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Review

Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system

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Abstract:
The present review gives an overview on the serotonin (5-hydroxytryptamine; 5-HT) system, its receptors and their relationship to central nervous system physiology and disorders. Additionally, we also introduce the recent knowledge about the 5-HT receptor ligands in preclinical research, clinical trials and as approved drugs.

Key words:
5-HT (serotonin), 5-HT receptors, 5-HT receptor ligands, 5-HT functional activity, 5-HT drugs, clinical trials

Abbreviations: AC – adenylate cyclase, ACh – acetylcholine, ACTH – adrenocorticotropic hormone, cAMP – cyclic adenosine monophosphate, CNS – central nervous system, CRH – corticotropin-releasing hormone, DA – dopamine, GABA – γ-aminobutyric acid, 5-HT - serotonin, L-5-HTP – L-5-hydroxytryptophan, NA – noradrenaline, TPH – tryptophan hydroxylase

Introduction

Serotonin (5-HT) is an important neurotransmitter in the mammalian central nervous system (CNS) involved in numerous physiological and behavioral disorders such as major depression, anxiety, schizophrenia, mania, autism, obesity and drug addiction. This review evaluates in detail the role of 5-HT receptors in the physiology and pathophysiology of the CNS and potential usefulness of 5-HT receptor ligands in the development of therapeutic strategies to the treatment of CNS disorders.

Serotonin (5-HT) in the CNS

Serotonin belongs to the evolutionarily oldest biogenic amines acting as neurotransmitters in the central nervous system. It was isolated from mammals in 1946 as a substance in the serum with tonic actions on

the vasculature, explaining its name. Seven years later it was also found in the brain and subsequently characterized as neurotransmitter. The first and rate-limiting step of 5-HT synthesis is the hydroxylation of L-tryptophan to L-5-hydroxytryptophan (L-5-HTP) catalyzed by tryptophan hydroxylase (TPH). Recently, it has been discovered that there are two TPH enzymes, TPH1 and TPH2, which define two independent 5-HT systems [96, 97]. TPH1 generates more than 95% of the bodily 5-HT in the gut, from where it is transported by platelets to all organs except the brain since it can not cross the blood-brain barrier. In the brain, TPH2 is exclusively responsible for the first step of 5-HT synthesis [1, 39, 82]. Then, the enzyme aromatic L-amino acid decarboxylase converts L-5-HTP to 5-HT. The neurotransmitter is taken up from neuronal cytoplasm to synaptic vesicles by vesicular monoamine transporter and stored therein. 5-HT is released from the synaptic vesicles to the synaptic space by a Ca^{2+}-dependent process, while its reuptake from synaptic space to 5-HT neurons is carried out by the membrane-bound 5-HT transporter occurring in axons, bodies and/or dendrites of 5-HT neurons. 5-HT is catabolized by mitochondrial type A monoamine oxidase. First, 5-HT is oxidized to aldehyde and then to 5-hydroxyindoleacetic acid. The main assemblages of 5-HT-synthesizing neurons are located in the brainstem. In the brain, 5-HT cells form 9 groups, so-called raphe nuclei, whose relatively small number of neurons by numerous descending and ascending projections innervate almost all brain areas. For this reason, 5-HT fulfills a significant role in the regulation of many vital functions of the organism (sleep, circadian rhythm, mood, cognition, reproductive behaviors, thermoregulation, nociceptive transmission, motor, endocrine, cardiovascular and respiratory functions, and intestinal peristalsis), and in etiology of the related pathological states (depression, anxiety, mania, schizophrenia, autism, obesity, drug addiction, migraine and hypertension) [1, 31, 37].

5-HT acts *via* its receptors. Based on structural (amino acid sequence), biochemical (postreceptor mechanisms of signal transduction) and pharmacological differences, 5-HT receptors were classified into seven families (5-HT_1-5-HT_7) and at least 14 different subtypes (Tab. 1). A majority of these receptors belong to the metabotropic receptor family (transmitting signals through G proteins), except for 5-HT_3 receptors included into the ionotropic receptor family [for review see: 4, 31, 42, 47, 51, 69].

The 5-HT_1 receptor family

The 5-HT_1 receptor family comprises the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} receptors which exhibit 40–63% overall sequence identity and couple preferentially to $G_{i/o}$ to inhibit cAMP formation ([42, 54, 69], Tab. 1).

5-HT_{1A} receptors

Structure, distribution and functional effects in the CNS

The 5-HT_{1A} receptor gene has been located on human chromosome 5q11.1-q13 and comprises of 421 amino acids in humans and mice or 422 amino acids in rats [42, 54]. It is widely distributed in the CNS, principally located in the hippocampus, cingulated and enthorhinal cortices, lateral septum and mesencephalic raphe nucleus. 5-HT_{1A} receptors are either autoreceptors in the raphe nuclei on the soma and dendities of 5-HT neurons (they control cell firing) or postsynaptic receptors in several limbic areas (they cause neuronal hyperpolarization due to activation of G-protein-coupled K^+ channels). In the raphe nucleus, activation of 5-HT_{1A} autoreceptors also inhibits voltage-dependent calcium currents [54]. 5-HT_{1A} receptors are involved in several physiological, behavioral, cognitive and developmental functions in rodents. Among others, stimulation of 5-HT_{1A} receptors facilitates acetylcholine (ACh) and noradrenaline (NA) release in the brain as well as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol blood levels [32, 49, 54]. On the other hand, activation of these receptors evokes reduction in 5-HT and glutamate brain levels and drop in growth hormone secretion [32, 49, 51]. The 5-HT_{1A} receptors are involved in motor behavior (activation evokes flat body posture, forepaw treading, tail flick, lower lip retraction and locomotor activation), copulatory behavior (activation reduces penile reflexes, frequency and length of intromission, and increases latency of ejaculation), pain perception (activation evokes analgesia) and emotional behavior (activation induces anxiolysis) [50, 51, 54]. The role of 5-HT_{1A} receptors in regulation of controlling emotion is supported by the studies on 5-HT_{1A} receptor knockout mice that showed elevated anxiety-related behavior [46, 67, 74] and antidepressant-like pheno-

type ([46], Tab. 1). Stimulation of 5-HT_{1A} receptors induces a discriminative stimulus, hyperphagia and hypothermia [47, 51, 54]. Recent literature data point significance for 5-HT_{1A} receptors in cognition [19], especially deficient of cognitive function and the negative symptoms in schizophrenia, although preclinical studies indicate mixed results in regard to the ability of 5-HT_{1A} partial agonists or antagonists to improve cognition in various paradigms [53, 59]. More recently, 5-HT_{1A} knock-out mice have a deficiency for cognitive processing of ambiguous aversive cues [9] while those over-expressing mutant mice in the cortex and hippocampus showed enhanced social recognition compared with wild-type mice [9, 52, 59]. Additionally, some atypical antipsychotic drugs (e.g. aripiprazole, bifeprunox, ziprasidone and those in clinical trials (1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-4-[5-(4-fluorophenyl)-pyridin-3-yl-methyl]-piperazine (SLV-313), (3-exo)-8-benzoyl-*N*-{[(2*S*)7-chloro-2,3-dihydro-1,4-benzodioxin-1-yl]methyl}-8-azabicyclo[3.2.1]octane-3-methanamine (SSR 181507)) that are more effective in reversing memory deficits than typical antipsychotics display partial agonism at 5-HT_{1A} receptors [60, 85, 93]. Some 5-HT_{1A} receptor agonists (e.g. xaliproden) display neurotrophic activity in many neurogenerative models *in vivo* and promotes effects of nerve growth factor on neurite outgrowth *in vitro* [104]. There are also other molecules (e.g. cyclobutyl{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide; WAY-211612) with dual 5-HT_{1A} receptor antagonist/selective 5-HT reuptake inhibitor properties that may represent a novel class of antidepressants [10].

Pharmacology

The discovery of the exogenous 5-HT_{1A} receptor ligand 8-hydroxy-di-n-propylaminotetralin (8-OH-DPAT) seemed to be a milestone in the characterization of these receptors ([69, 92], Tab. 2). 8-OH-DPAT displays also a moderate affinity for 5-HT_7 receptors and presently is used as a 5-$HT_{1A/7}$ receptor agonist. Several agonists show selectivity and full agonistic activity for 5-HT_{1A} receptors, particularly (R,S)-trans-8-hydroxy-2-[N-n-propyl-N-(3'-iodo-2'-propenyl)amino]-tetralin (8-OH-PIPAT), 1-[3-(3,4-methylenedioxyphenoxy)propyl]-4-phenyl piperazine (BP 554), 1-[2-(4-fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (S 14506), [(+)-R]-2-cyano-N,N-dipropyl-8-amino-6,7,8,9-tetrahydro-3H-benz[e]indole (U92016A) and xaliproden while other ligands, including anxiolytics (so-called "pirones") buspirone, gepirone and ipsapirone, are partial agonists. Flesinoxan and osemozotan show a high affinity for 5-HT_{1A} receptors, however, also a moderate affinity for dopamine (DA) D_2 and α_1-adrenoceptors, respectively. The most selective and silent 5-HT_{1A} receptor antagonists are 4-(2'-methoxy)-phenyl-1-[2'-(N-2''-pyridyl)-p-fluorobenzamido]ethylpiperazine (p-MPPF), 4-(2'-methoxy)phenyl-1-[2'-(N-2"-pyridinyl)-p-iodobenzamino]ethylpiperazine (p-MPPI), N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-(2-pyridyl)cyclohexane carboxamide maleate (WAY 100635) and (R)-N-[2-methyl-(4-indolyl-1-piperazinyl)ethyl]-N-(2-pyridinyl)-cyclohexane carboxamide (WAY 101405), all with good bioavailability and CNS penetration ([47, 92], Tab. 2).

