Review Article

Serotonin Receptors in Hippocampus

Laura Cristina Berumen,1 Angelina Rodríguez,1 Ricardo Miledi,2, 3 and Guadalupe García-Alcocer1

1 Facultad de Química, Universidad Autónoma de Querétaro, Centro Universitario S/N, Cerro de las Campanas, Querétaro 76010, Mexico
2 Instituto de Neurobiología, Universidad Nacional de México, Campus Juriquilla, Querétaro 76230, Mexico
3 Department of Neurobiology and Behaviour, University of California, Irvine, CA 92697-4550, USA

Correspondence should be addressed to Guadalupe García-Alcocer, leguga@email.com

Received 27 October 2011; Accepted 8 December 2011

Academic Editor: Jerrel Yakel

Copyright © 2012 Laura Cristina Berumen et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Serotonin is an ancient molecular signal and a recognized neurotransmitter brainwide distributed with particular presence in hippocampus. Almost all serotonin receptor subtypes are expressed in hippocampus, which implicates an intricate modulating system, considering that they can be localized as autosynaptic, presynaptic, and postsynaptic receptors, even colocalized within the same cell and being target of homo- and heterodimerization. Neurons and glia, including immune cells, integrate a functional network that uses several serotonin receptors to regulate their roles in this particular part of the limbic system.

1. Serotonin

Serotonin (5-hydroxytryptamine; 5-HT), named by Rapport et al. (1948) [1], is one of the ubiquitous molecules acting as messengers, well known as a neurotransmitter and neuromodulator. Serotonin (Figure 1) is mostly found outside the central nervous system [2]; it was first identified in enterochromaffin cells and named as “enteramine” by Vialli and Erspamer in 1937 and confirmed to be the same entity with the “clotted blood” vasoconstriction effects in 1952 [3].

2. Serotonin as an Ancient Molecular Signal

The serotonergic system is an ancient sensor of diverse stimuli and molecular signaling in single-celled eukaryotes, plants, and animals [4–6].

The regulated expression of genetic material in every cell is very important and a “regulatory lesson” learned over the years is that small metabolites are often regulatory signals to control gene expression. For “expensive” biosynthesis, as the required for the serotonin precursor tryptophan, common pathways are found in organisms that take advantage of the aromatic structures; tryptophan serves as the precursor not only of serotonin (Figure 2), but also of very important compounds as niacin in eukaryotes, indoleacetic acid in plants, and indole in bacteria. Regulatory strategies could be compatible with other metabolic goals as organisms evolved capable of obtaining tryptophan by feeding, with specific plasma membrane transporters [7, 8].

Beyond the heterotrophic theory of the very first living organisms [9], serotonin could be used as specific signal, after direct relation with tryptophan synthesis was controlled, and specific monoamine transporters that do not need the missing carboxyl group of the aminoacids [7, 10] were present; later, it acquired functions of “hormone” and growth factor, and serotonin activity as neurotransmitter was achieved at last [4]. In prenervous stages, serotonin regulates basic developmental processes from cleavage divisions after fertilization (proliferator) to morphogenetic cell movements during gastrulation (morphogen) in sea urchin [11]. Presence of serotonin and its metabolite 5-hydroxyindoleacetic acid in unicellular ciliate Tetrahymena pyriformis [12] and increasing RNA production in the 5-HT stimulated protozoa [13] suggested an active biogenic amine system with relevant functions; interaction with GTPases might represent some
of the earlier functions of serotonin (and biogenic amines) before it could be vesiculated and its exocytosis could be regulated for metazoan serotonergic systems [14, 15].

3. Serotonin as a Regulatory Molecule in Animals

This happy hormone, as recalled by Dr. Barnes [16], plays a modulatory role in almost every physiological function and is involved in many biological processes [2, 17]; furthermore, the three related metabolites, 5HT, tryptophan, and melatonin, are important regulators of feed intake, reproduction, immunity, neurological function, and antistress responses [18].

Serotonin is involved in natural reward-related physiology and behaviour, from feeding to sexual activity [19] with many actions correlated to the involved location (cellular-tissue-organ concentration) and the different signaling can also be associated with its more than fourteen receptor subtypes, regulating physiological processes through different, even opposing mechanisms; these indoleamine effects include also serotonylation and interaction with GTPases [2, 14, 15]. Serotonin influences body temperature, breathing rhythms (respiratory system), heart rate (cardiovascular function in general), eating and bowel motility (gastrointestinal system), ejaculatory latency and bladder control, muscle contraction/relaxation and locomotion, sleep, arousal, pain and sensory perception, emotions, and cognition [2, 5, 20] with a well-known signaling role in immune cells [21].

4. Serotonin in Central Nervous System

Serotonergic neurons, first discovered in the brainstem by Dahlström and Fuxe in 1964 [22], release 5-HT throughout the CNS [23, 24] as expected after the brain serotonin discovery [25]. 5-HT cell bodies are mainly localized in the raphe nuclei with their axons innervating almost every brain region [17]. The hippocampus is a principal target of serotonergic afferents along with all the limbic system [26]. The serotonin projections to hippocampus stem in a topographic order from the midbrain dorsal and median raphe nuclei [27–29]. The rat ventral hippocampus receive moderately dense projections from the caudal dorsal raphe and essentially none from the rostral dorsal raphe, with fine serotonergic axons and small varicosities widely distributed throughout the hippocampus. Furthermore, beaded serotonergic axons with large, spherical varicosities are also found in hippocampus; median raphe nucleus predominantly innervate the stratum lacunosum moleculare of the CA1 and CA3 regions and the dentate hilus [26, 28, 30, 31]. The density of serotonergic axons is highest in CA3, lower in dentate gyrus and lowest in CA1 [26, 30]. Almost all subtypes of serotonin receptors are expressed in hippocampus during ontogeny, so the regulation of the serotonergic system is more than complex [32, 33].

5. Serotonin Receptors

Heterogeneity in serotonin receptors was established by the late 1950s, with Gaddum and Picarelli [34] proposing two tryptamine receptors in the guinea-pig ileum: M and
D, blocked with morphine and dibenzyline, respectively; binding to serotonin receptors was also studied with [3H] 5-HT and [3H] LSD [35, 36] and more than twenty years later a new classification was proposed by Peroutka and Snyder (1979): 5-HT1 and 5-HT2 receptors based on radioligand binding techniques ([3H] 5-HT, [3H] LSD and [3H] spiroperidol) [37].

With the use of specific radiolabelled ligands, there was a new classification [38] proposing 5-HT3 receptors although 5-HT1-like receptors were still considered a heterogeneous entity. Others tried to adjust the new information and finally, with the advances in molecular biology, the serotonin receptors were cloned, finding more than three subtypes. The Serotonin Club Receptor Nomenclature Committee (SCRNC), reporting directly to the IUPHAR Committee for Receptor Nomenclature, described a new classification of 5-HT receptors [39]. This classification was based in different operational (selective agonists, antagonists, and ligand-binding affinities), structural (molecular structure), and transductional (intracellular transduction mechanisms) criteria.

Serotonergic receptors (Figure 3) were grouped in seven classes 5-HT1-7, all of them belonging to the G-protein-coupled receptor (GPCR) superfamily [40], except 5-HT3 which is a ligand-gated ion channel that belongs to the nicotinic acetylcholine receptor superfamily: cystein-loop transmitter gated superfamily which constitutes heteropentamers [5, 41, 42]. Particularly, subindex for the different receptors were arranged and the former 5-HT1C was renamed as 5-HT2C, for its transductional properties and molecular structure [39]. In the paper, subscript will be used for 5-HT subtype receptors after SCRNC, and normal line of type for previous findings in subtype receptor will be written.

6. Ion Channel Serotonin Receptor

The 5-HT3 receptor is a cation-selective ion channel which activation evokes neuronal excitation and neurotransmitter release. There are two well-recognized genes encoding A and B subunits, but additional C, D, and E genes expand the diversity to heterooligomer formation of the pentameric channel [45]. The different composition might reflect distinct pharmacology and relevance to their function representing each one a different subtype of receptor. These subunits can interact with other members of the Cys-loop superfamily, regarding the previous “M”-type serotonin of Gadum and Picarrelli classification [46].

