Pharmacology of Serotonin and Its Receptors

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Abstract

Serotonin (5-hydroxytryptamine) is found in platelets, neuronal bodies, and with higher concentrations in GIT enterochromaffin cells and lesser amount in the brain. Serotonin is responsible for various secondary actions as it is one of the most important neurotransmitters in the CNS. It comprises seven families, namely 5-HT_1 to 5-$HT_{6,}$ which are further divided into different subfamilies. 5-HT is associated with the pathophysiology of many diseases including vomiting, IBS, anxiety, schizophrenia, depression, hypertension, migraine, obsessive-compulsive panic disorders, eating disorders, and carcinoid diarrhea. The present chapter gives emphasis on the action of serotonin on different physiological systems via the serotonin receptors along with their receptor pharmacology, including the agonists, antagonists, and SSRIs.

Keywords

Serotonin · 5-hydroxytryptamine (5HT) · Serotonin receptors · SSRIs

Abbreviations

5-CT	5-Carboxamidotryptamine
5-HIAA	5-Hydroxyindoleacetic acid

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5-HTT	5-Hydroxytryptophan transporter
5-HTTP	5-Hydroxytryptophan
8-OH DPAT	8-Hydroxy-di-N-propylamino tetralin
AC	Adenylyl cyclase
Ach	Acetylcholine
ACTH	Adrenocorticotrophic hormone
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CSF	Cerebrospinal fluid
DAT	Dopamine transporter
DOB	2,5-Dimethyl-4-bromoamphetamine
DOI	2,5-Dimethoxy-4-iodoamphetamine
GABA	Gamma-aminobutyric acid
GIT	Gastrointestinal tract
IBS	Irritable bowel syndrome
IL	Intracellular
IM	Intramuscular
IV	Intravenous
MAO	Monoamine oxidase
MAT	Monoamine transporter
MH	Malignant hyperthermia
NE	Norepinephrine
NET	Norepinephrine transporter
NO	Nitric oxide
PAH	Pulmonary arterial hypertension
PL_A	Phospholipase A
PL_C	Phospholipase C
PNS	Peripheral nervous system
PPH	Primary pulmonary arterial hypertension
SERT	Serotonin transporter
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TM	Transmembrane
UTI	Urinary tract infection

6.1 Introduction

Serotonin is a chemical messenger that is available in each tissue of the human body as well as identified in plants and aerobic organisms like bacteria. Serotonin is a ubiquitous monoamine acting as a neurotransmitter and hormone (Mohammad-Zadeh et al. 2008), which is also recognized as 5-hydroxytryptamine (5-HT) (Shad 2017). Serotonin was first independently recognized in the late 1940s in the USA and Italy. At that time it was known as "Serotonin" in the USA and "Enteramine" in Italy. In 1950, it was confirmed that the structure of both the compounds were same. In the mid-1950s, serotonin was identified in the brain of animals (Glennon and

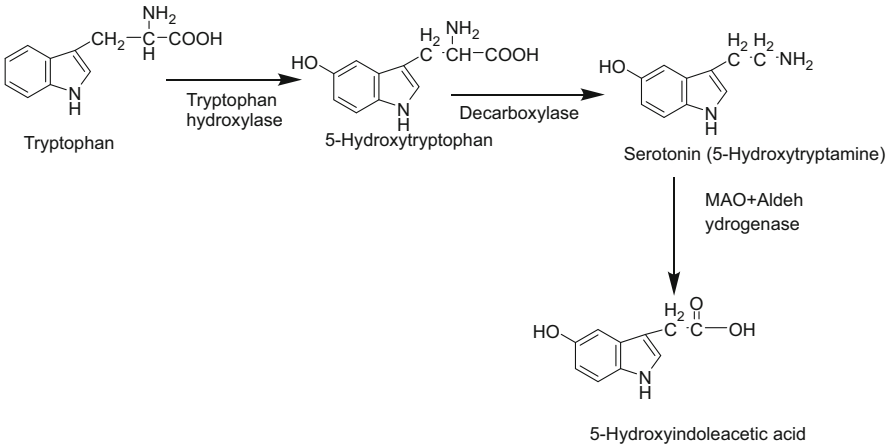

Fig. 6.1 Synthesis and degradation of serotonin (5-hydroxytryptamine) (Sources: Pytliak et al. 2011)

Dukat 2002). It is also found in the platelets, neurons, and GIT (enterochromaffin cells of the GIT mucosa). Over 90% (Shajib and Khan 2015) of the total amount in the body is present in the enterochromaffin cells of the gut and a lesser amount in the brain and retina (Pytliak et al. 2011; Peterlin and Rapoport 2007). In the brain, cell bodies of serotonergic neurons are mostly located in the brainstem midline with broad axonal ridge to all areas of the CNS (Peterlin and Rapoport 2007). Serotonin is associated with various diseases like schizophrenia, anxiety, depression, hypertension, migraine, carcinoid diarrhea, vomiting, irritable bowel syndrome, pulmonary hypertension, and eating disorders (Pauwels 2003; De Ponti 2004).

Serotonin secreted by the nuclei in the median raphe of CNS is transferred toward the spinal cord and other parts of the brain including the hypothalamus. Serotonin discharged from the enterochromaffin cells of GIT finds it own way out of the tissues into the blood, where it is taken up by the blood platelets (Zarrindast et al. 2014). Serotonin synthesis depends on two factors: (1) accessibility of tryptophan which is an amino acid obtained on or after nutritional ingestion, and (2) the action of rate-limiting enzymes tryptophan hydroxylase (Peterlin and Rapoport 2007). Serotonin synthesis starts through active uptake of tryptophan in neurons and enterochromaffin cell by use of amino acid transporters (Pytliak et al. 2011; Upadhyay 2003). Initially, in the presence of tryptophan hydroxylase, tryptophan is converted into 5-hydroxytryptophan, which is finally converted into 5-hydroxytryptamine (serotonin) with the help of aromatic L-amino acid decarboxylase (Fig. 6.1) (Berger et al. 2009). Serotonin is mainly degraded through oxidative deamination, catalyzed by monoamine oxidase A (MAO A), and followed by oxidation to 5-hydroxyindoleacetic acid (5-HIAA) (Ni and Watts 2006). In the brain, it is protected from enzymatic degradation by storing in synaptic vesicles of neurons. When 5-HT is released from the storage vesicles, it is either metabolized into 5-HIAA or reuptaken into the presynaptic

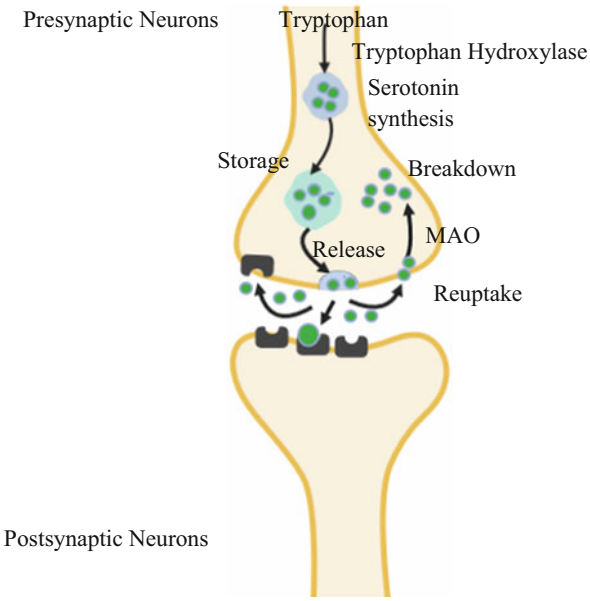

Fig. 6.2 Steps involved in synthesis and degradation of serotonin

neurons by the serotonin transporter (5-HTT or SERT) (Fig. 6.2) (Hamel and Currents 2007).

Serotonin possesses trophic factors in the early stages of pregnancy in humans. Serotonin secreted in mother's enterochromaffin cells of the GIT moves to the platelets in mother's blood. In the meantime from early stage of pregnancy, the fetus additionally begins its own 5-HT secretion process in the nuclei of the midbrain. After distribution of 5-HT by serotonergic neurons through the body and brain of the fetus, it expands division, relocation, and development of peripheral and central tissues (Shad 2017). Serotonin has vast numbers of physiological activity like modulation of platelet aggregation, contraction of vascular and nonvascular smooth muscle, regulation of appetite, mood, anxiety, controlling of body temperature, wakefulness, perception of sexual behavior, and hormone secretion (Upadhyay 2003; Kroeze et al. 2002). Serotonin and its receptors play a significant role in the functioning of the brain and therefore, dysregulation of serotonin system leads to various psychiatric and neurological disorders (Berger et al. 2009).

Serotonin, a notable neurotransmitter in the CNS, also plays a significant role in peripheral tissues as well as in immunity. The growing human body is the proof of recommending that a wide range of immune cells express the mechanism to create, store, react, and transport serotonin, including mast cells, T cells, macrophages, platelets, and dendritic cells. Moreover, there is rising evidence of a possible association between mood disorder, serotonin, and T cells. However, it is not clear how serotonin associates with immunity (Wu et al. 2019).

