Serotonin receptors and its agonists and antagonists

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**Introduction**

The greatest concentration, 90%, of Serotonin (5-HT, 5-hydroxytryptamine) is found in the enterochromaffin cells of the gastrointestinal tract. Most of the remainder of the body's 5HT is found in platelets and the central nervous system (Johnson, 2004). Rapport et al. discovered serotonin in 1948 as a potent vasotonic factor. For many years, the physiological effects of 5-HT, including its effects on the CNS, were attributed to only two major subtypes of 5-HT receptors (Gaddum & Picarelli, 1957).

5-HT is important for a variety of physiological functions, including platelet aggregation, smooth muscle contraction, appetite, cognition, perception, mood, and other CNS functions. These diverse physiological functions are mediated by large number of 5-HT receptor subtypes that are encoded by distinct genes. It now appears that there are at least 15 receptor subtypes that belong to four classes of receptors: 5-HT1/5, 5-HT2 (A, B, C), 5-HT3, and 5-HT4/6/7. 5-HT has been implicated in the etiology of numerous diseases states including depression, anxiety, social phobia, schizophrenia, obsessive-compulsive neurosis and panic disorder; in addition to migraine, hypertension, pulmonary hypertension, eating disorders, vomiting, and irritable bowel syndrome (Hoyer et al., 1994, Johnson, 2004 and Nagatomo et al, 2004).

![Serotonin balance and its clinical sequelae](image-url)

Fig. 1) Serotonin balance and its clinical sequelae
**Serotonin synthesis**

The biosynthesis of serotonin from the amino acid tryptophan is similar to that found for the catecholamines, and 5-hydroxytryptophan can cross the BBB to increase central levels of 5-HT. p-Chlorophenylalanine can competitively inhibit tryptophan hydroxylase to prevent serotonin synthesis. Although serotonin is metabolized by monoamine oxidase to 5-hydroxyindoleacetic acids, most of the serotonin released into the post-synaptic space is removed by the neuron through a reuptake mechanism inhibited by the tricyclic antidepressants. Serotonin also serves as a precursor for melatonin production in the pineal gland (Barnes et al, 1999).

![Synthesis and metabolism of serotonin](image)

Fig. 2) Synthesis and metabolism of serotonin
Fig 3) The serotonergic synapse. Illustration of the processes of serotonin synthesis and metabolism, presynaptic and vesicular 5-HT uptake, vesicular 5-HT release. And Pre- and postsynaptic 5-HT receptors and sites of action of some serotonergic drugs

Functions of Serotonin

1) Serotonin in central nervous system (Only 1-2% serotonin in body)
- involved in sleep induction
- involved in vascular tone: agonists is used in cluster headache and migraine
- Involved in mood: the basis of using selective serotonin uptake inhibitors
  - facilitates firing of motorneurons
  - involved in ability to differentiate sensory phenomena; reduction of its effect e.g. with the antagonist LSD, contributes to hallucinogenesis
  - involved in temperature regulation in the hypothalamus
  - free nerve endings: pain, possible role in acute inflammation (Siegel, 1999, Nelson, 2004).

Fig 4 shows the serotonin pathways, receptor sites and subtypes and the functions of serotonin in different paret's of the central nervous system
2-Serotonin in smooth muscle

In the gut, serotonin (5-hydroxytryptamine: 5-HT) exerts a variety of effects on intrinsic enteric neurons, extrinsic afferents, enterocytes and smooth muscle cells, which are related to the expression of multiple 5-HT receptor types and subtypes regulating motility, vascular tone, secretion and perception. Agonists and antagonists at 5-HT receptors have gained access to the market for the two major variants of the irritable bowel syndrome (IBS), a functional disorder characterized by abdominal pain associated with diarrhea and/or constipation in the absence of any organic abnormality. Indeed, the 5-HT₃ receptor antagonist alosetron is available in the US market for the treatment of women with severe, diarrhea-predominant IBS (D-IBS) refractory to conventional therapy, whereas tegaserod, a partial 5-HT₄ receptor agonist, has been approved by the FDA and other regulatory agencies for the treatment of women with constipation-predominant IBS (C-IBS) or functional constipation. This review is mainly intended to discuss the role of non-neuronal (paracrine) and neuronal 5-HT in the pathophysiology of functional
gastrointestinal disorders (FGIDs), such as IBS and functional dyspepsia, and the mechanisms through which drugs acting on 5-HT receptors regulate visceral motility, perception and secretion in these two conditions.  