7. Metabotropic Serotonin Receptors

The seven transmembrane domain (7TMD) serotonin receptors belong to the “type A” family of GPCR, rhodopsin-like receptors, grouped by Fredricksson et al. (2003) in the amine
receptor cluster [47]. They display a heterogeneous phylogenetic pattern with 5-HT1 forming one group and 5-HT1B-1F forming another group; the rest of 5-HT receptor subtypes can be related with other biogenic amine receptors clusters. In other classification [48], 7TMD 5-HT receptors can be grouped in type 1 family that contains GPCRs for small ligands binding in a cavity formed by TM-III to TM VI [49]. The 7TMD serotonin receptors are coupled to different G proteins. The 5-HT1 receptors couple to Ga11/Gαo proteins; the 5-HT2 receptors couple to Gαq proteins; the 5-HT4, 5-HT6 and 5-HT7 receptors couple to Gαs proteins, and the 5-HT5 receptors are related to Gαi/Gαo proteins [44]. Activation of Gαi coupled receptors (Figure 4) leads to the stimulation of adenyl cyclases elevating cyclic AMP (cAMP), which as a second messenger interacts with other proteins including ion channels and activating the protein kinase A (PKA). This phosphorylating enzyme also activates cAMP-responsive transcription factors like CREB modifying gene expression. The interaction with other exchange proteins directly activated by cAMP leads to alternative signaling cascades besides the classical PKA. The interaction with Gαs leads to inhibition of adenyl cyclases, decreasing production of cAMP [5]. The activation of Gαq11 coupled receptors (Figure 5) lead to the hydrolysis of membrane phosphoinositides resulting in the formation of diaclyl glycerol (DAG) and inositol phosphates (IP3). IP3 can interact with the calcium reservoirs, elevating intracellular levels and activating protein kinase C [5, 50]. Serotonin receptors may also be coupled to Gα12/13, mediating structural changes within the cell through activation of the Rho signaling pathway [41]. The Gβγ dimeric subunit can interact with a variety of enzymatic effectors within the cell, like their action on gated ion channels, regulation of particular isoforms of adenyl cyclase and phospholipase C, and phosphoinositide-3-kinase isoforms (and ERK signaling) [51]. If so many receptor subtypes of serotonin make it complex to understand, plethora of activities can be found with the coupling to multiple G-proteins. There are different parameters in the activation pathway of the GPCR receptors, considering multiple states instead of the traditional two-state model of activation and forming dimers that may have distinct pharmacology with respect to activation, signaling, and internalization and the organization in microdomains at the membrane level that may affect coupling and trafficking of G-proteins [52].
Promiscuous coupling of GPCRs to G-proteins is not a surprise, and they can also signal without coupling to them; they can activate a variety of cascades by arrestin-ergic signalling, beside the original function of these proteins in terminating coupling and endocytosis [53, 54].

In brief, there are thirteen genes coding for GPCR serotonin receptors that may couple almost every G-protein in the cell membrane and probably act without coupling to them, and two recognized genes coding for the subunits of cation-selective 5-HT₃ ligand-gated ion channel pentameric receptor.

This diversity is further complexed by the posttranslational and co/posttransductional modifications of the protein to be produced, without talking about oligomerization of the serotonin receptors and single-nucleotide polymorphisms. There are examples of this modifications in the different receptor families with alternative splicing, RNA editing, palmitoylation, glycosylation, phosphorylation, and proteolysis, to mention a few [55].

8. Serotonin Receptors
Expression in Hippocampus

All the serotonin receptor families are remarkably expressed in hippocampus, which is part of the limbic system, a whole structure related with memory processing, emotional association with memory, judgment, affect, and motivation or the organization of planned actions [26]. The innervation of serotonergic pathways in hippocampus and the diverse expression of serotonin receptors in this brain area reflect the overall functions related to 5-HT, in particular with cognition, mood and food intake. After recognition of hippocampal serotonergic afferents by histochemical methods (fluorescence, potassium dichromate), uptake of tritiated serotonin was achieved corroborating the wide spread of 5-HT pathways [56]. Molecular biology of the specific receptors for serotonin confirmed this knowledge.

8.1. 5-HT₁ Receptors. The hippocampus contains a high density of 5-HT₁ sites, most of which belong to the 5-HT₁ subtype [39]. Before classification of serotonin receptors on the basis of their molecular biology, distinction between the receptors in this group was based on the affinities for 8-hydroxy-2-((di-n-propylamino)tetratin (8-OH-DPAT) distinguishing 5-HT₁A, lysergic acid diethylamide (LSD) and mesulergine detecting 5-HT₁C, later renamed as 5-HT₂C, and rauwolscine for 5-HT₁D receptors, for example, but findings of new receptors with affinity for these ligands may clarify error in quantitation of the former groups.
8.2. *5-HT*₁₆. Fargin et al. characterized the genomic clone G-21 that corresponded to 5-HT₁₆ sequence [57]. Gozlan et al. (1983) [58] had previously reported the existence of 5 HT₁—like receptors in hippocampus on the basis of the binding experiments of [³H] 8-OH-DPAT. In 1986, Hoyer et al. [59] and Vergé et al. [60] confirmed these results and compared binding of 5-HT₁A and 5-HT₁B; later characterization was performed by chromatographic analyses of the serotonin 5-HT₁A receptor solubilized from the rat hippocampus [61]. Activation of somatodendritic autoreceptors diminished 5-HT synaptic transmission [62] suggesting that 5-HT₁A might represent presynaptic receptors as well as postsynaptic neurotransmission in hippocampus. At cellular levels, 5-HT₁₅A receptors are located postsynaptically in pyramidal and granular neurons of the hippocampus as well as extrasynaptic structures, by studies using highly selective 5-HT₁₅A antibodies that allowed confirmation and refinement of autoradiographic results [41]. They function as somatodendritic inhibitory receptors in raphe nuclei and presynaptically in hippocampus [63]. 5-HT₁₆A has also been detected in some astrocytes, radial glia, and ependymal and endothelial cells [64].

8.3. *5-HT*₁₆. Molecular cloning of rat 5-HT₁₆ receptor was performed by Voigt et al. in 1991 [65]. Previously, 5-HT₁B was defined as the nonsipiperone sensitive [³H]5-HT binding in brain [41]; localization of 5-HT₁B was described with low densities in hippocampus (gyrus dentatus > CA1 ≥ CA3) by affinity differences with [³H] 8-OH-DPAT [60] and binding studies with [¹²⁵I]iodocyanopindolol [66]. Immunohistochemistry analysis had also shown coexpression of 5-HT₁₆ in hippocampal cells with other serotonin receptors [67]. 5-HT₁₆ receptors are responsible for the presynaptic inhibition of neurotransmission at the local synapses between axon collaterals of CA1 pyramidal cells and other CA1 pyramidal neurons and interneurons [68]. Projection neurons from hippocampus reach the bed nucleus of the stria terminals, where presynaptic 5-HT₁₆ receptors are involved in the inhibition of glutamate transmission [69]. Furthermore, 5-HT₁₆ hippocampal GABAergic axon terminal heteroreceptors inhibit neurotransmitter release [70].

8.4. *5-HT*₁₇. Hamblin and Metcalf in 1991 [71] described sequence of human 5-HT₁D serotonin receptor and two genes known as 5-HT₁Da and 5-HT₁Db were reported [72]. It was clear later that 5-HT₁Db was the homologue receptor of rat 5-HT₁B, so called 5-HT₁B. Operational profiles between the former 5-HT₁Da and 5-HT₁Db receptors were almost indistinguishable, and similarities are still very present [41]. 5-HT₁Da remained as the homologue of rat 5-HT₁D, and so-called 5-HT₁D. 5-HT₁D binding sites resemble those of 5-HT₁B receptors in hippocampus with very low presence [41, 73]. 5-HT₁D₁B receptors are found at pre- and postsynaptic sites but presynaptic receptors are predominantly located on 5-HT hippocampal nerve terminals [63].

8.5. *5-HT*₁₆. There is not a clear characterization of 5-HT₁₆ due to the lack of specific ligands that might differentiate this receptor subtype; furthermore, expression of 5-HT₁₆ has not been found in rodents, because there is a stop codon in the correspondent mRNA [41]. Cloning of this receptor was achieved using cDNA synthesized from monkey cortex and human hippocampal cDNA library [74] though confirming its presence in hippocampus, previously reported by the existence of a 5-HT₁E subtype in human brain with findings in radioligand studies [75].

8.6. *5-HT*₁₅F. When 5-HT₁₅F was found [76], it was designated as 5-HT₁₅B due to its related pharmacological profile; 5-HT₁₅F-labeling was moderate in granule cells of the dentate gyrus and hippocampal pyramidal cells in CA1–CA3, confirming its expression in hippocampus [77].

8.7. *5-HT*₂. Receptors from this group were originally recognized by ligands like ketanserin, mesulergine, LSD, and spiperone, which were reported to have high affinities for 5-HT₂ receptors compared to 5-HT₁ group [78]. These receptors are coupled to phosphatidylinositol hydrolysis although some effects may involve intracellular calcium release via an independent mechanism [79]. Hoyer et al. [80] used Ketanserin binding though localizing 5-HT₂ receptors recognition sites in hippocampus.

8.8. *5-HT*₂A. On the basis of the similarity in exerting the cellular effects which reflected the structural relationship with the former 5-HT₁C receptor, Pritchett et al. (1988) used oligonucleotides encoding this serotonin receptor and found 5-HT₂A sequence [81]. Julius et al. (1990) also found an encoding sequence for 5-HT₂ which was expressed in hippocampus in a 10-fold lower level than in rat cortex [82]. The 5-HT₂A receptor refers to the classical D receptor described by Gaddum and Picarelli in 1957 and defined later as 5-HT₂ by Peroutka and Snyder in 1979 [37]. 5-HT₂A expression in human hippocampus was confirmed with RT-PCR technique [83]. Immunoreactivity for 5-HT₂A receptor in hippocampus was found primarily in the pyramidal cell layer of CA1–CA3 and in the granular layer of dentate gyrus [84]. Agonist studies with 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) indicate postsynaptic receptors for 5-HT₂A [63]; in prelimbic prefrontal cortex, most 5-HT₂A receptors were postsynaptically located, but presynaptic axons and varicosities locations were found [85]. Cellular localization of 5-HT₂A receptors in astrocytes has been found in hippocampus [86].

