

# Role of Serotonin Type-1A/B (Hydroxytryptamine) Receptors in Depression Revisited

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## ABSTRACT

Depression is among the common psychiatric disorders, therefore the common pathways and pathogenesis associated with depression is required to be studied. In few years, role of 5-hydroxytryptamine-1A/B (5-HT<sub>1A/B</sub>) receptors in depressive disorders have been revealed. Both preclinical and clinical studies reported that the potential agonist and antagonist at 5-HT<sub>1A/B</sub> receptors have significant modulatory effects in depression. However, the collective details regarding the involvement of 5-HT<sub>1A/B</sub> receptors and the molecular pathways associated in depression is lacking. Thus, the present review evidence the link between 5-HT<sub>1A/B</sub> receptors in the brain and depression, the possible pathways involved and their alterations in depression. Further, it reviews the preclinical evidences of 5-HT<sub>1A/B</sub> receptor modulators as antidepressant agents and their effectiveness. The current review also details the clinical relevance of 5-HT<sub>1A/B</sub> receptors etiopathogenesis of major depression in humans.

## Introduction

Depression is one of the most common psychiatric disorders that affect a large chunk of the population. It is estimated that roughly 6.6% of the US population suffers from some form of depression.<sup>[1]</sup> Worldwide it is estimated by WHO that 350 million people belonging to all age groups suffer from some or the other form of depression.<sup>[2]</sup> With such a huge portion of the population suffering from depression, the quest for the ideal antidepressant is never ending.


Depression can be defined as a psychiatric condition characterized by symptoms of pessimism, apathy, loss of interest in pleasurable activities, loss of hope with biological symptoms such as loss of appetite, loss of libido, and insomnia. The symptoms of depression can vary from being mild to severe depression that can also further

make a person susceptible to suicide.<sup>[3-5]</sup> Almost 1 million depressed patients commit suicide every year, which translates to 3000 suicide deaths every day. For every person who commits a suicide, 20 or more may attempt to end their life.<sup>[2]</sup> Therefore, the understanding of pathophysiology underlying the depressive episodes is necessary for better diagnosis and increasing the therapeutic outcome.

The role of monoamines in depression is well-established. Biological amines namely serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) have been proved to be involved in depression.<sup>[6-8]</sup> Biochemically, depression can be explained on the basis of the monoamine hypothesis, which states that monoamine imbalance or more specifically neurotransmitter deficiency in certain areas in the brain is responsible for depression. According to the monoamine hypothesis, depression can result due to decreased levels of 5-HT and NE in the brain.<sup>[9-11]</sup> 5-HT is primarily found in the raphe nuclei in the brain where it is responsible for mediating a variety of functions while NE is present in the locus coeruleus in the brain. These neurotransmitters have been reported to be involved in the regulation of mood and behavioral activities.<sup>[12-17]</sup> 5-HT mediates its action in the central nervous system (CNS) through the different receptor sub-types out of which 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> are primarily thought to be involved in depression.<sup>[18-21]</sup>

Hence, it's not surprising that the currently available drugs for depression aim at increasing the concentration of brain 5-HT levels through various mechanisms including blocking its reuptake or inhibiting its metabolism.<sup>[22-26]</sup>

The thrust for developing antidepressants has shifted from classical approaches, which mainly aimed at increasing serotonin concentrations at all the serotonin receptors nonselectively to developing molecules that selectively act as agonists or antagonists

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at individual receptor sub-classes. This development was the result of expansion of knowledge about the various 5-HT receptor subtypes, their characteristic function and the signaling mechanisms involved therein. This review is aimed at studying the advances in the 5-HT<sub>1A/1B</sub> receptors and their involvement in depression. Further, it reviewed the molecular pathways involved in the role of 5-HT<sub>1A/1B</sub> receptors associated with depression. The present review also enlisted the possible preclinical and clinical relevance of the 5-HT<sub>1A/1B</sub> receptors modulators in depressive disorders. Therefore, this detailed review will help to assess the future targets to be associated with depression and may help in better understanding of 5-HT<sub>1A/1B</sub> receptors in CNS circuits as well as their correlation with depression disorders.