6.2 Action of Serotonin in Physiological Systems

6.2.1 Cardiovascular System

Acting on 5-HT_2 receptors, 5-HT causes narrowing of vascular smooth muscle. Although serotonin acts as a vasoconstrictor, in the heart and skeletal muscle it acts as a vasodilator. Serotonin releases adrenaline from the adrenal medulla, which affects ganglionic transmission and elicits cardiovascular reflexes. Serotonin has positive inotropic and chronotropic activities on the heart, which may be blunted by concurrent incitement of afferent nerves from baroreceptors and chemoreceptor. On vagus nerve endings, activation of 5-HT_3 receptors evokes the Bezold-Jarisch reflex which causes hypotension and bradycardia. On arterial blood vessels serotonin shows inhibitory action, which causes endothelial nitric oxide production, synthesis of prostaglandin, and obstruction of NE release from sympathetic nerves (Sibley et al. 2018; Tripathi 2013; Katzung 2018).

6.2.2 GIT

The direct action of serotonin on 5-HT_2 smooth muscle receptors of GIT causes enhancing tone and facilitates peristalsis movement. In the enteric nervous system, activation of 5-HT_4 receptors causes increased release of acetylcholine. Serotonin inhibits gastric secretion but increases mucous production. Overproduction of serotonin in carcinoid tumors causes severe diarrhea (Katzung 2018). Serotonin is also involved in digestion right after food enters the body. Actuation of taste bud cells on the tongue causes serotonin release onto sensory afferent nerves that move the taste information to the CNS. When food enters in the GIT, serotonin regulates the peristaltic movement and secretions. Modified 5-HT signaling has been concerned in bowel disorders like irritable bowel syndrome (IBS) (Gershon and Tack 2007) and is efficiently treated by the medication targeting both 5-HT_3 and 5-HT_4 receptors. Excessive serotonin secretion in GIT can also activate the 5-HT_3 receptors present in afferent vagal nerves that innervate vomiting center present in the brainstem, which also justifies why 5-HT_3 antagonists like ondansetron are valuable antiemetic (Berger et al. 2009).

6.2.3 Nervous System

Serotonin shows a significant feature in the development of the brain (Nordquist and Oreland 2010). In the CNS, serotonergic neurons secrete serotonin which influences various functions like temperature regulation, appetite, mood, hormone secretion, cognition, sensory perception, and motor activity (Shajib and Khan 2015). A decrease in serotonin levels leads to various psychiatric disorders like depression, suicidal tendency, and violence. Notably, females are more prone to depressive disorders than males, because the rate of serotonin synthesis is only about half of

that in males. Depressive disorders are prominent in aged person which may be because of less serotonin synthesis (Sibley et al. 2018).

6.2.4 Respiratory System

Serotonin has stimulant effect on smooth muscles of bronchiole through 5-HT_{2A} receptors. It enhances acetylcholine secretion from bronchial vagal nerve endings. Usually, serotonin possesses hyperventilation but excess doses cause transient apnea through coronary chemoreflex. Serotonin causes relaxation and constriction of bronchi and bronchioles (Katzung 2018). Augmenting the release of Ach or releasing Ach from activated cholinergic nerves causes bronchoconstriction (Cazzola and Matera 2000).

6.2.5 Platelets

In platelets, the synthesis of serotonin does not occur but expresses the mechanisms for serotonin uptake, storage, and exocytotic release. Serotonin promotes platelet aggregation by binding to the platelet $5HT_{2A}$ receptors. Serotonin released from adherent platelets causes vasodilation, when the endothelium is undamaged, aiding proper blood flow, whereas in damaged endothelium serotonin causes constriction and further impairs the blood flow. These impacts of platelet-derived 5-HT are believed to be significant in vascular disease (Sibley et al. 2018; Rang et al. 2016).

6.3 Role of Serotonin

The various roles of serotonin are highlighted in Fig. 6.3.

6.3.1 Neurotransmitter

Serotonin is a neurotransmitter present in different parts of the brain. Serotonin is concerned with the regulation of sleep, temperature, mood, behavior etc., and the imbalance of serotonin causes different diseases like schizophrenia, depression, and anxiety (Tripathi 2013).

6.3.2 Malignant Hyperthermia (MH)

The episodes of MH can be activated by ecological stress such as heating, exercise, excitement, and anxiety. Some investigations performed on pigs specify that the sympathetic nervous system is concerned in MH as a minor response. Stresses like environmental, exercise, and heating also increase serotonin release in the CNS and distribute serotonin levels in blood, which induces MH (Wappler et al. 2001).

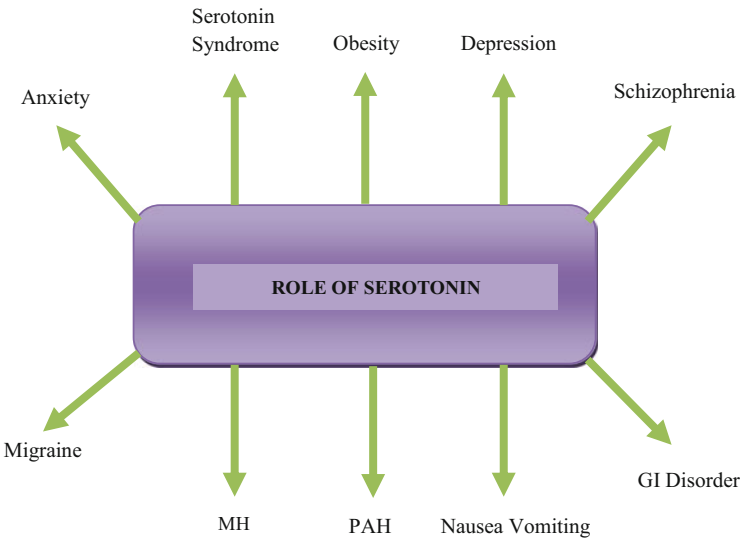

Fig. 6.3 Role of serotonin

6.3.3 Pulmonary Arterial Hypertension (PAH)

Serotonin increases pulmonary vascular smooth muscle cell proliferation, which causes pulmonary arterial vasoconstriction. Changes of serotonin yield cause increasing amount of free serotonin in the surrounding area of the pulmonary artery wall, which is an important pathophysiological process for the development of PAH. There are some conditions where changes in serotonin amount cause PAH such as increasing plasma concentration of free serotonin by lesser serotonin platelet storage, PPH patients with transplantation of the heart or lung, genetic defects in serotonin platelet storage, and low platelet count with PPH patients (Maclean et al. 2000).

6.3.4 Nausea and Vomiting

Serotonin plays an important role in nausea and vomiting induced by chemotherapeutic agents or antineoplastic agents. Vagal-dependent pathway is considered as the main mechanism to initiate vomiting after administration of antineoplastic agents (Hesketh 2008). Vomiting is activated when afferent impulses from the cerebral cortex to the vomiting center (located in medulla) travel through pharynx and vagal afferent nerves of the GIT. Efferent nerve impulses at that point make a journey from the vomiting center to the stomach muscles, salivary gland, cranial nerves, and respiratory system which cause vomiting. Chemotherapeutic agents cause vomiting by activation of neurotransmitters like serotonin, Ach, GABA situated in the chemoreceptor trigger zone, GIT, and vomiting center (Navari 2013).

6.3.5 Cancer

Recently it has been found that serotonin plays an important role in human tumor cells of different origins like glioma, carcinoid, and carcinomas. Serotonin is involved in the migration of cancer cells, tumor angiogenesis, and metastatic dissemination. Different studies show that the levels of serotonin play a major role in cancer cell growth (Sarrouilhe and Mesnil 2019).

6.3.6 Intestinal Motility and IBS

Serotonin has an important role in normal and dysfunctional GIT motility. Serotonin receptors especially 5-HT_3 and 5-HT_4 receptors are targeted to treat various GIT motility disorders. Different studies have been performed on rat to investigate the relevance of serotonin with colonic motility (Kendig and Grider 2015). Serotonin is a significant flagging particle in the gut particularly in enterocytes, smooth muscles, and enteric neurons. Most of the body serotonin is available in enterochromaffin cells. Serotonin promotes the activation of extrinsic and intrinsic afferent neurons to start the peristaltic and secretary reflexes and convey information to the CNS. Serotonin is reuptaken by the serotonin transporter (SERT) in the enterocytes or neurons. Exogenous serotonin application inspires such a large number of responses that it is hard to figure out which is physiologically relevant. This impact is to a great extent because of the nearness of multiple receptor subtypes, which seem, by all accounts, to be available on a few classes of myenteric neurons, on smooth muscle cells, and on epithelial cells. IBS is an unpredictable issue that is associated with altered gastrointestinal motility, discharge, and sensation. Changed serotonin signaling may prompt both intestinal and extraintestinal frameworks in IBS (Sikander et al. 2009).

6.3.7 Obesity

Serotonin receptors present in the CNS are related with the parameter of food ingestion leading to obesity (Thomsen et al. 2008). The capacity to store and prepare vitality is essential for physiologic capacity. Overabundance vitality is put away in fat tissue as triglycerides, which is discharged as free unsaturated fats when required, through cell forms firmly managed by insulin. Fat cell functioning is required to regulate the metabolism of lipid and body glucose level. Studies have been conducted to understand the effect of 5-HT on lipid digestion and glucose homeostasis and cytokine emission (Fex and Stenkula 2019). Obesity increases the risk of various diseases like diabetes mellitus, congestive heart failure, coronary heart diseases, stroke, hypertension, and osteoarthritis (Smith et al. 2009).