Buspirone (a 5-HT_{1A} partial agonist) has been introduced as anxiolytic agent being effective in generalized anxiety disorder, while its combination with sertraline and cognitive-behavioral therapy was more effective than placebo to promote smoking cessation [20]. The 5-HT_{1A} receptor agonist *N*-{3-[4-(4-cyclohexyl-methanesulfonylaminobutyl)piperazin-1-yl]phenyl}acetamide (PRX-00023) is in clinical trials for depression (phase II) and generalized anxiety disorder (phase I) treatments [76]. The 5-HT_{1A} receptor antagonist lecozotan [83] and the agonist xaliproden [104] have passed clinical trail phase II as cognitive enhancers in patients with Alzheimer's disease while tandospirone (a 5-HT_{1A} receptor partial agonist) was found to augment verbal memory in schizophrenic patients when used as an auxiliary drug to typical antipsychotics [86].

5-HT_{1B} receptors

Structure, distribution and functional effects in the CNS

The 5-HT_{1B} receptor gene has been located on human chromosome 6q13 and comprises of 390 amino acids in humans or 386 amino acids in mice and rats [47, 54, 80]. The highest expression of 5-HT_{1B} receptors in the CNS was found in the basal ganglia (particularly in the substantia nigra, globus pallidus, ventral pallidum, entopeduncular nucleus, caudate putamen) and the frontal cortex [54, 80]. 5-HT_{1B} receptors are either autoreceptors on the terminals of 5-HT neurons (they inhibit 5-HT release) or terminal heteroreceptors on γ-aminobutyric acid (GABA), ACh and gluta-

mate neurons (they control the release of these neurotransmitters) [54, 80]. Activation of the brain 5-HT_{1B} receptors is also linked with several other functional responses in rodents. Thus, these receptors couple negatively to adenylate cyclase (AC) under forskolin-stimulated conditions and inhibit evoked synaptic potentials in many brain areas. *In vivo* microdialysis studies have detected a facilitatory effect of 5-HT_{1B} receptor stimulation on release of DA; an indirect effect linked with an inhibition of GABA release, while an inhibitory response on glutamate, GABA and NA release and a modulatory control on ACh release [2, 7, 32, 41]. Other physiological and behavioral effects of 5-HT_{1B} receptor stimulation include facilitation of prolactin, ACTH, cortisol and renin secretion in the blood, hypophagia, hypothermia, sexual behavior (penile erection), motor behavior (locomotor hyperactivation; rotation, myoclonic jerks), a stimulus cue in drug discriminative paradigm and pain relieve [31, 49, 50, 81]. It was found that 5-HT_{1B} receptors are implicated in drug addiction as stimulation enhanced rewarding effects of abused substances [61, 68, 71, 72]. Interestingly, 5-HT_{1B} receptors control also impulsivity and aggression as 5-HT_{1B} receptor agonists display anti-aggressive properties in wild-type mice [80] while 5-HT_{1B} receptor knock-out mice are less anxious and more aggressive [81]. The 5-HT_{1B} receptor gene deletion in mice selectively enhances learning performance when the cognitive requirement of the task is elevated [101] and enhances vulnerability to cocaine [78].

Pharmacology

Several 5-HT_{1B} receptor ligands with high affinity for the receptors have been described (Tab. 2). The most selective agonists include 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-5H-pyrrolo[3,2-b]-pyridin-5-one (CP 93129), 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrrolo[3,2-b]pyridine hydrochloride (CP 94253), 3-[3-(2-dimethylaminoethyl)-*H*-indol-5--yl]-*N*-(4-methoxybenzyl) acrylamide (GR 46611), 2-{5-[3-(4-methylsulfonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indole-3-yl}ethylamine (L 694247) and 1'-methyl-5-{[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl}-2,3,6,7-tetrahydrospiro-[furo[2,3-f]indole-3,4'-piperidine (SKF 99101H) while so-called "triptans" (e.g. donitriptan, rizatriptan, zolmitriptan) do not show selectivity for 5-HT_{1B} receptors [69, 92]. N-{3-[3-(dimethylamine)ethoxy]-4-methoxyphenyl}-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-carboxamide hydrochloride (SB 216641), 1'-methyl-5-([2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl)-4-yl]carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] hydrochloride (SB 224289) and 3-[(3-dimethylamino)-propyl]-4-hydroxy-N-[4-(4-pyridinyl)-phenyl]benzamide (GR 55562) – the last drug being active following intracerebral administration – are antagonists with high affinity and selectivity for 5-HT_{1B} receptors, while N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl--4'-(5-methyl-[1,2,4]-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide (GR 127935) is a potent 5-$HT_{1B/1D}$ receptor antagonist [69, 92].

Rizatriptan, sumatriptan, zolmitriptan are only 5-$HT_{1B/1D}$ receptor ligands used in medicine for the acute treatment of migraine [6, 11, 48].

5-HT_{1D} receptors

Structure, distribution and functional effects in the CNS

In the human, the gene encoding the 5-HT_{1D} receptor is on chromosome 1p34.2-p36.2. The 5-HT_{1D} receptor comprises of 377 amino acids in humans or 374 amino acids in mice and rats [42, 48, 54]. The highest expression of 5-HT_{1D} receptors in the rat brain was found in the basal ganglia (particularly in the substantia nigra, globus pallidus and caudate putamen), the hippocampus and the cortex, while in the human brain in the basal ganglia (the substantia nigra, globus pallidus), the midbrain (the periaqueductal grey) and the spinal cord. 5-HT_{1D} receptors are either autoreceptors on the terminals of 5-HT neurons (they inhibit 5-HT release) or terminal heteroreceptors on GABA, ACh and glutamate neurons (they control the release of these neurotransmitters) [32, 47, 54]. Activation of the brain 5-HT_{1D} receptors is linked with inhibition of evoked synaptic potentials *via* $G_{i/o}$ inhibition of AC activity and cAMP formation, with reduction in 5-HT, glutamate, GABA and ACh release in many brain areas as well as with a drop in ACTH, cortisol and prolactin secretion [32, 47, 49]. It was proposed that 5-HT_{1D} receptors are involved in pain perception [54].

Pharmacology

Recently some high affinity 5-HT_{1D} receptor agonists have been recognized (Tab. 2), however, their limitation in functional assays is lack of 5-HT_{1D}/5-HT_{1B} receptor selectivity. The most selective agonists are (S)-(-)-1-{2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl}-N-methyl-isochroman-6-carboxamide (PNU 109291) and (*S*)-(-)-3,4-dihydro-1-[2-[4-(4-aminocarbonyl)-phenyl]-1-piperazinyl]ethyl-*N*-methyl-1*H*-2-benzopyran-6-carboxamide (PNU 142633) that display 12-, 600- and 3000-fold, respectively, selectivity over other 5-HT receptor subtypes [69, 92]. 1-{2-[4-(4-Fluorobenzoyl)-piperidin-1-yl]-ethyl}-3,3-dimethyl-1,2-dihydroindol-2-one (LY 310762) is a 5-HT_{1D} preferring antagonist and 3-[4-(4-chlorophenyl)piperazin-1-yl]-1,1-diphenyl-2-propanol (BRL 15572) is the high affinity 5-HT_{1D} receptor antagonist displaying 60-fold selectivity over 5-HT_{1B} receptors [47, 69, 92].

The mixed 5-$HT_{1B/1D}$ receptor agonists (i.e. "triptans" – rizatriptan, sumatriptan, zolmitriptan) are used in clinic as a first-line therapy for acute migraine [6, 11, 48].

5-HT_{1E} receptors

Structure, distribution and functional effects in the CNS

The human 5-HT_{1E} receptor gene locates to chromosome 6q14-q15; the gene is intronless and encodes a protein of 365 amino acids [42, 47, 54]. Its expression in the CNS of humans and animals was found similar in all species with the highest levels in the cortex (mainly in the frontal and entorhinal cortices), caudate putamen and claustrum while lower expression levels of the protein have been seen in the hippocampus and the amygdala [47, 51, 54]. It was proposed that 5-HT_{1E} receptors function as postsynaptic heteroreceptors as 5-HT lesions do not change the 5-HT_{1E} receptor binding levels [51, 54]. In recombinant cell system activation of 5-HT_{1E} receptors induces an inhibition of AC under forskolin-stimulated conditions [47, 51].

Pharmacology

In functional assays *in vitro* BRL 54443 is a potent agonist displaying the same affinity for 5-HT_{1E} and 5-HT_{1F} binding sites [92]. At present selective agonists and antagonists at 5-HT_{1E} receptors are unavailable.

5-HT_{1F} receptors

Structure, distribution and functional effects in the CNS

The human 5-HT_{1F} receptor gene is located on chromosome 3p11-p14.1 and consists of 366 amino acids [47, 51, 54]. It was recognized in several CNS areas (the dorsal raphe nucleus, hippocampus, cingulate and entorhinal cortices, claustrum, caudate nucleus, brainstem) and – based on localization – suggested to function as an autoreceptor [51, 54]. Stimulation of the 5-HT_{1F} receptor in rodents evokes neuronal hyperpolarization following $G_{i/o}$-mediated inhibition of AC and cAMP formation [47, 51]. The antimigraine drugs, so-called "triptans" (e.g. sumatriptan) show high affinity for the 5-HT_{1F} receptor and it was suggested as a brain target to control neurogenic inflammation as a cause of migraine [6, 73].

Pharmacology

There are selective and potent 5-HT_{1F} receptor agonists: 4-fluoro-N-[3-(1-methyl-4-piperidinyl)-lH-indol-5-yl]-benzamide (LY 334370) and (R)-(+)-N-(3-dimethylamino-1,2,3,4-tetrahydro-9H-carbazol-6-yl)-4-fluorobenzamide (LY 344864) that show 100- and 80-fold selectivity over other 5-HT receptors (the later agonist is also orally active) while another agonist 5-hydroxy-3-(1-methylpiperidin-4-yl)-1H-indole (BRL 54443) has similar affinity for 5-HT_{1F} and 5-HT_{1E} receptors [54, 92]. Nowadays there are no selective 5-HT_{1F} receptor antagonists.

