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## Serotonin: A Dive of Pleasure and Misery

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### ABSTRACT

Neurotransmitters are either excitatory or inhibitory. Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter in the brain. Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system and enterochromaffin cells in the gastrointestinal tract. Serotonin is believed to play an important part of the biochemistry of depression, bipolar disorder and anxiety. It is also believed to be influential on sexuality. The name "serotonin" is something of a misnomer and reflects the circumstances of the compound's discovery. This agent was later chemically identified as 5-hydroxytryptamine (5-HT) and as the broad range of physiological roles were elucidated, 5-HT became the preferred name in the pharmacological field.

**Key words:** - Neurotransmitter, receptor, 5-hydroxytryptamine, serotonin, excitatory, inhibitory.

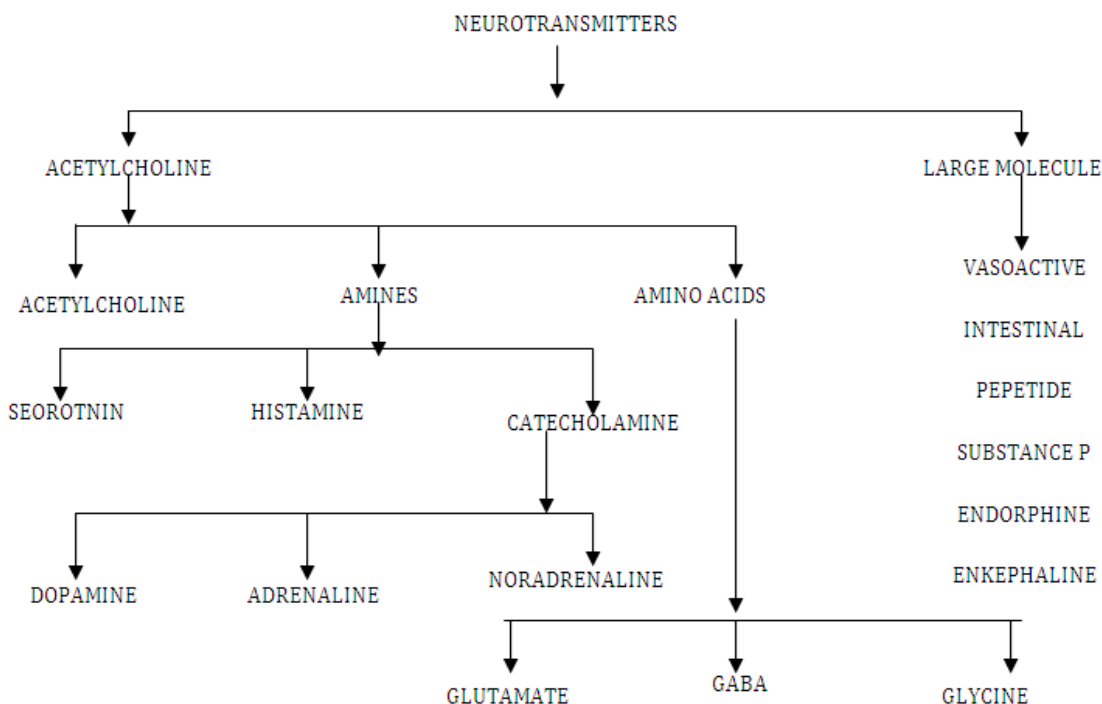
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### INTRODUCTION

5-Hydroxytryptamine (5-HT, serotonin, 3-[ $\beta$ -amino ethyl]-5-hydroxyindole) is widely distributed, occurring in vertebrates, tunicates, molluscs, arthropods, coelenterates, fruits, and nuts. The discovery of serotonin can be traced back to 1868 when it was shown that the serum of clotted blood contained a factor capable of causing vasoconstriction. Eventually the indolamine serotonin was discovered by Rapport et al. (1948) and was to have vasoconstrictor properties and to clot blood. Independently Erspamer (1940) had discovered a factor (called Enteramine) in gut mucosa that was later shown to be identical to serotonin. Twarog page (1953) finally discovered that serotonin was present in the mammalian brain and this led others to prove the neurotransmitter role for this Indolamine. The chemical name for serotonin is 5-hydroxytryptamine which is often abbreviated to 5-HT. Serotonin is naturally produced in the Pineal gland which lies deep at the centre of the human brain. The average adult human possesses only 5 to 10 mg of serotonin, 90 % of which is in the intestine and the rest in blood platelets and the brain. One role of this 'wonder drug' is allowing numerous functions in the human body including the control of appetite, sleep, memory and learning, temperature regulation, mood, behavior, cardiovascular function, muscle contraction, endocrine regulation and depression. Serotonin is also found in wasp stings and scorpion venom where its function is of an irritant, since intravenous injection of serotonin in humans leads to pain, gasping, coughing, a tingling and prickling sensation, nausea, cramps and other unpleasant symptoms. Serotonin taken orally does not pass into the serotonergic pathways of the central nervous system (CNS). This is due to the blood-brain barrier preventing serotonin in the blood stream from affecting serotonin levels in the brain. However, the amino acid tryptophan and its metabolite 5-hydroxytryptophan, from which serotonin is synthesized, are capable of crossing the blood-brain barrier. These agents are available as dietary supplements and may be effective serotonergic agents.

## 2. Different neurotransmitters regulating different functions of the central nervous system

Neurotransmitters of central nervous system can be classified by their function or their chemical structure. Because the function of neurotransmitters vary by location it is often useful to classify them according to their chemical structure<sup>1,2</sup>.