(Tonini and Pace, 2006)

Table 1) Role of serotonin in gastrointestinal function (Tonini and Pace, 2006)

3) Serotonin in cardiovascular system:

Serotonin is an important neurohormonal factor that has been implicated in cardiovascular function. It can regulate vascular tone, act directly on cardiomyocytes and stimulate chemosensitive nerves in the heart. The overall effect on blood vessels is dependent on vessel size, distribution of receptors, and modulation of noradrenergic
output. The onductance vessels tend to constrict. The transfer vessels: arterioles dilate, venules constrict and capillaries become more permeable; this favours the formation of oedema in the inflammatory response. Cardiovascular dysfunction is observed when serotonin signaling is altered or when variation in serotonin concentration occurs. Recent studies have provided evidence that, in the absence of peripheral serotonin synthesis, blood serotonin (which is almost exclusively stored in platelets) is markedly reduced, and that this drop leads to heart failure. This implies that the level of circulating serotonin is a key factor in maintaining normal cardiovascular activity. These findings offer new prospects for the use of serotonin in therapies for cardiovascular diseases. (Cote et al, 2004)

**Serotonin receptors**

Serotonin receptors are diverse and numerous. More than 15 different serotonin receptors have been cloned through molecular biological techniques. Overall, seven distinct families of 5-HT receptors have been identified. Only one of the 5-HT receptors is a ligand-gated ion channel; the other six belong to the G protein-coupled receptor family. The amino acid sequences of the 5-HT receptor families are remarkably similar to each other and to the adrenergic receptor, including a conserved aspartate residue in the third membrane-spanning segment. Serotonin receptors were divided into several subclasses based on functional similarities. The 5-HT1 receptors are coupled to the inhibition of adenylyl cyclase through the Gq/11 family of G proteins. In contrast, the 5-HT2 receptors stimulate phosphoinositide metabolism via Gq/11. (Hoyer et al., 1994 and Jhon et al, 2001).

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**Fig 6**) Serotonin synthesis, receptors and their signal pathway
The 5-HT₃ receptors are 5-HT-gated ion channels. The basic architecture of the G-protein-coupled 5-HT receptors is similar to that proposed for nearly all of the G-protein-coupled receptors (GPCRs). These receptors are integral membrane proteins with 7 putative hydrophobic transmembrane domains connected by 3 intracellular loops (termed i1–i3) and 3 extracellular loops (termed e1–e3). The amino terminus is oriented toward the extracellular space, whereas the carboxyl terminus is oriented toward the cytoplasm. The core proteins also possess conserved or common sites for post-translational modifications. The extracellular domains are typically glycosylated, and possess cysteine residues that may participate in disulfide bonds that provide structural constraints on the conformation of the receptors. The intracellular domains possess sites for interacting with G-proteins and other regulatory proteins, and sites for phosphorylation by diverse serine-threonine kinases. (Barnes et al., 1999)

Fig. 7) 5-HT receptors location and its signal transduction mechanisms

1) The 5-hydroxytryptamine₁ receptors:
There are 5 members of the 5-HT₁-receptor family, termed 5-HT₁A, 5-HT₁B, 5-HT₁D, 5-HT₁E, and 5-HT₁F. A receptor formerly termed the 5-HT₁C receptor is no longer felt to be
a member of the 5-HT<sub>1</sub> receptor family, having been reclassified as the 5-HT<sub>2C</sub> receptor based on similarities to other 5-HT<sub>2</sub> receptors in structure and second messenger systems (Hoyer et al., 1994). The 5-HT<sub>1</sub> receptors couple primarily through G<sub>i/o</sub>-proteins to the inhibition of adenylyl cyclase (AC) and to other signaling pathways and effectors. Family G-proteins, resulting in accumulation of phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to IP<sub>3</sub> and DAG. Generation of IP<sub>3</sub> results in elevation of intracellular Ca<sup>2+</sup> levels, whereas DAG activates the Ca<sup>2+</sup> and phospholipid-dependent protein kinase (John et al, 2001).

**The 5-hydroxytryptamine<sub>1A</sub> receptor**

In summary, The 5-hydroxytryptamine<sub>1A</sub> receptor acts through

* both inhibits and activates adenylyl cyclase
* activates and inhibits phosphatidylinositol-specific phospholipase C
* activates protein kinase C
* activates the extracellular signal-regulated mitogen-activated protein kinase
* stimulates phosphatidylinositol-3' kinase
* regulates K<sup>+</sup> channels (Kroeze et al 2002, Green, 2006);

The 5-HT<sub>1A</sub> receptor has also been implicated in morphogenesis and cell survival. Blockade of endogenous 5-HT<sub>1A</sub> receptors reverses serotoninergic stimulation of tooth germ development in mouse mandibular explant cultures (Moiseiwitsch et al., 1998 and Adayev et al., 1999)

**What is the basis for the multiplicity of 5-hydroxytryptamine<sub>1A</sub> receptor signaling?**

In that regard, the 5-HT<sub>1A</sub> receptor has been identified in both presynaptic and postsynaptic locations (Radja et al 1992). The signaling properties and pharmacology of the presynaptic and postsynaptic 5-HT<sub>1A</sub> receptors vary somewhat (Clarke et al., 1996), leading to speculation that there might be subtypes of 5-HT<sub>1A</sub> receptors (Barnes & Sharp, 1999). Langlois et al. (1996) demonstrated that 5-HT<sub>1A</sub> receptors transfected into polarized epithelial LLC-PK<sub>1</sub> cells were expressed on both basolateral and apical membranes. Receptors on both surfaces were able to inhibit cAMP accumulation, albeit with different efficiencies (Langlois et al., 1996). This study demonstrates that the variables that affect the multiplicity of signaling from single receptor types are not likely to be manifested as "all or none" effects. Thus, the specific coupling of single types of 5-HT receptors to signaling pathways is likely to result from the summation of effects specific to the host cell milieu (Lefebvre, et al 2001, Hall et al. 1999).

