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Abstract

Serotonin (5-hydroxytryptamine, 5-HT) is one of the extracellular messengers capable of activating the largest number of receptors (17 receptors belonging to 7 classes – $5\text{-HT}_{1\text{-}7}$ – defined first on a pharmacological basis and then on their gene sequence). Alternative splicing and RNA editing add to this diversity. Most of 5-HT receptors belong to the G protein-coupled receptor (GPCR) family except for 5-HT_3 receptors that are ionic channels. Their activation gives rise to a huge complexity of intracellular signaling events that depend or not on G protein activation and underlie the diversity of physiological functions of 5-HT. Assembly of 5-HT receptors into heteromers with distinct 5-HT receptors or other GPCRs, as well as their physical association with protein partners further increase the versatility of serotonergic signaling and the complexity of its regulation. These interactions also offer novel opportunities for therapeutic interventions in disorders related to dysfunctions of serotonergic systems.

Keywords

Serotonin, receptor, G protein, signaling, structure, heteromer, interactome, pharmacology

Introduction

Among the most ancient signaling molecules, it is not surprising to find amino acids (such as glutamate and GABA) and their derivatives such as serotonin (5-hydrotryptamine, 5-HT). 5-HT is present in plants and seeds. Since its discovery in Cowhage (*Mucuna pruriens*) in the 1950s, 5-HT has been found in more than 90 plant species, including banana, pineapple and walnuts (Erland et al., 2016). Banana skin contains 10 times more 5-HT than mammalian hippocampus. In addition to its anti-oxidant properties, 5-HT plays many physiological roles in plants such as growth, control of seasonal cycles, delay of senescence and responses to stress. However, no 5-HT receptors have been found in plants. It is only with the apparition of synapses 600 millions years ago that 5-HT receptors appeared in coelenterates (*Cnidaria*) (Hajj-Ali & Anctil, 1997). Their expansion was very rapid. Seven 5-HT receptor subtypes are present in *Caenorhabditis elegans*, four in mollusks (Aplysia), and four or five in *Drosophila melanogaster,* honeybees (*Apis mellifera*) and crickets (*Gryllus bimaculatus*) (Blenau & Thamm, 2011).

In invertebrates, particularly in insects, the classification and denomination of 5-HT receptors is based on the comparison of their primary sequences with those of vertebrate 5-HT receptors. Thus, drosophila and honeybee express homologues of vertebrate 5-HT_1 (5-HT_{1A} and 5-HT_{1B}), 5-HT_2 (5-HT_{2A} and 5-HT_{2B}) and 5-HT_7 receptors. With regard to evolution, it is worthy to note that invertebrate 5-HT_1 and 5-HT_7 receptors inhibit and stimulate cAMP production, respectively, reminiscent of vertebrate receptors. Due to the low interest of pharmaceutical companies for invertebrate 5-HT receptors, there are only a few drugs available for their characterization. Genetics and behavioral studies in invertebrates showed that 5-HT receptors are involved in important physiological functions, including sleep, associative learning, circadian rhythms, aggressive and social behaviors (Blenau & Thamm, 2011). The most spectacular effect of 5-HT upon social behavior is its ability to induce in a few hours a switch from solitary to gregarious behavior in desert locust (*Schistocerca gregaria*) (Anstey et al., 2009; Rogers & Ott, 2015).

In vertebrates, the classification of 5-HT receptors started in 1953 with the description by Gaddum of the antagonist effect of lysergic acid diethylamide (LSD) on 5-HT-elicited responses in several *in vitro* pharmacological tests (Gaddum, 1953). The psychotropic and hallucinogenic effects of LSD were known since April 1943, when Albert Hofmann was disturbed by unusual sensations and hallucinations after he accidentally ingested the drug.

In 1957, Gaddum and Picarelli proposed the first classification of 5-HT receptors. 5-HT-induced contractions of guinea-pig ileum were blocked in part by dibenziline (D), an irreversible blocker of SH groups, and in part by morphine (M). They proposed that two receptors were involved, the D and M receptors localized on smooth muscle and nerve ganglia, respectively (Gaddum & Picarelli, 1957) (Figure 1). We know, today, that D receptors correspond to muscle 5-HT_2 receptor, a G protein-coupled receptor (GPCR) (Bradley et al., 1986) whereas the M receptor corresponds to presynaptic cation-gated channels (5-HT_3 receptors) (Derkach et al., 1989).

In the 1970s and early 1980s, two novel methods based on new tools allowed a rapid advance in the discovery and classification of neurotransmitter receptors in general and of 5-HT receptors in particular. The first one was the binding of radiolabelled ligands on tissues. With regard to 5-HT receptors, the first ligands used were [^{3}H]-5-HT, [^{3}H]-LSD and [^{3}H]-spiperone (a D_2 and 5-HT_{2A} antagonist) and were followed by many others (Bennett & Aghajanian, 1974; Fillion et al., 1976; Hoyer et al., 1994; Peroutka et al., 1979, 1981; Peroutka & Snyder, 1979). The second method was the measurement of second messenger (cyclic AMP, inositol triphosphate (IP3), Ca^{2+}) production in cells or isolated membranes to monitor and pharmacologically characterize 5-HT-induced responses (Bockaert et al., 2006; Bockaert et al., 2008; Bouhelal et al., 1988; Dumuis et al., 1988). This last approach had the advantage of revealing immediately the agonist or antagonist nature of the compounds tested. This pharmacological period clearly characterized 4 classes of receptors (5-HT_1 to 5-HT_4) and most of their subtypes (Hoyer et al., 1994) (Figure 1). In 1988, the first 5-HT receptor (5-HT_{1A}) was cloned (Fargin et al., 1988), launching the cloning period. In addition to the cloning of 5-HT receptors belonging to pharmacologically defined classes, three receptors (the 5-HT_5, 5-HT_6

and 5-HT_7 receptors) were cloned. In total, at least 14 receptor subtypes have been cloned. All are GPCRs except for 5-HT_3 receptors that are ionic channels (Derkach et al., 1989; Hoyer et al., 1994; McCorvy & Roth, 2015) (Figure 1).

I- The four 5-HT receptor classes discovered before the cloning era

At the beginning of the 70s, there has been a great development of what was called "binding experiments" for searching and characterizing hormone and then neurotransmitter receptors. Laboratories used radioactive ligands, labeled with tritium [^{3}H] or iodine (generally [^{125}I]) to detect and pharmacologically characterize receptors. The three pioneer laboratories in binding experiments in the 5-HT receptor field are those of Fillion who used [^{3}H]-5-HT (Fillion et al., 1976), Aghajanian who used [^{3}H]-LSD (Bennett & Aghajanian, 1974) and Snyder who used both ligands together with [^{3}H]-spiperone (Peroutka et al., 1981). Peroutka and Snyder demonstrated that [^{3}H]-5-HT binds with a high affinity (nM) to a class of 5-HT receptors designated as 5-HT_1, whereas [^{3}H]-spiperone, and later on [^{3}H]-ketanserin, bind to another receptor, the 5-HT_2 receptor that has high affinity for spiperone but a low affinity (μM) for 5-HT (Peroutka et al., 1981; Peroutka & Snyder, 1979). [^{3}H]-LSD binds to both receptors.

5-HT_1 class

5-HT_1 receptors were rapidly subdivided into 5-HT_{1A} and 5-HT_{1B} receptors (Figure 1). The 5-HT_{1A} receptor was first described as the [^{3}H]-5-HT binding displaced by spiperone (Pedigo et al., 1981). Thereafter, 8-OH-DPAT, a selective and high-affinity 5-HT_{1A} receptor ligand, was discovered (Middlemiss & Fozard, 1983) and radiolabelled by Gozlan *et al.* (Gozlan et al., 1983). Further studies showed that 5-HT_{1A} receptor stimulation inhibits cAMP production in both hippocampal membranes (De Vivo & Maayani, 1986) and primary neurons (Bockaert et al., 1987; Weiss et al., 1986).

In contrast, 5-HT_{1B} receptor corresponded to [^{3}H]-5-HT binding not displaced by spiperone or 8-OH-DPAT and labeled with [^{125}I]-cyanopindolol, a β-adrenergic blocker (Hoyer et al., 1985). We found that this presynaptic receptor is negatively coupled to adenylyl cyclase in substantia nigra (Bouhelal et al., 1988). Initially, all binding experiments on 5-HT_{1B} receptor

were done in rodents. However, the surprise came when it was found that [^{125}I]-cyanopindolol does not bind to 5-HT$_{1B}$ receptor in guinea-pig, pig, and human brain. Thereafter, a receptor having very similar pharmacological properties (except for its low affinity for β-adrenergic antagonists) and the same ability to inhibit 5-HT release and cAMP production in those species was described. This receptor thought to be present only in some species such as pig and human (Hoyer & Middlemiss, 1989; Schoeffter & Hoyer, 1989) was called 5-HT$_{1D}$. The cloning of two genes (initially called *HT1RDα* and *HT1RDβ*) in human that share very similar sequences and encode receptors with common 5-HT$_{1B/D}$ pharmacology led to the proposal that the 5-HT$_{1B}$ receptor is coded by the *HT1RDβ* gene whereas the 5-HT$_{1D}$ receptor is coded by the *HT1RDα* gene in all species. It was later found that the absence of binding of [^{125}I]-cyanopindolol to the human 5-HT$_{1B}$ receptor is due to a single residue difference in the transmembrane 7 (TM7) (an asparagine in human and a threonine in rodents). The current gene nomenclature is *HTR1B* and *HTR1D* for the 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. The 5-HT$_{1B}$ receptor is largely predominant in terms of expression and function. The anti-migraine drug Sumatriptan, which was developed as a selective "5-HT$_1$-like" receptor agonist, is in fact a 5-HT$_{1B/1D}$ receptor agonist (Humphrey, 2008). However, triptans may also interact with 5-HT$_{1F}$ sites (Waeber & Moskowitz, 1995) (see below). Whether the effects of sumatriptan are mediated by vascular *vs.* neuronal receptors is still a matter of debate.