6.3.8 Migraine

Migraine pain is the most continuous neurological issue in the growing population around the world, influencing up to 12% of the all inclusive community and more common in women about 25%. It highly affects the general public because of its crippling nature and in that, decreased personal satisfaction and expanded absence from work. Cerebral pain is the essential clinical sign and it has been related with hereditary affectability of neurovascular responses to specific improvements or to cyclic changes in the central nervous system. Among the numerous synapses in the brain, the serotonergic system (5-HT) from the brainstem raphe core has been most convincingly ensnared in migraine pathophysiology. The changes in metabolism of serotonin and serotonin-mediated responses during the migraine pain recommend that migraine pain is a result of a central neurochemical imbalance that includes a low serotonergic character, although the correct flow between serotonergic neurotransmission to the sign and symptoms of migraine pain is still not completely understood (Hamel and Currents 2007).

6.4 Classification of Serotonin Receptors

Gaddum and Picarelli proposed the arrangement of 5-HT receptors in 1957, when it was exhibited that practical reactions of the guinea pig ileum could be mostly obstructed by morphine (M); at the same time the rest of the reaction can be obstructed by dibenzyline (D) and named them as M and D receptors, respectively (Göthert 2013).

Presently serotonin receptor families are classified into seven families (Table 6.1) naming 5-HT_1 to 5-HT_6. All classes are G-protein-coupled receptors (GPCRs)

Table 6.1 5-HT families and mechanisms

Family	Type	Mechanism of action	Signaling effect
5-HT_1	Gi/G_0-protein coupled	Decreasing intracellular concentration of cAMP	↓AC
5-HT_2	Gi/o-protein coupled	Increasing intracellular concentration of phospholipase A_2 and arachidonic acid	↑PL_C, PL_A
5-HT_3	Ligand-gated Na^+/K^+ channel	Depolarization of cell plasma membrane	Cations
5-HT_4	Gs-protein coupled	Increasing intracellular concentration of cAMP	↑AC
5-HT_5	Gi/G_0-protein coupled	Decreasing intracellular concentration of cAMP	↓AC
5-HT_6	Gs-protein coupled	Increasing intracellular concentration of cAMP	↑AC
5-HT_6	Gs-protein coupled	Increasing intracellular concentration of cAMP	↑AC

Sources: Pytliak et al. (2011), Leysen (2004), Sibley et al. (2018)

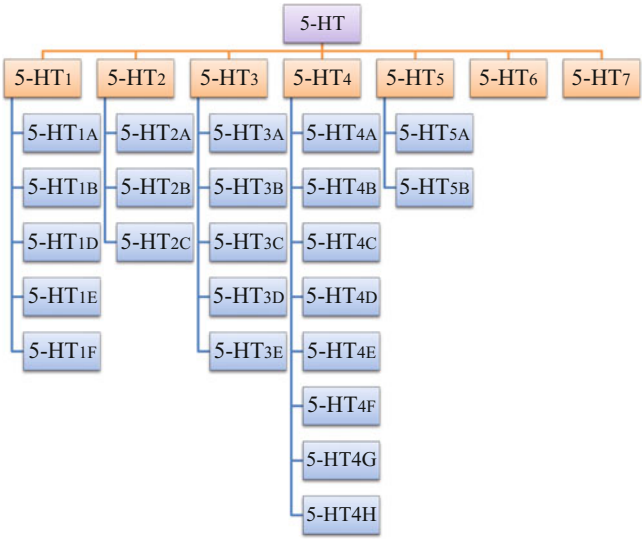

Fig. 6.4 Families and subfamilies of 5-HT

except 5-HT_3 receptor which is a ligand-gated ion channel (Kroeze et al. 2002). Based on sequence and pharmacological activity, all 5-HT receptors are further subdivided (Fig. 6.4) through alternative splicing, RNA editing, etc. (Barnes and Sharp 1999).

6.5 5-HT Receptors and Subfamilies

6.5.1 5-HT_1 Receptors Subfamily

The 5-HT_1 receptor is the largest class of 5-HT receptor, which has five subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} (Fig. 6.4). All the subfamilies of 5-HT_1 receptor show high affinity for the synthetic agonist, 5-carboxamidotryptamine (5-CT), except 5-HT_{1E} and 5-HT_{1F} receptors (Lanfumey and Hamon 2004). The mechanism of these receptors is to decrease adenylyl cyclase (AC) and cAMP levels by pairing to Gi/o protein. Additionally signal transduction mechanisms also have been described (Pytliak et al. 2011).

6.5.1.1 5-HT_{1A} Receptors

Mostly 5-HT_{1A} receptors are dispersed in the CNS, like in axon hillock of neurons, soma, dendrites, and the cell body. 5-HT_{1A} receptors control the production of adrenocorticotrophic hormone (ACTH) but they do not regulate prolactin discharge (Wang et al. 2009). In humans, 5-HT_{1A} receptor possesses a number of physiological and behavioral effects like aggression, anxiety, addiction, and appetite. They also regulate cardiovascular functions, heart rate, blood pressure, pupil dilation, and

Table 6.2 5-HT subtypes, their agonists and antagonists

Subtype	Localization	Agonists	Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus	Buspirone, 8-OH-DPAT	WAY 100135, Spiperone
5-HT_{1B}	Subiculum, globus pallidus, substantia nigra, basal ganglia	Sumatriptan, Methysergide, Zolmitriptan	GR-55562
5-HT_{1D}	Cranial vessels,globus pallidus, substantia nigra	Sumatriptan, Eletriptan	SB714786
5-HT_{1E}	Cortex, striatum	-	-
5-HT_{1F}	Dorsal raphe, hippocampus, periphery	Eletriptan, Naratriptan	-
5-HT_{2A}	Platelets, smooth muscle, cerebral cortex	α – CH_3-5HT, DOI	Ketanserin, Cyproheptadine, Methysergide, LY53857
5-HT_{2B}	Stomach fundus	α – CH_3-5HT, DOI	LY53857
5-HT_{2C}	Choroid plexus, substantia nigra, basal ganglia	α-Methyl-5-HT, Aripiprazole, Ergonovine, Lorcaserin	LY53857, Cyproheptadine, Methysergide, Mesulergine
5-HT_3	Parasympathetic nerves, solitary tract, area postrema, GI tract	2-CH_3-5HT,Quipazine	Ondansetron, Tropisetron
5-HT_4	Hippocampus, striatum, GI tract	Cisapride, Tegaserod, Prucalopride, Renzapride, Metoclopramide	GR113808
5-HT_{5A}	Cortex, hippocampus	-	SB-699551
5-HT_6	Hippocampus, striatum, nucleus accumbens	WAY-181187	SB-271046
5-HT_6	Hypothalamus, hippocampus, GI tract	5-CT, LP-12	SB-269970, Clozapine

Source: Pytliak et al. (2011), Katzung (2018), Sibley et al. (2018)

vasoconstriction (Glennon and Dukat 2002). The quantity of 5-HT_{1A} receptors is high in hippocampus, limbic area, lateral septum, cortical area, and also in raphe nuclei. But in cerebellum and basal ganglia, binding sites are rarely found. Some selective agonists of 5-HT_{1A} are Gepirone, Dipropyl-5-CT, 8-OH-DPAT, etc. (Table 6.2) (Barnes and Sharp 1999).

6.5.1.2 5-HT_{1B} Receptors

The 5-HT_{1B} receptors are available on axon terminal of non-serotonergic and serotonergic neurons. They reduce the discharge of neurotransmitters, including gamma aminobutyric acid (GABA), serotonin, acetylcholine, glutamate, and noradrenaline. 5-HT_{1B} receptors are available in different parts of the brain but mostly found in the frontal cortex, basal ganglia, and striatum. 5-HT_{1B} receptors are also

found on cerebral arteries and additional vascular tissues mediate vasomotor properties of 5-HT (Lanfumey and Hamon 2004).

6.5.1.3 5-HT$_{1D}$ Receptors

By using the radioligand technique, 5-HT$_{1D}$ receptors were identified in the CNS and broadly dispersed in the brain. They inhibit AC and paired with G-protein. They are involved in locomotion and anxiety. However, clinical significance of 5-HT$_{1D}$ receptors remains still largely unknown (Glennon and Dukat 2002).

6.5.1.4 5-HT$_{1E}$ Receptors

The role of 5-HT$_{1E}$ receptor is still unidentified because of the deficiency of selective animal models, specific antibodies, and pharmacological tools. Hypothetically based on their distribution in the brain like olfactory bulb, frontal cortex, and hippocampus, 5-HT$_{1E}$ receptor regulates memory. The gene of 5-HT$_{1E}$ receptor is composed of 365 amino acids and located in chromosome position 6q14-q15. Higher amount of receptor distribution is found in cortex, claustrum, and caudate putamen but lesser amount is observed in amygdala and hippocampus (Barnes and Sharp 1999).

6.5.1.5 5-HT$_{1F}$ Receptors

The 5-HT$_{1F}$ receptors are mostly mRNA recognized in the cortex, dorsal raphe, hippocampus, hypothalamus, striatum, and thalamus of the human brain. From its distribution it suggests that it may act as a 5-HT autoreceptor (Hoyer et al. 2002). There were no selective ligands for the 5-HT$_{1F}$ receptors, but recently two agonists are found, i.e., LY344864 and LY334370. Depending on the anatomical location where the 5-HT$_{1F}$ receptors are present, they play an important role in cognitive and visual functions (Barnes and Sharp 1999).