## Pathophysiology of depression

The pathophysiology of depression, which was first explained by the monoamine hypothesis gives us an insight about the mechanisms involved in the chain of events that finally lead to the depletion of serotonin in the CNS and the associated symptoms of depression.<sup>[27-29]</sup>

## Monoamine hypothesis

### The classic hypothesis of depression

The monoamine hypothesis was put forth from various observations with regards to pharmacological agents that interfered with the levels of monoamines in the brain. These also included the agents that were used to treat depression.<sup>[9,30-34]</sup>

The involvement of monoamines in depression was first observed with reserpine, a centrally acting sympatholytic drug, which caused depression like symptoms in animal models.<sup>[35,36]</sup> Further, it was also revealed that iproniazid, an antitubercular agent elevated depressed mood and it was hypothesized to work by inhibiting the monoamine oxidase enzymes, thereby elevating the levels of serotonin and NE.<sup>[37,38]</sup> Classical tricyclic antidepressants were found to act by inhibiting the reuptake of NE in the presynaptic neurons.<sup>[39-41]</sup> Similarly, other antidepressants which were actively used in therapy were all found to increase monoamine levels in the presynaptic neurons.

However, the increase in the levels of monoamines alone could not explain the lag in the improvement of symptoms that was observed after antidepressant therapy initiation.<sup>[42,43]</sup> It then led to the conclusion that increase in the levels of monoamines along with some other factors is involved in the process and that is when the concept of involvement of 5-HT receptors came into the picture.

### 5-hydroxytryptamine<sub>1A/1B</sub> receptors and their involvement in depression

The existence of three types of serotonin receptors was confirmed by the year 1986 and more receptor subtypes were further characterized and classified with advancements in molecular pharmacology.<sup>[44-48]</sup> Accordingly, current studies have revealed that seven subtypes of serotonin receptors are known from 5-HT<sub>1</sub> to 5-HT<sub>7</sub>, and some of them have been further sub-classified.

While the involvement of serotonin in depression was proved, it was obvious that 5-HT receptors have an equal role to play in

the pathogenesis and treatment of depression. Further advances also proved the existence of seven types of 5-HT receptors and their subtypes, playing, at least in part, a role in neuropsychiatric disorders such as depression. The involvement of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors in depression has been discussed in further in the following pages.

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

The 5-HT<sub>1A</sub> receptor is a trans membrane tertiary structure with sites for glycosylation and phosphorylation.<sup>[49,50]</sup> The human 5-HT<sub>1A</sub> receptor is localized on chromosome number 5.<sup>[51]</sup> The receptor is largely located in various areas of the brain including but not limited to hippocampus, cortical areas, and raphe nuclei.<sup>[52-54]</sup> The signaling in the 5-HT<sub>1A</sub> receptor is dependent on cyclic adenosine monophosphate (cAMP), potassium conductance and phosphatidylinositol turnover.<sup>[55-57]</sup>

The role of 5-HT<sub>1A</sub> receptors in depression was established from studies related to selective agonists and antagonists of the 5-HT<sub>1A</sub> receptor. 8-hydroxy-2-(di-n-propyl amine) tetralin and gepirone act as selective agonists at the 5-HT<sub>1A</sub> receptor while WAY100635 acts as a selective antagonist.<sup>[21,58-61]</sup> Work by Detke *et al.* have proved that selective agonists of 5-HT<sub>1A</sub> are involved in depression. Using the standard model for studying antidepressant activity namely the FST, Detke *et al.* were able to prove that selective agonists of 5-HT<sub>1A</sub> receptor show antidepressant activity which is observed as a decrease in the immobility time in the FST.<sup>[62,63]</sup>