**Fig 2.1: Classification of Neurotransmitters**

### 2.3 Serotonin bio-synthesis

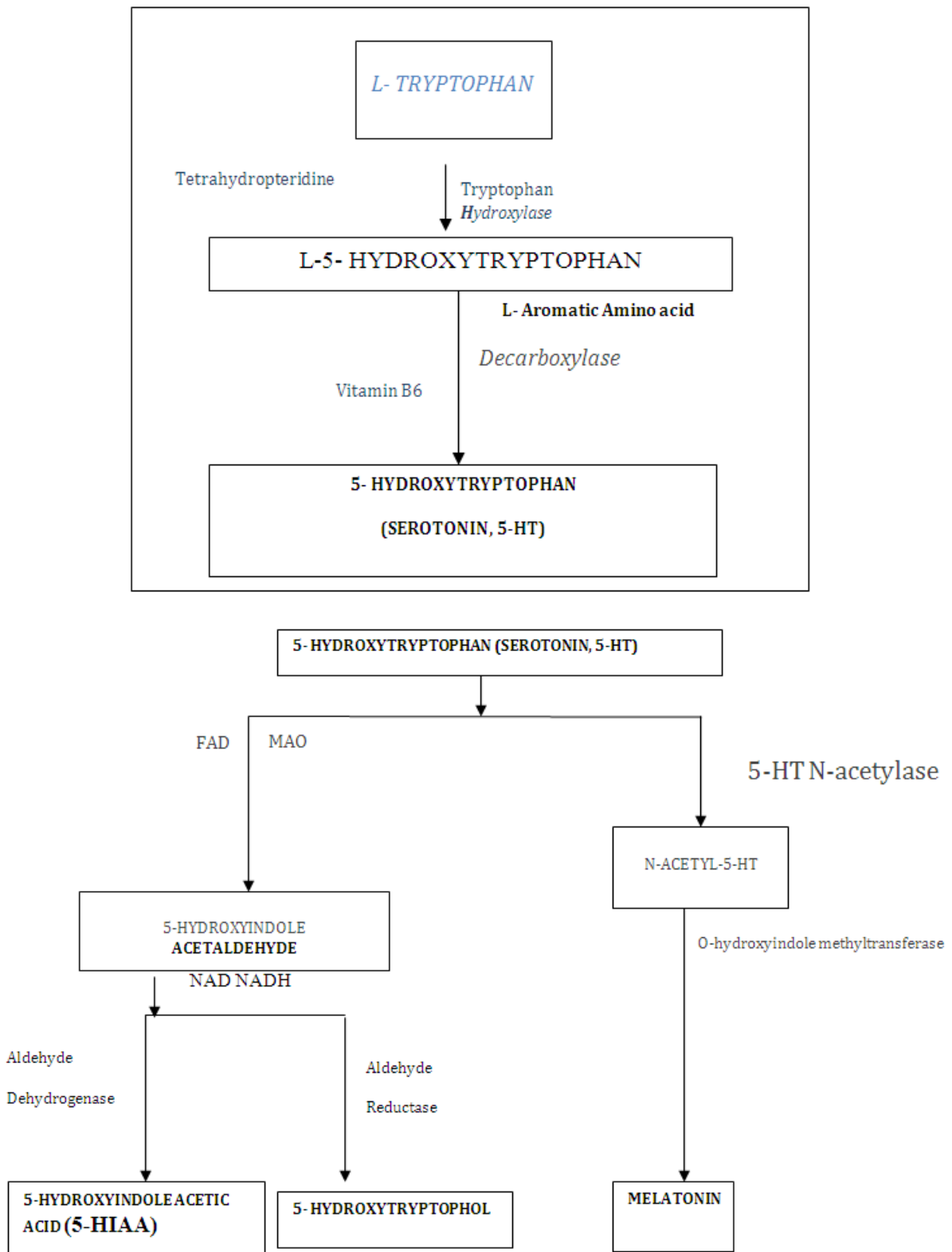
Endogenous 5-HT arises from a two-step biosynthetic pathway with precursor amino acid *tryptophan*, which is actively transported into the brain by a carrier protein that also transports other large neutral and branched chain amino acids.

1. 5-HT is synthesized by a pathway from tryptophan, Tryptophan is converted by tryptophan hydroxylase to 5-hydroxytryptophan. Tryptophan hydroxylase, a mixed-function oxidase (MAO) that requires O<sub>2</sub> and a reduced pteridine cofactor, is the rate-limiting enzyme in the synthetic pathway. Tryptophan hydroxylase is not regulated by end-product inhibition. Brain tryptophan hydroxylase is not generally saturated with substrate; consequently the concentration of tryptophan in the brain influences the synthesis of 5-HT.

L-5-hydroxytryptophan converts to 5-HT by the enzyme Aromatic L-amino acid decarboxylase.

5-HT is stored in the secretory granules by a vesicular transporter and released by exocytosis.

Newly formed 5-HT is rapidly accumulated in synaptic vesicles, where it is ; protected from MAO. 5-HT released by nerve-impulse flow is re-accumulated into the presynaptic terminal by the 5-HT transporter, SERT; thus, reuptake terminates the neurotransmitter action of 5-HT. 5-HT taken up by nonneuronal cells is destroyed by MAO<sup>3</sup>.



## 2.4 Metabolism of serotonin

The principal route of metabolism of 5-HT involves oxidative deamination by MAO, with subsequent conversion of the aldehyde to 5-hydroxyindole acetic acid (5-HIAA) by an aldehyde dehydrogenase. 5-HIAA from brain and peripheral sites of 5-HT storage and metabolism is excreted in the urine.