6.5.2 The 5-HT$_2$ Receptor

The 5-HT$_2$ receptor is a G-protein-coupled receptor and shows a typical heptahelical structure (Leysen 2004). The 5-HT$_2$ receptors have three subtypes, i.e., 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors (Fig. 6.4); they are coupled to Gi/o. The three 5-HT$_2$ receptor subtypes trigger phospholipase A_2 and promote the discharge of arachidonic acid (Leysen 2004). The families of 5-HT$_2$ receptor have different regional distributions within the brain. Therefore each subtype may be capable of mediating definite physiological functions (Knight et al. 2004). The 5-HT$_2$ receptors have showed various roles in CNS disorders like eating patterns, and influence sleep, migraine, schizophrenia, depression, and anxiety (Knight et al. 2004).

6.5.2.1 5-HT$_{2A}$ Receptor

Both centrally and peripherally 5-HT$_{2A}$ receptors occur. They are found in postsynaptic nonserotonergic neurons in the claustrum, olfactory nuclei, basal ganglia, and neocortex of the CNS. They inhibit the release of neurotransmitter like dopamine, glutamate, noradrenaline, and acetylcholine (Naughton et al. 2000). They also

regulate the endocrine responses like secretion of ACTH, corticosterone, oxytocin, renin, and prolactin (Bortolozzi et al. 2005; Feng et al. 2001). 5-HT_{2A} receptors are peripherally found in bronchial, urinary, platelets, and vascular smooth muscle tissues. They cause platelet aggregation, bronchoconstriction, and vasoconstriction. 5-HT_{2A} receptors are concerned in various CNS diseases like migraine, anxiety, depression, schizophrenia, psychosis, and hypertension (Naughton et al. 2000).

6.5.2.2 5-HT_{2B} Receptors

The mRNA of 5-HT_{2B} receptors is found in the human brain. In the brain, 5-HT_{2B} receptors are observed in dorsal hypothalamus, lateral septum, cerebellum nuclei, medial amygdala, and also in the nucleus of dorsal raphe. Along with the brain, these receptors are also found in the intestine, stomach, myocardium, and pulmonary smooth muscles (Leysen 2004). On cerebral arteries of endothelial cells, stimulation of 5-HT_{2B} receptors leads to the secretion of nitric oxide, which causes vascular relaxation in arteries. These vascular relaxations of cerebral arteries lead to migraine headache (Schmuck et al. 1996). Activation of 5-HT_{2B} receptors produces pulmonary hypertension on pulmonary arteries (Launay et al. 2002). In GIT, 5-HT_{2B} receptors cause hypersensitivity induced by serotonin in colonic smooth muscle. These receptors also involved in the IBS, cardiac valvulopathy, and neuroendocrine malignancy (Leysen 2004).

6.5.2.3 5-HT_{2C} Receptors

The mRNA and protein of 5-HT_{2C} receptors are observed in striatum, thalamic nuclei, brain stem nuclei, spinal cord, hippocampal formation, septal nuclei, midbrain nuclei in high amount (Leysen 2004). 5-HT_{2C} is quite similar to 5-HT_{2A} receptors; they show high homologous series of amino acids and also coupled to phosphoinositol hydrolysis. Some studies reported that in migraine, 5-HT_{2C} receptors have greater role than 5-HT_{2A} receptors. 5-HT_{2C} receptors are applied in the treatment of schizophrenia, drug abuse, urinary incontinence, Parkinson's disease, obesity, anxiety, depression, etc. Lorcaserin and WAY-163909 are the examples of 5-HT_{2C} receptor agonists, which are used in the treatment of obesity (Glennon and Dukat 2002).

6.5.3 5-HT_3 Receptors

The 5-HT_3 receptor is only 5-HT receptor which is a part of ionotropic ligand-gated ion channel. The structure and functions of 5-HT_3 receptors resemble the members of the cys-loop ligand-gated ion channel family (Thompson and Lummis 2007). The receptors are recognized on neurons of both central and peripheral origin, where they produce quick depolarization because of a transient internal current, resulting in the opening of nonselective cation channels (Na^+, Ca^{++} influx, K^+ efflux). 5-HT_3 receptors cause vomiting and nausea during radiotherapy and chemotherapy process, which are treated with 5-HT_3 antagonist like ondansetron, granisetron, tropisetron, palonosetron, and dolasetron (Table 6.2) (Hoyer et al. 2002; De Ponti 2004). At

higher concentration 5-HT_3 receptors are present in the brainstem especially in nucleus tractus solitarius and postrema, which are involved in the process of vomiting. The 5-HT_3 receptors are available in postsynaptic and presynaptic neurons and activation can regulate the release of neurotransmitters like GABA, dopamine, acetylcholine, and substance P (Lummis 2012). These receptors also control GIT secretion, motility, and peristalsis in enteric nervous system and also are involved in information transfer in the GIT (Galligan 2002). 5-HT_3 receptors have five subunits, i.e., 5-HT_{3A} to 5-HT_{3E} (Fig. 6.4). The structure of subunits differ from each other like 5-HT_{3A} varies with 32 amino acids, 5-HT_{3B} varies with three translational variants, and 5-HT_{3E} with five isoforms. 5-HT_3 receptor antagonists are used not only to treat chemotherapy-induced nausea and vomiting but also useful in the treatment of IBS, ischemic colitis, bipolar disorder, anorexia, anxiety etc. (Lummis 2012).

6.5.4 5-HT_4 Receptors

In the CNS, 5-HT_4 receptors alter neurotransmitter (dopamine, acetylcholine, GABA, and serotonin) discharge and increase synaptic diffusion. They may likewise assume a role in memory upgrade; in any case, positive clinical investigations are still energetically anticipated (Hoyer et al. 2002). 5-HT_4 receptors are subdivided into seven subtypes, i.e., 5-HT_{4A}-5-HT_{4H} (Fig. 6.4), which are coupled to Gs to activate AC and increase cAMP production (Sibley et al. 2018), though all subtypes contain analogous pharmacological activity and connected with AC activity (Pauwels 2003). 5-HT_4 receptors are found in the septum, hippocampus, prefrontal cortex, and basal ganglia, which are related with cholinergic, glutamatergic, and GABAergic neuro-transmission (King et al. 2008). 5-HT_4 receptors are also available in the heart, bladder, enteric neurons, and smooth muscle cells of GIT. On activation of the receptor, acetylcholine releases from motor neurons and inter neurons; this increases the motility of GIT (Tack et al. 2012). Some examples of 5-HT_4 receptor agonists are cisapride, mosapride, renzapride, naropride, clebopride, and metoclopramide (Table 6.2) belonging to the benzamide groups. Besides benzamide group agonists, other 5-HT_4 agonists are tegaserod, velusetrag (TD-5108), prucalopride, etc. (Tack et al. 2012).

6.5.5 5-HT_5 Receptors

These receptors have two subfamilies, i.e., 5-HT_{5A} and 5-HT_{5B} (Fig. 6.4). They are coupled to Gi/o to inhibit AC. Humans only express functional 5-HT_{5A} receptors. From their regions, it has been theorized that they might be engaged with feeding, anxiety, motor control, depression, adaptive behavior, learning, memory consolidation, and brain expansion (Thomas 2006). Disturbance of 5-HT neuron-glial associations might be engaged with the advancement of certain CNS pathologies including Alzheimer's disease, Down's syndrome, and some drug-actuated

development deficits. After analyzing the location of chromosome, it was found that for human 5-HT_{5A} receptors: position 7q36 and chromosome 7; 5-HT_{5B} receptors: position 2q11–13, chromosome 2. 5-HT_{5A} consists of 357 amino acids but in 5-HT_{5B} receptor, end codons are present in the gene. Studies on 5-HT_{5A} and 5-HT_{5B} are very less among the other serotonin receptors (Nelson 2004).

6.5.6 5-HT_6 Receptors

It is the first receptor of 5-HT which is coupled to AC (Woolley et al. 2004) and increases cAMP intracellular level by pairing to Gs protein. 5-HT_6 receptors are located predominantly inside limbic and extrapyramidal cerebral zones in the CNS, which suggest that it is important for motor control and cognition (Sibley et al. 2018). The accurate scientific importance of 5-HT_6 receptors remains still indistinguishable. 5-HT_6 receptors have a role in learning and memory process. It also plays a role in obesity. Additionally, the 5-HT_6 receptors have been recommended to be concerned in psychotic disease such as epilepsy and anxiety (Kitson 2007). The 5-HT_6 receptor was first discovered in rats and humans in 1993 and 1996, respectively with the help of molecular biology. The 5-HT_6 receptor shows a unique pharmacological activity of high affinity toward antipsychotic molecules and tricyclic and atypical antidepressant molecule like clozapine, loxapine, amitriptyline, and mianserin. In 1998, first selective 5-HT_6 receptor antagonist was reported in humans, i.e., Ro04–6790; chemically it is 4-amino-*N*-(2,6-bis-methyl-amino-pyrimidin-4-yl)-benzene sulphonamide. Ro04–6790 has less penetration through BBB, but when 30 mg/kg dose intraperitoneal was given it showed 70% receptor occupancy from CSF levels (Woolley et al. 2004).

