5-Hydroxytryptamine Receptor Subtypes and their Modulators with Therapeutic Potentials

Anand B. Pithadia, Sunita M. Jain

Abstract

5-hydroxytryptamine (5-HT) has become one of the most investigated and complex biogenic amines. The main receptors and their subtypes, e.g., 5-HT1 (5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1F), 5-HT2 (5-HT2A, 5-HT2B and 5-HT2C), 5-HT3, 5-HT4, 5-HT5 (5-HT5A, 5-HT5B), 5-HT6 and 5-HT7 have been identified. Specific drugs which are capable of either selectively stimulating or inhibiting these receptor subtypes are being designed. This has generated therapeutic potentials of 5-HT receptor modulators in a variety of disease conditions. Conditions where 5-HT receptor modulators have established their use with distinct efficacy and advantages include migraine, anxiety, psychosis, obesity and cancer therapy-induced vomiting by cytotoxic drugs and radiation. Discovery of 5-HT, its biosynthesis, metabolism, physiological role and the potential of 5-HT receptor modulators in various nervous, cardiovascular and gastrointestinal tract disorders, bone growth and micturition have been discussed in this article.

Keywords: 5-hydroxytryptamine (5-HT) receptors; Modulators; Biogenic amines

Introduction

In 1930s, Erspamer began to study the distribution of enterochromaffin cells, which stained with a reagent for indoles. The highest concentrations were found in gastrointestinal mucosa, followed by the platelets and the CNS.

Biosynthesis and Metabolism Pathway and Distribution

5-HT or Serotonin is biosynthesized from tryptophan amino acid. Tryptophan is converted to 5 hydroxy tryptophan by tryptophan hydroxylase which by action of dopa decarboxylase converted into serotonin. This synthesized serotonin is mainly stored in chramaffin and enteric neurons (90%). This biosynthesis not occur in CNS and Platelet but they take up 5-HT from circulation. 5-HT is metabolized by monoamine oxidase enzyme (MAO) to 5 Hydroxyindole acetaldehyde, which through aldehyde dehydrogenase converted into 5-Hydroxyindole Acetic Acid (5-HIAA). This 5-HIAA serve as marker for Malignant carcinoid syndrome in which higher concentration of 5-HT in body lead to 20 fold higher excretion of 5-HIAA. 5-HT is converted into N-acetyl 5-HT through enzyme 5-HT N-acetylase which is with help of hydroxyl indole c-methyl transferase converted into melatonin. Melatonin is an important hormone that maintains sleep cycle and also acts as antioxidant [2].

Physiological Role of Serotonin

Serotonin (5-hydroxytryptamine) is principally found stored in three main cell types - (a) serotonergic neurons in the CNS and in the intestinal myenteric plexus, (b) en-
terochromaffin cells in the mucosa of the gastrointestinal tract and (c) in blood platelets. Serotonergic neurons and enterochromaffin cells can synthesize serotonin from its precursor amino acid L-tryptophan, whereas platelets rely upon uptake of serotonin for their stores. Likewise, serotonergic neurons also have the capacity for amine uptake via serotonin transporters. In central nervous system serotonin acts as neurotransmitter as well as precursor for melatonin hormone synthesis in pineal gland. It regulates gastrointestinal motility and involved in haemostasis on platelets. The net effect of 5-HT is to cause platelet aggregation. It causes bronchoconstriction, positive inotropic and action on heart. All these actions are brought about by it’s interaction with various membrane receptors.

5-HT Receptor Subtypes

Gaddum and Picarelli in 1957 first suggested that 5-HT receptors located on guinea pig ileum smooth muscle cells could be blocked by dibenzyline and the serotonin mediated depolarization of intramural cholinergic neuron could be blocked by Morphine. They therefore classified 5-HT receptor subtypes as “D” and “M” subtypes Subsequent research demonstrated that certain action of 5-HT like vasoconstriction in the carotid vessels could neither be blocked by dibenzyline nor by morphine such reports initiated search for other “Non D, Non M” receptors [3]. Peroutka and Snyder (1979) used radioligand binding study to classify 5-HT receptor subtypes. However the classification scheme proved to be invalid. Hence widely accepted classification scheme is based on pharmacological properties, second messenger function and deduced amino acid sequence [4]. This classification scheme proposes 7 subfamilies of 5-HT receptors.