The 5-HT$_{1C}$ receptor had a brief existence in the 5-HT$_1$ class. Found in choroid plexus and later on in many brain areas using [^{3}H]-5-HT binding, it was rapidly shown to be coupled to phospholipase C (PLC), as shown for 5-HT$_{2A}$ receptors (Berg et al., 1998). After its cloning, it became evident that it has high sequence homology with 5-HT$_2$ receptors and a similar pharmacology. The 5-HT$_{1C}$ receptor was thus definitely classified in the 5-HT$_2$ family and renamed 5-HT$_{2C}$ receptor.

5-ht$_{1E}$ binding sites were first discovered using [^{3}H]-5-HT binding in human frontal cortical tissue and then in bovine but not in rat brain (Leonhardt et al., 1989). Their high affinity for [^{3}H]-5-HT and low affinity for drugs displaying affinity for 5-HT$_2$ receptors (i.e. mesulergine) led to its classification as a 5-HT$_1$ receptor. Its weak affinity for the prototypical 5-HT$_1$ receptor

agonist, 5-carboxamidotryptamine (5-CT), categorized it as a new member of the 5-HT_1 class (Leonhardt et al., 1989). A receptor with similar pharmacological properties to the 5-HT_{1E} binding sites (Levy et al., 1992) and thus named 5-HT_{1E} receptor was then cloned. However, the subsequently cloned 5-HT_{1F} shares a high degree of homology and pharmacology similarities with the 5-ht_{1E} binding sites, compared to other 5-HT receptors (Adham et al., 1993) and it is likely that the initially identified 5-ht_{1E} binding sites correspond to both 5-HT_{1E} and 5-HT_{1F} receptors. No drugs that can discriminate between these two receptor subtypes are currently available.

5-HT_2 class

The 5-HT_{2A} receptors correspond to the 5-HT_2 receptors initially identified as [^{3}H]-spiperone and [^{3}H]-ketanserin binding sites with low (micromolar) affinity for 5-HT and the "D receptor" identified by Gaddum and Picarelli (Peroutka & Snyder, 1979). They are not only expressed in the brain but also at the periphery, especially in platelets where they mediate aggregation and in smooth muscles where they trigger contraction.

The 5-HT_{2B} receptor was first characterized in rat stomach fundus where it stimulates muscle contraction and was transiently named "5-HT_{1F}". Its pharmacology has some similarities to that of 5-HT_{2C} receptors. After its cloning in 1992 in rodents (Foguet et al., 1992) and human (Hoyer et al., 1994; McCorvy & Roth, 2015), it became clear that this receptor belongs to the 5-HT_2 class but is distinct from 5-HT_{2C} receptors. It was thus named 5-HT_{2B} receptor (Figure 1). It has a wide distribution pattern both at the periphery and the brain (McCorvy & Roth, 2015). Activation of 5-HT_{2B} receptor is responsible for abnormal echocardiograms, pulmonary hypertension, cardiac valve deficiencies triggered by the fenfluramine metabolite norfenfluramine, a drug inducing a weight loss initially marketed by Wyeth (Roth, 2007).

The discovery and pharmacological characteristics of the 5-HT_{2C} receptor that was first thought to belong to the 5-HT_1 class, are described above.

5-HT$_3$ class

Initially named "M receptors" by Gaddum and Picarelli (Gaddum & Picarelli, 1957), 5-HT$_3$ receptors have been extensively studied for three decades in the periphery before the discovery that they are cation channels (Derkach et al., 1989) and that a radiolabelled compound ([^{3}H]-ICS 205-930 (tropisetron, 31-tropanyll-lH-indole-3-carboxylic acid ester) (Waeber et al., 1989) could be used for studying their distribution. 5-HT$_3$ receptors show a wide distribution in the brain, are responsible for the depolarizing effects of 5-HT and mediate peripheral neuronal transmitter release, emesis and nociception (Hoyer et al., 1994; Waeber et al., 1989). Five genes encoding 5-HT$_3$ receptor subunits (5-HT$_{3A-E}$) have been cloned in human and some other vertebrates (but not in rodents), while 5-HT$_3$ receptors seem to be absent in invertebrates (Niesler et al., 2008) (Figure 1). These subunits have a high level of homology with other members of the Cys-Cys loop ligand-gated channel superfamily (e.g. nicotinic, GABA$_A$ and glycine receptors). However, the most studied ones are 5-HT$_{3A}$ and 5-HT$_{3B}$ receptors. Native 5-HT$_3$ receptors have a pentameric structure, as revealed by electron microscopy (Boess et al., 1995). In order to form an active receptor, at least one 5-HT$_{3A}$ subunit has to be present. Functional receptors can be formed by co-assembling 5-HT$_{3A}$ subunits only, whereas receptors exclusively composed of 5-HT$_{3B}$ subunits are not functional (Barnes & Sharp, 1999). Native 5-HT$_3$ receptors are likely a co-assembling of 5-HT$_{3A}$ and 5-HT$_{3B}$ subunits and, possibly, some 5-HT$_{3C-E}$ subunits. The stoichiometry of the different subunits constituting native pentameric receptors has not yet been clearly determined (Niesler et al., 2008).

5-HT$_4$ receptor

In contrast to other G protein-coupled 5-HT receptors, the 5-HT$_4$ receptor has been discovered through its capacity to stimulate production of cAMP. Our laboratory identified an atypical 5-HT receptor positively coupled to the adenylyl cyclase both in colliculi neurons (Dumuis et al., 1988) and guinea-pig hippocampus (Bockaert et al., 1990). It was insensitive to 5-HT$_1$ and 5-HT$_2$ receptor antagonists and was inhibited (with a very low affinity) by some, but not all, 5-HT$_3$ receptor antagonists. Since it was obviously not a 5-HT$_{1-3}$ receptor, it was named "5-HT$_4$ receptor" (Figure 1). 2-methoxy-4-amino-5-chloro benzamides such as metoclopramide or

cisapride are potent agonists of the 5-HT_4 receptor (Dumuis et al., 1989). This pharmacology was sufficient to propose that the 5-HT_4 receptor described in neurons was similar to a gastro-prokinetic 5-HT receptor insensitive to 5-HT_{1-3} antagonists and stimulated by benzamides in guinea-pig ileum and more largely in gastro-intestinal tract (Bockaert et al., 1992). 5-HT_4 receptor agonists have been commercialized for gastro-intestinal problems such as idiopathic constipation and gastro-oesophagial reflux (Bockaert et al., 2008). A recent study showed that gut bacteria are able to produce tryptamine and to increase gastrointestinal transit by activating peripheral 5-HT_4 receptors (Bhattarai et al., 2018). De Vadder *et al.* demonstrated that maturation of peripheral nervous system is likewise under the control of gut microbiota through 5-HT release and 5-HT_4 receptor activation (De Vadder et al., 2018). In brain, several pathologies, such as Alzheimer's disease (AD), feeding disorders and depression, might benefit from 5-HT_4 receptor-directed therapies (Bockaert et al., 2011; Claeysen et al., 2012). Chronic administration of 5-HT_4 receptor agonists decreases the amyloid pathology and prevents the appearance of cognitive deficits in a mouse model of AD (Baranger et al., 2017; Giannoni et al., 2013). In line with these results, an innovative multitarget-directed ligand, named donecopride, has been developed against AD. This molecule simultaneously activates 5-HT_4 receptors and inhibits acetylcholinesterase (Lecoutey et al., 2014; Rochais et al., 2015).

II- The three 5-HT receptor classes discovered by homology cloning

The cloning of rhodopsin and some adrenergic and muscarinic receptors revealed the existence of a GPCR family that shares high sequence similarity throughout their seven transmembrane domains. Using cross-hybridization at reduced stringency with the full length β_2-adrenergic receptor, Fargin *et al.* (Fargin et al., 1988) cloned the first 5-HT receptor (the 5-HT_{1A} receptor). Thereafter, the cloning of 5-HT_{1-4} receptors described in the previous chapter by using similar technologies was quite rapid. However, some clones did not correspond to previously described receptors and thus allowed the discovery of three novel 5-HT receptors, the 5-HT_5, 5-HT_6 and 5-HT_7 receptors.

5-HT_5 receptors

In 1992, Plassat *et al.* cloned a new 5-HT receptor with a sequence quite different from those

of the previously identified 5-HT receptors and that display a high affinity for LSD (Plassat et al., 1992). Therefore, they named it 5-HT_5 (now 5-HT_{5A}). The same laboratory cloned one year later a second 5-HT_5 receptor that was called 5-ht_{5B} (Matthes et al., 1993). The development of 5-HT_{5A} receptor pharmacological tools has been difficult but led to the quite selective antagonists SB699551 (Corbett et al., 2005) and ASP5736 (Yamazaki et al., 2014) that are now widely used in functional studies. The distribution of 5-HT_{5A} receptors suggests a possible role in emotion regulation, cognition, anti-nociception, and control of circadian rhythm (Plassat et al., 1992). RNA-seq analysis confirmed that the expression of this receptor is restricted to the brain and the testis (Fagerberg et al., 2014). In contrast to the 5-HT_{5A} receptor, the 5-ht_{5B} was not conserved during evolution and leads to a pseudogene in human (Grailhe et al., 2001).