8.9. *5-HT*₂B. The “last” 5-HT2-like receptor subtype to be cloned was 5-HT₂B [87] from rat stomach fundus. The origin and comparable sequence to 5-HT₁C/2 led them to designate it as 5-HT₂F (for fundus) and renamed as 5-HT₂B after consensus of SCRNC in 1994. Cloned human 5-HT₂B receptors had a high degree of homology with mouse and rat receptors although with higher affinity for ketanserin and a lower affinity for yohimbine; it was found at very low presence in the whole brain [88]. Expression of 5-HT₂B receptors in cultured astrocytes from hippocampus with Ca²⁺ increases after stimulation with alpha-methyl 5-HT has been reported [89]. The presence of this receptor in astrocytes was verified with immunohistochemistry and
western blot analysis. Furthermore, microglial cell cultures expresses 5-HT$_{2B}$ receptors, and they are involved in the regulation of inflammatory cytokine production from blood cells [90].

8.10. 5-HT$_{2C}$. Lübbert and colleagues cloned in 1987 [91] the mouse 5-HT1C-mRNA (actually 5-HT$_{2C}$) extracted from choroid plexus tumors; Julius et al. (1988) characterized a cDNA encoding this protein and confirmed the receptor expression in neurons of many regions of central nervous system by in situ hybridization and RNA blot analysis [92]. It was first identified in porcine choroid plexus on the basis of its pharmacological properties [93] and localized by autoradiographic mapping in rat [94] and human brain, particularly in hippocampus [80].

The overall distribution of 5-HT$_{2C}$ receptor was reported by several studies with mRNA in situ hybridization [95–98]. The specificity of radioligand binding ($^{3}$H) mesulergine was compared with in situ hybridization by Mengod et al. (1990), finding high signal in the pyramidal layer of the CA3 field of rostral hippocampal formation, while intense hybridization was found in the strata oriens and radiatum of the caudal CA1 area and in the ventral subiculum [97]. Furthermore, Abramowski et al. (1995) compared $^{3}$H mesulergine binding with specific antibody-binding in rat and human brain [99]; Clemett et al. (2000) also studied the presence of 5-HT$_{2C}$ protein with immunohistochemistry and western blotting with abundant expression in rat hippocampus [100].

8.11. 5-HT$_{3}$ Receptors. 5-HT$_{3}$ receptor belongs to the ligand-gated ion channel superfamily and corresponds to the M receptor of Gaddum and Picarelli [41, 101]; five subunits have been cloned although only 5-HT$_{3A}$ and 5-HT$_{3B}$ are recognized for rodents [102–106]. The various subtypes of 5-HT$_{3}$ may well-correspond to the pentameric heterodimer assembled between all subunits and their splice variants, and also with other members of the cys-loop superfamily, like a4-nAChR nicotinic receptor [46, 107] although this association has not been detected in porcine native 5-HT$_{3}$ brain receptors [108]. On the contrary, association and coimmunoprecipitation of 5-HT$_{3}$ and P2X$_{2}$ ATP-gated channels has been reported [109].

All subunits have been found mainly in human intestine [110]. 5-HT$_{3}$ mRNA was found in rat hippocampus primarily on interneurons, mediating indirect inhibitory effects on pyramidal neuron populations [111]. On the contrary, 5-HT$_{3}$ was found in human hippocampus with predominant immunoreactivity associated with pyramidal neurons in CA$_{2}$ and CA$_{1}$; transcripts were also identified so hippocampal cells can produce 5-HT$_{3A}$ and 5-HT$_{3B}$ functionally isoforms of this ion channel [112].

8.12. 5-HT$_{4}$ Receptors. The 5-HT$_{4}$ receptor was first described in the central nervous system [113] stimulating adenylate cyclase; with some useful radioligands, it was showed to be distributed in hippocampus. It was cloned [114] and mRNA was localized in hippocampus by in situ hybridization [115].

The 5-HT$_{4}$ receptor gene is very complex and has several possible splice variants; there are at least nine receptor splice variants reported with a number of carboxy-terminal variants but no difference in affinity for agonists or antagonists [41]. There is evidence that suggests that 5-HT$_{4}$ receptor activity enhances cognition and provides neuroprotection, particularly on hippocampal effects [116]; 5-HT$_{4}$ receptors on hippocampal cholinergic axon terminals are neurotransmitter release facilitating [70].

8.13. 5-HT$_{5}$ Receptors. The 5-HT$_{3}$ receptor group consists of two members: 5-HT$_{5A}$ and 5-HT$_{5B}$; human 5-HT$_{5B}$ has been described, but it fails to encode a functional protein due to the presence of stop codons in the sequence [117–119]. They still lack physiological correlation, in part for the lack of selective agonists; the transductions pathways have not been well established although negatively coupling to adenylate cyclase has been reported [41, 43, 120].

8.14. 5-HT$_{5A}$. Cloning and distribution of 5-HT$_{5A}$ receptor has been reported, finding high concentration in hippocampus [119, 121, 122]. Although this receptor is a well-recognized GPCR protein, the negatively coupling to adenylated cyclase is not well established [120, 123–125], and furthermore, its coupling to multiple signal transduction pathways has been reported [126]. The 5-HT$_{5A}$ receptor is expressed predominantly by astrocytes with very weak neuronal immunoreactivity [120].

8.15. 5-HT$_{5B}$. Cloning and distribution of 5-HT$_{5B}$ receptor has been reported as well, finding this receptor in hippocampus [119, 127]. The levels of expression of 5-HT$_{5B}$ mRNA in hippocampus were high, with predominant expression in CA1 pyramidal cells [128]. It is a pseudogene in man [129], and it has been proposed that the upregulation found (particularly in hippocampus) for mice 5-HT$_{5B}$ receptor, in response to social isolation stress, might be undertaken in humans by another receptor like 5-HT$_{5A}$ [130].

8.16. 5-HT$_{6}$. Ruat et al. (1993) cloned 5-HT$_{6}$ receptor [131], starting from the sequence of rat histamine H2 receptor with two transcripts evidenced. mRNA was detected in hippocampus and in transfected COS-7 cells 5-HT$_{6}$ receptor was positively coupled to adenylate cyclase. Hybridization signal of 5-HT$_{6}$ mRNA was detected in CA1, CA2, and CA3 fields of hippocampus as well as in dentate gyrus [128].

8.17. 5-HT$_{7}$. Ruat et al. (1993) also cloned the putative 5-HT$_{7}$ receptor and localized it at hippocampus [132]. It is differentially expressed in CA1 cells preferentially localized on the cell body but absent in interneurons [133]. The expression in the limbic areas suggests that these receptors mediate serotonergic controls in functions like mood, learning, or neuroendocrine and vegetative behaviors. The emerging functions of hippocampus involve several neurotransmitter networks, where 5-HT$_{7}$ receptors can be functioning. AMPA receptor-mediated transmission between CA3 and CA1 pyramidal neurons is enhanced.
postsynaptically by 5-HT\textsubscript{7}, while 5-HT\textsubscript{1A} receptors inhibit this transmission both pre- and postsynaptically [134].

9. Serotonergic Modulation in Hippocampus

Among the various major neurotransmitter signaling, like monoaminergic, glutamatergic, and nitrergic neurotransmitter systems that might be involved in some plastic modifications of hippocampus particularly after stress exposure [135], serotonergic system is very interesting for its complexity and regulation.

Almost all pre- and postsynaptic serotonin receptors have been identified in hippocampus; furthermore, the 5-HT transporter (SERT, 5-HTT) plays a key role in serotonergic neurotransmission, and it is condition-regulated in hippocampus [136, 137]. In addition, tryptophan hydroxylase (TPH), the rate-limiting enzyme for producing serotonin, plays another key role in the regulation of this system; TPH1 and TPH2 have been found in hippocampus [138]. The other key enzyme in serotonergic system is monoamine oxidase A, responsible for 5-HT degradation [139], expressed in hippocampus as well.

Regulation of serotonin system is very important and disturbances in this matter are related to anatomical, functional and behavioural anomalies, including neurologic and psychiatric disorders as obsessive-compulsive disorder, bulimia, chronic impulsivity, obesity and drug addiction, aggression, -major- depression, suicide, anxiety, schizophrenia, mania, autism, Alzheimer’s disease and also sudden infant death syndrome [43, 139–142].

The function of serotonin as neurotransmitter seems to be developed at last in evolution, and ionotropic channels are related to rapid neuronal activation, particularly in enteric nervous system [4]. Serotonin, as metabotropic effector, has been recognized as a trophic factor, particularly during development including morphogenetic activities as cell proliferation, migration and differentiation [137, 143]; during adulthood, depletion in serotonin decreases neurogenesis in the dentate gyrus [144] though 5-HT plays a critical role in the neuronal organization of the hippocampus [145].

