

# Section-II



## Chapter-1

# INTRODUCTION

## 1. INTRODUCTION

Serotonin, 5-hydroxytryptamine (5-HT), is one of the members of monoamine neurotransmitters, all of which have a chemical template comprising of a basic amino group separated from an aromatic nucleus by a two carbon aliphatic chain. In mammals, 5-HT is biosynthetically derived from two enzymatic steps [1]:

1. Ring hydroxylation of the essential amino acid tryptophan by tryptophan hydroxylase, the rate-limiting step followed by
2. Side chain decarboxylation by aromatic amino acid decarboxylase.

A second isoform of tryptophan hydroxylase was identified in 2003 by Walther *et al.* [2, 3] The original enzyme expressed in the gut is now called *tph1*, and the isoform expressed exclusively within the brain is named *tph2* [4, 5]. In the brain, serotonin is formed within axon terminals, where it is released in response to an action potential and then diffuses across the synapse to activate postsynaptic receptors. The serotonin receptor family is larger than any other family of G-protein coupled (GPCR) neurotransmitter receptors - 13 distinct genes are encoding for these G-protein coupled seven-transmembrane class of receptors. In addition, there is one ligand-gated ion channel, the 5-HT<sub>3</sub> receptor.

### 1.1. The Discovery of serotonin

The involvement of multidisciplinary groups led to identification of serotonin as an important neurotransmitter which really makes a very interesting detective story [6, 7]. Vittorio Erspamer did the early work on serotonin in Rome, Italy, who revealed that an acetone extract of enterochromaffin cells from gastrointestinal mucosa contained a substance that caused contraction of the smooth muscle of the rat uterus. He further concluded that this substance is an indole on the basis of chemical tests he performed and named it as 'enteramine' [8]. Several papers were published on enteramine by Erspamer and his group in the subsequent years till 1952. Later it was recognized that the active component in enteramine was indistinguishable to a substance named serotonin that had just been identified by Maurice Rapport, Arda Green, and Irvine Page. Irvine Page was the Director of the Division of Research at the Cleveland Clinic and had concerns in the isolation of vasoconstrictor substances in the blood that might be responsible for hypertension. His laboratory had discovered that a vasoconstricting substance was instantly produced when blood is coagulated. Arda Green and Maurice Rapport; one a notable biochemist and the other a talented organic chemist isolated and purified the material [9]. Rapport afterwards illustrated the purification of serotonin from approximately "900 liters of serum collected from almost two tons of beef blood" over the way of his structure elucidation work [10]. The

substance was finally purified, crystallized, and named serotonin in 1948, the name being derived from the fact that the substance was produced in the serum (“ser”), and constricted or increased tone (“tonin”) in blood vessels [11, 12]. A classical chemical structure elucidation approach led Rapport to propose that serotonin was 5-hydroxytryptamine (5-HT) [12].

## 1.2. Serotonin receptors

In the last 20 years, seven unique groups of 5-HT receptors have been recognized and different subpopulations have been depicted for a few of these (e.g. Nichols and Nichols 2008).

### 1.2.1. 5-HT<sub>1</sub> receptors

This group comprises of five receptor subtypes (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub> and 5-HT<sub>1F</sub>), which are structurally indistinguishable in 40-63 % people. There is no 5-HT<sub>1C</sub> receptor, as it was renamed as the 5-HT<sub>2C</sub> receptor. These receptors are mostly coupled with G<sub>i</sub>/G<sub>0</sub> proteins and suppress generation of family. Completely functional 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors have been found in numerous tissues of different species [13].

The **5-HT<sub>1A</sub>** receptor is the most widely disseminated of all the 5-HT receptors. In the main sensory system, 5-HT<sub>1A</sub> receptors are available in high density in the hippocampus, cerebral cortex, amygdala, septum and raphe nucleus, however they have been demonstrated in little amount in the thalamus and basal ganglia too [14]. On the other hand, they could be discovered additionally in myenteric plexus and entire gastrointestinal tract. In the brain, 5-HT<sub>1A</sub> receptors go about as autoreceptors and postsynaptic receptors. They are involved in the impediment of "release" of neurons, regulation of the generation of ACTH (however not prolactin), and regulation of conduct and consuming [15]. They likely assume an essential part in the rise of anxiety. This perception was affirmed by studies with knockout gene for this subtype of 5-HT<sub>1</sub> receptor in mice. The animals indicated expanded fear in numerous test conditions [16]. Also, 5-HT<sub>1A</sub> antagonist (buspiron, gepiron) are utilized for the medicine of depression and anxiety. Antagonist of 5-HT<sub>1A</sub> receptor and  $\beta$ -blocker pindolol enhance the adequacy of specific serotonin reuptake inhibitors – SSRI's in medication of gloom [17]. The antianxiety actions of 5-HT<sub>1A</sub> (fractional) agonists may give fundamentally presynaptic somatodendritic 5-HT<sub>1A</sub> receptors (prompting lessened arrival of 5-HT in terminal zones), in as much as the stimulant activity of 5-HT<sub>1A</sub> agonists might basically give postsynaptic 5-HT<sub>1A</sub> receptors [18]. Certain 5-HT<sub>1A</sub> agonists show antiaggressive behaviour, and estimation of the density of 5-HT<sub>1A</sub> receptors in frontal cortex of suicide exploited people uncovers that suicide victimized people had a fundamentally higher ratio [19, 20].

