Serotonin Receptors – From Molecular Biology to Clinical Applications

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Summary
Serotonin (5-hydroxytryptamine) is an ubiquitary monoamine acting as one of the neurotransmitters at synapses of nerve cells. Serotonin acts through several receptor types and subtypes. The profusion of 5-HT receptors should eventually allow a better understanding of the different and complex processes in which serotonin is involved. Its role is expected in the etiology of several diseases, including depression, schizophrenia, anxiety and panic disorders, migraine, hypertension, pulmonary hypertension, eating disorders, vomiting and irritable bowel syndromes. In the past 20 years, seven distinct families of 5-HT receptors have been identified and various subpopulations have been described for several of them. Increasing number of 5-HT receptors has made it difficult to unravel the role of 5-HT receptor subpopulations due to the lack of suitable selective agents. The present review describes the different populations and nomenclature of recently discovered 5-HT receptors and their pharmacological relevance.

Key words
Serotonin • Serotonin receptors • Antidepressants • Behavior

Introduction
Serotonin – 5-hydroxytryptamine (5-HT) is an ubiquitary monoamine acting as one of the neurotransmitters at synapses of nerve cells. It has a similar chemical structure with tryptamine, dimethyltryptamine, diethyltryptamine, melatonin and bufothein belonging to the group of indolalkylamines (Doggrell 2003).

In addition to the nerve endings, serotonin was found in the bodies of neurons, enterochromafinne stomach cells and platelets. Biosynthesis of serotonin begins with hydroxylation of an essential amino acid L-tryptophan. L-tryptophan is transported through the blood-brain barrier into the brain using the neutral amino acids transmitter, on which competes with other amino acids – phenylalanine, leucine and methionine. Tryptophanhydroxylase is the first step and speed limiting factor of 5-HT synthesis. This enzyme was found in the brain only in the serotonergic neurons. It enables conversion of tryptophan into 5-hydroxytryptophan, followed by the decarbolization mediated by aromatic L-amino acid decarboxylase onto 5-hydroxytryptamine (serotonin) – Figure 1 (Berger 2009).

Serotonin was discovered in the late 1940s and within a next decade, there were indications for its existence in the central nervous system of animals and its neurotransmitter function. By the late 1950s, evidence for 5-HT receptor heterogeneity was found in the periphery and in 1979, two distinct populations of 5-HT binding sites were identified in rat brain: 5-HT₁ and 5-HT₂ sites (Peroutka 1984). In the recent 20 years, seven distinct families of 5-HT receptors have been identified (Table 1) and various subpopulations have been described for several of these (e.g. Nichols and Nichols 2008).
Fig. 1. Synthesis of serotonin from tryptophan (the hydroxylation of tryptophan through tryptophanhydroxylase is a speed limiting step in the serotonin production). Source: own figure

**Table 1.** Families of 5-HT receptors.

<table>
<thead>
<tr>
<th>Family</th>
<th>Potential</th>
<th>Type</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁</td>
<td>Inhibitory</td>
<td>Gᵢ/G₀-protein coupled</td>
<td>Decreasing intracellular concentration of cAMP</td>
</tr>
<tr>
<td>5-HT₂</td>
<td>Excitatory</td>
<td>Gₛ-protein coupled</td>
<td>Increasing intracellular concentration of IP3 and DAG</td>
</tr>
<tr>
<td>5-HT₃</td>
<td>Excitatory</td>
<td>Ligand-gated Na⁺/K⁺ channel</td>
<td>Depolarization of cell plasma membrane</td>
</tr>
<tr>
<td>5-HT₄</td>
<td>Excitatory</td>
<td>Gₛ-protein coupled</td>
<td>Increasing intracellular concentration of cAMP</td>
</tr>
<tr>
<td>5-HT₅</td>
<td>Inhibitory</td>
<td>Gᵢ/G₀-protein coupled</td>
<td>Decreasing intracellular concentration of cAMP</td>
</tr>
<tr>
<td>5-HT₆</td>
<td>Excitatory</td>
<td>Gₛ-protein coupled</td>
<td>Increasing intracellular concentration of cAMP</td>
</tr>
<tr>
<td>5-HT₇</td>
<td>Excitatory</td>
<td>Gₛ-protein coupled</td>
<td>Increasing intracellular concentration of cAMP</td>
</tr>
</tbody>
</table>


At least 20 subpopulations of 5-HT receptors have been cloned, yet (Table 2).

