

Serotonin Receptors

Key References

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Overview

Serotonin (5-hydroxytryptamine, 5-HT) is widely distributed throughout the mammalian body, being synthesized from L-tryptophan in enterochromaffin cells of the gastro-intestinal tract as well as in serotonergic neurons. The monoamine is a major neurotransmitter in the CNS, but while it is avidly taken up by peripheral sympathetic neurons and co-stored with norepinephrine, evidence for discrete peripheral serotonergic neurons remains equivocal. In the periphery, the primary source of serotonin is the platelets, which sequester serotonin via an active transport mechanism and store it as a serotonin:ATP complex. It is released when platelets aggregate at a site of vascular injury, promoting hemostasis. Serotonin is also released from enterochromaffin cells following exposure to radiation or cancer chemotherapeutic agents such as cisplatin. The ensuing activation of 5-HT₃ receptors on vagal afferents in the gut wall and/or within the area postrema promotes nausea and vomiting. Hence in both of these situations the monoamine stimulates a host organism defense response.

The classification and nomenclature of serotonin receptors is organized according to criteria established by the IUPHAR Subcommittee for the Classification and Nomenclature of Serotonin Receptors. Thirteen distinct human subtypes of serotonin receptor are recognized on the basis of structural, transductional and operational characteristics. A fourteenth putative subtype (5-HT_{5B}) has been identified in rodents, but not in the human where its coding sequence is interrupted by stop codons. These receptor subtypes fall into seven structurally-defined classes (5-HT₁ to 5-HT₇). However, in a few cases, unambiguous physiological roles have still not been demonstrated hence a lower case appella-

tion is ascribed e.g. 5-HT_{1E}, 5-HT_{1F} to distinguish these gene products from receptors with proven operational functionality.

Further structural and operational diversity arises from allelic polymorphism and alternative splicing. For example, seven isoforms of the 5-HT₄ receptor and four isoforms of the human 5-HT₇ receptor are known to be produced by alternative splicing of the receptor mRNA. In addition, up to seven isoforms of the 5-HT_{2C} receptor, varying in the amino acid composition of the second intracellular loop, have been shown to be produced by editing of the receptor pre-mRNA. All of these isoforms exhibit different tissue distributions, implying tissue-specific functions. While precise roles remain uncertain, these differences may govern rates of receptor desensitization/internalization, intracellular trafficking and the specificity and/or efficiency of coupling to G proteins. One final form of receptor diversity may be represented by receptor homo- and hetero-dimerization. This has been shown for 5-HT_{1B} and 5-HT_{1D} receptors in recombinant systems, though its relevance in a native setting has yet to be demonstrated.

In the last 50 years, drugs directly or indirectly targeting serotonin receptors have emerged as an important category of therapeutic agents, providing treatments for a broad range of clinical conditions. Chief among these drugs are selective serotonin reuptake inhibitors (SSRIs) which are widely used in the treatment of depression and various anxiety disorders. By selectively blocking the serotonin transporter, these drugs are thought to work via modulation of 5-HT_{1A} receptors, a concept reinforced by the proven efficacy of 5-HT_{1A} receptor agonists, such as buspirone, in the treat-

ment of anxiety. Selective antagonists at 5-HT₃ receptors have transformed cancer therapy by preventing chemotherapy- and radiation-induced vomiting. Likewise, selective 5-HT_{1B} receptor agonists, exemplified by sumatriptan, zolmitriptan and rizatriptan, have established a new standard in the acute treatment of migraine headache. Other 5-HT receptor subtypes being targeted by emerging treatments include: the 5-HT_{2A} receptor, where antagonists are being sought for the treatment of schizophrenia; the 5-HT_{2B} receptor, antagonism of which offers promise in both irritable bowel syndrome (IBS) and migraine prophylaxis; the 5-HT_{2C} receptor, at which selective agonists are predicted to increase satiety and reduce obesity; the 5-HT₄ receptor, at which antagonists or low efficacy agonists are sought as potential treatments for IBS and finally, the putative 5-HT₆ receptor, selective blockade of which may offer potential in the treatment of cognitive dysfunction.