Several metabotropic effects of serotonin have been related to brain-derived neurotrophic factor (BDNF) expression [144] and BDNF itself promotes the development and function of serotonergic neurons [140]. This kind of interaction between neurtrophilic factors and neurotransmitters has been reported also with steroids; the regulation of HPA axis by serotonin and vice versa is well documented [146, 147]; sexual steroids have this intricate correlation as well [148]. The key for understanding these relationships is the existence of multiple receptors and ligand interaction for molecular signaling.

On the other hand, hippocampus-dependent memory formation uses long-term potentiation (LTP) as a pivotal role. Cross-talk between the cAMP signal transduction system and LTP has been reported, with a critical linkage between Ca\textsuperscript{2+} and cAMP signaling [149]. At this level, all of the serotonin receptors seem to be directly involved in the normal function of hippocampus in mood regulation and memory formation; neurogenesis is thought to be one of the involved processes for long lasting changes related to hippocampal function, particularly because dentate gyrus is one of the prominent areas of adult brain neurogenesis [150].

The 5-HT\textsubscript{1A} is the most likely involved receptor in regulation of neurogenesis in the dentate gyrus [150]; it is expressed on raphe serotonin neurons as an autoreceptor [151], acting as a negative regulator of neuronal activity in presynaptic locations in hippocampus, with very important function in the balance of serotonin reservoirs. 5-HT\textsubscript{1A} also inhibits neuronal firing, activating G-protein-gated inwardly rectifying potassium (GIRK) currents and inhibiting Ca\textsuperscript{2+} channels [44]; it is involved in the inhibition of long-term potentiation (LTP) by the inhibition of NMDA function [152].

As one of the most “important” members of serotonin receptors, 5-HT\textsubscript{1A} receptor is the best characterized and its ligands are used extensively. The mutant (knockout) mice lacking this receptor exhibits enhanced anxiety-related behaviour [153, 154]. The “specific” 5-HT\textsubscript{1A} ligand 8-OH-DPAT has been used to establish the roles of this receptor as trophic factor and in neurotransmission as well, but 5-HTT (SERT) recognizes this ligand and likewise modulates anxiety-related behaviour [136, 155].

The therapeutic effects of serotonin-selective reuptake inhibitors (SSRI), “specifically” acting on SERT function, are well documented, and several theories are proposed to explain the retarded actions in successfully treated patients [156–158]. SSRIs are the most widely prescribed class of antidepressants, which increases synaptic levels of 5-HT in hours or days, but exerts the therapeutic response several weeks later [159]. The increasing levels of 5-HT cause a desensitization of 5-HT\textsubscript{1A} autoreceptors with a lesser inhibition caused by this receptor in raphe neurons, leading to a facilitation of 5-HT signaling [160]. There is a differential response of SSRI’s desensitizing 5-HT\textsubscript{1A} presynaptic or postsynaptic receptors; the specific serotonin receptor antagonist WAY 100635 also promotes differential changes in autoreceptors compared to postsynaptic 5-HT\textsubscript{1A} receptors [160, 161].

SERT and 5-HT\textsubscript{1A} are the most studied therapeutic targets although several serotonin receptors are involved in hippocampus activities, particularly 5-HT\textsubscript{4}, 5-HT\textsubscript{5A}, and 5-HT\textsubscript{7} that activate cAMP signaling increasing CREB, which may increase the expression of BDNF [150]. Furthermore, 5-HT\textsubscript{4} activation may cause a faster direct activation of 5-HT neurons, increasing their firing and causing desensitization of 5-HT\textsubscript{1A} [159]. 5-HT\textsubscript{2} receptors involve an alternative signaling pathway to cAMP, where increasing Ca\textsuperscript{2+} levels is of particular importance, relying on the crosstalk between cAMP signaling and Ca\textsuperscript{2+}-regulated adenyl cyclases. Knockout phenotype for 5-HT\textsubscript{2A} shows decreased, anxiety while the one for 5-HT\textsubscript{2C} shows increased appetite, overweight, and cognitive impairment. Serotonin receptor 5-HT\textsubscript{2C} is probably the most important receptor related to food intake and energy balance (satiety and obesity), with viable targeting for weight control [20].

The most representative neurotransmitter receptor for serotonin in rapid actions is the ionotropic 5-HT\textsubscript{3}, which
Figure 6: Serotonin receptors in hippocampus. The functional glia-neuron-vascular cells network uses several serotonin receptors (5-HTRs). The 7TMD images of each subtype receptor are represented with the defined number of exons that code for the mature protein (Bockaert et al., 2006) [44]; putative intron location in correspondent pre-mRNA is marked by a lightning symbol (‡); alternative splicing sites are marked with stars (⋆ ⋆ ⋆). Neuron metabotropic 5-HTRs are mainly somatodendritic volume receptors although there is an association with synaptic specializations for some of them. 5-HT\textsubscript{3} with the five 4TMD subunits of a ligand activated ion channel is shown as synaptic receptor although this fact remains to be determined in hippocampus. Microglia is also included in the network for its relevance in pathophysiological responses, with 5-HT\textsubscript{2B} receptor expression (Capone et al., 2007) [90]. The 12TMD image of the serotonin transporter (SERT; 5-HTT) and vesicular monoamine transporter (VMAT) are represented in the serotonergic neuron and only SERT in the astrocyte.

is also involved in LTP modulation in hippocampus [162]. The knockout phenotype for 5-HT\textsubscript{3A} has reduced pain perception and variants of the 5-HT\textsubscript{3A} receptor have been associated with bipolar disorder and schizophrenia [43].

Serotonergic neuronal-glial interactions (Figure 6) have been proposed to play a significant role in the development of several CNS pathologies [163]. Some serotonin receptors are mainly expressed in glia. 5-HT\textsubscript{3A} correlates with astrocyte maturity and activity, increasing its levels after induced gliosis [120] although its expression in pyramidal cells of hippocampus has been reported [117]. Addition of cAMP analogues to astrocyte cultures decreases 5-HT\textsubscript{3A} expression and increases 5-HT\textsubscript{5A}, therefore suggesting a direct neuronal regulation of astrocyte homeostasis, as cAMP intracellular
increases might activate and sensitize astrocytes to respond at serotonin signaling from neurons that can suppress gliosis in vivo [120].

Each cell type can modify its serotonin receptor expression depending on the differentiation time and relationship in a particular network. Mouillet-Richard et al. (2000) have shown the differentiating changes than induced serotonergic 1C11-HT cells can exhibit [164], sequentially expressing three different serotonin receptor subtypes (5-HT1B/1D, 5-HT2A, and 5-HT2A). Although cell cultures do not represent reliable conditions of in vivo differentiation, they help us understand how cells can adapt to changing media. The 5-HT2 receptors are referred to as programmable receptors that may not influence development although this process affect their number, affinity, or function; the coupling efficiency of the receptor may change in time, in correlation to a developmental change of phosphatidylinositol hydrolysis-second messenger system [165].

In conclusion, the specific changes that modulate serotonin signaling can be performed by serotonin itself; the levels of serotonin that can be reached in the synapses, or as a volume transmission, is of outstanding importance to understand the rate of change in the 5-HT signaling itself, time of action might conduce to one response or the contrary, considering that all the cell types in hippocampus are involved in this modulation and function. Serotonin can act directly into neuron and glia after SERT incorporation, an ancient function for this biogenic amine and probably with more importance during development.

Conflict of Interests

The authors do not have conflict of interests. Support for publication is received from Universidad Autónoma de Querétaro.

Acknowledgments

The authors appreciate the suggestions of Jesica Escobar in the preparation of this paper. They would also like to acknowledge Salvador and Diego Lecona for editing the English content of this paper.