**5-HT₁ receptors**

This group consists of five receptor subtypes (5-HT₁A, 5-HT₁B, 5-HT₁D, 5-HT₁E and 5-HT₁F), which are structurally identical in humans to 40-63 %. There is no 5-HT₁C receptor, as it was reclassified as the 5-HT₂C receptor. They are mostly (but not exclusively) associated with Gᵢ/G₀ proteins and inhibit production of cAMP. Fully functional 5-HT₁A, 5-HT₁B and 5-HT₁D receptors have been found in many tissues of various species (Hoyer and Martin 1997).

The 5-HT₁A receptor is the most extensively distributed of all the 5-HT receptors. In the central nervous system, 5-HT₁A receptors are present in high density in the cerebral cortex, hippocampus, septum, amygdala, and raphe nucelus, but they were proven in small amounts in the basal ganglia and thalamus as well (el Mestikawy et al. 1993). However, they can be found also in myentericus plexus and whole gastrointestinal tract. In the brain, 5-HT₁A receptors act as autoreceptors as well as postsynaptic receptors. They are involved in the inhibition of "discharge" of neurons, regulation of the production of ACTH (but not prolactin), and regulation of behavior and eating (Wang et al. 2009). They play probably an important role in the emergence of anxiety. This observation was confirmed by studies with knockout gene for this subtype of 5-HT₁ receptor in mice. The animals showed increased fear in many experimental conditions (Klemenhagen et al. 2006). Moreover, 5-HT₁A antagonists (buspiron, gepiron) are used or developed for the treatment of anxiety and depression. Antagonists of 5-HT₁A receptor and β-blocker pindolol improve the effectiveness of selective serotonin reuptake inhibitors – SSRIs in treatment of depression (Artigas et al. 2006). The antianxiety actions of 5-HT₁A (partial) agonists may provide primarily presynaptic somatodendritic 5-HT₁A receptors (leading to reduced release of 5-HT in terminal areas), whereas the antidepressant action of 5-HT₁A agents may primarily provide postsynaptic 5-HT₁A receptors (De Vry 1995). Certain 5-HT₁A agents display antiaggressive behavior, and measurement of the density of 5-HT₁A receptors in frontal cortex of suicide victims reveals that nonviolent suicide victims had a significantly higher Bmax, compared with controls and violent
Table 2. Subpopulations of 5-HT receptors families.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects and functions</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>CNS: Aggression, Anxiety, Addiction, Appetite, Emesis, Impulsivity, Memory, Mood, Nausea, Nociception, Respiration, Sleep, Sociability, Thermoregulation, Sexual behavior Cardiovascular system: Blood pressure, Heart rate, Cardiovascular function, Vasoconstriction, Penile erection</td>
<td>buspiron, dihydroergotamine, eltoprazine, ergotamine, flesinoxan, flibenserin, gepirone, ipsapirone, methysergide, quetiapine, tandospirone, urapidil, yohimbine, ziprasidone</td>
<td>spiperone, alprenolol, asenapine, cyanopindolol, idocyanopindolol, lecozotan, methiothepin, oxprenolol, pindolol, propanolol</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
<td>CNS: Aggression, Anxiety, Learning, Addiction, Locomotion, Memory, Mood, Sexual behavior Vessels: Pulmonary vasoconstriction, Penile erection</td>