5-HT_6 receptor

It is also in the 1990s that the 5-HT_6 receptor was originally cloned in rat (Monsma et al., 1993; Ruat, Traiffort, Arrang, et al., 1993) and a few years later in human (Kohen et al., 1996) and mouse (Kohen et al., 2001). It is almost exclusively detected in brain. Selective agonists including WAY181187, WAY208466 (Schechter et al., 2008) and ST1936 (Borsini et al., 2015) as well as antagonists such as SB258585, SB271046 and SB399885 (Hirst et al., 2006) have been synthetized. [^{125}I]-SB258585 is the most selective radioligand available (Hirst et al., 2006). Studies of brain distribution of 5-HT_6 receptors, assessed by mRNA localization, [^{125}I]-SB258585 binding and immunohistochemistry, indicate their presence in hypothalamus, hippocampus, mesencephalon, cerebral cortex, olfactory bulb, with the higher density in dorsal striatum in rat and human but not in mice (Gerard et al., 1997; Hirst et al., 2003; Marazziti et al., 2013). The neuronal expression profile indicates localization in both glutamatergic and GABAergic neurons in the cortex (in particular GABAergic neurons that express 5-HT_3 receptors) and the hippocampus. In the striatum, 5-HT_6 receptors are found in medium sized spiny neurons expressing D_1 or D_2 dopaminergic receptors and some cholinergic neurons (Helboe et al., 2015). Further studies revealed that 5-HT_6 receptors are mainly located in primary cilium and also in dendrites (Brailov et al., 2000; Brodsky et al., 2017). A specific sequence in the third intracellular loop of the mouse 5-HT_6 receptor and other GPCRs known

to be targeted in primary cilium has been demonstrated to be responsible for this intriguing localization (Berbari et al., 2008).

Preclinical studies revealed that 5-HT_6 receptor blockade induces pro-cognitive effects in a wide range of cognition paradigms in rodents, raising some hope that 5-HT_6 receptors could be an interesting target for treating cognitive deficits of neuropsychiatric disorders such as AD and other dementia (de Jong & Mork, 2017) as well as schizophrenia (Meffre et al., 2012). However, a first clinical trial of Idalopirdine, a 5-HT_6 receptor antagonist developed by Lundbeck/Otsuka, given in association with the acetylcholinesterase inhibitor Donepezil, failed in Phase III for AD (Mullard, 2016). Two others trials are on-going. Similarly, a Phase IIb trial performed with another antagonist developed by Axovant, Intepirdine (SB742458), in patients with dementia with Lewy bodies, was also negative. The 5-HT_6 receptor has also been proposed as target for the treatment of depression (Svenningsson et al., 2007) and obesity (Heal et al., 2008).

5-HT_7 receptor

The 5-HT_7 was the last 5-HT receptor to be cloned from 1993 by several groups in mouse (Plassat et al., 1993), rat (Lovenberg et al., 1993; Meyerhof et al., 1993; Ruat, Traiffort, Leurs, et al., 1993) human (Bard et al., 1993), guinea-pig (Tsou et al., 1994) and pig (Bhalla et al., 2002). "5-HT_7 like" receptors have also been cloned in *Xenopus laevis* (Nelson et al., 1995), *C. elegans* (Hobson et al., 2003) and honeybee (Schlenstedt et al., 2006). The pharmacology of 5-HT_7 receptors is characterized by a high affinity for agonists generally known to act on 5-HT_1 receptors, such as 5-carboxytryptamine and 8-OH-DPAT, and antagonists known to act on 5-HT_2 receptors, such as cyproheptadine and clozapine. Crystal structure of the 5-HT_7 receptor should reveal the residues responsible for this singularity. Notably, LSD, which is an agonist (often partial) of most 5-HT receptor subtypes, is an antagonist of the 5-HT_7 receptor (Wacker et al., 2013). The most potent and selective 5-HT_7 receptor agonists are the aminotetraline derivatives AS19 and E-55888 (Brenchat et al., 2009). SB269970 is the prototypic 5-HT_7 receptor antagonist that has been used as a radiolabelled form ([^{3}H]-SB269970) in binding experiments (Hagan et al., 2000; D. R. Thomas et al., 2000). In human, high 5-HT_7 receptor density was found in thalamus, hypothalamus, hippocampus, caudate nucleus, putamen and

substantia nigra (Varnas et al., 2004). Immunohistochemistry confirmed this localization and showed additional expression in suprachiasmatic nuclei (Neumaier et al., 2001), spinal cord dorsal horn (Doly et al., 2005) and myenteric neurons (Tonini et al., 2005). Experiments using selective antagonists and sometimes 5-HT_7 receptor knockout mice have implicated this receptor in numerous CNS functions, including neuronal morphogenesis, circadian rhythm, rapid eye movement (REM) sleep, thermoregulation, and memory (Matthys et al., 2011). 5-HT_7 receptor antagonists have been suggested to be of interest for the treatment of cognitive deficits of schizophrenia. They attenuate reversal learning deficits as well as deficit in novel object recognition induced by phencyclidine (PCP) treatment in the rat (Horiguchi et al., 2011; McLean et al., 2009). Blockade of 5-HT_7 receptors may also have therapeutic implications for treating negative symptoms in schizophrenia since SB269970 administration ameliorates both ketamine and PCP-induced social withdrawal in rats (Nikiforuk et al., 2013). On the other hand, activation of 5-HT_7 receptors corrects molecular, electrophysiological, and behavior abnormalities in mice models of Fragile X syndrome (FXS) (Costa et al., 2015). Finally, in rat models of neuropathic pain, SB269970 reduces hyperalgesia and tactile allodynia (Amaya-Castellanos et al., 2011).

III- Some light on the pharmacology and signaling of 5-HT receptors given by their 3D structure

Several 5-HT receptor structures have been solved by X-ray crystallography or cryo-EM (Garcia-Nafria et al., 2018; Hassaine et al., 2014; Peng et al., 2018; Wacker et al., 2013; Wacker et al., 2017; C. Wang et al., 2013). 5-HT_{1B} receptors have been crystallized in presence of ergotamine and dihydroergotamine (C. Wang et al., 2013), the 5-HT_{2B} receptor in presence of ergotamine (Wacker et al., 2013) and LSD (Wacker et al., 2017) and the 5-HT_{2C} receptor in presence of ergotamine and ritanserin, an inverse agonist (Peng et al., 2018). The ergotamine binding site in 5-HT_{1B} receptors is defined by helices III, V, VI, and the extracellular loop (ecl)2. It includes two pockets, an orthosteric pocket equivalent to that of other aminergic GPCRs and an extended pocket localized less deeply within the receptor that binds the cyclic tripeptide moiety of ergotamine (Figure 2A) (Wacker et al., 2013). The ergoline ring of

ergotamine, as 5-HT, binds to the receptor through a salt bridge formed between its positively charged nitrogen and the conserved D129$^{3.32}$. A hydrophobic cleft, composed of C133$^{3.36}$, I130$^{3.33}$, W327$^{6.48}$, F330$^{6.51}$ and F331$^{6.52}$ side chains, packs the planar ergoline ring. The orthosteric pocket of the 5HT$_{2B}$ receptor is very similar to that of the 5-HT$_{1B}$ receptor. The extended pocket of the 5-HT$_{1B}$ receptor located above the orthosteric pocket is broader than that of the 5-HT$_{2B}$ receptor, because the equivalent of M218$^{5.39}$ in the 5-HT$_{2B}$ receptor is a smaller threonine residue (T209$^{5.39}$) (C. Wang et al., 2013). The phenyl ring of the cyclic tripeptide moiety of ergotamine contacts with L347$^{6.58}$ and V348$^{6.59}$ in the 5-HT$_{2B}$ receptor, whereas it rotates to occupy a cavity close to T209$^{5.39}$ at helix V in the 5-HT$_{1B}$ receptor (Figure 2B). The extended pocket in the 5-HT$_{1B}$ receptor described above receives the large substitution at the 5' position of the indole of triptans, the most frequently prescribed anti-migraine medications, whereas the narrow pocket of the 5-HT$_{2B}$ receptor is not favorable for the binding of these drugs (C. Wang et al., 2013). Simulation of norfenfluramine binding to 5-HT$_{1B}$ and 5-HT$_{2B}$ receptors indicates that in the 5-HT$_{2B}$ receptor, F217$^{5.38}$ and M218$^{5.39}$ form a hydrophobic pocket otherwise absent in the 5-HT$_{1B}$ receptor, which receives the trifluoromethyl group of norfenfluramine (C. Wang et al., 2013). One of the interesting characteristics of ergotamine and LSD is their potent arrestin-biased signaling *vs.* G_q signaling at 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors. The high residency of LSD in 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors (more than 200 min) and the slow but important recruitment of arrestin that is important for LSD hallucinogenic effects is due to LSD interaction with the ecl2 loop (L209 in the 5-HT$_{2B}$ receptor) forming a lid above the binding site (Wacker et al., 2017). Cryo-EM structure of agonist-bound 5-HT$_{1B}$ receptor coupled to G_o indicates that the intracellular domain of the receptor is in a similar conformation to that observed for other amine receptors in complex with G_s, but with a smaller receptor:G protein interface, suggesting difference in coupling and signaling kinetics (Garcia-Nafria et al., 2018).

Crystallization of the 5-HT$_{2C}$ receptor bound to ergotamine (Peng et al., 2018) confirmed the binding orthosteric pocket of 5-HT$_{1B}$ and 5-HT$_{2B}$ receptors and provided a complete resolution of extracellular loops that were disordered in the other serotonin receptor crystal structures

(Peng et al., 2018) (Figure 2C). The 5-HT_{2C}-ritanserin crystals revealed the inactive form of serotonin receptors, a conformation close to the inactive state structure of β_2-adrenergic receptor (Rasmussen et al., 2011). Interestingly and compared with the orthosteric pocket in other aminergic receptors, the inverse agonist ritanserin bound to one helical turn deeper in the transmembrane domains (Peng et al., 2018) (Figure 2D). This deep pocket includes interactions with residues $F328^{6.52}$ and $W324^{6.48}$, two key elements of GPCR activation by "toggle switch" of helix VI. The deep binding of ritanserin seems to prevent this activation switch, highlighting inverse agonist action mode on this receptor.