The 5-HT_2 receptor family

The 5-HT_2 receptor family consists of three subtypes named the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. They exhibit 46-50% overall sequence identity and couple to $G_{q/11}$ and the phosphoinositol hydrolysis signal transduction system to stimulate the inositol 1,4,5-trisphosphate accumulation and intracellular Ca^{2+} release ([4, 5, 51, 69], Tab. 1).

Tab. 1. Serotonin (5-HT) receptors: the signalling pathways, knockout mouse phenotypes (if existing), and the drugs in current clinical use are shown for all 7 families of 5-HT receptors

Family	Subtype	Main signalling pathway	Main expression sites in the CNS	Knock-out phenotype*	Clinically used drugs
5-HT_1	5-HT_{1A}	$G_{i/o}$ AC i	Widespread in brain (mainly hippocampus, cortex, raphe nuclei)	Increased anxiety [46, 67, 74] Antidepressant-like phenotype [46] Cognitive impairment [9]	"pirones" Ag
	5-HT_{1B}	$G_{i/o}$ AC i	Widespread in brain (mainly basal ganglia, cortex)	Increased aggression [80] Decreased anxiety [80] Enhanced learning performance [101] Enhanced cocaine response [78]	"triptans" Ag
	5-HT_{1D}	$G_{i/o}$ AC i	Basal ganglia, hippocampus, cortex		"triptans" Ag
	5-HT_{1E}	$G_{i/o}$ AC i	Cortex, caudate putamen, claustrum	(not existing in mice)	
	5-HT_{1F}	$G_{i/o}$ AC i	Dorsal raphe nucleus, hippocampus, cortex, claustrum, caudate nucleus, brainstem		"triptans" Ag
5-HT_2	5-HT_{2A}	$G_{q/11}$ PLC s	Cortex, claustrum, hippocampus, hypothalamus, basal ganglia	Decreased anxiety [98]	sarpogrelate Ant
	5-HT_{2B}	$G_{q/11}$ PLC s	Cerebellum, septum, hypothalamus, amygdala		
	5-HT_{2C}	$G_{q/11}$ PLC s	Choroid plexus, cortex, hippocampus, amygdala, striatum, substantia nigra	Increased appetite, overweight [87] Spontaneous convulsions [87] Cognitive impairment [87] Enhanced cocaine response [77]	
5-HT_3	Pentamer of 5-HT_{3A} with $5\text{-HT}_{3B, C, D}$ and $_E$	Ion channel	Widespread in brain (mainly area postrema, nucleus tractus solitarius, dorsal vagal complex, limbic structures)	Reduced pain perception (5-HT_{3A}) [50]	"setrons" Ant
5-HT_4	5-HT_4	G_s AC s	Basal ganglia, cortex, septum, hippocampus	Decreased stress response [23] Increased convulsive response [23]	"serods" Ag "saprides" Ag
5-HT_5	5-HT_{5A}	$G_{i/o}$ AC i	Hippocampus, hypothalamus, olfactory bulb, cortex, thalamus, striatum, pons	Increased exploratory activity [36] Altered LSD response [36]	
	5-HT_{5B}	?	Habenula, raphe nuclei, hippocampus (in rodents); pseudogene (in humans)		
5-HT_6	5-HT_6	G_s AC s	Widespread in brain (mainly striatum, amygdala, hippocampus, cortex)	Altered alcohol response [16]	
5-HT_7	5-HT_7	G_s AC s	Thalamus, hippocampus, cortex, amygdala, suprachiasmatic nucleus	Antidepressant-like phenotype [38] Disturbed circadian rhythms [84] Disturbed thermoregulation [44]	

* – related to the CNS function. Abbreviations: AC – adenylate cyclase; CNS – central nervous system; LSD – lysergic acid diethylamide; PLC – phospholipase C; i – inhibition; s – stimulation; Ag – agonist, Ant – antagonist; ? – lack of data

5-HT$_{2A}$ receptors

Structure, distribution and functional effects in the CNS

The 5-HT$_{2A}$ receptor gene is located on human chromosome 13q14-q21 and comprises of 471 amino acids in humans, rats and mice [47, 51]. It is widely distributed in the CNS, the highest expression was found in the cortex, claustrum, hippocampus, hypothalamus and basal ganglia. 5-HT$_{2A}$ receptors are expressed on DA, GABA, glutamate and ACh neurons where function as somatodendritic heteroreceptors [19, 51, 55]. Activation of the brain 5-HT$_{2A}$ receptors is linked with neuronal depolarization in several brain areas [5, 55]. *In vivo* microdialysis studies indicate a facilitatory effect of 5-HT$_{2A}$ receptor stimulation on release of DA, glutamate and GABA while inhibitory responses on NA release [7, 17, 26, 32, 56]. Other physiological and behavioral effects of 5-HT$_{2A}$ receptor stimulation in rodents include facilitation of oxytocin, renin, prolactin, ACTH and cortisol blood secretion, induction of hyperthermia, motor behaviors (head twitches, wet dog shakes), a stimulus cue in drug discriminative paradigm and pain control [49-51, 55]. These receptors are known to control the neurochemical and behavioral responses of addicted substances [18, 29-31] as well as regulate sleep architecture [88]. Global disruption of 5-HT$_{2A}$ receptor signaling in mice reduced inhibition in conflict anxiety paradigms without affecting fear-conditioned and depression-related behaviors [98]. Interestingly, 5-HT$_{2A}$ receptors are proposed as an important brain target for the developing antipsychotic drugs as mixed 5-HT$_{2A}$ and DA D$_2$ receptor antagonists show beneficial effects for the treatment of negative symptoms of schizophrenia [12, 75]. It was also found that a high 5-HT$_{2A}$ receptor affinity and an antagonistic profile enhance antidepressant-like properties of drugs (e.g. nefazodone) [25].

Pharmacology

There are several agonists that show high affinity for 5-HT$_{2A}$ receptors (Tab. 2). The commonly used 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), 1-(2,5-dimethoxy-4-bromophenol)-2-aminopropane (DOB) and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) are mixed 5-HT$_{2A/2B/2C}$ receptor ligands in binding assays while in the *in vivo* functional studies they behave like agonists at 5-HT$_{2A}$ receptors [69, 92]. The most potent 5-HT$_{2A}$ receptor antagonists are 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)piperidine oxalate (4F 4PP), R-(+)-α-(2,3-dimethoxyphenyl)-1-[4-fluorophenylethyl]-4-piperidinemethanol (M 100907), (2R,4R)-5-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-ethyl]-1-methyl-3-pyrrolidinol (R 96544) and sarpogrelate; the first two drugs display also > 100 selectivity over other 5-HT receptors. Other 5-HT$_{2A}$ receptor antagonists like cinanserin (DA D$_4$), ketanserin (5-HT$_{2C}$, 5-HT$_{1D}$, α_1-adrenoceptor), risperidone (DA D$_2$) and 1(Z)-[2-(dimethylamino)ethoxyimino]-1(2-fluorophenyl)-3-(4-hydroxyphenyl)-2(E)-propene (SR 46349B) (5-HT$_{2B}$) possess high affinity for other neurotransmitter receptors (in brackets) [12, 75, 92] while nefazodone is a 5-HT/NA uptake inhibitor [25].

The selective 5-HT$_{2A}$ antagonist sarpogrelate is clinically used as an anti-platelet agent for the treatment of peripheral arterial disease [63], while other non-selective receptor blockers are either antidepressants (e.g. nefazodone; [25]) or antipsychotics (e.g. olanzapine, risperidone; [75]). Antagonists/inverse agonists of 5-HT$_{2A}$ receptors, such as eplivanserin, pimavanserin, pruvanserin and volinanserin, are currently being investigated as therapeutics that could improve the treatment of sleep maintenance and quality in people with insomnia [88].

5-HT$_{2B}$ receptors

Structure, distribution and functional effects in the CNS

The 5-HT$_{2B}$ receptor gene is located on human chromosome 2q36.3-2q37.1 and comprises of 481 amino acids in humans, 504 amino acids in mice and 479 amino acids in rats [5, 55]. Its localization in the CNS is restricted to some brain regions including the cerebellum, lateral septum, hypothalamus and amygdala and based on autoradiographic studies was hypothesized to act as a heteroreceptor [4, 51]. Stimulation of the rodent brain 5-HT$_{2B}$ receptors has been reported to evoke changes in motor behavior (reduced grooming), emotional behavior (anxiolysis), food intake (hyperphagia) and pain perception [47, 55]. Recent studies link 5-HT$_{2B}$ receptors with the precipitation of migraine and the action of 5-HT$_2$ receptor antagonists (e.g. cyproheptadine, pizotifen) that display a high affinity for 5-HT$_{2B}$ receptors [48].

