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## Association of 5-HT<sub>1A</sub> Receptors with Affective Disorders

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Cesar Soria-Fregozo, Maria Isabel Perez-Vega,  
Juan Francisco Rodríguez-Landa,  
León Jesús Germán-Ponciano,  
Rosa Isela García-Ríos and Armando Mora-Perez

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### Abstract

Serotonin or 5-hydroxytryptamine (5-HT) is synthesized in both the brain and peripheral system, which exert their actions at a wide family of receptors classified as 5-HT<sub>1</sub> to 5-HT<sub>7</sub>. Pharmacological, behavioral, and clinical studies involve particularly to the 5-HT<sub>1A</sub> receptors (5-HT<sub>1A</sub>-R) - auto-receptors (presynaptic) and heteroreceptors (postsynaptic) - in the control of motivated behavior, and consequently in the physiopathology of affective disorders and in the action mechanism of antidepressant drugs. In this way, some research support that 5-HT<sub>1A</sub>-R participates in the delayed effect of different types of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), and tricyclic drugs, principally. The therapeutic effect of serotonergic drugs as the SSRIs, starting with the binding to auto-receptors, which produces increases of 5-HT in the synaptic cleft as consequence of blockade of serotonin reuptake. While these molecular events occur initially, in the long-term are produced plastic changes at neuronal level, as well as down-regulation of the 5-HT<sub>1A</sub>-R, which is associated with the therapeutic effects of antidepressant drugs. The purpose of this chapter is to analyze and discuss the current information about of 5-HT<sub>1A</sub>-R-mediated signaling cascades, the intracellular signaling of 5-HT<sub>1A</sub>-R, in addition to their expression and pharmacology that are important to treatment of affective disorders symptoms.

**Keywords:** 5-HT<sub>1A</sub> receptors, affective disorders serotonin

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## 1. Introduction

5-Hydroxytryptamine (5-HT) regulates many important physiological processes, including body temperature, sleep, appetite, pain, motor activity, and affective disorders. One type of 5-HTergic functions is performed by the release of 5-HT into targeted areas and its action via at least 16 different pre-and postsynaptic 5-HT receptor (5-HTR) [1]. 5-HTRs are subdivided into seven groups—from 5-HT<sub>1</sub>-R to 5-HT<sub>7</sub>-R—according to their distribution, molecular structure, cell response, and function. Except for the 5-HT<sub>3</sub>-Rs, which are ligand-gated ion channels, all other 5-HTR are G-protein-coupled receptors that influence different transduction pathways (**Table 1**). 5-HT<sub>1A</sub>-R auto-receptors located on the soma of 5-HTergic neurons are key components of the negative feedback loop that inhibits neuronal signaling and 5-HT release [2], while 5-HT<sub>1A</sub>-R heteroreceptors located on postsynaptic 5-HTergic and non-5-HTergic neurons [3, 4], particularly those in the limbic system, are involved in emotional states.

## 2. Distribution and ontogeny of the 5-HT<sub>1A</sub>-R

The 5-HT can interact with different types of receptors, whose effect depends on the activation of different subtypes and location of these [1, 3] (**Table 1**). In this sense, the use of such techniques as ligand binding, immunohistochemistry, and hybridization *in situ* in the brains of the rat, mouse, cat, and human has reported significant levels of 5-HT<sub>1A</sub>-R in almost all regions of the brain [5–9]. A study performed in cats used positron emission tomography (PET) and 2'-methoxyphenyl-(N-2'-pyridinyl)-p-fluoro-benzamidoethylpiperazin marked with fluorine (MPPF [<sup>18</sup>F]) in combination with *in vitro* autoradiography with [<sup>3</sup>H] MPPF, 8-hydroxy-2-(di-n-propylamino)tetralin ([<sup>3</sup>H] 8-OH-DPAT) and [<sup>3</sup>H] paroxetine, to visualize the distribution of the 5-HT<sub>1A</sub>-R. These showed high levels of expression in the hippocampus, cingulate, septum, infralimbic cortex, and raphe nuclei, with low levels being detected in the cerebellum [9]. However, studies with PET using [<sup>11</sup>C] WAY-100635 reported some regional heterogeneity of the 5-HT<sub>1A</sub>-R in the human cerebellum [10]. The absence of 5-HT<sub>1A</sub>-R expression was observed in

| Receptor family   | Subtype            | Mechanism                | Cellular response |
|-------------------|--------------------|--------------------------|-------------------|
| 5-HT <sub>1</sub> | 1A, 1B, 1D, 1E, 1F | Adenylate cyclase        | Inhibitory        |
| 5-HT <sub>2</sub> | 2A, 2B, 2C         | Phospholipase C          | Excitatory        |
| 5-HT <sub>3</sub> | 3A, 3B, 3C         | Ligand-gated ion channel | Excitatory        |
| 5-HT <sub>4</sub> | 5A                 | Adenylate cyclase        | Excitatory        |
| 5-HT <sub>5</sub> | 5A, 5B             | Adenylate cyclase        | Inhibitory        |
| 5-HT <sub>6</sub> | 56                 | Adenylate cyclase        | Excitatory        |
| 5-HT <sub>7</sub> |                    | Adenylate cyclase        | Excitatory        |

**Table 1.** Classification and mechanism of the 5-HT receptor.

the cerebellar white matter, while the other regions displayed detectable levels of this receptor. On the other hand, studies of the cellular distribution of this receptor and its messenger ribonucleic acid (mRNA) have reported that approximately 60% of all glutamatergic cells express the transcript 5-HT<sub>1A</sub>-R, and about 25% of cells that express the enzyme glutamate decarboxylase (GAD) contain mRNA for 5-HT<sub>1A</sub>-R [5]. In addition, studies using immunohistochemistry, *in vitro* autoradiography with [<sup>3</sup>H] 8-OH-DPAT, and *in situ* hybridization have reported mRNA and protein expression for the 5-HT<sub>1A</sub>-R in the pyramidal neurons of layer 2 of the prefrontal, insular, and occipital cortex [9], but labeling with [<sup>3</sup>H] 8-OH-DPAT is only detected the layers 1 and 2 of the prefrontal and occipital cortex and in the pyramidal neurons of the cloister and the anterior olfactory nucleus. Neurons of the hippocampal CA1 region expressed the mRNA of the 5-HT<sub>1A</sub>-R, and [<sup>3</sup>H] 8-OH-DPAT labeling was observed in the stratum oriens and stratum radiatum. Low receptor expression was observed in CA3 pyramidal neurons, but the granule neurons in the dentate gyrus contained moderate concentrations of this receptor.

