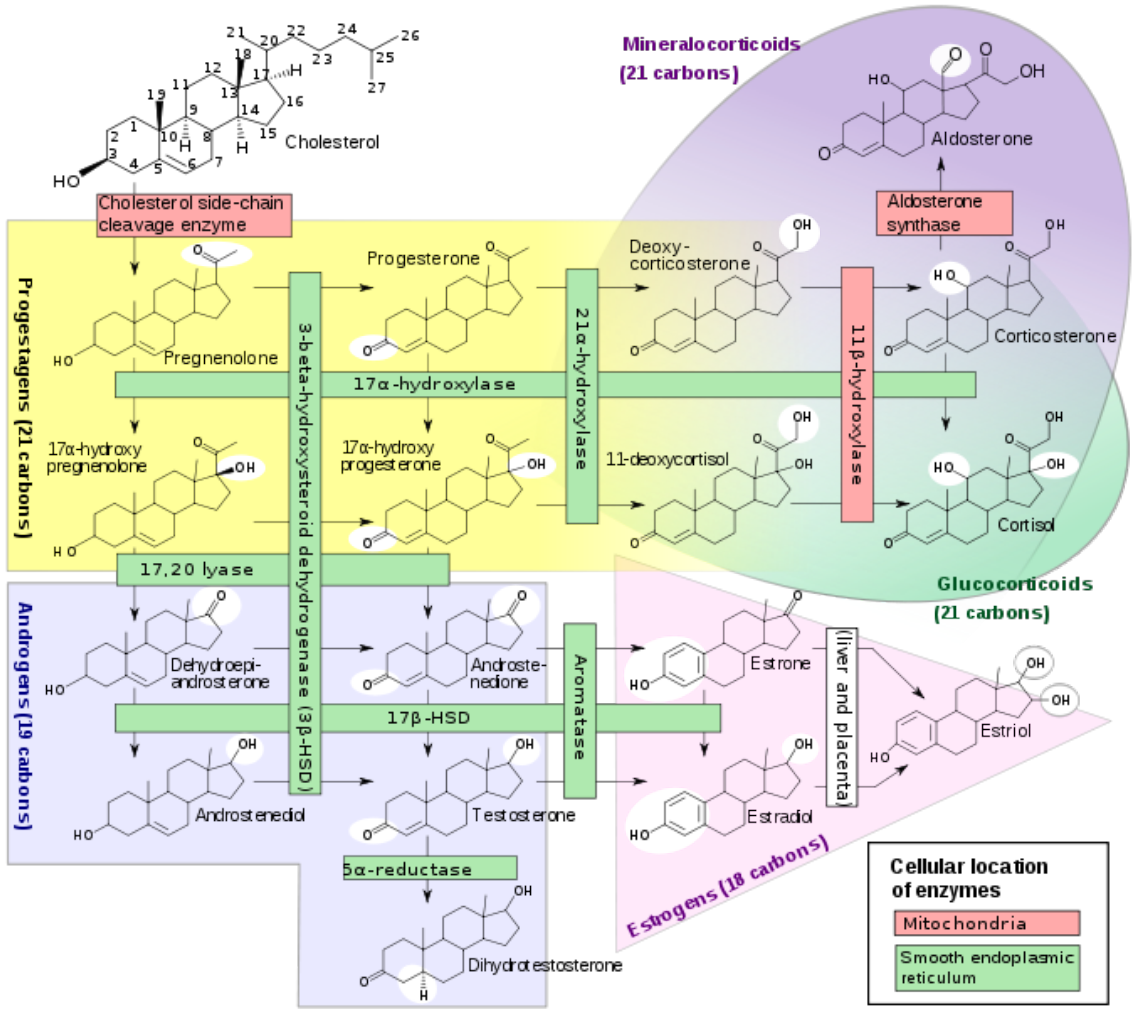


11-deoxycorticosterone

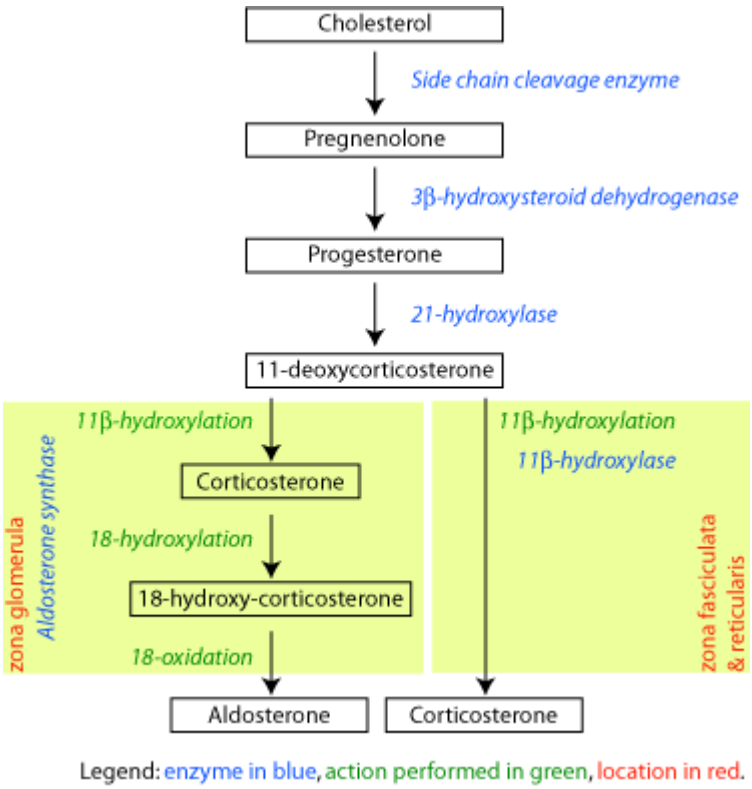


Steroid numbering - #21 is near center top

Pathway



Human steroidogenesis, showing both reactions of 21-Hydroxylase at center top.



Corticosteroid biosynthetic pathway in the rat.

Clinical significance

A defect within the CYP21B gene causes a disturbance of the development of the enzyme, which leads to congenital adrenal hyperplasia due to 21-hydroxylase deficiency. A related pseudogene is located near this gene; gene conversion events involving the functional gene and the pseudogene are thought account for many cases of steroid 21-hydroxylase deficiency.

Chapter 2

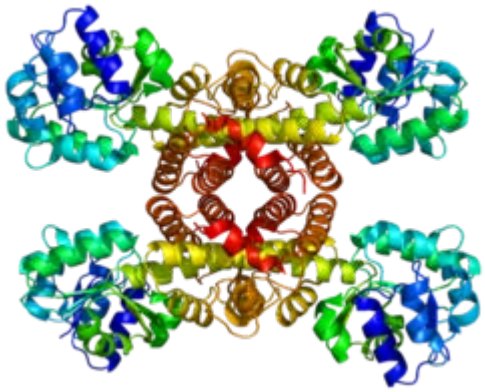
3-Hydroxyisobutyrate Dehydrogenase and 5-HT_{1E} Receptor

3-hydroxyisobutyrate dehydrogenase

3-hydroxyisobutyrate dehydrogenase

Identifiers	
EC number	1.1.1.31
CAS number	9028-39-1
Databases	
IntEnz	IntEnz view
BRENDA	BRENDA entry
ExPASy	NiceZyme view
KEGG	KEGG entry
MetaCyc	metabolic pathway
PRIAM	profile
PDB	structures
Gene Ontology	AmiGO / EGO

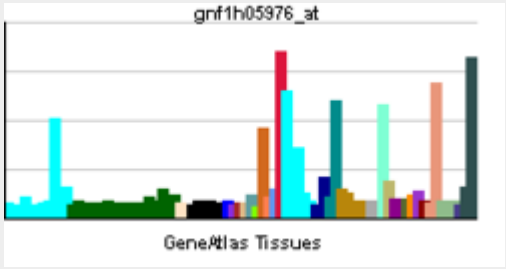
3-hydroxyisobutyrate dehydrogenase



PDB rendering based on 2gf2.

Identifiers	
Symbols	HIBADH; MGC40361; NS5ATP1
External IDs	OMIM: 608475 MGI: 1889802 HomoloGene: 15088 GeneCards: HIBADH Gene
EC number	1.1.1.31

RNA expression pattern



Orthologs

Species	Human	Mouse
Entrez	11112	58875
Ensembl	ENSG00000106049	ENSMUSG00000029776
UniProt	P31937	A0ZNJ2
RefSeq	NM_152740	NM_145567

(mRNA)		
RefSeq (protein)	NP_689953	NP_663542
Location (UCSC)	Chr 7: 27.53 - 27.67 Mb	Chr 6: 52.48 - 52.57 Mb

In enzymology, a **3-hydroxyisobutyrate dehydrogenase** (EC 1.1.1.31) also known as **β-hydroxyisobutyrate dehydrogenase** or **3-hydroxyisobutyrate dehydrogenase, mitochondrial** (HIBADH) is an enzyme that in humans is encoded by the *HIBADH* gene.

3-Hydroxyisobutyrate dehydrogenase catalyzes the chemical reaction:

3-hydroxy-2-methylpropanoate + $NAD^+ \rightleftharpoons$ 2-methyl-3-oxopropanoate + NADH + H^+

Thus, the two substrates of this enzyme are 3-hydroxy-2-methylpropanoate and NAD^+, whereas its 3 products are 2-methyl-3-oxopropanoate, NADH, and H^+.

This enzyme belongs to the family of oxidoreductases, specifically those acting on the CH-OH group of donor with NAD+ or NADP+ as acceptor. The systematic name of this enzyme class is **3-hydroxy-2-methylpropanoate:NAD+ oxidoreductase**. This enzyme participates in valine, leucine and isoleucine degradation.

Function

3-hydroxyisobutyrate dehydrogenase is a dimeric mitochondrial enzyme that catalyzes the NAD^+-dependent, reversible oxidation of 3-hydroxyisobutyrate, an intermediate of valine catabolism, to methylmalonate semialdehyde.

Structural studies

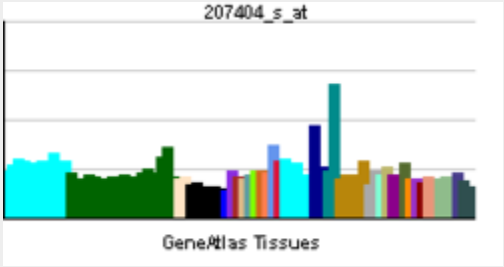
As of late 2007, 5 structures have been solved for this class of enzymes, with PDB accession codes 1WP4, 2CVZ, 2GF2, 2H78, and 2I9P.

5-HT_{1E} receptor

5-HT_{1E} serotonin receptor

Identifiers	
Symbols	HTR1E; 5-HT1E
External IDs	OMIM: 182132 HomoloGene: 55491 IUPHAR: 5-ht_{1e} GeneCards: HTR1E Gene

RNA expression pattern



Orthologs		
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Ensembl	ENSG00000168830	n/a
UniProt	P28566	n/a
RefSeq (mRNA)	NM_000865	n/a
RefSeq (protein)	NP_000856	n/a
Location (UCSC)	Chr 6: 87.7 - 87.78 Mb	n/a

5-hydroxytryptamine (serotonin) 1E receptor (5-HT_{1E}) is a highly expressed human G-protein coupled receptor that belongs to the 5-HT1 receptor family (G_i-coupled serotonin receptor). The human gene is denoted as **HTR1E**.

Function

The function of the 5-HT_{1E} receptor is unknown due to the lack of selective pharmacological tools, specific antibodies, and permissive animal models. The 5-HT_{1E} receptor gene lacks polymorphisms amongst humans (few mutations), indicating a high degree of evolutionary conservation of genetic sequence, which suggests that the 5-HT_{1E} receptor has an important physiological role in humans. It is hypothesized that the 5-HT_{1E} receptor is involved in the regulation of memory in humans due to the high abundance of receptors in the frontal cortex, hippocampus, and olfactory bulb, all of which are regions of the brain integral to memory regulation.

This receptor is unique among the serotonin receptors in that it is not known to be expressed by any rodent species, all of which lack the gene encoding the 5-HT_{1E} receptor. However the genomes of the pig, rhesus monkey, and several lagomorphs (including the guinea pig and rabbit) each encode a homologous 5-HT_{1E} receptor gene. The guinea pig is the most likely candidate for future study of 5-HT_{1E} receptor function *in vivo*. The expression of 5-HT_{1E} receptors in the guinea pig brain has been pharmacologically confirmed; 5-HT_{1E} receptor expression patterns of the human and guinea pig brains appear to be similar.

The most closely related receptor to the 5-HT_{1E} is the 5-HT_{1F} receptor. They share 57% amino acid sequence homology and have some pharmacological characteristics in common. Both receptors are G_i-coupled (inhibit adenylate cyclase activity) and both receptors have high affinities for 5-HT and low affinities for 5-carboxyamidotryptaine and mesulergine. However, due to major differences in brain expression patters, these receptors are unlikely to mediate similar functions in humans. For example, 5-HT_{1E} receptors are abundant in the hippocampus but are not detectable in the striatum (caudate and putamen of the human brain), while the opposite is true for the 5-HT_{1F} receptor. Thus, conclusions about the function of the 5-HT_{1E} receptor cannot be ascribed to the function of the 5-HT_{1F} receptor, and vice versa.

Selective ligands

No highly selective 5-HT_{1E} ligands are available yet. [^{3}H]5-HT remains the only radioligand available with high affinity for the 5-HT_{1E} receptor (5nM).

Agonists

- BRL-54443 (5-Hydroxy-3-(1-methylpiperidin-4-yl)-1H-indole) - mixed 5-$HT_{1E/1F}$ agonist

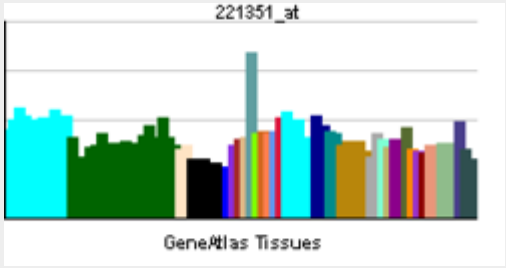
Chapter 3

5-HT_{1A} Receptor

5-hydroxytryptamine (serotonin) receptor 1A

Identifiers	
Symbols	HTR1A; 5-HT1A; 5HT1a; ADRB2RL1; ADRBRL1
External IDs	OMIM: 109760 MGI: 96273 HomoloGene: 20148 IUPHAR: 5-HT_{1A} GeneCards: HTR1A Gene

RNA expression pattern



Orthologs		
Species	**Human**	**Mouse**
Entrez	3350	15550
Ensembl	ENSG00000178394	ENSMUSG00000021721
UniProt	P08908	Q8BGS4
RefSeq (mRNA)	NM_000524	NM_008308

RefSeq (protein)	NP_000515	NP_032334
Location (UCSC)	Chr 5: 63.29 - 63.29 Mb	Chr 13: 106.56 - 106.57 Mb

The **5-HT_{1A} receptor** is a subtype of 5-HT receptor that binds the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). It is a G protein-coupled receptor (GPCR) that is coupled to G_i/G_o and mediates inhibitory neurotransmission. *HTR1A* denotes the human gene encoding for the receptor.