**5-HT<sub>1B</sub>** receptors are available in the CNS, where they actuate presynaptic hindrance and behavioral impacts. Notwithstanding, they display vascular impacts too, for example, aspiratory vasoconstriction. 5-HT<sub>1B</sub> receptors are available in numerous parts of the human cerebrum. The most amazing finding is that they might be found in the striatum, basal ganglia and the frontal cortex. The capacity of the receptor relies upon its area: in the frontal cortex it is accepted to go about as a terminal receptor suppressing the arrival of dopamine. In the striatum and the basal ganglia, the 5-HT<sub>1B</sub> receptor is thought to go about as an autoreceptor, inhibiting the arrival of serotonin. Optional part of 5-HT<sub>1B</sub> receptors is to serve as controlling terminal heteroreceptors for discharge of different neurotransmitters, e.g. acetylcholine, glutamate, dopamine, norepinephrine and  $\gamma$ -aminobutyric acid (GABA). Notwithstanding the cerebrum, this subtype was additionally found in cerebral and different areas [21]. Knockout mice deficit of 5-HT<sub>1B</sub> gene indicates an elevation in antagonism [22]. Revelation of antimigraine properties of the sumatriptan (nonselective 5-HT<sub>1D/1B</sub> agonist) expanded enthusiasm toward this subtype of 5-HT<sub>1</sub> receptors. Different agonists (dihydroergotamine, zolmitriptan, naratriptan, rizatriptan) are utilized or formed within this indication. Nonetheless, different numbers of different impacts of 5-HT<sub>1D/1B</sub> agonists were observed, plus its antimigraine class, e.g. prokinetic impact on gastrointestinal tract, its position in the medication of a mental imbalance, antiplatelet impacts and so forth [23].

Interpretation of **5-HT<sub>1D</sub>** is low contrasted with the 5-HT<sub>1B</sub> receptor and both the receptors display 63 % structural homology. 5-HT<sub>1D</sub> receptors go about as autoreceptors in the dorsal raphe nuclei, however these were additionally found in the heart where they regulate the arrival of serotonin [24]. In the main sensory system, 5-HT<sub>1D</sub> receptors are included in motion and nervousness. They prompt likewise the vascular vasoconstriction in the cerebrum. Ergotamine works basically through the 5-HT<sub>1B</sub> receptor, since the impact through the 5-HT<sub>1D</sub> receptor is as different to the mode of action of ergotamine, i.e. vasoconstriction [25]. In any case, the clinical importance of 5-HT<sub>1D</sub> receptors stays still obscure to a great extent. There has been theory that these receptors may be included in tension, sadness and other neuropsychiatric issues. With the accessibility of the 5-HT<sub>1D</sub> competitors, it has been indicated for instance that Gr127935 obstructs the impact of antidepressants in the mouse tail suspension test [26]. Moreover, the restriction of 5-HT<sub>1D</sub> receptors in human cerebrum is thought to be predictable with potential inclusion in Huntington's disease [27]. These days accessible antimigraine medicaments for all intents and purposes don't separate 5-HT<sub>1B</sub> from 5-HT<sub>1D</sub> receptors. Trials with a particular 5-HT<sub>1D</sub>

agonist (distinguished so far as PNU 109291) demonstrated huge concealment of meningeal neurogenic irritation and nociception in trigeminal ganglia [28].