Turning now to the ontogeny of the 5-HT<sub>1A</sub>-R, immunohistochemistry has shown that almost all neurons of the hippocampus begin to express the 5-HT<sub>1A</sub>-R at the end of mitosis [11]. It is well known that at day 5 of postnatal age (P5), this receptor is expressed mainly in the cell bodies, while at day P10 it appears in the cell bodies and proximal apical dendrites. At the end of neuronal maturation (P21), a relatively scarce distribution is seen in the dendrites of the stratum radiatum and oriens of the hippocampus. During the early postnatal development of the hippocampus, glial cells that are positive to S100 (protein saturated ammonium sulfate soluble) and glial fibrillary acidic protein (GFAP) temporarily express the 5-HT<sub>1A</sub>-R and more than 90% of astrocytes that are positive to S100 in CA1, CA3, and the dentate gyrus also show moderate immunoreactivity to the 5-HT<sub>1A</sub>-R in P7, though this decreases sharply in P16. Although the specific distribution of the 5-HT<sub>1A</sub>-R has been studied in different brain regions, this does not ensure that receptor signaling activity will always be proportional to the levels of receptor expression. 5-HT<sub>1A</sub>-R signaling in neurons is important for functionality, and this intracellular effect is regulated by the coupling of second messengers.

### 3. Presynaptic and postsynaptic 5-HT<sub>1A</sub>-R and their signaling effects

The main electrophysiological response to the activation of the 5-HT<sub>1A</sub>-R in neurons is mediated by the hyperpolarization of K<sup>+</sup> channels [12, 13], which attenuates the propagation of action potentials, causing a consequent decrease in the release of the neurotransmitter. The hyperpolarizing effect is observed in both pre- and postsynaptic terminals; however, the desensitization profiles of those receptors and molecules activated in the pre- and postsynaptic terminals seem to differ. One of the mechanisms that cause desensitization of G-protein-coupled receptors is internalization, and studies have demonstrated the internalization (i.e., transfer of the plasmatic membrane in the cytoplasm) of the 5-HT<sub>1A</sub> auto-receptors in the dorsal raphe nucleus (DRN) of rats after acute treatment with the specific 8-OH-DPAT agonist to the 5-HT<sub>1A</sub>-R, or with recapture inhibitors of the 5-HT (selective inhibitors of serotonin reuptake, SSRIs). Although this phenomenon has not been observed in the hippocampus, we know that in this structure the 5-HT<sub>1A</sub>-Rs are located in the soma and dendrites of neurons (heteroreceptors) [14]. The

SSRIs in the presynaptic terminals, in turn, increase the release of 5-HT, which binds to the 5-HT<sub>1A</sub>-R auto-receptors present in the soma of the raphe neurons, thus inhibiting neuronal firing. Subsequently, these auto-receptors are internalized, causing the end of 5-HT<sub>1A</sub>-R signaling in the presynaptic neurons, and again at onset of the 5-HT release of the raphe neurons in the synapse with the dendritic terminals of the postsynaptic neurons. In the absence of the 5-HT<sub>1A</sub> auto-receptors, the 5HT released binds only to the postsynaptic 5-HT<sub>1A</sub>-R, thereby eliciting the anxiolytic effect of the SSRIs [15]. On the other hand, agonists to 5-HT<sub>1A</sub>-R, such as buspirone or flesinoxan, show an antidepressant effect, probably due to the desensitization of the 5-HT<sub>1A</sub> auto-receptors [16, 17]. Thus, the acute agonist treatment has its effect due to interaction with the auto-receptors present in the soma of the raphe neurons. The hyperpolarizing effect of the activation of this auto-receptor inhibits the release of 5-HT in the presynaptic terminal. It has been reported that under this treatment, the free or excess agonist can activate the postsynaptic (dendritic) 5-HT<sub>1A</sub>-R, resulting in the inhibition of postsynaptic neurons. Thus, an overstimulation of the receptor by an agonist causes desensitization and internalization of the 5-HT<sub>1A</sub>-R in raphe neurons, but not in postsynaptic neurons. The absence of 5-HT<sub>1A</sub> auto-receptors in the presynaptic raphe terminal facilitates neural firing by blocking inhibition by 5-HT, which is attached to the 5-HT<sub>1A</sub>-R in the postsynaptic neurons and causes the anxiolytic effect.

The activation of both pre- and postsynaptic 5-HT<sub>1A</sub>-R and their subsequent signaling seems to differ in at least one biochemical pathway. It has been shown that HN2-5 cells derived from neurons in the hippocampus, as well as in organotypic cultures of slices of the hippocampus, which are agonists to the 5-HT<sub>1A</sub>-R, stimulate the protein kinase pathway activated by mitogen (MAPK) [18]. However, in the raphe-derived cell line RN46A, activation of this receptor by agonists inhibits the basal activity of the MAPK pathway [19]. Nonetheless, it has been reported that activation of the 5-HT<sub>1A</sub>-R located both pre- and postsynaptically with the agonist inhibits intracellular cyclic adenosine monophosphate (cAMP) [20]. There are also reports that activation of 5-HT<sub>1A</sub>-R in a postsynaptic neuron-derived cell line and in non-neuronal cells promotes synthesis of phospholipase C (PLC), but this response has not been reported in presynaptic (serotonergic) or raphe-derived neurons [20, 21].

