The 5-HT1A receptors: from molecular biology to neuropsychiatric symptoms

R. Navinés, E. Gómez and C. Gastó

Instituto de Psiquiatría y Psicología. Hospital Clínico. Barcelona. Spain

Receptores 5-HT1A: de la biología molecular a la clínica neuropsiquiátrica

Summary

Among the multiple serotonin receptors identified to date, the 5-hydroxytryptamine (5-HT) 1A subtype is among the best known because selective ligands have been available for more than 15 years. Radioactive derivatives of these ligands make it possible to demonstrate the presence of 5-HT1A binding sites mainly in the limbic areas and in the raphe nuclei in the brain, where they correspond to post-synaptic receptors and pre-synaptic autoreceptors respectively. On stimulation of 5-HT1A autoreceptors, they regulate serotonin release in the distal regions of the neuron by inhibitory firing activity. In this way, they help to maintain the serotonin in the terminal regions at physiological levels, which favors correct neuronal functioning.

This review article summarizes key data on localization, study technique, molecular biology, signal transduction, differential functional properties of pre-synaptic versus post-synaptic 5-HT1A receptors, and behavioral effects and clinical correlates of their activation, especially cognitive and emotional responses. Mention is made about the role of these receptors in the neurogenesis process of certain brain areas and of the possible clinical and therapeutic implications of these processes.

Key words: *Serotonin (5-HT). 5-HT1A receptor. Molecular biology. Signal transdution. Cognition. Emotion. Neurodevelopment.*

Resumen

De entre los múltiples receptores de serotonina identificados hasta el momento, el subtipo 5-HT1A es uno de los más conocidos, en parte porque desde hace más de 15 años se ha dispuesto de ligandos selectivos para su estudio. Utilizando derivados radioactivos de estos ligandos se ha podido demostrar la presencia de receptores 5-HT1A principalmente en áreas límbicas, donde actúan como receptores postsinápticos y en los núcleos del rafe cerebrales, donde actúan como autorreceptores presinápticos. Estos últimos al ser estimulados, regulan la liberación de serotonina en las regiones distales de la neurona mediante la atenuación de su disparo. De esta forma ayudan a mantener la serotonina en las regiones terminales en niveles fisiológicos, lo cual favorece el correcto funcionamiento neuronal.

En este artículo se revisa el conocimiento actual sobre los receptores 5-HT1A en lo referente a su localización, métodos para su investigación, estructura molecular, mecanismos de transducción receptorial, diferencias funcionales entre los receptores 5-HT1A pre y postsinápticos e implicaciones funcionales, especialmente en lo que concierne a respuestas cognitivas y emocionales. Se hace mención al papel de estos receptores en los procesos de neurogénesis de ciertas áreas cerebrales y a las posibles implicaciones clínicas y terapéuticas de dichos procesos.

Palabras clave: *Serotonina (5-HT). Receptores 5-HT1A. Biología molecular. Transducción. Cognición. Emoción. Neurodesarrollo.*

SEROTONINERGIC RECEPTORS: 5-HT1A SUBTYPE

The 5-hydroxytryptamine (5-HT, serotonin) and serotonergic receptors have been involved in the etiology of several diseases, especially in mental disorders such as depressive disorders, schizophrenia, eating disorders, anxiety disorders and obsessive-compulsive disorders. Some of the treatments used for these disorders are known to act through the modulation of the serotoninergic tone[1-2].

During the past 10 years, several types of serotoninergic receptors have been characterized and at least 15 different subtypes have been identified up to date. Initially, these receptors were characterized using pharmacological and immunological strategies. Recently, molecular biology techniques have made it possible to clone and sequence these receptors on locating the different genes that they encode[3].

Of the different subtypes[4-6], the 5-HT1A receptors are the ones that have been studied most, partially because

Correspondence:
Cristóbal Gastó
Instituto de Psiquiatría y Psicología
Hospital Clínico
Villarroel, 170
08036 Barcelona (Spain)
E-mail: esgomez@clinic.ub.es

the first selective agonists and selective radioligands of the serotoninergic receptors available were those of this subtype[7]. These receptors are widely distributed in the central nervous system[8] and have been involved in the regulation of several physiological functions and behaviors, such as thermoregulation, cardiovascular function, response to pain, cognitive functions, response to stress, anxiety, mood state, impulsivity-aggressivity responses, appetite, sleep-awakeness cycle and sexual behavior[9-10]. Given the importance of the 5-HT1A receptors in the physiology of these functions and behaviors, the following presents a review of the literature on the findings observed in regards to localization, structure, transduction mechanisms, functional differences between pre and post-synaptics and some of the main functions in which these receptors have been involved (table 1).