6.5.7 5-HT_7 Receptors

In human beings, 5-HT_7 receptors enhance the activation of AC by pairing to Gs protein. It is mainly distributed in the CNS (Sibley et al. 2018). 5-HT_7 receptors incite relaxation in human colonic smooth muscle and in the guinea pig ileum. 5-HT_7 receptors have a task in reducing the peristalsis by 5-HT. 5-HT_7 receptors are also expressed in extravascular GIT smooth muscles and CNS (De Ponti 2004). Recent studies have provided evidences on the modulation of 5-HT_7 receptors for the treatments of various CNS disorders like anxiety and depression. Also, the 5-HT_7 receptor agonist facilitates memory and has antiamnesic effects (Meneses 2015). AS-19, LP-44, and LP-211 are recently available as highly selective 5-HT_7 agonists (Ciranna 2006). The mRNA and protein of 5-HT_7 receptors, which are present in hypothalamic nuclei play a role in regulation of body temperature. 5-HT_7 receptors also regulate circadian rhythms and REM sleep (Thomas and Hagan 2004).

6.6 Clinical Pharmacology of Serotonin

6.6.1 5-HT Receptor Agonist

Azapirones like buspirone, gepirone, and ipsapirone are agonists of 5-HT_{1A} receptor which is partially active. These are used as anxiolytic drugs and may work on the autoreceptors to reduce serotonergic activity (Katzung 2018).

Dexfenfluramine (Fig. 6.5) is another agonist of 5-HT receptors, which is a selective agonist. It may be broadly used as a hunger suppresser but it was withdrawn due to cardiac valvulopathy (Katzung 2018).

Lorcaserin (Fig. 6.5) is approved for weight loss medication which is a 5-HT_{2C} agonist (Fig. 6.7) (Katzung 2018). The drug is thought to reduce food consumption and increase satiety by selectively activating $5HT_{2C}$ receptors on hypothalamus. Chemically lorcaserin is 1R-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzapine (Smith et al. 2009). In humans, lorcaserin shows 100-fold selectivity for 5-HT_{2C} versus the closely related 5-HT_{2B} receptor and 17-fold selectivity over the 5-HT_{2A} receptor (Thomsen et al. 2008; Smith et al. 2008). There is no useful action at additional 5-HT receptors when the concentration of lorcaserin is less than 1 micromol per liter. This leads to the minimal adverse effects than that of nonselective 5-HT receptor agonist (Smith et al. 2009). The clinical dose recommendation for 18 years and older patient of lorcaserin is 10 mg, two times in a day. On oral administration, lorcaserin absorbed rapidly greater than 90%. The C_{max} is about 1.5–2 h and $t_{1/2}$ is about 11 h. About 70% drugs are bound to plasma protein. Lorcaserin is metabolized in the liver and the main metabolite is lorcaserin sulfamate. It is excreted by the kidney through urine and the main metabolite is *N*-carbamoylglucuronides (Bai and Wang 2011). Common adverse effects are vomiting, nausea, diarrhea, constipation, fatigue, UTI, upper respiratory tract infections, rashes, headache, dizziness and back pain; memory and attention deficiency are also seen in 1.9% of patients (Brashier et al. 2014).

The 8-hydroxydipropylamino tetraline (8-OH DPAT) is an aminotetralin derivative and highly selective 5-HT_{1A} agonist. It is used as an experimental tool and not used therapeutically because of its low oral bioavailability (Tripathi 2013).

Sumatriptan and other triptans are selective 5-$HT_{1B/1D}$ agonist and effective to treat acute migraine pain attacks (Fig. 6.7). Migraine pain is a disease characterized by pulsating pain in the head lasting for 4–8 h and often associated with vomiting, nausea, sensitivity to sound and light, flashes of light, and other symptoms. Dilatation of certain cranial vessels causes migraine pain; selective 5-$HT_{1B/1D}$ agonists (triptans) constrict the dilated cerebral blood vessels. Triptans have three mechanisms of action which relieve the migraine pain. The mechanisms are by direct effect on vascular smooth cells which causes vasoconstriction of cranial vessels, reduction of nociceptive neurotransmission, and reduction of discharge of vasoactive neuropeptides (Tepper et al. 2002).

In 1984, Sumatriptan (Fig. 6.5) was discovered. It is the first selective 5-$HT_{1B/1D}$ agonist among the triptans. At first, it was introduced as injectable, followed by tablet, nasal spray, and suppositories (Dahlöf 2001). Sumatriptan demonstrates its

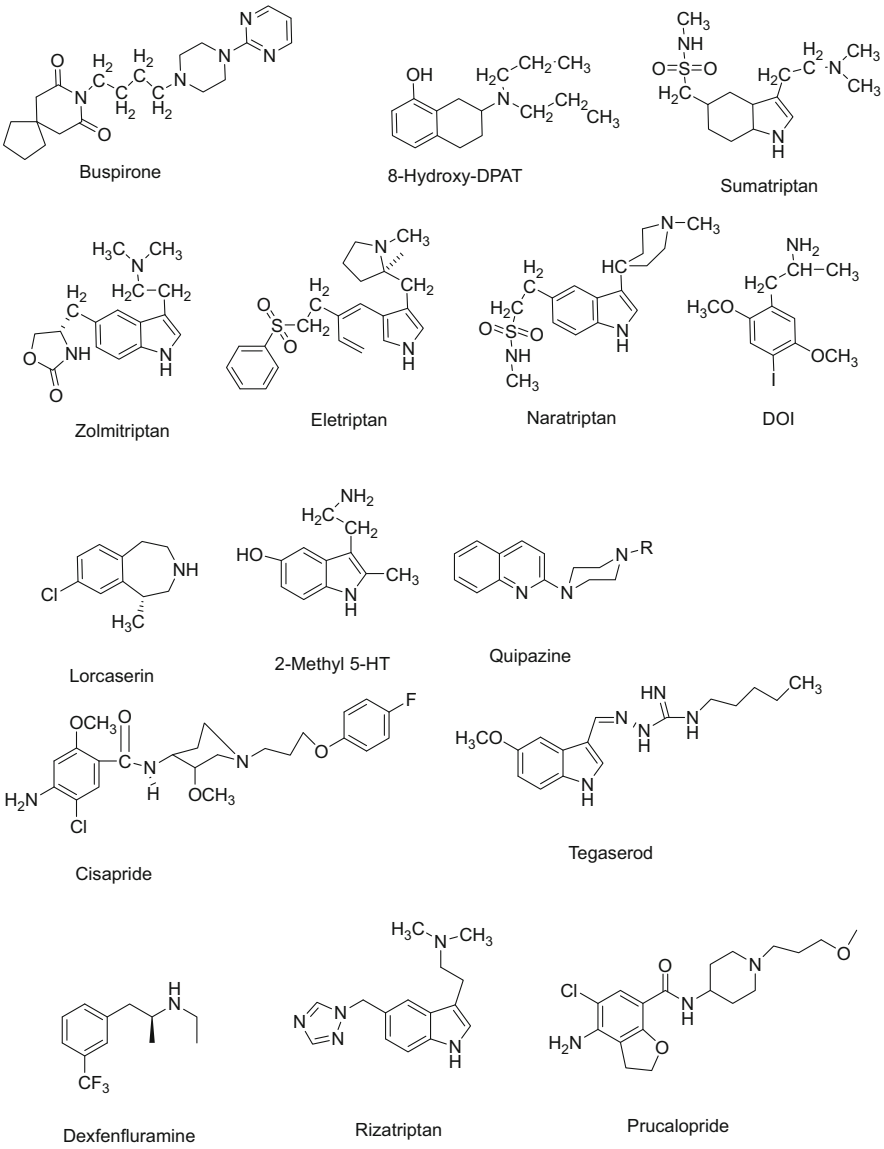

Fig. 6.5 5-HT receptor agonists (Sources: Glennon and Dukat 2002)

remedial impact by incitement of the $5HT_{1B}$ receptor on cranial vascular smooth muscle that causes vasoconstriction, which relieves the headache (Fuseau et al. 2002; Dahlöf 2001). Sumatriptan has definite limits like high headache reappearance, contraindications in patients with coronary artery disease, and low oral bioavailability (Villaln et al. 2003).

The bioavailability of sumatriptan is about 15% in intranasal, 14% after oral, and 96% after subcutaneous administrations. Incomplete absorption and presystemic metabolism cause low bioavailability. The therapeutic dose is 8–66 ng/ml. After subcutaneous administration C_{max} is 25 min and after oral or intranasal administration the C_{max} is 60–90 min. The $t_{1/2}$ is 1.5–2.6 h (Femenia-Font et al. 2005). Adverse effects of sumatriptan are difficulty and abnormal thinking, tiredness, dizziness, agitation, fatigue, tremor, vertigo, etc. (Dodick and Martin 2004).

Zolmitriptan (Fig. 6.5) is another Triptans which have higher oral bioavailability than sumatriptan, about 40% (Tepper et al. 2002). Chemically zolmitriptan is (*S*)4-[3-[2-dimethylamino-ethyl]-1*H*-indol-5-yl]methyl-2-oxazolidinone (Goads and Boes 2001). It is a selective 5-$HT_{1B/1D}$ receptor agonist. It is used effectively in the treatment of migraine and adolescent migraine (Lewis et al. 2007). It is also used in the treatment of cluster headache (Bahra et al. 2000). The $t_{1/2}$ is 3 h and T_{max} is 2 h. Zolmitriptan is metabolized in the liver and eliminated with cytochrome P_{450} pathways (Goads and Boes 2001).