#### **4. Aberrant 5-HT<sub>1A</sub>-R expression, anxiety and depression disorders**

In recent decades, such psychiatric disorders as anxiety (mainly generalized anxiety) and depression (mainly severe) have increased in prevalence and are now responsible for 3.12 and 6.86%, respectively, of years lived with disability (YLDs), according to estimates by the Global Burden of Diseases in 2015. Anxiety is a normal human emotion that allows us to respond to everyday stress situations, where the stressor—work, for example—can be identified. However, anxiety becomes a disorder when it no longer allows the individual to remain functional in her/his daily activities and when no trigger can be identified [22]. Both anxiety and depression have been attributed to a varied etiology that includes the person's social, economic, family, employment and academic condition, combined with the persistence of an inherent biological factor. In this sense, the findings of clinical and preclinical studies have identified a dysfunctionality of the serotonergic system associated with low availability

of L-tryptophan (a precursor of 5-HT), low concentrations of 5-hydroxyindoleacetic acid (5-HIAA)—the main metabolite of 5-HT in the cerebrospinal fluid—a reduction in the synthesis, release, recapture, and metabolism of 5-HT, a decrease in the density of 5-HT<sub>1A</sub>-R pre- and postsynaptic, low neural activity in brain areas involved in regulating the emotions (such as the septum and prefrontal cortex), factors that increase the propensity (serotonergic vulnerability) to suffer mood disorders like anxiety and depression. This is reinforced by the fact that serotonergic antidepressant treatments are prescribed to reverse these types of alterations [23–25]. In addition, functional brain imaging and postmortem studies of the limbic structures of depressed patients—which are responsible for integrating the emotions, and include the striatum, amygdala, and frontal cortex—have reported a low capacity for recapture 5-HT coupled with a decrease in the expression of 5-HT (5-HTT) transporters, which are responsible for recapturing the unused 5-HT in the 5-HT synapse and so regulate the magnitude and duration of serotonergic neurotransmission [26]. Alterations of this kind in the 5-HTT have also been detected in patients with major depression using PET, which reveals a low capacity for 5-HT recapture in the thalamus, an area involved in controlling cortical excitability that contributes to establishing anxiety in patients so affected [27].

In addition, the involvement of deregulation of pre- and postsynaptic 5-HT<sub>1A</sub>-R in anxiety and depression is widely known, since it has been observed in patients with panic disorder by PET studies. There, reports indicate a reduction in the availability of both pre- and postsynaptic 5-HT<sub>1A</sub>-R in brain areas that regulate cognitive and emotional responses, such as the raphe, the orbitofrontal cortex, the temporal cortex, and the amygdala [28]. In support of this, preclinical studies have reported that knockout mice for 5-HT<sub>1A</sub>-R present an anxious phenotype that includes observations of such behaviors as a decrease of thigmotaxis (i.e., exploratory activity in central areas of an open field), increased fear in aversive environments, increased reactivity to stress, autonomic activation, and neuroendocrine alterations in models of experimental anxiety using the open-field, elevated-zero maze, and novel-object tests. However, an antidepressant-like effect has been observed in the tail suspension model of experimental depression, more markedly in females than in males. This is not associated with morphological abnormalities in brain tissues or changes in cell bodies or 5-HTergic fibers, nor is there evidence of changes in brain levels of 5-HT and 5-HIAA in the striatum, dorsal raphe, or frontal cortex [29, 30], though there is an increase in the turnover of 5-HT [31] and the firing of 5-HTergic neurons [32] in knockout mice to 5-HT<sub>1A</sub>-R. However, the possibility of such long-term changes cannot be discarded [33]. This situation can be interpreted as a disinhibition of 5-HTergic neuronal activity that increases the release of 5-HT in limbic areas, causing the establishment of anxiety through its interaction with other receptor subtypes, but without modifying levels of 5-HT or its metabolite, since the amount of stored 5-HT greatly exceeds the extracellular 5-HT content.

In support of this, differences in the function of the pre- and postsynaptic 5-HT<sub>1A</sub>-R in different brain areas seem to be decisive in establishing anxiety and depression, given that stimulation of the postsynaptic 5-HT<sub>1A</sub>-R in the dorsal hippocampus and amygdala produces anxiogenic effects, while anxiolytic effects are seen in areas such as the middle and dorsal raphe (where the 5-HT<sub>1A</sub> auto-receptors are located) [33–35]. In contrast, stimulation of the presynaptic receptors produces anxiolytic effects by suppressing 5-HTergic neuronal

activity with the resulting decrease of 5-HT in axonal terminals of limbic areas [36]. These findings suggest that there are differences in the role played by pre- and postsynaptic 5-HT<sub>1A</sub>-R receptors in regulating emotions. This may be reflected in the fact that acute administration of antidepressants causes a reduction in neural activity due to the immediate stimulation of the 5-HT<sub>1A</sub> auto-receptors, while chronic antidepressant treatments cause desensitization and, consequently, the downregulation of the 5-HT<sub>1A</sub> auto-receptors, though with no changes in postsynaptic 5-HT<sub>1A</sub>-R. This leads to the recovery of 5-HTergic neuronal activity, which matches the long latency to the onset of the therapeutic effects of SSRIs antidepressants.

It is important to note that mice require proper 5-HTergic signaling through 5-HT<sub>1A</sub>-R stimulation of the prosencephalon during the early postnatal period as this produces lasting chemical and structural changes in the brain that are essential for effective response behaviors in the face of normal anxiety during adulthood [37]. Thus, clinically effective antidepressant or anti-anxiety treatments must stimulate the 5-HT<sub>1A</sub> auto-receptors with direct agonists (such as buspirone) or indirect agonists like fluoxetine to obtain therapeutic efficacy. This suggests that in both the developmental and adult stage efficient activation of the 5-HT<sub>1A</sub> auto-receptors can produce changes that decrease expressions of pathological anxiety.