**The 5-hydroxytryptamine<sub>1B</sub> receptor**

In summary, the 5-hydroxytryptamine<sub>1B</sub> receptor act through (Kroeze et al 2002, Green, 2006) :

* regulates adenylyl cyclase
  * activates phospholipases e.g PLC, PLD
  * stimulates endothelial nitric oxide production
  *Other signals of the 5-hydroxytryptamine<sub>1B</sub> receptor: Several groups have demonstrated that presynaptic 5-HT<sub>1B</sub> receptors decrease 5-HT release. Human 5-HT<sub>1B</sub>
receptors stably transfected in C6 glioma cells activate Ca\(^{2+}\)-dependent K\(^{+}\) channels (Le Jeong et al, 2005.).

<table>
<thead>
<tr>
<th>Subfamily</th>
<th>Effectors</th>
<th>Site</th>
<th>Actions</th>
<th>Agonists (Used in)</th>
<th>Antagonists (Used in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT(_{1A})</td>
<td>Gi</td>
<td>*CNS: cortex, Hippocampus, thalamus, amygdale, raphe</td>
<td>*Control sleep, feeding, anxiety and ACTH release.</td>
<td>*Azapiron(^{±}), Buspiron(^{±}), Jaspiron(^{±}), gepirone (^{±}), Vilazodone(^{±}), spiperone (Anxiety, depression)</td>
<td><em>pindolol</em> (^{<em>}), Sarizotane (^{</em>}) (L-dopa dyskinesia) *Spiroxatrine (Alzheimer) *SLV310 (psychosis)</td>
</tr>
<tr>
<td>(Auto R., Inhibitory)</td>
<td>Go</td>
<td>Close Ca channel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT(_{1B})</td>
<td>Gi ((\downarrow)AC)</td>
<td>*CNS: cortex, BG, striatum, Hypothalamus *Cerebral &amp; pulmonary arteries</td>
<td>*Control motor activity, behavior *Control BV tone.</td>
<td>*Ergometrin, *Donitriptan, sumatriptan almotriptan elecatriptan, frovatriptan, naratriptan ,rizatriptan (migraine, hypophagia)</td>
<td>-AR-A2, Elzasonan (Depression, anxiety)</td>
</tr>
<tr>
<td>(Auto R., Inhibitory)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT(_{1D})</td>
<td>Gi ((\downarrow)AC)</td>
<td>Dorsal raphe, heart, meningeal arteries</td>
<td>BV tone &amp; inflammation</td>
<td>*Sumatriptan, almotriptan , elecatriptan, frovatriptan, naratriptan ,Rizatriptan (Migraine)</td>
<td>-</td>
</tr>
<tr>
<td>(Auto R., Inhibitory)</td>
<td></td>
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<tr>
<td>5-HT(_{1E})</td>
<td>Gi ((\downarrow)AC)</td>
<td>Cortex</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT(_{1F})</td>
<td>Gi ((\downarrow)AC)</td>
<td>Brain, mesentery</td>
<td>Neurogenic, inflammation</td>
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\(\pm\) = Partial agonist, \(\neq\) = Inverse agonist, BG = Basal ganglia, AC = Adenyl cyclase

**Table 2) 5HT\(_{1}\) receptors subfamilies, sites, functions and its agonists and antagonists and its clinical uses ligands.** (Miyake et al, 1995; John et al, 2001; Raymond et al, 2001; De Vry et al, 2004; Hayashi et al, 2004; Palvimaki et al, 2005; Jeong et al, 2005; Qvigstad et al, 2005; Green, 2006; Nelson (2004); Nagatomo et al, 2004; Ferreira et al, 2004; Tonini M and Pace F, 2006; Cote F et al, 2004)

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**Fig.8) 5-HT\(_{1A}\) and 5-HT\(_{1D}\) autoreceptor**
The 5-hydroxytryptamine$_{1D}$ receptor

In summary, the 5-hydroxytryptamine$_{1D}$ acts through:

* inhibits adenylyl cyclase
* regulates ion channels
* inhibits 5-hydroxytryptamine, glutamate release (LeJeong et al., 2005 & Green, 2006).

The 5-HT$_{1E}$ receptor

The 5-HT$_{1E}$ receptor originally was identified as a component of [$^3$H]5-HT binding to human cortical homogenates that was resistant to a cocktail of antagonists of 5-HT$_{1A}$, 5-HT$_{1B/D}$, and 5-HT$_2$ receptors. The intronless 5-HT$_{1E}$ receptor gene was subsequently cloned from human and rat and the human gene encodes a protein of 365 amino acids. This protein shares 39% homology with the 5-HT$_{1A}$ receptor and 47% identity (64% in the transmembrane regions) with the 5-HT$_{1B/D}$ receptors. The 5-HT$_{1E}$ receptor gene has been localized to human chromosome 6q14-q15 (Zgombick et al., 1996).

There are few details about signaling pathways linked to the 5-HT$_{1E}$ receptor. Low concentrations of agonist have been shown to inhibit AC in HeLa and BS-C-1 cells transfected with the 5-HT$_{1E}$ receptor. The 5-HT$_{1E}$ receptor can also stimulate AC, as high concentrations of agonist also promote increases in cAMP in BS-C-1 cells. The 5-HT$_{1E}$ receptor has not yet been demonstrated to stimulate PLC and/or PLA$_2$. In BS-C-1 cells, 5-HT had no effect on inositol phosphate release, intracellular Ca$^{2+}$ levels, or AA mobilization (Adham et al., 1994).