Tab. 2. Pharmacology of 5-HT receptors

	LIGANDS	5-HT RECEPTOR FAMILY	REFERENCES
		5-HT_1	
5-HT_{1A}	agonists	8-OH-DPAT, 8-OH-PIPAT, BP 554, flesinoxan, LY 228729, osemozotan (=MKC-242), PRX-00023, S 14506, U 92016A, xaliproden (=SR 57746A)	47, 69, 92
	partial agonists	BMY 7378, buspirone, F13714, gepirone, ipsapirone, MDL 73005EF, NAN-190, SDZ 216525, tandospirone, WAY 100135	
	antagonists	lecozotan (SRA-333), p-MPPF, p-MPPI, robalzotan (=AZD 7371,NAD-299), WAY 100635, WAY 101405	
5-HT_{1B}	agonists	almotriptan, CGS 12066B, CP 94253, CP 93129, donitriptan, eletriptan, GR 46611, naratriptan, RU 24969, rizatriptan, RU 24969, SKF 99101H, zolmitriptan	47, 69, 92
	antagonists	AR-A00002, GR 55562, GR 127935, NAS-181, SB 216641, SB 224289, SB 616234	
5-HT_{1D}	agonists	almotriptan, eletriptan, frovatriptan, GR 46611, L 694247, L 703664, LY 310762, naratriptan, PNU 109291, PNU 142633, rizatriptan, sumatriptan, zolmitriptan	47, 69, 92
	antagonists	BRL 15572	
5-HT_{1E}	agonists	BRL 54443	92
	antagonists	?	
5-HT_{1F}	agonists	BRL 54443, LY 344370, LY 334 864, naratriptan, rizatriptan, sumatriptan, zolmitriptan	54, 92
	antagonists	?	
		5-HT_2	
5-HT_{2A}	agonists	DOB, DOI, DOM, PNU 22394, TCB-2	12, 69, 75, 92
	antagonists	4F 4PP, ACP 103, AR 116081, cinanserin, eplivanserin, ketanserin, M11939, nefazodone, PNU 96415E, primavanserin, privanserin, R 96544, risperidone, sarpogrelate, SR 46349B, volinaserin (=M100907)	
5-HT_{2B}	agonists	α-Me-5-HT, 5-methoxytryptamine, BW 723C86	51, 69, 70, 92
	antagonists	EGIS-7625, LY 23728, LY 266097, LY 287375, LY 272015, RS 127445, SB 200646, SB 204741, SB 215505, SB 221284	
5-HT_{2C}	agonists	1-methylpsilocin, ALEPH-2, CP 809101, lorcaserin (=APD 356), mCPP, MK 212, Org 12962, Ro 60-0175, WAY 629, WAY 161503, WAY 163909, YM 348	40, 55, 69, 92
	partial agonists	IL 639, PNU 22394	
	antagonists	RS 102221, SB 242084, SDZ SER-082	
		5-HT_3	
5-HT_3 receptors	agonists	1-phenylbiguanide, 2-methyl-5-HT, m-chlorophenylbiquanide, SR 57227A	91, 92
	partial agonists	MD-354, RS 56812	
	antagonists	bemesetron, dolasetron, granisetron, itasetron, ondansetron, palonosetron, Y 25130, zatosetron	
		5-HT_4	
5-HT_4	agonists	BIMU 1, BIMU 8, cisapride, LS 650155, ML 10302, mosapride, RS 67506, TD-5108, zacopride	12, 15, 27, 69, 92
	partial agonists	CJ 033466, ML 10302, PF 00885706, PF 01354082, prucalopride (=R093877), PRX-03140, RS 17017, RS 67333, RS 67506, SL65.0155, tegaserod (=HTF-919), VRX-03011	
	antagonists	GR 113808, GR 125487, LY 353433, RS 23597-190, RS 39604, RS 67532, SB 204070, SB 203186, SB 207266, SDZ 205557	
		5-HT_5	
5-HT_5	agonists	?	92, 99
	antagonists	SB 699551	
		5-HT_6	
5-HT_6	agonists	E-6801, EMD 386088, R-13c, WAY 466 (=WAY 208466WAY 181187, WAY 208466 (=WAY 466) BCG20-761, BVT 74316, LY 483518, MS-245, PRX-07034, Ro 04-6790,	27, 34, 40, 69, 92, 99
	antagonists	Ro 630563, Ro 4368554, SAM-531, SB 258510A, SB 258585, SB 271046, SB 357134, SB 399885, SB 742457, SGS-518, SUVN-502, SYN-114	
		5-HT_7	
5-HT_7 receptors	agonists	AS 19, LP 12, LP 44	45, 90, 92, 99
	antagonists	DR 4004, DR 4365, DR 4446, SB 258719, SB 258741, SB 2656104-A, SB 269970, SB 691673	

? - lack of data

Pharmacology

α-Methyl-5-hydroxytryptamine (α-Me-5-HT), 5-methoxytryptamine and α-methyl-5-(2-thienylmethoxy)-1H-indole-3-ethanamine (BW 723C86) are full agonists at 5-HT_{2B} receptors that show some affinity for 5-HT_{2A} (21-, 25- and 100-fold lower than for 5-HT_{2B} receptors, respectively) and 5-HT_{2C} (264-, 400- and 10-fold lower than for 5-HT_{2B} receptors, respectively) receptor sites [51, 69, 92]. N-(1-Methyl-1H-indol-5-yl)-N'-3-pyridinylurea (SB 200646) and 2,3-dihydro-5-(methylthio)-N-3-pyridinyl-6-(trifluoromethyl)-1H-indole-1-carboxamide (SB 221284) are mixed 5-$HT_{2B/2C}$ receptor antagonists [69, 92]. The most selective 5-HT_{2B} receptor antagonists include 1-[(3,4-dimethoxyphenyl)methy]-2,3,4,9-tetrahydro-6-methyl-1H-pyrido[3,4-b]indole (LY 272015), 4-(4-fluoro-1-naphthalenyl)-6-(1-methylethyl)-2-pyrimidinamine (RS 127445) and N-(1-methyl-1H-indolyl-5-yl)-N''-(3-methyl-5-isothiazolyl)urea (SB 204741) that display 20-, 1000- and 135-fold selectivity over 5-HT_{2A} and 5-HT_{2C} sites ([70, 92]; Tab. 2).

Cyproheptadine and pizotifen, the non-selective 5-HT_{2B} receptor antagonists, are clinically used in migraine prophylaxis [48].

5-HT_{2C} receptors

Structure, distribution and functional effects in the CNS

The 5-HT_{2C} receptor gene is located on human chromosome Xq24 and comprises of 458 amino acids in humans, 459 amino acids in mice and 460 amino acids in rats [5, 8, 55]. At least 14 functional isoforms of the 5-HT_{2C} receptor have been identified; they are products of posttranslational modification of the receptor mRNA by adenine deaminase editing with no pharmacological differences between the variants [8, 55]. The highest 5-HT_{2C} receptor levels in both humans and rodents are present in the choroid plexus, while much lower distribution is found in the cerebral cortex, hippocampus, amygdala, striatum (ventral and dorsal parts) and substantia nigra [5, 55, 56]. 5-HT_{2C} receptors are localized to GABA, glutamate and DA neurons where act as somatodendritic heteroreceptors [5, 47, 55]. Activation of the brain 5-HT_{2C} receptors evokes neuronal depolarization in several brain areas. *In vivo* neurochemical findings show an inhibitory effect of 5-HT_{2C} receptor stimulation on release of DA and NA [26, 32, 55, 56]. Other physiological and behavioral effects of 5-HT_{2C} receptor stimulation in rodents include facilitation of neuroendocrine function (prolactin and ACTH blood secretion), induction of hyperthermia, hypophagia, motor behaviors (hypolocomotion, oral dyskinesis), sexual responses (penile erections) and a stimulus cue in drug discriminative paradigm [35, 47, 55]. They also control emotional behavior (anxiogenesis) [35, 55] and pain perception [50]. Mutant mice lacking 5-HT_{2C} receptors suffer from obesity, spontaneous convulsions and cognitive impairment [87], are insensitive to 5-HT_{2C} receptor agonist-induced hypolocomotor and anxiogenic effects [87] and show enhanced behavioral responses to cocaine [77]. Hyperphagic or proconvulsant responses in 5-HT_{2C} knock-out mice are probably the developmental or neuroadaptive answers since 5-HT_{2C} receptor antagonists do not induce such effects [55, 87]. Importantly, activation of 5-HT_{2C} receptors makes a tonic, inhibitory influence on DA-ergic and NA-ergic transmission in the cortical areas [26, 56] and involvement of these receptors in some mental health disorders (e.g. schizophrenia, drug addiction, obesity, obsessive–compulsive disorder or depression) has been suggested [18, 29, 30, 58, 79, 95].

Pharmacology

There are some high affinity 5-HT_{2C} receptor agonists that display diverse receptor selectivity (Tab. 2). The most commonly used are 6-chloro-2-(1-piperazinyl)pyrazine (MK 212) and (S)-6-chloro-5-fluoro-α-methyl-1H-indole-1-ethanamine (Ro 60-0175). MK 212 has 25-fold selectivity for 5-HT_{2C} receptors over 5-HT_{2A} sites [69, 92] while in the case of Ro 60-0175 there is no affinity separation for 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors in binding assays, however, this drug in the *in vivo* functional studies evokes only 5-HT_{2A} receptor-related responses [55, 69, 92]. A most selective alternative to the above agonists are 2-[(3-chlorophenyl)methoxy]-6-(1-piperazinyl)pyrazine (CP 809191) and 8,9-dichloro-2,3,4,4a-tetrahydro-1H-pyrazino[1,2-a]quinoxalin-5(6H)-one (WAY 163909) that display 100- and 66-fold selectivity over other 5-HT receptor subtypes [69, 92]. 1,2,3,4,5,6- Hexahydro-6-methylazepino[4,5-b]indole (PNU 22394) is a partial agonist at 5-HT_{2C} receptors [92]. The most selective and potent 5-HT_{2C} receptor antagonists (100-fold selectivity over other 5-HT receptors) are

8-[5-(2,4-dimethoxy-5-(4-trifluoromethylphenylsulfonamido)phenyl-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione (RS 102221) (the drug shows low bioavailability) and 6-chloro-2,3-dihydro-5-methyl-N-{6-[(2-methyl-3-pyridinyl)oxy]-3-pyridinyl}-1H-indole-1-carboxyamide (SB 242084). (+)-*cis*-4,5,7a,8,9,10,11,11a-Octahydro-7H-10-methylindolo[1,7-bc][2,6]-naphthyridine (SDZ SER-082) is a mixed 5-$HT_{2C/2B}$ receptor antagonist [55, 92].

Currently, a new generation of 5-HT_{2C} selective agonists has been developed (including 2-chloro-6-(1-piperazinyl)-3-(trifluoromethyl)pyridine (Org 12962), (S)-2-(6-bromo-2,3-dihydroindol-1-yl)-1-methylethylamine (VER-3323) and 6,7-dichloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (YM 348) and at least one, lorcaserin, is currently undergoing clinical trials to produce weight loss in the obesity [40, 93].