Donaldson et al. [38] reported that a decrease in the 5-HT<sub>1A</sub> auto-receptors in the 21st postnatal leads to increased long-term anxiety levels but does not modify depressive behaviors. In this regard, lifelong abolition of the 5-HT<sub>1A</sub> auto-receptors suffices to increase anxiety behaviors in adult mice [39], though without necessarily affecting depressive-like behaviors in the forced swimming test [40]. Based on these results, it has been suggested that 5-HT<sub>1A</sub> auto-receptors are involved in establishing anxious and depressive phenotypes, while the heteroreceptor is implicated in the depressive phenotype observed in experimental tests of depression [40]. Moreover, Albert and François [41] suggest that a reduction in the activity of postsynaptic receptors is involved in anxiety and that an increase in the transcription of 5-HT<sub>1A</sub> auto-receptors is associated with both depression and resistance to chronic treatment with SSIR drugs [41]. Hence, the reduced expression of the auto-receptors with no modification of postsynaptic 5-HT<sub>1A</sub>-R expression is enough to produce depression-like behaviors in mice [42].

## 5. Therapeutic agents that function by regulating 5-HT<sub>1A</sub>-R signaling

5-HT<sub>1A</sub>-R is involved in the pathology and treatment of mental disorders, such as anxiety and depression [23, 43, 44]. Several studies have suggested that the 5-HT<sub>1A</sub>-Rs are potential targets for these psychiatric disorders [45–49]. In this regard, agonists (total and partial) to the 5-HT<sub>1A</sub>-R have shown antidepressant and anxiolytic properties and have been employed as adjunct treatments to improve the therapeutic action of several antidepressant and anxiolytic drugs in several preclinical and clinical studies [50–53]. They offer a different pharmacological mechanism from that of the monoamine oxidase inhibitors (MAOI), tricyclic drugs, SSIRs, and other antidepressants.

Buspirone is perhaps the most widely studied partial 5-HT<sub>1A</sub>-R agonist. It belongs to the chemical class of the azapirones [54, 55] and has been used primarily due to its anxiolytic effects and absence of side effects such as sedation and dependence that are often associated with benzodiazepines [56]. It is also utilized to treat patients who are resistant to the SSRI<sub>s</sub>, due to its capacity to stimulate the release of catecholamines [57]. In this regard, a clinical trial carried out with ambulatory patients diagnosed with generalized anxiety disorder (GAD) found that after weeks 3 and 4, buspirone showed efficacy in relieving patients' symptoms with a therapeutic effect comparable to that of lorazepam. Also, after discontinuing this therapy, the individuals treated with buspirone showed no withdrawal symptoms, while those medicated with lorazepam saw their symptoms worsen in week 9 after ceasing treatment [58]. Similarly, buspirone (15 mg/day) prescribed for 4 weeks to ambulatory patients with GAD produced a significant reduction of anxiety symptoms compared to alprazolam. Moreover, the patients treated with buspirone experienced fewer adverse effects and symptoms of abstinence than those who received alprazolam [59]. The anxiolytic properties of buspirone have been confirmed in animal models. For example, in a study conducted with Swiss Albino mice that received buspirone at 2.5 and 5 mg/kg, i.p., the drug significantly increased the number of step-through by 46 and 61%, respectively [60]. This demonstrates that buspirone is effective in treating anxiety disorders without causing adverse effects or signs of benzodiazepine dependence.

Gepirone is another component of the class of the azapirones that has shown antidepressant properties [61] due to its partial 5-HT<sub>1A</sub>-R antagonism, which improves 5-HTergic activity [62]. The structure of this azapirone is similar to that of buspirone, and it has similar anxiolytic properties that have been identified in clinical studies [63, 64]. But it also has antidepressant action. In a study of patients with major depressive disorder (DDM), prolonged-release gepirone (60–80 mg/day) administered for 3 weeks produced a significant reduction in total HAM-D17 scores (Hamilton Depression Scale) compared to a placebo group, thus improving the symptomatology of patients [65]. Similarly, gepirone (40–80 mg/day) prescribed for 8 weeks improved the sexual function of male patients diagnosed with DDM, in addition to its antidepressant action [66].

Tandospirone is a partial 5-HT<sub>1A</sub>-R agonist that has been shown to have antidepressant effects. In a study with male Sprague-Dawley rats, chronic treatment (28 days) with tandospirone at 10 mg/kg inhibited changes induced by psychosocial stress in the neurogenesis of the dorsal and ventral hippocampus, thus producing a type of antidepressant effect. It has been suggested that chronic administration of tandospirone desensitizes the 5-HT<sub>1A</sub>-R in the raphe. This decreases self-inhibition mediated by the somatodendritic receptor and, consequently, increases the firing rate and release of 5-HT [67].