The 5-hydroxytryptamine$_{1F}$ receptor

The 5-HT$_{1F}$ receptor gene encodes a protein of 366 amino acids, with 70% homology to the 5-HT$_{1E}$ receptor, 60% to the 5-HT$_{1B}$ receptor (60%), and 63% to the 5-HT$_{1D}$ receptor. 5-HT$_{1F}$ receptor mRNA was detected in human brain, uterus, and mesentery, but not in kidney, liver, spleen, heart, pancreas, and testes. When stably expressed in NIH 3T3 cells, the 5-HT$_{1F}$ receptor negatively couples to AC (Adham et al., 1994).

The 5-HT$_{1F}$ receptor has been shown to couple to PI-PLC in a cell-specific manner. When transfected into NIH 3T3 cells, no elevation of inositol phosphates or Ca$^{2+}$ was observed, whereas in LM (tk-) cells, the receptor stimulated accumulation of inositol phosphates and induced a rapid increase of Ca$^{2+}$. PLC activation was blocked by pertussis toxin, supporting a role for the $G_{i/o}$ protein. The significance of the coupling to PLC is uncertain, as the transfected cells used in this study expressed high levels of receptors (4.4 pmol/mg of protein). The 5-HT$_{1F}$ receptor has been demonstrated to decrease capsaicin-induced c-fos expression in the rat trigeminal nucleus caudalis, although the signaling pathway of this effect was not defined (Mitsikostas et al., 1999).

2-The 5-hydroxytryptamine$_{2}$ receptors

There are three members of the 5-HT$_2$ receptor family, termed 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ (Hoyer et al., 1994). The 5-HT$_{2A}$ receptor is probably the 5-HT M receptor...
described by Gaddum and Picarelli (1957). The 5-HT$_2B$ receptor was formerly referred to as the 5-HT$_2F$ receptor [or serotonin receptor like (SRL)] (Foguet et al., 1992), and the 5-HT$_3C$ receptor was previously referred to as the 5-HT$_1C$ receptor. The 5-HT$_2$ receptors couple consistently to the PLC-β second messenger pathway (Peroutka, 1995). Unlike the 5-HT$_1$ receptors, the 5-HT$_2$ receptor genes have introns. Although the 5-HT$_2$ receptors are similar in structure, pharmacology, and signaling pathways, there are a few differences in their signaling properties (Grotewiel et al. 1999).

**The 5-hydroxytryptamine$_{2A}$ receptor**

In summary, 5-HT$_{2A}$ act through (Kroeze et al. 2002, Green, 2006, Bhatnagar et al., 2000, Bhatnagar et al. 2000; Luparini et al. 2004).:

- Activates phospholipase C
- Activates other phospholipases
- Activates the extracellular signal-regulated mitogen-activated protein kinase
- Activates the Janus kinase/signal transducers and activators of transcription pathway
- Regulates channels e.g. Ca$^{2+}$,Ca$^{2+}$-activated small conductance K$^+$ channel
- Causes production of reactive oxygen and nitrogen species
- Regulates transport processes e.g Na$^+$-proton exchange exchanger, Type 1 Na$^+$-proton exchanger in renal mesangial cells

**The 5-hydroxytryptamine$_{2B}$ and 2C receptors:**

The 5-Hydroxytryptamine$_{2B}$ receptor:

5-HT$_{2A}$ was first described as the receptor that mediates contraction of the gastric fundus (Vane, 1959). The receptor was cloned from rat and mouse in 1992 (Foguet et al., 1992) and from human in 1 (Kursar et al., 1994). The human receptor protein is 481 amino acids in length (Kursar et al., 1994), and it has 2 introns similar to the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. The human receptor has 45% homology with the 5-HT$_{2A}$ receptor and 42% homology with the 5-HT$_{2C}$ receptor (Sharp and Hjorb, 1999). The human 5-HT$_{2B}$ receptor gene is localized to chromosome 2q36.3-2q37.1. mRNA encoding the 5-HT$_{2B}$ receptor is expressed with greatest abundance in the human liver and kidney. Lower levels of expression have been detected in the pancreas and spleen (Bonhaus et al., 1995), but the presence of mRNA for the 5-HT$_{2B}$ receptor in the brain appears to be relatively limited (Kursar 1994, Duxon et al., 1997).