IV- Gene structure of 5-HT receptors and editing

The gene structure of human 5-HT receptors differs between receptor classes (Figure 3), in line with their phylogeny (Barnes & Sharp, 1999). Only 5-HT_1 receptors are encoded by monointronic genes. The coding sequences of 5-HT_2 receptors are split into three to four exons. Splicing site positions are conserved between 5-HT_{2A-C} receptors. 5-HT_3 receptors genes are highly fragmented and two to five splice variants have been actually described for each gene, with the exception of 5-HT_{3C} receptor gene. Most of these splice variants differ in the N-terminal region of the protein. The 5-HT_{2A} receptor gene presents an in frame internal splicing site, leading to different coding sequences within the transmembrane domains III and IV. The fragmented gene of the 5-HT_4 receptor gene encodes at least ten splice variants (Bender et al., 2000). Nine of them differ in the length and composition of the C-terminal domain after a common splicing site. An internal in-frame splice variant, in combination with the 5-$HT_{4(b)}$ isoform has also been described. This alternative modification of ecl2 might combine with all the C-terminal variations, leading to a plethora of possibilities. The 5-HT_{5A} and 5-HT_6 receptors are encoded by two and three exons, respectively, whereas the 5-ht_{5B} receptor has been lost during evolution and corresponds to a pseudogene in human (Grailhe et al., 2001). Similarly to the 5-HT_4 receptor, three C-terminal splice variants are generated from a common splicing site in the 5-HT_7 receptor gene.

In addition to the 5-HT receptors and splice variants encoded by the 17 human genes, RNA editing of the 5-HT_{2C} receptor generates additional diversity. Five positions in its second coding

exon can undergo adenosine to inosine (A to I) substitution: four major sites termed A to D and one less-frequent site, termed E. The second intracellular loop of the receptor is then theoretically capable of presenting 24 different variations from the non-edited form (INI) to the fully edited form (VGV) (Fitzgerald et al., 1999). Editing of the 5-HT_{2C} receptor is tissue-specific and regulated by 5-HT. Low levels of 5-HT favor the expression of forms presenting a high affinity for 5-HT (Gurevich, Englander, et al., 2002). In suicide patients, altered editing of the 5-HT_{2C} receptor results in the expression of edited receptor forms exhibiting decreased basal activity and decreased agonist affinity and potency (Gurevich, Tamir, et al., 2002). In addition to its role in major depression, altered editing of the 5-HT_{2C} receptor has been reported in Prader-Willy syndrome patients (Glatt-Deeley et al., 2010) and autistic individuals (Eran et al., 2013).

V- Canonical signaling events engaged by 5-HT receptors

5-HT_{1A} receptor

A wealth of information on 5-HT_{1A} receptor signaling has been collected through transfection of the receptor in diverse heterologous systems. In most models, its activation of $G\alpha_i$ leads to the inhibition of adenylyl cyclase, lowering intracellular cAMP concentration (Figure 4A). However, other pathways seem to be involved in the regulation of cAMP levels by 5-HT_{1A} receptors. Indeed, 5-HT_{1A} receptor can increase cAMP formation in cellular models expressing the adenylyl cyclase II variant, including hippocampal neurons (Albert et al., 1999; Cadogan et al., 1994; Shenker et al., 1987). One of the principal 5-HT_{1A} receptor effectors is the G protein-gated inward rectifying gK^+ (GIRK) channel (Figure 4), which opens following the stimulation of 5-HT_{1A} receptor, leading to the inhibition of voltage-gated Ca^{2+} channels. Interestingly, this functional coupling between 5-HT_{1A} receptors and GIRK channels is enhanced in tyrosine hydroxylase 2 knockout mice, which exhibit a functional sensitization of 5-HT_{1A} receptors (Mlinar et al., 2017). Heterologous expression of 5-HT_{1A} receptor in HeLa cells, as well as endogenous expression of the receptor in Jurkat cells can lead to activation of $G\beta\gamma$, which stimulates PLC, leading to the production of IP3 and diacyl glycerol (DAG) (Raymond et al., 1999). Remarkably, endogenous 5-HT_{1A} receptors can have opposite effects on signaling

pathways depending on where they are expressed. For example, they can activate Extracellular signal-Regulated Kinase (ERK)1/2 in the hypothalamus in a Calmodulin (CaM)-dependent manner, similar to what is observed in heterologous systems (Della Rocca et al., 1999; Turner et al., 2007), whereas they inhibit ERK1/2 phosphorylation in the hippocampus (Crane et al., 2007). In contrast, an activation of the Akt pathway has been demonstrated in the hippocampus and the medial prefrontal cortex (mPFC), where an activation of the mTOR (mammalian Target Of Rapamycin) has also been described (Cowen et al., 2005; Fukumoto et al., 2018a, 2018b). In the same brain area, activation of 5-HT_{1A} receptors leads to the inhibition of NMDA transmission, an effect that seems to require the Regulator of G protein signaling (RGS)4 function to be inhibited, which suggests a coupling between RGS4 and 5-HT_{1A} receptor (Figure 4A) (Gu et al., 2007). 5-HT_{1A} receptor stimulation transactivates PDGFβ receptors in SH-SY5Y neuroblastoma cells and primary cortical neurons, providing a signaling link between the serotonergic system and growth factors in neurons. This transactivation pathway is Pertussis toxin-sensitive and depends on Src tyrosine kinase, PLC and intracellular Ca^{2+} (Kruk et al., 2013). Another source of diversity for 5-HT_{1A} receptor signaling comes from the difference in the pharmacology as well as the ability of the receptor to desensitize depending on its presynaptic *vs.* postsynaptic localization. 5-HT_{1A} receptors have also been shown to stimulate nitric oxide synthase (NOS), Nicotinamide Dinucleotide phosphate oxidase-like enzyme, and Protein Kinase C (PKC) (Adayev et al., 2003; Polter & Li, 2010; Raymond et al., 1999).

5-$HT_{1B/D/E/F}$ receptors

Unlike the 5-HT_{1A} receptor that is expressed in somato-dendritic compartment, 5-HT_{1B} receptors are preferentially located on axon terminals, where their activation potentiates serotonin reuptake (Montanez et al., 2014). Endogenous 5-HT_{1B} receptors are coupled to $G_{i/o}$ proteins, leading to the inhibition of the adenylyl cyclase pathway. This has been demonstrated first in the substantia nigra (Bouhelal et al., 1988) and then confirmed in other brain areas such as the hippocampus (Lu et al., 2018). In addition, heterologous expression of the receptor showed a possible regulation of PLC and PLD, Akt, neuronal nitric oxide synthase (nNOS) and ERK1/2 (Raymond et al., 2001). 5-HT_{1B} receptor stimulation also inhibits Ca^{2+} channels and

activates K^+ channels.

Little is known about the signal transduction of other 5-HT_1 receptor subtypes. Studies in heterologous systems showed that they are also negatively coupled to adenylyl cyclase. The 5-HT_{1D} receptor has recently been shown to activate an axin1-βcatenin-metalloproteinase-7 pathway, promoting tumor invasion in colorectal cancer (Sui et al., 2015). Other evidences of a role for 5-HT_{1B} and 5-HT_{1D} receptors in cancer dissemination through the regulation of matrix metalloproteinases (MMPs) have been shown. In pancreatic cancer, the knockdown of both 5-HT_{1B} and 5-HT_{1D} receptors using RNA interference significantly decreases cell invasion. This results from a decrease in the MMP2 and integrin/Src/FAK signaling pathway (Gurbuz et al., 2014).

5-HT_{2A} receptor

The 5-HT_{2A} receptor is canonically coupled to the $G\alpha_{q/11}$ proteins and thus activates PLC (Conn & Sanders-Bush, 1984), leading to IP3 and DAG production and the activation of PKC (Figure 4B). 5-HT_{2A} receptor-mediated PKC activation leads to the phosphorylation of presynaptic GluN2B-containing NMDA receptors and postsynaptic GluA2-containing AMPA receptors, to gate synaptic plasticity at thalamo-cortical synapses (Barre et al., 2016; Berthoux et al., 2018). 5-HT_{2A} receptor activation by hallucinogenic agonists such as LSD, psilocybin, mescaline and 2,5-dimethoxy-4-iodoamphetamine (DOI) also leads to the activation of a $G\alpha_{i/o}$-Src pathway in PFC neurons, whereas receptor stimulation by non-hallucinogenic agonists such as ergotamine and the anti-Parkinson agent lisuride only triggers the activation of the G_q-PLC pathway (Gonzalez-Maeso et al., 2007). These differences in signaling mechanisms elicited by both agonist categories leads to specific patterns of gene expression in cortical neurons: both agonist subclasses induce *c-fos* expression in neurons expressing 5-HT_{2A} receptors, while only hallucinogens induce *egr-1* and *egr-2* expression (Gonzalez-Maeso et al., 2007). Intriguingly, only hallucinogenic agonists induce 5-HT_{2A} receptor phosphorylation at the serine residue (Ser^{280}) located in its third intracellular loop, an effect underlying the lower propensity of hallucinogens to promote receptor desensitization and internalization, compared with non-hallucinogenic agonists (Karaki et al., 2014). This biased phosphorylation and attenuated

desensitization of receptor may be responsible for more sustained receptor activation by hallucinogens *vs.* non-hallucinogenic agonists that might underlie their different behavioral outcomes. Collectively, these findings suggest that hallucinogenic and non-hallucinogenic agonists induce different conformational states of the 5-HT_{2A} receptor and represent a striking example of functional selectivity translated into contrasting patterns of behavior (Gonzalez-Maeso & Sealfon, 2009).