Brexpiprazole is a second-generation antipsychotic that exerts partial antagonism to the 5-HT<sub>1A</sub>-R and D2. A study in adults diagnosed with DDM, but inadequate responses to antidepressants, showed that brexpiprazole as an adjunct therapy improved patients' symptoms. In that research, a series of drugs—escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, and venlafaxine—all significantly improved scores on the Clinical Global Impressions Scale (CGI-I scale), Zung Self-Rating Depression Scale (SDS), and HAM-D17

scale when administered jointly with brexpiprazole (2 mg) for 6 weeks. Improvement was remarkable from the first week of treatment [68]. Finally, flesinoxan is a phenylpiperazine derivative initially developed as an antihypertensive [69]. This drug has total antagonism to 5-HT<sub>1A</sub>-R with high affinity [70]. Various studies have demonstrated its antidepressant properties, particularly in treatment-resistant DDM patients [71]. For example, in a double-blind, placebo-controlled and fixed-dose study of treatment-resistant DDM patients, flesinoxan (1.2 mg/day) administered for 6 weeks improved scores on the HAM-D17, Montgomery-Asberg Depression Rating Scale (MADRS) and CGI scales with improvement in subjects' mood. Nausea and dizziness were the most common side effects reported [72]. The therapeutic effects of flesinoxan have also been reported in animal models. In research with male Sprague-Dawley rats after olfactory bulbectomy, subjects were given flesinoxan (1 and 3 mg/kg, s.c.) for 17 days. They presented reduced total immobility time on the forced swimming test [73]. This therapeutic action may be associated with the desensitization effect of the 5-HT<sub>1A</sub>-R in the nucleus of the dorsal raphe as an action mechanism [71].

The antidepressant activity of agonists to the 5-HT<sub>1A</sub>-R in presynaptic and postsynaptic neurons has been widely reported. Studies using the model of experimental learned helplessness in relation to depression have reported that stimulation of the 5-HT<sub>1A</sub>-R with 8-OH-DPAT at dosages of 0.03, 0.06, 0.125, 0.25, and 1 mg/kg i.p. for 5 days shows an antidepressant effect. To explore the role of the pre- and postsynaptic 5-HT<sub>1A</sub>-R, in that study, 8-OH-DPAT (0.1 and 1 µg/0.5 µl) was microinjected into the raphe and septum. While this showed an antidepressant effect when microinjected into the septum, no such effect was seen in the raphe of male rats [74]. This indicates that stimulation of the postsynaptic 5-HT<sub>1A</sub> receptors is responsible for establishing the antidepressant effect caused by 5-HT<sub>1A</sub>-R agonists when managed through a systemic pathway, since stimulation of the 5-HT<sub>1A</sub> somatodendritic auto-receptors in the raphe inhibits the release of 5-HT and the electrical activity of the raphe [75].

In recent years, administration of vilazodone has shown antidepressant [75, 76] and anxiolytic effects by eliminating physical and somatic symptoms in women with generalized anxiety disorder, after 8 weeks of treatment at daily doses of 20–40 mg [77, 78]. This effect is due to the action mechanism of this SSRI, which is a partial agonist of postsynaptic 5-HT<sub>1A</sub> receptors. In addition, it desensitizes 5-HT<sub>1A</sub> auto-receptors in the raphe more quickly than fluoxetine or paroxetine [79], is 30 times more powerful than serotonin transporter (SERT), and causes a larger increase of extracellular 5-HT in the ventral hippocampus and frontal cortex [80]. These facts justify the short latency to the appearance of therapeutic effects. Similar data have been reported in models of experimental anxiety using ultrasonic vocalizations. Observations suggest that vidazolam produces an anxiolytic effect that can be reversed by coadministration with an antagonist of the presynaptic 5-HT<sub>1A</sub> receptors such as WAY-100635.

This substance also produced an anxiolytic effect in the model of predator-induced stress at doses of 20–40 mg/kg and in the defensive burial model at doses of 10–40 mg/kg. However, no anxiolytic effect was seen in the elevated arms maze model [81]. Antidepressant effects at doses of 1 mg/kg were found in models of experimental depression based on the forced swimming and tail suspension tests [82].

## 6. Recent advances in the use of serotonin-norepinephrine reuptake inhibitors (SNRIs) for treating affective disorders

Affective disorders are characterized by vigorousness in neurotransmission pathways at the cerebral level with reductions in serotonergic, noradrenergic, and dopaminergic concentrations, among other neurochemical and neuroanatomical changes. Consequently, therapeutic strategies designed to treat affective disorders include combinations of drugs and, in other cases, chemical compounds that act on one or more neurotransmission systems [83]. In this way, serotonin-norepinephrine reuptake inhibitors (SNRIs) have the capacity to block serotonin and noradrenalin reuptake in the brain, and so have been used successfully to treat such affective disorders as depression, emotional disorders like anxiety, and other illnesses related to the control of overweightness, fibromyalgia, peripheral diabetic neuropathic pain, and attention deficit-hyperactivity disorders, among others (Table 2).

The SNRIs were introduced into therapeutic use in the USA in 1993 under the name venlafaxine, a chemical compound included in a group of molecules named phenylethylamines, whose action mechanism principally involves the reuptake inhibition of serotonin and noradrenaline, though a lower degree of dopamine reuptake inhibition has also been reported. Through their dual action, these substances quickly increase concentrations of both neurotransmitters, apparently producing better therapeutic actions in major depression disorders than conventional antidepressant drugs that act upon only a single neurotransmission system. But SNRIs can produce side effects that include loss of appetite, reduced body weight and sleep, fatigue, headaches, nausea/vomiting, sexual dysfunction, and urinary retention, among others. To a lesser degree, they can also produce anxiety and high blood pressure. It is important to point out that some patients treated with SNRIs have increased suicidal thoughts, though this is still subject to controversy [84]. Despite their side effects, SNRIs are used frequently to control several depressive disorders due to their therapeutic efficacy.

| Active compound | Therapeutic use   | Reference      |
|-----------------|---|----------------|
| Venlafaxine     | MDD, AD, syndrome of chronic pain, BDD                  | [85, 86]       |
| Desvenlafaxine  | MDD in adult patients                                   | [89]           |
| Duloxetine      | MDD, DPNP, fibromyalgia                                 | [96, 104, 107] |
| Atomoxetine     | ADHD in adults and pediatric patients under 6 years old | [103, 108]     |
| Sibutramine     | Treatment of obesity                                    | [106]          |
| Milnacipran     | MDD, fibromyalgia                                       | [85, 105]      |
| Levomilnacipran | MDD, AD in adult patients                               | [90]           |

Abbreviations: MDD, major depression disorder; BDD, bipolar depression disorder; AD, anxiety disorder; DPNP, diabetic peripheral neuropathy pain; ADHD, attention deficit hyperactivity disorder.