A close relative of 5-HT, melatonin (5-methoxy-N-acetyltryptamine), is formed by sequential N-acetylation and O-methylation. Melatonin is the principal indoleamine in the pineal gland, where it may be said to constitute a pigment of the imagination, it also serves a role in regulating biological rhythms and shows promise in the treatment of jet lag and other sleep disturbances<sup>3</sup>.

## 2.5 Serotonin Pathways in the CNS

The distribution of 5-HT-containing neurons resembles that of noradrenergic neurons. The cell bodies are grouped in the pons and upper medulla, close to the midline (raphe), and are often referred to as *raphe nuclei*. The rostrally situated nuclei project, via the medial forebrain bundle, to many parts of the cortex, hippocampus, basal ganglia, limbic system and hypothalamus. The caudally situated cells project to the cerebellum, medulla and spinal cord<sup>1</sup>.

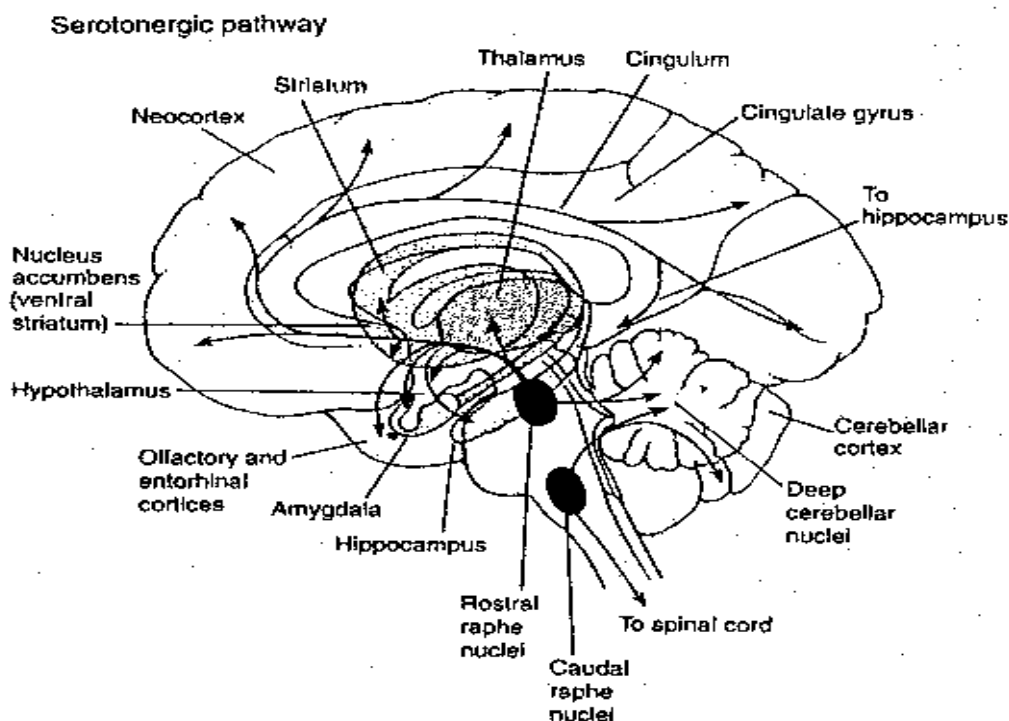


Figure 1.5 serotonin pathways in brain

## 2.6 Serotonin receptors

The multiple 5-HT receptor subtypes comprise the largest known neurotransmitter receptor family. Four 5-HT receptor families are recognized: 5-HT<sub>1</sub> through 5-HT<sub>4</sub>.

### 5-HT<sub>1</sub> Receptors

All 5 members of the 5-HT<sub>1</sub> receptor subfamily inhibit adenylyl cyclase. At least one 5-HT<sub>1</sub> receptor subtype 5-HT<sub>1A, B, C, D, F</sub>.

- The 5-HT<sub>1A</sub> receptor activates a receptor-operated K<sup>+</sup> channel and inhibits a voltage-gated Ca<sup>++</sup> channel, a common property of receptors coupled to the pertussis toxin-sensitive Gi/Go family of G proteins.

- The 5-HT<sub>1A</sub> receptor is found in the raphe nuclei of the brainstem, where it functions as an inhibitory, somatodendritic autoreceptor on cell bodies of serotonergic neurons.
- Another subtype, the 5-HT<sub>1D</sub> receptor, functions as an autoreceptor on axon terminals, inhibiting 5-HT release.
- 5-HT<sub>1B/D</sub> cause constriction of cranial blood vessel. Antimigrain drug sumatriptan is selective 5-HT<sub>1B/D</sub> agonist.

### 5-HT<sub>2</sub> Receptors

The three subtypes of 5-HT<sub>2</sub> receptors couple to pertussis toxin-insensitive. They are G proteins (*e.g.*, Gq and Gil) coupled receptors and PLC to generate *diacylglycerol* and *inositol trisphosphate*

- 5-HT<sub>2A</sub> receptors are broadly distributed in the CNS, primarily in serotonergic terminal areas. High densities of 5-HT<sub>2A</sub> receptors are found in prefrontal, parietal, and somatosensory cortex, claustrum, and in platelets. It mediate most of the direct action of 5-HT like vasoconstriction, intestinal uterine, and bronchial contraction, platelet aggregation and activation of cerebral neurons.
- 5-HT<sub>2B</sub> receptors originally were described in stomach fundus.
- 5-HT<sub>2c</sub> receptors have a very high density in the choroid plexus, an epithelial tissue that is the primary site of cerebrospinal fluid production. The 5-HT<sub>2c</sub> receptor has been implicated in feeding behaviour and susceptibility to seizure.

### 5-HT<sub>3</sub> Receptors

The 5-HT<sub>3</sub> receptor is the only monoamine neurotransmitter receptor. Activation of 5-HT<sub>3</sub> receptors elicits a rapidly desensitizing depolarization mediated by the gating of cations.