RESEARCH TECHNIQUES OF 5-HT1A RECEPTORS AND BRAIN LOCATION

At present, there are two groups of techniques for the visualization of the receptors in the human brain[11]. The first group includes the invasive techniques, which make it necessary to obtain tissue by biopsy or necropsy and its manipulation in the laboratory to selectively label the molecular entity of interest. These include: *a*) autoradiograph; *b*) immunohistochemical, and *c*) hybridization *in situ*. The second group is made up by the non-invasive or imaging techniques such as positron emission tomography (PET) or single proton emission computer tomography (SPECT) which, combined with the magnetic resonance imaging techniques (MRI) make the *in vivo* visualization of the distribution of the selective ligands of these receptors in the brain possible.

TABLE 1. General characteristics of the 5-HT1A receptors

Regions with greater density	Raphe nucleus Hipocampus
Drugs agents	
Selective	8-OH-DPAT Ipsapirone Buspirone
Non-selective	RV 24969 D-LSD (–) Pindolol
Effector mechanisms	Inhibition of the adenyl cyclase enzyme Activaction of phospholipases (C, A2 & D) Activation of potassium channels Inhibition of calcium channels
Effects in the neuronal membrane	Hiperpolarization
Functional correlations	Thermoreglation Cognitive functions (learning, memory, attention) Axiety, impulsivity, aggresivity Emotional state

Autoradiograph techniques

The autoradiography is a technique that consists in the labeling of tissue sections obtained by microtomy with a radioligand and their visualization (autoradiogram) after exposure to a radiosensitive photographic emulsion[12-15]. The map of the 5-HT1A receptors in the rat brain was established by this technique as soon as the first selective 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) was available[7,16]. Later, many new radioligands were synthesized (table 2). Practically all these autoradiograph studies in the rat brain have found that the 5-HT1A receptors are especially abundant in the following areas[17]: in the hippocampus (*gyrus dentatus* and Ammon's horn), in the lateral septum, in the entorhinal and frontal cortex, and principally in the dorsal raphe nucleus. They have also been found in the dorsal horn of the funiculi medullae spinalis, and in less density in some thalamic and hypothalamic nuclei. On the contrary, they have not been identified in extrapyramidal structures as black matter, caudate nucleus, *globus pallidus* and cerebellum (table 3).

Immunohistochemical techniques

Immunohistochemical techniques are based on the detection of the receptors by specific 5-HT1A anti-receptor antibodies. These antibodies have been obtained

TABLE 2. Radioligand used most in autoradiographic techniques

First radioligands

- [H^3]8-hidroxy-dimethyl triphosphate
- [H^3]ipsapirone
- [H^3]5-metoxhy-3-(di-n-propilamine)croman
- [H^3]5-methyl-urapidil

Radioiodined ligands

- [I^{125}]Bolton-Hunter-8-methoxy-2[N-propyl-N-(3'-iodine-4'hydroxyphenyl)-propionamide-N-propylamina] tetralin (I^{125})-BH-8-MeO-N-PAT)
- [I^{125}]trans-8-hydroxy-PIPAT

Last generation radioligands

- [H^3]5-metoxy-3-(di-n-propilamine)croman ([H^3]5-MeO-DPAC)
- [H^3]alnespiron
- [H^3]1-[2(4-fluorobenzoyl-amino)ethyl]-4-(7-methoxynaphtyl)piperazine [3H]S14506
- [H^3]N-[2-[4-(2-methoxiphenyl)-1-piperazinyl]etil]N-(2-piperadinyl]-cyclohexane-carboxamide ([H3]WAY-100635
- [I^{125}]4-(2'-methoxy-phenyl)1-[2'-(N-2"-pyridinyl)-p-iodine-benzamide]-ethilpiperazine-[I^{125}]p-MPPI

TABLE 3. Localization of 5-HT1A r eceptors

Hippocampus (*gyrus dentatus* and Ammon's horn)
Lateral septum
Entorhinal and frontal cortex
Dorsal raphe nucleus
Dorsal horn of the spinal cords
Thalamic andhypthalamic nuclei

by injecting rabbits with a synthetic peptide corresponding to a highly selective region of the third intracellular portion of the 5-HT1A receptor of the rat[18]. Using these techniques, it has been found that immunoreactivity against the 5-HT1A receptors presents exclusively in the neuronal bodies and dendrites in the dorsal raphe nucleus, indicating the presynaptic localization of these receptors. Distally, its localization coincides with that found by previously mentioned autoradiograph techniques[19-20].

In situ hybridization technique

The *in situ* hybridization technique is based on the detection of the messenger Ribonucleic Acid (mRNA) in brain tissue, using a complementary nucleic acid sequence labelled radioactively with phosphorus or selenium isotopes and non-isotopically with biotin or alkaline phosphatase. Hybridization is produced by the formation of hydrogen bonds between complementary bases, and this signal is visualized by autoradiographic methods[21-24].