**Table 2.** Principal serotonin-norepinephrine reuptake inhibitors and their therapeutic uses.

Indeed, in some cases they work better than classic antidepressant drugs (e.g., SSRIs and tricyclic drugs) in certain groups of patients. For example, a clinical study of patients diagnosed with major depression disorder (aged 18–65) found remission of symptoms after 24 weeks of treatment with venlafaxine (initial dose of 75 mg/day, maximum dose of 225 mg/day) and milnacipran (50 mg twice a day), with a greater effect than that produced by 20 mg/day of the SSRI paroxetine [85]. However, in patients diagnosed with Alzheimer's and major depression disorders, the SSRIs sertraline and venlafaxine had a greater effect than the tricyclic antidepressant desipramine, all at doses of 150 mg/day during 12 weeks of treatment [86]. In a randomized, double-blind, parallel group study that evaluated the effect of long-term treatment (12 weeks) with venlafaxine in adult patients, there was a significant reduction of depressive symptoms compared to patients under the same conditions but treated with a lithium monotherapy [87]. Another SNRI used to treat major depression disorder is desvenlafaxine [88]. An integrated analysis of the efficacy of this drug found that treatment with 50 and 100 mg/day reduced depression symptoms in patients diagnosed with major depression disorder compared to a placebo group [89].

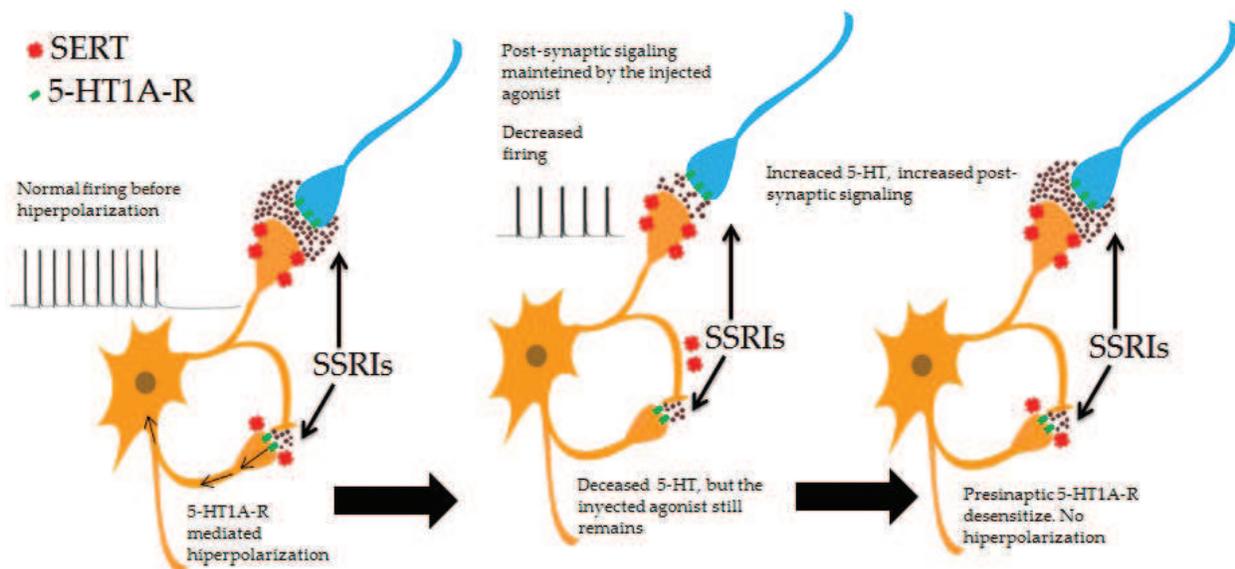
Similarly, treatment with levomilnacipran (40–120 mg) in patients aged 18–80 diagnosed with some depression disorder, significantly reduced symptoms after 8–10 weeks of treatment [90]. These data show that the effect of SNRIs in treating major depression disorders depends on the characteristics of patients and the dosage schedule. One double-blind, controlled, randomized study compared two treatment schedules with venlafaxine: one fixed (75 mg/day) the other flexible (75–225 mg/day). It found that the fixed program gave a better response to this antidepressant treatment than the flexible approach [91]. Similarly, the use of SNRIs in young depressed patients (7–18) did not produce better therapeutic effects than a placebo treatment, though duloxetine has shown therapeutic potential in such patients [92]. A meta-analysis of the efficacy of venlafaxine, duloxetine, fluoxetine, and imipramine in children and adolescents found that SNRIs and tricyclic antidepressants do not seem to offer a significant advantage in treating major depression disorder in this population, as only fluoxetine produced an adequate therapeutic effect in those patients [93].

SNRIs are also often used to treat depressive symptoms associated with menopause. It is well known that in this biological phase, women are more susceptible and vulnerable to socio-environmental factors that predispose them to develop emotional and affective disorders [94]. Menopausal women diagnosed with major depression disorders and vasomotor symptoms treated with duloxetine for 8 weeks experienced a reduction in their depressive and vasomotor symptoms, positive anxiolytic effects, and improved sleep quality, so it is believed that SNRIs may be an effective therapeutic option for treating mood and emotional disorders, as well as the more general symptoms associated with menopause [95]. In addition to its role as an effective treatment for major depression disorders associated with menopause, duloxetine is used to control other symptoms, such as hot flashes and anxiety [96]. Meanwhile, menopausal women treated with venlafaxine (75–300 mg/day) or fluoxetine (20–60 mg/day) felt a reduction in their depressive symptoms after 6 weeks of treatment, with no significant differences between these two antidepressants [97]. Administration of desvenlafaxine (50, 100, or 200 mg/day) to peri- and postmenopausal women also reduced depressive symptom compared to a placebo [98].