The capacity of the **5-HT<sub>1E</sub>** receptor is obscure because of the absence of particular pharmacological tools, particular antibodies and moderate animal models. The 5-HT<sub>1E</sub> receptor gene needs polymorphisms amongst people, showing a high level of evolutionary protection of hereditary succession, which proposes that the 5-HT<sub>1E</sub> receptor has an essential physiological role in people. It is theorized that the 5-HT<sub>1E</sub> receptor is included in the regulation of memory in people because of the high expression of the receptors in the frontal cortex, hippocampus and olfactory knob, all of which are areas of the cerebrum basic to memory regulation [29]. Functional studies in cells steadily communicating 5-HT<sub>1E</sub> receptors demonstrate that the receptor is negatively coupled to adenylyl cyclase. Then again, cloned human 5-HT<sub>1E</sub> receptors may couple to adenylyl cyclase by means of two different pathways. [30]. It has been demonstrated, that 5-HT produces a Gi-mediated obstruction of forskolin-active site aggregation at low fixations, in as much as it additionally evokes a critical, despite the fact that with lower proficiency, potentiation of site collection at higher focuses because of coupling to Gs [31]. Methiothepin, which binds to 5-HT<sub>1E</sub> receptors just with typical addition, is a powerless focused antagonist [32].

The **5-HT<sub>1F</sub> receptor** shows moderate transmembrane homology with a few other 5-HT<sub>1</sub> receptors: 5-HT<sub>1E</sub> (70 %), 5-HT<sub>1D $\alpha$</sub>  (63 %), 5-HT<sub>1D $\beta$</sub>  (60 %), and 5-HT<sub>1A</sub> (53 %). Regardless of similitudes to 5-HT<sub>1E</sub> receptors, 5-HT<sub>1F</sub> receptors tie 5-methoxytryptamine and certain ergotamine derivatives with high natural inclination. The cloned human 5-HT<sub>1F</sub> receptor couples to chains of adenylyl cyclase [33]. Agonist impacts of 5-HT were antagonized totally and clearly aggressively by the nonselective 5-HT antagonist methiothepin [34]. Identification of 5-HT<sub>1F</sub> receptors in the uterus and coronary supply routes propose a conceivable part in vascular compression [35]. Despite the fact that circulation in the cerebrum seems restricted, there are distributional likenesses with 5-HT<sub>1D $\beta$</sub>  receptors [36].

### 1.2.2. 5-HT<sub>2</sub> receptors

This class has three subtypes – 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub>, indicating 46-50 % structural homology, ideally interfaced to Gq11 protein and expanding inositol trisphosphate hydrolysis and intracellular Ca<sup>2+</sup> fixation. This is the principle excitatory receptor subtype among the G-protein coupled receptors for serotonin (5-HT), albeit 5-HT<sub>2A</sub> might likewise have an inhibitory effect on specific ranges, for example, the ocular cortex and the orbitofrontal cortex [37].

**5-HT<sub>2A</sub>** receptor is communicated in numerous central and peripheral tissues. 5-HT<sub>2A</sub> receptors intercede the withdrawal response of smooth muscles. Moreover, expanded platelet collection and expanded fine penetrability succeeding appearance to serotonin (most likely because of enactment of this receptor subtype) were depicted [38]. In the CNS, 5-HT<sub>2A</sub> receptors are available fundamentally in the outside layer, claustrum and basal ganglia. Initiation of 5-HT<sub>2A</sub> receptor prompts stimulation of discharge of ACTH, corticosterone, oxytocin, renin, and prolactin [39, 40]. Obstruction of 5-HT<sub>2A</sub> receptor impacts conduct. 5-HT<sub>2A</sub> antagonists with diverse receptor tying ability (ritanserine, risperidone, olanzepine, seroquel and so forth.) are utilized or are, no doubt produced for the medicine of schizophrenia [41]. Late studies recommend that 5-HT<sub>2A</sub> receptors may assume a more conspicuous part in the behavioral movements of stimulants than 5-HT<sub>2C</sub> [42].

Initiation of **5-HT<sub>2B</sub>** receptor prompts withdrawal of smooth muscle of stomach fundus. 5-HT<sub>2B</sub> immunoreactivity was distinguished in the cerebellum, parallel septum, hypothalamus and average some pieces of the amygdala [43, 44]. Immediate infusion of a specific agonist BW723c86 in amygdala has anxiolytic effects in rats [45]. 5-HT<sub>2B</sub> receptor framework mediates likewise endothelium-subordinate unwinding in detached rodent veins and longitudinal muscle density in the human digestive system [46, 47]. In addition, performance of 5-HT<sub>2B</sub> receptor in mouse fibroblasts has mitogenic effect through the initiation of MAP kinase (mitogen initiated protein kinase) [48]. Antagonists of 5-HT<sub>2B</sub> receptors (e.g. SB 200646) are generally new and may discover clinical requisition in the medication and curative action of headache [49]. It gives the idea that this receptor is additionally communicated in heart valves and may be in charge of valvulopathies described in patients utilizing arrangements for decrease of the longing holding dexfenfluramine [50].