5-HT_{2A} receptors activate several other pathways, including PLA2 (Barclay et al., 2011) and PLD (Figure 4B) (Felder et al., 1990). Interestingly, PLD activation occurs through a mechanism independent of heterotrimeric G proteins that requires a physical interaction between the receptor C-terminal domain and PLD1 (Felder et al., 1990). As many GPCRs, 5-HT_{2A} receptor stimulation also induces activation of ERK1/2 pathway in various cell types, including neurons. Highlighting another example of functional selectivity at the 5-HT_{2A} receptor, activation of ERK1/2 by the 5-HT precursor 5-hydroxytryptophan (5-HTP) depends on β-arrestin2, whereas DOI-elicited ERK1/2 phosphorylation is β-arrestin-independent (Schmid et al., 2008). Likewise, 5-HTP but not *N*-methyltryptamines induces Akt stimulation through a β-arrestin2-dependent mechanism (Schmid & Bohn, 2010). Furthermore, the hallucinogenic-like effects, e.g. the head twitch response, induced by 5-HTP is β-arrestin-dependent, whereas DOI or *N*-methyltryptamines elicit similar behavioral responses in wild type and β-arrestin2 knockout mice (Schmid & Bohn, 2010; Schmid et al., 2008). β-arrestin-dependent ERK1/2 activation has also been involved in the counteractive effect of 5-HT_{2A} receptors on 5-HT_{1A} receptor-operated inhibition of NMDA receptor currents in PFC pyramidal neurons, providing one molecular substrate for the complex interactions between prefrontal serotonergic and NMDA receptors that underlie cognitive and emotional control by these systems (Yuen et al., 2008). Transactivation of growth factor receptors has also been involved in 5-HT_{2A} receptor-mediated ERK1/2 phosphorylation (Quinn et al., 2002; Tsuchioka et al., 2008). In rat C6 glioma cells, it depends on FGFR2 receptor transactivation and leads to the release of glial cell line-derived neurotrophic factor (Figure 4B) (Tsuchioka et al., 2008). In smooth muscle cells, 5-HT_{2A} receptor-mediated ERK1/2 activation is PLC/PKC-dependent and

ultimately results in MMP-13 production. This activation could be crucial for the collagen removal required post-partum to restore uterus reproductive function (Shum et al., 2002).

5-HT_{2A} receptors engage the Janus Kinase-2 (JAK)2/Signal transducers and activators of transcription (STAT)3 pathway in various cell types (Figure 4B). In trophoblast choricarcinoma cells, 5-HT_{2A} receptor stimulation activates both JAK2/STAT3 and MEK1/2-ERK1/2 pathways, which results in an increased DNA synthesis and improved viability of the cells (Oufkir et al., 2010; Oufkir & Vaillancourt, 2011). Activation of the JAK2/STAT3 pathway has also been demonstrated in rat frontal cortex, where it leads to the extinction of receptor-stimulated PLC activation (Singh et al., 2010).

Finally, 5-HT_{2A} (and 5-HT_{2C}) receptor stimulation by DOI induces transglutaminase (TGase)-catalyzed transamidation and activation of the small G proteins Rac1 and Cdc42 in primary cultured cortical neurons (Figure 4B), a process that causes a transient dendritic spine enlargement (Mi et al., 2017).

5-HT_{2B} receptor

The 5-HT_{2B} receptor is also coupled to the $G_{q/11}$ proteins and activates PLC. 5-HT_{2B} receptor stimulation in mouse fibroblasts induces ERK1/2 activation through transactivation of the platelet-derived growth factor (PDGF) receptor to promote cyclin D1 expression. Moreover, 5-HT_{2B} receptor stimulation increases activity of the Src family kinases, c-Src, Fyn, and c-Yes but only Src contributes to Cyclin D1 expression and cell cycle control by the receptor (Nebigil et al., 2000). In astroglial cells, activation of the receptor induced by fluoxetine treatment triggers ERK1/2 phosphorylation that depends on EGF receptor transactivation (Li et al., 2008). Furthermore, 5-HT_{2B} receptors are coupled to PLA2 (Tournois et al., 1998) and can activate both constitutive and inducible NOS (Manivet et al., 2000; Tournois et al., 1998).

5-HT_{2C} receptor

Both non-edited and edited forms of the 5-HT_{2C} receptor are coupled to $G_{q/11}$ proteins and activate PLC (Figure 4), but the editing results in decreased constitutive activity of the receptor and reduced agonist affinity and potency (Herrick-Davis et al., 1999; Niswender et al., 1999).

5-HT_{2C} receptor stimulation also induces PLD activation *via* coupling to $G\alpha_{13}$ protein, and the transactivation of the small G-protein RhoA (Figure 4C) (McGrew et al., 2004). Notably, the fully edited ($5HT_{2C\text{-}VGV}$) receptor does not activate the PLD pathway (McGrew et al., 2004), further supporting that editing represent a key regulatory mechanism of 5-HT_{2C} receptor-operated signaling. Agonist-dependent and independent 5-HT_{2C} receptor activation also leads to ERK1/2 phosphorylation through a G-independent, β-arrestin-dependent mechanism, which requires the receptor to be bound to CaM (Figure 4C) (Labasque et al., 2010; Labasque et al., 2008). Recent studies revealed that the β-arrestin-dependent stimulation of ERK1/2 pathway by the 5-HT_{2C} receptor, as well as other GPCRs that engage ERK signaling through a β-arrestin-dependent mechanism, requires β-arrestin2 phosphorylation on Thr^{383} (Cassier et al., 2017). Finally, stimulation of 5-HT_{2C} receptors induces the transamidation of the small G proteins Rac1 and Cdc42 in primary cortical cultures (Mi et al., 2017).

5-HT_3 receptors

As cationic channels permeable to Na^+, K^+ and Ca^{2+}, 5-HT_3 receptors give rise to fast, depolarizing responses and Ca^{2+} increase through voltage-sensitive Ca^{2+} channels in neurons upon activation (Maricq et al., 1991). Postsynaptic receptors mediate fast synaptic transmission while presynaptic receptors promote the release of 5-HT or other neurotransmitters in various brain regions.

5-HT_4 receptor

Stimulation of native 5-HT_4 receptors activates the G_s/cAMP/PKA pathway in colliculi neurons, guinea-pig hippocampus and nucleus accumbens (Figure 4D) (Bockaert et al., 1990; Dumuis et al., 1988; Dumuis et al., 1989). Coupling to other G proteins such as G_q and $G_{i/o}$ have also been described in heterologous systems (Bockaert et al., 2006; Ponimaskin et al., 2002). 5-HT_4 receptors are also coupled to $G\alpha_{13}$ (Figure 4D), an effect that leads to a RhoA-dependent neurite retraction and cell rounding in NIE-115 cells (Ponimaskin et al., 2002). Further supporting a prominent role of 5-HT_4 receptors in the regulation of neuronal architecture, receptor coupling to $G\alpha_{13}$ in cultured hippocampal neurons results in the reduction of neurite length and of the total number of neurites (Kvachnina et al., 2005). Notably, splice

variants of the receptor not only exhibit variable levels of constitutive activity (Claeysen et al., 1999) but can also display specificity towards the G protein with which they are coupled. For example, the 5-$HT_{4(b)}$ receptor activates both G_s and $G_{i/o}$ proteins, whereas the 5-$HT_{4(a)}$ receptor is only coupled to G_s (Pindon et al., 2002). The 5-HT_4 receptor also engages the ERK1/2 pathway through a β-arrestin-independent mechanism that requires Src activation (Figure 4D) (Barthet et al., 2009), consistent with the inability of the receptor to promote β-arrestin2 phosphorylation at Thr^{383} (Cassier et al., 2017). Activation of 5-HT_4 receptors also induces activation of the exchange factor Epac (Figure 4D), which in turn stimulates Rac and α-secretase-mediated amyloid precursor protein (APP) processing. This results in the release of the neuroprotective extracellular APP fragment sAPPα from both CHO cells and primary cultured cortical neurons (Maillet et al., 2003). More recently, an interaction between the 5-HT_4 receptor and the α-secretase ADAM10 has been described (Cochet et al., 2013). This interaction results in an increase in sAPPα release through the PKA/Epac signaling pathway (Cochet et al., 2013).

5-HT_{5A} receptor

Amongst the two 5-HT_5 receptor variants identified, only the 5-HT_{5A} variant is functional in humans (Grailhe et al., 2001). The 5-HT_{5A} receptor is coupled to $G_{i/o}$ proteins and inhibits cAMP production in recombinant cells, but little is known about the coupling of native receptors (Noda et al., 2003). In the cerebral cortex of rodents, 5-HT_5 receptor stimulation induces an inward rectifying outward current that is suppressed by blockers of Kir3 channels (Goodfellow et al., 2012). The 5-HT_5 receptor has been involved in pain (Munoz-Islas et al., 2014), cognitive deficits in a rat model of schizophrenia (Avila-Rojas et al., 2015; Nikiforuk et al., 2016) and in the acoustic startle circuits (Curtin et al., 2013).

5-HT_6 receptor

As firstly established in mouse striatal neurons in primary culture (Sebben et al., 1994), the 5-HT_6 receptor is canonically coupled to G_s protein and activates adenylyl cyclase (Figure 4E) (Sebben et al., 1994). In striatal neurons, 5-HT_6 receptor-operated cAMP signaling can regulate DARPP32 enzymatic activity (Svenningsson et al., 2002). The 5-HT_6 receptor binds to and

activates the tyrosine kinase Fyn, a process that leads to ERK1/2 phosphorylation (Figure 4E) (Yun et al., 2007). 5-HT_6 receptor activation also induces the translocation of Jun activation domain-binding protein-1 (Jab1) into the nucleus, leading to an increase in c-Jun phosphorylation and the interaction between Jab1 and c-Jun (Yun et al., 2010). The 5-HT_6 receptor can also activate the mTOR pathway in various brain regions, including the prefrontal cortex (Figure 4E). mTOR activation under the control of 5-HT_6 receptors, has been involved in both cognitive deficits observed in rodent developmental models of schizophrenia (Meffre et al., 2012) and seizure activity in epilepsy (L. Wang et al., 2015). Finally, 5-HT_6 receptors activate Cyclin-dependent kinase (Cdk)5 in an agonist-independent manner through a mechanism involving a reciprocal interplay between the receptor and Cdk5 whereby phosphorylation of receptor Ser^{350} by associated Cdk5 is required for 5-HT_6 receptor-operated Cdk5 activation (Figure 4E). Cdk5 in turn activates a Cdc42 pathway, leading to neuronal differentiation and the initiation of neurite growth (Duhr et al., 2014). 5-HT_6 receptor-elicited Cdk5 signaling has also been involved in the fine-tuning of neuronal migration by the receptor (Jacobshagen et al., 2014).