References

[1] M. M. Rapport, A. A. Green, and I. H. Page, “Serum vasoconstrictor (serotonin). IV. Isolation and characterization,” The Journal of Biological Chemistry, vol. 176, pp. 1243–1251, 1948.
[2] M. Berger, J. A. Gray, and B. L. Roth, “The expanded biology of serotonin,” Annual Review of Medicine, vol. 60, pp. 355–366, 2009.
[3] V. Ersasper and B. Asero, “Identification of entarame, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine,” Nature, vol. 169, no. 4306, pp. 800–801, 1952.
[4] K. Turlejski, “Evolutionary ancient roles of serotonin: long-lasting regulation of activity and development,” Acta Neurobiologica Experimentalis, vol. 56, no. 2, pp. 619–636, 1996.
[5] D. E. Nichols and C. D. Nichols, “Serotonin receptors,” Chemical Reviews, vol. 108, no. 5, pp. 1614–1641, 2008.
[6] S. Park, K. Kang, S. W. Lee, M. J. Ahn, J. M. Bae, and K. Back, “Production of serotonin by dual expression of tryptophan decarboxylase and tryptamine 5-hydroxylase in Escherichia coli,” Applied Microbiology and Biotechnology, vol. 89, no. 5, pp. 1387–1394, 2011.
[7] G. Rudnick, “What is an antidepressant binding site doing in a bacterial transporter,” ACS Chemical Biology, vol. 2, no. 9, pp. 606–609, 2007.
[8] C. Yanofsky, “RNA-based regulation of genes of tryptophan synthesis and degradation, in bacteria,” RNA, vol. 13, no. 8, pp. 1141–1154, 2007.
[9] A. Lazzano, “Historical development of origins research,” Cold Spring Harbor Perspectives in Biology, vol. 2, no. 11, Article ID a002089, 2010.
[10] D. L. Murphy, M. A. Fox, K. R. Timpano et al., “How the serotonin story is being rewritten by new gene-based discoveries principally related to SLC6A4, the serotonin transporter gene, which functions to influence all cellular serotonin systems,” Neuropharmacology, vol. 55, no. 6, pp. 932–960, 2008.
[11] G. A. Buznikov, H. W. Lambert, and J. M. Lauder, “Serotonin and serotonin-like substances as regulators of early embryogenesis and morphogenesis,” Cell and Tissue Research, vol. 305, no. 2, pp. 177–186, 2001.
[12] E. J. Eisman, “The serotonergic system in Tetrahymena pyriformis,” La Ricerca in Clinica e in Laboratorio, vol. 17, no. 1, pp. 77–82, 1987.
[13] G. Csaba, “Presence in and effects of pineal indoleamines at very low level of phylogeny,” Experientia, vol. 49, no. 8, pp. 627–634, 1993.
[14] N. Paulmann, M. Grohmann, J. P. Voigt et al., “Intracellular serotonin modulates insulin secretion from pancreatic β-cells by protein serotonylation,” PLoS Biology, vol. 7, no. 10, Article ID e100229, 2009.
[15] C. P. Mercado, E. Ziu, and F. Kilic, “Communication between 5-HT and small GTPases,” Current Opinion in Pharmacology, vol. 11, no. 1, pp. 23–28, 2011.
[16] N. M. Barnes, “5-HT: the promiscuous and happy hormone! editorial overview,” Current Opinion in Pharmacology, vol. 11, no. 1, pp. 1–2, 2011.
[17] Y. Charnay and L. Léger, “Brain serotonergic circuitries,” Dialogues in Clinical Neuroscience, vol. 12, no. 4, pp. 471–487, 2010.
[18] K. Yao, J. Fang, Y. L. Yin, Z. M. Feng, Z. R. Tang, and G. Wu, “Tryptophan metabolism in animals: important roles in nutrition and health,” Frontiers in Bioscience, vol. 3, pp. 286–297, 2011.
[19] D. J. Hayes and A. J. Greenshaw, “5-HT receptors and reward-related behaviour: a review,” Neuroscience and Biobehavioral Reviews, vol. 35, no. 6, pp. 1419–1449, 2011.
[20] F. M. Feijó, M. C. Bertoluci, and C. Reis, “Serotonin and hypothalamic control of hunger: a review,” Revista da Associação Médica Brasileira, vol. 57, no. 1, pp. 74–77, 2011.
[21] G. P. Ahern, “5-HT and the immune system,” Current Opinion in Pharmacology, vol. 11, no. 1, pp. 29–33, 2011.
[22] A. Dahlström and K. Fuxe, “Localization of monoamines in the lower brain stem,” Experientia, vol. 20, no. 7, pp. 398–399, 1964.
[23] H. W. Steinbusch, “Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals,” Neuroscience, vol. 6, no. 4, pp. 557–618, 1981.
[24] W. Wisden, “Cre-ating ways to serotonin,” *Frontiers in Neuroscience*, vol. 4, p. 167, 2010.

[25] B. M. Twarog and I. H. Page, “Serotonin content of some mammalian tissues and urine and a method for its determination,” *The American Journal of Physiology*, vol. 175, no. 1, pp. 157–161, 1953.

[26] J. G. Hensler, “Serotonergic modulation of the limbic system,” *Neuroscience and Biobehavioral Reviews*, vol. 30, no. 2, pp. 203–214, 2006.

[27] M. E. Molliver, “Serotonergic neuronal systems: what their anatomic organization tells us about function,” *Journal of Clinical Psychopharmacology*, vol. 7, supplement 6, pp. 35–235, 1987.

[28] T. F. Freund, A. I. Gulyás, L. Acády, T. Görcs, and K. Tóth, “Serotonergic control of the hippocampus via local inhibitory interneurons,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 87, no. 21, pp. 8501–8505, 1990.

[29] M. Bijak, “Monoamine modulation of the synaptic inhibition in the hippocampus,” *Acta Neurobiologica Experimentalis*, vol. 56, no. 1, pp. 385–395, 1996.

[30] L. A. Mamounas, C. A. Mullen, E. O’Hearn, and M. E. Molliver, “Dual serotoninergic projections to forebrain in the rat: morphologically distinct 5-HT axon terminals exhibit differential vulnerability to neurotoxic amphetamine derivatives,” *Journal of Comparative Neurology*, vol. 314, no. 3, pp. 558–586, 1991.

[31] R. P. Vertes, “A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat,” *Journal of Comparative Neurology*, vol. 313, no. 4, pp. 643–668, 1991.

[32] G. García-Alcocer, G. Sarabia-Altamirano, A. Martínez-Torres, and R. Miledi, “Developmental expression of 5-HT5A receptor mRNA in the rat brain,” *Neuroscience Letters*, vol. 379, no. 2, pp. 101–105, 2005.

[33] G. García-Alcocer, L. C. B. Segura, M. G. Peña, A. Martínez-Torres, and R. Miledi, “Ontogenetic distribution of 5-HT2C, 5-HT3A, and 5-HT7 receptors in the rat hippocampus,” *Gene Expression*, vol. 13, no. 1, pp. 53–57, 2005.

[34] J. H. Gaddum and Z. P. Picarelli, “Two kinds of tryptamine receptor,” *British Journal of Pharmacology and Chemotherapy*, vol. 12, no. 3, pp. 323–328, 1957.

[35] J. I. Bennett and G. K. Aghajanian, “D LSD binding to brain homogenates: possible relationship to serotonin receptors,” *Life Sciences*, vol. 15, no. 11, pp. 1935–1944, 1974.

[36] G. Fillion, M. P. Fillion, J. Jacob, and J. C. Rousselle, “5 HT and LSD high affinity binding sites to brain synaptosomal membranes,” *British Journal of Pharmacology*, vol. 58, no. 3, pp. 425P–426P, 1976.

[37] S. J. Peroutka and S. H. Snyder, “Multiple serotonin receptors: differential binding of [3H]5-hydroxytryptamine, [3H]lysergic acid diethylamide and [3H]spiroperidol,” *Molecular Pharmacology*, vol. 16, no. 3, pp. 687–699, 1979.

[38] P. B. Bradley, G. Engel, and W. Feniuk, “Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine,” *Neuropharmacology*, vol. 25, no. 6, pp. 563–576, 1986.

[39] D. Hoyer, D. E. Clarke, J. R. Fozard et al., “International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin),” *Pharmacological Reviews*, vol. 46, no. 2, pp. 157–203, 1994.

[40] D. Hoyer, J. P. Hannon, and G. R. Martin, “Molecular, pharmacological and functional diversity of 5-HT receptors,” *Pharmacology Biochemistry and Behavior*, vol. 71, no. 4, pp. 333–354, 2002.

[41] J. Hannon and D. Hoyer, “Molecular biology of 5-HT receptors,” *Behavioural Brain Research*, vol. 195, no. 1, pp. 198–213, 2008.

[42] G. L. Collingridge, R. W. Olsen, J. Peters, and M. Spedding, “A nomenclature for ligand-gated ion channels,” *Neuropharmacology*, vol. 56, no. 1, pp. 2–5, 2009.

[43] M. Filip and M. Bader, “Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system,” *Pharmacological Reports*, vol. 61, no. 5, pp. 761–777, 2009.

[44] J. Bockaert, S. Claeysen, C. Bécamel, A. Dumuis, and P. Marin, “Neuronal 5-HT metabotropic receptors: fine-tuning of their structure, signaling, and roles in synaptic modulation,” *Cell and Tissue Research*, vol. 326, no. 2, pp. 553–572, 2006.

[45] N. M. Barnes, T. G. Hales, S. C. R. Lummis, and J. A. Peters, “The 5-HT3 receptor—the relationship between structure and function,” *Neuropharmacology*, vol. 56, no. 1, pp. 273–284, 2009.

[46] J. A. van Hooft, A. D. Spier, J. L. Yakel, S. C. R. Lummis, and H. P. M. Vijverberg, “Promiscuous assembly of serotonin 5-HT1, and nicotinic a4 receptor subunits into Ca2+–permeable ion channels,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 19, pp. 11456–11461, 1998.

[47] R. Fredriksson, M. C. Lagerström, L. G. Lundin, and H. B. Schöth, “The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints,” *Molecular Pharmacology*, vol. 65, no. 6, pp. 1256–1272, 2003.