Because of the absence of particular ligands for **5-HT<sub>2C</sub>** receptor, the learning of its association stays unremarkable. A 5-HT<sub>2C</sub> antagonist agomelatine came out as a convincing superior because of its antagonism of 5-HT<sub>2C</sub> receptors, along these appearances bringing on a rise in dopamine and norepinephrine levels in specific regions of the cerebrum [51]. Fluoxetine and different SSRIs authorize 5-HT<sub>2C</sub> work by increasing the level of serotonin in the synapse. Interestingly, some atypical antipsychotics obstruct 5-HT<sub>2C</sub> receptors halfway. Notwithstanding hindering serotonin reuptake, fluoxetine does additionally go about as a coordinate 5-HT<sub>2C</sub> antagonist [52]. On the hypothesis of a huge association between headache prophylaxis, 5-HT<sub>2C</sub> receptors are also involved in the establishment of headache symptoms; in any case, the available proof did not take into consideration a necessity between 5-HT<sub>2C</sub> with respect to 5-HT<sub>2B</sub> receptors [53]. Activation of this receptor subtype

has additionally anxiogenic effect and prompts hypophagia, hypoactivity and oral dyskinesia [54].

### 1.2.3. 5-HT<sub>3</sub> receptors

5-HT<sub>3</sub> receptors comprise of 5 subunits organized around a central constituent part directing stoma which is penetrable to sodium, potassium and calcium ions. The coupling of the neurotransmitter serotonin to the 5-HT<sub>3</sub> receptor opens the sidetrack which prompts an excitatory reaction in neurons. 5-HT<sub>3</sub> receptors are present on neurons of both, central and border origin. 5-HT<sub>3</sub> receptors also demonstrate on presynaptic nerve terminals, where they are considered to interfere or regulate neurotransmitter discharge. To attain the full impact of initiation of this receptor, heteromeric synthesis of its two subtypes – 5-HT<sub>3A</sub> and 5-HT<sub>3B</sub> is obliged [55]. 5-HT<sub>3</sub> antagonists (ondansetron, granisetron, tropisetron etc.) were affirmed for being clinically viable in the medication of chemotherapy- or radiation induced sickness, while they are inadequate against movement disorder and apomorphine induced emesis [56]. There are likewise signs that they may be compelling in the medication of headache. Preclinical studies propose that 5-HT<sub>3</sub> antagonists may improve memory and be of use in the medication of nervousness, distress, anguish and dementia. At last, there is proof that 5-HT<sub>3</sub> antagonists may suppress the behavioural results of withdrawing everlasting medication with drugs of abuse, including nicotine, alcohol, cocaine, and amphetamine [57]. There is just little confirmation about the conceivable helpful provision of 5-HT<sub>3</sub> agonists; it appears that some partial agonists have an anxiolytic profile [58]. Alosetron introduced to treat colon irritation however was withdrawn from market due its unwanted side effects [59].

### 1.2.4. 5-HT<sub>4</sub> receptors

Seven variants (5-HT<sub>4A-H</sub>) of the receptor were recognized which are distinguished in the C-terminal portion arrangement. Additionally, 5-HT<sub>4H</sub> subtype was portrayed with insertion of 14 amino acids into the second extracellular loop. Nonetheless, all variants have comparable pharmacology and are connected with adenylyl cyclase pathways. The subtypes of serotonin receptors show constitutive (ligand autonomous) action, regardless of the possibility that it helps the capacity of the receptor just in a little degree. This action clarifies the differences between expected and observed effects of agonists and antagonists of the 5-HT<sub>4</sub> receptors. Some normal agonists exhibited rather noiseless or antagonistic impacts relying upon the level of ligand free action [60]. A few studies pointed particular tissue distribution of individual isoforms of 5-HT<sub>4</sub> receptors, e.g. 5-HT<sub>4D</sub> receptor was discovered just in the human digestive system [61]. Activation of 5-HT<sub>4</sub> receptor results in the influx of acetylcholine in the ileum and the constrictions of the throat and colon in pigs. The

combination of 5-HT<sub>4</sub> agonists on human heart quickly constructs its contractile force [62]. 5-HT<sub>4</sub> receptors in the CNS increase the influx of different neurotransmitters (acetylcholine, dopamine, serotonin and GABA) and improve synaptic transmission which may influence the advancement of memory [63]. 5-HT<sub>4</sub> receptor agonist cisapride was utilized within clinical practice as gastroprokinetic operator (however has been withdrawn from the market because of its cardiovascular side effects) [64]. Specific 5-HT<sub>4</sub> ligands are prone to be utilized as a part of the medication of different ailments, e.g. dysrhythmias, neurodegenerative disorders and urinary incontinence [65, 66]. 5-HT<sub>4</sub> receptors may be included in memory and learning and they are altogether diminished in patients with Alzheimer's disease [67]. In any case, utilization of very strong and particular 5-HT<sub>4</sub> agonists may bring about cardiovascular unfavourable reactions. A high density of 5-HT<sub>4</sub> receptors in the nucleus accumbens lead to contemplations that these receptors may be included in the prize framework and may impact association toward one's conduct [68]. On the other hand, 5-HT<sub>4</sub> agonists, for example, metoclopramide, mosapride, renzapride and zacopride go about as 5-HT<sub>3</sub> antagonists also. These compounds can't be considered very specific.