The 5-hydroxytryptamine$_{2B}$ receptor act through ((Kroeze et al. 2002, Green, 2006):

- activates phospholipase C
- can stimulate cyclic AMP accumulation
- activates the extracellular signal-regulated kinase and cell cycle components
- The causes production of reactive nitrogen species

And 5-hydroxytryptamine$_{2C}$ receptor act through:

- activates phospholipase C
- receptor can modulate cyclic AMP accumulation
- regulates channels e.g K$^+$ and Cl$^-$ channels
<table>
<thead>
<tr>
<th>Subfamily</th>
<th>Effectors</th>
<th>Site</th>
<th>Actions</th>
<th>Agonists (Used in)</th>
<th>Antagonists (Used in)</th>
</tr>
</thead>
</table>
| 5-HT<sub>2A</sub> | Gq: *↑PLC  
→↑IP3  
*↑PLA→AA | CNS: Cortex, BG  
Sooth muscle, Blood vessels, Platelets | *Learning, antiaggressive, behaviour)  
*Contract SM,  
*↑PLC→↑IP3  
*↑PLA→AA  
*VC/VD (↑NO) & ↑capillary permeability  
* Platelet aggregation,  
*methyl-5-HT, LSD  
*Citalopram (aggression) | *Methysergide  
*respiridone, Ketanserine, mianserin (migraine, depression)  
*Ritanserin (Schizophrenia)  
*Eplivanserin, pruvanserin (sleep disorder) |
| 5-HT<sub>2B</sub> | Gq  
*↑PLC→↑IP3  
*↑PLA→AA | CNS: Amygdale, Stomach | *Anxiolytic, hyperphagia, Contraction (prokinetic) | locaserin  
RS127445, SB200648 |
| 5-HT<sub>2C</sub> | Gq: *↑PLC→↑IP3  
*↑PLA→AA | CNS: Cortex, Choroids plexus | *Anxiety, sleep, Food intake  
*CSF secretion  
*MCCP (obesity)  
-D-Fenfluramine, sibutramine, fluoxetine | - Agomelatine  
(Depression, anxiety, sleep disorders)  
-ACP103 (L-dopa dysthesia)  
- Eplivanserin, pruvanserin (sleep disorder) |


Also, 5-HT has significant ability to modulate membrane excitability in subthalamicneurons; modulation is accomplished by decreasing potassium conductance by activating 5-HT4 and 5-HT2C receptors (Xiang et al 2005). The 5-HT plays a critical role in the control of vagaloutflow of the heart. Blocking 5-HTA1 receptors attenuate bradycardia evoked by stimulating baroreceptor and cardiopulmonary afferent but notarterial chemoreceptor, whereas antagonizing 5-HT7 receptors markedly attenuated all these reflex bradycardias (Jordan 2005).

3) The 5-hydroxytryptamine<sub>3</sub> Receptors

Unlike most of the other 5-HT receptors, where functional assays were slow to be identified (and, in some cases, have yet to be identified). Due to the pharmacological similarity between 5-HT3 receptors and 5-HT-M receptors. 5-HT3 receptors are unique among the families of 5-HT receptors, in that they are nonselective Na<sup>+</sup>/K<sup>+</sup> ion channel receptors. They are found in the periphery and also in the central nervous system, particularly in the area postrema, entorhinal cortex, frontal cortex, and hippocampus. Differences in agonist potencies and efficacies, and antagonist potencies, in various
functional assays led to early speculation about 5-HT$_3$ receptor heterogeneity or at least interspecies variation among 5-HT$_3$ receptors. Furthermore, the distribution of 5-HT$_3$ binding sites in human brain was not identical to that in rodent brain, and the results of radioligand binding studies using postmortem human brain revealed differences from other species. Support for interspecies differences has come from molecular biological studies. 5-HT$_3$ receptor cDNA was initially isolated from a mouse neuroblastoma cell line; later, a splice variant was isolated, human 5-HT$_3$ receptors (hippocampus, amygdala) have been cloned (Miyake et al, 1995)

**4. The 5-hydroxytryptamine$_4$ receptor:**

Three types of 5-HT receptors couple primarily to the activation of AC: the G$_s$-coupled 5-HT$_4$, 5-HT$_6$, and 5-HT$_7$ receptors (Hamblin et al., 1998). Unlike the 5-HT$_6$ and 5-HT$_7$ receptors, the 5-HT$_4$ receptor was well-characterized pharmacologically and functionally prior to its cloning. The major functional effects of the 5-HT$_4$ receptors are prokinetic actions in the gut and positive inotropy, chronotropy, and lusitropy in atria, but not ventricles (Kaumann, 1991).

The human 5-HT$_4$ gene is thought to be highly complex, with multiple introns. It maps to chromosome 5q31-q33. In 1995, Gerald et al. reported the isolation of two rat brain 5-HT$_4$ receptors. These were originally termed 5-HT$_{4S}$ and 5-HT$_{4L}$ to indicate that they are short (387 amino acids) and long versions (406 amino acids) of the 5-HT$_4$ receptor (Bockaert et al., 1998). Similar murine cDNA homologues of these receptors were subsequently reported, and these were proposed to be renamed 5-HT$_{4a}$ and 5-HT$_{4b}$ receptors, to be more in keeping with the recommendations of the Nomenclature Committee of the International Union of Pharmacology. 5-HT$_{4a}$, 5-HT$_{4b}$, and 5-HT$_{4c}$ receptors are expressed in the brain, the atrium, and the gut, whereas the 5-HT$_{4d}$ receptor has only been detected in the gut. The human 5-HT$_{4d}$ receptor is localized in the atrium and the brain, but not in the gut. Functional ventricular 5-HT(4) receptors are induced by myocardial infarction and CHF of the rat heart. We propose that they are a model for ventricular 5-HT(4) receptors of human failing heart and may play a pathophysiological role in heart failure (Kroeze et al 2002 & Qvigstad et al 2005, Green, 2006).