[48] T. K. Kumari, B. Pant, and K. R. Pardasani, “A model for the evaluation of domain based classification of GPCR,” *Bioinformation*, vol. 4, no. 4, pp. 138–142, 2009.

[49] J. Bockaert and J. P. Pin, “Molecular tinkering of G protein-coupled receptors: an evolutionary success,” *EMBO Journal*, vol. 18, no. 7, pp. 1723–1729, 1999.

[50] T. D. Werry, K. J. Gregory, P. M. Sexton, and A. Christopoulos, “Characterization of serotonin 5-HT2C receptor signaling to extracellular signal-regulated kinases 1 and 2,” *Journal of Neurochemistry*, vol. 93, no. 6, pp. 1603–1615, 2005.

[51] N. M. Wetzschureck and S. Offermanns, “Mammalian G proteins and their cell type specific functions,” *Physiological Reviews*, vol. 85, no. 4, pp. 1159–1204, 2005.

[52] K. DeFea, “β-arrestins and heterotrimeric G-proteins: collaborators and competitors in signal transduction,” *British Journal of Pharmacology*, vol. 153, supplement 1, pp. S298–S309, 2008.

[53] K. A. DeFea, “β-arrestins as regulators of signal termination and transduction: how do they determine what to scaffold?” *Cellular Signalling*, vol. 23, no. 4, pp. 621–629, 2010.

[54] B. L. Roth, “Irving Page lecture 5-HT(2A) serotonin receptor biology: interacting proteins, kinases and paradoxical regulation,” *Neuropharmacology*, vol. 61, no. 3, pp. 348–354, 2011.

[55] M. A. Davies, C. Y. Chang, and B. L. Roth, “Polymorphic and posttranscriptional modifications of 5-HT receptor structure, functional and pathological implications,” in *The Serotonin Receptors*, B. L. Roth, Ed., pp. 59–90, Humana Press, New Jersey, NJ, USA, 2006.
[56] E. C. Azmitia and W. F. Marovitz, “In vitro hippocampal uptake of tritiated serotonin (3H-5HT): a morphological, biochemical, and pharmacological approach to specificity,” *Journal of Histochemistry and Cytochemistry*, vol. 28, no. 7, pp. 636–644, 1980.

[57] A. Fargin, J. R. Raymond, M. J. Lohse, B. K. Kobilka, M. G. Caron, and R. J. Lefkowitz, “The genomic clone G-21 which resembles a β-adrenergic receptor sequence encodes the 5-HT1A receptor,” *Nature*, vol. 335, no. 6188, pp. 358–360, 1988.

[58] H. Gozlan, S. El Mestikawy, and L. Pichat, “Identification of presynaptic autoreceptors using a new ligand: 3H-PAT,” *Nature*, vol. 305, no. 5930, pp. 140–142, 1983.

[59] D. Hoyer, A. Pazos, A. Probst, and J. M. Palacios, “Serotonin receptors in the human brain. I. Characterization and autoradiographic localization of 5-HT(1A) recognition sites. Apparent absence of 5-HT(1B) recognition sites,” *Brain Research*, vol. 376, no. 1, pp. 85–96, 1986.

[60] D. Vergé, G. Daval, M. Marcinkiewicz et al., “Quantitative autoradiography of multiple 5-HT1 receptor subtypes in the brain of control or 5,7-dihydroxytryptamine-treated rats,” *Journal of Neuroscience*, vol. 6, no. 12, pp. 3474–3478, 1986.

[61] S. El Mestikawy, D. Taussig, H. Gozlan, M. B. Emerit, M. Ponchant, and H. Hamon, “Chromatographic analyses of the serotonin 5-HTA receptor solubilized from the rat hippocampus,” *Journal of Neurochemistry*, vol. 53, no. 5, pp. 1555–1566, 1989.

[62] Y. Chaput, P. Blier, and C. de Montigny, “In vivo electrophysiological evidence for the regulatory role of autoreceptors on serotonergic terminals,” *Journal of Neuroscience*, vol. 6, no. 10, pp. 2796–2801, 1986.

[63] S. Muchimapura, R. Mason, and C. A. Marsden, “Effect of isolation rearing on pre- and post-synaptic serotonergic function in the rat dorsal hippocampus,” *Synapse*, vol. 47, no. 3, pp. 209–217, 2003.

[64] E. C. Azmitia, P. J. Gannon, N. M. Kheck, and P. M. Whitaker-Azmitia, “Cellular localization of the 5-HT(1A) receptor in primate brain neurons and glial cells,” *Neuropsychopharmacology*, vol. 14, no. 1, pp. 35–46, 1996.

[65] M. M. Voigt, D. J. Laurie, P. H. Seeburg, and A. Bach, “Molecular cloning and characterization of a rat brain cDNA encoding a 5-hydroxytryptamine 1B receptor,” *EMBO Journal*, vol. 10, no. 13, pp. 4017–4023, 1991.

[66] D. Hoyer, G. Engel, and H. O. Kalkman, “Characterization of the 5–HT1B recognition site in rat brain: binding studies with [125I]iodocyanopindolol,” *European Journal of Pharmacology*, vol. 118, no. 1-2, pp. 1–12, 1985.

[67] M. Egeland, J. Warner-Schmidt, P. Greengard, and P. Svenningsson, “Co-expression of serotonin 5-HT(1B) and 5-HT(4) receptors in p11 containing cells in cerebral cortex, hippocampus, caudate-putamen and cerebellum,” *Neuropharmacology*, vol. 61, no. 3, pp. 442–450, 2011.

[68] B. Mlinar, C. Falsini, and R. Corradetti, “Pharmacological characterization of 5-HT1B receptor-mediated inhibition of local excitatory synaptic transmission in the CA1 region of rat hippocampus,” *British Journal of Pharmacology*, vol. 138, no. 1, pp. 71–80, 2003.

[69] J. D. Guo and D. G. Rainnie, “Presynaptic 5-HT1B receptor-mediated serotonergic inhibition of glutamate transmission in the bed nucleus of the stria terminalis,” *Neuroscience*, vol. 165, no. 4, pp. 360–360, 2010.

[70] K. B. Fink and M. Göthert, “5-HT receptor regulation of neurotransmitter release,” *Pharmacological Reviews*, vol. 59, no. 4, pp. 360–417, 2007.

[71] M. W. Hamblin and M. A. Metcalf, “Primary structure and functional characterization of a human 5-HT(1D)-type serotonin receptor,” *Molecular Pharmacology*, vol. 40, no. 2, pp. 143–148, 1991.

[72] R. L. Weinshank, J. M. Zgombick, M. J. Macchi, T. A. Brancheck, and P. R. Harting, “Human serotonin 1D receptor is encoded by a subfamily of two distinct genes: 5-HT1D α and 5-HT1D β,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 89, no. 8, pp. 8630–8634, 1992.

[73] A. T. Bruinvels, J. M. Palacios, and D. Hoyer, “Autoradiographic characterisation and localisation of 5-HT1D compared to 5-HT1B binding sites in rat brain,” *Naunyn-Schmiedeberg’s Archives of Pharmacology*, vol. 347, no. 6, pp. 569–582, 1993.

[74] G. McAllister, A. Charlesworth, C. Snodin et al., “Molecular cloning of a serotonin receptor from human brain (5HT1E): a fifth 5HT1-like subtype,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 89, no. 12, pp. 5517–5521, 1992.

[75] S. Leonardt, K. Herrick-Davis, and M. Titeler, “Detection of a novel serotonin receptor subtype (5-HT1E) in human brain: interaction with a GTP-binding protein,” *Journal of Neurochemistry*, vol. 53, no. 2, pp. 465–471, 1989.

[76] N. Amlaiky, S. Ramboz, U. Boschart, J. L. Plasat, and R. Hen, “Isolation of a mouse “5HT1E-like” serotonin receptor expressed predominantly in hippocampus,” *Journal of Biological Chemistry*, vol. 267, no. 28, pp. 19761–19764, 1992.

[77] N. Adham, H. T. Kao, L. E. Schechter et al., “Cloning of another human serotonin receptor (5-HT1F): a fifth 5-HT1 receptor subtype coupled to the inhibition of adenylyl cyclase,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 2, pp. 408–412, 1993.

[78] A. Pazos, R. Cortés, and J. M. Palacios, “Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors,” *Brain Research*, vol. 346, no. 2, pp. 231–249, 1985.

[79] C. Ullmer, H. G. Boddeke, K. Schmuck, and H. Lübbert, “5-HT2B receptor-mediated calcium release from ryanodine-sensitive intracellular stores in human pulmonary artery endothelial cells,” *British Journal of Pharmacology*, vol. 117, no. 6, pp. 1081–1088, 1996.

[80] D. Hoyer, A. Pazos, A. Probst, and J. M. Palacios, “Serotonin receptors in the human brain. II. Characterization and autoradiographic localization of 5-HT1C and 5-HT2 recognition sites,” *Brain Research*, vol. 376, no. 1, pp. 97–107, 1986.