These studies with selective drugs of 5-HT<sub>1A</sub> receptor also demonstrated that two types of receptors exist namely, presynaptic, and postsynaptic receptors.<sup>[64]</sup> Studies have also revealed that the number of 5-HT<sub>1A</sub> receptors is increased following antidepressant therapy in rodents in the hippocampus.<sup>[65,66]</sup> This theory is further cemented by the fact that the expression of 5-HT<sub>1A</sub> was largely decreased in suicide victims with a history of depression.<sup>[67,68]</sup>

### 5-hydroxytryptamine<sub>1B</sub> receptor

The 5-HT<sub>1B</sub> receptor is a G-protein coupled receptor that shares many of its features with 5-HT<sub>1D</sub> receptor. It is found extensively in the striatum, basal ganglia and the frontal cortex and is encoded by Chromosome 6, at 6q13.<sup>[69-73]</sup> The 5-HT<sub>1B</sub> receptor signaling is dependent on the Go/Gi subset of the G-protein coupled receptors and adenylyl cyclase is the secondary messenger involved in the signal transduction of the 5-HT<sub>1B</sub> receptor.<sup>[74]</sup>

As stated earlier that the 5-HT<sub>1B</sub> shares many of its features with the 5-HT<sub>1D</sub> receptor subtype. Studies have indicated that these receptors share more than 75% of their features.<sup>[75,76]</sup> This could mean that agonists at the 5-HT<sub>1D</sub> receptor could also be explored for their antidepressant like activity.

### Signaling in 5-hydroxytryptamine<sub>1A/1B</sub> receptor

As stated above 5-HT<sub>1B</sub> receptors function via Go/Gi variants of the G-protein coupled receptors which in turn inhibits the release of the adenylyl cyclase. Though adenylyl cyclase inhibition seems to be the major signal transduction pathway involved, there are many other mechanisms by which 5-HT<sub>1B</sub> receptors act which might explain the role they play in the pathophysiology of depression.<sup>[77]</sup>

### Inhibition of adenylyl cyclase and cyclic adenosine monophosphate-responsive element-binding levels

Inhibition of adenylyl cyclase is of the most important mechanisms by which 5-HT<sub>1B</sub> receptors in the CNS function. Inhibition of adenylyl cyclase occurs since the 5-HT<sub>1B</sub> receptors are coupled to inhibitory Go/Gi subunits and this leads to mobilization of calcium stores inside the cell and activation of certain calmodulin kinases. This in turn leads to stimulation of cAMP-responsive element-binding (CREB) protein and further downstream processes occur.<sup>[78,79]</sup>

It is also worthwhile to examine the signaling mechanisms involved with respect to 5-HT<sub>1A</sub> receptors. 5-HT<sub>1A</sub> receptors are coupled to Gi subunit of G-protein coupled receptors. Thus, stimulation of these receptors leads to calcium ion mobilization, which in-turn is responsible for an activation of calcium dependent calmodulin kinases. Chronic antidepressant treatment has also supported this view. CREB acts as one of the substrates for binding with protein kinase-A (PK-A) and calcium dependent calmodulin kinases.<sup>[78]</sup>

Chronic antidepressant treatment in rats has revealed that in the majority of cases the levels of CREB increased. The levels of phosphorylated CREB, CREB-alpha and CREB-beta in the hippocampus have been found to be increased by several antidepressants.<sup>[79]</sup> This gives us a conclusive evidence that CREB and adenylyl cyclase are involved in depression.