- The 5-HT<sub>3</sub> receptor corresponds to the originally described JM receptor.
- These receptors are located on parasympathetic terminals in the GI tract, including vagal and splanchnic afferents. In the CNS, a high density of 5-HT<sub>3</sub> receptors is found in the solitary tract nucleus and the area postrema.

### 5-HT<sub>4</sub> Receptors

5-HT<sub>4</sub> receptors are widely distributed throughout the body.

- In the CNS, the receptors are found on neurons of the superior and inferior colliculi and in the hippocampus.
- In the GI tract, 5-HT<sub>4</sub> receptors are located on neurons of the myenteric plexus and on smooth muscle and secretory cells.

### 2.7 Additional Cloned 5-HT Receptors

- Two subtypes of the 5-HT<sub>5</sub> receptor have been cloned; the 5-HT<sub>5A</sub> receptor couples to inhibit adenylyl cyclase; functional coupling of the cloned 5-HT<sub>5B</sub> receptor has not been described.
- Two other cloned receptors, 5-HT<sub>6</sub> and 5-HT<sub>7</sub>, are linked to activation of adenylyl cyclase.
- Circumstantial evidence suggests that 5-HT<sub>7</sub> receptors play a role in smooth-muscle relaxation in the GI tract and the vasculature<sup>2,3,4</sup>.

### 2.9 Role of serotonin in central nervous system and other systems

Serotonin has tremendous influence over several brain functions, including the control of perception, cognition, sleep, appetite, pain, and mood and mediates these effects through interactions with receptors located throughout the central and peripheral nervous systems.

Studies shows that while both serotonin and hallucinogens act at the serotonin 2A receptor, serotonin utilizes a very specific pathway and its actions are independent of those produced by hallucinogens Future drug discovery efforts to identify lead compounds for treatment of depression may consider focusing upon those that only engage that pathway.

This may be particularly important, for the treatment of depression because traditional therapies, which focus on elevating serotonin levels, can sometimes produce serious side effects such as a serotonin syndrome. This syndrome is often accompanied by hallucinations, and is especially serious when antidepressant treatments such as selective serotonin reuptake inhibitors (SSRIs) are mixed with monoamine oxidase inhibitors (MAOIs).

**2.8 The Main 5 HT Receptor Subtype**

Receptor type	Distribution	Main effect	Second messenger	Partial agonist	Partial Antagonist
5-HT <sub>1A</sub>	Raphe Nucleus, Hippocampus	Neuronal Inhibition Behavioural Effects: sleep, Feeding, Thermoregulation, Anxiety	↓cAMP	5-CT 8-OH-DPAT Buspirone (PA)	Spiperone Methiothepin Ergotamine (PA)
5-HT <sub>1B</sub>	Sustantia Nigra, Globus Pallidus, Basal ganglia	Presynaptic Inhibition Behavioural effects Pulmonary Vasoconstriction	↓cAMP	5-CT Ergotamine (PA)	Methiothepin
5-HT <sub>2A</sub>	CNS PNS Smooth Muscle Platelets	Neuronal Excitation Behavioural effects Smooth muscle Contraction (gut, bronchi, etc.) Platelet Aggregation, Vasoconstriction, vasodilatation	↑IP <sub>3</sub> /DAG	a-Me-5HT LSD (CNS) LSD (periphery)	Ketanserin Cyproheptadine Pizotifen (non-selective) Methysergide
5-HT <sub>2B</sub>	Gastric fundus	Contraction	↑IP <sub>3</sub> /DAG	a-Me-5HT	-
5-HT <sub>2C</sub>	CNS Choroid Plexus	Cerebrospinal fluid Secretion	↑IP <sub>3</sub> /DAG	a-Me-5HT LSD	Methysergide
5-HT <sub>3</sub>	PNS CNS	Neuronal Excitation (autonomic, nociceptive neurons) Emesis Behavioural Effects: anxiety	None- ligand-gated Cation Channel	2-Me-5-HT Chlorophenyl-Biguanide	Ondansetron Tropisetron Granisetron
5-HT <sub>4</sub>	PNS (G1 tract) CNS	Neuronal Excitation GI motility	↑cAMP	5-Methoxy-tryptamine Metoclopramide Tegaserod	Various Experimental Compounds (e.g. GR113808, SB207266)
5-HT <sub>5</sub>	Hippocampus	Not known	Not known	Not known	Not known
5-HT <sub>6</sub>	Striatum	Synaptic Modulation?	↑cAMP	Not Known	Not known
5-HT <sub>7</sub>	Hypothalamus; GI tract Blood vessels	Nociception/ Lisuride Pirenperone Thermo reg.	↑cAMP	5-CT LSD No selective Agonists	Various 5-HT <sub>2</sub> Antagonists No selective antagonists

Similarly, in the brainstem, nerve impulses along presynaptic fibers might release serotonin in minute amounts at synaptic junctions. This release of free serotonin might act as a chemical mediator of responsive brain centers that in turn send impulses along postsynaptic fibers. Ordinarily, free serotonin could be considered to be present at the synapse for only a short time following presynaptic impulses.