**5. The 5-hydroxytryptamine$_5$ receptors**

Currently, little is known about 5-HT$_5$ receptors. As functional 5-HT$_5$ receptors have not been identified in vivo yet, the lower case designation is used. Cloning experiments have revealed two subtypes of the 5-HT$_5$ receptor, termed 5-HT$_{5a}$ and 5-HT$_{5b}$. Both 5-HT$_{5a}$ and 5-HT$_{5b}$ receptors have been cloned from rat and mouse, but only the 5-HT$_{5a}$ receptor has been cloned from human. The human 5-HT$_{5A}$ receptor gene encodes a protein of 357 amino acid residues, has a single intron, and is located on chromosome 7q36 (Rees et al., 1994).

The 5-HT$_5$ receptors have high affinity for lysergic acid diethylamide (LSD) and 5-carboxamidotryptamine. Both receptors are expressed in multiple brain regions, but not in peripheral tissues (Rees et al, 1994). Waeger et al (1995) were able to identify putative 5-
hts receptors by comparative autoradiography with $[^3]H$5-carboxamidotryptamine and $[^{125}]I$LSD in wild-type and 5-hts receptor knockout mice. Studies with $[^3]H$5-carboxamidotryptamine (in the presence of 8-OH-DPAT, GR127935, and spiperone) revealed no binding in knockout mice, but intermediate levels of binding in wild-type mice in the olfactory bulb and neocortex. This binding probably represents the 5-hts receptor. (Waeber et al., 1998).

<table>
<thead>
<tr>
<th>Subfamily</th>
<th>Effector</th>
<th>Site</th>
<th>Actions</th>
<th>Agonists (Used in)</th>
<th>Antagonists (Used in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT3</td>
<td>Open cation channel</td>
<td>*CNS: cortex, NTS, area postrema *Peripheral sensory nerves (vagus, splanchnic) *Enteric neurone</td>
<td>*Anxiety, vomiting, Gut motility *Pain, itching, ↑transmitter release. *↑Transmitter release, ↑Secretion</td>
<td>2-methyl-5-HT</td>
<td>-Ondansetron, Dolasetron, granisetron, tropisetron (Used in chemotherapy induced emesis) -Alosetrone, Clansetron, mosapride, rinzapride (used in IBS with diarrhea)</td>
</tr>
<tr>
<td>5HT4</td>
<td>Gs (↑AC)</td>
<td>*Enteric neurone * Atria, *Brain (stimulatory)</td>
<td>↑Transmitter release, relaxation &amp; ↑Secretion (Prokinetic) *↑ HR *↑</td>
<td>*Tegaserod↑ Mosapride, Prucaloprid, renzapiride (IBS+ constipation &amp; GIT disorders)</td>
<td>-</td>
</tr>
<tr>
<td>5-HT5A</td>
<td>? Gs (?AC)</td>
<td>Brain</td>
<td>Brain development</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5HT5B</td>
<td>? Gs (?AC)</td>
<td>Hippocampus</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5-HT6</td>
<td>Gs (↑AC)</td>
<td>Limbic system, cortex, hippocampus</td>
<td>Cognition, feeding, affected disorders, seizures.</td>
<td>EDMT</td>
<td>-Gw742457 (psychosis) – BVTS-5182S (Obesity)</td>
</tr>
<tr>
<td>5-HT7</td>
<td>Gs (↑AC)</td>
<td>BV, SM, brain stem, hypothalamus, hippocampus</td>
<td>VD, sleep, temperature control</td>
<td>5CT, 5-MeOt</td>
<td>SB258719, SB258741. -Paliperidone (psychosis)</td>
</tr>
</tbody>
</table>

7. The 5-hydroxytryptamine$_7$ receptor

The 5-hydroxytryptamine$_7$ receptor act through (Kroeze et al 2002, Green, 2006))
* activates adenylyl cyclase
* activates the extracellular signal-regulated kinase
* modulates slow afterhyperpolarization

6. The 5-hydroxytryptamine$_6$ receptor

(The human 5-HT$_6$ receptor is a 440 amino acid protein. The gene contains two introns that correspond to regions of the putative i3 and e3 loops. The gene for the receptor maps to the human chromosome region 1p35-p36 (Kohen et al., 1996). The 5-HT$_6$ receptor stimulates AC and has high affinity for typical and atypical antipsychotics, including clozapine. The receptor is expressed in several brain regions, most prominently in the caudate nucleus, the olfactory tubercle, the striatum, the hippocampus, and the nucleus accumbens. Low levels of 5-HT$_6$ receptor mRNA are also expressed in the adrenal gland and the stomach. Surprisingly, 5-HT$_6$ receptors appear to regulate cholinergic (rather than dopaminergic) neurotransmission in the brain, implicating it as a target for the treatment of learning and memory disorders (Bourson et al 1998, Wolley et al 2004, Kroeze et al 2002, Green, 2006).

Selective Serotonin reuptake inhibitors

Serotonin transport across the plasma membrane:

- Serotonin uptake is a carrier-mediated process requiring the presence of Na$^+$ and Cl$^-$ ions. Sodium binds first to the carrier, followed by 5-HT (1).
- Chloride is needed for transport but not for transmitter binding. The carrier is translocated in the membrane by an unknown mechanism, after which 5-HT and the ions dissociate from their binding sites (2).
- Potassium then binds to the carrier (3), is translocated to the outside of the membrane (4), and dissociates from the carrier to complete the cycle.