<td>dihydroergotamine, eletriptan, eltoprazine, ergotamine, methysergide, sumatriptan, zolmitriptan</td>
<td>yohimbine, alprenolol, asenapine, cyanopindolol, idocyanopindolol, isamoltane, metergoline, methiothepin, oxprenolol, pindolol, propanolol</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1D&lt;/sub&gt;</td>
<td>CNS: Locomotion, Anxiety Vessels: Cerebral vasoconstriction</td>
<td>sumatriptan, almotriptan, dihydroergotamine, eletriptan, ergotamine, frovatriptan, methysergide, naratriptan, rizatriptan, yohimbine, zolmitriptan</td>
<td>ketanserin, metergoline, methiothepin, rRauwolscine, ritanserin</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1E&lt;/sub&gt;</td>
<td>CNS: Memory</td>
<td>eletriptan, methysergide, tryptamine</td>
<td>methiothepin</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1F&lt;/sub&gt;</td>
<td>Blood Vessels: Vasoconstriction CNS: Locomotion? Anxiety?</td>
<td>eletriptan, naratriptan, sumatriptan</td>
<td>methiothepin</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2B&lt;/sub&gt;</td>
<td>CNS: Anxiety, Appetite, Sleep Gastrointestinal tract: GI motility Vessels: Vasoconstriction Cardiovascular system: Cardiovascular function</td>
<td>α-methyl-5-HT, fenfluramine, LSD (in CNS), norfenfluramine</td>
<td>agomelatine, asenapine, ketanserin, LSD (PNS), methysergide, ritanserin, tegaserod, yohimbine</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
<td>CNS: Anxiety, Appetite, Addiction, Locomotion, Mood, Sexual behaviour, Sleep, Thermoregulation Gastrointestinal tract: GI motility Vessels: Vasoconstriction, Penile erection</td>
<td>α-methyl-5-HT, aripiprazole, ergonovine, lorcaserin, LSD (in CNS)</td>
<td>agomelatine, asenapine, clozapine, cyproheptadine, eltoprazine, etoperidone, fluoxetine, ketanserin, lisuride, LSD (in PNS), methysergide, mianserin, mirtazapine, nefazodone, olanzapine, risperidone, ritanserin, trazodone, ziprasidone</td>
</tr>
<tr>
<td>5-HT3</td>
<td>CNS, PNS: Anxiety, Addiction, Anxiety, Nausea, Emesis, Learning, Memory, Neuronal excitation</td>
<td>α-methyl-5-HT, quipazine</td>
<td>alosetron, clozapine, dolasetron, granisetron, memantine, metoclopramide, mianserin, mirtazapine, olanzapine, ondansetron, quetiapine, tropisetron</td>
</tr>
<tr>
<td>5-HT4</td>
<td>CNS: Anxiety, Appetite, Learning, Memory, Mood, Respiration</td>
<td>cisapride, metoclopramide, mosapride, prucalopride, renzapride, tegaserod, zacopride</td>
<td>L-lysine, piboserod</td>
</tr>
<tr>
<td>5-HT5</td>
<td>CNS: Locomotion, Sleep</td>
<td>ergotamine, valeric acid</td>
<td>asenapine, dimebolin, methiothepin, ritanserin</td>
</tr>
<tr>
<td>5-HT6</td>
<td>CNS: Anxiety, Cognition, Learning, Memory, Mood</td>
<td>EMD-386.088, EMDT</td>
<td>aripiprazole, asenapine, clozapine, dimebolin, iloperidone, olanzapine</td>
</tr>
<tr>
<td>5-HT7</td>
<td>CNS: Anxiety, Memory, Mood, Respiration, Sleep, Thermoregulation</td>
<td>5-carboxytryptamin, LSD</td>
<td>aripiprazole, asenapine, clozapine, iloperidone, ketanserin, metiotepin, olanzapine, ritanserin</td>
</tr>
</tbody>
</table>


suicides (Matsubara et al. 1991). The presence of alcohol is also associated with a decreased density of 5-HT1A receptors in certain brain regions (Storvik et al. 2009).