### 3. Drug Affecting Serotonin System

**Table 3.1: Drug Related To Synthesis, Storage and Metabolism**

Drug	Action
Tryptophan	5-HT precursor
p-Chlorophenyallanine (PCPA)	Synthesis inhibitors (tryptophan Hydroxylase inhibitor)
Tricyclic antidepressant, Fluoxetine and Sertaline are SSRI	Uptake inhibitor
Reserpine	Storage inhibitor
Nonselective MAO inhibitor (Tranlycypromine) Selective MAO-A inhibitor Clorgyline	Degradation inhibitor
5,6, Dihydroxy Tryptamine	Neuronal degeneration

**Table 3.2 : Serotonin Antagonist**

Drug	Receptor	Action
Cyproheptadine		Intestinal manifestation of carcinoid, post gastrectomy dumping syndrome.
Methylsergide	5-HT <sub>2A/2C</sub> , 5-HT <sub>1</sub>	Migraine, carcinoid, post-gastrectomy dumping syndrome.
Keatserine, Retanserine	5-HT <sub>2</sub>	Antihypertensive
Clozapime	5-HT <sub>2A/2C</sub>	Antipsychotic
Risperidon	5HT <sub>2A+</sub> , D <sub>2</sub>	Antipsychotic
Ondansetron	5-HT <sub>3</sub>	Nootropic activity

### 4. Serotonin and cns related disease

#### 4.1 Depression

Depression is complicated illness which can involve number of contributing risk factors such as physical, emotional, biochemical, and psychological, genetic and social factors. The symptoms of depression may vary from person to person, and also depend on severity of the depression. Depression causes changes in thinking, feeling, behaviour, and physical well-being. Depressed person may experience problems with concentration and decision-making. Negative thoughts and thinking are characteristic of depression. Sometime irritability is a problem of depressed patient and they may have more difficulty controlling their temper. In the extreme, depression is characterized by feelings of helplessness and hopelessness. Social withdrawals, dramatic change in appetite, lack of sexual desire are some behavioural symptoms of depression. The different types of depression are categorized by factors such as severity and cause. Different types of depression include bipolar disorder, cyclothymic disorder, dysthymic disorder, major depression, postnatal depression (PND), seasonal affective disorder (SAD).

#### 4.2 Pathophysiology of depression: the monoamine theory

The monoamine theory of depression became a widely accepted theory<sup>5</sup>. The main biochemical theory of depression is the *monoamine hypothesis*, proposed by Schildkraut in 1965, which stated that depression is caused by a functional deficit of monoamine transmitters such as catecholamines and serotonin at certain sites in the brain'. The abnormalities of monoamine in depression are related to deficiency with monoaminergic transmission in the brain, synthesis, storage and metabolism of monoamine, activity of known monoaminergic pathways. Along with functional deficit of monoamine transmitter, wrong neurotransmitter receptor function is associated to depression. There is reduction in the function of serotonin receptors, postsynaptic  $\alpha_2$  adrenergic receptor, GABA, dopamine receptor.

#### 4.3 Intracellular hypothesis

Despite the range of alterations observed in neurotransmitter levels and their interaction with the respective receptors, signalling pathway abnormalities have been shown to be directly related to a series of neurotransmission system alteration. In depressed condition there are changes in intracellular events which result from signal to second intracellular messenger such as G-protein, adenylyclase etc. Studies showed that an increased in stimulatory G - protein level in the frontal, temporal and occipital cortices of individuals with depression. Postmortem studies and studies of peripheral cells in the patient with depression have consistently shown an increases in adenylyclase, an enzyme that converts ATP in the cyclic AMP(cAMP) which activate protein kinase A(PKA), an enzyme that

regulate various neurobiological changes. It was also observed that increase levels of phosphatidylinositol (PIP2) in the platelet of depressive patient.

#### 4.4 Serotonin and depression

The serotonin (5-HT) hypothesis of depression is more than 40 years old<sup>1</sup>. This hypothesis proposes that diminished activity of 5-HT pathways plays a causal role in the pathophysiology of depression<sup>8</sup>. This serotonin depletion hypothesis of depression based on following evidence:

#### 4.5 Tryptophan Depletion and Depression

"Tryptophan depletion" is one approach to elucidate the role of 5-HT in depression<sup>8</sup>. There are several reports that for plasma L-tryptophan (L-TRP), availability is significantly lower in subjects with major depression than in normal controls<sup>9</sup>. Because the amino acid L-tryptophan (L-TRP) is precursor of 5-HT and conversion of tryptophan to 5-hydroxytryptophan by tryptophan hydroxylase is the rate-limiting step in 5-HT synthesis. This tryptophan depletion is able to produce a transient lowering of brain 5-HT activity. Thus tryptophan depletion interferes with 5-HT synthesis and decreased serotonergic activity in major depression. Decreased plasma L-TRP concentrations are most likely related to lower central presynaptic 5-HT activity<sup>10</sup>. One hypothesis to explain lower plasma L-TRP concentrations and altered L-TRP pharmacokinetics in depression is enhanced catabolism of L-TRP in the liver by induction of pyrrolase, the first rate-limiting enzyme of the kynurenine-nicotinamide pathway<sup>10</sup>.

#### 4.6 Plasma or platelet serotonin contents:

Blood platelets are able to take up, store, and release 5-HT by mechanisms that are sufficiently similar to those of central 5-HT neurons<sup>10</sup>. It presents as an easily accessible marker of 5-HT function, which in the absence of the sophisticated neuro-imaging techniques that are now becoming available, has provided much information regarding the adaptations to the serotonergic system in major depression and other psychiatric disorders. 5-HT turnover is reduced in depressed subjects who have committed suicide<sup>10</sup>.