It is now known that the gene that encodes the 5-HT1A receptor is located in the distal part of chromosome 13 in the rat and in chromosome 5 (5q11.2q13) in humans. Thus, it has been possible to investigate the regional distribution of the mRNA that encodes this receptor in the rat. The findings observed with this technique suggest that the 5-HT1A receptors are not transported to much distance from the sites where they are synthesized, in the neurons of the dorsal raphe nuclei. One part is directed to portions of the soma and dendrites of these presynaptic neurons, while another part is transported distally, primarily to the hippocampus, where they acquire a post-synaptic localization. In fact, only half of the 5-HT1A receptors are localized in the cellular bodies, while the rest are localized in non-serotoninergic nerve endings[25]. The mRNA distribution of these receptors in the brain is similar to that obtained when autoradiographic and immunohistochemical techniques are used[19-20].

Positron emission tomography and single photon emission tomography

The positron emission (PET) and single photon emission (SPECT) tomography techniques are based on *in vi - vo* detection of photons emitted by radioisotopes introduced in blood in the human and experimental animal brain[11]. At present, there is a considerable number of radioligands that mainly belong to three families: *a*) derivatives of 5-HT1A 8-OH-DPAT agonist; *b*) from a structure similar to the 5-HT1A WAY-100635 antagonist, and *c*) apomorphinic derivatives[26]. Studies by these techniques have made it possible to investigate differences in density (Bmax) and affinity (Kd) of radioligands of 5-HT1A receptor *in vivo* in different brain structures and neuropsychiatric diseases, and the occupation of these receptors by several drugs[27-28].

MOLECULAR STRUCTURE OF THE 5-HT1A RECEPTORS

The first studies performed on the structure of the 5-HT1A receptors purified in rat hippocampus demonstrated that the 5-HT1A complex-receptor corresponded to a glycoprotein with a molecular weight around 150 kilodalton (Kd), which, in presence of guanosine triphosphate (GTP), was dissociated into two components of 60 and 90 Kf. The minor component, that of 60 Kd, corresponded to the receptor itself, while the 90 Kd component corresponded to an associated G-protein[29-30].

1. *The 5-HT1a receptor* consists in a protein of 422 amino acids, whose polypeptidic sequence contains seven fragments or transmembranal portions of about 20 amino acids each one. There is a high degree of homology in the transmembrane sequence of all the G-protein coupled serotonin receptors, except in the amino terminal region and in the third intracellular region, that are specific for each type of receptor and thus, they permit the production of specific anti-receptor antibodies[18,31]. The terminal amino group is located in the exterior of the cell, while the carboxy-terminal group is located intracellularly. In the second and third intracellular region, there are mainly sites for phosphorylation by binding with protein-kinase enzymes (PK). The fragment or link of intracellular localization that binds the fifth and sixth transmembranal fragments constitutes the receptor region through which this interacts with a complex family of intracellular proteins, the G-proteins, that are essential for the translation of the signal received by the receptor[32] (fig. 1).
2. *The G-proteins* have been so named because they recognize or interact with the guanosine triphosphate (GPT). Their structure is made up of three subunits: alpha, beta and gamma. The alpha subunit is the most variable and it is the one that possesses the site binding to the guanine GTP and guanosine diphosphate (GDP) nucleotides. Several isoforms of the different subunits have been identified. The alpha subunit type confers its functional specificity and its name to the different G-proteins: *a*) The Gs and Gi proteins were initially identified by their action of stimulating or inhibi-