Distribution

The 5-HT_{1A} receptor is the most widespread of all the 5-HT receptors. In the central nervous system, 5-HT_{1A} receptors exist in the cerebral cortex, hippocampus, septum, amygdala, and raphe nucelus in high densities, while low amounts also exist in the basal ganglia and thalamus. The 5-HT_{1A} receptors in the raphe nucleus are largely somatodendritic autoreceptors, whereas those in other areas such as the hippocampus are postsynaptic receptors.

Function

Neuromodulation

5-HT_{1A} receptor agonists decrease blood pressure and heart rate via a central mechanism, by inducing peripheral vasodilation, and by stimulating the vagus nerve. These effects are the result of activation of 5-HT_{1A} receptors within the rostral ventrolateral medulla. The sympatholytic antihypertensive drug urapidil is an α_1-adrenergic receptor antagonist and α_2-adrenergic receptor agonist, as well as 5-HT_{1A} receptor agonist, and it has been demonstrated that the latter property contributes to its overall therapeutic effects. Vasodilation of the blood vessels in the skin via central 5-HT_{1A} activation increases heat dissipation from the organism out into the environment, causing a decrease in body temperature.

Activation of central 5-HT_{1A} receptors triggers the release or inhibition of norepinephrine depending on species, presumably from the locus coeruleus, which then reduces or increases neuronal tone to the iris sphincter muscle by modulation of postsynaptic α_2-adrenergic receptors within the Edinger-Westphal nucleus, resulting in pupil dilation in rodents, and pupil constriction in primates including humans.

5-HT_{1A} receptor agonists like buspirone and flesinoxan show efficacy in relieving anxiety and depression, and buspirone and tandospirone are currently approved for these indications in various parts of the world. Others such as gepirone, flesinoxan, flibanserin, and PRX-00023 have also been investigated, though none have been fully developed and approved as of yet. Some of the atypical antipsychotics like aripiprazole are also partial

agonists at the 5-HT_{1A} receptor and are sometimes used in low doses as augmentations to standard antidepressants like the selective serotonin reuptake inhibitors (SSRIs).

5-HT_{1A} autoreceptor desensitization and increased 5-HT_{1A} receptor postsynaptic activation via general increases in serotonin levels by serotonin precursor supplementation, serotonin reuptake inhibition, or monoamine oxidase inhibition has been shown to be a major mediator in the therapeutic benefits of most mainstream antidepressant supplements and pharmaceuticals, including serotonin precursors like L-tryptophan and 5-HTP, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), and monoamine oxidase inhibitors (MAOIs). 5-HT_{1A} receptor activation likely plays a significant role in the positive effects of serotonin releasing agents (SRAs) like MDMA ("Ecstasy") as well.

5-HT_{1A} receptors in the dorsal raphe nucleus are co-localized with neurokinin 1 (NK_1) receptors and have been shown to inhibit the release of substance P, their endogenous ligand. In addition to being antidepressant and anxiolytic in effect, 5-HT_{1A} receptor activation has also been demonstrated to be antiemetic and analgesic, and all of these properties may be mediated in part or full, depending on the property in question, by NK_1 receptor inhibition. Consequently, novel NK_1 receptor antagonists are now in use for the treatment of nausea and emesis, and are also being investigated for the treatment of anxiety and depression.

5-HT_{1A} receptor activation has been shown to increase dopamine release in the medial prefrontal cortex, striatum, and hippocampus, and may be useful for improving the symptoms of schizophrenia and Parkinson's disease. As mentioned above, some of the atypical antipsychotics are 5-HT_{1A} receptor partial agonists, and this property has been shown to enhance their clinical efficacy. Enhancement of dopamine release in these areas may also play a major role in the antidepressant and anxiolytic effects seen upon postsynaptic activation of the 5-HT_{1A} receptor.

Activation of 5-HT_{1A} receptors has been demonstrated to impair cognition, learning, and memory by inhibiting the release of glutamate and acetylcholine in various areas of the brain. Conversely, 5-HT_{1A} receptor antagonists such as lecozotan have been shown to facilitate certain types of learning and memory in rodents, and as a result, are being developed as novel treatments for Alzheimer's disease.

Other effects of 5-HT_{1A} activation include decreased aggression or increased serenic behavior, increased sociability, increased impulsivity, inhibition of addictive behavior, facilitation of sexual behavior and arousal, inhibition of penile erection, decreased food intake or anorexia, prolongation of REM sleep latency, and enhanced breathing or hyperventilation and reversal of opioid-induced respiratory depression.

Endocrinology

5-HT_{1A} receptor activation induces the secretion of various hormones including cortisol, corticosterone, adrenocorticotropic hormone (ACTH), oxytocin, prolactin, growth hormone, and β-endorphin. The receptor does not affect vasopressin or renin secretion, unlike the 5-HT_2 receptors. It has been suggested that oxytocin release may contribute to the prosocial, antiaggressive or serenic, and anxiolytic properties observed upon activation of the receptor. β-Endorphin secretion likely contributes to antidepressant, anxiolytic, and analgesic effects.

Autoreceptors

5-HT_{1A} receptors can be located on the cell body or soma, dendrites, axons, and both presynaptically and postsynaptically in nerve terminals or synapses. Those located on the soma and dendrites are called somatodendritic, and those located presynaptically in the synapse are aptly titled presynaptic. As a group, they are known as autoreceptors. Stimulation of 5-HT_{1A} autoreceptors inhibits the release of serotonin in nerve terminals. For this reason, 5-HT_{1A} receptor agonists tend to exert a biphasic mode of action; they decrease serotonin release and postsynaptic 5-HT_{1A} receptor activity in low doses, and further decrease serotonin release but increase postsynaptic 5-HT_{1A} receptor activity at moderate to high doses by directly stimulating the receptors in replacement of serotonin.

This autoreceptor-mediated inhibition of serotonin release has been postulated to be one of the reasons for the therapeutic lag that is commonly reported for most mainstream serotonergic antidepressants such as the SSRIs. The autoreceptors must first densensitize before the concentration of extracellular serotonin in the synapse can become elevated appreciably. Though the responsiveness of the autoreceptors is somewhat reduced with chronic treatment, they still remain effective at constraining large increases in extracellular serotonin concentrations. For this reason, serotonin reuptake inhibitors that also have 5-HT_{1A} receptor antagonistic or partial agonistic properties such as vilazodone and SB-649,915 are currently being investigated as novel antidepressants with a faster onset of action and greater efficacy than many of those currently available.

Unlike most drugs that elevate extracellular serotonin levels like the SSRIs and MAOIs, SRAs such as fenfluramine and MDMA ("Ecstasy") fully bypass serotonin autoreceptors like 5-HT_{1A} by forcing release to occur regardless of their inhibition. This is why SRAs display immediate and full effects in contrast to drugs like the SSRIs, which require several weeks of chronic dosing before therapeutic benefits are seen, and also why SRAs are much stronger than SSRIs and related compounds in effect as they produce far more robust and balanced increases in extracellular serotonin concentrations. For these reasons, selective serotonin releasing agents (SSRAs) including MDAI, MMAI, and 4-MTA have been proposed as novel antidepressants with an immediate onset of action and far greater efficacy in comparison to most current treatments.

Sufficient doses of 5-HT_{1A} receptor agonists themselves, like SRAs, are capable of fully bypassing the 5-HT_{1A} autoreceptor-mediated inhibition of serotonin release and therefore

decreased 5-HT_{1A} postsynaptic receptor activation as well, by directly agonizing the postsynaptic receptors in lieu of serotonin. It is mentionable, however, that, unlike SRAs, 5-HT_{1A} receptor agonists are incapable of bypassing the inhibitory effect of 5-HT_{1A} autoreceptors located as heteroreceptors in non-serotonergic synapses where 5-HT_{1A} postsynaptic receptors are not present, which, instead of serotonin, modulate the release of other neurotransmitters such as dopamine or glutamate.

Ligands

The distribution of 5-HT_{1A} receptors in the human brain may be imaged with the positron emission tomography using the radioligand [^{11}C]WAY-100,635. For example, one study has found increased 5-HT_{1A} binding in type 2 diabetes. Another PET study found a negative correlation between the amount of 5-HT_{1A} binding in the raphe nuclei, hippocampus and neocortex and a self-reported tendency to have spiritual experiences. Labeled with tritium, WAY-100,635 may also be used in autoradiography.

Agonists

- 5-CT
- 5-MeO-DMT
- 5-MT
- 8-OH-DPAT
- Adatanserin
- αET
- Alnespirone
- αMT
- Aripiprazole
- Asenapine
- Befiradol
- Binospirone
- Bufotenin
- Buspirone
- Cannabidiol
- Clozapine
- Dihydroergotamine
- DMT
- Ebalzotan
- Eltoprazine
- Eptapirone
- Ergotamine
- Etoperidone
- F-11,461
- F-12,826
- F-13,714
- F-14,679
- F-15,599

- Flesinoxan
- Flibanserin
- Gepirone
- Ipsapirone
- Lesopitron
- Lisuride
- LSD
- Lu AA21004
- LY-293,284
- LY-301,317
- MDMA
- Methysergide
- MKC-242
- NBUMP
- Nefazodone
- Osemozotan
- Perospirone
- Piclozotan
- Psilocin
- Psilocybin
- PRX-00023
- Rauwolscine
- Repinotan
- RU-24,969
- S-15,535
- Sarizotan
- SSR-181,507
- Sunepitron
- Tandospirone
- Tiospirone
- Trazodone
- U-92,016-A
- Urapidil
- Vilazodone
- Yohimbine
- Xaliproden
- Zalospirone
- Ziprasidone

Antagonists

- Alprenolol
- AV-965
- BMY-7,378
- Cyanopindolol
- Dotarizine

- Flopropione
- GR-46,611
- Iodocyanopindolol
- Isamoltane
- Lecozotan
- Methiothepin
- MPPF
- NAN-190
- Oxprenolol
- Pindobind
- Pindolol
- Propranolol
- Quetiapine
- Robalzotan
- SB-649,915
- SDZ-216,525
- Spiperone
- Spiramide
- Spiroxatrine
- UH-301
- WAY-100,135
- WAY-100,635
- Xylamidine

Genetics

The 5-HT_{1A} receptor is coded by the *HTR1A* gene. There are several human polymorphisms associated with this gene. A 2007 review listed 27 single nucleotide polymorphisms (SNP). The most investigated SNPs are C-1019G (rs6295), C-1018G, Ile28Val (rs1799921), Arg219Leu (rs1800044), and Gly22Ser (rs1799920). Some of the other SNPs are Pro16Leu, Gly272Asp, and the synonymous polymorphism G294A (rs6294). These gene variants have been studied in relation to psychiatric disorders with no definitive results.

Interactions

The 5-HT_{1A} receptor has been shown to interact with brain-derived neurotrophic factor (BDNF), which may play a major role in its regulation of mood and anxiety. It has also been shown to interact with sphingosine-1-phosphate receptor 1 ($S1PR_1$).

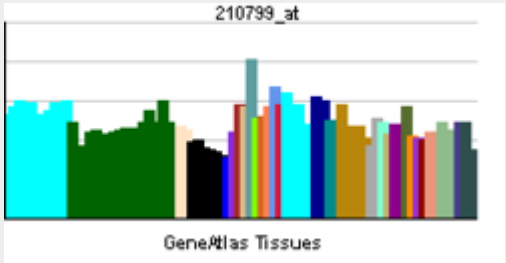
Chapter 4

5-HT_{1B} Receptor and 5-HT_{1D} Receptor

5-HT_{1B} receptor

5-hydroxytryptamine (serotonin) receptor 1B

Identifiers	
Symbols	HTR1B; 5-HT1B; 5-HT1DB; HTR1D2; HTR1DB; S12
External IDs	OMIM: 182131 MGI: 96274 HomoloGene: 669 IUPHAR: 5-HT_{1B} GeneCards: HTR1B Gene
RNA expression pattern	



Orthologs		
Species	**Human**	**Mouse**

Entrez	3351	15551
Ensembl	ENSG00000135312	ENSMUSG00000049511
UniProt	P28222	Q0VES5
RefSeq (mRNA)	NM_000863	NM_010482
RefSeq (protein)	NP_000854	NP_034612
Location (UCSC)	Chr 6: 78.23 - 78.23 Mb	Chr 9: 81.43 - 81.43 Mb

5-hydroxytryptamine receptor 1B also known as the **5-HT$_{1B}$ receptor** is a protein that in humans is encoded by the *HTR1B* gene. The 5-HT$_{1B}$ receptor is a 5-HT receptor subtype.

Tissue distribution and function

The 5-HT$_{1B}$ receptor acts on the CNS, where it induces presynaptic inhibition and behavioural effects. It also has vascular effects, such as pulmonary vasoconstriction.

Blocking the 5-HT$_{1B}$ receptor increases the number of osteoblasts, bone mass, and the bone formation rate.

5-HT$_{1B}$ receptors are present in many parts of the human brain. The highest concentrations are found in the basal ganglia, striatum and the frontal cortex. The function of the receptor differs between the areas: in the frontal cortex it is believed to act as a terminal receptor, inhibiting the release of dopamine. In the striatum and the basal ganglia, the 5-HT$_{1B}$ receptor is thought to act as an autoreceptor, inhibiting the release of serotonin.

Knockout mice lacking the 5-HT$_{1B}$ gene have shown an increase of aggression and a higher preference for alcohol.

Ligands

Agonists

- ergotamine (vasoconstrictor in migraine)
- sumatriptan (vasoconstrictor in migraine)
- zolmitriptan
- 5-Carboxamidotryptamine
- CGS-12066A

- CP-93,129 (peripherally acting)
- CP-94,253
- CP-135,807 (mixed 5-$HT_{1B/1D}$ agonist)
- RU-24969 (mixed 5-$HT_{1A/1B}$ agonist)

Antagonists and inverse agonists

- methiothepin (antipsychotic)
- yohimbine (aphrodisiac)
- metergoline
- isamoltane
- AR-A000002
- SB-216,641
- SB-224,289 (inverse agonist)
- SB-236,057 (inverse agonist)

Genetics

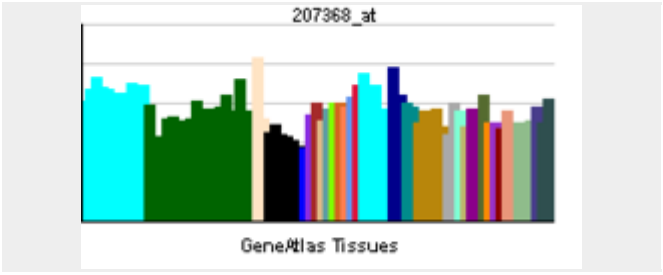
In humans the protein is coded by the gene *HTR1B*.

A genetic variant in the promotor region, *A-161T*, has been examined with respect to personality traits and showed no major effect.