[81] D. B. Pritchett, A. W. Bach, M. Wozny et al., “Structure and functional expression of cloned rat serotonin 5HT-2 receptor,” *EMBO Journal*, vol. 7, no. 13, pp. 4135–4140, 1988.

[82] D. Julius, K. N. Huang, T. J. Livelli, R. Axel, and T. M. Jessell, “The 5HT2 receptor defines a family of structurally distinct but functionally conserved serotonin receptors,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 87, no. 3, pp. 928–932, 1990.

[83] P. W. Burnet, S. L. Eastwood, and P. J. Harrison, “Detection and quantitation of 5-HT1A and 5HT(2A) receptor mRNAs in human hippocampus using a revel-se transcriptase-polymerase chain reaction (RT-PCR) technique and their correlation with binding site densities and age,” *Neuroscience Letters*, vol. 178, no. 1, pp. 85–89, 1994.
[84] Q. H. Li, K. Nakadate, S. Tanaka-Nakadate, D. Nakatsu, Y. Cui, and Y. Watanabe, “Unique expression patterns of 5-HT2A and 5-HT2C receptors in the rat brain during postnatal development: western blot and immunohistochemical analyses,” *Journal of Comparative Neurology*, vol. 469, no. 1, pp. 128–140, 2004.

[85] L. A. Miner, J. R. Backstrom, E. Sanders-Bush, and S. R. Sosack, “Ultrastructural localization of serotonin2A receptors in the middle layers of the rat prelimbic prefrontal cortex,” *Neuroscience*, vol. 116, no. 1, pp. 107–117, 2003.

[86] T. Xu and S. C. Pandey, “Cellular localization of serotonin(2A) (5HT(2A)) receptors in the rat brain,” *Brain Research Bulletin*, vol. 51, no. 6, pp. 499–505, 2000.

[87] J. D. Kursar, D. L. Nelson, D. B. Wainscott, M. L. Cohen, and M. Baez, “Molecular cloning, functional expression, and pharmacological characterization of a novel serotonin receptor (5-hydroxytryptamine2F) from rat stomach fundus,” *Molecular Pharmacology*, vol. 42, no. 4, pp. 549–557, 1992.

[88] D. W. Bonhaus, C. Bach, A. DeSouza et al., “The pharmacology and distribution of human 5-hydroxytryptamine2B (5-HT2B) receptor gene products: comparison with 5-HT(2A) and 5-HT(2C) receptors,” *British Journal of Pharmacology*, vol. 115, no. 4, pp. 622–628, 1995.

[89] N. Sanden, T. Thorlin, F. Blomstrand, P. A. Persson, and E. Hansson, “5-Hydroxytryptamine2B receptors stimulate Ca2+ increases in cultured astrocytes from three different brain regions,” *Neurochemistry International*, vol. 36, no. 4–5, pp. 427–434, 2000.

[90] C. Capone, C. Fabrizi, P. Piovesan et al., “2-Aminotetralin derivative protects from ischemia/reperfusion brain injury with a broad therapeutic window,” *Neuropsychopharmacology*, vol. 32, no. 6, pp. 1302–1311, 2007.

[91] H. Lübbert, B. J. Hoffman, T. P. Snutch et al., “cDNA cloning of a serotonin 5-HT1C receptor by electrophysiological assays of mRNA-injected Xenopus oocytes,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 84, no. 12, pp. 4332–4336, 1987.

[92] D. Julius, A. B. MacDermott, R. Axel, and T. M. Jessell, “Molecular characterization of a functional cDNA encoding the serotonin 1c receptor,” *Science*, vol. 241, no. 4865, pp. 558–564, 1988.

[93] A. Pazos, D. Hoyer, and J. M. Palacios, “The binding of serotonergic ligands to the porcine chordoidplexus: characterization of a new type of serotonin recognition site,” *European Journal of Pharmacology*, vol. 106, no. 3, pp. 539–546, 1984.

[94] A. Pazos and J. M. Palacios, “Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors,” *Brain Research*, vol. 346, no. 2, pp. 205–230, 1985.

[95] B. J. Hoffman and E. Mezey, “Distribution of serotonin 5-HT1C receptor mRNA in adult rat brain,” *FEBS Letters*, vol. 247, no. 2, pp. 453–462, 1989.

[96] S. M. Molineaux, T. M. Jessell, R. Axel, and D. Julius, “5-HT1C receptor is a prominent serotonin receptor subtype in the central nervous system,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 86, no. 17, pp. 6793–6797, 1989.

[97] G. Mengod, H. Nguyen, H. Le, C. Waeber, H. Lübbert, and J. M. Palacios, “The distribution and cellular localization of the serotonin 1C receptor mRNA in the rodent brain examined by in situ hybridization histochemistry. Comparison with receptor binding distribution,” *Neuroscience*, vol. 35, no. 3, pp. 377–391, 1990.
European Journal of Pharmacology, vol. 146, no. 1, pp. 187–188, 1988.

[114] C. Gerald, N. Adham, H. T. Kao et al., “The 5-HT4 receptor: molecular cloning and pharmacological characterization of two splice variants,” EMBO Journal, vol. 14, no. 12, pp. 2806–2815, 1995.

[115] M. T. Vilarró, R. Cortés, C. Gerald, T. A. Branchek, J. M. Pacalios, and G. Mengod, “Localization of 5-HT4 receptor mRNA in rat brain by in situ hybridization histochemistry,” Molecular Brain Research, vol. 43, no. 1-2, pp. 356–360, 1996.

[116] E. G. Mohler, S. Shacham, S. Noiman et al., “VRX-03011, a novel 5-HT4 agonist, enhances memory and hippocampal acetylcholine efflux,” Neuropearmacology, vol. 53, no. 4, pp. 563–573, 2007.

[117] J. L. Plassat, U. Boschert, N. Amlaiky, and R. Hen, “The mouse 5HT5 receptor reveals a remarkable heterogeneity within the 5HT1D receptor family,” EMBO Journal, vol. 11, no. 13, pp. 4779–4786, 1992.

[118] M. G. Erlander, T. W. Lovenberg, B. M. Baron et al., “Two members of a distinct subfamily of 5-hydroxytryptamine receptors differentially expressed in rat brain,” Proceedings of the National Academy of Sciences of the United States of America, vol. 90, no. 8, pp. 3452–3456, 1993.

[119] H. Matthés, U. Boschert, N. Amlaiky et al., “Mouse 5-hydroxytryptamine5A and 5-hydroxytryptamine5B receptors define a new family of serotonin receptors: cloning, functional expression, and chromosomal localization,” Molecular Pharmacology, vol. 43, no. 3, pp. 313–319, 1993.

[120] M. J. Carson, E. A. Thomas, P. E. Danielsen, and J. G. Sutcliffe, “The 5-HT5A serotonin receptor is expressed predominantly by astrocytes in which it inhibits cAMP accumulation: a mechanism for neuronal suppression of reactive astrocytes,” GLIA, vol. 17, no. 4, pp. 317–326, 1996.

[121] M. Pasqualetti, M. Ori, I. Nardi, M. Castagna, G. B. Cassano, and D. Marazziti, “Distribution of the 5-HT5A serotonin receptor mRNA in the human brain,” Molecular Brain Research, vol. 56, no. 1-2, pp. 1–8, 1998.

[122] K. R. Oliver, A. M. Kinsey, A. Wainwright, and D. J. S. Sirinathsinghji, “Localization of 5–h5A receptor-like immunoreactivity in the rat brain,” Brain Research, vol. 867, no. 1-2, pp. 131–142, 2000.

[123] B. J. Francken, M. Jurzak, J. F. Vanhauwe, W. H. Luyten, and J. E. Leysen, “The human 5–h5A receptor couples to G(i)/G(o) proteins and inhibits adenylate cyclase in HEK 293 cells,” European Journal of Pharmacology, vol. 361, no. 2-3, pp. 299–309, 1998.

[124] B. J. B. Francken, K. Josson, P. Lijnen, M. Jurzak, W. H. M. L. Luyten, and J. E. Leysen, “Human 5-hydroxytryptamine(5A) receptors activate coexpressed G(i) and G(o) proteins in Spodoptera frugiperda 9 cells,” Molecular Pharmacology, vol. 57, no. 5, pp. 1034–1044, 2000.

[125] B. J. B. Francken, J. F. Vanhauwe, K. Josson, M. Jurzak, W. H. Luyten, and J. E. Leysen, “Reconstitution of human 5-hydroxytryptamine5A receptor-G protein coupling in E. coli and SF9 cell membranes with membranes from SF9 cells expressing mammalian G proteins,” Receptors and Channels, vol. 7, no. 4, pp. 303–318, 2001.

[126] M. Noda, S. Yasuda, N. Okada et al., “Recombinant human serotonin5A receptors stably expressed in C6 glioma cells couple to multiple signal transduction pathways,” Journal of Neurochemistry, vol. 84, no. 2, pp. 222–232, 2003.

[127] W. Wisden, E. M. Parker, C. D. Mahle et al., “Cloning and characterization of the rat 5–HT3b receptor. Evidence that the 5–HT3b receptor couples to a G protein in mammalian cell membranes,” FEBS Letters, vol. 333, no. 1-2, pp. 25–31, 1993.