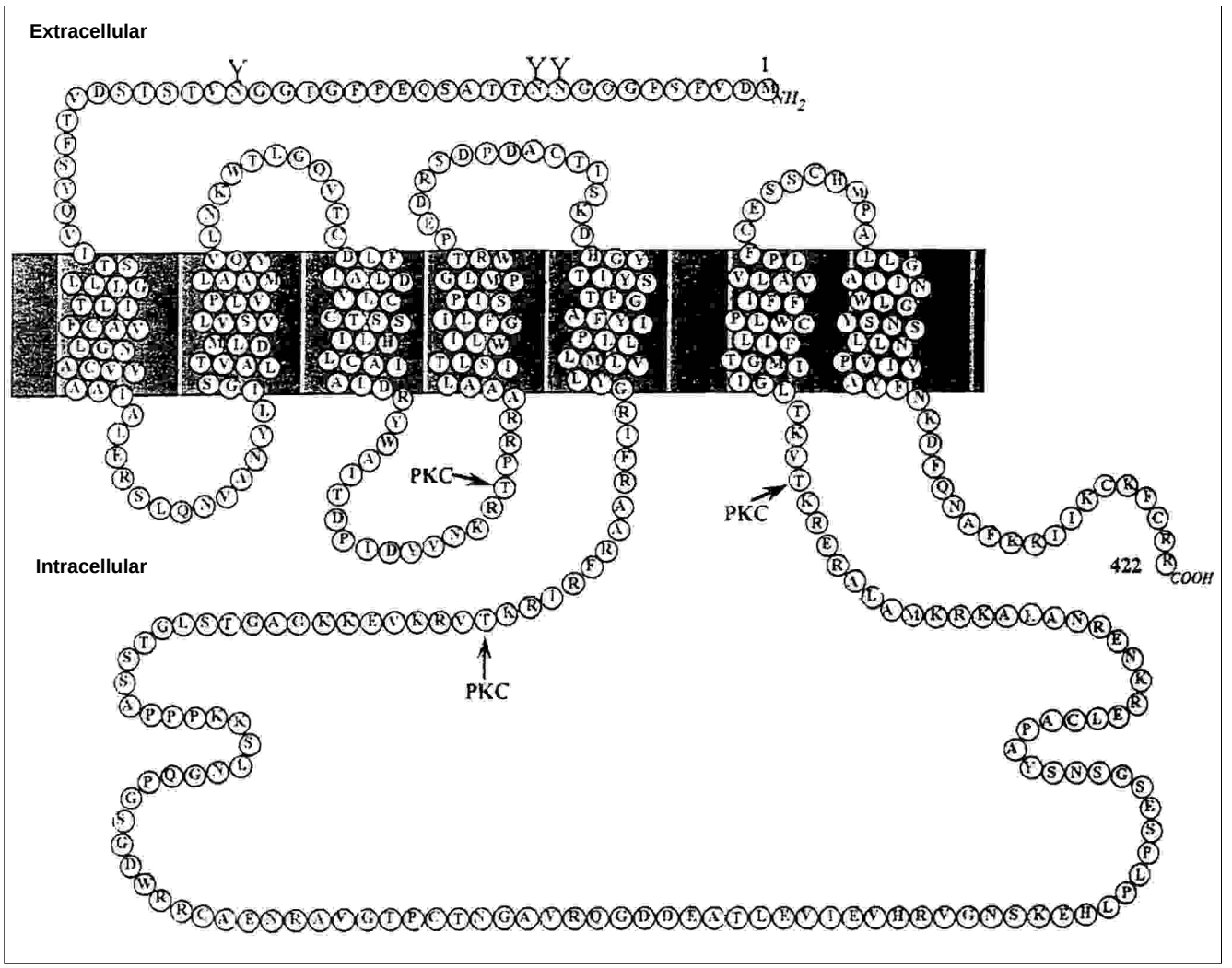

Figure 1. Molecular structure of the 5-HT1A receptors.

ting, respectively, the adenyl cyclase. The 5-HT1A receptors basically interact with the Gi proteins; *b*) the Gq protein stimulates the phospholipase enzyme C, and *c*) the Go probably opens and closes ionic channels directly[33]. All of them can be activated by stimulation of the 5-HT1A receptors. The fact that the same type of receptor can be bond to different types of G-proteins makes it possible to explain the different effects induced by agonists and antagonists of these receptors in different brain areas[30].

INTRACELLULAR TRANSDUCTION MECHANISMS ASSOCIATED TO 5-HT1A RECEPTORS

The G-proteins are considered the transductor molecules of the chemical signal because they couple the binding of the chemical messenger to the receptor, with the cellular response. The inactive form of the G-protein is bond to the GDP and its three subunits remain associated. The interaction of the agonist with the 5-HT1A receptor changes its conformation and favors the exchange of GDP in GTP in the alpha subunit of the G-protein[34]. The activated G-protein is uncoupled from the receptor in the alpha-GTP and the beta-gamma dimer. It is not exactly known if it is the alpha-GTP subunit and/or beta-gamma complex subunits, that interact with two types of effector proteins, positively or negatively modulating them: *a*) with intracellular enzymes that generate second messengers, and *b*) with ionic channels[35].

The activation of the 5-HT1A receptors principally affects the enzymatic system of the adenyl cyclase, but also the enzymatic system of the phospholipase C and the phospholipase A2 and D, and the K^+ and Ca^{2+} channels (fig. 2).