Table 1a, b, and c give information about the serotonergic receptor subtypes with their signal transduction mechanism, their location, physiological action, agonist and antagonists.

Theapeutic Uses of Drugs Acting on Serotonin Receptors

The various indications where 5-HT receptor modulators have been reported to be of beneficial are given below.

Central Nervous System

Depression

The hypothesis in affective disorders focuses on an involvement of neurotransmitters noradrenaline (norepinephrine), 5-HT and dopamine. It has been found that some depressed patients appear to have reduced cerebral concentration of 5-HIAA (5-Hydroxy indole acetic acid) (the metabolite of 5-HT), whereas others appear to have reduced level of methoxyhydroxyphenylglycerol (MHPG), a metabolite of noradrenaline. More consistent changes have been reported in the plasma concentration of L-tryptophan (the precursor for serotonin). The classical mechanism of antidepressant drugs is by increasing effective synaptic concentration of monoamines-NE, 5-HT and dopamine, either by blocking the oxidative enzyme in synaptic terminals that degrade these monoamines (e.g. MAO Inhibitors) or by blocking the reuptake of these transmitters i.e., reuptake blockers. It has been shown that many antidepressant drugs like imipramine,desipramine, amitriptyline, nortriptyline, doxepin, amoxapine, maprotiline, mianserin and trazodone are also antagonists at 5-HT1c receptors in the brain. Selective 5-HT reuptake inhibitors, e.g., fluoxetine, fluvoxamine, paroxetine, citalopram and sertraline are effective as tricyclic anti-depressants (TCAs) and MAO-I (monoamine oxidase inhibitors) in treating depression of moderate degree but probably less effective than TCAs in treating severe depression [5].

Psychosis

The idea that 5-HT dysfunction could be involved in schizophrenia was based on the fact that LSD (Lysergic acid diethylamide) produce schizophrenia like symptoms. Many effective anti-psychotic drugs in addition to blocking dopamine receptors, also act as 5-HT receptors antagonists. Clozapine, an atypical anti-psychotic drug has more effect on limbic system and 5-HT2 receptors, which may explain its reduce risk of extrapyramidal symptoms [6]. Risperidone, which blocks both 5-HT2 and D2 receptors does improve both positive and negative symptoms of schizophrenia, while ritanserin, a very potent and selective 5-HT2 receptor antagonist, showed significant improvement in Type II schizophrenics [those with primarily negative symptoms]. Drugs acting on 5-HT3 receptors e.g. ondansetron have also been investigated as new anti-psychotics [7].Further studies are required to prove their usefulness or otherwise.

Migraine

5-HT1B and 5-HT1D receptors are found mainly as presynaptic inhibitory receptors in basal ganglia. 5-HT1D receptor subtype which is expressed in cerebral blood vessels is believed to be involved in migraine. Sumatriptan, 5-HT1D receptor agonist is used to treat acute attack of migraine. It constrict large arteries and inhibit trigeminal nerve transmission. Sumatriptan cause pain at site of injection and also cause hypertension, so contraindicated to patient with IHD (Ischemic Heart Disease) while zolmitriptan is fast acting and don’t cause chest pain. Naratriptan,eletriptan, almotriptan and rizatriptan are other agonists of 5-HT1D and 5-HT1B receptors, active as antimigraine agents at lower dose than sumatriptan. They have properties similar to those of sumatripan but a better bioavailability by oral route and are presented in the form of tablets. Their thera-
Table 1a. Serotonergic receptor subtypes

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Second Messanger</th>
<th>Location</th>
<th>Physiological Action</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
<td>Inhibit adenylate Cyclase</td>
<td>CNS: subiculum substantia nigra PNS: Vascular smooth muscle</td>
<td>1. Serotonergic auto receptor 2. Terminal heteroreceptor to control release of Ach and nor adrenaline 3. Contraction of vascular smooth muscle</td>
<td>5-CT 8-OH-DPAT Sumatriptan Ergotamine (PA)</td>
<td>GR55562 SB224289 SB236057 Methiothepin Cynopindolol</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1E&lt;/sub&gt;</td>
<td>Inhibit adenylate Cyclase</td>
<td>CNS: cortex striatum PNS: m-RNA in vascular tissue</td>
<td>Unknown</td>
<td>5-CT (weak agonist)</td>
<td>5-HT</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1F&lt;/sub&gt;</td>
<td>Inhibit adenylate Cyclase</td>
<td>CNS: Spinal cord Hippocampus PNS: Uterus, mesentery, Vascular smooth muscle</td>
<td>Trigeminal (V) neuro inhibition in guinea pig and rat.</td>
<td>No selective agonist or antagonist are available</td>
<td></td>
</tr>
</tbody>
</table>