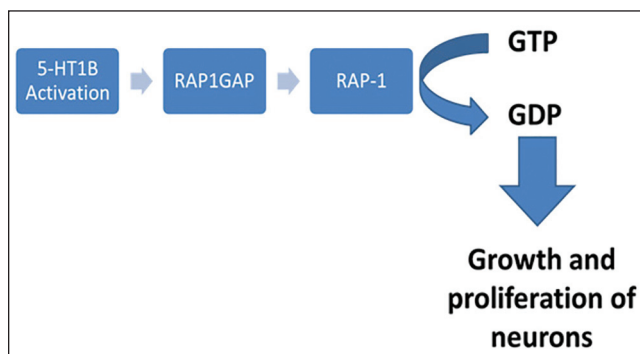
### Inhibition of (Ras-proximate-1 or Ras-related protein 1-GTPase-activating-protein) Rap-1-GTPase-activating-protein activity

The 5-HT<sub>1B</sub> receptors can also mediate signals via the Rap1-GTPase-activating-protein (GAP). Rap1-GAP activates the RAP-1 which in-turn is responsible for conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP). This is critical in the CNS because it is proposed that the balance between the levels of GDP and GTP are responsible for the proliferation, differentiation and growth of the neurons. The stimulation of the 5-HT<sub>1B</sub> receptors is thought to be involved in enhanced neurite growth in the thalamus.

The nexus between depression and neurogenesis is now well-known throughout the scientific community. Various studies relating to depression and action of antidepressants have proved that neurogenesis is one of the mechanisms of action by which majority of antidepressants act. Reduction in the hippocampal volume has been observed in depression and antidepressant drugs like fluoxetine and imipramine is involved in neurogenesis. It is also postulated that neurogenesis is essential for the action of antidepressants in the forced swim test which is one of the standard model used in assessment of antidepressive activity. The lag in the time required for the action of antidepressant is also thought to be because of the time required for neurogenesis growth of neurons and neurogenesis in depression [Figure 1].<sup>[79,80]</sup>

### Signaling through phospholipase-C activation

Serotonergic receptors also act by phospholipase-C (PL-C) activation, which leads to release of inositol-3-phosphate and calcium ions, but this mechanism is reported to be important only for those serotonergic receptors, which are present in the smooth muscles rather than in the CNS.<sup>[81]</sup>



**Figure 1:** Diagram explaining the involvement of RAP1 in neuronal growth and proliferation (RAP1GAP = Ras-proximate-1 or Ras-related protein 1-GTPase-activating-protein, RAP1: Ras-related protein 1, GDP = Guanosine diphosphate, GTP = Guanosine triphosphate)

### Signaling through extracellular signal regulated kinase

Phosphorylation of extracellular signal regulated kinase (ERK) is also involved in 5-HT<sub>1B</sub> signaling. ERK also known as mitogen activated PKs is a mitogen activated class of kinases. Signaling through ERK involves dimerization of the intracellular domain of the receptor which further leads to attachment of proteins like growth factor receptor-bound protein 2. Other molecules like son of seven less also bind to this phosphorylated complex and activation of Ras-bound GDP occurs which involves phosphorylation of the GDP to GTP. In the subsequent steps, other proteins and downstream mediators like p70, S6 are involved that activate mitogen activated proteins leading to activation of CREB like molecules that are responsible for regulating the transcription.<sup>[82,83]</sup>

### Nitric oxide synthase in serotonergic signaling

Recent studies have also shown that nitric oxide might also be involved in serotonin signaling and its function. Binding of serotonin to its receptors activates two types of proteins namely PK-C and PK-G. The former is responsible for inhibition of serotonin reuptake while the latter stimulates serotonin reuptake. It is now known that neuronal nitric oxide synthase (nNOS) binds to serotonin reuptake and presence of 5-HT leads to synthesis of nitric oxide and cyclic guanosine monophosphate (cGMP). This also serves as a feedback mechanism in the body wherein the released NO by this process activates PK-G which has said earlier is responsible for increasing the reuptake of serotonin. Serotonin reuptake inhibitors which are one of the most widely used drugs in depression are believed to inhibit this synthesis of nitric oxide and cGMP [Figure 2].<sup>[84-87]</sup>