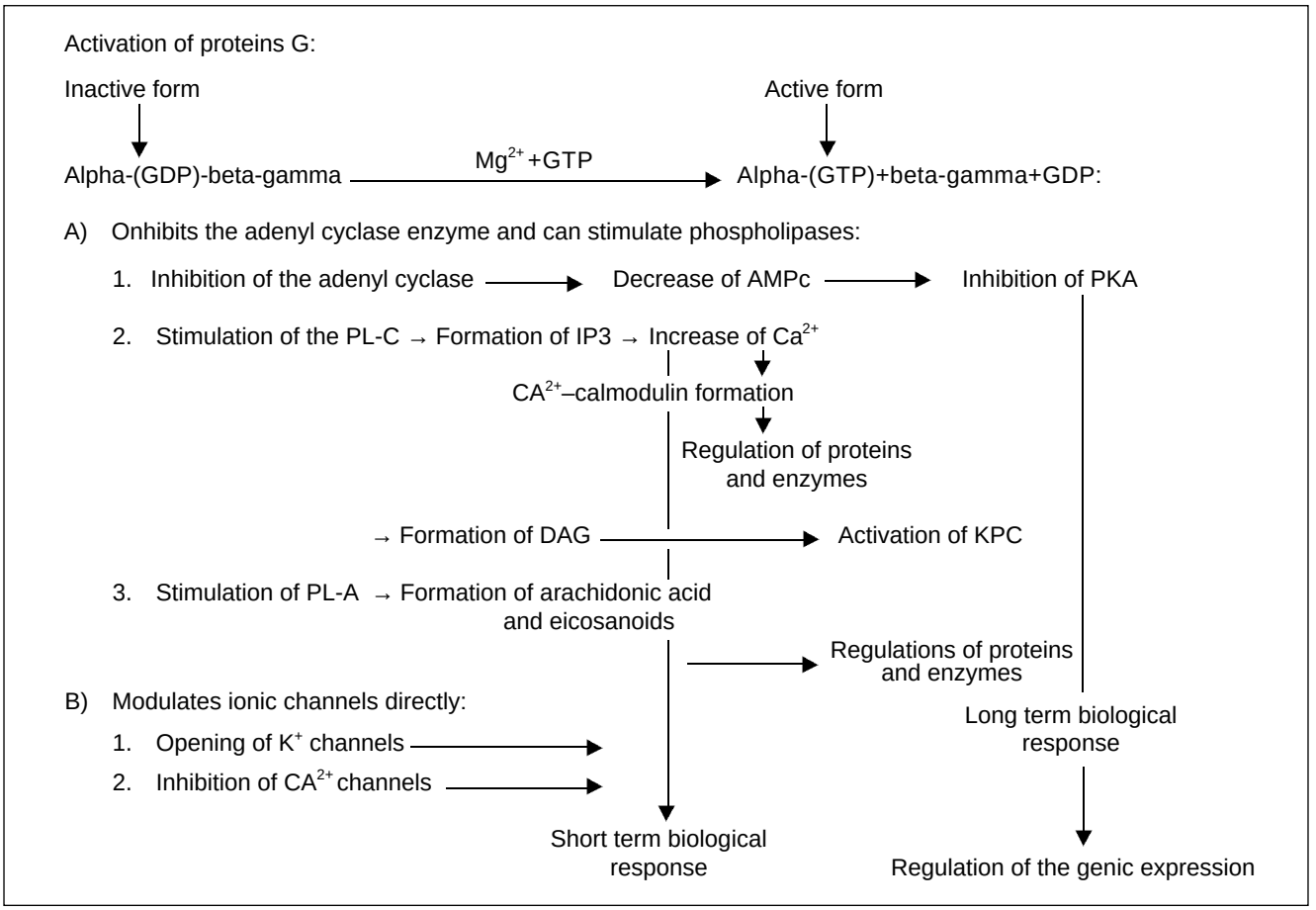

Figure 2. Stimulation of 5-HT1A receptor (binding of theneurotransmitter to receptor).

Adenyl cyclase system

At present, it seems to be clear that the activation of the 5-HT1A receptors produces an inhibition of the adenyl cyclase enzyme mediated by the activation of the Gi protein[30]. This inhibition produces a decrease of cyclic AMP inside the cell and secondarily an inhibition of a cAMP dependent protein kinase, the protein-kinase A (PK-A)[36].

This protein phosphorylates a large number of target proteins, among them the voltage dependent Ca^{2+} channels, the beta-adrenergic receptor, the tyrosine hydroxylase enzyme, or in the interior of the cell, transcription regulatory molecules such as the CREB protein (Cyclic-AMP Response Element Binding protein). The CREB protein, on the one hand, binds to deoxyribonucleic acid (DNA), promoting the expression of specific genes. On the other hand, it regulates the c-fos gene, which in turn is one of the components of the transcription factor of the type 1 activating protein (AP-1)[37]. The importance of this protein comes from its capacity to regulate the genic expression of tyrosine-hydroxylase, limiting step in the synthesis of catecholamines, proenkephalin and neurotensin[38]. Thus, the inactivation of the PK-A enzyme secondary to the inhibition of adenyl cyclase regulates the expression of these genes and thus the synthesis of enzymes such as tyrosine-hydroxylase[39-40].