#### 4.7 5-HT pathway in depression

Basal ganglia structures (e.g., frontal cortex, striatum and substantia nigra) are primarily innervated by those in the dorsal raphe<sup>12</sup>. It was suggested that the pathway connecting the median raphe nucleus (MRN) to the hippocampus system involve in depression<sup>13</sup>

#### 5-HT receptor

Out of 14 distinct mammalian 5-HT receptor subtypes 5-HT<sub>1</sub> and 5-HT<sub>2</sub> subtypes are involved in depression. Many studies on serotonergic alteration in brain region tissue by employing brain imaging technique. 5-HT<sub>1A</sub> receptors are likely to be the main target of the MRN (Median Raphe Nucleus)-hippocampus. A reduced number of hippocampus 5-HT<sub>1A</sub> receptors in post-mortem brains of depressed suicides have been reported<sup>14</sup>. This suggests that reduction in 5-HT<sub>1A</sub> function is associated with depression. The number of 5-HT<sub>1</sub> binding sites was significantly lower in hippocampus, whereas the affinity of 5-HT<sub>1</sub> binding sites was significantly lower in the amygdala. These results may provide some evidence of increased cortical 5-HT<sub>1</sub> receptors in (depressed) suicides, and decreased density of 5-HT<sub>1</sub> receptors in the hippocampus and amygdala of depressed subjects. Major depression is characterized by a down-regulation or hyporesponsivity of postsynaptic 5-HT<sub>1A</sub> receptors<sup>10</sup>.

#### 5-HT<sub>2</sub> receptor

Post-mortem tissue studies are found an increase in 5-HT<sub>2</sub> receptors in cortical regions of depressed suicide victims, especially the prefrontal cortex<sup>9</sup>. 5-HT<sub>2</sub> binding in the blood platelets of depressed patients increased. Increased 5-HT<sub>2</sub> binding (B<sub>max</sub>) in depressed patients is also supported by the increased 5-HT<sub>2</sub> receptor functional response as measured by phosphoinositide turnover and 5-HT-induced platelet aggregation. Mikuni et al. reported that the effects of 5-HT to increase intracellular calcium in platelets was greater in depressed patients than in controls, which is consistent with the hypothesis of 5-HT<sub>2</sub> receptor up-regulation in depression<sup>10</sup>.

and dendrites, type ID at terminals). This mechanism involved over several weeks with a return or increase of presynaptic activity, production, and release of 5-HT<sup>3</sup>.



### Antagonist

The Phenylpiperazine Nefazodone has a prominent direct antagonistic effect at 5-HT<sub>2A</sub> receptors that may contribute to antidepressant. Finally, the atypical antidepressants Mirtazapine and Mianserin are structural analogs of 5-HT with potent antagonistic effects at several postsynaptic 5-HT receptor types (including 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub> receptors) and can produce gradual down-regulation of 5-HT<sub>2A</sub> receptors<sup>3</sup>. Moreover the antidepressant efficacy of ritanserin a pure 5-HT<sub>2</sub> antagonist has been established<sup>13</sup>.

### 4.8 Monoamine Oxidase Inhibitors (MAOIS)

MAO regulates the metabolic degradation of catecholamines, 5-HT, and other endogenous amines in the CNS and peripheral tissues. *The MAOs comprise two structurally related flavin-containing enzymes, designated MAO-A and MAO-B.* MAO-A preferentially deaminates Epinephrine, NE, and 5-HT, is selectively inhibited by Clorgyline, Moclobemide and MAO-B metabolizes Phenethylamine, is inhibited by Selegiline. Selective MAO-A inhibitors are more effective in treating major depression than MAO-B inhibitors. Selegiline also has antidepressant effects, particularly at doses >10 mg that also inhibit MAO-A or yield amphetamine-like metabolites. Several shortacting selective inhibitors of MAO-A (e.g., Brofaromine and Moclobemide) and Toloxatone, nonselective, irreversible MAO inhibitor, have at least moderate antidepressant effects<sup>3</sup>.

### 5. Nootropic Activity

Cognitive functions can be defined as an animal's capability to collect, encode, treat, store and use any kind of knowledge about its environment. Learning is defined as the acquisition of information and skills, and subsequent retention of that information is called memory<sup>15</sup>.

#### 5.1 The role of serotonergic-cholinergic interaction in the medication of cognitive behaviour

Cholinergic systems have been closely linked to cognitive processes such as attention, learning function. Along with acetylcholine other neurotransmitter systems such as serotonin (5-hydroxytryptamine, 5-HT) is thought to be involved in these processes. There is increasing evidence that 5-HT and ACh neurotransmitter systems have considerable functional interactions in learning and memory processes<sup>16</sup> drugs acting at serotonergic systems influence human as well as animal cognition; serotonergic neurons degenerate in disorders associated with dementia and animals with serotonergic lesions exhibit alterations in tasks aimed at measuring cognitive behaviour. There is considerable evidence that acetylcholine release is under an inhibitory 5-hydroxytryptaminergic tone. Therefore; decrease serotonin release is responsible for increase release of acetylcholine from striatum<sup>7</sup>.

There have been a great many reports regarding the existence of serotonergic perturbations associated with age-related cognitive disorders such as Alzheimer in the frontal cortex and hippocampus produced either by the long-term residual neurotoxic effects of p-chloroamphetamine (i.e., 24-h and 1-week injection) or by neurotoxic lesions of the dorsal raphe nucleus, failed to affect retention scores<sup>18</sup>. Evidence from invertebrates to human studies indicates that serotonin (5-hydroxytryptamine; 5-HT) system modulates short- (STM) and long-term memory (LTM)<sup>19</sup>. Anatomical interaction

Medial septum (MS); the vertical limb of the diagonal band of Broca (vDBB) the horizontal limb of the diagonal band of Broca (hDBB) and the nucleus basalis magnocellularis (NBM) of basal forebrain and the pedunculopontine tegmental nucleus (PPTg) and the laterodorsal tegmental nucleus (LTDg), of cholinergic brainstem nuclei are important cholinergic pathways involve in learning activity. Dorsal raphe nucleus (DR) and Medial raphe nucleus (MR), both pathways of serotonin interact with above cholinergic pathways.