### p11 expression and depression

Studies indicate that 5-HT<sub>1B</sub> interacts with p11 and it is now shown to be involved in depression as proved by suitable animal models. p11 is a calcium binding protein and is involved in translocation of annexin and ion channels and increased levels of p11 have been found in the raphe nuclei on treatment with standard antidepressants. Further mice models with increased p11 expression showed decreased immobility time in tail suspension test suggesting that they might be involved in depression along with 5-HT<sub>1B</sub> receptors.<sup>[88]</sup>

### Role of 5-hydroxytryptamine<sub>1A/B</sub> receptors in depression

#### The preclinical evidences

Initially, it was thought that 5-HT<sub>1A</sub> receptors have the major say when it comes to depression. Various studies involving knockout models also supported this theory. The 5-HT<sub>1A</sub> receptors are present in various like the frontal cortex, septum, amygdala that are predominant areas for serotonin released from the raphe nuclei to act. They are also the predominant receptors that function as auto receptors in the raphe nuclei.<sup>[89,90]</sup>

However, the possibility of involvement of receptors other than 5-HT<sub>1B</sub> emerged from knocks out studies and use of specific agonists of the 5-HT<sub>1B</sub> sub type. For example, studies carried out using 5-HT<sub>1B</sub> agonist CP 94253 decreased the immobility time in the forced swim test.<sup>[91]</sup>

Studies involving nonselective 5-HT<sub>1A</sub>/5-HT<sub>1B</sub> receptors agonist RU24969 showed antidepressant activity in the forced swimming test and tail suspension test animal models.<sup>[92-94]</sup> When the animals were pretreated with GR127935, a 5-HT<sub>1B</sub> antagonist, the effects of RU24969 were blocked. However, this was not seen with selective 5-HT<sub>1A</sub> antagonist, WAY100135. This study suggested the critical involvement of 5-HT<sub>1B</sub> receptors in depression. The role of 5-HT<sub>1B</sub> can be further supported by studies that involved administration of selective 5-HT<sub>1B</sub> antagonist GR127935 that reversed the antidepressant activity of standard drugs like citalopram.<sup>[92,95,96]</sup>

5-hydroxytryptamine<sub>1B</sub> receptors are located both pre and postsynaptically. They function as both auto receptors responsible for synthesis of serotonin and hetero receptors, which are not involved in the synthesis of serotonin, but control the release of other neurotransmitters [Figure 3].<sup>[97]</sup>

Further, it is known that antidepressant treatment changes the expression of the 5-HT<sub>1B</sub> receptors in animal models. Chronic antidepressant therapy decreases the mRNA responsible for formation of the 5-HT<sub>1B</sub> receptors in the rat dorsal raphe nucleus. This decreased mRNA then decreases the efficiency of the 5-HT<sub>1B</sub> receptors, which leads to increased levels of serotonin [Figure 4].<sup>[98,99]</sup>

Hence, all these evidences prove the involvement of 5-HT<sub>1B</sub> receptors in depression and agonists of this receptor could prove to be a suitable target to develop drugs to treat depression.

### Role of 5-hydroxytryptamine<sub>1A/B</sub> receptors in depression

#### The clinical relevance

Although the effectiveness of targets in preclinical settings plays an important mediator to provide an idea for developing novel therapeutics of disorders, it will not always be correlated well. The present review thus highlighted the clinical relevance of the 5-HT<sub>1A/B</sub> receptor functioning in clinically depressed patients. 5-HT<sub>1A</sub> auto-receptors exist presynaptically regulate the release of 5-HT in synapse.<sup>[30]</sup> Thus, it can be attributed to the antidepressant like effects of various antidepressants in clinical use such as fluoxetine that act also by blocking 5-HT<sub>1A</sub> presynaptic receptors. This mechanism was first postulated for antidepressant-like activity of pindolol in depressed patients.<sup>[58]</sup> However, lack of selectivity of the candidates the clinical data is insufficient for the conclusive statement of the above notion. The clinical evidences demonstrating the potential role of 5-HT<sub>1B</sub> as a target in depression are quite few and require the future studies to be conducted.