![Fig.9) Hypothesized mechanism of serotonin transport across the plasma membrane](image-url)
Clinical indications of SSRI:

1. Major Depression & 2nd to medical condition (e.g., Post stroke)
2. Paraphillias, sexual addictions & premature ejaculation.
3. Obesity & Weight gain in smokers & Bulimia nervosa.
4. Emotional liability following brain injury.
5. Migraine prophylaxis.
6. Diabetic neuropathy.
7. Seasonal Affective Disorder.
8. Obsessive-compulsive disorder
9. Panic Disorder & Social phobia
10. Borderline personality disorder.
11. Depersonalization syndrome
12. Alcoholism

Schizophrenia

Schizophrenic symptoms can represent either an excess or distortion of normal function (positive symptoms) or a decrease or loss of normal function (negative symptoms).

<table>
<thead>
<tr>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thought disorders e.g. delusion.</td>
<td>1. Poverty of thought and speech.</td>
</tr>
<tr>
<td>2. Abnormal perception e.g. hallucination.</td>
<td>2. Impaired volition</td>
</tr>
<tr>
<td>3. Inappropriate affect (affective response is</td>
<td>3. Blunt affect and anhedonia</td>
</tr>
<tr>
<td>incompatible with the ideas or thoughts expressed)</td>
<td></td>
</tr>
<tr>
<td>4. Disorganized behavior.</td>
<td>4. Social withdrawal</td>
</tr>
</tbody>
</table>

Table 5) Positive and negative symptoms of schizophrenia
**Antipsychotic (Neuroleptics)**

*All have epileptogenic potentials  * All available in Oral preparation

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High affinity (blocker) to D2.</strong></td>
<td>*High 5HT₂, D₄ &amp; weak D₂ (blocker) affinity.</td>
</tr>
<tr>
<td><strong>Decrease negrostriatal &amp; mesolimbic dopaminergic activity.</strong></td>
<td>*Decrease mainly the mesolimbic dopaminergic activity.</td>
</tr>
<tr>
<td><strong>More effective in treatment of positive symptoms</strong></td>
<td>*Affect both negative and positive symptoms.</td>
</tr>
</tbody>
</table>

* More adverse effect :
  1- Extrapyrdimal side effect (EPS), the higher potency, the higher EPS.
  2- Sedation (D₂, H₁ & α₁ blockade).
  3- Anticholinergic.
  4- Postural hypotension.
  5- Hyperprolactinaemia & sexual dysfunction:
    e.g. a- Phenothizines.
    b- Thioxantines (flupenthixol).
    c- Butyrophenone (flupenthixol).
    d- Diphenylbutyl piperidine

* Diabetes + Drug’s specific adverse effect:
  **e.g :**
  a- **Clozapin** (fatal agranulocytosis, high anticholinergic & sedation, weight gain).
  b- **Resperidon** (EPS in dose > 6 mg/day).
  c- **Sertindol** (nasal congestion, sexual dysfunction).
  d- **Olanzapine** (sedation & weight gain).
  e- **Quetiapine** (postural hypotension).

**Table 6)** Typical and Atypical antipsychotic

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Fig.11) Comparative receptor binding profile of atypical antipsychotic
Migraine

Migraine is a chronic, neurological disorder generally manifesting itself in attacks with severe headache, nausea and an increased reactivity to sensory stimuli. The discovery of the triptans (selective 5-HT_{1B/1D} receptor agonists) gave an alternative therapeutic approach to the acute treatment of migraine. Sumatriptan, the first to be developed, is the most extensively studied medication in the history of migraine. Its emergence onto the market generated intense pharmaceutical research and the development of a number of second-generation agents, including almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan. (Linde, 2006)

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Severity</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| Migrains| Unilateral| Usually severe| *Prodrome* (anxiety, irritability, euphoria or drowsiness, sensitive to sound, light, smell): hours to days before headache  
*Aura*: 5-20 m before headache, visual (zigzag lines, paraesthesia & visual defect) is the comment  
*Headache*: Throbbing, nausea Last a long time.  
*Postdrome*: follow severe attacks (exhaustion and scalp tenderness) |
| Cluster | Unilateral| Usually severe| Autonomic: affect eye and nose Brief 15-90 m)                               |
| Tension | Diffuse   | Rarely severe | Dull, nonthrobby, no nausea Worsened by stress                             |