5-HT1B receptors are present in the CNS, where they induce presynaptic inhibition and behavioural effects. However, they exhibit vascular effects as well, such as pulmonary vasconstriction. 5-HT1B receptors are present in many parts of the human brain. The highest concentrations can be found in the basal ganglia, striatum and the frontal cortex. The function of the receptor depends on its location: 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-HT1B receptor is thought to act as an autoreceptor, inhibiting the release of serotonin. Secondary role of 5-HT1B receptors is to serve as controlling terminal heteroreceptors of secretion of other neurotransmitters, e.g. acetylcholine, glutamate, dopamine, norepinephrine and γ-aminobutyric acid. In addition to the brain, this subtype was also found in cerebral and other arteries (Jin et al. 1992). Knockout mice lacking the 5-HT1B gene has shown an increase of aggression and a higher preference for alcohol (Groenink et al. 2006). Discovery of antimigraine properties of the sumatriptan (nonselective 5-HT1D/1B agonist) increased interest in this subtype of 5-HT1 receptors. Other agonists (dihydroergotamine, zolmitriptan, naratriptan, rizatriptan) are used or developed in this indication. However, various number of other effects of 5-HT1D/1B agonists was observed, besides its antimigraine activity, e.g. prokinetic influence on gastrointestinal tract, its position in the treatment of autism, antiplatelet effects etc. (Morelli et al. 2007).

Expression of 5-HT1D is very low compared to the 5-HT1B receptor and both receptors exhibit 63 % structural homology. 5-HT1D receptors act as autoreceptors in the dorsal raphe nuclei, but were also found in the heart where they modulate the release of serotonin (Pullar et al. 2007). In the central nervous system, 5-HT1B receptors are involved in locomotion and anxiety. They induce also the vascular vasconstriction in the brain. Ergotamine works primarily through the 5-HT1B receptor, since the effect through the 5-HT1D receptor is contrary to the mode of action of ergotamine, i.e. vasconstriction (Hamblin and Metcalf 1991). However, the clinical significance of 5-HT1D receptors remains still largely unknown. There has been speculation that these receptors might be involved in anxiety, depression and other neuropsychiatric disorders,
but this remains, for the most part, to be substantiated. With the availability of the 5-HT_{1D} antagonists, it has been shown for example that GR127935 blocks the effect of antidepressants in the mouse tail suspension test (O’Neill et al. 1996). Furthermore, the localization of 5-HT_{1D} receptors in human brain is thought to be consistent with potential involvement in Huntington’s disease (Pasqualetti et al. 1996).

Nowadays available antimigraine medicaments practically do not differentiate between 5-HT_{1B} and 5-HT_{1D} receptors. Trials with selective 5-HT_{1D} agonist (identified so far as PNU 109291) showed significant suppression of meningeal neurogenic inflammation and nociception in trigeminal ganglia (Cutrer et al. 1999).

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, 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 (Shimron-Abarbanell et al. 1995).

Functional studies in cells stably expressing 5-HT_{1E} receptors indicate that the receptor is negatively coupled to adenylyl cyclase. However, cloned human 5-HT_{1E} receptors may couple to adenylyl cyclase via two distinct pathways. In general, the type of second messenger pathway activated by receptors depends upon the cellular environment in which they are expressed and upon the density of receptors (Adham et al. 1994). It has been shown, that 5-HT produces a G_{i}-mediated inhibition of forskolin-stimulated cAMP accumulation at low concentrations, whereas it also elicits a significant, although with lower efficiency, potentiation of cAMP accumulation at higher concentrations due primarily to coupling to G_{i} (Dukat et al. 2004). Methiothepin, which binds at 5-HT_{1E} receptors only with modest affinity, is a weak competitive antagonist (Zgombick et al. 1992).

The 5-HT_{1F} receptor exhibits intermediate transmembrane homology with several other 5-HT_{1} receptors: 5-HT_{1E} (70 %), 5-HT_{1D/a} (63 %), 5-HT_{1D/b} (60 %), 5-HT_{1A} (53 %). Despite similarities to 5-HT_{1E} receptors, 5-HT_{1F} receptors bind 5-methoxytryptamine and certain ergotamine derivatives with high affinity. The cloned human 5-HT_{1F} receptor couples to inhibition of adenylyl cyclase (Adham et al. 1993). Agonist effects of 5-HT were antagonized completely and apparently competitively by the nonselective 5-HT antagonist methiothepin (Adham et al. 1997). Detection of 5-HT_{1F} receptors in the uterus and coronary arteries suggest a possible role in vascular contraction (e.g. Nilsson et al. 1999). Although distribution in the brain appears limited, there are distributional similarities with 5-HT_{1D/B} receptors (Bhalla et al. 2002).