5-HT_{1D} receptor

5-hydroxytryptamine (serotonin) receptor 1D

Identifiers	
Symbols	HTR1D; 5-HT1D; HT1DA; HTR1DA; HTRL; RDC4
External IDs	OMIM: 182133 MGI: 96276 HomoloGene: 20240 IUPHAR: 5-HT_{1D} GeneCards: HTR1D Gene
RNA expression pattern	



Orthologs		
Species	**Human**	**Mouse**
Entrez	3352	15552
Ensembl	ENSG00000179546	ENSMUSG00000070687
UniProt	P28221	Q3ZB48
RefSeq (mRNA)	NM_000864	NM_008309
RefSeq (protein)	NP_000855	NP_032335
Location (UCSC)	Chr 1: 23.39 - 23.39 Mb	Chr 4: 135.7 - 135.72 Mb

5-hydroxytryptamine (serotonin) receptor 1D, also known as **HTR1D**, is a 5-HT receptor, but also denotes the human gene encoding it. 5-HT_{1D} acts on the central nervous system, and affects locomotion and anxiety. It also induces vascular vasoconstriction in the brain.

Ligands

Agonists

- 5-(Nonyloxy)tryptamine,
- sumatriptan (vasoconstrictor in migraine)
- 5-Carboxamidotryptamine (5-CT)
- 5-(t-Butyl)-N-methyltryptamine
- CP-286,601
- PNU-109,291 ((S)-3,4-Dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-N-methyl-1H-2-benzopyran-6-carboxamide)
- PNU-142,633 ((1S)-1-[2-[4-[4-(Aminocarbonyl)phenyl]-1-piperazinyl]ethyl]-3,4-dihydro-N-methyl-1H-2-benzopyran-6-carboxamide)

- GR-46611 (3-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-N-(4-methoxybenzyl)acrylamide)
- L-694,247 (2-[5-[3-(4-Methylsulfonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indol-3-yl]ethanamine)
- L-772,405

Antagonists

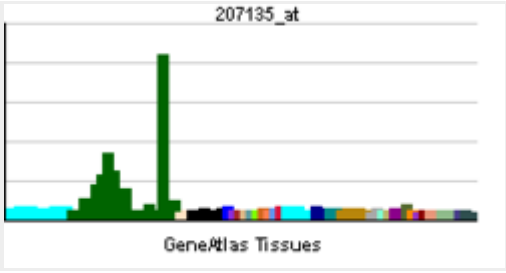
- Ziprasidone (atypical antipsychotic)
- methiothepin (antipsychotic)
- yohimbine (aphrodisiac)
- metergoline
- ergotamine (vasoconstrictor in migraine)
- BRL-15572
- GR-127,935 (mixed 5-$HT_{1B/1D}$ antagonist)
- LY-310,762
- LY-367,642
- LY-456,219
- LY-456,220

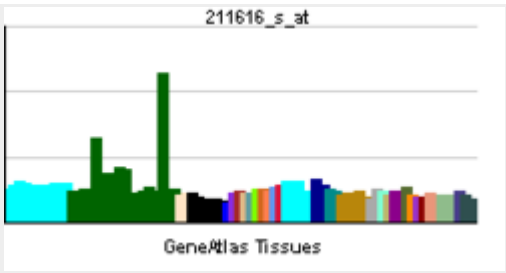
Chapter 5

5-HT_{2A} Receptor

5-hydroxytryptamine (serotonin) receptor 2A

Identifiers	
Symbols	HTR2A; 5-HT2A; HTR2
External IDs	OMIM: 182135 MGI: 109521 HomoloGene: 68073 IUPHAR: 5-HT_{2A} GeneCards: HTR2A Gene
RNA expression pattern	





Orthologs

Species	Human	Mouse
Entrez	3356	15558
Ensembl	ENSG00000102468	ENSMUSG00000034997
UniProt	P28223	Q543D4
RefSeq (mRNA)	NM_000621	NM_172812
RefSeq (protein)	NP_000612	NP_766400
Location (UCSC)	Chr 13: 46.31 - 46.37 Mb	Chr 14: 73.37 - 73.44 Mb

The mammalian **5-HT_{2A} receptor** is a subtype of the 5-HT_2 receptor that belongs to the serotonin receptor family and is a G protein-coupled receptor (GPCR). This is the main excitatory receptor subtype among the GPCRs for serotonin (5-HT), although 5-HT_{2A} may also have an inhibitory effect on certain areas such as the visual cortex and the orbitofrontal cortex. This receptor was given importance first as the target of psychedelic drugs like LSD. Later it came back to prominence because it was also found to be mediating, at least partly, the action of many antipsychotic drugs, especially the atypical ones.

5-HT_{2A} also happens to be a necessary receptor for the spread of the human polyoma virus called JC virus.

History

Serotonin receptors were split into two classes by Gaddum and Picarelli when it was discovered that some of the serotonin-induced changes in the gut could be blocked by morphine, whilst the remainder of the response was inhibited by dibenzyline leading to the naming of M and D receptors respectively. 5-HT_{2A} is thought to correspond to what was originally described as D subtype of 5-HT receptors by Gaddum and Picarelli. In the pre-molecular-cloning era when radioligand binding and displacement was the only major tool, spiperone and LSD were shown to label two different serotonin receptors, and neither of them displaced morphine, leading to naming of the 5-HT_1, 5-HT_2 and 5-HT_3 receptors, corresponding to high affinity sites from LSD, spiperone and morphine respectively. Later it was shown that the 5-HT_2 was very close to 5-HT_{1C} and thus were clubbed together, renaming the 5-HT_2 into 5-HT_{2A}. Thus the 5-HT_2 receptor family is composed of three separate molecular entities: the 5-HT_{2A} (erstwhile 5-HT_2 or D), the 5-HT_{2B} (erstwhile 5-HT_{2F}) and the 5-HT_{2C} (erstwhile 5-HT_{1C}) receptors.

Distribution

5-HT_{2A} is expressed widely throughout the central nervous system (CNS). It is expressed near most of the serotoninergic terminal rich areas, including neocortex (mainly prefrontal, parietal, and somatosensory cortex) and the olfactory tubercle. Especially high concentrations of this receptor on the apical dendrites of pyramidal cells in layer V of the cortex may modulate cognitive processes, by enhancing glutamate release followed by a complex range of interactions with the 5-HT_{1A}, $GABA_A$, adenosine A_1, AMPA, $mGluR_{2/3}$, mGlu5, and OX_2 receptors. In the rat cerebellum, the protein has also been found in the Golgi cells of the granular layer, and in the Purkinje cells.

In the periphery, it is highly expressed in platelets and many cell types of the cardiovascularsystem, in fibroblasts, and in neurons of the peripheral nervous system. Additionally, 5-HT2A mRNA expression has been observed in human monocytes.

Signaling cascade

The 5-HT_{2A} receptor is known primarily to couple to the $G\alpha_q$ signal transduction pathway. Upon receptor stimulation with agonist, $G\alpha_q$ and β-γ subunits dissociate to initiate downstream effector pathways. $G\alpha_q$ stimulates phospholipase C (PLC) activity, which subsequently promotes the release of diacylglycerol (DAG) and inositol triphosphate (IP3), which in turn stimulate protein kinase C (PKC) activity and Ca^{2+} release.

There are many additional signal cascade components that include the formation of arachidonic acid through PLA2 activity, activation of phospholipase D, Rho/Rho kinase, and ERK pathway activation initiated by agonist stimulation of the receptor.

Effects

Physiological processes mediated by the receptor include:

- CNS: neuronal excitation, behavioural effects, learning, anxiety
- smooth muscle: contraction (in gastrointestinal tract & bronchi)
- vasoconstriction / vasodilatation
- platelets: aggregation
- Activation of the 5-HT_{2A} receptor with DOI produces superpotent anti-inflammatory effects in cardiovascular related tissues, as well as potent anti-inflammatory effects in non-cardiovascular tissues. Other 5-HT_{2A} agonists like LSD also have potent anti-inflammatory effects against TNF-alpha-induced inflammation.

Ligands

Agonists

Activation of the 5-HT_{2A} receptor is necessary for the effects of the "classic" psychedelics like LSD, psilocin and mescaline, which act as full or partial agonists at this receptor, and represent the three main classes of 5-HT_{2A} agonists, the ergolines, tryptamines and phenethylamines, respectively. A very large family of derivatives from these three classes has been developed, and their structure-activity relationships have been extensively researched. Agonists acting at 5-HT_{2A} receptors located on the apical dendrites of pyramidal cells within regions of the prefrontal cortex are believed to mediate hallucinogenic activity.

Full agonists

- (R)-DOI
- N-(2-hydroxybenzyl)-2C-I and its 2-methoxy-analog
- TCB-2
- Br-DFLY.

Partial agonists

Methysergide, a congener of methylergonovine, used in treatment of migraine blocks 5-HT_{2A} and 5-HT_{2C} receptors, but sometimes acts as partial agonist, in some preparations. The atypical antipsychotic aripiprazole is also a weak partial agonist.

Peripherally selective agonists

One effect of 5-HT_{2A} receptor activation is a reduction in intraocular pressure, and so 5-HT_{2A} agonists can be useful for the treatment of glaucoma. This has led to the development of compounds such as AL-34662 that are hoped to reduce pressure inside the eyes but without crossing the blood-brain barrier and producing hallucinogenic side effects. Animal studies with this compound showed it to be free of hallucinogenic effects at doses up to 30 mg/kg, although several of its more lipophilic analogues did produce the head twitch response known to be characteristic of hallucinogenic effects in rodents.

Silent antagonists

- Although ergot alkaloids are mostly nonspecific 5-HT receptor antagonists, a few ergot derivatives such as metergoline bind preferentially to members of the 5-HT_2 receptor family.

- Ketanserin, the prototypic 5-HT_2 receptor antagonist potently blocks 5-HT_{2A}receptors, less potently blocks 5-HT_{2C} receptors, and has no significant effect on 5-HT_3 or 5-HT_4 receptors or any members of the 5-HT_1 receptor family. Thus discovery of Ketanserin was a landmark in the pharmacology of 5-HT_2

receptors. Ketanserin, though capable of blocking 5-HT induced platelet adhesion, however does not mediate its well known antihypertensive action through 5-HT_2 receptor family, but through its high affinity for $alpha_1$ adrenergic receptors. It also has high affinity for H_1 histaminergic receptors equal to that at 5-HT_{2A} receptors. Compounds chemically related to ketanserin such as ritanserin are more selective 5-HT_{2A} receptor antagonists with low affinity for alpha-adrenergic receptors. However, ritanserin, like most other 5-HT_{2A} receptor antagonists, also potently inhibits 5-HT_{2C} receptors.

- Nefazodone operates by blocking post-synaptic serotonin type-2A receptors and to a lesser extent by inhibiting pre-synaptic serotonin and norepinephrine (noradrenaline) reuptake.

- Atypical antipsychotic drugs like clozapine, olanzapine, quetiapine, risperidone are relatively potent antagonists of 5-HT_{2A} as are some of the lower potency old generation/typical antipsychotics. Other antagonists are MDL-100,907 (prototype of another new series of 5-HT_{2A}antagonists) and cyproheptadine.

- Pizotifen is a non-selective antagonist.

- 2-alkyl-4-aryl-tetrahydro-pyrimido-azepines are subtype selective antagonists (35g: 60-fold).

- AMDA and related derivatives are another family of selective 5-HT_{2A} antagonists.

- Hydroxyzine

Inverse agonists

- AC-90179 - potent and selective inverse agonist at 5-HT_{2A}, also 5-HT_{2C} antagonist.

- Nelotanserin (APD-125) - selective 5-HT_{2A} inverse agonist developed by Arena Pharmaceuticals for the treatment of insomnia. APD-125 was shown to be effective and well tolerated in clinical trials, but development of APD-125 was halted in December 2008 because the substance did not meet the trial's endpoints.

- Eplivanserin (Sanofi Aventis), a sleeping pill that reached phase II trials (but for which the application for approval was withdrawn), acts as a selective 5-HT_{2A} inverse agonist.

- Pimavanserin (ACP-103) - more selective than AC-90179, orally active, antipsychotic *in vivo*, now in human clinical trials.