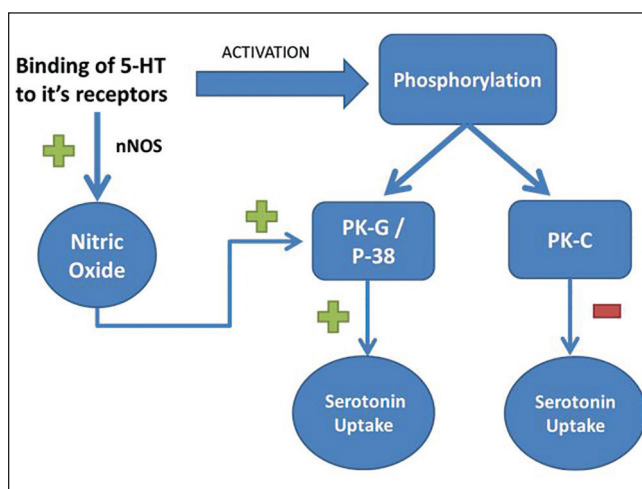


Figure 2: Flowchart explaining the effect of nitric oxide on serotonin uptake (nNOS: Neuronal nitric oxide synthase, PK-G = Protein kinase-G, PK-C = Protein kinase-C. - = Inhibitory effects, + = increasing effects)

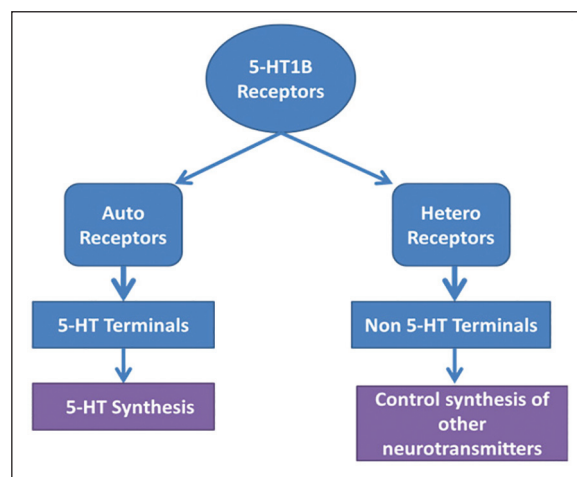


Figure 3: Flowchart explaining the functions of the auto and hetero receptors 5-hydroxytryptamine<sub>1B</sub> receptors

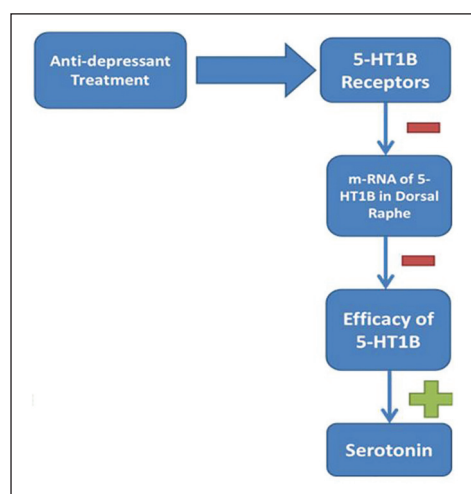


Figure 4: Flowchart explaining the mechanism of action of antidepressants through the 5-hydroxytryptamine<sub>1B</sub> receptors (- = Inhibitory effects, + = Increasing effects)



## Conclusion

The present review revealed that the 5-HT<sub>1A/B</sub> receptors are predominantly involved in depression. These receptor subtypes act by different molecular events such as inhibition of adenylate cyclase and Rap-1-GAP activity, signaling through PL-C, ERK, nNOS and p11 signaling, and regulate a number of pathways involved in depression. Further preclinical and clinical studies confirmed the potential activity of these in the etiopathogenesis of depression.

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