#### **1.2.5. 5-HT<sub>5</sub> receptors**

Rodents have been indicated to have two practical 5-HT<sub>5</sub> receptor subtypes, 5-HT<sub>5A</sub> and 5-HT<sub>5B</sub>. Nonetheless, the gene coding the 5-HT<sub>5B</sub> subtype in humans incorporates stop codons making it non-useful which brings about single explanation of just 5-HT<sub>5A</sub> subtype in human cerebrum [69]. The pharmacological property of 5-HT<sub>5</sub> receptors is still to a great extent unclear. In light of their restriction, it has been speculated that they may be included in encouraging, tension, sadness, learning, memory and mental health [70]. 5-HT<sub>5A</sub> receptors may be likewise included in neuron-mediated systems for regulation of astrocyte physiology with significance to gliosis. Interruption of 5-HT neuron-glia collaborations may be included in the improvement of specific CNS pathologies including Alzheimer's disease and Down's syndrome [71].

#### **1.2.6. 5-HT<sub>6</sub> receptors**

Two variants of 5-HT<sub>6</sub> receptor have been described yet. Complete 5-HT<sub>6</sub> receptor is made out of 440 amino acid deposits and patterned dominantly in limbic and extrapyramidal cerebral zones. The second variant (most likely the consequence of cancellation of 286 amino acid deposits) is communicated magnificently in caudatum and substantia nigra [72]. The accurate clinical enormity of 5-HT<sub>6</sub> receptors stays still unclear. Particularly atypical antipsychotics and different antidepressants recommend a possible association between 5-HT<sub>6</sub> receptors and specific psychiatric conditions [73]. This prompted

a theory that one of the parts of 5-HT<sub>6</sub> receptors may control cholinergic neurotransmission and that 5-HT<sub>6</sub>-specific antagonists may be valuable in the medication of nervousness and memory impairments. Particular antagonists of this type of serotonin receptors have an effect on conduct and appear to enhance the spatial memory in animal models [74].

### 1.2.7. 5-HT<sub>7</sub> receptors

The human 5-HT<sub>7</sub> receptor is formed from 445 amino acids and builds the initiation of adenylyl cyclase through G<sub>s</sub> protein pathway. This receptor additionally enacts MAP kinase. Receptor isoforms (5-HT<sub>7A-D</sub>) which contrast in their C-terminal end were portrayed, and all of them showed the same pharmacological properties. 5-HT<sub>7</sub> receptors are additionally communicated in CNS and extravascular smooth muscles (e.g. in the gastrointestinal tract). Atypical antipsychotics, for example, risperidone, clozapine and antidepressants have high natural inclination for 5-HT<sub>7</sub> receptors [75]. Antagonists of 5-HT<sub>7</sub> receptor imitate the effects of SSRIs and may discover demand in the medication of unhappiness and sleep issues [76]. A wide range of physiological functions have been mediated by serotonin by interacting with multiple receptors. These serotonin receptors are implicated in different psychopathological and pathological state.

Amongst all of the serotonin receptors, 5-HT<sub>2C</sub> receptor is of great importance because it mediates several neurological and metabolic responses. Therapeutic potentials of 5-HT<sub>2C</sub> receptor are discussed below.