8-OH DPAT, 8- Hydroxy -2 - (di-n-propylamino) Tetraline; PA, Partial Agonist; LSD, Lysergic Acid Diethylamide; 5-CT, 5 Carboxamidotryptamine; CSF, Cerebrospinal Fluid; 5-HT, 5 Hydroxytryptamine; CTZ, Chemoreceptor Trigger Zone

5-HT Receptor Subtypes

therapeutic use is also the treatment of migraine attacks. 5-HT2 receptor antagonists e.g. dihydroergotamine, methysergide, pizotifen and cyproheptadine are mainly use for migraine prophylaxis [8]. Methysergide is rarely used because of development of “Retroperitoneal fibrosis” or “Ormond’s disease” which is characterize by development of fibrotic mass in peritoneal cavity like kidney. Cyproheptadine in addition to 5-HT2A blocking activity also has anti-allergic action due to histamine receptor antagonistic activity antimuscarinic and Ca<sup>2+</sup> antagonistic activities. It is used in children to enhance appetite and also reduce dumping after gastrin surgery (Post Gastrctomy Dumping Syndrome) [9].

Pithadia et al

Pain

5-HT stimulates nociceptive (pain mediating) sensory nerve ending, an effect mediated by 5-HT3 receptors. Thus 5-HT3 receptors could play a role in nociception at spinal level [10]. It is further reported that 5-HT3 receptor stimulation in the spinal cord results in GABA release that may inhibit nociceptive signal transmission at sites post-synaptic to primary afferent terminals. These findings may herald the development of new non-opioid, non-addictive analgesics. The relief by 5-HT3 receptor antagonists in migraine and visceral discomfort associated with irritable bowel syndrome is known [11]. Further clinical evaluation is however needed to establish this concept. There is considerable evidence of a role for 5-HT mediation in cardiac pain. It has been suggested that combined antagonism of 5HT2 and 5-HT3 receptors may provide more effective therapy for the treatment of angina [12].

Anxiety

Buspirone is a partial agonist at 5-HT1A receptors used to treat various anxiety disorders. It shows high specific

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Second Messenger</th>
<th>Location</th>
<th>Physiological Action</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT3B</td>
<td>Phospholipase C activation</td>
<td>CNS: cerebellum hypothalamus PNS: Vascular endothelium, stomach</td>
<td>Endothelium dependant vaso relaxation via NO production and stomach fundus contraction</td>
<td>5-CT Sumatriptan BW723C86</td>
<td>RS127445 SB204741</td>
</tr>
<tr>
<td>5-HT2C</td>
<td>Phospholipase C activation</td>
<td>CNS: choroid plexus, hippocampus, hypothala-mus</td>
<td>Modulation of transferin production and modulation of CSF volume</td>
<td>α -methyl 5-HT 5-CT</td>
<td>Quipazine Methylsergide Olanzapine Mesulergine</td>
</tr>
<tr>
<td>5-HT3 M receptor</td>
<td>Ligand gated ion channel</td>
<td>CNS: area postrema PNS: Abdominal visceral afferent neuron</td>
<td>1. Stimulate vomiting by acting on CTZ and by vagal neuro excitation 2. Stimulate nociceptive (pain mediating) nerve ending led to pain</td>
<td>2-me5-HT 5-MeOT</td>
<td>Ondesetron Tropisetron Granisetron</td>
</tr>
<tr>
<td>5-HT4</td>
<td>Activation of adenylate cyclase</td>
<td>CNS: Hippocampus PNS: GIT</td>
<td>Neuronal excitation Increase GI motility</td>
<td>Mosapride Cisapride Zacopride</td>
<td>GR113808 SB204070</td>
</tr>
<tr>
<td>5-HT5A</td>
<td>Unknown</td>
<td>CNS: olfactory bulb, Hebenula</td>
<td>Unknown</td>
<td>No selective agonist or antagonist are available</td>
<td></td>
</tr>
<tr>
<td>5-HT5B</td>
<td>Unknown</td>
<td>CNS: olfactory bulb, Hebenula</td>
<td>Unknown</td>
<td>No selective agonist or antagonist are available</td>
<td></td>
</tr>
</tbody>
</table>