Serotonin 5-HT₁ Receptors

CURRENTLY ACCEPTED NAME	5-HT _{1A} (S160)	5-HT _{1B} ^a	5-HT _{1D} ^a	5-HT _{1E} ^b	5-HT _{1F} ^b
ALTERNATE NAME	None	5-HT _{1D} ^b	5-HT _{1D} ^a	5-HT _{1E} ^a	5-HT _{1E} ^b 5-HT ₆
STRUCTURAL INFORMATION	421 aa (human)	390 aa (human)	377 aa (human)	365 aa (human)	366 aa (human)
SUBTYPE SELECTIVE AGONISTS	R(+)-8-OH-DPAT (H140), U-92016A, R(+)-UH-301 (U109)	Sumatriptan, ^c Zolmitriptan, L-694,247 (L129), CGS12066 (C106)	Sumatriptan, Zolmitriptan, L-694,247 (L129)	BRL 54443 (B173)	LY-334370, LY-344864, BRL 54443 (B173)
SUBTYPE SELECTIVE ANTAGONISTS	WAY 100635 (W108), S(-)-UH-301 (U108), NAN-190 (N3529), S(-)-Pindolol (P152), Spiperone (S7395)	GR 55562 (G0419), ^c SB-216641 (S8942), GR 127935 (G5793), SB-224289 (S201)	GR 127935 (G5793), BRL 15572 (B9929)	Not known	Not known
SIGNAL TRANSDUCTION MECHANISM	G _{i/o} (cAMP modulation)	G _{i/o} (cAMP modulation)	G _{i/o} (cAMP modulation)	G _{i/o} (cAMP modulation)	G _{i/o} (cAMP modulation)
RADIOLIGANDS OF CHOICE	[³ H]-WAY 100635 [³ H]-8-OH-DPAT	[³ H]-Sumatriptan ^c [³ H]-GR 125743	[³ H]-Sumatriptan [³ H]-GR 125743	[³ H]-5-HT	[³ H]-LY-334370 [¹²⁵ I]-LSD
TISSUE EXPRESSION	Hippocampus, amygdala, raphe nuclei, myenteric plexus	Striatum, hippocampus raphe nuclei, sympathetic neurons, vascular smooth muscle	Striatum, hippocampus dorsal raphe, trigeminal ganglion, vascular smooth muscle	Parietal cortex, caudate putamen, olfactory tubercle, amygdala, glial cells	Cortex, thalamus, hippocampus, uterus, mesentery
PHYSIOLOGICAL FUNCTION	Somatodendritic autoreceptor in raphe and hippocampus, somatodendritic hetero- receptor in myenteric plexus	Presynaptic autoreceptor in hippocampus and sympathetic neurons, contraction of smooth muscle	Somatodendritic autoreceptor in raphe and hippocampus, sympathetic presynaptic autoreceptor	Not known	Trigeminal neuro- inhibition
DISEASE RELEVANCE	Anxiety disorders	Implicated in aggression, migraine	Potentially migraine	Not known	Potentially migraine

Abbreviations

BRL 15572: 3-[4-(3-Chlorophenyl)piperazine-1-yl]-1,1-diphenyl-2-propanol

BRL 54443: 3-(1-Methylpiperidin-4-yl)-1H-indol-5-ol

CGS12066: 7-Trifluoromethyl-4-(4-methyl-1-piperazinyl)pyrrolo[1,2-a]quinoxaline

8-OH-DPAT: 8-Hydroxy-2-(di-n-propylamino)tetralin

GR 55562: 3-[3-Dimethylaminopropyl]-4-hydroxy-N-[4-pyridinyl]phenyl]benzamide

GR 125743: N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]3-methyl-4-(4-pyridinyl) benzamide

GR 127935: N-[Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'(5-methyl-1,2,4-oxadiazol-3-yl)[1,1-biphenyl]-4-carboxamide

L-694,247: 2-[5-[3-(4-Methylsulphonylamino)benzyl]-1,2,4-oxadiazol-5-yl]1H-indol-3-yl]ethanamine

LSD: Lysergic acid diethylamide

LY-334370: 4-Fluoro-N-[3-(1-methyl-4-piperidinyl)-1H-indol-5-yl]-benzamide

LY-344864: (R)-N-[3-Dimethylamino-2,3,4,9-tetrahydro-1H-carbazol-6-yl]-4-fluorobenzamide

NAN-190: 1-(2-Methoxyphenyl)-4-(4-[2-phthalimido]butyl)-piperazine

SB-216641: N-[3-(2-Dimethylamino)ethoxy-4-methoxyphenyl]-2'-methyl-4'(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1'-biphenyl)-4-carboxamide

SB-224289: 2,3,6,7-Tetrahydro-1'-methyl-5-[2'-methyl-4'(5-methyl-1,2,4-oxadiazol-3-yl)]biphenyl-4-carbonyl]furo[2,3-f]in dole-3-spiro-4'-piperidine hydrochloride

U-92016A: (+)-R-2-Cyano-N,N-dipropyl-8-amino-6,7,8,9-tetrahydro-3H-benz[e]indole

UH-301: 5-Fluoro-8-hydroxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene

WAY 100635: N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl)-cyclohexanecarboxamide trichloride

FOOTNOTES

a Human receptors now assume primacy in serotonin receptor nomenclature - *Trends Pharmacol. Sci.*, **17**, 103-105 (1996). The terms 5-HT_{1B} and 5-HT_{1D} now refer to the human receptors previously termed 5-HT_{1Db} and 5-HT_{1Da}, respectively. Non-human orthologs are subsumed within these classes.

b The use of lower case denotes the identification of a gene product only; the endogenous receptor has yet to be characterized.

c Rodent ortholog exhibits different pharmacology: Selective agonist - CP-93,129, selective antagonist - cyanopindolol; radioligand - [¹²⁵I]-iodocyanopindolol.