### 1.3. 5HT<sub>2C</sub> receptor and its therapeutic potentials

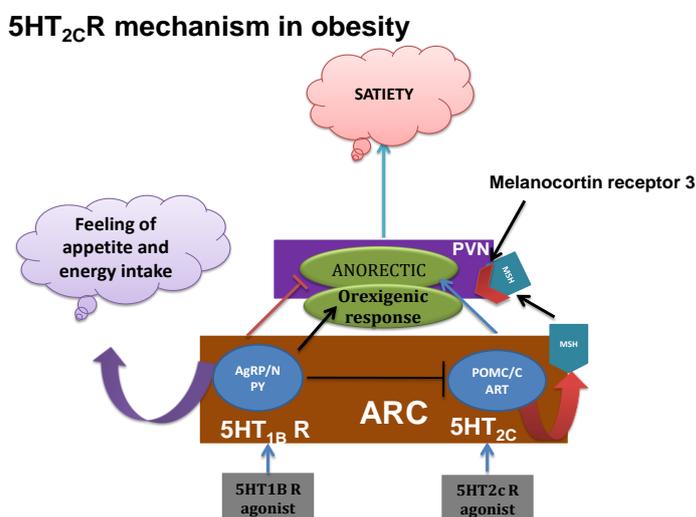
The first cloned serotonin receptor was 5-HT<sub>2C</sub> receptor [77] which was initially named 5-HT<sub>1C</sub> receptor. When additional receptors were identified and on the basis of G-protein coupling and sequence homology, this receptor was reclassified as 5-HT<sub>2C</sub> receptor. The 5-HT<sub>2C</sub> receptor is homologous to 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors on the basis of amino acid sequence, and due to this reason, there are very few isoform-selective antagonists and agonists discovered till date for this receptor. 5-HT<sub>2C</sub> receptor is highly expressed in the choroid plexus, where it may be regulating ion exchange between the brain and the cerebrospinal fluid. Cortex, basal ganglia, amygdala, thalamus and hippocampus are the regions in brain where mRNA and protein of 5-HT<sub>2C</sub> receptor are widely expressed [78]. 5-HT<sub>2C</sub> receptors dominantly regulate mood, anxiety, feeding, and reproductive behavior. Dopamine release is also regulated by 5-HT<sub>2C</sub> receptors in the nucleus accumbens, striatum, prefrontal cortex, amygdala, hippocampus and hypothalamus regions. The therapeutic potentials of 5-HT<sub>2C</sub> receptor have been established on the basis of number of observations received. Better therapeutic approaches can be possible by designing novel chemical agents

which may interact with 5-HT<sub>2C</sub> receptor in different diseases. Some major diseases and their molecular mechanisms in which 5-HT<sub>2C</sub> receptor modulators play important roles are discussed here. Serotonin level in brain is enhanced when an agonist binds with 5-HT<sub>2C</sub> receptor and therefore it is an important upshot to treat several related disorders. Only 5-HT<sub>2C</sub> agonist structures and related disorders are discussed herein [77].

### 1.3.1. Obesity

Obesity persists to be an escalating health predicament world-wide and can lead to the development of many diseased conditions, including hypertension, type-2 diabetes, osteoarthritis, ischemia, stroke and various forms of cancer including that of the colon and the kidney [79]. It is now well established that 5-HT neurotransmission in brain induces hypophagia and it regulates the feeding habits. The molecular mechanism for obesity is discussed here.

Activation of the 5-HT<sub>2C</sub> receptor on pro-opiomelanocortin (POMC) neurons promotes satiety and reduced energy intake via release of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$  MSH) and activation of melanocortin receptors 3 and 4 on neurons located within hypothalamic paraventricular nuclei (PVN). The anorectic POMC/MC pathway is negatively regulated by AgRP/NPY (agouti-related peptide/neuropeptide Y) neurons located within the arcuate nucleus (Figure 1).



**Figure 1:** 5-HT<sub>2C</sub> receptor and molecular mechanism of obesity

Activation of 5-HT<sub>1B</sub> receptors and release of NPY from these neurons suppresses POMC activity, promoting appetite and energy intake. Activation of anorexigenic POMC neurons and suppression of orexigenic AgRP/NPY neurons is postulated to underlie the satiation properties of serotonin and serotonergic pharmaceutical compounds. As a 'selective'

5-HT<sub>2C</sub> agonist, lorcaserin would be expected to interact with POMC but not AgRP/NPY neurons<sup>5</sup>, and to increase satiety and reduce food intake, resulting in a net anorexigenic effect. Serotonin acts in a milieu of other episodic and chronic regulatory signals that converge on central sites of appetite control, including the arcuate nucleus. These signals convey information about energy balance and can come from the periphery (e.g., cholecystokinin, leptin, insulin, ghrelin) and from central sites (e.g., orexin, melanin concentrating hormone, pituitary adenylate cyclase-activating peptide).

Several therapeutic strategies have been tried to control obesity. Before the withdrawal from the market, [±]-fenfluramine and the more active enantiomer dexfenfluramine were considered to be the most effective drugs among the weight loss agents at that time. Dexfenfluramine was the first anti-obesity drug to be approved for a duration of usage in excess of 3 months in the INDEX study [80]. Norfenfluramine, an active metabolite of fenfluramine, is a potent 5-HT<sub>2C</sub> receptor agonist that has similar efficacy as fenfluramine and the results suggest that much of fenfluramine's efficacy results from 5-HT<sub>2C</sub> receptor activation by norfenfluramine. However, fenfluramine and dexfenfluramine were withdrawn from the market following heart valve abnormalities and psychotropic effects, possibly related to the non-selectivity with the central 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors.