The 5-HT_3 receptor family

5-HT_3 receptor family is a cation-selective ligand-gated ion channel assembled as a pentamer of several subunits (Tab. 1). Molecular composition of the 5-HT_3 receptor family include multiple isoforms (5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E}) that are products of different genes located on human chromosome 11 (5-HT_{3A} and 5-HT_{3B}: 11q23.1-q23.2) being a local duplication event, or on human chromosome 3 (5-HT_{3C} 5-HT_{3D} and 5-HT_{3E}: 3q27.1) [3, 66]. Alternative splicing of the 5-HT_{3A} subunit results in at least four subunits named 5-$HT_{3A(a)}$, 5-$HT_{3A(b)}$, 5-HT_{3AT} and 5-HT_{3AL}. These variants show similar physiological and pharmacological profiles [3, 51, 91]. To provide functional properties of the 5-HT_3 receptor, the heteromeric combination of 5-HT_{3A} and 5-HT_{3B} subunits is necessary [3, 47].

5-HT_3 receptors

Structure, distribution and functional effects in the CNS

The 5-HT_{3A} receptor comprises of 478 amino acids in humans, 487 amino acids in mice and 483 amino acids in rats. The 5-HT_{3B} receptor comprises of 441 amino acids in humans and 437 amino acids in rodents. The 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} receptor comprise of 447, 279 and 471 amino acids, respectively, and were found only in humans [3, 24, 42].

The 5-HT_3 receptor binding is widely distributed in the CNS with the highest densities in the area postrema, nucleus tractus solitarius, trigeminal nucleus, dorsal vagal complex and several limbic structures [3, 91]. The 5-HT_{3A} receptor subunit is found in the dorsal vagal complex, hippocampus, cerebral cortex, amygdala and caudate nucleus while 5-HT_{3B} receptor subunit is located mainly in the hippocampus, amygdala and caudate nucleus [3, 37, 51]. 5-HT_3 receptors are heteroreceptors localized to GABA, glutamate and ACh neurons [24, 91]. The brain 5-HT_3 receptors mediate rapid neuronal depolarization and excitation in several areas due to a transient inward current, resulting from the opening of nonselective cation channels (Na^+ and Ca^{2+} influx, K^+ efflux) [24, 91]. Activation of 5-HT_3 receptors facilitates *in vivo* 5-HT, cholecystokinin, DA and GABA release, decreases glutamate release and modulates ACh release [3, 21, 24, 32, 49, 91]. Their stimulation enhances ACTH and prolactin secretion [32, 49]. Other functional effects of 5-HT_3 receptor stimulation in rodents include induction of motor behavior (contralateral turning following direct intra-striatal agonist infusions), a stimulus cue in the discriminative stimulus paradigm, dysfunction of cognition, causing pain and sensitization of nociceptive neurons, induction of nausea and vomiting [19, 24, 50, 91]. The 5-HT_3 receptors also control emotional behavior (stimulation causes anxiogenesis) [3, 91] and, due to their facilitatory role with respect to DA function, are thought to be engaged in induction of psychosis and drug addiction [3, 28].

Pharmacology

Several, high affinity 5-HT_3 receptor agonists have been developed (Tab. 2). 2-Methyl-5-hydroxytryptamine is a 5-HT_3 receptor agonist and 5-HT_6 receptor ligand [91, 92]. *m*-Chlorophenylbiguanide and 1-(6-chloro-2-pyridinyl)-4-piperidinamine (SR 57227) are potent and selective 5-HT_3 receptor agonists; the later agonist is active *in vivo* and penetrates to the brain [91, 92]. The best characterized partial agonists include *m*-chlorophenylguanidine (MD-354) and (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)-2-(1-methyl-1H-indol-3-yl)-2-(1-methyl-1H-indol-3-yl)-2-oxoacetamide (RS 56812). There are several 5-HT_3 receptor selective antagonists such as bemesetron, dolasetron, granisetron, itasetron, ondansetron, N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-

4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide (Y 25130) and zatosetron [91, 92].

Several 5-HT_3 receptor antagonists, so-called "setrons" (e.g. granisetron, ondansetron), have been introduced to clinic for the prevention of acute, delayed, and overall chemotherapy-induced nausea and vomiting [13]; palonosetron is in phase III clinical trials [64, 93]. Another clinical application of the above 5-HT_3 receptor antagonists is the treatment of irritable-bowel syndrome [33].

The 5-HT_4 receptor family

The 5-HT_4 receptor family consists of the receptor that exists in multiple isoforms (5-HT_{4A}, 5-HT_{4B}, 5-HT_{4C}, 5-HT_{4D}, 5-HT_{4E}, 5-HT_{4F}, 5-HT_{4G}, 5-HT_{4H}, 5-HT_{4HB}) being post-translational modification of C-terminus and showing similar pharmacology [15, 42]. 5-HT_4 receptors are functionally coupled positively to AC *via* G_s and enhance cAMP formation ([15, 42], Tab. 1).

5-HT_4 receptors

Structure, distribution and functional effects in the CNS

The human 5-HT_4 receptor gene was mapped to chromosome 5q31-q33 and comprises of 387 amino acids in humans and rodents [15, 47, 69]. In the brain only the 5-HT_{4A}, 5-HT_{4B} and 5-HT_{4C} receptor isoforms were found (the 5-HT_{4D} isoform was detected in the gut), especially in the nigrostriatal and mesolimbic DA systems (the substantia nigra, ventral tegmental area, dorsal and ventral striatum) as well as in the prefrontal cortex, septum and hippocampus [4, 14, 15]. 5-HT_4 receptors are heteroreceptors on GABA, ACh and glutamate cell bodies and/or terminals. Activation of the brain 5-HT_4 receptors induces neuronal excitability and slowing of repolarization by reducing the Ca^{2+}-evoked K^+ currents responsible for afterhypolarization that lead to the enhancement of several neurotransmitter release in the brain areas. Following 5-HT_4 receptor stimulation, an increase of ACh or GABA (a direct effect), 5-HT or DA (an indirect effect) release as well as of ACTH and cortisol secretion in the plasma were reported [14, 15]. Behavioral effects of 5-HT_4 receptor stimulation in rodents include facilitation of memory consolidation [19, 52, 57] and reduction in the physiological drive to eat [15], while the receptor antagonism mediates anxiety (antagonists display both anxiolytic and anxiogenic properties in different animals models) [14, 15, 51]. Male 5-HT_4 knock-out mice exhibit a hyposensitivity to anorexic stress and an enhancement to pentylenetetrazol-induced convulsive responses [23].

Pharmacology

The high affinity 5-HT_4 receptor agonists (Tab. 2) include benzamides (e.g. cisaparide and zacopride) and benzimidazolones (e.g. 1-(3-ethyl-2,3-dihydro-N-[endo-8-methyl-8-azabicyclo(3.2.1)-oct-3-yl]-2-oxo-1H)benzimidazole-1-carboxamide (BIMU 1), endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-(1-methyl)-ethyl-2-oxo-1 H-benzimidazole-1-carboxamide (BIMU 8)), however, they display diverse receptor selectivity. BIMU 1, BIMU 8 and zacopride are also highly potent 5-HT_3 receptor ligands [15, 69, 92]. The group of partial agonists at 5-HT_4 receptors comprises 5-amino-6-chloro-2-methyl-N-{[1-(2-methylpropyl)-4-piperidinyl]methyl}-imidazo[1,2-a]-pyridine-8-carboxamide (CJ 033466), PRX-03140 (the chemical name not available; synthesized by Epix Pharmaceuticals, Inc.), 1-(4-amino-5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)-1-pentanone (RS 17017), 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-butyl-4-piperidinyl]-1-propanone (RS 67333), 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-2-methylsulfonylamino)ethyl-4-piperidinyl]-1-propanone (RS 67506), 5-(8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl-)-3-[1-(2-phenylethyl)-4-piperidynyl]-1,3,4-oxadiazo-(3H)-one (SL65.0155), tegaserod and 6,7-dihydro-4-hydroxy-7-isopropyl-6-oxo-N-[3-(piperidin-1-yl)propyl]thieno[2,3-b]pyridine-5-carboxamide (VRX-03011). The most selective and potent 5-HT_4 receptor antagonists (more than 300-fold selectivity over other 5-HT receptors) are 1-[2-[(methylsulfonyl)amino]-ethyl]-4-piperidinylmethyl ester (GR 113808), 5-fluoro-2-methoxy-[1-[2-[(methylsulfonyl)amino]-ethyl]-4-piperidinyl]-1H-indole-3methylcarboxylate (GR 125487) and 1-(4-amino-5-chloro-2-(3,5-dimethoxybenzyloxy-phenyl)-5-(1-piperidinyl)-1-pentanone (RS 67532); all of them show good bioavailability [15, 69, 92].

Some 5-HT_4 receptor agonists – so called "saprides" (e.g. cisapride, mosapride) or 5-HT_4 receptor partial agonists – so called "serods" (e.g. tegaserod), have been on the market for gastro-intestinal patholo-

gies [33]. Since 5-HT_4 receptors have recognized effects on memory, depression and feeding in animal models, there is still hope that 5-HT_4 receptor drugs will be commercialized for brain disorders. Presently, the 5-HT_4 partial agonists PRX-03140 and SL65.0155 are in phase II clinical trails for Alzheimer's disease [27, 93].

The 5-HT_5 receptor family

The 5-HT_5 receptor family consists of two subunits named the 5-HT_{5A} and 5-HT_{5B} receptors (Tab. 1) that have 70-88% overall sequence homology and a comparable pharmacology in radioligand binding studies [42, 47, 51, 65]. In the rat and the human, recombinant 5-HT_{5A} receptor is negatively coupled to AC cyclase activity and induces preferentially inhibition of forskolin-stimulated cAMP production [4, 47].