Two important considerations derive from anatomical data: first, there are serotonergic projections to the basal forebrain and it appears that the MS and vDBB receive projections mainly from the MRN, whereas the DRN appears to be the primary source of serotonergic projections to hDBB and NBM. Similarly, there are projections from DR and central superior raphe nuclei to the PPTg and LTDg where serotonergic projections also synapse directly at cholinergic neurons. Thus; there are anatomical evidences for direct interactive processes between serotonergic and cholinergic systems, whatever the behavioural significance. Second, there is also evidence for ongoing indirect interactive processes at the level of convergent Projection areas of the two neurotransmitter systems: Serotonergic neurons innervate the hippocampus, the primary target of MS and vDBB cholinergic neurons, cortical areas and the amygdala, which are both innervated by the NBM. Moreover, there are serotonergic projections to thalamic and hypothalamic nuclei and to the substantia nigra, which also receive dense cholinergic innervations from brainstem cholinergic nuclei and/or NBM. Based on these anatomical findings, it may be

suggested that there are different serotonergic-cholinergic interactive systems. One system could be described as the MR-MS/vDBB-hippocampal, the other as the DR-NBMcortical/ amygdaloid system. A third system important in interactive terms could be the DR/MR-PPTg/LTDg thalamic and/or nigral system and activation or inhibition of the different systems could have different effects on cognitive behaviour<sup>20</sup>.

## 5.2 Serotonin receptor and memory

There are different distributions of serotonergic receptor subtypes within the brain and thus serotonergic-cholinergic drug interaction of importance for the context of this review are the 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>7</sub>.

### 5-HT<sub>1A</sub> receptor

The 5-HT<sub>1A</sub> receptor is highly concentrated in cortical and limbic brain areas associated with memory functions. 5-HT<sub>1A</sub> receptor present at the somatodendritic inhibitory autoreceptor and postsynaptic located in hippocampus pyramidal and granule cells are involved in cognitive function. Drugs acting at the 5-HT<sub>1A</sub> receptor can, depending on the dosages, inhibit or enhance 5-HT<sub>1A</sub> receptor function, resulting in varying modulatory effects on key neurotransmitters (glutamate, GABA, and acetylcholine (ACh)) involved in cognition<sup>21</sup>.

Studies using the original full 5-HT<sub>1A</sub> agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), other agonists such as tandospirone, and partial agonists such as buspirone, in rodents have shown a range of responses in cognitive tasks from improvement to impairment. 8-OH-DPAT showed a biphasic dose effect, with low doses (presynaptic specific) causing facilitation and high doses (pre plus postsynaptic receptor activation) causing impairment. Administration of 8-OH-DPAT into the raphe nuclei, which contain serotonergic neuron cell bodies, causes inhibition of 5-HT neuronal firing via activation of the dendritic inhibitory 5-HT<sub>1A</sub> autoreceptors in this brain area, which results in decreased 5-HT release from terminal 5-HT-neurone projection areas. Therefore; decrease serotonin release is responsible for increase release of acetylcholine from striatum<sup>17</sup>.

Administration of 8-OH-DPAT with high doses (pre plus postsynaptic receptor activation) causing impairment, because these high dose of act on postsynaptic 5-HT<sub>1A</sub> receptor located in hippocampus. In the hippocampus, postsynaptic 5-HT<sub>1A</sub> receptor has been localized to excitatory pyramidal and granular cells of the hippocampus. Pyramidal cell firing is inhibited by 5-HT<sub>1A</sub> receptor agonists, and such agonists have also been shown to interfere with NMDA receptor-mediated excitation. There are many examples, using a range of tests, showing that selective 5-HT<sub>1A</sub>-receptor antagonists, including WAY-10635 and NAD-299, reverse deficits in learning and memory induced by 5-HT<sub>1A</sub> agonists. The cognitive improvements observed with 5-HT<sub>1A</sub> antagonists being mediated by postsynaptic 5-HT<sub>1A</sub> receptors, it is still unclear which other neurotransmitters and mechanisms are involved. Both WAY-100635 and WAY-101405 increase extracellular acetylcholine in the hippocampus. Alternatively, the action might be through enhancement of glutamate function, which increases after treatment with Lecoctan, another selective 5-HT<sub>1A</sub>-receptor antagonist<sup>21</sup>.

### 5-HT<sub>3</sub> receptor:

5-HT<sub>3</sub> receptors mediate inhibition of acetylcholine release in cortical tissue. Radioligand binding studies show a high density of 5-HT<sub>3</sub> receptor in the cholinergic rich cortex ; so reduction in cortical cholinergic function can effected by 5-HT<sub>3</sub> receptor. Release of acetylcholine from rat entorhinal cortex was stimulated by potassium. Selective 5-HT<sub>3</sub> receptor agonist 2-methyl 5-HT inhibited potassium stimulated acetylcholine release . 5-HT<sub>3</sub> antagonist such as Ondansetron and Ganisetron enhanced basal and potassium stimulated Ach release from slices of rat entorhinal cortex and striatum. 5-HT<sub>3</sub> receptors present on GABAergic interneurons of hippocampus and cortex are involved in cognitive function<sup>27</sup>. In the entorhinal cortex, 5-HT<sub>3</sub> receptor antagonist block the excitatory influence of 5-HT on 5-HT<sub>3</sub> receptor on GABA neuron and inhibit the inhibitory influence of GABA on cholinergic neurons and increase activity of cholinergic system<sup>2</sup>.