Recent preclinical data suggested that selective 5-HT<sub>2C</sub> receptor agonists might be implicated in the regulation of feeding. In 1995, Tecott *et. al.* [81] demonstrated that 5-HT<sub>2C</sub> knockout mice are overweight and resistant to the hypophagic effect of meta-chlorophenylpiperazine (*m*-CPP). *m*-CPP is a non-selective 5-HT<sub>2C</sub> receptor agonist that reduces feeding both acutely and chronically, and thus it produces chronic reduction in body weight. These results implied that a highly selective 5-HT<sub>2C</sub> agonist with a similar efficacy as fenfluramine in humans, without the side effects related to 5-HT<sub>2A</sub> or 5-HT<sub>2B</sub>, could be an attractive target for the discovery of novel treatments for feeding disorders.

### 1.3.2. Anxiety

In mood and anxiety disorders the receptor which is mostly occupied is 5-HT<sub>2C</sub> receptor and is therefore a target for the development of novel anxiolytic drugs [82]. The molecular mechanism responsible in anxiety is discussed below.

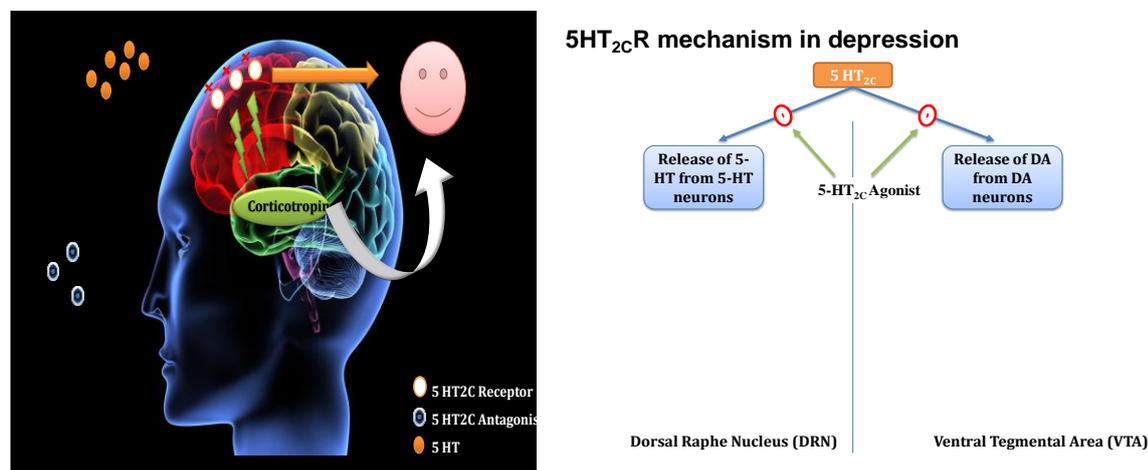
Anxiety which is mainly regulated by amygdala region of the brain, expresses high levels of 5-HT<sub>2C</sub> receptor. There are evidences that demonstrate that activation of amygdala by 5-HT<sub>2C</sub> receptor agonists is strongly associated with anxiety state [83]. So antagonism of 5-HT<sub>2C</sub> receptor might be beneficial for the treatment of anxiety [84, 85]. 5-HT<sub>2C</sub> receptor

mediated modulation of anxiety depends on its ability to regulate corticotropine releasing hormone against stress conditions [86].

In several anxiety animal models, 5-HT<sub>2C</sub> receptor antagonists reduce anxiety-like behaviour at least in an acute fashion [87, 88]. For example, SB-242084, a potent and selective 5-HT<sub>2C</sub> receptor antagonist is anxiolytic in the social interaction test and the Geller-Seifter conflict test of anxiety [89]. Like *m*-CPP, 6-chloro-2-(1-piperazinyl)pyrazine (MK-212), a non-selective 5-HT<sub>2C</sub> agonist, exerts its anxiogenic actions via activation of 5-HT<sub>2C</sub> receptor [90, 91]. SB-242084 blocks the anxiogenic effects of *m*-CPP in rats. Activation of 5-HT<sub>2C</sub> receptors contributes to the anxiogenic effects following acute treatment with SSRIs, which are common antidepressants [92, 93]. Taken together, these studies propose that 5-HT<sub>2C</sub> receptor activation is an essential component of anxiogenesis. A report suggests that 5-HT<sub>2C</sub> antagonists may be effective anxiolytic agents devoid of many usual side effects associated with benzodiazepines (e.g., tolerance and dependence) and SSRIs (e.g., insomnia, agitation and sexual dysfunction).