## 7. Mechanism of action of selective serotonin reuptake inhibitors (SSRIs) and affective disorders

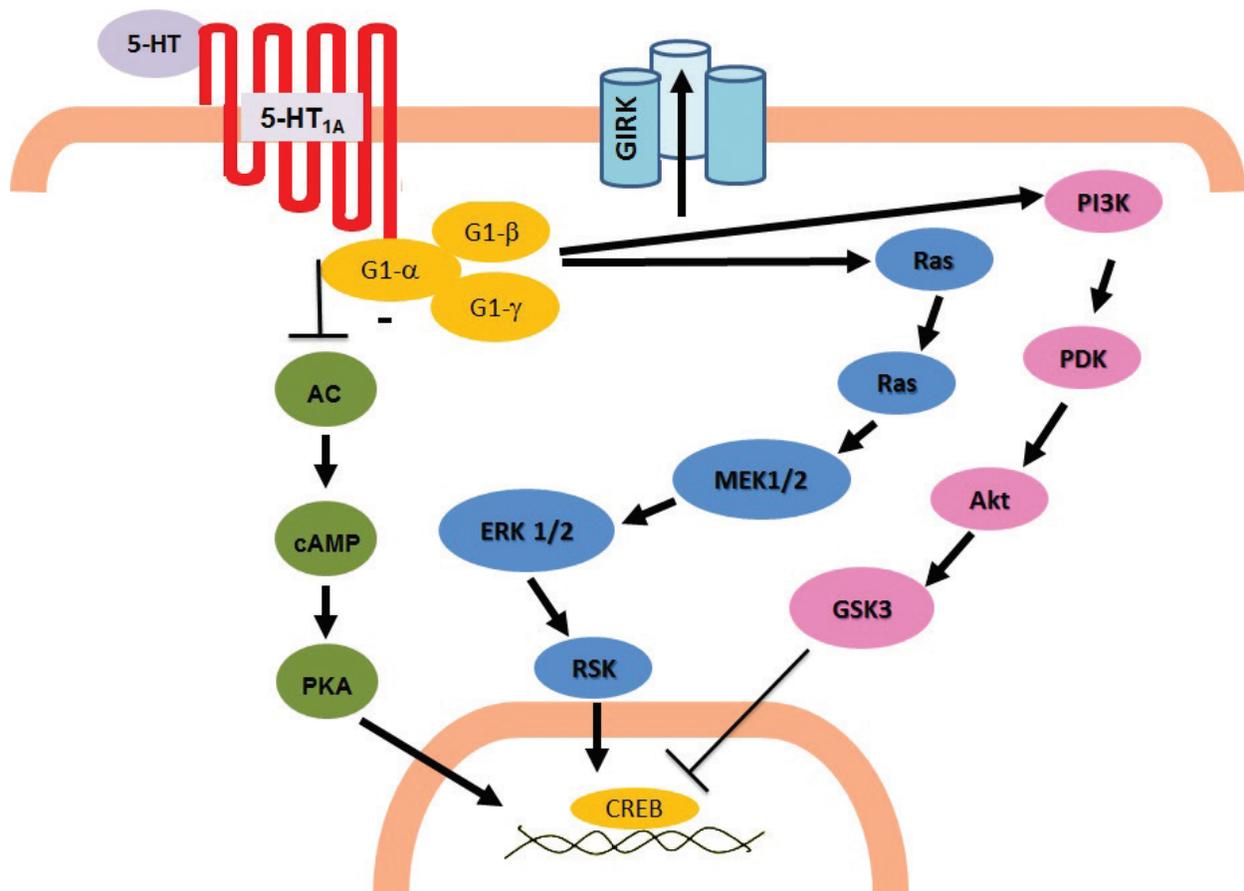
The action mechanism of SSRIs consists in inhibiting the 5-HT transporters (SERT) in the soma of raphe dorsal neurons (**Figure 1**). It has been shown that SSRIs, such as fluoxetine, that have an antidepressant effect possess a mechanism that inhibits SERT, thus increasing the availability of 5-HT in the synaptic cleft. This is accompanied by an increase in 5-HTergic neurotransmission associated with the establishment of the antidepressant effect [99]. This pharmacological effect is not immediate, suggesting that the 5-HT<sub>1A</sub> transporter blockade, *per se*, does not produce therapeutic effects during acute treatment, since in the first week of antidepressant therapy with SSRIs increases 5-HTergic neurotransmission due to the availability of 5-HT, which causes an overstimulation of the 5-HT<sub>1A</sub> auto-receptors, located in the cell body and dendrites of neurons in the raphe. Therefore, its neuronal activity, which is in charge of releasing 5-HT, is reduced in limbic areas, though we know that treatment with SSRI antidepressants requires 2–3 weeks to establish its therapeutic effect, because regulation of 5-HTergic neurotransmission in depressed patients requires the desensitization and subsequent internalization of the 5-HT<sub>1A</sub> auto-receptors of presynaptic neurons that eliminate the negative feedback on the raphe, thus increasing its neuronal activity and normalizing the release of 5-HT to the synaptic cleft that, finally, translates into an antidepressant effect.