8-OH DPAT, 8-Hydroxy-2-(di-n-propylamino) Tetraline; PA, Partial Agonist; LSD, Lysergic Acid Diethylamide; 5-CT, 5 Carboxamido-tryptamine; CSF, Cerebrospinal Fluid; 5-HT, 5 Hydroxytryptamine; CTZ, Chemoreceptor Trigger Zone
for 5-HT1A receptors, which are inhibitory autoreceptors that reduce the release of 5-HT and other mediators. Buspirone and related compounds ipsapirone and gepirone don’t cause sedation or motor in coordination nor have withdrawal effects as with other anxiolytics like barbiturates [13].

**Parkinsonism**

Of the three cardinal symptoms of parkinsonism, i.e., rigidity, tremor and bradykinesia, tremor may be mediated by 5-HT2 receptors. This was revealed by the success of ritanserin, a potent and selective 5-HT2 receptor antagonist, in reducing the tremor of parkinsonism patients [14].

**Treatment of drug abuse**

5-HT3 receptor antagonism has also been shown to reduce the alcohol intake in animals and in human. However, more preclinical and clinical studies are required, to arrive at any meaningful conclusion about the usefulness of 5-HT3 receptor blockers in treatment of drug abuse [15].

**Temperature regulation**

Changes in temperature were determined following injection of noradrenaline, adrenaline, isoprenaline, dopamine and 5-hydroxytryptamine (5-HT) into the cerebral ventricles of the conscious mouse. 5-HT (10-160 µg) caused a fall in body temperature. The activity may be involving 5-HT2 receptor. Hence 5-HT could be the effective target to control body temperature [16].

**Anti-emetic Action**

The central neural regulation of vomiting is vested in two separate units in medulla. These are vomiting centers and chemoreceptor trigger zone (CTZ). Impulses from CTZ pass to vomiting centre and integrate the visceral and somatic functions involved in vomiting. The main neurotransmitters considered to be involved in the control of vomiting are acetylcholine, dopamine, histamine and 5-HT. Receptors for these neurotransmitters have been demonstrated in relevant areas. 5-HT3 receptors in brain particularly in the area postrema, a region of medulla in the vomiting reflex, and selective 5-HT3 receptor antagonists are useful as anti-emetic drugs [17]. Ondansetron, tropisetron and dolasetron are of particular value in preventing and treating vomiting cause either by radiation therapy in cancer patients or by administration of cytotoxic drugs such as cisplatin [17].

**Gastrointestinal tract**

5-HTIA, 5-HTlc, 5-HT2, 5-HT3 and 5-HT4 receptors have been identified in the gut, in either the enteric nervous system or on smooth muscles [18-20]. The actions of 5-HT1-like receptors may include inhibition of release and smooth muscle contraction. 5-HT2 receptors located on the smooth muscle cells, when stimulated directly cause contraction of gastrointestinal smooth muscle and gut vascular smooth muscle. Some selective 5-HT2 receptor agonists stimulate contraction of the lower oesophageal sphincter [21]. 5-HT3 receptors are located on post-synaptic enteric and sensory neurones, on enteric neuronal membranes, in the vagus, on gastric endocrine glands and in the CNS. They are impli-

---

**Table 1c. Serotonergic receptor subtypes**

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Second Messanger</th>
<th>Location</th>
<th>Physiological Action</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT&lt;sub&gt;s&lt;/sub&gt;</td>
<td>Activation of adenylate cyclase</td>
<td>CNS: caudate putamen, hippocampus PNS: Superior cervical ganglia</td>
<td>Modulation of CNS Ach release</td>
<td>No selective agonist available</td>
<td>SB271046 Methiothepin</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Activation of adenylate cyclase</td>
<td>CNS: hypothalamus PNS: gastrointestinal and vascular smooth muscle</td>
<td>Smooth muscle relaxation</td>
<td>5-HT Sumatriptan 8-OH DPAT</td>
<td>SB258719 Methiothepin</td>
</tr>
</tbody>
</table>

8-OH DPAT, 8- Hydroxy -2 -(di-n-propylamino) Tetraline; PA, Partial Agonist; LSD, Lysergic Acid Diethylamide; 5-CT, 5 Carboxamidotryptamine; CSF, Cerebrospinal Fluid; 5-HT, 5 Hydroxytryptamine; CTZ, Chemoreceptor Trigger Zone
cated in the modulation of cholinergic transmission in the enteric nervous system, where their stimulation has been reported to facilitate acetylcholine (ACh) release. 5-HT4 receptors are believed to be located in the nerve terminals on both cholinergic interneurones and motor neurones. Their stimulation leads to increased release of ACh and they accelerate upper gastrointestinal transit as well as increase in colonic motor activity [22].