5-HT_5 receptors

Structure, distribution and functional effects in the CNS

The 5-HT_{5A} receptor gene is located on human chromosome 7 (position 7q36) and on mouse chromosome 5 (position 5B) and comprises of 357 amino acids in humans and rodents [47, 65]. The 5-HT_{5B} receptor gene is located on human chromosome 2 (position 2q11-q13) and on mouse chromosome 1 (position 1F) and comprises of 370-371 amino acids in rodents [47, 65]. Both genes contain an intron. In the brain, the 5-HT_{5A} isoform-labeled structures include hippocampus, hypothalamus, olfactory bulb, cerebral cortex, thalamus, striatum, pons and habenula and the receptor transcripts are predominantly expressed by astrocytes, however, they may also colocalized with neurons [51, 65]. The presence of the 5-HT_{5B} receptor transcript has been demonstrated in the hippocampus, habenula and dorsal raphe nucleus in rodents [51, 65]. It was suggested that 5-HT_5 receptors are heteroreceptors on GABA neurons or terminal autoreceptors in the mouse frontal cortex. The 5-HT_{5A} knock-out mice display increased exploratory activity and altered LSD response, but no change in anxiety-related behaviors [36].

Pharmacology

There are no selective agonists for 5-HT_5 receptor at present. The one recognized 5-HT_5 receptor antagonist N-[2-(dimethylamino)ethyl]-N-[[4'-[[(2-phenylethyl)amino]methyl][1,1'-biphenyl]-4-yl]methyl]cyclopentanepropanamide (SB 699551) displays a 100-fold selectivity for 5-HT_{5A} receptors over other 5-HT receptors [92, 99].

The 5-HT_6 receptor family

The 5-HT_6 receptor family consists of the receptor that exists in two splice variants (as the gene contains two introns) with no pharmacological differences between the variants [42, 47, 51]. The 5-HT_6 receptors are positively coupled to AC *via* G_s and cAMP formation ([47, 51]; Tab. 1).

5-HT_6 receptors

Structure, distribution and functional effects in the CNS

The 5-HT_6 receptor gene is located on human chromosome 1p35-p36 and comprises of 440 amino acids in humans and mice while of 438 amino acids in rats [47, 102]. The highest 5-HT_6 receptor levels are located in the striatum (the dorsal and ventral parts), amygdala, hippocampus, cortex and olfactory tubercle [5, 102]. 5-HT_6 receptors are localized postsynaptic to 5-HT neurons on ACh, GABA and glutamate neurons where their immunoreactivity is associated with dendritic processes [32, 102]. Activation of the brain 5-HT_6 receptors evokes neuronal depolarization in several brain areas. *In vivo* neurochemical findings indicate a facilitatory effect of 5-HT_6 receptor stimulation on release of 5-HT, DA and GABA release while a fall in ACh synaptic levels [32, 49, 102]. As indicated following antagonists or antisense oligonucleotides administration, 5-HT_6 receptors have a role in motor behaviors (a specific behavioral syndrome of yawning, stretching and chewing appears), food intake and body weight (reduction) as well as learning and memory processes (enhancement in retention of spatial learning) [19, 47, 51, 52, 62, 102] while 5-HT_6 knock-out mice display altered alcohol response [16].

To note, several antipsychotic (e.g. clozapine, olanzapine and seroquel) and antidepressant (e.g. amitryptyline, doxepin and nortryptyline) drugs have high affinity and an antagonistic profile for 5-HT_6 receptors and these receptors are proposed as an important brain target for the developing treatment strategy for schizophrenia and depression [51, 99, 102].

Pharmacology

5-Chloro-2-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (EMD 386088) is a potent agonist that shows moderate affinity for 5-HT_6 receptors and displays selectivity over other 5-HT receptor subtypes [69, 99]. Recently synthesized selective agonists with nanomolar affinity for 5-HT_6 receptors are 6-chloro-N-(3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)imidazo-[2,1-b]thiazole-5-sulfonamide (E-6801), N1-(6-chloro-imidazo[2,1-b][1,3]thiazole-5-sulfonyl)tryptamine (WAY 181187) and WAY 208466 (the chemical name not available; synthesized by Wyeth Research) ([69, 92, 99]; Tab. 2). The most potent and selective 5-HT_6 receptor antagonists include 4-amino-N-[2,6-bis(methylamino)-4-pyrimidinyl]-benzene sulfonamide (Ro 04-6790) (no affinity at a range of other receptors), 4-iodo-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-benzenesulfon-amide SB 258585 (>160-fold selectivity over other 5-HT receptors) and N-(3,5-dichloro-2-methoxyphenyl)-4-methoxy-3-(1-piperazinyl)benzenesulfonamide (SB 399885) (>200-fold selectivity over other 5-HT receptors) [69, 92, 99].

Several 5-HT_6 receptor antagonists are in clinical trials for cognitive dysfunction in Alzheimer's dementia (phase II: SB 742457 (a quinolinylpiperazine derivative, the full chemical name not available; synthesized by GlaxoSmithKline), SAM-531 (the full chemical name not available; synthesized by Wyeth Research) or phase I: PRX-07034 (the full chemical name not available; synthesized by Epix Pharmaceuticals, Inc.), SYN-114 (the full chemical name not available; synthesized by Synosia/Roche), SUVN-502 (the full chemical name not available; synthesized by Suven) or in schizophrenia (phase II: SGS-518 (the full chemical name not available; synthesized by Lundbeck/Lilly)) [27, 34, 62, 93, 94, 103]. In addition, 5-HT_6 receptor antagonists BVT 74316 (the chemical name not available), PRX-07034 and SUVN-502 have recently entered I phase of clinical trials for the treatment of obesity [40, 43, 93, 94].

The 5-HT_7 receptor family

The 5-HT_7 receptor family consists of the receptors that exist in four splice variants (5-HT_{7A}, 5-HT_{7B}, 5-HT_{7C}, 5-HT_{7D}) which differ in the C-terminus with no major pharmacological differences and signal transduction pathways (they are positively coupled to AC *via* G_s and elevate cAMP ([42, 47, 51]; Tab. 1). The 5-HT_{7A} and 5-HT_{7B} variants exist both in humans and rats; the 5-HT_{7C} isoform was found only in rats, while the 5-HT_{7D} isoform was located to humans [42, 51].

5-HT_7 receptors

Structure, distribution and functional effects in the CNS

The 5-HT_7 receptor has been located on human chromosome 10q23.3-q24.4 and comprises of 445 amino acids in humans and of 448 amino acids in rodents [45, 47, 51]. The high density of 5-HT_7 receptors has been localized to the thalamus, hippocampus, cerebral cortex, amygdala and suprachiasmatic nucleus, while moderate binding densities were reported to the hypothalamus, central grey and dorsal raphe nucleus [45, 90]. The cellular localization of 5-HT_7 receptors was found on the postsynaptic membranes on GABA and glutamate neurons. Activation of 5-HT_7 receptors induces the postspike medium-duration after-hyperpolarization and enhancement of the after-depolarization. These receptors control some neuroendocrine responses (stimulation facilitates ACTH and cortisol secretion). Moreover, 5-HT_7 receptors have been consistently implicated in the etiology of circadian rhythm regulation, sleep architecture, mood, seizure activity, pain perception, cognition and thermoregulation [22, 45, 90]. A role for 5-HT_7 receptors in the regulation of circadian rhythms was confirmed in the 5-HT_7 receptor knock-out mice [84], which also show a phenotype similar to antidepressant treated mice [38] and disturbed thermoregulation [44]. Recently it was demonstrated that several antidepressant and antipsychotic drugs bind to 5-HT_7 receptors with high affinity that may suggest the possibility that actions at these receptors may therapeutically complement the antidepressant efficacy and antipsychotic drug action, respectively [89, 90, 100].

Several high affinity 5-HT_7 receptor ligands have been synthesized (Tab. 2). The most potent agonists are (2S)-(+)-5-(1,3,5-trimethylpyrazol-4-yl)-2-(dimethylamino)tetralin (AS 19), 4-(2-diphenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinehexanamide (LP 12) and 4-[2-(methylthio)phenyl]-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-1-piperazinehexanamide (LP 44). LP 12 has a 33-fold selectivity for 5-HT_7 receptors over 5-HT_{1A}, 5-HT_{2A} and DA D_2 sites, while LP 44 shows a 200-fold selectivity for 5-HT_7 receptors over 5-HT_{1A} and 5-HT_{2A} receptors [45, 92]. According to the information provided by Tocris [92], AS 19 is a selective 5-HT_7 receptor agonist with a potency of IC_{50} = 0.83 nM. The most selective and potent 5-HT_7 receptor antagonists include 3-methyl-N-[(1R)-1-methyl-3-(4-methyl-1-piperidinyl)-propyl]-N-methylbenzenesulfonamide (SB 258719) and (2R)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)-ethyl]pyrrolidine (SB 269970) (>100- and >60-fold selectivity over other 5-HT receptors, respectively); the latter antagonist shows also good bioavailability [45, 92, 99].

Conclusions

The present state of knowledge of the 5-HT system justifies the opinion that it controls many physiological events in the organism while pharmacological interventions in the 5-HT neurotransmission can efficiently counteract the effects of many disturbances in the CNS. Identification of 5-HT brain targets and their detailed characterization led to utilize this knowledge to develop receptor-specific drugs and better treat CNS disorders.