Other enzymatic systems

The 5-HT1A receptors also affect other enzymatic systems such as the phospholipase C (PL-C) and the phospholipase A2 and D (PL-A2, FL-D) systems. Through the activation of these systems, the second messengers that are generated (inositol-1,4,5,-triphosphate [IP3], diacylglycerol [DAG], calcium [Ca^{2+}], prostaglandins and thromboxanes, leukotrienes, etc.), can: *a*) regulate the conductance of the ionic channels; *b*) regulate the mobilization and homeostasis of Ca^{2+}; *c*) modify the activity of key cellular enzymes and proteins, and *d*) alter the genic expression[33,35]. The responses produced, as in the case of the adenyl cyclase system, given the time used in the chemical reactions that occur, generally appear slowly, although an amplification effect of the signal in each sequence of the chemical cascade also occurs[41-42]. Thus, the 5-HT1A receptors have been related with the coding of the neural information in the long term.

Ionic channels

Activation of the 5-HT1A receptors, through their interaction with a Go protein subtype, causes the opening of the K+ channels with the consequent neuronal hyperpolarization and reduction of the electric activity of the serotoninergic neurons[43]. This causes an inhibition of the neuronal discharge and release of neurotransmitter. Through the Go proteins, the 5-HT1A receptors can also produce inhibition of the Ca^{2+} channels[44]. The response produced, acting on the ionic channel level, appears rapidly, and thus consists in the appearance of inhibitory postsynaptic potentials.

FUNCTIONAL DIFFERENCES OF THE PRE AND POST-SYNAPTIC 5-HT1A RECEPTORS

Type 1A serotoninergic receptors have two specific localizations, one pre-synaptic, in the bodies of the raphe nuclei neurons, and another post-synaptic, principally in the hypothalamic neurons. Both groups of receptors present differential characteristics[45].

1. In the raphe nuclei, the 5-HT1A receptors act as somatodendritic autoreceptors[46] while in the serotoninergic neuronal projections, they act as post-synaptic heteroreceptors[47]. Thus, the serotonin and 5-HT1A receptor agonists have a dual effect on serotoninergic neurotransmission: acting on the autoreceptors, they inhibit the electrical activity of the serotoninergic neurons of the raphe nuclei, and thus reduce the distal release of serotonin and serotoninergic neurotransmission[48]. In contrast, acting directly on the post-synaptic receptors, the agonists copy the effect of the serotonin release and thus facilitate the serotoninergic neurotransmission. Based on this dual action, it has been demonstrated by both *in vivo* as well as *vitro* electrophysiological studies that the chronic stimulation of these receptors, the result of treatment during 2 or 3 weeks with selective serotonin reuptake inhibitor (SSRI) drugs, produces desensitization of the somatodendritic 5-HT1A autoreceptors, without affecting the post-synaptic receptors[49]. Furthermore, after these treatments, the capacity of the 5-HT1A agonists to hyperpolarize the neuronal membranes is markedly reduced in the serotoninergic neurons of the dorsal raphe, but without affecting the hippocampal neurons.
2. The relationship between the serotoninergic system and the hypothalamo-pituitary-adrenal axis is also different according to localization. The expression of the 5-HT1A receptors is regulated in the hippocampus negatively by corticosterone but not in the raphe dorsal nucleus. Thus, adrenelectomy, which means the suppression of endogenous corticosterone, increases the concentration of mRNA complementary to the DNA that encodes the 5-HT1A receptor in the hippocampus, and the fixation with 5-HT1A receptor markers in the hippocampus[50], but these parameters are not affected in the dorsal raphe nucleus[51]. Specific stimulation with mineral corticoids seems to be responsible for the desensitization of these receptors in the hippocampus[52], while this same effect is due to the stimulation of the dorsal raphe nucleus receptors with glucocorticoids[53]. Furthermore, under situations of stress, when endogenous corticosterone is secreted, desensitization affects the somatodendritic 5-HT1A autoreceptors, but not the post-synaptic 5-HT1A heteroreceptors[54].
3. Differences have also been found in regards to the functionality and regulating capacity of these receptors in different areas[17,35]. For example, the influence of the agonists and antagonists of the 5-HT1A receptors in the stimulation or inhibition of the potassium channels coupled to the receptors varies from one area to another[55,48].