Irritable bowel syndrome (IBS)
5-HT4 agonists increase intestinal motility and could be used in the treatment of gastroesophageal reflux, intestinal paresis (constipation), irritable bowel syndrome. The first drug of this group is tegaserod. A frequent adverse effect of tegaserod is diarrhea and a rare more severe effect is ischemic colitis. Depending on whether diarrhoea or constipation is the presenting problem, IBS is sub-classified as either diarrhoea predominant IBS or constipation predominant IBS. Though the exact pathophysiology remains unclear, it has been reported that patients of IBS have a higher resting tone of the intestinal smooth muscles and have an excessively sensitive colon. Patients with IBS may also in some cases have a reduced tolerance to gas infusion into the small bowels and the threshold for perception of intestinal contraction may be lower than normal [23]. 5-HT3– receptor blockade has been shown to slow colonic transit in healthy volunteers and has also been reported to reduce visceral hypersensitivity [24]. Thus 5-HT3 receptor antagonists like ondansetron were thought to be of benefit in diarrhea predominant IBS cases. Stimulation of 5HT4 receptors facilitate cholinergic neurotransmission in the gut and thereby increase colonic motor activity. Thus, 5HT4 receptor agonists like cisapride, zacopride, renzapride have a potential role in the constipation predominant IBS patients [25].

Malignant carcinoid syndrome
Carcinoid syndrome is a rare disorder associated with malignant tumors enterochromaffin cells, usually arising in the small intestine and metastasising to liver. These tumors secrete variety of hormones. 5-HT is the important one. The syndrome is readily diagnosed by measuring excretion of 5-HIAA (5-hydroxyindole acetic acid); the main metabolite of 5-HT in the urine. The concentration of which increase up to 20-fold. 5-HT2 antagonists such as cyproheptadine are effective in controlling some of the symptoms of carcinoid syndrome. A complementary therapeutic approach is to use a long acting analogue of somatostatin analogue, namely octreotide, which suppress the hormone secretion from various neuroendocrine cells, including carcinoid cells [26].

Dyspepsia
Dyspepsia is defined as pain or discomfort centered in the upper abdomen in the absence of any structural or biochemical abnormality. 5-HT3 receptor antagonists have been reported to reduce visceral pain reflex in the gut, and studies in the rat showed that granisetron and tropisetron (but not ondansetron) reduced the pain response induced by duodenal distension [27]. Thus 5-HT3 receptor antagonists would theoretically benefit patients of dyspepsia who have increased visceral sensitivity.

Non-cardiac chest pain
Sometimes referred to as chest pain of undetermined etiology (CPUE), it is an ill defined entity requiring urgent elimination of other differential diagnosis. Some authors have reported that visceral nociceptive abnormalities in the oesophagus may contribute in the etiopathogenesis of CPUE [28]. As 5-HT3 receptor antagonists can reduce the visceral pain reflex in the gut, they would theoretically be of benefit in the management of such cases.

Gastro-oesophageal reflux disease
The symptoms of pain and anxiety, seen in gastro-oesophageal reflux disease (GERD) are due to a pathological acid reflux into the oesophagus which may result from a combination of decreased lower oesophageal sphincter tone and impaired acid clearance [29, 30]. 5-HT4 receptor agonists having prokinetic action have been found clinically useful in such conditions.

Cardiovascular system
Ketanserin, a 5-HT2 receptor antagonist with high affinity for peripheral 5-HT2 sites, reduces blood pressure by causing vasodilation and reducing total peripheral resistance. The reflex tachycardia seen with other vasodilators is not seen with ketanserin [31]. This 5-HT2 receptor blockade may be very useful in protecting the microcirculatory bed against the detrimental effects of serotonin, which is massively released by aggregation of platelets, particularly when the vascular bed is predamaged by atherosclerosis, diabetes mellitus and old age. Ketanserin has also been reported to be more effective in the elderly [32].