Naratriptan (Fig. 6.5) has 60% more bioavailability than sumatriptan, greater lipophilicity, less readily metabolized, and better CNS penetration (Tepper et al. 2002). It belongs to triptans, a second-generation antimigraine drug. Naratriptan is 5-$HT_{1B/1D}$ receptor agonists. Chemically naratriptan is (*N*-methyl-3-1-methyl-4-piperidinyl)-1-H-indole-5-ethanesulphonamide hydrochloride. Among the orally administered triptans, naratriptans have highest bioavailability. The approximate dose is 35 microgram per Kg. The pharmacokinetics of naratriptan is that it has longest $t_{1/2}$ of about 5–6 h after oral administration. 70% of naratriptan eliminates unchanged; only a considerable part is subjected to P450 metabolism. Naratriptan has fewer side effects (Lambert 2005).

Rizatriptan (Fig. 6.5) has high bioavailability than sumatriptan, is more potent, and has a rapid onset of action (Tepper et al. 2002). Chemically rizatriptan is *N,N*-dimethyl-2-[5-(*1*H-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine. Metabolism of rizatriptan occurs in the liver by MAO-A. Rizatriptan-*N*-oxide and triazolomethyl indole-3-acetic acid are two major metabolites of rizatriptan; both are inactive. N-monodesmethyl-rizatriptan is a minor active metabolite of rizatriptan. After oral administration, bioavailability is 45%, C_{max} is 1–1.5 h, $t_{1/2}$ is about 2–3 h, and 14% bound to plasma protein. In 1998, the FDA approved rizatriptan and it is available as oral disintegrating tablets in a dose of 5 mg or 10 mg (Wellington and Jarvis 2002; Kacperski and O'brien 2012). Rizatriptan is used in the migraine with aura and migraine without aura treatment in adult patients (Wellington and Jarvis 2002).

Cisapride (Fig. 6.5) is a benzamide derivative (Crowell 2004) and it agonizes the 5-HT_4, which is used to treat GIT disorders like gastroesophageal motility and reflux (Fig. 6.7) (Katzung 2018). Cisapride speeds up the process of stomach emptying and intestinal passage but it has limitations on varying bowel functions. Some studies confirmed that it is used in chronic constipation. But nowadays it is available only for considerate use in the USA because of its toxicity like patient deaths and cardiac dysrhythmias (Crowell 2004).

Tegaserod (Fig. 6.5) is a partial agonist highly selective for the 5-HT_4 receptor (Camilleri 2001), which is used for IBS and constipation. It is an

indolecarbazimidamide (Tack et al. 2012), a new class of compound which shows GIT prokinetic effects (Crowell 2004). The chemical name of tegaserod is [3-(5-methoxy-1*H*-indole-3-ylmethylene)-N-pentyl-carboximidamide]hydrogen maleate (Müller-Lissner et al. 2001). After oral administration, tegaserod quickly absorbed and widely distributed in tissues. Presystemically, it is metabolized and excreted through bile as *N*-gluconides. From toxicity studies, it is confirmed that tegaserod is safe and there were no drug-drug interactions found clinically (Camilleri 2001). It is effective for the treatment of gastroesophageal reflux disease, lower bowel motility disorders, constipation, and predominant irritable bowel syndrome (Camilleri 2001).

Prucalopride (Fig. 6.5) is a benzofurancarboxamide (Tack et al. 2012), a newer 5-HT_4 agonist, stimulates peristalsis movement, and accelerates colonic transit (De Ponti 2004). It shows more potent laxative efficacy than tegaserod (Spiller 2002). Chemically prucalopride is (4-amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidinyl]-7 benzofurancarboxamidemonohydrochloride (Briejer et al. 2001). Prucalopride is quickly absorbed from GIT after oral administration. It is excreted by urine about more than 60% and through feces about 6%. The dose recommendation for elderly person is started with 1 mg daily and it may be increased to 2 mg daily if required (Frampton 2009).

Velusetrag (TD-5108) is 5-HT_4 agonist which has high affinity and selectivity. Velusetrag is a derivative of dihydroquinoline carboxylic acid. It is an effective stimulant of GIT motility. It is more potent than other 5-HT_4 agonist in stimulating colonic transit (Tack et al. 2012).

6.6.2 5-HT Antagonist

These are a variety of compounds, which block serotonergic receptors and antagonize the action. Some newly developed antagonists are described below:

Cyproheptadine (Fig. 6.6) has potent 5-HT_2 blocking action. The major clinical uses include management of the smooth muscle manifestations, carcinoid tumor, and cold-induced urticaria. It is used in children for increasing appetite and poor eater for weight gaining. Cyproheptadine also reduces muscle spasms following spinal cord (Hoyer et al. 2002) injury, in which constitutive activity of 5-HT_{2C} receptors is connected with rising Ca^{2+} currents leading to spasms. It has some side effects like dry mouth, drowsiness, weight gain, and confusion ataxia (Tripathi 2013).

Methysergide (Fig. 6.6) antagonizes some action of 5-HT on smooth muscles including blood vessels. It is a 5-$HT_{2A/2C}$ antagonist. It is used in migraine prophylaxis and in the treatment of carcinoid and postgastrectomy dumping syndrome. Long-term use causes abdominal, pulmonary, and endocardial fibrosis (Tripathi 2013). Clinically, methysergide is available in tablet form of 1 mg. Long-term uses of methysergide has adverse effects like pleura pulmonary fibrosis, fibrotic thickening, and retroperitoneal fibrosis (Dahlöf and Maassen Van Den Brink 2012).

Ketanserin (Fig. 6.6) is a 5-HT_2 receptor antagonist. Among 5-HT_2 receptors, ketanserin shows stronger blockade in 5-HT_{2A} than 5-HT_{2C}. It antagonizes

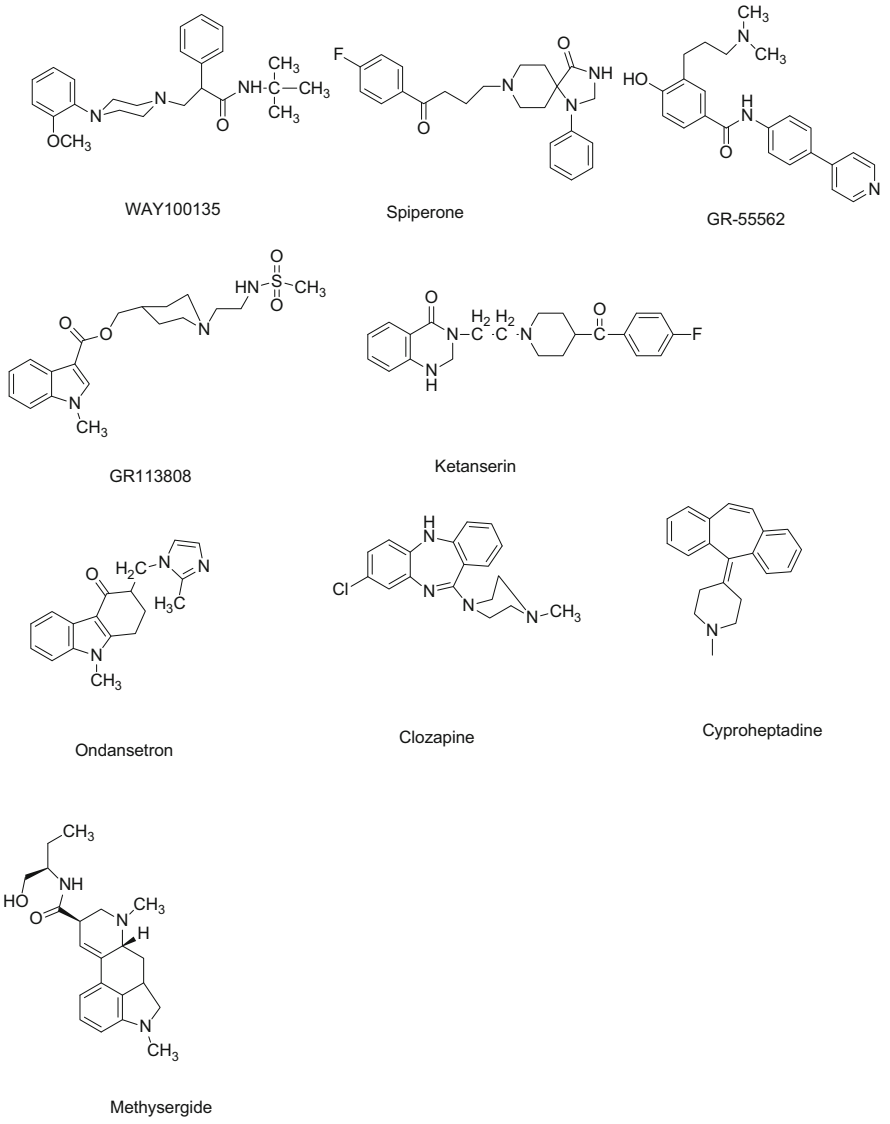

Fig. 6.6 5-HT receptor antagonists (Sources: Glennon and Dukat 2002)

vasoconstriction, platelet aggregation, and contraction of airway smooth muscles which are induced by serotonin. It is an effective antihypertensive drug (Katzung 2018). Another 5-HT_2 antagonist is ritanserin; it has no α-blocking action. It alters the bleeding time and reduces thromboxane formation (Katzung 2018).