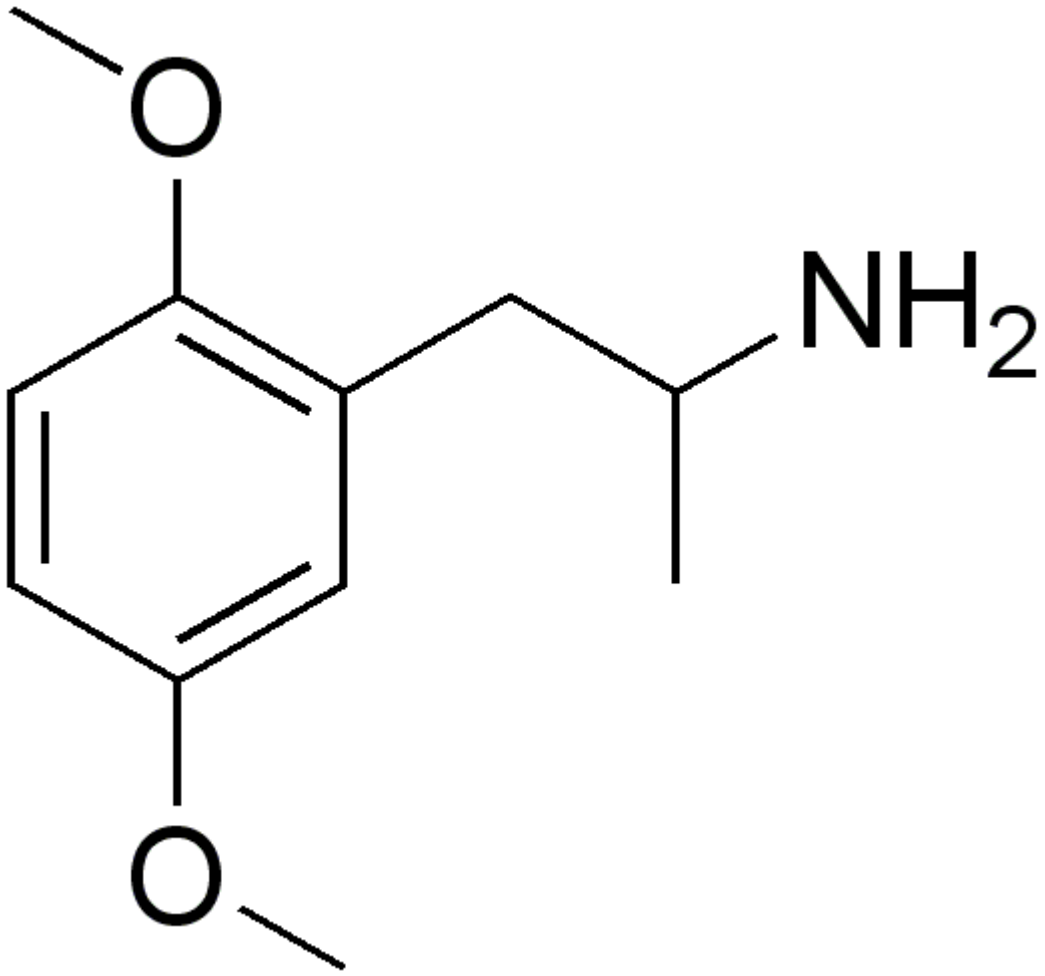
- Volinanserin

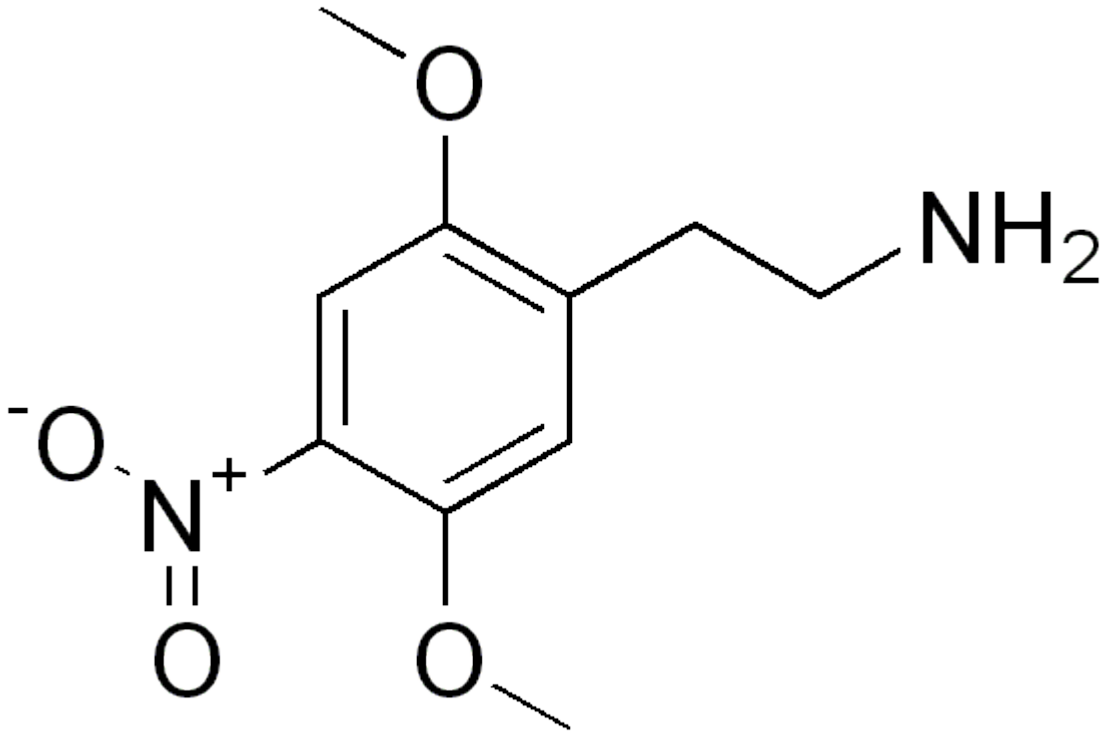
Examples

Agonists	Antagonists
• α-methyl-5-HT	• cyproheptadine
• AMT	• ketanserin
• DMT	• mirtazapine
• LSD	• nefazodone
• mescaline	• pizotifen
• psilocin	• trazodone
• TCB-2	• atypical antipsychotics

Functional selectivity

5-HT_{2A}-receptor ligands may differentially activate the transductional pathways. Studies evaluated the activation of two effectors, PLC and PLA2, by means of their second messengers. Compounds displaying more pronounced functional selectivity are 2,5-DMA and 2C-N. The former induces IP accumulation without activating the PLA2 mediated response, while the latter elicits AA release without activating the PLC mediated response.


O
NH2
O



Recent research has suggested potential signaling differences within the somatosensory cortex between 5-HT_{2A} agonists that produce headshakes in the mouse and those that do not, such as lisuride, as these agents are also non-hallucinogenic in humans despite being active 5-HT_{2A} agonists. The difference in signal transduction between the two 5-HT_{2A} agonists serotonin and DOI may be due to the presence of the intracellular proteins called β-arrestins, more specifically arrestin beta 2.

Role of lipophilicity

A set of ligands were evaluated. For agonists, a highly significant linear correlation was observed between binding affinity and lipophilicity. For ligands exhibiting partial agonist or antagonist properties, the lipophilicity was consistently higher than would be expected for an agonist of comparable affinity.

Genetics

Chromosome 13.

The 5-HT_{2A} receptors is coded by the *HTR2A* gene. In humans the gene is located on chromosome 13. The gene has previously been called just HTR2 until the description of two related genes *HTR2B* and *HTR2C*. Several interesting polymorphisms have been identified for HTR2A: A-1438G (rs6311), C102T (rs6313) and His452Tyr (rs6314). Many more polymorphisms exist for the gene. A 2006 paper listed 255.

Associations with psychiatric disorders

Several studies have seen links between the -1438G/A polymorphism and mood disorders, such as bipolar disorder and major depressive disorder. A weak link with an odds ratio of 1.3 has been found between the T102C polymorphism and schizophrenia. This polymorphism has also been studied in relation to suicide attempts, with a study finding excess of the C/C genotypes among the suicide attempters. A number of other studies were devoted to finding an association of the gene with schizophrenia, with diverging results.

These individual studies may, however, not give a full picture: A review from 2007 looking at the effect of different SNPs reported in separate studies stated that "genetic association studies [of *HTR2A* gene variants with psychiatric disorders] report conflicting and generally negative results" with no involvement, small or a not replicated role for the genetic variant of the gene.

Treatment response

One study has found that genetic variations between individuals in the HTR2A gene may to some extent account for the difference in outcome of antidepressant treatment, so that patients suffering from major depressive disorder and treated with Citalopram may

benefit more than others if they have one particular genotype. In this study 768 single nucleotide polymorphism (SNP) across 68 genes were investigated and a SNP—termed rs7997012—in the second intron of the HTR2A gene showed significant association with treatment outcome.

Genetics seems also to be associated to some extent with the amount of adverse events in treatment of major depression disorder.

Neuroimaging

The 5-HT_{2A} receptors may be imaged with PET-scanners using the fluorine-18-altanserin and MDL 100,907 radioligands that binds to the neuroreceptor, e.g., one study reported a *reduced* binding of altanserin particularly in the hippocampus in patients with major depressive disorder. Another PET study reported *increased* altanserin binding in the caudate nuclei in obsessive compulsive disorder patients compared to a healthy control group.

Patients with Tourette's syndrome have also been scanned and the study found an increased binding of altanserin for patients compared to healthy controls. The altanserin uptake decreases with age reflecting a loss of specific 5-HT_{2A} receptors with age. A study has also found a positive correlation among healthy subjects between altanserin binding and the personality trait neuroticism as measured by the NEO PI-R personality questionnaire.

Role in virus endocytosis

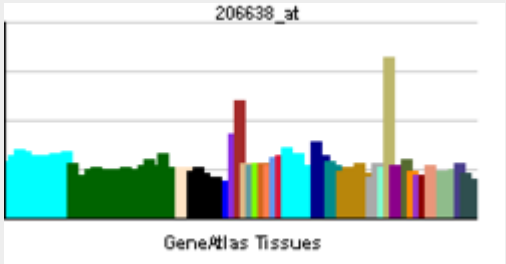
5-HT_{2A} is a necessary receptor for clathrin mediated endocytosis of the human polyoma virus called JC virus, the causative agent of progressive multifocal leukoencephalopathy (PML), that enters cells like oligodendrocytes, astrocytes, B lymphocytes, and kidney epithelial cells. These cells need to express both the alpha 2-6–linked sialic acid component of the $5HT_{2A}$ receptor in order to endocytose JCV.

Chapter 6

5-HT_{2B} Receptor and 5-HT_{2C} Receptor

5-HT_{2B} receptor

5-hydroxytryptamine (serotonin) receptor 2B

Identifiers	
Symbols	HTR2B; 5-HT(2B); 5-HT2B
External IDs	OMIM: 601122 MGI: 109323 HomoloGene: 55492 IUPHAR: 5-HT_{2B} GeneCards: HTR2B Gene
RNA expression pattern	

Orthologs		
Species	**Human**	**Mouse**
Entrez	3357	15559
Ensembl	ENSG00000135914	ENSMUSG00000026228

UniProt	P41595	Q7TNN4
RefSeq (mRNA)	NM_000867	NM_008311
RefSeq (protein)	NP_000858	NP_032337
Location (UCSC)	Chr 2: 231.68 - 231.7 Mb	Chr 1: 87.93 - 87.94 Mb

5-hydroxytryptamine (serotonin) receptor 2B, also known as **HTR2B**, is a 5-HT_2 receptor, but also denotes the human gene encoding it.

Function

The 5-HT_2 receptors (of which the 5-HT_{2B} receptor is a subtype) mediate many of the central and peripheral physiologic functions of serotonin. Cardiovascular effects include contraction of blood vessels and shape changes in platelets; central nervous system effects include neuronal sensitization to tactile stimuli and mediation of some of the effects of phenylisopropylamine hallucinogens.

The 5-HT_{2B} receptor subtype is involved in:

- CNS: presynaptic inhibition, behavioural effects
- Vascular: pulmonary vasoconstriction
- Cardiac: The 5-HT_{2B} receptor regulates cardiac structure and functions as demonstrated by the abnormal cardiac development observed in 5-HT_{2B} receptor null mice. The 5-HT_{2B} receptor stimulation can also lead to pathological proliferation of cardiac valves fibroblasts, which with chronic overstimulation of 5-HT_{2B} can lead to a severe valvulopathy. Moreover, 5-HT_{2B} receptors were recently shown to be overexpressed in human failing heart and antagonists of 5-HT_{2B} receptors were uncovered to prevent both angiotensin II or beta-adrenergic agonist-induced pathological cardiac hypertrophy in mouse.

- Serotonin transporter: 5-HT_{2B} receptors regulate serotonin release via the serotonin transporter, and are important both to normal physiological regulation of serotonin levels in blood plasma, and with the abnormal acute serotonin release produced by drugs such as MDMA.

Ligands

As of 2009, few highly selective 5-HT_{2B} receptor ligands have been discovered, although numerous potent non-selective compounds are known, particularly agents with concomitant 5-HT_{2C} binding. Research in this area has been limited due to the

cardiotoxicity of $5HT_{2B}$ agonists, and the lack of clear therapeutic application for $5HT_{2B}$ antagonists, but there is still a need for selective ligands for scientific research.

Agonists

Selective

- BW-723C86: fair functional subtype selectivity; almost full agonist. Anxiolytic *in vivo*.
- Ro60-0175 functionally selective over 5-HT_{2A}, potent agonist at both 5-HT_{2B} and 5-HT_{2C}
- VER-3323: selective for 5-$HT_{2B/2C}$ over 5-HT_{2A}
- α-Methyl-5-HT - moderately selective over 5-HT_{2A} and 5-HT_{2C}

Non-selective

- MDMA (Ecstasy)
- MDA
- MEM
- Pergolide
- Cabergoline
- Norfenfluramine
- Chlorphentermine
- Aminorex
- mCPP
- Bromo-dragonfly
- Psilocin
- DMT
- 5-MeO-DMT

Antagonists

- Sarpogrelate (mixed 5-HT_{2A} / 5-HT_{2B} antagonist)
- Lisuride (primarily dopamine agonist, but 5-HT_{2B} antagonist effects as well)
- Tegaserod (primarily 5-HT_4 agonist, but also 5-HT_{2B} antagonist)
- RS-127,445: high affinity; subtype selective (1000x), selective over at least eight other 5-HTR types; orally bioavailable.
- SDZ SER-082: mixed 5-$HT_{2B/2C}$ antagonist
- EGIS-7625: high selectivity over 5-HT_{2A}
- PRX-08066
- SB-200,646
- SB-204,741
- SB-206,553: mixed 5-HT_{2B} / 5-HT_{2C} antagonist and PAM at α7 nAChR
- SB-215,505
- SB-228,357
- LY-272,015

Possible Applications

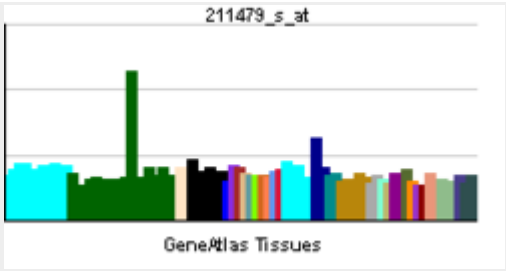
5-HT_{2B} antagonists have previously been proposed as treatment for migraine headaches, and RS-127,445 was trialled in humans up to Phase I for this indication, but development was not continued. More recent research has focused on possible application of 5-HT_{2B} antagonists as treatments for chronic heart disease.

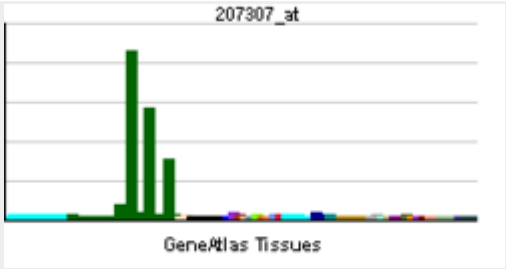
5-HT_{2C} receptor

5-hydroxytryptamine (serotonin) receptor 2C

Identifiers	
Symbols	HTR2C; 5-HT2C; HTR1C
External IDs	OMIM: 312861 MGI: 96281 HomoloGene: 20242 IUPHAR: 5-HT_{2C} GeneCards: HTR2C Gene

RNA expression pattern





Orthologs

Species	Human	Mouse
Entrez	3358	15560

Ensembl	ENSG00000147246	ENSMUSG00000041380
UniProt	P28335	Q8BUB1
RefSeq (mRNA)	NM_000868	XM_978183
RefSeq (protein)	NP_000859	XP_983277
Location (UCSC)	Chr X: 113.72 - 114.05 Mb	Chr X: 142.21 - 142.44 Mb

The **5-HT_{2C} receptor** is a subtype of 5-HT receptor that binds the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). It is a G protein-coupled receptor (GPCR) that is coupled to G_q/G_{11} and mediates excitatory neurotransmission. *HTR2C* denotes the human gene encoding for the receptor, that in humans is located at the X chromosome. As males have one copy of the gene and in females one of the two copies of the gene is repressed, polymorphisms at this receptor can affect the two genders to differing extent.

Distribution

5-HT_{2C} receptors are widely distributed across the peripheral human brain.

Function

The 5-HT_{2C} receptor is one of the many binding sites for serotonin. Activation of this receptor by serotonin inhibits dopamine and norepinephrine release in certain areas of the brain.

5-HT_{2C} receptors significantly regulate mood, anxiety, feeding, and reproductive behavior. 5-HT_{2C} receptors regulate dopamine release in the striatum, prefrontal cortex, nucleus accumbens, hippocampus, hypothalamus, and amygdala, among others.

Research indicates that some suicide victims have an abnormally high number of 5-HT_{2C} receptors in the prefrontal cortex. There is some mixed evidence that agomelatine, a 5-HT_{2C} antagonist, is an effective antidepressant. Antagonism of 5-HT_{2C} receptors by agomelatine results in an increase of dopamine and norepinephrine activity in the frontal cortex. Conversely, fluoxetine and other SSRIs indirectly stimulate 5-HT_{2C} activity by increasing levels of serotonin in the synapse. Many atypical antipsychotics block 5-HT_{2C} receptors, but their clinical use is limited by multiple undesirable actions on various neurotransmitters and receptors. Fluoxetine acts as a direct 5-HT_{2C} antagonist in addition to inhibiting serotonin reuptake, however, the clinical significance of this action is variable.