Serotonin 5-HT₂ Receptors

CURRENTLY ACCEPTED NAME	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}
ALTERNATE NAME	D 5-HT ₂	5-HT _{2F}	5-HT _{1C}
STRUCTURAL INFORMATION	471 aa (human)	479, 481 aa (human)	458 aa (human) ^a
SUBTYPE SELECTIVE AGONISTS	α-Me-5-HT (M110), DOI (D101), DOB (D7412)	α-Me-5-HT (M110), BW723C86 (B175)	α-Me-5-HT (M110), m-CPP (C5554), YM348, Tegaserod (partial)
SUBTYPE SELECTIVE ANTAGONISTS	Ketanserin (S006), AMI-193, ML 100907, R102444	SB-204741 (S0693), SB-200646 (S0568), SB-206553 (S180), RS 127445, EGIS-7625, LY 272015	RS 102221, SB-200646 (S0568), SB-206553 (S180), SB-242084 (S8061)
SIGNAL TRANSDUCTION MECHANISM	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-Ketanserin	[³ H]-5-HT	[³ H]-Mesulergine
TISSUE EXPRESSION	Cortex, hippocampus striatum, vascular and non-vascular smooth muscle blood platelets	Vascular and GI smooth muscle, stomach fundus, uterus, vascular endothelium	Choroid plexus, striatum, hippocampus, hypothalamus
PHYSIOLOGICAL FUNCTION	Possibly neuro-inhibition, platelet activation, smooth muscle contraction	Smooth muscle contraction, NO-dependent vasorelaxation	CSF volume regulation
DISEASE RELEVANCE	Implicated in schizophrenia	Potentially migraine, anxiety, irritable bowel syndrome	Potentially migraine and obesity

Abbreviations

AMI-193: 8-[3-(4-Fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one

BW723C86: 1-[5-(2-Thienylmethoxy)-1H-3-indolyl]propan-2-amine hydrochloride

m-CPP: 1-(m-Chlorophenyl)piperazine

DOB: 2,5-Dimethoxy-4-bromoamphetamine

DOI: 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane

EGIS-7625: (1-Benzyl-4-[(2-nitro-4-methyl-5-amino)-phenyl]-piperazine)

LY272015: 6-Methyl-1,2,3,4-tetrahydro-1-[3,4-dimethoxyphenyl] methyl-9H-pyrido[3,4b]indole hydrochloride

ML 100907: (±)-2,3-Dimethoxyphenyl-1-[2-(4-piperidine)-methanol]

R 102444: (2R,4R)-4-Lauroyloxy-2-[2-[2-(3-methoxy)phenyl]ethyl]phenoxy]ethyl-1-methylpyrrolidine hydrochloride

RS 102221: 8-[5-(5-Amino 2,4-dimethoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4,5]decane-2,4-dione

RS 127445: 2-Amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine

SB-200646: N-(1-Methyl-5-indolyl)-N-(3-pyridyl)urea hydrochloride

SB-204741: N-(1-Methyl-5-indolyl)-N-(3-methyl-5-isothiazolyl)urea

SB-242084: 6-Chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl]indoline

SB-206553: N-3-Pyridinyl-3,5-dihydro-5-methyl-benzo(1,2-b:4,5-b')dipyrrole-1(2H)carboxamide

Tegaserod: 2-[(5-Methoxy-1H-indol-3-yl)methylene]-N-pentylhydrazinecarboximidamide

YM348: S-2-(7-Ethyl-1H-furo[2,3-g]indazol-1-yl)-1-methylethylamine

FOOTNOTES

^a Up to seven functional isoforms are produced by mRNA editing.