[128] A. M. Kinsey, A. Wainwright, R. Heavens, D. J. Sirinathsinghji, and K. R. Oliver, “Distribution of 5-h(5A), 5-h(5B), 5-h(6) and 5-HT(7) receptor mRNAs in the rat brain,” Molecular Brain Research, vol. 88, no. 1-2, pp. 194–198, 2001.

[129] R. Graiile, G. W. Grabtree, and R. Hen, “Human 5-HT3 receptors: the 5–HT3A receptor is functional but the 5–HT3B receptor was lost during mammalian evolution,” European Journal of Pharmacology, vol. 418, no. 3, pp. 157–167, 2001.

[130] T. Maeawa, S. Kim, D. Nakai et al., “Social isolation stress induces ATF-7 phosphorylation and impairs silencing of the 5-HT 5B receptor gene,” The EMBO Journal, vol. 29, no. 1, pp. 196–208, 2010.

[131] M. Ruat, E. Traiffort, J. M. Arrang et al., “A novel rat serotonin (5-HT6) receptor: molecular cloning, localization and stimulation of cAMP accumulation,” Biochemical and Biophysical Research Communications, vol. 193, no. 1, pp. 268–276, 1993.

[132] M. Ruat, E. Traiffort, R. Leurs et al., “Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT7) activating CAMP formation,” Proceedings of the National Academy of Sciences of the United States of America, vol. 90, no. 18, pp. 8547–8551, 1993.

[133] U. Bickmeyer, M. Heine, T. Manzke, and D. W. Richter, “Differential modulation of I(h) by 5-HT receptors in mouse CA1 hippocampal neurons,” European Journal of Neuroscience, vol. 16, no. 2, pp. 209–218, 2002.

[134] L. Costa, C. Trovato, S. A. Musumeci, M. V. Catania, and L. Ciranna, “5-HT(1A) and 5-HT(7) receptors differently modulate AMPA receptor-mediated hippocampal synaptic transmission,” Hippocampus. In press.

[135] S. R. Joca, F. R. Ferreira, and F. S. Guimarães, “Modulation of stress consequences by hippocampal monoaminergic, glutamatergic and nitrergic neurotransmitter systems,” Stress, vol. 10, no. 3, pp. 227–249, 2007.

[136] H. Schoemaker and S. Z. Langer, “[3H]8-OH-DPAT labels the serotonin transporter in the rat striatum,” European Journal of Pharmacology, vol. 124, no. 3, pp. 371–373, 1986.

[137] K. P. Lesch and R. Mössner, “Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders?” Biological Psychiatry, vol. 44, no. 3, pp. 179–192, 1998.

[138] K. Sugden, A. Tichopad, N. Khan, I. W. Craig, and U. M. D’Souza, “Genes within the serotonergic system are differentially expressed in human brain,” BMC Neuroscience, vol. 15, pp. 10–50, 2009.

[139] N. Nordquist and L. Oreland, “Serotonin, genetic variability, behaviour, and psychiatric disorders—a review,” Upsala Journal of Medical Sciences, vol. 115, no. 1, pp. 2–10, 2010.

[140] K. Martinowich and B. Lu, “Interaction between BDNF and serotonin: role in mood disorders,” Neuropsychopharmacology, vol. 33, no. 1, pp. 73–83, 2008.

[141] L. J. Siever, “Neurobiology of aggression and violence,” American Journal of Psychiatry, vol. 165, no. 4, pp. 429–442, 2008.

[142] K. Waters, “Serotonin in the sudden infant death syndrome,” Drug News and Perspectives, vol. 23, no. 9, pp. 537–548, 2010.
[143] J. R. Moiseiwitsch and J. M. Lauder, “Serotonin regulates mouse cranial neural crest migration,” Proceedings of the National Academy of Sciences of the United States of America, vol. 92, no. 16, pp. 7182–7186, 1995.

[144] J. M. Brezun and A. Daszuta, “Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats,” Neuroscience, vol. 89, no. 4, pp. 999–1002, 1999.

[145] J. M. Brezun and A. Daszuta, “Serotonergic reinnervation reverses lesion-induced decreases in PSA-NCAM labeling and proliferation of hippocampal cells in adult rats,” Hippocampus, vol. 10, no. 1, pp. 37–46, 2000.

[146] L. Lanfumey, R. Mongeau, C. Cohen-Salmon, and M. Hamon, “Corticosteroid-serotonin interactions in the neurobiological mechanisms of stress-related disorders,” Neuroscience and Biobehavioral Reviews, vol. 32, no. 6, pp. 1174–1184, 2008.

[147] S. Haj-Dahmane and R. Y. Shen, “Modulation of the serotonin system by endocannabinoid signaling,” Neuropharmacology, vol. 61, no. 3, pp. 414–420, 2011.

[148] M. Banasr, M. Hery, J. M. Brezun, and A. Daszuta, “Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus,” European Journal of Neuroscience, vol. 14, no. 9, pp. 1417–1424, 2001.

[149] H. Wang and D. R. Storm, “Calmodulin-regulated adenyl cyclases: cross-talk and plasticity in the central nervous system,” Molecular Pharmacology, vol. 63, no. 3, pp. 463–468, 2003.

[150] R. L. Djavadian, “Serotonin and neurogenesis in the hippocampal dentate gyrus of adult mammals,” Acta Neurobiologiae Experimentalis, vol. 64, no. 2, pp. 189–200, 2004.

[151] P. R. Albert, B. le Francois, and A. M. Millar, “Transcriptional dysregulation of 5-HT1A autoreceptors in mental illness,” Molecular Brain, vol. 4, no. 1, p. 21, 2011.

[152] U. Staubli and N. Otaky, “Serotonin controls the magnitude of LTP induced by theta bursts via an action on NMDA-receptor-mediated responses,” Brain Research, vol. 643, no. 1-2, pp. 10–16, 1994.

[153] A. M. Gardier, “Mutant mouse models and antidepressant drug research: focus on serotonin and brain-derived neurotrophic factor,” Behavioural Pharmacology, vol. 20, no. 1, pp. 18–32, 2009.

[154] R. Saxena and A. Chattopadhyay, “Membrane organization and dynamics of the serotonin1A receptor in live cells,” Journal of Neurochemistry, vol. 116, no. 5, pp. 726–733, 2011.

[155] A. Schmitt, J. Benninghoff, R. Moessner et al., “Adult neurogenesis in serotonin transporter deficient mice,” Journal of Neural Transmission, vol. 114, no. 9, pp. 1107–1119, 2007.

[156] R. S. Duman, G. R. Heninger, and E. J. Nestler, “A molecular and cellular theory of depression,” Archives of General Psychiatry, vol. 54, no. 7, pp. 597–606, 1997.

[157] I. Hindmarch, “Beyond the monoamine hypothesis: mechanisms, molecules and methods,” European Psychiatry, vol. 17, supplement 3, pp. 294–299, 2002.

[158] T. Sharp and P. J. Cowen, “5-HT and depression: is the glass half-full?” Current Opinion in Pharmacology, vol. 11, no. 1, pp. 45–51, 2011.

[159] R. S. Duman, “A silver bullet for the treatment of depression?” Neuron, vol. 55, no. 3, pp. 679–681, 2007.

[160] R. Corradetti, N. Laaris, N. Hanoun et al., “Antagonist properties of (-)-pindolol and WAY 100635 at somatodendritic and postsynaptic 5-HT1A receptors in the rat brain,” British Journal of Pharmacology, vol. 123, no. 3, pp. 449–462, 1998.

[161] E. le Poul, C. Boni, N. Hanoun et al., “Differential adaptation of brain 5-HT1A and 5-HT1B receptors and 5-HT transporter in rats treated chronically with fluoxetine,” Neuropsychopharmacology, vol. 39, no. 1, pp. 110–122, 2000.

[162] M. B. Passani, A. M. Pugliese, M. Azzurrini, and R. Corradetti, “Effects of DAU 6215, a novel 5-hydroxytryptamine3 (5-HT3) antagonist on electrophysiological properties of the rat hippocampus,” British Journal of Pharmacology, vol. 112, no. 2, pp. 695–703, 1994.

[163] L. Hertz, “Neuronal-astrocytic interactions in brain development, brain function and brain disease,” Advances in Experimental Medicine and Biology, vol. 296, pp. 143–159, 1991.

[164] S. Mouillet-Richard, V. Mutel, S. Loric, C. Tournois, J. M. Launay, and O. Kellermann, “Regulation by neurotransmitter receptors of serotonergic or catecholaminergic neuronal cell differentiation,” Journal of Biological Chemistry, vol. 275, no. 13, pp. 9186–9192, 2000.

[165] P. M. Whitaker-Azmitia, “The role of serotonin and serotonin receptors in development of the mammalian nervous system,” in Receptors in the Developing Nervous System, I. S. N. Zagon and P. J. McLaughlin, Eds., vol. 2, pp. 43–50, Chapman and Hall, London, UK, 1993.