An overactivity of 5-HT_{2C} receptors may contribute to depressive and anxiety symptoms in a certain population of patients. Activation of 5-HT_{2C} by serotonin is responsible for many of the negative side effects of SSRI and SNRI medications, such as sertraline, paroxetine, venlafaxine, and others. Some of the initial anxiety caused by SSRIs is due to excessive signalling at 5-HT_{2C}. Over a period of 1–2 weeks, the receptor begins to downregulate, along with the downregulation of 5-HT_{2A}, 5-$HT1_A$, and other serotonin receptors. This downregulation parallels the onset of the clinical benefits of SSRIs. 5-HT_{2C} receptors exhibit constitutive activity in vivo, and may retain the ability to influence neurotransmission in the absence of ligand occupancy. Thus, 5-HT_{2C} receptors do not require binding by a ligand (serotonin) in order to exhibit influence on neurotransmission. Inverse agonists may be required to fully extinguish 5-HT_{2C} constitutive activity, and may prove useful in the treatment of 5-HT_{2C}-mediated conditions in the absence of typical serotonin activity.

5-HT_{2C} receptors mediate the release and increase of extracellular dopamine in response to many drugs, including caffeine, nicotine, amphetamine, morphine, cocaine, and others. 5-HT_{2C} antagonism increases dopamine release in response to reinforcing drugs, and many dopaminergic stimuli. Feeding, social interaction, and sexual activity all release dopamine subject to inhibition by 5-HT_{2C}. Increased 5-HT_{2C} expression reduces dopamine release in both the presence and absence of stimuli.

Many GPCRs downregulate in response to agonists for the receptor, and upregulate in response to antagonists. The 5-HT_{2A} and 5-HT_{2C} receptors appear to downregulate in response to both antagonists and agonists. Chronic treatment with antipsychotic drugs, which possess 5-HT_2 antagonist activity, results in downregulation of both 5-HT_{2A} and 5-HT_{2C}, as does chronic treatment with SSRIs and other 5-HT agonists. However, chronic SSRI treatment may increase 5-HT_{2C} expression, specifically in the choroid plexus.

Conditions that increase cytokine levels in the human body may have potential to raise 5-HT_{2C} gene expression in the brain. This could possibly comprise a link between viral infections and associated depression. Cytokine therapy has been shown to increase 5-HT_{2C} gene expression, resulting in increased activity of 5-HT_{2C} receptors in the brain.

Endocrinology

Serotonin is involved in basal and stress-induced regulation of hypothalamus and pituitary gland hormones such as prolactin, adrenocorticotropic hormone (ACTH), vasopressin and oxytocin, mainly via actions of receptor subtypes 5-HT_{2A} and 5-HT_{2C}. As such, the 5-HT_{2C} receptor is a significant modulator of Hypothalamic–pituitary–adrenal axis (HPA axis). The HPA axis is the main controller of acute sympathetic stress responses related to fight-or-flight response. Prolonged activation and disturbances of the HPA axis contribute to depressive and anxiety symptoms seen in many psychopathological conditions.

Stimulation of 5-HT_{2C} receptors leads to increase of corticotropin releasing hormone (CRH) and vasopressin mRNA in the paraventricular nucleus and proopiomelanocortin in

the anterior pituitary lobe. In rats, restraint stress (which can produces depressive symptoms if being chronic) induces secretion of prolactin, ACTH, vasopressin and oxytocin which is partially mediated via 5-HT_{2C} receptor. Responses during such conditions as dehydration or haemorrhage causes the release oxytocin via serotonergic response that is partly mediated via 5-HT_{2C}. In addition, peripheral release of vasopressin involves serotonergic response which is partially mediated via 5-HT_{2C}.

Expression of the 5-HT_{2C} receptor in the CNS is modulated by female sex hormones estradiol and progesterone. Combination of the hormones decrease the receptor concentration in the ventral hippocampus in rats and could thus affect mood.

Genetics

Many human polymorphisms have been identified influencing the expression of 5-HT_{2C}. Significant correlations are suggested, specifically in relation to psychiatric disorders such as depression, OCD, and anxiety-related conditions. Polymorphisms also correlate with susceptibility to a number of conditions including drug abuse and obesity. There are indications that the alternative splicing of the 5-HT2C receptor is regulated by a snoRNA called SNORD115, the deletion of which is associated with Prader–Willi syndrome. As the human gene is located in the X chromosome, males have only one copy of the gene whereas women have two, meaning that mutations in the gene affect the phenotype of men even when the allele would be recessive in nature. As women have two copies of the gene, but only one allele is expressed in each cell, they are a mosaic for polymorphisms, meaning that one genetic variant may be prevalent in one tissue and another variant will be prevalent in a different tissue (as with all other x-linked genetic variations).

Ligands

Agonists

- A-372,159
- AL-38022A
- Aripiprazole
- CP-809,101
- Fenfluramine
- Lisuride
- Lorcaserin
- Mesulergine
- MK-212
- Naphthylisopropylamine
- Norfenfluramine
- Org 12,962
- ORG-37,684
- Oxaflozane
- PNU-22394
- Psychedelics
    - Lysergamides (LSD, etc)

Antagonists

- Agomelatine
- Eltoprazine
- Etoperidone
- Fluoxetine
- FR-260,010
- Lu AA24530
- Methysergide
- Nefazodone
- Norfluoxetine
- O-Desmethyltramadol
- RS-102,221
- SB-200,646
- SB-221,284
- SB-242,084
- SDZ SER-082

Inverse Agonists

- Antidepressants
    - Tricyclics (Amitriptyline, Clomipramine, Imipramine, Nortriptyline, etc)
    - Tetracyclics (Mirtazapine, Mianserin, Amoxapine, etc)
- Antihistamines (Cyproheptadine, Hydroxyzine, Latrepirdine, etc)
- Antipsychotics
    - Typicals (Chlorpromazine,

    - Phenethylamines (2C-B, DOI, DOM, Mescaline, etc)
    - Piperazines (mCPP, TFMPP, etc)
    - Tryptamines (5-MeO-DMT, Bufotenin, DMT, Psilocin, etc)
- Ro60-0175
- Vabicaserin
- WAY-629
- WAY-161,503
- YM-348
- Tramadol
- Trazodone
    - Fluphenazine, Loxapine, Thioridazine, etc)
    - Atypicals (Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone, etc)
- Cinanserin
- Deramciclane
- Ketanserin
- LY-53,857
- Metergoline
- Methiothepin
- Pizotifen
- Ritanserin
- SB-206,553
- SB-228,357
- SB-243,213

Interactions

The 5-HT_{2C} receptor has been shown to interact with MPDZ.

RNA editing

5HT2CR pre-mRNA can be the subject of RNA editing. It is the only serotonin receptor as well as being the one of the large family of 7 transmembrane receptors (7TMRs) known to be edited. Different levels of editing result in a variety of effects on receptor function.

Type

The type of RNA editing that occurs in the pre-mRNA of the 5HT2CR is Adenosine to Inosine (A to I) editing.

A to I RNA editing is catalyzed by a family of adenosine deaminases acting on RNA (ADARs) that specifically recognize adenosines within double-stranded regions of pre-mRNAs and deaminate them to inosine. Inosines are recognised as guanosine by the cells translational machinery. There are three members of the ADAR family ADARs 1-3 with ADAR1 and ADAR2 being the only enzymatically active members. ADAR3 is thought to have a regulatory role in the brain. ADAR1 and ADAR2 are widely expressed in tissues while ADAR3 is restricted to the brain. The double stranded regions of RNA are formed by base-pairing between residues in the close to region of the editing site with residues usually in a neighboring intron but can be an exonic sequence. The region that

base pairs with the editing region is known as an Editing Complementary Sequence (ECS)

ADARs bind interact directly with the dsRNA substrate via their double stranded RNA binding domains. If an editing site occurs within a coding sequence, it can result in a codon change. This can lead to translation of a protein isoform due to a change in its primary protein structure. Therefore editing can also alter protein function. A to I editing occurs in a non coding RNA sequences such as introns, untranslated regions (UTRs), LINEs, SINEs(especially Alu repeats) The function of A to I editing in these regions is thought to involve creation of splice sites and retention of RNAs in the nucleus amongst others.

Location

Editing occurs in 5 different closely located sites within exon 5 which is corresponds to the second intracellular loop of the final protein. The sites are known as A, B, C′ (previously called E), C and D and are predicted to occur within amino acid positions 156, 158 and 160. Several codon changes can occur due to A to I editing at these sites.32 different mRNA variants can occur leading to 24 different protein isoforms.

1. An Isoleucine to Valine (I/V) at amino acid position 157,161.
2. An Isoleucine to a Methionine(I/M) at amino acid position 157
3. An Aspartate to a Serine (N/S)at 159
4. An Aspartate to Aspargine(N/D) at 159
5. An Asparagine to a Glycine(N/G) at 159.

These codon changes which can occur due to A to I editing at these sites can lead to a maximum of 32 different mRNA variants leading to 24 different protein isoforms. The number of protein isoforms is less than 32 since some amino acids are encoded by more than one codon. Another editing site , site F has also been located in the exon complementary sequence (ECS) of intron 5. The ECS required for formation of double stranded RNA structure is found within intron 5.

Conservation

RNA editing of this receptor occurs at 4 locations in the rat. Editing also occurs in the mouse. The initial demonstration of RNA editing in rat. The predominant isoform in rat brain is VNV which differs from the most common type found in humans. The editing complementary sequence is known to be conserved across Mammalia.

Regulation

5HT2c receptor is the only serotonin receptor edited despite its close sequence similarites to other family memebers. 5HT2CR is different due to possessing a imperfect inverted repeat at the end of exon 5 and the begining of intron 5 allowing formation of an RNA duplex producing the dsRNA required by ADARs for editing. Disruption of this inverted

repeat was demonstrated to cease all editing. ref name="pmid9153397"/> The different 5HT2CR mRNA isoforms are expresssed differently throughourt the brain, yet not all of the 24 have been detected perhaps due to tissue specific expression or low frequency editng of a particular type. Those isoforms that are not expressed at all or at a very low frequency are linked by being edited only at site C' and/or site B but not at site A. Some examples of differences in frequency of editing and site edited in different parts of the human brain of 5HT2CR include low frequency of editing in cerebellum and nearly all editing is at site D while in the hippocampus editing frequency is higher with site A being the main editing site. Site C' is only found edited in the thalamus. The most common isoform in human brain is the VSV isoform.

Mice knock out and other studies have been used to determine which ADAR enzyme are involved in editing. Editing at A and B sites has been demonstrated to be due to ADAR1 editing. Also since ADAR1 expression is increased in response tothe presence of interferon α, it was also observed that editing at A and B sites was also increased because of this. C' and D sites require ADAR2 and editing is decreased by the presence of ADAR1 with editing of C' site only obsered in ADAR1 double knock out mice. The C site has been shown to be mainly edited by ADAR2 but in presence of upregulated expression of ADAR1 , there was an increase in editing of this site and the enzymes prescence can also result in limited editing in ADAR 2 knock out mice. This demonstrates that there must be some form interaction between the two A to I editing enzymes. Also such interactions and tissue specific expression of ADARs interaction may explain the variety in editing patterns in different regions of the brain.

Consequences

Second, the editing pattern controls the amount of the 5-HT2CR mRNA that leads to the expression of full-length protein through the modulation of alternative splice site selection 76,77. Among three alternative splice donor sites (GU1 to GU3; Fig. 4C), GU2 is the only site that forms the mature mRNA to produce the functional, full-length 5-HT2CR protein. Unedited pre-mRNAs tend to be spliced at the GU1 site, resulting in the truncated, non-functional protein if translated 76,77. However, most pre-mRNAs edited at more than one position are spliced at GU2 77. Thus, when editing is inefficient, increased splicing at GU1 may act as a control mechanism to decrease biosynthesis of the 5-HT2CR-INI and thereby limit serotonin response. Third, RNA editing controls the ultimate physiological output of constitutively active receptors by affecting the cell surface expression of the 5-HT2CR. The 5-HT2CR-VGV, which displays the lowest level of constitutive activity, is fully expressed at the cell surface under basal conditions and is rapidly internalized in the presence of agonist 78. In contrast, the 5-HT2CR-INI is constitutively internalized and accumulates in endosomes 78.

Structure

As mentioned editing results in several codaon changes.The editing sites are found in the second intracellular domain of the protein which is also the receptors G protein coupling

domain.Therefore editing of these sites can effect the affinity of the receptor for G protein binding.

Function

Editing results in reduced affinity for specific G proteins which in turn affects internal signalling via second messengers (Phospholipase C signalling system).The fully edited isoform ,VGV, considerably reduces 5-HT potency, G-protein coupling and agonist binding, compared to the unedited protein isoform , INI. 72-76. Most evidence for the effect of editing on function comes from downstream measurements of receptor activity , radio ligand binding and functional studies.Inhibitory effects are linked to the extent of editing.Those isoforms with a higher level of editing require higher levels of serotonin to activate the phospholipase c pathway. Unedited INI form has a greater tendency to isomerise to a active form which can more easily interact with G proteins. This indicates that RNA editng here may be a mechanism for regulating neuronal excitability by stabilising receptor signalling.

Editing is also thought to function in cell surface expression of the receptor subtype.The fully edited VGV which has the lowest level of constitutive activity is fully expressed at the cell surface while the non edited INI is internalised and accumulates in endosome.

Editing is also thought to influence splicing.Three different spliced isoforms of the receptor exist .Editing regulates the amount of 5HT2CR mRNA which leads to translation of the full length protein selection of alternative splice sites. t76,77. These splice sites termed Gu1, Gu2 , GU3.Only GU2 site splicing results in translation of the full length receptor while editing at GU1 is known to result in translation of a truncated protein.This is thought to be a regulatory mechanism to decrease the amount of unedited isoform INI to limit serotonin response when editing is inefficent. Most of the pre-mRNAs which are edited are splced at the GU2 site.

Dysregulation

Serotonin family of receptors are often linked to pathology of several human mental conditions such as Schizophrenia , anxiety, Bipolar disorder and major depression. There have been several experimental investigations into the effects of alternative editing patterns of the 5HT2CR and these conditions with a wide variability in results especially those relating to schizophrenia. Interestingly some studies have noted that there is an increase in in RNA editing at site A in depressed suicide victims. E site editing was observed to be increased in individuals suffering from major depression. In rat models this increase is also observed and can be reversed with fluoxetine with some suggestion that E site editing maybe linked to major depression.