### 5HT<sub>2A/2C</sub> receptors

At the systems level, the activation of 5HT<sub>2A/2C</sub> receptors induces a facilitatory effect on cholinergic release in the rat frontal cortex<sup>24</sup> it was observed to enhance learning. This suggests the use of 5HT<sub>2A/2C</sub> agonists as therapeutic tools for the treatment of severe memory deficits in humans.

### 5-HT<sub>4</sub> receptor

The number of hippocampal 5-HT<sub>4</sub> receptors is reduced in patients with Alzheimer's disease. 5-HT<sub>4</sub> receptor agonists stimulate adenylate cyclase, thereby increasing cAMP levels and decreased in hyperpolarisation that may

cause increase in neuronal excitability and increase the release of acetylcholine in the rat frontal cortex. These basic modifications in neuronal excitability and/or neurotransmitter release by 5-HT<sub>4</sub> ligands in anatomical structures linked to memory and suggest an active involvement of these receptors in learning. RS67333, a selective 5-HT<sub>4</sub> agonist, antagonizes the performance induced by atropine in rats on the Morris water maze; his effect is reversed by RS67532, a selective 5-HT<sub>4</sub> antagonist<sup>24</sup>.

## 6. Mechanism of serotonin

Serotonin reuptake transporters (SERTs) are dependent on extracellular Na<sup>+</sup> and extracellular Cl<sup>-</sup>. Unlike Na<sup>+</sup>, Cl<sup>-</sup> can be at least partly substituted for by NO<sub>2</sub><sup>-</sup>, Br<sup>-</sup>, and other anions. Intracellular potassium (K<sup>+</sup>) is also used in the process but can be replaced by other ions, most notably hydrogen (H<sup>+</sup>). The driving force for the energetically unfavorable transport of serotonin is the Na<sup>+</sup> influx down its concentration gradient. The Na<sup>+</sup>/K<sup>+</sup> pump (Na<sup>+</sup>/K<sup>+</sup> ATPase) maintains the extracellular Na<sup>+</sup> concentration as well as the intracellular K<sup>+</sup> concentration. Na<sup>+</sup>/K<sup>+</sup> ATPase pumps three Na<sup>+</sup> ions out for each two K<sup>+</sup> ions pumped into the cell. The electrical potential produced, in addition to creating the Na<sup>+</sup> concentration used by the transporter protein, also leads to the loss of Cl<sup>-</sup> ions from the cell which is also used in transport. The first step occurs when Na<sup>+</sup> binds to the carrier protein. Serotonin, in its protonated form (5HT<sup>+</sup>), then binds to the transporter followed by Cl<sup>-</sup>. Chloride ions are not required for 5HT<sup>+</sup> binding to occur but are necessary for net transport to take place. The initial complex of serotonin, Na<sup>+</sup>, and Cl<sup>-</sup> creates a conformational change in the transporter protein. The protein, which began by facing the outside of the neuron, moves to an inward position where the neurotransmitter and ions are released into the cytoplasm of the neuron. Intracellular K<sup>+</sup> then binds to the SERT to promote reorientation of the carrier for another transport cycle. The unoccupied binding site becomes, once again, exposed to the outside of the cell and the K<sup>+</sup> is released outside the cell.

### 6.1 Factors affect serotonin level reduction

- Stress
- PCB's, pesticides and plastic chemicals exposure
- Under-methylation
- Inadequate sunlight exposure
- Tryptophan (precursor) deficiency
- Iron, calcium, magnesium, zinc, B3, B6, folate & vitamin C deficiency
- Inadequate sleep
- Glutathione deficiency
- Chronic infections
- Food allergies
- Genetic serotonin receptor abnormalities
- Chronic opioid, alcohol, amphetamine & marijuana use
- Human growth hormone deficiency
- Progesterone deficiency
- Impaired blood flow to brain
- Insulin resistance or deficiency

## 7. Use of serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter in the brain that has an enormous influence over many brain functions. The functions of serotonin are numerous and appear to involve control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including sexual and hallucinogenic behavior), cardiovascular function, muscle contraction, endocrine regulation, and depression. Due to the widespread distribution of serotonin in the nervous system, it is not surprising that this neurotransmitter can be linked to many types of behavior. Serotonin is perhaps the most implicated in the treatment of various disorders, including anxiety, depression, obsessive-compulsive disorder, schizophrenia, stroke, obesity, pain, hypertension, vascular disorders, migraine, and nausea. The linkage of serotonin to depression has been known for the past five years. From numerous studies, the most concrete evidence of this connection is the decreased concentration of serotonin metabolites like 5-HIAA (5-hydroxyindole acetic acid) in the cerebrospinal fluid and brain tissues of depressed people. If depression, as suggested, is a result of decreased levels of serotonin in the brain, pharmaceutical agents that can reverse this effect should be helpful in treating depressed patients. Therefore, the primary targets of various antidepressant medications are serotonin transports of the brain. Since serotonin is activated when released by neurons into the synapse,

antidepressants function at the synapse to enhance serotonin activity. Normally, serotonin's actions in the synapse are terminated by its being taken back into the neuron then releases it at which point "it is either recycled for reuse as a transmitter or broken down into its metabolic by products and transported out of the brain. As a result, antidepressants work to increase serotonin levels at the synapse by blocking serotonin reuptake. The newest medications used to suppress depression are collectively known as selective serotonin inhibitors (SSRIs). Unfortunately, although these SSRIs are effective in treating depression and are the least toxic of the antidepressants, they do produce some harmful side effects. In fact, some have defined the presence of certain side effects due to SSRIs as "serotonin syndrome."

The serotonin syndrome is generally caused by a combination of two or more drugs, one of which is often a selective serotonergic medication.

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