5-HT_7 receptor

5-HT_7 receptors are positively coupled to adenylyl cyclase *via* $G\alpha_s$ and induce cAMP production (Figure 4F) (Bard et al., 1993; Lovenberg et al., 1993; Ruat, Traiffort, Leurs, et al., 1993). They are also coupled to $G\alpha_{12}$ (Kvachnina et al., 2005) in NIH/3T3 cells and hippocampal neurons, where their stimulation leads to the activation of RhoA and Cdc42, and triggers neurite growth (Kvachnina et al., 2005). Both agonist-dependent and independent activation of 5-HT_7 receptors induce formation of dendritic spines and synaptogenesis in cortical and striatal neurons through the activation of Cdk5 and Cdc42 (Figure 4F) (Speranza et al., 2017). Likewise, activation of 5-HT_7/G_{12} signaling potentiates formation of dendritic spines and enhances synaptic activity in hippocampal neurons at early post-natal stages. In a recent study, Bijata *et al.* demonstrated that the effects of the 5-HT_7 receptor upon dendritic spine morphogenesis and synaptic plasticity depend on local activation of MMP-9 that in turn cleaves CD44 bound to the receptor, leading to Cdc42 activation (Bijata et al., 2017). In

hippocampal neurons, the 5-HT_7 receptor also activates ERK1/2 (Errico et al., 2001), but the underlying mechanism is not fully understood. It may involve PKA-dependent phosphorylation of the guanine nucleotide exchange factor Ras-GRF1 and subsequent Ras activation (Norum et al., 2003; Norum et al., 2005).

VI- Homo and heterodimerization of 5-HT receptors and their consequences on 5-HT receptor signaling and functions

Accumulating evidence indicates that GPCRs are not only monomeric entities that couple to G proteins upon activation by a single ligand molecule, but that they form dimers or even higher order oligomers composed of unique or different receptor proteins, which exhibit specific pharmacological and signaling properties underlying unique physiological outcomes. It is thus not surprising that the ability to form dimers, and in some cases oligomers, has now been shown for many 5-HT receptors, including 5-HT_{1A} (Kobe et al., 2008), 5-HT_{2A} (Brea et al., 2009; Teitler & Klein, 2012), 5-HT_{2C} (Herrick-Davis et al., 2015), 5-HT_4 (Pellissier et al., 2011), and 5-HT_7 (Teitler & Klein, 2012) receptors. Different factors regulate 5-HT receptor oligomerization. These include receptor density, with low expression levels favoring monomeric forms while higher expression levels favor association of dimers into tetramers, cholesterol level in the membrane and ligand binding. For instance, if 5-HT_{1A} receptors have the propensity to form homodimers in absence of ligand, agonists (8-OH-DPAT) enhance while antagonists (SCH58216 and methysergide) decrease dimer formation (Lukasiewicz et al., 2007). Homodimer formation not only leads to new pharmacological entities with specific binding and signal transduction properties but it might also be important for receptor trafficking to the membrane when it occurs early during receptor synthesis, as shown for the 5-HT_{2C} receptor (Herrick-Davis et al., 2006).

Certain 5-HT receptors are not only capable of forming homodimers, or homo-oligomers, but can also form heteromers with different 5-HT receptor subtypes (Table 1). Due to technical difficulties, their ability to form heteromers has mostly been demonstrated *in vitro* using cell lines and in most cases remains to be established *in vivo*. However, evidence of the presence of heteromers composed of different 5-HT receptor subtypes *in vivo* is emerging. For instance, 5-

HT_{2A} and 5-HT_{2C} receptors were found to form a complex that might be involved in the control of impulsivity in the rat mPFC (Anastasio et al., 2015), and the ability of both receptors to heteromerize was recently confirmed by three complementary biophysical techniques (Felsing et al., 2018). 5-HT_{2B} receptors also form heteromers with 5-HT_{2C} receptors. Heteromerization with 5-HT_{2C} receptors blunts both 5-HT_{2A} and 5-HT_{2B} receptor-operated signaling in transfected cells and neurons, suggesting that 5-HT_2 receptors form functionally asymmetric heterodimers *in vitro* and *in vivo* (Moutkine et al., 2017). Co-immunoprecipitation studies suggest that the 5-HT_{1A} receptor forms hetero-oligomers with several 5-HT receptor subtypes, but only heteromers with 5-HT_{2A} or 5-HT_7 receptors have been validated. The existence of 5-HT_{1A}:5-HT_{2A} receptor heteromers has been demonstrated in the pyramidal cell layer of CA1-CA3 regions of the dorsal hippocampus using *in situ* proximity ligation assay and was further validated in cellular models by BRET (Borroto-Escuela et al., 2017). The number of 5-HT_{1A}:5-HT_{2A} clusters in CA1 and CA2 regions decreases 24 h after a forced swim test session, suggesting that 5-HT_{1A}:5-HT_{2A} heteromerization is a dynamic process that might be involved in depression-like behavior (Borroto-Escuela et al., 2017). 5-HT_{1A}:5-HT_7 receptor heteromerization inhibits 5-HT_{1A} receptor-mediated activation of G_i without affecting 5-HT_7 receptor-operated signaling, and decreases the ability of the 5-HT_{1A} receptor to activate GIRK channels in hippocampal neurons (Renner et al., 2012). Moreover, 5-HT_{1A}:5-HT_7 heteromerization promotes 5-HT-induced 5-HT_{1A} receptor internalization and receptor-operated ERK1,2 activation.

Accumulated evidence also indicates that 5-HT receptors can form heteromers with GPCRs not activated by 5-HT, with important consequences on their signaling and functional outcomes (Table 1). 5-HT_{1A} receptors heteromerize with galanin receptor 1 (GalR1) (Borroto-Escuela, Narvaez, et al., 2010), the zinc receptor GPR39 (Tena-Campos et al., 2015), D_2 dopaminergic receptor (Lukasiewicz et al., 2016) and μ-opioid receptor (MOR) (Cussac et al., 2012). GalR1-5-HT_{1A} receptor heteromerization induces a reciprocal inhibition of signaling engaged by both receptors *via* allosteric mechanisms (Borroto-Escuela, Narvaez, et al., 2010). Intriguingly, GalR1-5-HT_{1A} receptor heteromers can further associate with GPR39 to form heterotrimers and

the presence of $GalR_1$ seems to inhibit both 5-HT_{1A} and GPR39-operated signaling (Tena-Campos et al., 2015). Likewise, 5-H_{1A}:D_2 heteromer formation seems to profoundly affect signal transduction properties of both receptors and the response to antipsychotics (Lukasiewicz et al., 2016). Though the existence 5-HT_{1A}:D_2 heteromers has been established in mouse prefrontal cortex (Kolasa et al., 2018), the irrefutable proof that the observed effects of heteromerization on signal transduction of both receptors result from heteromer formation and not solely receptor co-expression is still lacking. The existence of MOR:5-HT_{1A} heteromers *in vivo* also remains to be established. Data obtained in cell lines suggest a crosstalk within MOR:5-HT_{1A} heteromers to activate $G\alpha_o$ and ERK1/12 pathways (Cussac et al., 2012).

The 5-HT_{2A} receptor forms heteromers with a number of GPCRs, including $mGlu_2$ (Gonzalez-Maeso et al., 2008), cannabinoid CB_1 (Vinals et al., 2015), D_2 (Borroto-Escuela, Romero-Fernandez, et al., 2010) and cortiocotropin releasing factor $(CRF)_1$ receptors (Narla et al., 2015), the latter involving PDZ-based interactions. Evidence of their existence *in vivo* has only been established for 5-HT_{2A}:$mGlu_2$ (Gonzalez-Maeso et al., 2008) and 5-HT_{2A}:CB_1 heteromers (Vinals et al., 2015). 5-HT_{2A}:$mGlu_2$ heteromerization strongly influences signal transduction elicited by both receptors by modulating their coupling to G proteins and phosphorylation profile (Fribourg et al., 2011; Murat et al., 2018). Numerous data also suggest that 5-HT_{2A}:$mGlu_2$ heteromers represent the actual receptor entity that underlies the psychomimetic effects of hallucinogens as well as the action of second and last-generation antipsychotics that acts at 5-HT_{2A} and $mGlu_2$ receptors, respectively (Benvenga et al., 2018; Delille et al., 2013; Fribourg et al., 2011; Moreno et al., 2011). 5-HT_{2A}:CB_1 heteromer formation switches G protein coupling of 5-HT_{2A} receptor from G_q to G_i (Vinals et al., 2015). 5-HT_{2A}:CB_1 heteromers also mediate Δ-9-tetrahydrocannabinol (THC)-induced memory impairment but not its analgesic effects, suggesting that they might be relevant targets to dissociate the beneficial antinociceptive properties of THC from its side effects upon cognition (Vinals et al., 2015). Functional crosstalk within 5-HT_{2A}-D_2 and 5-HT_{2A}/CRF_1 receptor heteromers has also been suggested (Borroto-Escuela, Romero-Fernandez, et al., 2010; Narla et al., 2015).