PHYSIOLOGICAL, BEHAVIORAL AND CLINICAL CORRELATIONS

Traditionally, the serotoninergic system was described basically as a modulator system, however in recent years, its primary role has been demonstrated in different biological functions and behaviors. The 5-HT1A receptors have been involved in cognitive processes (learning and memory, attention)[56], emotional ones (anxiety, impulsivity, aggressive behaviors and emotional state)[57,58] and in the neurogenesis of certain brain regions, both in the gestational period as well as after[59]. The alteration of these receptors, both in number and density as well as in function, is involved in the pathogenesis of different neuropsychiatric diseases (table 4).

Learning and memory

Stimulation of the 5-HT1A receptors negatively affects the work memory or executive memory[60]. Several studies in experimental animals support this hypothesis:

1. Systemic as well as intra-hippocampal injection of 8-OH-DTP, a specific agonist of these receptors, hinder the acquisition of tasks in which spatial memory is involved in rodents.
2. Combining both types of injection with a 5-HT1A receptor antagonist, Carli et al.[61] demonstrated that the selective activation of the 5-HT1A receptors in the hippocampus hinders spatial but not visual discrimination.
3. In rats, the systemic as well as local injection of a 5HT1A antagonist antagonizes the negative effect of the intra-hippocampal injection of scopolamine in the learning tasks that require spatial memory[62].
4. Similarly, learning difficulty caused by the destruction of hypothalamic neurons in the rodent

TABLE 4. Alterations described on the 5-HT1A receptors in neuropsychiatric disease

Disease	*Autoreceptors*	*Post-synaptic receptors*
Depression	Increase of density Desensitization or less functionality	No differences in density in frontal cortex Greater functionality
Ansiety	Increase of density Desentization or less functionality	No differences in density Desensitization or less functionality
Diseases with increase impulsivity (alcoholism, borderline personality, bulimia)	Increase of density Desentization or less functionality	No differences in density Desensitization or less functionality
Eschizophrenia	Increase of density No differences in functionality	No differences in density Less functionality
Dementia	Decrease of density No differences in functionality	Decrease of density Greater functionality

can be relieved with the administration of an antagonist of these receptors[63].

5. Administration of a 5-HT1A receptor agonist with an anticholinergic such as scopolamine before training worsens learning of certain tasks performed in the labyrinth test in rats. However, if it is administered after training, it does not hinder the test, which suggests that this receptor plays a role in the learning processes, but not in the retention memory, although there are controversies in this regards[64-65]. The 5-HT1A receptors involved in this effect are probably the post-synaptic receptors located in pyramidal cells of the hippocampus.

In summary, the activation of the 5-HT1A receptors has a negative effect in learning and executive memory (of work), while its selective inactivation antagonizes this effect and those associated with a cholinergic dysfunction.

Attention

Attention has been studied in animals using models that try to understand the mechanisms normally used to filter or control the sensorial stimuli that are received[66-67]. Functional measures of these mechanisms have been developed based on the so- called startle response. It has been verified that when a stimulus that produces a startle response is preceded by another previous stimulus having low intensity, the startle reflex response is reduced. This effect is called prepulse inhibition of startle (PIS)[68]. Several studies support that this response is mediated by the 5-HT1A receptors, especially the autoreceptors, besides other serotoninergic receptors such as those of 5-HT1B and 5-HT2 type[69]:

1. In rats, the PIS is reduced by systemic treatment with direct agonists of the 5-HT1A receptors[70].
2. Reduction in the PIS induced by the compounds that increase 5-HT release in the presynaptic endings is avoided by previous treatment with a serotonin reuptake inhibitor[71].
3. The alteration of the PIS induced by direct agonists of the 5-HT1A receptor in rats can be blocked by its antagonists[72].

In summary, reduction or alteration of the startle response after previous stimulus is mediated by the activation of the 5-HT1A receptors, especially the autoreceptors, although it seems that other receptors such as the 5-HT1B and 5-HT2 participate. According to this model, serotonin probably plays a role in attention as well as in behavioral inhibition.

Anxiety, impulsivity and aggressivity

The 5-HT1A receptors play an important role in the modulation of stress and in the anxiety responses, and it seems that this anxiolytic effect is mediated, at least partially, by the pre-synaptic type receptors[73]:

1. It has been verified that the partial agonists of these receptors, as the gepirone, ipsapirone and tandospirone azapirones, decrease anxiety[74-75].
2. Rats with reduced levels or with eliminated 5-HT1A receptors are less reactive but more anxious[58].

On the other hand, serotonin seems to play an important role in humans and other species, determining vulnerability for aggressive and violent behaviors, since an inverse relationship between the activity of the sero- toninergic (and especially of the 5-HT1A receptors) and the aggressive behaviors has been found in several studies[3]:

1. It has been described that individuals who present impulsive and/or violent behaviors (antisocial personality disorders, alcoholism) present blunted responses in the neuroendocrine tests that use 5-HT1A agonist as activators of the hormonal response.
2. An alteration in the density of these receptors in the brain of individuals who have presented violent suicidal behaviors has been found.
3. Rats with reduced levels or with eliminated 5-HT1A receptors are less reactive and possibly less aggressive[58].