Table 7) Types of headache

Fig 12) Location of headache
A migraine trigger causes the release of neuropeptide from 5HT-1D receptors in the trigeminal vascular junction which in turn induce sterile inflammation of the meningeal arteries via 5HT-1D receptors. The throbbing of the meningeal arteries is transmitted into the thalamus and interpreted as pain. Abnormal neurologic impulses produce a central effect with nausea, vomiting, dizziness and light and sound sensitivity. Triptans block 5HT-1D and 5HT-1B receptors, thus deactivating the mechanisms that propagates migraine (Rapoport et al 2006).
The irritable bowel syndrome (IBS) is part of the spectrum of functional bowel disorders characterised by a diverse consortium of abdominal symptoms including abdominal pain, altered bowel function (bowel frequency and/or constipation), bloating, abdominal distension, the sensation of incomplete evacuation and the increased passage of mucus. It is not surprising therefore that no single, unifying mechanism has as yet been put forward to explain symptom production in IBS. The currently favoured model includes both central and end-organ components which may be combined to create an integrated hypothesis incorporating psychological factors (stress, distress, affective disorder) with end-organ dysfunction (motility disorder, visceral hypersensitivity) possibly aggravated by sub-clinical inflammation as a residuum of an intestinal infection. There is currently no universally effective therapy for IBS. Standard therapy generally involves a symptom-directed approach; anti-diarrhoeal agents for bowel frequency, soluble fibre or laxatives for constipation and smooth muscle relaxants and anti-spasmodics for pain. New drug development has focused predominantly on agents that modify the effects of 5-hydroxytryptamine (5-HT) in the gut, principally the 5-HT$_3$ receptor antagonists for painful diarrhoea predominant IBS and 5-HT$_4$ agonists for constipation predominant IBS. More speculative new therapeutic approaches include anti-inflammatory agents, antibiotics, probiotics, antagonists of CCK1 receptors, tachykinins and other novel neuronal receptors. (Farthing, 2004, Bradesi et al, 2006).

![Fig. 15] Localization of potential relevant molecular targets in irritable bowel syndrome with the specific
5-HT₃ antagonists Alosetron and cilansetron have been evaluated in randomized, controlled trials and both are considered to have efficacy in female patients with diarrhea-predominant IBS. Indeed, in a first major study, alosetron was shown to have a 12% therapeutic advantage over placebo, using an end point of adequate relief of IBS pain and discomfort for at least two weeks per month. Several other Phase III studies have confirmed these results. Cilansetron was shown to have similar efficacy in a Phase III study in a similar female IBS population. One of the major problems with the use of both alosetron and cilansetron is a high prevalence of ischemic colitis, which might be linked to a direct or indirect action of 5-HT₃ antagonists on colonic blood flow. (Bradesi et al, 2006).

Tegaserod a selective 5-HT₄ receptor partial agonist, has prokinetic properties by virtue of stimulating peristalsis and increasing both intestinal and colonic transit, and also by modulating sensory pathways. Clinical trials in constipated female IBS patients, with end points comprising a global improvement, and an improvement in bowel frequency, stool consistency or abdominal pain at three months, indicate a 9.3% higher percentage than placebo. The limited side effects observed included transient diarrhea and a higher than expected rate of cholecystectomy (Shoenfeld, 2004).

Renzapride (mixed 5-HT₄ agonist and 5-HT₃ antagonist) has been evaluated in IBS treatment. As a 5-HT₄ agonist, it might stimulate gastrointestinal and colonic contractions and transit. Evidence of a potentially favorable outcome in the treatment of IBS with renzapride is based on Phase IIb trials in constipated IBS or mixed-symptom IBS. A dose-related acceleration of colonic transit in constipated IBS patients and an improvement in stool consistency and passage have been demonstrated after two weeks of treatments (Camilleri et al, 2004).

**Obesity**

Central biogenic amine systems have long been studied for their effects on feeding behavior, energy balance, and maintenance of body weight. Those monoaminergic systems that use dopamine, norepinephrine and serotonin as neurotransmitters have been the main targets of study. A number of antiobesity medications that affect monoaminergic activity have appeared on the market and/or in clinical trials. Early examples of such agents are the so-called CNS stimulants, e.g., the amphetamines, phentermine, ephedrine, etc. These agents release monoamines from neuronal stores, and their antiobesity activity seems to be tied most closely to their ability to release NE. Inhibitors of neuronal reuptake of NE or 5-HT have been shown to reduce feeding and weight gain both preclinically and clinically. However, the magnitude and sustainability of such effects in clinical trials has generally not been great enough to register or label these agents for the treatment of obesity. Sibutramine, however, is an exception. This compound is metabolized in vivo to produce metabolites that have varying degrees of inhibition of NE, 5-HT, and/or DA uptake. Sibutramine is the only drug affecting monoaminergic systems currently approved for the
long-term control of obesity. Research continues on serotonergic and histaminergic systems to determine if targets such as the 5-HT$_{2C}$ and H$_3$ receptors may be suitable for developing antiobesity agents. Because the clinical antiobesity effects of monoaminergic drugs have been modest, future directions include looking at combinations of different monoaminergic mechanisms and/or combinations of monoaminergic drugs with non-monoaminergic mechanisms. Nelson and Gehlert, 2006).

In light of the extensive data supporting the therapeutic potential of 5-HT$_{2C}$ receptor agonists for the treatment of obesity, numerous reports on the development of 5-HT$_{2C}$ receptor agonist compounds have appeared in the literature in recent years. Research efforts at several pharmaceutical companies have resulted in the identification of potent and subtype-selective 5-HT$_{2C}$ receptor agonists with promising properties as potential antiobesity agents. (Nilsson, 2006)

![Chemical structures of some anorectic drugs and 5-HT$_{2C}$ agonist](image)

**Fig.16** Chemical structures of some anorectic drugs and 5HT$_{2C}$ agonist (Smith et al, 2006)
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