The 5-HT_{2C} receptor forms functional heteromers with MT_2 melatonin receptors in human

cortex and hippocampus that may be of special interest as target for the treatment of mood disorders in light of the "synergistic" melatonin agonist/5-HT_{2C} antagonist profile of the antidepressant agomelatine (Kamal et al., 2015). The 5-HT_{2C} receptor also forms complexes with another receptor involved in the control of food intake, the ghrelin GHS-R1a receptor (Schellekens et al., 2015). Blocking 5-HT_{2C} receptor signaling potentiates ghrelin orexigenic effect, whereas lorcaserin, a 5-HT_{2C} receptor agonist approved for the treatment of obesity, attenuates ghrelin-induced food intake (Schellekens et al., 2015). The role of heteromerization in these effects remains to be established.

VII- 5-HT receptor-interacting proteins and their role in 5-HT receptor-operated signal transduction and functions

Over the past 20 years, it has become evident that GPCRs, including G protein-coupled 5-HT receptors, are not solely capable of interacting with other GPCRs, G proteins and β-arrestins, but that they additionally recruit specific proteins called GIPs (GPCR-interacting proteins) that strongly influence GPCR intracellular fate and signal transduction properties (Bockaert et al., 2004). Some 5-HT receptors are certainly amongst the GPCRs for which the largest number of interacting proteins has been characterized, mostly thanks to two-hybrid screens or affinity purification coupled to mass spectrometry (AP-MS) proteomic strategies (Marin et al., 2012). However, the characterization of 5-HT receptor interactomes differs from one receptor to another and still remains to be done for several 5-HT receptors (Table 2).

5-HT_{1A} receptor

CaM was the first interacting partner of the 5-HT_{1A} receptor identified. CaM is recruited *via* two binding motifs located in the receptor i3 loop and thereby interferes with receptor phosphorylation by PKC and desensitization (Turner et al., 2004). The 5-HT_{1A} receptor also binds to Yif1B, the orthologue of the yeast Yif1p implicated in vesicular trafficking between the endoplasmic reticulum and the Golgi apparatus, *via* its C-terminal domain (Carrel et al., 2008). Yif1B functions as a scaffold protein that recruits a complex composed of Yip1A, Rab6, Kif5B and dynein, involved in dendritic targeting of the receptor (Al Awabdh et al., 2012).

5-HT$_{1B}$ receptor

The 5-HT$_{1B}$ receptor interacts with the adaptor protein p11, also designated as S100A10, which has been involved in depression-like behaviors and responses to antidepressants as well as to cocaine in rodents. P11 increases localization of 5-HT$_{1B}$ receptors at the cell surface and data suggest that 5-HT$_{1B}$ receptor:p11 interaction may play a role in response to antidepressants (Svenningsson et al., 2006). Further studies suggested a role of this interaction in L-DOPA treatment of Parkinson's disease (Zhang et al., 2008) and the regulation of emotional memory by 5-HT$_{1B}$ receptors (Eriksson et al., 2013).

5-HT$_{2A}$ receptor

The 5-HT$_{2A}$ receptor recruits several PDZ domain-containing proteins (PDZ proteins) through its C-terminal PDZ-binding motif (-SCV). These include the major postsynaptic protein PSD-95 and other proteins of the postsynaptic density (Becamel et al., 2004), which profoundly influence receptor trafficking and signaling. 5-HT$_{2A}$ receptor:PSD95 interaction modulates receptor targeting (Xia, Hufeisen, et al., 2003), trafficking (Xia, Gray, et al., 2003), psychomimetic effects of hallucinogens and responses to antipsychotics acting on 5-HT$_{2A}$ receptors (Abbas et al., 2009) as well as neuropathic pain (Pichon et al., 2010; Vogrig et al., 2013). The 5-HT$_{2A}$ receptor also binds to PDZK1/NHERF3 but, surprisingly, through a PDZ-independent mechanism. 5-HT$_{2A}$ receptor/PDZK1 association negatively regulates 5-HT$_{2A}$ receptor endocytosis and, correspondingly, promote receptor-operated PLC activation (Walther et al., 2015). Likewise, 5-HT$_{2A}$ receptor association with SAP97 decreases receptor internalization rate and enhance receptor-induced inositol phosphate production (Dunn et al., 2014). More recently, using a PDZ overlay assay, Hammad *et al.* showed that 5-HT$_{2A}$ receptors physically interact with the three members of the MAGI PDZ protein family (MAGI-1, MAGI-2 and MAGI-3) (Hammad et al., 2018). All three proteins share a similar structure containing one guanylate kinase-like (GK) domain, two tryptophan (WW) domains and six PDZ domains. MAGI proteins promote 5-HT$_{2A}$ receptor internalization and differentially modulate receptor-induced signaling pathways: their association with the receptor enhances the recruitment of

PLCβ3 to the receptor and PLC signaling, whereas it inhibits ERK1/2 activation, the latter effect being PDZ-independent (Hammad et al., 2018).

The 5-HT_{2A} receptor also recruits a number of non-PDZ proteins that influence their signal transduction and functions. As shown for 5-HT_{1A} receptors, 5-HT_{2A} receptors bind to CaM, which influences receptor phosphorylation and desensitization (Turner & Raymond, 2005). They also associate with p90 ribosomal S6 kinase (RSK)2, a downstream kinase of the ERK1,2 pathway that phosphorylates a serine residue located in the receptor i3 loop (Sheffler et al., 2006). Notably, RSK2 expresses a C-terminal PDZ binding motif and RSK2/PDZ protein interactions have been demonstrated to be important for the role of RSK2 in regulation of synaptic transmission (G. M. Thomas et al., 2005). 5-HT_{2A} receptors associate with caveolin-1 in various cell types (Bhatnagar et al., 2004). Both form a complex with KV1.5 channels upon receptor stimulation by 5-HT (Cogolludo et al., 2006). Finally, 5-HT_{2A} receptors associate with PLD1 (Felder et al., 1990) and the ADP-ribosylation factors ARF1 and, to a lesser extent, ARF6 (Robertson et al., 2003). Physical interaction between PLD1 and ARF proteins seems to be essential for 5-HT_{2A} receptor-operated PLD activation.

5-HT_{2B} receptor

The 5-HT_{2B} receptor interactome remains much less characterized, when compared to the 5-HT_{2A} receptor one. The presence of a PDZ binding motif at its C-terminus suggests its interaction with PDZ proteins. As 5-HT_{2A} and 5-HT_{2C} receptors, the 5-HT_{2B} receptor recruits the multi-PDZ protein 1 (MUPP1) (Becamel et al., 2001), but the role of this interaction remains to be elucidated. It has been shown that the activation of NOS by the 5-HT_{2B} receptor is PDZ-dependent (Manivet et al., 2000), but the nature of the PDZ protein(s) involved also remains to be established.

5-HT_{2C} receptor

In line with the presence of PDZ binding motif at its C-terminal extremity, the 5-HT_{2C} recruits a number of PDZ proteins through PDZ-based interactions. MUPP1 was the first receptor PDZ binding partner identified (Ullmer et al., 1998). Further studies showed that 5-HT_{2C}

receptor:MUPP1 interaction is dynamically regulated by agonist-dependent receptor phosphorylation at a serine residue located in the PDZ binding motif (Ser^{458}) (Parker et al., 2003). Association of the 5-HT_2 like *Caenorhabditis elegans* receptor SER-1 with a multi-PDZ domain containing protein similar to MUPP1 is involved in 5-HT-stimulated egg laying in the worm (Xiao et al., 2006), suggesting that this interaction play a key in some receptor functions. The receptor also binds to additional PDZ proteins, such as PSD-95 and MPP3, which differentially regulate receptor trafficking (Becamel et al., 2002; Gavarini et al., 2006). As previously mentioned, interaction of CaM with the juxta-membrane region of the receptor C-terminus is critical for the G-independent, β-arrestin-dependent, activation of ERK1/2 by the receptor (Labasque et al., 2008). The interaction of PTEN (phosphatase and tensin homolog deleted on chromosome 10) with the receptor i3 loop leads to inhibition of agonist-induced receptor phosphorylation. Disruption of 5-HT_{2C} receptor/PTEN interaction prevents the increase in firing rate of ventral tegmental area dopaminergic neurons induced by THC, thus mimicking the effect of agonist receptor stimulation (Ji et al., 2006). More recently, Kleene *et al.* showed an interaction between the receptor i3 loop and the cell adhesion molecule close homolog of L1 (CHL1) and that CHL1 regulates receptor association with β-arrestin and PTEN and signaling pathways engaged by constitutively active 5-HT_{2C} receptors (Kleene et al., 2015). Finally, 5-HT_{2C} receptors expressed in hypothalamus interact with Abelson helper integration site 1 (Ahi1) protein. This interaction promotes 5-HT_{2C} receptor degradation in the lysosomal pathway and thereby contributes to its control of food intake (H. Wang et al., 2012).