Ophthalmology
5-HT receptor modulators may have some potential in the treatment of ocular conditions such as glaucoma. A single topical application of 0.5 % ketanserin, a 5-HT2 receptor antagonist with additional alpha-1 adrenoceptor blocking activity, has recently been reported to lower intra-ocular pressure (IOP) for 6–8 hours. This decrease in IOP was due to increased outflow and was not accompanied by any change in systolic or diastolic blood pressure, heart rate, pupil size, corneal thickness or tear secretion [33].

Diabetes
In overnight fasted rats 5-HT was found to produce dose dependant increase in serum glucose level. 5-HT may cause hyperglycemia as shown in Figure 1. It has been reported that 5-HT2A receptor agonist α methyl 5-HT increase serum glucose while 5-HT2A receptor antagonist sarprogralate reduce serum glucose level. In same study 5-HT3 receptor agonist 1-Phenyl biguanide potentiate hyperglycemia effect of 5-HT while 5-HT receptor antagonist ondsetron inhibit the same action [34, 35].

**Obesity**

Sibutramine is an inhibitor of 5-HT/Noradrenaline reuptake at the hypothalamic sites that regulate food intake. Sibutramine reduce food intake and cause dose dependant weight loss, the weight loss being associated with decrease in obesity related risk factors [36, 37].

**Bone growth**

Selective serotonin-reuptake inhibitors (SSRIs) antagonize the serotonin (5-hydroxytryptamine) transporter (5-HTT), and are frequently prescribed to children and adolescents to treat depression. However, recent findings of functional serotonergic pathways in bone cells and preliminary clinical evidence demonstrating detrimental effects of SSRIs on bone growth. The current work investigated the impact of 5-HTT inhibition on the skeleton in: (a) mice with a null mutation in the gene encoding for the 5-HTT; and (b) growing mice treated with a SSRI. In both models, 5-HTT inhibition had significant detrimental effects on bone mineral accrual. 5-HTT null mutant mice had a consistent skeletal phenotype of reduced mass, altered architecture, and inferior mechanical properties, whereas bone mineral accrual was impaired in growing mice treated with a SSRI. These phenotypes resulted from a reduction in bone formation without an increase in bone resorption and were not influenced by effects on skeletal mechanosensitivity or serum biochemistries. These findings indicate a role for the 5-HTT in the regulation of bone accrual in the growing skeleton and point to a need for further research into the prescription of SSRIs to children and adolescents [38].

**Micturition**

Traditionally, central 5-HT-pathways are considered to be inhibitory in the control of micturition. However, at least in the rat, 5-HT1A and 5-HT7 receptors have excitatory actions. The use of antagonists for these two receptors indicates that both play an essential role in micturition in the rat and probably in the guinea pig. Interestingly, both receptors seem to have a similar role supraspinally, although they have opposing effects on adenylyl cyclase. The paucity of evidence compared with rat indicating that 5-HT plays an important role in the control of micturition may just reflect the lack of experiments carried out in this species. Overall the data indicate that 5-HT is an important transmitter involved in the control of micturition. However, further experiments are required to elucidate its precise role and the seeming difference in importance it has in this function between species [39].

**Conclusions**

Basic scientific research has expanded at a great pace, and more and more potent and selective agonists and antagonists for different 5-HT receptor subtypes are discovered. The study at molecular level revealing more subtypes of each receptor family. Scientists are finding precise and specific involvement of such receptor subtypes in different physiological processes and pathological states. Therefore, drugs acting specifically on 5-HT, suggesting their therapeutic potentials in conditions either in CNS or in peripheral tissues. The 5-HT receptor modulating drugs have now established their therapeutic role in various disease conditions like emesis, anxiety and migraine, in various other neurological conditions, as well as peripheral disorders. More studies in future will guide therapeutic potential of 5-HT modulating drugs in other conditions.

**Acknowledgements**

The authors declare no conflicts of interest related to this article.

**References**

1. Rapport MM, Green AA, Page IH. Serum vasoconstric-


22. Ormsbee HS, Barone FC, Barnette MS et al. SK and F 103829, a novel serotonergic agent that contracts the lower oesophageal sphincter. Gastroenterology 1987;92:1562.


33. Costagliola C, Iuliano G, Rinaldi M, Russo V, Scibelli G, Mastropasqua L. Effect of topical ketanserin ad-