### 1.3.3. Depression

The pathophysiology of depression states that there is larger involvement of serotonergic neurotransmission and the role of the serotonergic neurotransmitter system in depression is now well established. The molecular mechanism behind involvement of 5-HT<sub>2C</sub> receptor in depression is discussed below.



**Figure 2:** 5-HT<sub>2C</sub> agonist positively regulates firing of 5-HT and DA in DRN and VTA.

5-HT<sub>2C</sub> receptors have influence on the firing of monoamine neurotransmitters. There are some contradictions in case of depression and 5-HT<sub>2C</sub> regulation. The evidences suggest that 5-HT<sub>2C</sub> receptors control firing of 5-HT and DA neurons in the dorsal raphe nucleus (DRN) and ventral tegmental area (VTA) both positively and negatively respectively

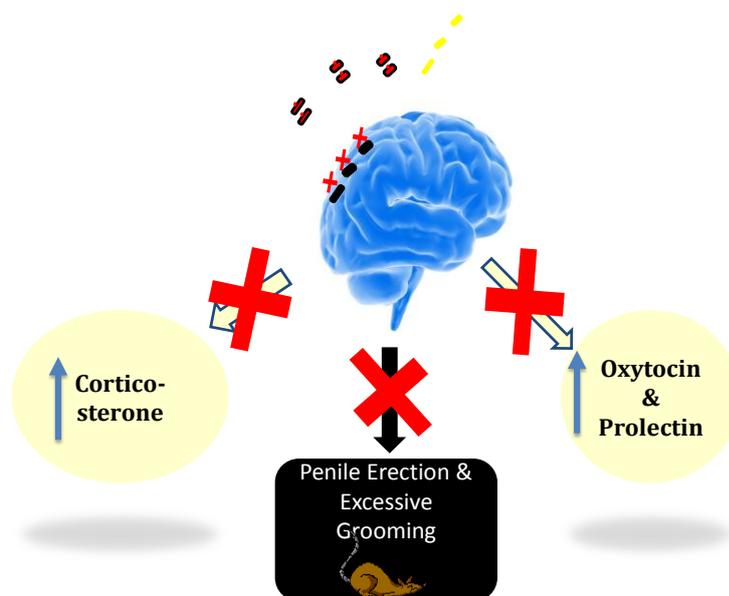
[94-100]. Considering positive regulation, 5-HT<sub>2C</sub> receptor agonists increase the firing of 5-HT and DA neurons (**Figure 2**). 5-HT<sub>2C</sub> receptors are coupled to Gq11 and G13 proteins [101-103]. Gq11-mediated signal transduction pathway involves activation of phospholipase C (PLC) and neuronal excitation via inositol triphosphate (IP<sub>3</sub>)-induced Ca<sup>2+</sup> influx into the neuronal cytoplasm [104]. In addition to that, 5-HT<sub>2C</sub> receptors accelerate the firing of GABA interneurons in the ventral tegmental area [96]. Thus 5-HT<sub>2C</sub> receptor agonists could be an effective tool for the treatment of depression all alone or in combination with SSRI.

The density of 5-HT<sub>2C</sub> receptor and its sensitivity are correlated in humans and experimental models of depression [105, 106]. Therefore, to develop novel antidepressant agents, the role 5-HT<sub>2C</sub> receptor in depression deserves due consideration and should be considered at the time of designing of the compounds to treat depression. Major depressive disorder (MDD) is a foremost health crisis. Increased suicidal propensity and mortality add to the burden of the MDD.

#### 1.3.4. Penile erection

5-HT<sub>2C</sub> receptor mediated penile erection is well known. *m*-CPP, a nonselective 5-HT<sub>2</sub> receptor agonist, is able to induce penile erection and excessive grooming in animal models

### 5HT<sub>2C</sub>R mechanism in penile erection



**Figure 3:** 5-HT<sub>2C</sub> agonist showing penile erection and grooming by increasing corticosterone and prolactin levels. Red ones are selective antagonists and yellow ones are selective agonists for 5-HT<sub>2C</sub> receptor.

along with increased levels of oxytocin, prolactin and corticosterone (**Figure 3**). Paraventricular nucleus is believed to control these behavioural and neuroendocrine responses. RO 60-0175, a selective 5-HT<sub>2C</sub> receptor agonist, mimics m-CPP-induced penile erection. SB-200646 and SB-206553 behave as potent antagonists at 5-HT<sub>2C</sub> vs 5-HT<sub>2A</sub> receptors [107, 108] mediated reversal of penile erection behaviour confirming their 5-HT<sub>2C</sub> receptor selectivity. 5-HT<sub>2C</sub> receptors at the lumbosacral level are strongly associated with the supraspinal serotonergic control of erection [109].