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References:

1. Alenina N, Kikic D, Todiras M, Mosienko V, Qadri F, Plehm R, Boyé P et al.: Growth retardation and altered autonomic control in mice lacking brain serotonin. Proc Natl Acad Sci USA, 2009, 106, 10332–10337.
2. Ase AR, Reader TA, Hen R, Descarries L: Regionally selective changes in neurotransmitter receptors in the brain of the 5-HT_{1B} knockout mouse. J Chem Neuroanat, 2008, 35, 356–363.
3. Barnes NM, Hales TG, Lummis SC, Peters JA: The 5-HT_3 receptor – the relationship between structure and function. Neuropharmacology, 2009, 56, 273–284.
4. Barnes NM, Sharp T: A review of central 5-HT receptors and their function. Neuropharmacology, 1999, 38, 1083–1152.
5. Baxter G, Kennett G, Blaney F, Blackburn T: 5-HT_2 receptor subtypes: a family re-united? Trends Pharmacol Sci, 1995, 16, 105–110.
6. Belvís R, Pagonabarraga J, Kulisevsky J: Individual triptan selection in migraine attack therapy. Recent Pat CNS Drug Discov, 2009, 4, 70–81.
7. Benloucif S, Keegan MJ, Galloway MP: Serotonin-facilitated dopamine release in vivo: pharmacological characterization. J Pharmacol Exp Ther, 1993, 265, 373–377.
8. Berg KA, Clarke WP, Cunningham KA, Spampinato U: Fine-tuning $serotonin_{2C}$ receptor function in the brain: molecular and functional implications. Neuropharmacology, 2008, 55, 969–976.
9. Bert B, Fink H, Rothe J, Walstab J, Bönisch H: Learning and memory in 5-HT_{1A}-receptor mutant mice. Behav Brain Res, 2008, 195, 78–85.
10. Beyer CE, Lin Q, Platt B, Malberg J, Hornby G, Sullivan KM, Smith DL, et al.: Preclinical characterization of WAY-211612: a dual 5-HT uptake inhibitor and 5-HT_{1A} receptor antagonist and potential novel antidepressant. Br J Pharmacol, 2009, 157, 307-319.
11. Bigal ME, Krymchantowski AV, Ho T: Migraine in the triptan era: progresses achieved, lessons learned and future developments. Arq Neuropsiquiatr, 2009, 67, 559–569.
12. Blier P, Szabo ST: Potential mechanisms of action of atypical antipsychotic medications in treatment-resistant depression and anxiety. J Clin Psychiatry, 2005, 66, Suppl 8, 30–40.
13. Board T, Board R: The role of 5-HT_3 receptor antagonists in preventing postoperative nausea and vomiting. AORN J, 2006, 83, 209–16, 219–20.
14. Bockaert J, Claeysen S, Compan V, Dumuis A: 5-HT_4 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 39–51.
15. Bockaert J, Claeysen S, Compan V, Dumuis A. 5-HT_4 receptors: history, molecular pharmacology and brain functions. Neuropharmacology, 2008, 55, 922–931.
16. Bonasera SJ, Chu HM, Brennan TJ, Tecott LH: A null mutation of the serotonin 6 receptor alters acute responses to ethanol. Neuropsychopharmacology, 2006, 31, 1801–1813.
17. Bowers BJ, Henry MB, Thielen RJ, McBride WJ: Serotonin 5-HT_2 receptor stimulation of dopamine release in the posterior but not anterior nucleus accumbens of the rat. J Neurochem, 2000, 75, 1625–1633.
18. Bubar MJ, Cunningham KA: Serotonin 5-HT_{2A} and 5-HT_{2C} receptors as potential targets for modulation of

psychostimulant use and dependence. Curr Top Med Chem, 2006, 1971–1985.
19. Buhot MC: Serotonin receptors in cognitive behaviors. Curr Opin Neurobiol, 1997, 7, 243–254.
20. Carrão JL, Moreira LB, Fuchs FD: The efficacy of the combination of sertraline with buspirone for smoking cessation. A randomized clinical trial in nondepressed smokers. Eur Arch Psychiatry Clin Neurosci, 2007, 257, 383–388.
21. Chen JP, van Praag HM, Gardner EL: Activation of 5-HT_3 receptor by 1-phenylbiguanide increases dopamine release in the rat nucleus accumbens. Brain Res, 1991, 543, 354–357.
22. Cifariello A, Pompili A, Gasbarri A: 5-HT_7 receptors in the modulation of cognitive processes. Behav Brain Res, 2008, 195, 171–179.
23. Compan V, Zhou M, Grailhe R, Gazzara RA, Martin R, Gingrich J, Dumuis A et al.: Attenuated response to stress and novelty and hypersensitivity to seizures in 5-HT_4 receptor knock-out mice. J Neurosci, 2004, 24, 412–419.
24. Costall B, Naylor RJ: 5-HT_3 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 27–37.
25. Davis R, Whittington R, Bryson HM: Nefazodone. A review of its pharmacology and clinical efficacy in the management of major depression. Drugs, 1997, 53, 608–636.
26. De Deurwaerdere P, Spampinato U: Role of serotonin$_{2A}$ and serotonin$_{2B/2C}$ receptor subtypes in the control of accumbal and striatal dopamine release elicited in vivo by dorsal raphe nucleus electrical stimulation. J Neurochem, 1999, 73, 1033-1042.
27. Doraiswamy PM, Xiong GL: Pharmacological strategies for the prevention of Alzheimer's disease. Expert Opin Pharmacother, 2006, 7, 1–10.
28. Engleman EA, Rodd ZA, Bell RL, Murphy JM: The role of 5-HT_3 receptors in drug abuse and as a target for pharmacotherapy. CNS Neurol Disord Drug Targets, 2008, 7, 454–467.
29. Filip M: Role of serotonin (5-HT)$_2$ receptors in cocaine self-administration and seeking behavior in rats. Pharmacol Rep, 2005, 57, 35–46.
30. Filip M, Bubar MJ, Cunningham KA: Contribution of serotonin (5-hydroxytryptamine; 5-HT) 5-HT_2 receptor subtypes to the hyperlocomotor effects of cocaine: acute and chronic pharmacological analyses. J Pharmacol Exp Ther, 2004, 310, 1246–1254.
31. Filip M, Frankowska M, Zaniewska M, Gołda A, Przegaliński E: The serotonergic system and its role in cocaine addiction. Pharmacol Rep, 2005, 57, 685–700.
32. Fink KB, Göthert M: 5-HT receptor regulation of neurotransmitter release. Pharmacol Rev, 2007, 59, 360–417.
33. Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P: Efficacy of 5-HT_3 antagonists and 5-HT_4 agonists in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol, 2009, 104, 1831–1843.
34. Geldenhuys WJ, Van der Schyf CJ: The serotonin 5-HT_6 receptor: a viable drug target for treating cognitive deficits in Alzheimer's disease. Expert Rev Neurother, 2009, 9, 1073–1085.
35. Giorgetti M, Tecott LH: Contributions of 5-HT_{2C} receptors to multiple actions of central serotonin systems. Eur J Pharmacol, 2004, 488, 1–9.
36. Grailhe R, Waeber C, Dulawa SC, Hornung JP, Zhuang X, Brunner D, Geyer MA, Hen R: Increased exploratory activity and altered response to LSD in mice lacking the 5-HT_{5A} receptor. Neuron, 1999, 22, 581–591.
37. Greek AR: Neuropharmacology of 5-hydroxytryptamine. Br J Pharmacol, 2006, 147, Suppl 1:S145–S152.
38. Guscott M, Bristow LJ, Hadingham K, Rosahl TW, Beer MS, Stanton JA, Bromidge F, et al.: Genetic knockout and pharmacological blockade studies of the 5-HT_7 receptor suggest therapeutic potential in depression. Neuropharmacology, 2005, 48, 492-502.
39. Gutknecht L, Waider J, Kraft S, Kriegebaum C, Holtmann B, Reif A, Schmitt A, Lesch KP: Deficiency of brain 5-HT synthesis but serotonergic neuron formation in Tph2 knockout mice. J Neural Transm, 2008, 115, 1127–1132.
40. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE: Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. Drugs, 2007, 67, 27–55.
41. Hallbus M, Magnusson T, Magnusson O: Influence of 5-$HT_{1B/1D}$ receptors on dopamine release in the guinea pig nucleus accumbens: a microdialysis study. Neurosci Lett, 1997, 225, 57-60.
42. Hannon J, Hoyer D: Molecular biology of 5-HT receptors. Behav Brain Res, 2008, 195, 198–213.
43. Heal DJ, Smith SL, Fisas A, Codony X, Buschmann H: Selective 5-HT_6 receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. Pharmacol Ther, 2008, 117, 207–231.
44. Hedlund PB, Danielson PE, Thomas EA, Slanina K, Carson MJ, Sutcliffe JG: No hypothermic response to serotonin in 5-HT_7 receptor knockout mice. Proc Natl Acad Sci USA, 2003, 100, 1375–1380.
45. Hedlund PB, Sutcliffe JG: Functional, molecular and pharmacological advances in 5-HT_7 receptor research. Trends Pharmacol Sci, 2004, 25, 481–486.
46. Heisler LK, Chu HM, Brennan TJ, Danao JA, Bajwa P, Parsons LH, Tecott LH: Elevated anxiety and antidepressant-like responses in serotonin 5-HT_{1A} receptor mutant mice. Proc Natl Acad Sci USA, 1998, 95, 15049–15054.
47. Hoyer D, Hannon JP, Martin GR: Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav, 2002, 71, 533–554.
48. Johnson KW, Phebus LA, Cohen ML: Serotonin in migraine: theories, animal models and emerging therapies. Prog Drug Res, 1998, 51, 219–244.
49. Jørgensen HS: Studies on the neuroendocrine role of serotonin. Dan Med Bull, 2007, 54, 266–288.
50. Kayser V, Elfassi IE, Aubel B, Melfort M, Julius D, Gingrich JA, Hamon M, Bourgoin S: Mechanical, thermal and formalin-induced nociception is differentially altered in 5-HT_{1A}-/-, 5-HT_{1B}-/-, 5-HT_{2A}-/-, 5-HT_{3A}-/- and 5-HTT-/- knock-out male mice. Pain, 2007, 130, 235–248.
51. Kennett GA: Serotonin receptors and their function. Tocris, 1998.