5-HT_{2} receptors

This class has three subtypes – 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}, showing 46-50 % structural homology, preferably linked to G_{q/11} protein and increasing inositol trisphosphate hydrolysis and intracellular Ca^{2+} concentration. This is the main excitatory receptor subtype among the G-protein coupled receptors 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 (Hannon and Hoyer 2002).

5-HT_{2A} receptor is expressed in many central and peripheral tissues. 5-HT_{2A} receptors mediate the contraction answer of smooth muscles. Furthermore, increased platelet aggregation and increased capillary permeability following exposure to serotonin (probably due to activation of this receptor subtype) were described (Cook et al. 1994). In the CNS, 5-HT_{2A} receptors are present mainly in the crust, claustrum and basal ganglia. Activation of 5-HT_{2A} receptor leads to stimulation of secretion of ACTH, corticosterone, oxytocin, renin, and prolactin (Bortolozzi et al. 2005, Feng et al. 2001). Inhibition of 5-HT_{2A} receptor influences behavior. 5-HT_{2A} antagonists with different receptor binding affinity (risperidone, ritanserine, soroquel, olanzepine etc.) are used or are being developed for the treatment of schizophrenia (Kim et al. 2009). Recent studies suggest that 5-HT_{2A} receptors may play a more prominent role in the behavioral actions of hallucinogens than 5-HT_{2C} (Chang et al. 2009).

Activation of 5-HT_{2B} receptor leads to contraction of smooth muscle of stomach fundus. 5-HT_{2B} immunoreactivity was detected in the cerebellum, lateral septum, hypothalamus and medial part of the amygdala. (Cox et al. 1995, Schmuck et al. 1994). Direct injection of a selective agonist BW 723C86 in amygdala have anxiolytic effects in rats (Kennett et al. 1998). 5-HT_{2B} receptor system mediates also endothelium-dependent relaxation in isolated rat veins and longitudinal muscle
contraction in the human intestine (Ellis et al. 1995, Borman et al. 2002). Moreover, activation of 5-HT2B receptor in mouse fibroblasts has mitogenic effect through the activation of MAP kinase (mitogen activated protein kinase) (Nebigil et al. 2000). Antagonists of 5-HT2B receptors (e.g. SB 200646) are relatively new and may find clinical application in the treatment and prevention of migraine (Kennet et al. 1994). It appears that this receptor is also expressed in heart valves and may be responsible for valvulopathies described in patients using preparations for reduction of the appetite containing dexfenfluramin (Bhattacharyya et al. 2009).

Due to the lack of selective ligands for 5-HT2C receptor, the knowledge of its action remains modest. A 5-HT2C antagonist agomelatine functions as an antagonist of this receptor, heteromeric combination of its subtypes – 5-HT 3A and 5-HT3B is required (Dubin et al. 1997). 5-HT3A and 5-HT3B receptors, therefore, act as a single unit. This receptor is activated by serotonin, which binds to a specific site on the receptor. Activation of this receptor leads to the release of neurotransmitters such as sodium, potassium, calcium, and chloride ions. The binding of serotonin to the 5-HT3A receptor opens the channel which in turn leads to an excitatory response in neurons. 5-HT3B receptors are also present in presynaptic nerve terminals, where they are considered to mediate or modulate neurotransmitter release. To achieve the full effect of activation of this receptor, heteromeric combination of its two subtypes – 5-HT3A and 5-HT3B is required (Dubin et al. 1999). 5-HT3 antagonists (ondansetron, granisetron, tropisetron etc.) were confirmed for being clinically effective in the treatment of chemotherapy- or radiation-induced nausea and vomiting, whereas they are ineffective against motion sickness and apomorphine-induced emesis (Gyermek 1995). There are also indications that they may be effective in the treatment of migraine or migraine associated pain. Preclinical studies suggest that 5-HT3 antagonists may enhance memory and be of benefit in the treatment of anxiety, depression, pain and dementia. Finally, there is evidence that 5-HT3 antagonists may suppress the behavioral consequences of withdrawing chronic treatment with drugs of abuse, including alcohol, nicotine, cocaine, and amphetamine (Thompson and Lummis 2007). There is only little evidence about the possible therapeutic application of 5-HT3 agonists; it seems that some partial agonists possess an anxiolytic profile (Rodd et al. 2007). Alosetron was developed to treat colon irritable but was withdrawn from market due its adverse side effects (Crowell 2004).