Ondansetron (Fig. 6.6) is a newer selective 5-HT_3 antagonist, which has shown efficacy in controlling nausea and vomiting process of chemotherapy and radiotherapy of cancer (Fig. 6.7) (Katzung 2018). In the CNS region, ondansetron inhibits

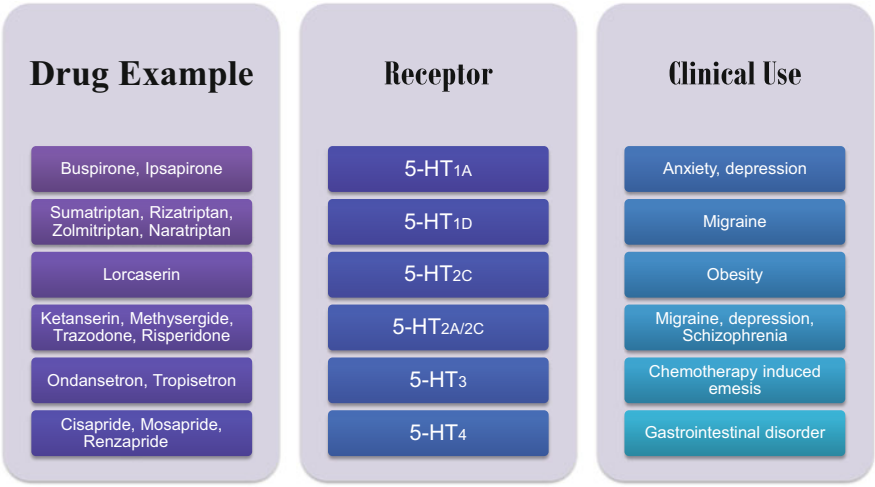

Fig. 6.7 Example of drugs with clinical uses

5-HT_3 receptors or antagonizes including the region of nucleus tractus solitarius, amygdala, postrema, and dorsal raphe nucleus. In the PNS, by antagonizing 5-HT_3 receptors, ondansetron blocks the myenteric neurons and depolarization of vagal afferent nerves, which cause a decrease of 5-HT_3 receptor-mediated nociceptive reaction. The bioavailability of oral ondansetron is low due to hepatic first-pass metabolism. The highest plasma concentration of ondansetron is about 1.5 h after oral administration (Ye et al. 2001). Plasma protein binding capacity of ondansetron is about 70–76%. It has 140 L volume of distribution after IV or IM or oral routes of administration. The $t_{1/2}$ is about 3–3.5 h. Metabolism occurs in the liver by cytochrome P450 enzyme pathway. Ondansetron is excreted about 5% through urine. Ondansetron is used to treat nausea and vomiting induced by postoperative, chemotherapy, radiation therapy and bone marrow transplantation etc. (Culy et al. 2001).

Palonosetron is another newer 5-HT_3 antagonist, which has been shown more efficacy than first-generation 5-HT_3 antagonist (ondansetron or granisetron) in clinical trials phase III to treat emesis during chemotherapy. Palonosetron has different chemical structure from the other drugs in its class. It is a compound tricyclic ring system attached to quinuclidine moiety. It shows longer activity (Rojas et al. 2008). Palonosetron has long $t_{1/2}$ which is about 40 h and slower elimination. Due to its long $t_{1/2}$, it shows better efficacy about 48 h after surgery (Srivastava et al. 2016).

6.7 Serotonin Transporter

Serotonin transporter (SERT or 5-HTT) is a member of monoamine transporter (MAT) (Xue et al. 2019). SERT terminates the actions of serotonin by various ways like enzymatic degradation, restriction of diffusion in synapse, and reuptake to presynaptic neuron from extracellular site (Glennon and Dukat 2002). The SERT is located in the cytoplasm of neuron; the protein consists of amino acids (in humans 630 amino acids) and 12 reversed topological transmembrane (TM) spanning helices with COOH and NH_2 group at end point (Fig. 6.8) (Beecher et al. 2019). Transmembrane domain has been interlined by 2 intracellular (IL1 and IL5) and 3 extracellular (EL2, EL3, and El5) hydrophilic loops (Beecher et al. 2019). SERT is 50% homologous to norepinephrine transporter (NET) and dopamine transporter (DAT) of MAT (Glennon and Dukat 2002). The SERT protein binds with sodium ion and chloride ion to form a complex for transportation of serotonin (Glennon and Dukat 2002; Barnes and Neumaier 2011). SERT has vital roles in homeostasis in the CNS, GIT, and blood platelets. SERT has in affective role in many disorders like stress, obsessive compulsive disease, poor mood, anxiety, sexual dysfunction, and depression (Beecher et al. 2019).

Some tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) are used to block the SERT, which causes inhibition of uptake and increasing the amount of neurotransmitter in the synapse (Schloss and Williams 1998). Some examples of SERT inhibitors are fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, imipramine, and desipramine (Fig. 6.9) (Rudnick 2006; Glennon and Dukat 2002).

The bioavailability of fluoxetine is less than 90% due to hepatic first-pass metabolism after oral administration. It has long $t_{1/2}$ about 1–4 days. Fluoxetine is excreted through urine. More than 90% of fluvoxamine is absorbed after oral administration. About 100% of drug excreted through urine. Metabolism of fluvoxamine occurs in the liver. Clinically paroxetine is a potent chiral SSRI. It is

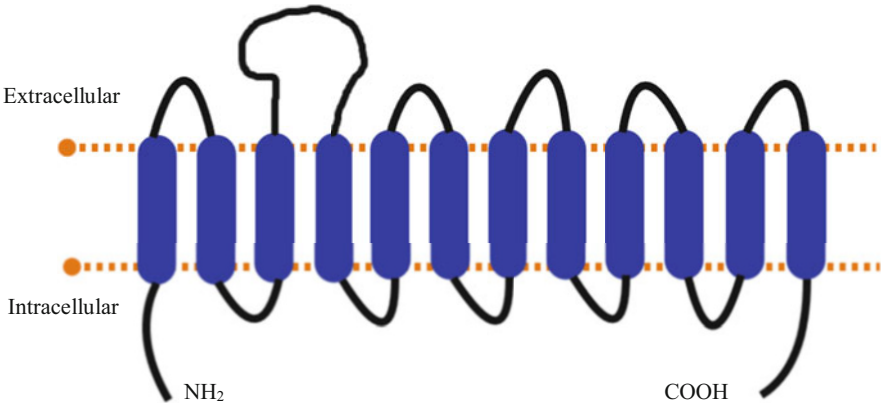

Fig. 6.8 Serotonin transporter

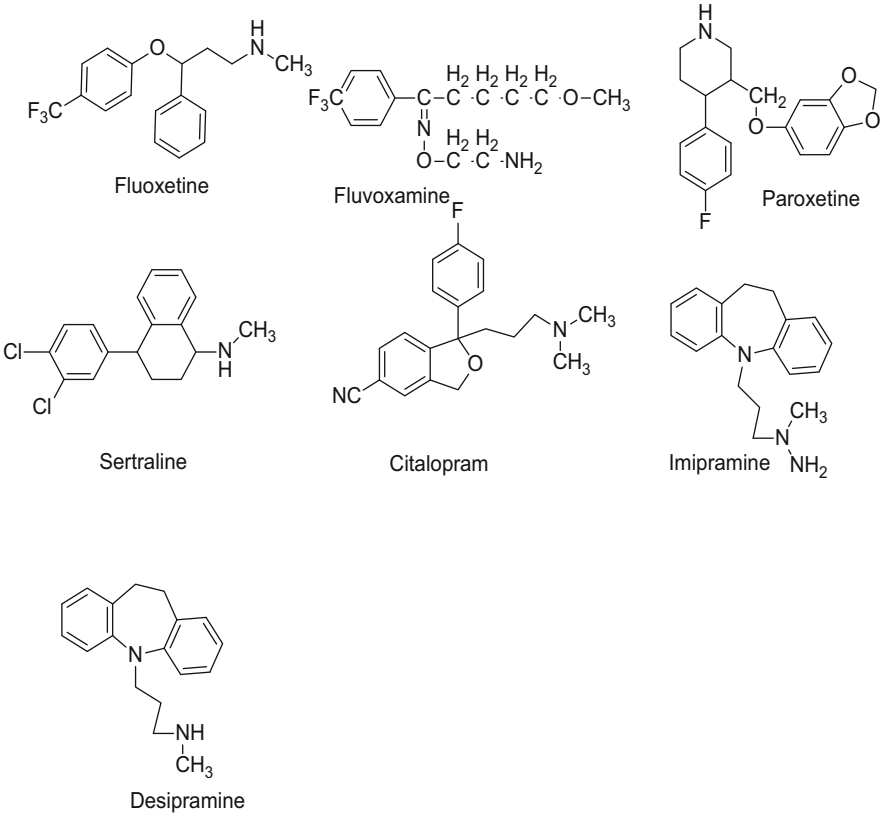

Fig. 6.9 Structure of some SERT inhibitors (Sources: Glennon and Dukat 2002)

absorbed from GIT and metabolized in the liver. Complete absorption takes place from the GIT in case of sertraline. The C_{max} of sertraline is 6–8 h (Hiemke and HÄrtter 2000).