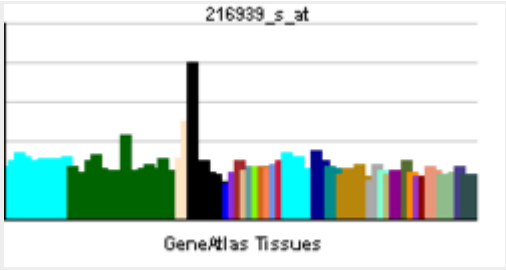
Chapter 7

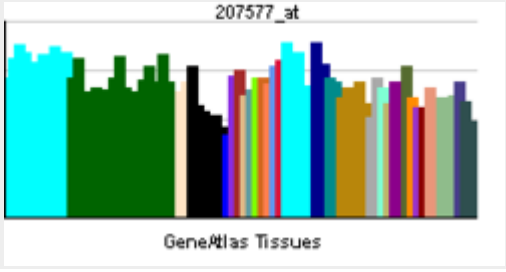
5-HT_4 Receptor and 5-HT_{5A} Receptor

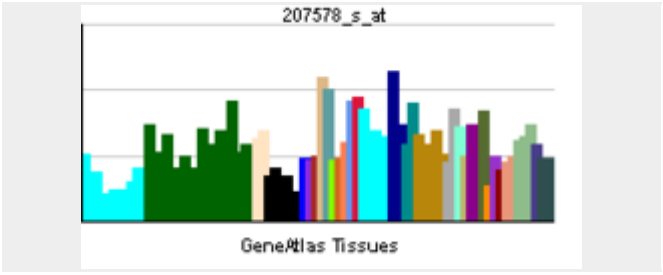
5-HT_4 receptor

5-hydroxytryptamine (serotonin) receptor 4

Identifiers	
Symbols	HTR4; 5-HT4; 5-HT4R
External IDs	OMIM: 602164 MGI: 109246 HomoloGene: 20243 IUPHAR: 5-HT_4 GeneCards: HTR4 Gene
RNA expression pattern	







Orthologs		
Species	**Human**	**Mouse**
Entrez	3360	15562
Ensembl	ENSG00000164270	ENSMUSG00000026322
UniProt	Q13639	Q3URB5
RefSeq (mRNA)	NM_000870	NM_008313
RefSeq (protein)	NP_000861	NP_032339
Location (UCSC)	Chr 5: 147.81 - 148.01 Mb	Chr 18: 62.45 - 62.59 Mb

5-hydroxytryptamine receptor 4 is a protein that in humans is encoded by the *HTR4* gene.

This gene is a member of the family of serotonin receptors, which are G protein coupled receptors that stimulate cAMP production in response to serotonin (5-hydroxytryptamine). The gene product is a glycosylated transmembrane protein that functions in both the peripheral and central nervous system to modulate the release of various neurotransmitters. Multiple transcript variants encoding proteins with distinct C-terminal sequences have been described, but the full-length nature of some transcript variants has not been determined.

Location

The receptor is located in the alimentary tract, urinary bladder, heart and adrenal gland as well as the central nervous system (CNS). In the CNS the receptor appears in the putamen, caudate nucleus, nucleus accumbens, globus pallidus and substantia nigra and to a lesser extent in the neocortex, raphe and pontine nuclei and some areas of the thalamus. It has not been found in the cerebellum.

Isoforms

Internalization is isoform-specific.

Ligands

Several drugs which act as 5-HT_4 selective agonists have recently been introduced into use in both scientific research and clinical medicine. Some drugs which act as 5-HT_4 agonists are also active as 5-HT_3 antagonists, such as mosapride, metoclopramide, renzapride and zacopride, and so these compounds cannot be considered highly selective. Research in this area is ongoing.

SB-207,145 radiolabeled with carbon-11 is used as a radioligand for 5-HT_4 in positron emission tomography pig and human studies.

Agonists

- BIMU-8
- Cisapride
- CJ-033,466
- Mosapride
- Prucalopride
- Renzapride
- RS-67506
- RS-67333 - partial agonist
- SL65.0155 - partial agonist
- Tegaserod
- Zacopride

Antagonists

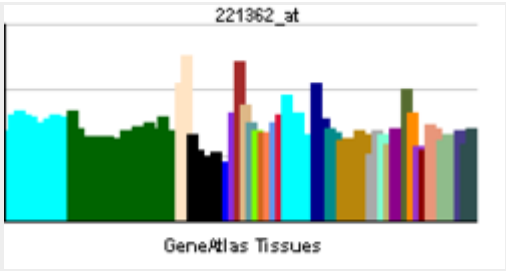
- Piboserod
- GR-113,808 (1-methyl-1H-indole-3-carboxylic acid, [1-[2-[(methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl ester)
- GR-125,487
- RS-39604 (1-[4-Amino-5-chloro-2-(3,5-dimethoxyphenyl)methyloxy]-3-[1-[2-methylsulphonylamino]piperidin-4-yl]propan-1-one)
- SB-203,186
- ([Methoxy-^{11}C]1-butylpiperidin-4-yl)methyl 4-amino-3-methoxybenzoate

5-HT_{5A} receptor

5-hydroxytryptamine (serotonin) receptor 5A

Identifiers	
Symbols	HTR5A; 5-HT5A; MGC138226
External IDs	OMIM: 601305 MGI: 96283 HomoloGene: 22461 IUPHAR: 5-ht_{5a} GeneCards: HTR5A Gene

RNA expression pattern



Orthologs		
Species	**Human**	**Mouse**
Entrez	3361	15563
Ensembl	ENSG00000157219	ENSMUSG00000039106
UniProt	P47898	Q3URB0
RefSeq (mRNA)	NM_024012	NM_008314
RefSeq (protein)	NP_076917	NP_032340
Location (UCSC)	Chr 7: 154.49 - 154.51 Mb	Chr 5: 28.17 - 28.19 Mb

5-hydroxytryptamine (serotonin) receptor 5A, also known as **HTR5A**, is a protein which in humans is encoded by the *HTR5A* gene.

Function

The gene described in this record is a member of 5-hydroxytryptamine receptor family and encodes a multi-pass membrane protein that functions as a receptor for 5-hydroxytryptamine and couples to G proteins, negatively influencing cAMP levels via G_i and G_o. This protein has been shown to function in part through the regulation of intracellular Ca^{2+} mobilization.

Rodents have been shown to possess two functional 5-HT_5 receptor subtypes, 5-HT_{5A} and 5-HT_{5B}, however while humans possess a gene coding for the 5-HT_{5B} subtype, its coding sequence is interrupted by stop codons making the gene non-functional, and so only the 5-HT_{5A} subtype is expressed in human brain.

Clinical signficance

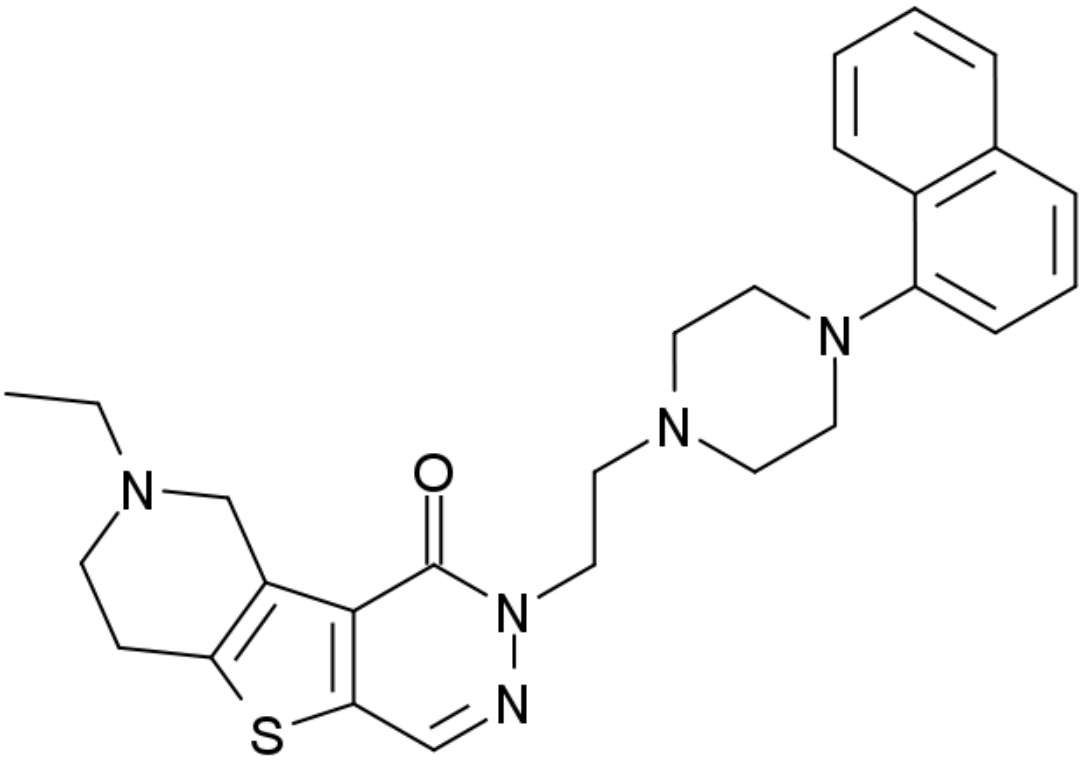
The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated in a wide range of psychiatric conditions and also has vasoconstrictive and vasodilatory effects.

Selective Ligands

Few highly selective ligands are commercially available for the 5-HT_{5A} receptor. When selective activation of this receptor is desired in scientific research, the non-selective serotonin receptor agonist 5-Carboxamidotryptamine can be used in conjunction with selective antagonists for its other targets (principally 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} and 5-HT_7). Research in this area is ongoing.

Agonists

- Valerenic acid, a component of valerian, has been shown to act as a $5HT_{5A}$ partial agonist.
- Another ligand which has been recently disclosed is shown below, claimed be a selective 5-HT_{5A} agonist with K_i = 124 nM.



Antagonists

- Latrepirdine (non-selective)
- SB-699,551

Chapter 8

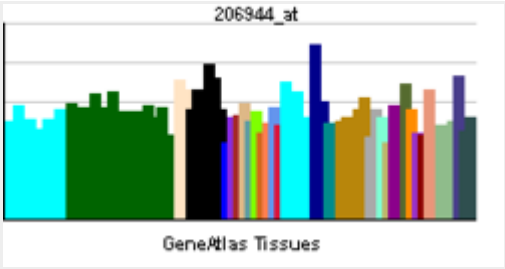
5-HT_6 Receptor and 5-HT_7 Receptor

5-HT_6 receptor

5-hydroxytryptamine (serotonin) receptor 6

Identifiers	
Symbols	HTR6; 5-HT6; 5-HT6R
External IDs	OMIM: 601109 MGI: 1196627 HomoloGene: 673 IUPHAR: 5-HT_6 GeneCards: HTR6 Gene

RNA expression pattern



Orthologs		
Species	**Human**	**Mouse**
Entrez	3362	15565
Ensembl	ENSG00000158748	ENSMUSG00000028747
UniProt	P50406	Q14AW8

RefSeq (mRNA)	NM_000871	NM_021358
RefSeq (protein)	NP_000862	NP_067333
Location (UCSC)	Chr 1: 19.86 - 19.88 Mb	Chr 4: 138.33 - 138.35 Mb

The **5-HT$_6$ receptor** is a subtype of 5-HT receptor that binds the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). It is a G protein-coupled receptor (GPCR) that is coupled to G_s/G_o and mediates excitatory neurotransmission. *HTR6* denotes the human gene encoding for the receptor.

Distribution

The 5-HT$_6$ receptor is expressed almost exclusively in the brain. It is distributed in various areas including, but not limited to, the olfactory tubercle, cerebral cortex (frontal and entorhinal regions), nucleus accumbens, striatum, caudate nucleus, hippocampus, and the molecular layer of the cerebellum. Based on its abundance in extrapyramidal, limbic, and cortical regions it can be suggested that the 5-HT$_6$ receptor plays a role in functions like motor control, emotionality, cognition, and memory.

Function

Blockade of central 5-HT$_6$ receptors has been shown to increase glutamatergic and cholinergic neurotransmission in various brain areas, whereas activation enhances GABAergic signaling in a widespread manner. Antagonism of 5-HT$_6$ receptors also facilitates dopamine and norepinephrine release in the frontal cortex, while stimulation has the opposite effect.

Despite the 5-HT$_6$ receptor having a functionally excitatory action, it is largely co-localized with GABAergic neurons and therefore produces an overall inhibition of brain activity. In parallel with this, 5-HT$_6$ antagonists improve cognition, learning, and memory, and agents such as latrepirdine, Lu AE58054, and SB-742,457 are being developed as novel treatments for Alzheimer's disease and other dementias. 5-HT$_6$ antagonists have also been shown to reduce appetite and produce weight loss, and as a result, PRX-07034, BVT-5,182, and BVT-74,316 are being investigated for the treatment of obesity.

Recently, the 5-HT$_6$ agonists WAY-181,187 and WAY-208,466 have been demonstrated to be active in rodent models of depression, anxiety, and obsessive-compulsive disorder (OCD), and such agents may be useful treatments for these conditions. Additionally, it can be inferred that 5-HT$_6$ activation likely plays a major role in the therapeutic benefits

of serotonergic antidepressants like the selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).

Ligands

A large number of selective 5-HT_6 ligands have now been developed and this is a productive current area of research.

Full agonists

- EMD-386,088 - potent and selective $5HT_6$ agonist (EC_{50} 1nM)
- 2-Ethyl-5-methoxy-N,N-dimethyltryptamine (EMDT)
- WAY-181,187
- WAY-208,466
- N1-(6-chloroimidazo[2,1-b][1,3]thiazole-5-sulfonyl)tryptamine (compound 11q)
- *N*-(inden-5-yl)imidazothiazole-5-sulfonamide (43): K_i = 4.5nM, EC_{50} = 0.9nM, E_{max} = 98%

Partial Agonists

- E-6801
- E-6837

Antagonists

- BVT-5182
- BVT-74316
- EGIS-12233 - mixed 5-HT_6 / 5-HT_7 antagonist
- Latrepirdine (non-selective) and analogues
- Lu AE58054
- MS-245
- PRX-07034
- SB-258,585
- SB-271,046
- SB-357,134
- SB-399,885
- SB-742,457
- Ro04-6790
- Atypical antipsychotics (olanzapine, asenapine, clozapine)
- WAY-255315 / SAM-315: Ki = 1.1nM, IC = 13nM

Genetics

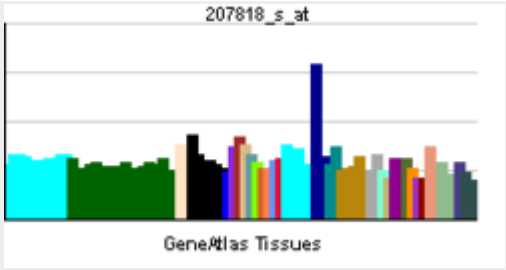
The receptor is encoded by the *HTR6* gene. As the protein is a neuroreceptor it is possible that genetic variations in the gene would have an effect on brain, and research studies have investigated whether polymorphisms is associated with brain-related variables, such

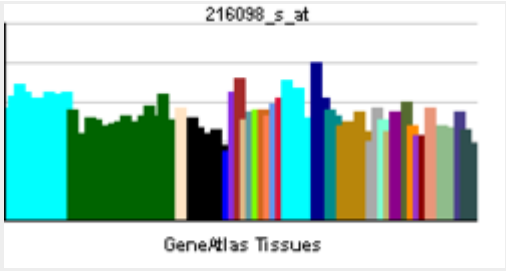
as neuropsychiatric disorders. For example, in 2004 one Chinese study reported an association between the C267T (rs1805054) polymorphism and Alzheimer's disease. Others have studied the polymorphism in relation to Parkinson's disease.