Emotional state

There is much evidence that the serotoninergic function is involved in the physiopathology of depression,

although the exact nature of this disorder is still unknown[76]. The 5-HT1A receptors are very important in the investigation of this disorder, given that the 5-HT1A autoreceptors are involved in the modulation of serotoninergic transmission[46,77-78], and the post-synaptic 5-HT1A receptors are located in the brain cortical areas and limbic regions involved in the emotional states. Studies performed by techniques that assess density (Bmax) and affinity (Kd) of these receptors (fixation techniques of radioligands to 5-HT1A receptors in brain tissue samples of post-mortem subjects) or that assess the functionality or sensitivity of them (neuroendocrine techniques) have found disorders in these parameters in depressive patients[45]. The first ones, as a whole, do not support the existence of important differences in the density of the 5-HT1A receptors of the brain cortex of subject affected by depression, although they suggest an increase in the presynaptic receptors on the level of the raphe nuclei[79-81]. Although the findings discovered with neuroendocrine tests are not conclusive, in general, they seem to indicate that both the presynaptic 5-HT1A receptors as well as the post-synaptic 5-HT1A receptors are desensitized or hypofunctioning in depression[45].

Influence of 5-HT1A receptors in neurodevelopment

In addition to the role of serotonin as a neurotransmitter, recent studies have investigated the possibility that this neurotransmitter may participate in the modulation of brain development both during the embryonic period as well as in adult life[82-83]. On the contrary to most of the brain regions whose development occurs relatively fast during gestation, the gyrus dentatus region of the hippocampus develops during an extensive period that begins in gestation and continues during adult life. This region has a high density for 5-HT1A receptors[84]. It has been suggested that serotonin, through the activation of the serotoninergic receptors, especially of the 5-HT1A, participates in the neurogenesis of this region[85].

1. Several conditions associated with a decrease in the neurogenesis such as malnutrition[86], aging[87-88], elevated levels of corticosteron and stress[89], and the activation of the NMDA receptors[90], decrease the density of the 5-HT1A receptors and inhibit the release of serotonin in the gyrus dentatus[91-93].
2. In contrast, interventions that stimulate the genesis of granule cells of this region, such as the provocation of[95] adrenalectomy[89], and antagonists of the NMDA receptors[90], increase the density of these receptors or the release of serotonin in this region[93,96-97].
3. On the other hand, administration of compounds that increase serotonin levels in the hippocampus, as phenfluramine or 5HT1A receptor agonists, increase the proliferation of granule cells in this region[98]. All these data indicate that the stimulation of the 5-HT1A receptors participates in the production of granule cells in hippocampus.

The role of the hippocampal formations in learning and in memory has been recognized for decades[99], although the underlying mechanisms involved in these functions continue to be unknown. It has been suggested that the brain development that occurs during adult life in mammals is greatly involved in learning and memory processes, and the 5-HT1A receptors would mediate these processes.

1. Suppression of the neurogenesis induced by stress and reported after treatments with corticosterone generates deficits in learning and in memory[100-101].
2. Some degenerative disorders such as Alzheimer's disease mean a prominent loss of 5-HT1A receptors[102]. Thus, at present, the use of antagonists of the 5-HT1A receptors is being proposed as treatment of dementia[103].
3. Stimulation of the 5-HT1A receptors in rodents has a neuroprotector effect of the hippocampal injury produced after a vascular accident[104-105]; thus, the development of drugs that modulate these receptors could prevent neuronal changes that occur after cerebral ischemia conditions[106].

CONCLUSION

5-HT1A receptors are presently well characterized and their localization is known because radioligands for them have been available since years ago. The different techniques existing for their visualization have made it possible to demonstrate their presence principally in the raphe nuclei and in the cerebral limbic areas, where they correspond to pre-synaptic and post-synaptic localizations, respectively. These receptors belong to the group of receptors associated to G-proteins and their stimulation basically causes activation of potassium channels, inhibition of calcium channels and inhibition of adenyl cyclase enzyme, besides other enzymatic changes that end up generating second messengers. The second messengers may activate kinase protein enzymes, through which many proteins, channels, enzymes and/or transcriptional factors such as CREB or the c-fos suffer phosphorylation processes and are responsible, in the last place, for modifying the genic expression and consequently, cell functions, cellular metabolism, neurotransmitter synthesis and release, sensitivity of receptors, or membrane potential. These receptors participate in the regulation of different physiological functions and behaviors, and are involved in the pathogenesis of functions such as learning, memory and attention, in anxious and affective disease, and recent studies also support an influence in neurodevelopment.

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