6.8 Serotonin Toxicity or Serotonin Syndrome

Serotonin toxicity or syndrome is due to excess concentrations of 5-HT in the brain or CNS (Birmes et al. 2003). It is characterized by different dose-related adverse effects. Generally, it includes a group of symptoms like autonomic instability, neuromuscular excitability, and cognitive behavioral changes, called serotonin syndrome (Ener et al. 2003). Depending on the increased level of serotonin in the CNS, the toxic effect ranges from mild to severe. Overdose of drug and rising therapeutic doses cause moderate toxicity. The combination of two or more serotonergic drugs causes severe toxicity (Buckley et al. 2014). For analysis of serotonin syndrome, the patient's complete history is required including serotonergic drug uses, its signs and

symptoms, and the elimination of extra situation (Birmes et al. 2003). On clinical ground severe toxicity is diagnosed and characterized by a quickly rising temperature and inflexibility. Mild toxicity is difficult to recognize from numerous ailments or other unfriendly medication impacts (Buckley et al. 2014). Sternbach criteria are used for the analysis of serotonin syndrome, but it is still complicated in cases of benign symptoms or normal neurological test results (Birmes et al. 2003). Serotonin syndrome or toxicity is treated primarily by caring, charcoal lavage, consisting of external cooling with blankets, and dialysis in the case of lithium overdose (Ener et al. 2003). Generally, discontinuation of serotonergic medications is done to overcome from toxicity (Buckley et al. 2014). Benzodiazepines are used in some neurological symptoms, including serious myoclonus and hyperreflexia. In severe toxicity cases cyproheptadine is recommended (Frank 2008).

6.9 Clinical Studies on Serotonin and Its Receptors

Serotonin agonists and mood: A randomized phase I study was initiated in 40 participants by the University of Chicago to determine the efficacy of very low doses serotonergic agonist on a human volunteer with depression. The study will measure the changes from the baseline in the Profile of Mood States (POMS) in the subjects. This study was initiated in May 2018 and estimated to be completed by May 2020 (ClinicalTrials.gov Identifier: NCT03790358).

Serotonin 1_A agonists and cognition in schizophrenia: A phase III study was performed in 60 participants by Vanderbilt University to observe the cognitive functioning of schizophrenia patient with antipsychotic treatment. For 6 weeks patients were assigned to take their antipsychotic drugs with active medication buspar or placebo. Before and after treatment, memory and problem-solving abilities were evaluated. The study was initiated in January 2003 and completed in October 2004 (ClinicalTrials.gov Identifier: NCT00178971).

5-HT_4 agonist and chronic constipation: A phase II study was performed in 360 participants by Theravance Biopharma to compare the effectiveness and safety in chronic constipation of TD-5108 drug (Investigational drug) with a sugar pill (placebo). The study was performed to determine the efficacy and safety of a 5-HT_4 agonist in chronic constipation. The study was initiated in October 2006 and completed in May 2007 (ClinicalTrials.gov Identifier: NCT00391820).

Lorcaserin hydrochloride and smoking cessation: A randomized phase II study was performed in 603 participants by Arena Pharmaceuticals to evaluate the effect of lorcaserin hydrochloride in smokers for smoking cessation. The study was performed by giving treatment with lorcaserin and placebo. The effect was measured on the last 4 weeks of treatment. The study was initiated in March 2014 and completed in November 2014 (ClinicalTrials.gov Identifier: NCT02044874).

Sarpogrelate and coronary artery disease: A randomized phase IV study was performed in 40 participants by Seoul National University Bundang Hospital to determine the effect of sarpogrelate, a serotonin receptor antagonist, on coronary artery disease. The study was performed in Korean type 2 diabetic patients with

atherosclerosis disease and to review the comparisons of sarpogrelate with aspirin. The study was initiated in July 2015 and completed in April 2016 (ClinicalTrials.gov Identifier: NCT02607436).

Granisetron and sympathomimetics during cesarean section: An observational study was performed in 240 participants by Johann Wolfgang Goethe University Hospital to determine the effect of granisetron on usage of sympathomimetics during cesarean section. The study was performed in patient with cesarean section to quantify the usage and dose of sympathomimetics used. The study was initiated in October 2017 and completed in February 2016 (ClinicalTrials.gov Identifier: NCT03318536).

Ramosetron Plus DX, Dexamethasone, Granisetron plus DX, and vomiting and nausea: A randomized phase III study was performed in 287 participants by Astellas Pharma Inc. to compare Ramosetron Plus DX and Dexamethasone to Granisetron plus DX. The comparisons were measured on safety and efficiency parameter for the treatment of vomiting and nausea induced by chemotherapy. The study was initiated in January 2006 completed in March 2006 (ClinicalTrials.gov Identifier: NCT00272285).

5-HT_3 antagonists and cardiac safety: An observational study was performed in 250 participants by the University of British Columbia to evaluate cardiac safety of commonly used antiemetic drugs like ondansetron. The study was performed to determine the increased cardiac safety of ondansetron. The study was initiated in June 2014 and estimated to be completed by July 2020 (ClinicalTrials.gov Identifier: NCT02436798).

Emend and emetogenic chemotherapy: A non-randomized phase II study was performed in 22 participants by the University of Illinois at Chicago to review the effect of emend or aprepitant on chemotherapy-induced nausea and vomiting for multiple days. The drugs used in the study were aprepitant, dexamethasone, and ondansetron. The study was initiated in November 2005 and completed in January 2009 (ClinicalTrials.gov Identifier: NCT00711555).

5-HT_6 antagonist and bipolar disorder: A randomized study was initiated in 68 participants by King's College London to determine the efficacy of JNJ-18038683, a 5-HT_6 antagonist on cognitive impaired people with bipolar disorder and healthy volunteer using functional MRI. The study was also designed to validate 5-HT_6 antagonist for the treatment of bipolar disorders and effects of 5-HT_6 antagonist for brain functioning in healthy volunteers. The study was initiated in August 2018 and estimated to be completed by July 2020 (ClinicalTrials.gov Identifier: NCT03633357).

5-HT_3 antagonist and opioid withdrawal: A randomized study was performed in 133 participants by Stanford University to examine the uses of ondansetron on reducing the withdrawal symptoms of opioid and to prevent the sequence of physical dependence of opioid. The drugs used in the study were ondansetron, naloxone, and morphine. The study was initiated in April 2011 and completed in October 2016 (ClinicalTrials.gov Identifier: NCT01549652).

Ondansetron and lactulose-induced diarrhea: A randomized phase IV study was initiated in 16 participants by the University of Nottingham to determine the efficacy

of ondansetron (5-HT_3 antagonist) on the quantity of water in large and small bowel. The study will measure the mode of action of ondansetron in lactulose-induced diarrhea. The study was initiated in October 2018 and estimated to be completed by August 2019 (ClinicalTrials.gov Identifier: NCT03833999).

Aprepitant in preventing nausea and vomiting: A phase II study was performed in 22 participants by Wake Forest University Health Sciences to evaluate the effect of aprepitant in preventing nausea and vomiting in patients undergoing chemotherapy and radiation therapy for pancreatic cancer. The drugs used in the study were aprepitant, gemcitabine hydrochloride, capecitabine, and fluorouracil. The study was initiated in August 2006 and completed in August 2012 (ClinicalTrials.gov Identifier: NCT01534637).

Granisetron and myofascial pain: A randomized phase IV study was performed in 40 participants by Karolinska Institute to evaluate the effect of granisetron on myofascial pain in the orofacial muscles. The study was initiated in March 2007 and completed in July 2015 (ClinicalTrials.gov Identifier: NCT02230371).

ONZETRA® Xsail® and episodic migraine: A randomized phase III study was undertaken in 420 participants by Avanir pharmaceuticals to evaluate the safety and efficacy of ONZETRA® Xsail® (sumatriptan nasal powder) for the acute treatment of episodic migraine with or without aura in adolescents. The study was designed to examine the efficacy and safety of sumatriptan nasal powder for treating migraine in 12–17 years old patients. The study was initiated in November 2017 and completed by November 2019 (ClinicalTrials.gov Identifier: NCT03338920).

Ondansetron and CNS distribution: A non-randomized phase I study has been performed in 18 participants by Washington University School of Medicine to determine the time course of plasma and CSF concentrations of IV ondansetron in healthy subjects, with and without selective inhibition of Pgp efflux transporter. The study was initiated in May 2019 and estimated to be completed by June 2020 (ClinicalTrials.gov Identifier: NCT03809234).

Ondansetron and hypotension: A randomized phase IV study has been performed in 100 participants by Hospital de base to verify the hypothesis that ondansetron IV (5-HT3 receptor antagonist) decreases the occurrence of hypotension induced by spinal anesthesia. The study was initiated in March 2019 and estimated to be completed by March 2020 (ClinicalTrials.gov Identifier: NCT03973411).

6.10 Conclusion

Among the monoamines, serotonin or 5-hydroxytryptamine (5-HT) is unique and its effects are served by one ligand-gated ion channel and G-protein-coupled receptors. Seven families and different subfamilies of 5-HT receptor have been recognized. In recent two decades, a tremendous research work has been carried out to recognize the different 5-HT receptor families and subfamilies, and their uniqueness, revealing various connections between 5-hydroxytryptamine receptors and diseases. However, further studies would provide better insight about functions, effect of some receptors and their subtypes in health or disease.

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