52. King MV, Marsden CA, Fone KC: A role for the 5-HT_{1A}, 5-HT_4 and 5-HT_6 receptors in learning and memory. Trends Pharmacol Sci, 2008, 29, 482–492.
53. Lacivita E, Leopoldo M, Berardi F, Perrone R: 5-HT_{1A} receptor, an old target for new therapeutic agents. Curr Top Med Chem, 2008, 8, 1024–1034.
54. Lanfumey L, Hamon M: 5-HT_1 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 1–10.
55. Leysen JE: 5-HT_2 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 11–26.
56. Lucas G, Spampinato U: Role of striatal serotonin$_{2A}$ and serotonin$_{2C}$ receptor subtypes in the control of in vivo dopamine outflow in the rat striatum. J Neurochem, 2000, 74, 693–701.
57. Maillet M, Robert SJ, Lezoualc'h F: New insights into serotonin 5-HT_4 receptors: a novel therapeutic target for Alzheimer's disease? Curr Alzheimer Res, 2004, 1, 79–85.
58. Marston OJ, Heisler LK: Targeting the serotonin 2C receptor for the treatment of obesity and type 2 diabetes. Neuropsychopharmacology, 2009, 34, 252–253.
59. Meltzer HY, Sumiyoshi T: Does stimulation of 5-HT_{1A} receptors improve cognition in schizophrenia? Behav Brain Res, 2008, 195, 98–102.
60. Meneses A, Perez-Garcia G: 5-HT_{1A} receptors and memory. Neurosci Biobehav Rev, 2007, 31, 705–727.
61. Miranda F, Sandoval-Sánchez A, Cedillo LN, Jiménez JC, Millán-Mejía P, Velázquez-Martínez DN: Modulatory role of 5-HT_{1B} receptors in the discriminative signal of amphetamine in the conditioned taste aversion paradigm. Pharmacol Rep, 2007, 59, 517-524.
62. Mitchell ES, Neumaier JF: 5-HT_6 receptors: a novel target for cognitive enhancement. Pharmacol Ther, 2005, 108, 320–333.
63. Miyazaki M, Higashi Y, Goto C, Chayama K, Yoshizumi M, Sanada H, Orihashi K, et al.: Sarpogrelate hydrochloride, a selective 5-HT_{2A} antagonist, improves vascular function in patients with peripheral arterial disease. J Cardiovasc Pharmacol, 2007, 49, 221–227.
64. Navari RM: Palonosetron: a second-generation 5-hydroxytryptamine receptor antagonist. Future Oncol, 2006, 2, 591-602.
65. Nelson DL: 5-HT_5 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 53–58.
66. Niesler B, Kapeller J, Hammer C, Rappold G: Serotonin type 3 receptor genes: HTR3A, B, C, D, E. Pharmacogenomics, 2008, 9, 501–504.
67. Parks CL, Robinson PS, Sibille E, Shenk T, Toth M: Increased anxiety of mice lacking the serotonin$_{1A}$ receptor. Proc Natl Acad Sci USA, 1998, 95, 10734–10739.
68. Parsons LH, Weiss F, Koob GF: Serotonin$_{1B}$ receptor stimulation enhances cocaine reinforcement. J Neurosci, 1998, 18, 10078–10089.
69. Pauwels PJ: 5-HT Receptors and their ligands. Tocris Reviews, 2003, No. 25.
70. Poissonnet G, Parmentier JG, Boutin JA, Goldstein S: The emergence of selective 5-HT_{2B} antagonists structures, activities and potential therapeutic applications. Mini Rev Med Chem, 2004, 4, 325–330.
71. Przegaliński E, Filip M, Papla I, Siwanowicz J: Effect of serotonin (5-HT)$_{1B}$ receptor ligands on cocaine sensitization in rats. Behav Pharmacol, 2001, 12, 109–116.
72. Przegaliński E, Gołda A, Filip M: Effects of serotonin (5-HT)$_{1B}$ receptor ligands on cocaine-seeking behavior in rats. Pharmacol Rep, 2008, 60, 798–810.
73. Ramadan NM, Skljarevski V, Phebus LA, Johnson KW: 5-HT_{1F} receptor agonists in acute migraine treatment: a hypothesis. Cephalalgia, 2003, 23, 776–785.
74. Ramboz S, Oosting R, Amara DA, Kung HF, Blier P, Mendelsohn M, Mann JJ et al.: Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. Proc Natl Acad Sci USA, 1998, 95, 14476–14481.
75. Richtand NM, McNamara RK: Serotonin and dopamine interactions in psychosis prevention. Prog Brain Res, 2008, 172, 141–153.
76. Rickels K, Mathew S, Banov MD, Zimbroff DL, Oshana S, Parsons EC Jr, Donahue SR, et al.: Effects of PRX-00023, a novel, selective serotonin 1A receptor agonist on measures of anxiety and depression in generalized anxiety disorder: results of a double-blind, placebo-controlled trial. J Clin Psychopharmacol, 2008, 28, 235–239.
77. Rocha BA, Goulding EH, O'Dellis LE, Mead AN, Coufal NG, Parsons LH, Tecott L: Enhanced behavioral, reinforcing, and neurochemical effects of cocaine in serotonin 5-HT_{2C} receptor mutant mice. J Neurosci, 2002, 22, 10039–10045.
78. Rocha BA, Scearce-Levie K, Lucas JJ, Hiroi N, Castanon N, Crabbe JC, Nestler EJ, Hen R: Increased vulnerability to cocaine in mice lacking the serotonin-1B receptor. Nature, 1998, 393, 175–178.
79. Rosenzweig-Lipson S, Dunlop J, Marquis KL: 5-HT_{2C} receptor agonists as an innovative approach for psychiatric disorders. Drug News Perspect, 2007, 20, 565–571.
80. Sari Y: Serotonin$_{1B}$ receptors: from protein to physiological function and behavior. Neurosci Biobehav Rev, 2004, 28, 565–582.
81. Saudou F, Amara DA, Dierich A, LeMeur M, Ramboz S, Segu L, Buhot MC, Hen R: Enhanced aggressive behavior in mice lacking 5-HT_{1B} receptor. Science, 1994, 265, 1875–1878.
82. Savelieva KV, Zhao S, Pogorelov VM, Rajan I, Yang Q, Cullinan E, Lanthorn TH: Genetic disruption of both tryptophan hydroxylase genes dramatically reduces serotonin and affects behavior in models sensitive to antidepressants. PLoS One, 2008, 3, e3301.
83. Schechter LE, Smith DL, Rosenzweig-Lipson S, Sukoff SJ, Dawson LA, Marquis K, Jones D, et al.: Lecozotan (SRA-333): a selective serotonin 1A receptor antagonist that enhances the stimulated release of glutamate and acetylcholine in the hippocampus and possesses cognitive-enhancing properties. J Pharmacol Exp Ther, 2005, 314, 1274–1289.
84. Sprouse J, Li X, Stock J, McNeish J, Reynolds L: Circadian rhythm phenotype of 5-HT_7 receptor knockout mice: 5-HT and 8-OH-DPAT-induced phase advances of SCN neuronal firing. J Biol Rhythms, 2005, 20, 122–131.
85. Sumiyoshi T, Bubenikova-Valesova V, Horacek J, Bert B: Serotonin$_{1A}$ receptors in the pathophysiology of

schizophrenia: development of novel cognition-enhancing therapeutics. Adv Ther, 2008, 25, 1037–1056.
86. Sumiyoshi T, Higuchi Y, Matsui M, Arai H, Takamiya C, Meltzer HY, Kurachi M: Effective adjunctive use of tandospirone with perospirone for enhancing verbal memory and quality of life in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry, 2007, 31, 965–967.
87. Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, Julius D: Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors. Nature, 1995, 374, 542–546.
88. Teegarden BR, Al Shamma H, Xiong Y: 5-HT_{2A} inverse-agonists for the treatment of insomnia. Curr Top Med Chem, 2008, 8, 969–976.
89. Terron JA: The 5-HT_7 receptor: A target for novel therapeutic avenues. IDrugs, 1998, 1, 302–310.
90. Thomas DR, Hagan JJ: 5-HT_7 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 81–90.
91. Thompson AJ, Lummis SC: 5-HT_3 receptors. Curr Pharm Des, 2006, 12, 3615–3630.
92. Tocris: Life Science Catalogue 2009–2010.
93. Tomillero A, Moral MA: Gateways to clinical trials. December 2008. Methods Find Exp Clin Pharmacol, 2008, 30, 761–782.
94. Upton N, Chuang TT, Hunter AJ, Virley DJ: 5-HT_6 receptor antagonists as novel cognitive enhancing agents for Alzheimer's disease. Neurotherapeutics, 2008, 5, 458–469.
95. Wacker DA, Miller KJ: Agonists of the serotonin 5-HT_{2C} receptor: preclinical and clinical progression in multiple diseases. Curr Opin Drug Discov Devel, 2008, 11, 438–445.
96. Walther DJ, Bader M: A unique central tryptophan hydroxylase isoform. Biochem Pharmacol, 2003, 66, 1673–1680.
97. Walther DJ, Walther DJ, Peter JU, Bashammakh S, Hörtnagl H, Voits M, Fink H, et al.: Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science, 2003, 299, 76.
98. Weisstaub NV, Zhoi M, Lira A,Lambe E, Goznalez-Maeso J, Hornung JP, Sibille E, et al.: Cortical 5-HT_{2A} receptor signaling modulates anxiety-like behaviors in mice. Science, 2006, 313, 536–540.
99. Wesołowska A: In the search for selective ligands of 5-HT_5, 5-HT_6 and 5-HT_7 serotonin receptors. Pol J Pharmacol, 2002, 54, 327–341.
100. Wesołowska A, Kowalska M: Influence of serotonin 5-HT_7 receptor blockade on the behavioral and neurochemical effects of imipramine in rats. Pharmacol Rep, 2008, 60, 464-474.
101. Wolff M, Savova M, Malleret G, Hen R, Segu L, Buhot MC: Serotonin 1B knockout mice exhibit a task-dependent selective learning facilitation. Neurosci Lett, 2003, 338, 1–4.
102. Woolley ML, Marsden CA, Fone KC: 5-ht_6 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 59–79.
103. www.clinicaltrials.gov
104. Xaliproden: SR 57746, SR 57746A, xaliproden hydrochloride, xaliprodene. Drugs R D, 2003, 4, 386–388.

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