5-HT4 receptors

Seven variants of the receptor were identified so far (5-HT4A-H) which differ in the C-terminal segment sequence. Moreover, 5-HT4B subtype was described with insertion of 14 amino acids into the second extracellular loop. However, all variants have similar pharmacology and are associated with adenylyl cyclase activity. This subtype of serotonin receptors exhibits also constitutive (ligand independent) activity, even if it contributes to the function of the receptor only in a small extent. This activity explains the differences between expected and observed effects of agonists and antagonists of the 5-HT4 receptors. Some expected agonists exhibited rather silent or antagonistic effects depending on the level of ligand independent activity (Hoyer et al. 2002). Several studies pointed specific tissue distribution of individual isoforms of 5-HT4 receptors, e.g. 5-HT4D receptor was found only in the human intestine. Besides the activation of the adenylyl cyclase, some isoforms of 5-HT4 receptors are associated directly with a potassium channel and voltage-operated calcium channels (Pauwels et al. 2003).

Activation of 5-HT4 receptor leads to the release of acetylcholine in the ileum and the contractions of the esophagus and colon in pigs. In addition, it participates in the modulation of gastrointestinal motility and secretory responses of intestinal mucosa (Hansen et al. 2008). Voltage-controlled ion channels are stimulated through
5-HT\textsubscript{4} receptors, in particular in the small intestine and heart atria (Pau et al. 2007). The infusion of 5-HT\textsubscript{4} agonists to isolated human heart leads to increase of its contractile power (Mialet et al. 2000). 5-HT\textsubscript{4} receptors in the CNS modulate release of other neurotransmitters (acetylcholine, dopamine, serotonin and gamma-aminobutyric acid – GABA) and enhance synaptic transmission which may affect the development of memory (Ciranna 2006).

5-HT\textsubscript{4} receptors agonist cisapride was used in clinical practice as gastroprokinetic agent (but has been withdrawn from the market due to its cardiac toxicity), whereas partial agonist of this serotonin receptor subtype tegaserod found its application in the treatment of symptoms of colon irritable (De Ponti and Crema 2002). Selective 5-HT\textsubscript{4} ligands are likely to be used in the treatment of various diseases, e.g. dysrhythmias, neurodegenerative diseases and urinary incontinence (Pau et al. 2003, Ramage 2006). 5-HT\textsubscript{4} receptors may be involved in memory and learning and they are significantly decreased in patients with Alzheimer's disease (Reynolds et al. 1995). However, use of highly potent and selective 5-HT\textsubscript{4} agonists might result in cardiovascular adverse side effects. A high density of 5-HT\textsubscript{4} receptors in the nucleus accumbens lead to considerations that these receptors may be involved in the reward system and may influence self-administration behavior (Reynolds et al. 1995). However, 5-HT\textsubscript{4} agonists such as mosapride, metoclopramide, renzapride and zacopride act as 5-HT\textsubscript{3} antagonists as well. These molecules cannot be considered highly selective.