The postsynaptic mechanism and cellular signaling of the 5-HT<sub>1A</sub>-R in relation to mood control are very complex. In this regard, it has been reported that some accompany the establishment of the therapeutic effect of SSRI antidepressants. One of the most important effects is the desensitization of the 5-HT<sub>1A</sub> auto-receptors. Normally in 5-HTergic neurotransmission, once the 5-HT is released into the synaptic cleft, it mainly has a three-point coupling. The



**Figure 1.** Mechanism of SSRIs: the 5-HT transporters (SERT) in the soma of raphe dorsal neurons; modified according to Garcia-Garcia et al. [40].

first is to the postsynaptic serotonergic receptors, mainly 5-HT<sub>1A</sub>. These receptors are coupled to the inhibition of protein G (Gi/o) and the consequent decrease in AMPc synthesis due to the inhibition of adenylate cyclase which, in conjunction with other second messengers, are responsible for activating the opening of ion channels, including Na<sup>+</sup> and K<sup>+</sup>, for its input and output, respectively (**Figure 2**). This contributes to the hyperpolarization of the postsynaptic neurons so that they can go with the flow of neural inhibition. The second coupling is with the SERT, which are responsible for the reuptake of unused synapse 5-HT, which is returned to the presynaptic neuron through recycling, where it is stored for later release or to be metabolized to reset the synthesis of 5-HT. The energetic cost of its production is very high. The third coupling is with the 5-HT<sub>1A</sub> auto-receptors and, to a lesser extent, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub>. This causes inhibition of the opening of Ca<sup>2+</sup> channels from the presynaptic neuron, which then inhibits the release of 5-HT into the synaptic cleft, thus regulating the intensity and duration of the nerve impulse from the presynaptic neuron (i.e., negative feedback or self-inhibition), mainly in neurons of the raphe, exerting the end the signaling of the presynaptic neurons and the resumption of the release of 5-HT neurons from the raphe to the postsynaptic neurons through the limbic areas [100]. In this context, chronic administration of SSRIs induces internalization of the 5-HT<sub>1A</sub> auto-receptors and the neurons of the raphe [101], since the increase in the availability of 5-HT in the cleft overstimulates those auto-receptors while also desensitizing and internalizing them. This process is associated with the phosphorylation of the carboxylic chain



**Figure 2.** Model of the transduction pathways that may be activated by the 5-HT<sub>1A</sub>-R; modified according to Polter and Li [100].

and the third intracellular loop of the receptor. The absence of 5-HT<sub>1A</sub> auto-receptors induces the binding of 5-HT only to postsynaptic 5-HT<sub>1A</sub> receptors, which in turn triggers the antidepressant effect of SSRIs, though only after 2–3 weeks of treatment. However, this desensitization effect on the auto-receptors depends on the type of SSRIs administered, as it has not been observed when sertraline is administered chronically in humans [102].

## 8. Conclusion

Multiple antidepressant drugs are known to function through the 5-HT<sub>1A</sub>-R. New findings related to dysfunctions in the serotonergic system, specifically in both pre- and postsynaptic 5-HT<sub>1A</sub>-R in the signaling pathways that modulate the 5-HT<sub>1A</sub>-R, demonstrate that 5HTergic alterations—whether in the expression or functionality associated with such disorders as anxiety and depression, and their subsequent association with alterations in signaling pathways that indirectly modulate and involve survival and neuronal development—can interfere with responses to antidepressant treatment. However, we require additional studies that accurately identify signaling mechanisms in different brain areas and differentiate their functions between the pre- and postsynaptic 5-HT<sub>1A</sub>-R present in intact animals and animals subjected to clinically effective antidepressant and anti-anxiety treatments. Since we know that differences in the distribution of receptors in the brain determine the physiological and behavioral functions, a better understanding of the underlying mechanisms associated with abnormal activity of the 5-HT<sub>1A</sub>-R will contribute to the search for novel therapeutic strategies that explore new ways of enhancing treatment of the most common psychiatric disorders around the world, including those of anxiety and depression, which severely impair the quality of life of individuals.

In general, the participation of the 5-HT<sub>1A</sub>-R in psychiatric disorders such as anxiety and depression has been widely explored in numerous clinical studies and animal models. All findings seem to indicate that including agonist components to the 5-HT<sub>1A</sub>-R in drug treatment of individuals with anxiety and depression is a promising option for improving the efficiency and implementation of the therapeutic effect of conventional drugs. It is important to emphasize that stimulation of the 5-HT<sub>1A</sub>-R activates indirect signaling mechanisms that have not yet been studied, so further research is necessary to explore possible alternative signaling mechanisms that accompany the establishment of the antidepressant effects mediated by 5-HT<sub>1A</sub>-R. Finally, in order to better understand the etiology of many disorders of brain development and advance in the elaboration of drugs that target 5-HT<sub>1A</sub>-R, it is important to study the profile of this receptor's activity in brain signaling during development.

In summary, there is ample clinical evidence to support the idea that SNRIs may be used to treat major depression disorder and other psychiatric disorders in certain groups of patients. However, the scarcity of controlled clinical studies and the wide age range of patients included in existing work, in addition to the scarce comparisons of the effects of SNRIs and classic antidepressant drugs (e.g., SSRIs and tricyclic antidepressants), raise the challenge of determining whether SNRIs produce greater, similar, or lower therapeutic effects than traditional therapeutic schedules. Nonetheless, the data currently available open doors for future research designed to explore new therapeutic options that will benefit patients with major depression disorders or other affective or emotional alterations.

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## Author details

Cesar Soria-Fregozo<sup>1\*</sup>, Maria Isabel Perez-Vega<sup>1</sup>, Juan Francisco Rodríguez-Landa<sup>2</sup>, León Jesús Germán-Ponciano<sup>3</sup>, Rosa Isela García-Ríos<sup>4</sup> and Armando Mora-Perez<sup>1</sup>

\*Address all correspondence to: csoria@culagos.udg.mx

1 Laboratory of Biomedical Sciences/Histology, University Center of Los Lagos, University of Guadalajara, Lagos de Moreno, Jalisco, Mexico

2 Laboratory of Neuropharmacology, Institute of Neuroethology, University Veracruzana, Xalapa, Veracruz, México

3 Postgraduate in Neuroethology, Institute of Neuroethology, Universidad Veracruzana, Xalapa, Veracruz, México

4 Department of Health Sciences, University Center of Tonalá, University of Guadalajara, México

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