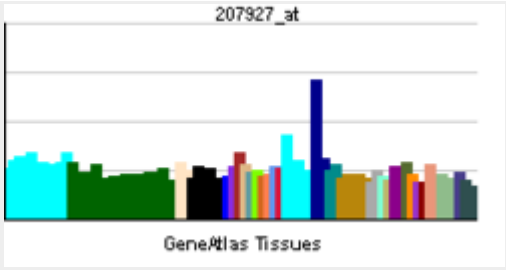
5-HT$_7$ receptor

5-HT$_7$ serotonin receptor

Identifiers	
Symbols	HTR7; 5-HT7
External IDs	OMIM: 182137 MGI: 99841 HomoloGene: 20244 IUPHAR: 5-HT$_7$ GeneCards: HTR7 Gene
RNA expression pattern	







Orthologs		
Species	**Human**	**Mouse**

Entrez	3363	15566
Ensembl	ENSG00000148680	ENSMUSG00000024798
UniProt	P34969	Q14A50
RefSeq (mRNA)	NM_000872	NM_008315
RefSeq (protein)	NP_000863	NP_032341
Location (UCSC)	Chr 10: 92.49 - 92.61 Mb	Chr 19: 36.03 - 36.12 Mb

The **5-HT_7 receptor** is a member of the GPCR superfamily of cell surface receptors and is activated by the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) The 5-HT_7 receptor is coupled to G_s (stimulates the production of the intracellular signaling molecule cAMP) and is expressed in a variety of human tissues, particularly in the brain, the gastrointestinal tract, and in various blood vessels. This receptor has been a drug development target for the treatment of several clinical disorders. The 5-HT_7 receptor is encoded by the intron containing *HTR7* gene, which in humans is transcribed into 3 different splice variants.

Function

In humans, the neurotransmitter serotonin (5-Hydroxytryptamine (5-HT)) plays an important role in various cognitive and behavioral functions. The serotonin receptor encoded by the *HTR7* gene belongs to the superfamily of G protein-coupled receptors (GPCRs). When the 5-HT_7 receptor is activated by serotonin, it sets off a cascade of events starting with release of the stimulatory G protein G_s from the GPCR complex. G_s in turn activates adenylate cyclase which increases intracellular levels of the second messenger cAMP.

The 5-HT_7 receptor plays a role in smooth muscle relaxation within the vasculature and in the gastrointestinal tract. The highest 5-HT_7 receptor densities are in the thalamus and hypothalamus, and it is present at higher densities also in the hippocampus and cortex. The 5-HT_7 receptor is involved in thermoregulation, circadian rhythm, learning and memory, and sleep. It is also speculated that this receptor may be involved in mood regulation, suggesting that it may be a useful target in the treatment of depression.

Variants

Three splice variants have been identified in humans (designated h5-$HT_{7(a)}$, h5-$HT_{7(b)}$, and h5-$HT_{7(d)}$), which encode receptors that differ in their carboxy terminals. The h5-$HT_{7(a)}$ is the full length receptor (445 amino acids), while the h5-$HT_{7(b)}$ is truncated at

amino acid 432 due to alternative splice donor site. The h5-$HT_{7(d)}$ is a distinct isoform of the receptor: the retention of an exon cassette in the region encoding the carboxyl terminal results a 479-amino acid receptor with a c-terminus markedly different from the h5-$HT_{7(a)}$. A 5-$HT_{7(c)}$ splice variant is detectable in rat tissue but is not expressed in humans. Conversely, rats do not express a splice variant homologous to the h5-$HT_{7(d)}$, as the rat 5-HT_7 gene lacks the exon necessary to encode this isoform. Drug binding affinities are similar across the three human splice variants; however, inverse agonist efficacies appear to differ between the splice variants.

Discovery

In 1983, evidence for a 5-HT_1-like receptor was first found. Ten years later, 5-HT_7 receptor was cloned and characterized. It has since become clear that the receptor described in 1983 is 5-HT_7.

Clinical signficance

This receptor gene is a candidate locus for involvement in autistic disorder and other neuropsychiatric disorders.

Ligands

Numerous ligands bind to the 5-HT_7 receptor with moderate to high affinity.

Agonists

Agonists mimic the effects of the endogenous ligand, which is serotonin at the 5-HT_7 receptor (↑cAMP).

- 5-Carboxamidotryptamine (5-CT)
- 5-methoxytryptamine (5-MT, 5-MeOT)
- 8-OH-DPAT (mixed 5-HT_{1A}/5-HT_7 agonist)
- AS-19
- LP-12 (4-(2-Diphenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinehexanamide)
- LP-44 (4-[2-(Methylthio)phenyl]-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-1-piperazinehexanamide)
- N_ω-Methylserotonin
- *N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)-4-aryl-1-piperazinehexanamides (can function as either an agonist or antagonist depending on side chain substitution)

Antagonists

Neutral antagonists (also known as silent antagonists) bind the receptor and have no intrinsic activity but will block the activity of agonists or inverse agonists. Inverse agonists inhibit the constitutive activity of the receptor, producing functional effects

opposite to those of agonists (at the 5-HT_7 receptor: ↓cAMP). Neutral antagonists and inverse agonists are typically referred to collectively as "antagonists" and, in the case of the 5-HT_7 receptor, differentiation between neutral antagonists and inverse agonists is problematic due to differing levels inverse agonist efficacy between receptor splice variants. For instance, mesulergine and metergoline are reported to be neutral antagonists at the h5-$HT_{7(a)}$ and h5-$HT_{7(d)}$ receptor isoforms but these drugs display marked inverse agonist effects at the h5-$HT_{7(b)}$ splice variant.

- 3-{4-[4-(4-chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-6-fluoro-1,3-dihydro-2*H*-indol-2-one
- Amisulpride
- Amitriptyline
- Amoxapine
- Aripiprazole
- Clomipramine
- Clozapine
- Cyproheptadine
- N,N-Dimethyltryptamine
- EGIS-12233 (mixed 5-HT_6/5-HT_7 antagonist)
- Fluphenazine
- Fluperlapine
- ICI 169,369
- Imipramine
- Ketanserin
- Loxapine
- LSD
- Maprotiline
- Mesulergine
- Methysergide
- Mianserin
- Olanzapine
- Ritanserin
- SB-258,719
- SB-258,741
- SB-269,970 (highly 5-HT_7 selective)
- SB-656,104-A
- SB-691,673
- Sertindole
- Spiperone
- Sulpiride
- Tenilapine
- TFMPP
- Trifluoperazine
- Ziprasidone
- Zotepine

Inactivating antagonists

Inactivating antagonists are non-competitive antagonists that render the receptor persistently insensitive to agonist, which resembles receptor desensitization. Inactivation of the 5-HT_7 receptor, however, does not arise from the classically described mechanisms of receptor desensitization via receptor phosphorylation, beta-arrestin recruitment, and receptor internalization. Inactivating antagonists all likely interact with the 5-HT_7 receptor in an irreversible/pseudo-irreversible manner, as is the case with [^{3}H]risperidone.

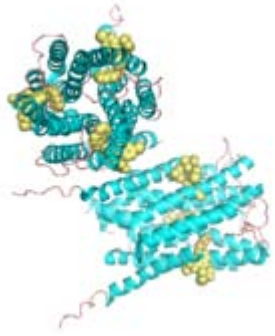
- Bromocriptine
- Lisuride
- Metergoline
- Methiothepin
- Paliperidone
- Risperidone

Chapter 9

5-Lipoxygenase-Activating Protein and Methionine Synthase

5-Lipoxygenase-activating protein

arachidonate 5-lipoxygenase-activating protein



Crystallographic structure of the inhibitor-bound human 5-lipoxygenase-activating protein.

Identifiers	
Symbols	ALOX5AP; FLAP
External IDs	OMIM: 603700 MGI: 107505 HomoloGene: 1231 GeneCards: ALOX5AP Gene
Orthologs	

Species	Human	Mouse
Entrez	241	11690
Ensembl	ENSG00000132965	ENSMUSG00000060063
UniProt	P20292	P30355
RefSeq (mRNA)	NM_001629	NM_009663
RefSeq (protein)	NP_001620	NP_033793
Location (UCSC)	Chr 13: 30.21 - 30.24 Mb	Chr 5: 150.08 - 150.1 Mb

Arachidonate 5-lipoxygenase-activating protein also known as **5-lipoxygenase activating protein**, or **FLAP**, is a protein that in humans is encoded by the *ALOX5AP* gene.

Function

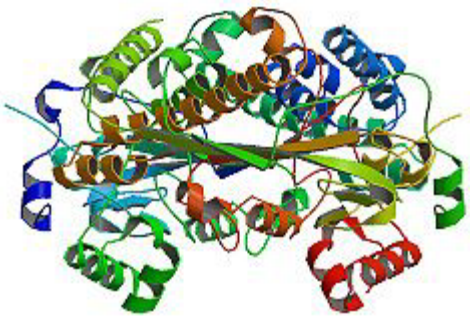
FLAP is necessary for the activation of 5-lipoxygenase and therefore for the production of leukotrienes. It is an integral protein within the nuclear membrane. FLAP is necessary in synthesis of leukotriene, which are lipid mediators of inflammation that is involved in respiratory and cardiovascular diseases. FLAP functions as a membrane anchor for 5-lipooxygenase and as an amine acid-bind protein. How FLAP activates 5-lipooxygenase is not completely understood, but there is a physical interaction between the two. FLAP structure consist of 4 transmembrane alpha helices, but they are found in 3's(trimer) forming a barrel. The barrel is about 60 A high and 36 A wide.

Clinical significance

Gene polymorphisms in FLAP are suspected of playing a role in Alzheimer's disease. Leukotrienes, which need the FLAP protein to be made, have an established pathological role in allergic and respiratory diseases. Animal and human genetic evidence suggests they may also have an important role in atherosclerosis, myocardial infarction, and stroke. The structure of FLAP provides a tool for the development of novel therapies for respiratory and cardiovascular diseases and for the design of focused experiments to probe the cell biology of FLAP and its role in leukotriene biosynthesis.

Methionine synthase

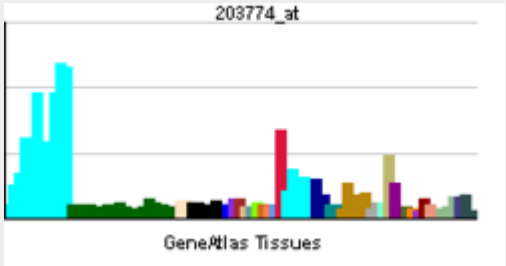
5-methyltetrahydrofolate-homocysteine methyltransferase



PDB rendering based on 2o2k.

Identifiers	
Symbols	MTR; FLJ45386
External IDs	OMIM: 156570 MGI: 894292 HomoloGene: 37280 GeneCards: MTR Gene
EC number	2.1.1.13

RNA expression pattern



Orthologs		
Species	**Human**	**Mouse**
Entrez	4548	238505
Ensembl	ENSG00000116984	ENSMUSG00000021311

UniProt	Q99707	n/a
RefSeq (mRNA)	NM_000254	XM_138431
RefSeq (protein)	NP_000245	XP_138431
Location (UCSC)	Chr 1: 235.03 - 235.13 Mb	Chr 13: 12.27 - 12.31 Mb

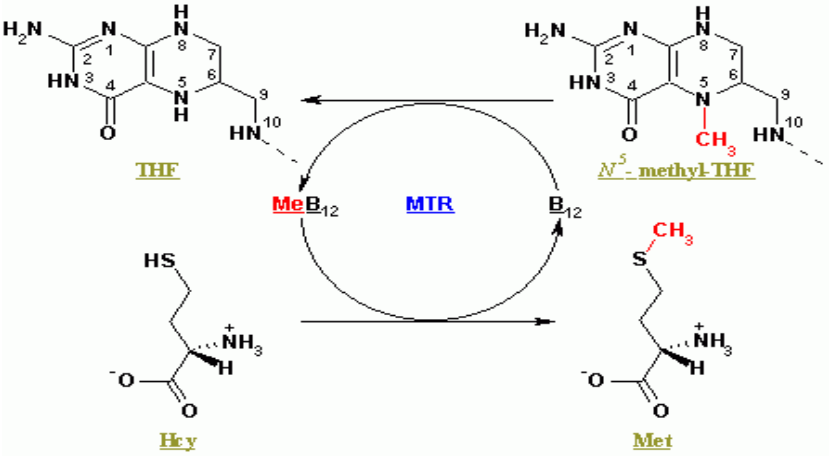
Methionine synthase also known as **MS**, **MeSe**, **MetH** is an enzyme that in humans is encoded by the *MTR* gene (5-methyltetrahydrofolate-homocysteine methyltransferase). This enzyme is responsible for the production of methionine from homocysteine. Methionine synthase forms part of the S-adenosylmethionine (SAMe) biosynthesis and regeneration cycle.

Function

Methionine synthase catalyzes the final step in methionine biosynthesis.

Methionine synthase contains the cofactor methylcobalamin (MeB_{12}) and uses the substrates N^5-methyl-tetrahydrofolate (N^5-mTHF) and homocysteine.

The enzyme works in two steps in a ping-pong reaction. First, methylcobalamin is formed by a methyl group transfer from N^5-mTHF with formation of MeB_{12} and tetrahydrofolate (THF). In the second step, MeB_{12} transfers this methyl group to homocysteine, regenerating the cofactor cobalamin and releasing the product methionine.



The reaction reaction catalyzed by methionine synthase

Methionine synthase is the only mammalian enzyme that metabolizes 5-mTHF to regenerate the active cofactor, THF. Deficiency in methionine synthase function may be due to genetic mutations, reduced levels of its cobalamin cofactor (vitamin B_{12}), or decreased levels of the enzyme (methionine synthase) reductase (required for the sustained activity of methionine synthase).

Clinical significance

Mutations in the MTR gene have been identified as the underlying cause of methylcobalamin deficiency complementation group G, or methylcobalamin deficiency cblG type. The consequence of reduced methionine synthase activity is megaloblastic anemia.

Genetics

Several polymorphisms in the MTR gene have been identified.

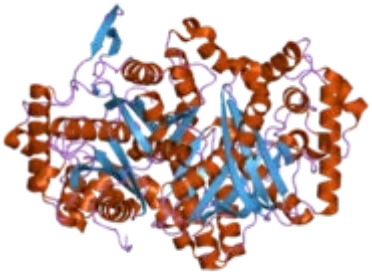
- 2756A→G ($Asp^{919}Gly$)

Chapter 10

ACAA1, ACF (Gene) and ACD (Gene)

ACAA1

acetyl-Coenzyme A acyltransferase 1



PDB rendering based on 2iik.

Identifiers	
Symbols	ACAA1; PTHIO; THIO; ACAA
External IDs	OMIM: 604054 MGI: 2148491 HomoloGene: 37497 GeneCards: ACAA1 Gene
EC number	2.3.1.16
Orthologs	

Species	Human	Mouse
Entrez	30	113868
Ensembl	ENSG00000060971	ENSMUSG00000036138
UniProt	P09110	Q921H8
RefSeq (mRNA)	NM_001607	NM_130864
RefSeq (protein)	NP_001123882	NP_570934
Location (UCSC)	Chr 3: 38.14 - 38.15 Mb	Chr 9: 119.25 - 119.26 Mb

3-Ketoacyl-CoA thiolase, peroxisomal also known as **acetyl-Coenzyme A acyltransferase 1** is an enzyme that in humans is encoded by the *ACAA1* gene.