5-HT\textsubscript{5} receptors

Rodents have been shown to possess two functional 5-HT\textsubscript{5} receptor subtypes, 5-HT\textsubscript{5A} and 5-HT\textsubscript{5B}. However, the gene coding the 5-HT\textsubscript{5B} subtype in humans includes stop codons making it non-functional what results in solitary expression of only 5-HT\textsubscript{5A} subtype in human brain (Grailhe et al. 2001). The pharmacological function of 5-HT\textsubscript{5} receptors is still largely unknown. Based on their localization, it has been speculated that they may be involved in motor control, feeding, anxiety, depression, learning, memory consolidation, adaptive behavior and brain development (Thomas 2006). 5-HT\textsubscript{5A} receptors may be also involved in neuron-mediated mechanism for regulation of astrocyte physiology with relevance to gliosis. Disruption of 5-HT neuron-glial interactions may be involved in the development of certain CNS pathologies including Alzheimer's disease, Down's syndrome and some drug-induced developmental deficits (Nelson 2004).

5-HT\textsubscript{6} receptors

Two variants of 5-HT\textsubscript{6} receptor were described yet. Complete 5-HT\textsubscript{6} receptor is composed of 440 amino acid residues and located predominantly in limbic and extrapyramidal cerebral zones. The second variant (probably the result of deletion of 286 amino acid residues) is expressed predominantly in caudatum and substantia nigra (Kohen et al. 1996).

The exact clinical significance of 5-HT\textsubscript{6} receptors remains still unclear. Especially atypical antipsychotics and various antidepressants suggest a possible connection between 5-HT\textsubscript{6} receptors and particular psychiatric disorders. Repeated intracerebroventricular administration of antisense oligonucleotides in rats in order to prevent expression of 5-HT\textsubscript{6} receptors produced a behavioral syndrome that including the increase of cholinergic function (Bourson et al. 1995). This led to speculation that one of the roles of 5-HT\textsubscript{6} receptors might be the control of cholinergic neurotransmission and that 5-HT\textsubscript{6}-selective antagonists may be useful in the treatment of anxiety and memory deficits. Selective antagonists of this type of serotonin receptors have an impact on behavior and seem to improve the spatial memory of laboratory animals (Johnson et al. 2008).

5-HT\textsubscript{7} receptors

The human 5-HT\textsubscript{7} receptor is composed from 445 amino acids and increases the activation of adenylyl cyclase via G\textsubscript{s} protein pathway. This receptor also activates MAP kinase. 5 receptor isoforms (5-HT\textsubscript{7A-D}) which differ in their C-terminal end were described, although all exhibit the same pharmacological properties (Hedlund and Sutcliffe 2004). 5-HT\textsubscript{7} receptors are expressed abundantly in the vessels and are responsible for the persistent vasodilation of anesthesed experimental animals (Terrón and Martínez-García 2007). 5-HT\textsubscript{7} receptors are also expressed in extravascular smooth muscles (e.g. in the gastrointestinal tract) and CNS (Ruat et al. 1993).

Atypical antipsychotics such as clozapine, risperidone and antidepressants have high affinity for 5-HT\textsubscript{7} receptors. The long-term antidepressant treatment leads to down-regulation of these receptors, whereas acute (but not chronic) stress increases their number (Knight et al. 2009). Antagonists of 5-HT\textsubscript{7} receptor mimic the effects of SSRIs and may find application in
the treatment of depression and sleep disorders (Mnie-Filali et al. 2007).

Conclusions

Serotonin is unique among the monoamines in that its effects are subserved by distinct G-protein-coupled receptors and one ligand-gated ion channel. It is evident that in the last two decades, a vast amount of new information has become available concerning the various 5-HT receptor types and subtypes, and their characteristics. This derives from two main research approaches – operational pharmacology using selective ligands, and molecular biology. It still remains to be seen which functions some of the many subtypes play in health or disease. There are multiple links between 5-HT receptors and disease, as illustrated by a large list of medications active at one or the other receptors, other drugs being active at several receptors at the time. The complexity of the system is probably even larger than suspected.

The challenge for the next years of serotonin research is to clear to what extent diversity in receptors fulfills specific physiological or pathophysiological roles. This research may then assist in designing drugs with an adequate profile at the target organ and specific disease. But, the diversity in receptors described above suggests that under physiological and pathological conditions, the status of the receptors may vary from one patient to another, explaining differences in responder rates to a specific drug. However, we may expect a different therapeutic potential for each 5-HT receptor subtype listed in this letter.

Conflict of Interest

There is no conflict of interest.

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