Additional Serotonin Receptor Classes

CURRENTLY ACCEPTED NAME	5-HT ₃	5-HT ₄	5-HT ₅ ^{a,b}	5-HT ₆ ^b	5-HT ₇ (S177 (h), S162 (r))
ALTERNATE NAME	M	None	5-HT _{5a} 5-HT _{5b}	None	5-HT ₁ -like 5-HTY
STRUCTURAL INFORMATION	478 aa (human) ^c	387 aa (human [a]) ^d 388 aa (human [b]) 378 aa (human [e])	357 aa (human) ^e	440 aa (human)	445 aa (human [a]) ^d 432 aa (human [b]) 479 aa (human [d])
SUBTYPE SELECTIVE AGONISTS	SR 57227A (S1688), 2-Methyl-5-HT (M109), 1-(m-Chlorophenyl- biguanide (C144), 5-HTQ (H133)	BIMU 8, RS 67506, ML 10302, SC 53116	LSD (L7007)	LSD (L7007), 5-CT (C117)	5-CT (C117)
SUBTYPE SELECTIVE ANTAGONISTS	Granisetron, Ondansetron (O3639), Tropisetron	GR 113808 (G5918), SB-204070 (S3313), RS 100235	Not known	Ro 04-6790 (R140), Ro 63-0563	SB-258719, SB-269970 (S7389), Clozapine (C6305)
SIGNAL TRANSDUCTION MECHANISM	Ligand-gated cation channel	G _s (increase cAMP)	Not known	G _s (increase cAMP)	G _s (increase cAMP)
RADIOLIGANDS OF CHOICE	[³ H]-(S)-Zacopride [³ H]-BRL 43694	[³ H]-GR 113808 [¹²⁵ I]-SB-207710	[³ H]-5-CT [¹²⁵ I]-LSD	[³ H]-5-CT [¹²⁵ I]-LSD	[³ H]-5-CT
TISSUE EXPRESSION	Striatum, hippocampus, substantia nigra, autonomic nerve terminals, sensory neurons	Striatum, brainstem, substantia nigra, cardiac muscle, parasympathetic nerve terminals, smooth muscle	Hippocampus, cortex, cerebellum, habenula, spinal cord	Caudate, putamen, nucleus accumbens, hippocampus, sup cervical ganglion	Hippocampus, hypothalamus, raphe nuclei, GI and vascular smooth muscle, sympathetic ganglia
PHYSIOLOGICAL FUNCTION	Sympathetic and para- sympathetic neuro- excitation	Smooth muscle relaxation, cardiac contraction, cholinergic neuroexcitation	Not known	Potentially modulation of central cholinergic neurones	Smooth muscle relaxation, CNS neuromodulation
DISEASE RELEVANCE	Chemo- and radiation- induced emesis, IBS	IBS, potentially cognition, potentially heart failure	Not known	Potential role in psychoses	Circadian phase shifts

Abbreviations

BIMU 8: (endo-N-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1H-benzimidazol-1-carboxamide hydrochloride

5-CT: 5-Carboxamidotryptamine

GR 113808: [1-2[(Methylsulphonyl)amino]ethyl]-4-piperidinyl)methyl-1-methyl-1H-indole-3-carboxylate

5-HTQ: N,N,N-Trimethylserotonin iodide

IBS: Irritable Bowel Syndrome

LSD: Lysergic acid diethylamide

ML 10302: 2-(1-Piperidinyl)ethyl-4-amino-5-chloro-2-methoxybenzoate

Ro 04-6790: 4-Amino-N-(2,6 bis-methylamino-pyrimidin-4-yl)-benzene sulfonamide

Ro 63-0563: 4-Amino-N-(2,6 bis-methylamino-pyridin-4-yl)-benzene sulfonamide

RS 67506: 1-(4-Amino-5-chloro-2-methoxyphenyl)-3-(1-n-butyl-4-piperidinyl)-1-propanone

RS 100235: 1-(8-Amino-7-chloro-1,4-benzodioxan-5-yl)-5-((3-(3,4-dimethoxyphenyl)prop-1-yl)piperidin-4-yl)propan-1-one

SB-204070: 1-Butyl-4-piperidinylmethyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate

SB-207710: 1-Butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate

SB-258719: (R)-3,N-Dimethyl-N-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzenesulfonamide

SB-269970: (R)-1-[3-Hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine

SC 53116: (1S-cis)-4-Amino-5-chloro-N-[(hexahydro-1H-pyrrolizin-1-yl)methyl]-2-methoxybenzamide

SR 57227A: 4-Amino-(6-chloro-2-pyridyl)-1-piperidine hydrochloride

h: human

r: rat

FOOTNOTES

a Two genes encoding putative 5-HT₅ receptors have been identified in rodents and termed 5-HT_{5A} and 5-HT_{5B}. No human ortholog of the 5-HT_{5B} has been found.

b The use of lower case denotes the identification of a gene product only; the endogenous receptor has yet to be characterized.

c Splice variants of the α -subunit exist in mouse.

d Splice variants are denoted [a], [b] etc.

e Putative rat rodent 5-HT_{5B} receptor: 371 370 aa.