Function

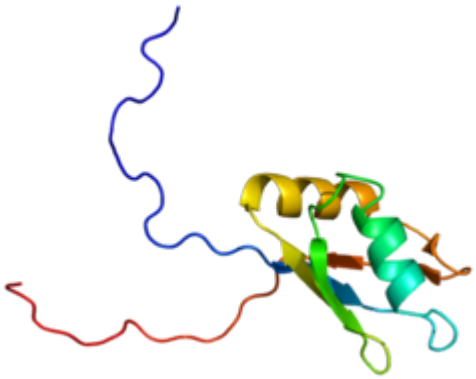
This gene encodes an enzyme operative in the beta oxidation system of the peroxisomes.

Clinical significance

Deficiency of this enzyme leads to pseudo-Zellweger syndrome.

ACF (gene)

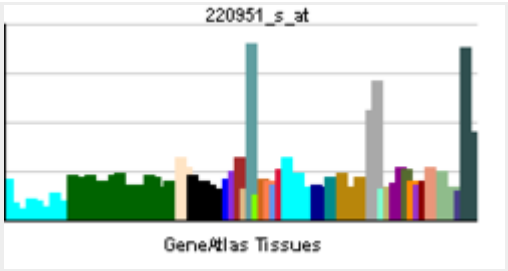
Apobec-1 complementation factor



PDB rendering based on 2cpd.

Identifiers	
Symbols	ACF; ASP; ACF64; ACF65; MGC163391; RP11-564C4.2
External IDs	MGI: 1917115 HomoloGene: 16363 GeneCards: ACF Gene

RNA expression pattern



Orthologs

Species	Human	Mouse
Entrez	29974	69865
Ensembl	ENSG00000148584	ENSMUSG00000052595
UniProt	Q9NQ94	Q5YD48
RefSeq (mRNA)	NM_014576	XM_001000199

RefSeq (protein)	NP_055391	XP_001000199
Location (UCSC)	Chr 10: 52.24 - 52.32 Mb	Chr 19: 31.93 - 32.01 Mb

APOBEC1 complementation factor is a protein that in humans is encoded by the *A1CF* gene.

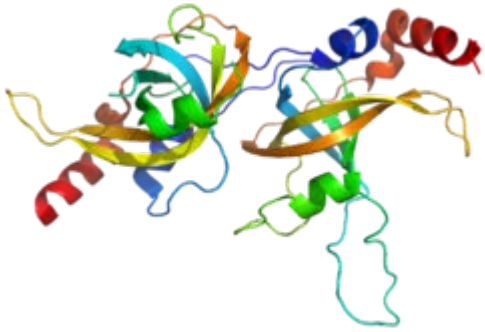
Mammalian apolipoprotein B mRNA undergoes site-specific C to U deamination, which is mediated by a multi-component enzyme complex containing a minimal core composed of APOBEC-1 and a complementation factor encoded by this gene. The gene product has three non-identical RNA recognition motifs and belongs to the hnRNP R family of RNA-binding proteins. It has been proposed that this complementation factor functions as an RNA-binding subunit and docks APOBEC-1 to deaminate the upstream cytidine. Studies suggest that the protein may also be involved in other RNA editing or RNA processing events. Alternative splicing occurs at this locus and three full-length transcript variants, encoding three distinct isoforms, have been described. Additional splicing has been observed but the full-length nature of these variants has not been determined.

Interactions

ACF (gene) has been shown to interact with CUGBP2, SYNCRIP and APOBEC1.

ACD (gene)

Adrenocortical dysplasia homolog (mouse)

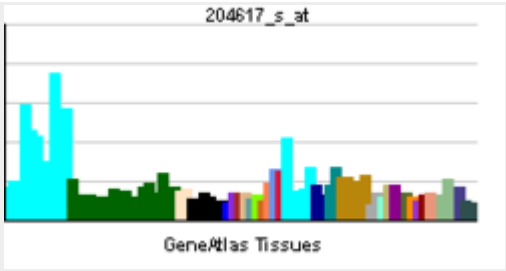


PDB rendering based on 2i46.

Identifiers

Symbols	ACD; TPP1; PIP1; PTOP; TINT1
External IDs	OMIM: 609377 MGI: 87873 HomoloGene: 23391 GeneCards: ACD Gene

RNA expression pattern



Orthologs

Species	**Human**	**Mouse**
Entrez	65057	497652
Ensembl	ENSG00000102977	ENSMUSG00000038000
UniProt	Q96AP0	Q5EE38
RefSeq (mRNA)	NM_022914	NM_001012638
RefSeq (protein)	NP_075065	NP_001012656
Location (UCSC)	Chr 16: 66.25 - 66.25 Mb	Chr 8: 108.58 - 108.59 Mb

Adrenocortical dysplasia protein homolog is a protein that in humans is encoded by the *ACD* gene.

This gene encodes a protein that is involved in telomere function. This protein is one of six core proteins in the telosome/shelterin telomeric complex, which functions to maintain telomere length and to protect telomere ends. Through its interaction with other components, this protein plays a key role in the assembly and stabilization of this complex, and it mediates the access of telomerase to the telomere. Multiple transcript variants encoding different isoforms have been found for this gene. This gene, which is also referred to as TPP1, is distinct from the unrelated TPP1 gene on chromosome 11, which encodes tripeptidyl-peptidase I.

Interactions

ACD (gene) has been shown to interact with POT1 and TINF2.

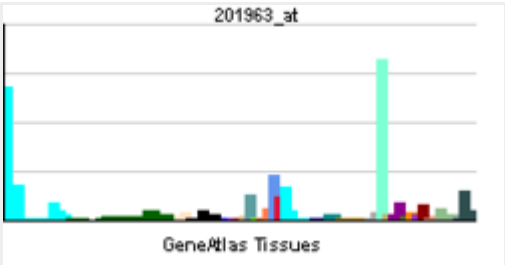
Chapter 11

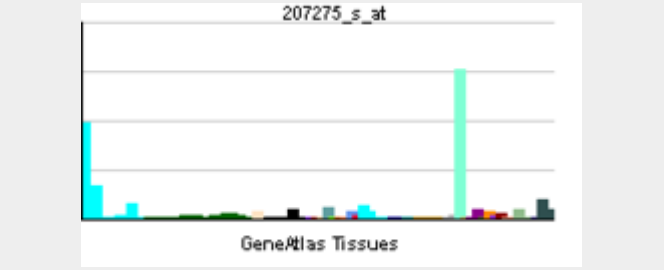
ACSL Proteins

ACSL1

Acyl-CoA synthetase long-chain family member 1

Identifiers	
Symbols	ACSL1; ACS1; FACL1; FACL2; LACS; LACS1; LACS2
External IDs	OMIM: 152425 MGI: 102797 HomoloGene: 37561 GeneCards: ACSL1 Gene
RNA expression pattern	





Orthologs		
Species	**Human**	**Mouse**
Entrez	2180	14081
Ensembl	ENSG00000151726	ENSMUSG00000018796
UniProt	P33121	Q6GTG6
RefSeq (mRNA)	NM_001995	XM_991183
RefSeq (protein)	NP_001986	XP_996277
Location (UCSC)	Chr 4: 185.91 - 185.98 Mb	Chr 8: 47.97 - 48.03 Mb

Long-chain-fatty-acid—CoA ligase 1 is an enzyme that in humans is encoded by the *ACSL1* gene.

The protein encoded by this gene is an isozyme of the long-chain fatty-acid-coenzyme A ligase family. Although differing in substrate specificity, subcellular localization, and tissue distribution, all isozymes of this family convert free long-chain fatty acids into fatty acyl-CoA esters, and thereby play a key role in lipid biosynthesis and fatty acid degradation.

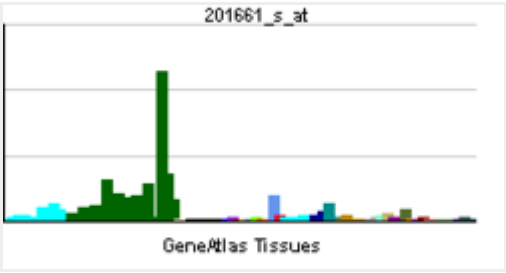
In melanocytic cells ACSL1 gene expression may be regulated by MITF.

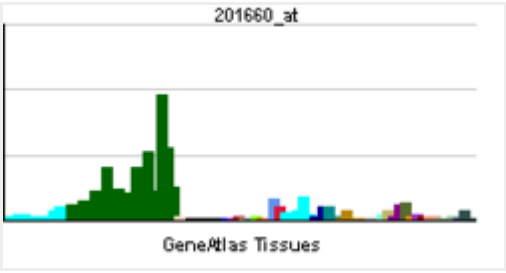
ACSL3

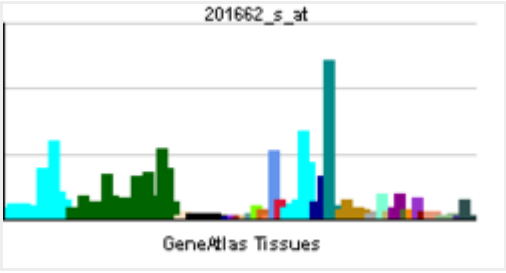
Acyl-CoA synthetase long-chain family member 3

Identifiers	
Symbols	ACSL3; ACS3; FACL3; PRO2194
External IDs	OMIM: 602371 MGI: 1921455 HomoloGene: 3278 GeneCards: ACSL3 Gene

RNA expression pattern







Orthologs

Species	Human	Mouse
Entrez	2181	74205
Ensembl	ENSG00000123983	n/a
UniProt	O95573	n/a

RefSeq (mRNA)	NM_004457	NM_001033606
RefSeq (protein)	NP_004448	NP_001028778
Location (UCSC)	Chr 2: 223.43 - 223.52 Mb	n/a

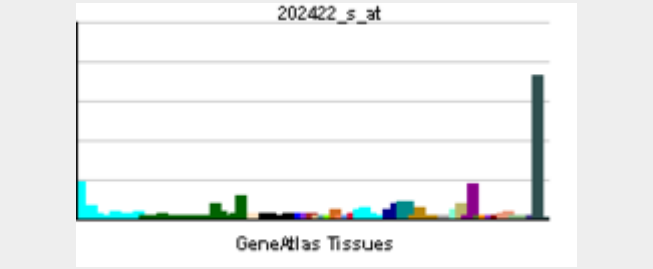
Long-chain-fatty-acid—CoA ligase 3 is an enzyme that in humans is encoded by the *ACSL3* gene.

The protein encoded by this gene is an isozyme of the long-chain fatty-acid-coenzyme A ligase family. Although differing in substrate specificity, subcellular localization, and tissue distribution, all isozymes of this family convert free long-chain fatty acids into fatty acyl-CoA esters, and thereby play a key role in lipid biosynthesis and fatty acid degradation. This isozyme is highly expressed in brain, and preferentially utilizes myristate, arachidonate, and eicosapentaenoate as substrates. The amino acid sequence of this isozyme is 92% identical to that of rat homolog. Two transcript variants encoding the same protein have been found for this gene.

ACSL4

Acyl-CoA synthetase long-chain family member 4

Identifiers	
Symbols	ACSL4; ACS4; FACL4; LACS4; MRX63; MRX68
External IDs	OMIM: 300157 MGI: 1354713 HomoloGene: 56282 GeneCards: ACSL4 Gene
RNA expression pattern	



Orthologs		
Species	**Human**	**Mouse**
Entrez	2182	50790
Ensembl	ENSG00000068366	ENSMUSG00000031278
UniProt	O60488	Q5D071
RefSeq (mRNA)	NM_004458	NM_001033600
RefSeq (protein)	NP_004449	NP_001028772
Location (UCSC)	Chr X: 108.77 - 108.86 Mb	Chr X: 137.56 - 137.64 Mb

Long-chain-fatty-acid—CoA ligase 4 is an enzyme that in humans is encoded by the *ACSL4* gene.

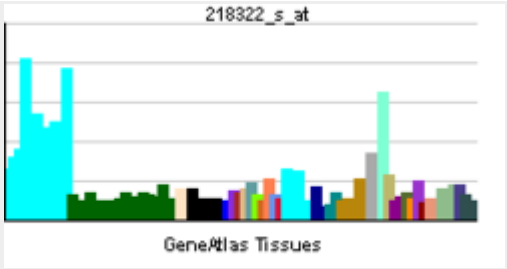
The protein encoded by this gene is an isozyme of the long-chain fatty-acid-coenzyme A ligase family. Although differing in substrate specificity, subcellular localization, and tissue distribution, all isozymes of this family convert free long-chain fatty acids into fatty acyl-CoA esters, and thereby play a key role in lipid biosynthesis and fatty acid degradation. This isozyme preferentially utilizes arachidonate as substrate. The absence of this enzyme may contribute to the mental retardation or Alport syndrome. Alternative splicing of this gene generates 2 transcript variants.

ACSL5

Acyl-CoA synthetase long-chain family member 5

Identifiers	
Symbols	ACSL5; ACS2; ACS5; FACL5
External IDs	OMIM: 605677 MGI: 1919129 HomoloGene: 69208 GeneCards: ACSL5 Gene

RNA expression pattern



Orthologs		
Species	**Human**	**Mouse**
Entrez	51703	433256
Ensembl	ENSG00000197142	ENSMUSG00000024981
UniProt	Q9ULC5	Q3UC67
RefSeq (mRNA)	NM_016234	NM_027976
RefSeq (protein)	NP_057318	NP_082252
Location (UCSC)	Chr 10: 114.12 - 114.18 Mb	Chr 19: 55.31 - 55.35 Mb

Long-chain-fatty-acid—CoA ligase 5 is an enzyme that in humans is encoded by the *ACSL5* gene.

The protein encoded by this gene is an isozyme of the long-chain fatty-acid-coenzyme A ligase family. Although differing in substrate specificity, subcellular localization, and tissue distribution, all isozymes of this family convert free long-chain fatty acids into fatty acyl-CoA esters, and thereby play a key role in lipid biosynthesis and fatty acid degradation. This isozyme is highly expressed in uterus and spleen, and in trace amounts in normal brain, but has markedly increased levels in malignant gliomas. This gene

functions in mediating fatty acid-induced glioma cell growth. Three transcript variants encoding two different isoforms have been found for this gene.

ACSL6

acyl-CoA synthetase long-chain family member 6

Identifiers		
Symbols	ACSL6; FACL6; LACS2; FLJ16173; LACS5; KIAA0837; ACS2	
External IDs	OMIM: 604443 MGI: 894291 HomoloGene: 100939 GeneCards: ACSL6 Gene	
Orthologs		
Species	**Human**	**Mouse**
Entrez	23305	216739
Ensembl	ENSG00000164398	ENSMUSG00000020333
UniProt	Q9UKU0	Q91WC3
RefSeq (mRNA)	NM_001009185	NM_001033599
RefSeq (protein)	NP_056071	NP_659072
Location (UCSC)	Chr 5: 131.31 - 131.38 Mb	Chr 11: 54.12 - 54.18 Mb

Acyl-CoA synthetase long-chain family member 6 is an enzyme that in humans is encoded by the *ACSL6* gene. Long-chain acyl-CoA synthetases such as ACSL6, catalyze the formation of acyl-CoA from fatty acids, ATP, and CoA.