5-HT_4 receptor

Consistent with the presence of a PDZ binding motif at the C-terminus of some 5-HT_4 receptor variants (e.g. SCF and VPV in 5-HT_{4a} and 5-HT_{4e} variants, respectively), these variants recruit specific sets of PDZ proteins (Joubert et al., 2004). For instance, the 5-HT_{4a} receptor interacts with sortin nexin (SNX)27 and NEHRF1 (EBP50), that target the receptor to microvilli where it is co-localized with activated ezrin, and early endosomes, respectively (Joubert et al., 2004). Further studies identified SNX27 as an essential adaptor protein linking GPCRs to the retromer and contributing to their endosome-to-plasma membrane traffic (Temkin et al., 2011). The

function of other 5-HT_4 receptor-PDZ protein interactions identified remains to be elucidated. The 5-HT_4 receptor directly interacts with Src and its activation promotes auto-phosphorylation of Src bound to the receptor at Tyr^{416}. Src association with the receptor and its subsequent phosphorylation are required for the engagement of ERK1/2 signaling by the 5-HT_4 receptor (Barthet et al., 2009). Reminiscent of the 5-HT_{1B} receptor, the 5-HT_4 receptor interacts with p11 (Warner-Schmidt et al., 2009). P11 increases 5-HT_4 receptor surface expression, thereby enhancing receptor-operated signaling, and is required for the behavioral antidepressant response induced by 5-HT_4 receptor stimulation (Warner-Schmidt et al., 2009). Likewise, induction of p11 expression by BDNF or imipramine in cardiomyocytes reveals 5-HT_4 receptor-mediated effects on Ca^{2+} handling (Meschin et al., 2015). The 5-HT_4 receptor also physically associates with the α-secretase ADAM10 and Amyloid Precursor Protein (APP) to promote its non-amyloidogenic cleavage and the release of the neuroprotective soluble APP fragment sAPPα in an agonist-independent manner (Cochet et al., 2013). More recently, a systematic screen of protein-protein interactions implicating clinically relevant GPCRs identified G protein-regulated inducer of neurite outgrowth 2 (GPRIN2) (Sokolina et al., 2017), a protein known to interact with G proteins (Chen et al., 1999) and the Parkinson's disease-associated receptor GPR37 (Dusonchet et al., 2009), as novel 5-HT_{4d} receptor interacting partners (Sokolina et al., 2017). Co-expression of GPR37 and GPRIN2 with the 5-HT_{4d} receptor potentiates receptor-elicited cAMP production while it prevents ERK1/2 phosphorylation in HEK-293 cells (Sokolina et al., 2017).

5-HT_6 receptor

The Src family tyrosine kinase Fyn was the first 5-HT_6 receptor interacting protein identified by means of a two-hybrid screen using the receptor C-terminal domain as bait (Yun et al., 2007). Further studies showed that 5-HT_6 receptor:Fyn interaction promotes receptor cell surface expression and its coupling to G proteins and, reciprocally, that 5-HT_6 receptor activation increases Fyn kinase activity (Yun et al., 2007). Furthermore, activation of ERK1/2 signaling depends on Fyn (Yun et al., 2007). The same group of investigators identified two additional 5-HT_6 receptor partners, namely, Jun activation domain-binding protein1 (Jab1) (Yun et al.,

2010) and the microtubule-associated protein Map1b (Kim et al., 2014). 5-HT_6 receptor stimulation promotes Jab1 translocation to the nucleus, its association with c-Jun, and c-Jun phosphorylation (Yun et al., 2010). Both Jab1 and Map1b increase 5-HT_6 receptor cell surface expression and consequently receptor-mediated signal transduction (Kim et al., 2014; Yun et al., 2010).

An AP-MS proteomic strategy revealed that 5-HT_6 receptors recruit several proteins of the mTOR pathway (Meffre et al., 2012). These include mTOR itself and raptor, which, together with mTOR, constitutes the mTOR complex 1 (mTORC1), Tti1 and Tel2, which form a complex required for the assembly and stability of mTORC1, neurofibromin1 (NF1), a Ras GTPase activating protein identified as an upstream modulator of the mTOR pathway (Johannessen et al., 2005) and Vps34, a class III phosphatidylinositol 3-kinase (PI3K) necessary for mTORC1 activation in response to amino acids and implicated in autophagosome formation (Backer, 2008). Physical interaction between the 5-HT_6 receptor and mTOR seems to be essential for receptor-operated mTOR activation, which has been involved in cognitive deficits observed in neurodevelopmental models of schizophrenia (Meffre et al., 2012) as well as seizure activity of epileptic brain (L. Wang et al., 2015) in rodents. A more recent study revealed that 5-HT_6 receptor-neurofibromin interaction is critical for agonist-independent receptor-operated cAMP signaling in prefrontal cortex (Deraredj Nadim et al., 2016). Another study showed that the 5-HT_6 receptor directly interacts with SNX14 and that this interaction promotes receptor internalization and degradation (Ha et al., 2015). Finally, the 5-HT_6 receptor was found to associate with a network of proteins, including Cdk5 and some of its regulator or substrates. These proteins are known to control actin cytoskeleton dynamics and key neurodevelopmental processes such as neuronal migration, neurite growth, and synapse morphogenesis (Duhr et al., 2014; Jacobshagen et al., 2014; Jessberger et al., 2009). As mentioned in chapter V, functional studies showed that agonist-independent activation of Cdk5 signaling by 5-HT_6 receptors plays a key role in its control of neuronal migration and differentiation during brain development (Duhr et al., 2014; Jacobshagen et al., 2014).

5-HT_7 receptor

Using a yeast two-hybrid screening, Matthys et al. showed that the C-terminal domain of the 5-HT_{7a} receptor directly interacts with RhoBTB3, an atypical Rho GTPase, which strongly inhibits proteasomal degradation of the receptor (Matthys et al., 2012). 5-HT_7 receptors also bind to S100B, a Ca^{2+}-binding protein that serves as a biochemical predictor of behavioral responses to chronic fluoxetine treatment, *via* its i3 loop (Stroth & Svenningsson, 2015). This interaction negatively regulates 5-HT_7 receptor-dependent cAMP production in transfected HeLa cells and mouse cortical astrocytes. It might also play a role in mood disorders as depressive-like behavior in the forced swim test (FST) observed in transgenic mice over-expressing S100B is normalized by pharmacological 5-HT_7 receptor blockade (Stroth & Svenningsson, 2015). Finally, a recent study highlighted a physical interaction between the 5-HT_7 receptor and CD44, an MMP-9 substrate cleaved upon receptor activation in neurons and involved in receptor-mediated dendritic spine remodeling, synaptic pruning and impairment of LTP (Bijata et al., 2017).

Concluding remarks

Over the two last decades, our knowledge of G protein-dependent signaling mechanisms engaged by 5-HT receptors has probably achieved maturity. An important challenge is now to precisely determine where 5-HT receptors activate G proteins in the cells and the dynamics of G protein activation. Recently described single-molecule microscopy methods that allow direct visualization of GPCR:G protein interactions in living cells with unprecedented spatiotemporal resolution, will certainly provide a unique opportunity to address this question (Calebiro & Sungkaworn, 2018). Beyond G protein signaling, identification of 5-HT receptor interactomes using genetics or proteomics strategies has proven efficiency to identify novel signaling pathways engaged by these receptors, as recently exemplified by the identification of novel 5-HT_6 and 5-HT_7 receptor-operated signaling pathways that underlie their role in neural development. Determination of crystal structures of 5-HT receptors will also be an important step in the understanding of 5-HT receptor activation process and of the mechanism of action

of 5-HT receptor ligands, as well as in the development of drugs acting at 5-HT receptors. Given the importance of heteromer formation and the association of 5-HT receptors with GIPs in their signal transduction properties and functions, the next step will certainly be to determine structures of complexes made of 5-HT receptors and their protein partners.

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Figure legends

Figure 1. Classification of serotonin receptors: an historic view

The evolution of 5-HT receptor classification from the first proposal made by Gaddum and Picarelli to the current consensus is depicted. During the "Pharmacological Period", 8 receptor subtypes have been characterized. During the "Molecular Biology Period", 17 genes (designated as HTRs) and one pseudogene (designated as Htr) have been cloned, leading to the current classification of 17 functional 5-HT receptors.

Figure 2. Solved structures of 5-HT receptors

Comparison of the overall architecture of 5-HT_{1B} (A), 5-HT_{2B} (B) and 5-HT_{2C} receptors (C and D) bound to the agonist ergotamine (ERG) or the inverse agonist ritanserin (RIT). The limits of the classical orthosteric site are indicated using dashed lines: upper limit in blue, lower limit in pink.

Figure 3. Gene structures of human 5-HT receptor coding sequences

This figure was generated using released data of the human genome project available on the NCBI site (http://www.ncbi.nlm.nih.gov) using Gene Database and Consensus CDS Reference Sequences. GRCh38.p12 assembly was used to localize the exons except for Htr_{5B} that was annotated using GRCm38.p4 assembly. First column: gene names and chromosomic localizations. Second column: exon composition of the coding sequences and part of the receptor encoded by each exon (open boxes, exons; bridges, splicing events; black boxes, trans-membrane domains; curved lines, loops or N- or C-terminal domains; colours, alternative exons). Third column: name and size of the gene products and splice variants (aa, amino acids). Fourth column: size of the complete coding sequence on the human genome (b, bases; kb, kilo bases).

Figure 4. Signaling pathways engaged by 5-HT receptors.

Only the 5-HT receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_4, 5-HT_6 and 5-HT_7 receptors) for which signal transduction mechanisms have been extensively characterized, including in authentic tissues, are depicted. cAMP, cyclic adenosine monophosphate; Cdk5, cyclin-dependent kinase 5; Epac, Exchange protein directly activated by cAMP; ERK, Extracellular

signal-regulated kinase; FGFR2, Fibroblast Growth Factor Receptor 2; gCa^{2+}, calcium conductance; gK^{+}, potassium conductance; GIRK, G protein-coupled inwardly-rectifying potassium channel; Jab1, c-Jun activation domain-binding protein-1; Jak2, Janus kinase 2; MMP9, Matrix metalloproteinase 9; mTOR, mammalian Target Of Rapamycin; mTORC1, mTOR Complex 1; NF1, neurofibromin; PLA2, Phospholipase A2; PLC, phospholipase C; PLD1, phospholipase D1; PKC, protein kinase C; Ras-GRF1, Guanine nucleotide exchange factor for Ras; STAT3, Signal Transducer and Activator of Transcription 3.

Receptor 1	Receptor 2	Demonstration of interaction *in vitro*	Demonstration of interaction *in vivo*	Impact on signaling	Physiological / pathological roles	References
5-HT_{1A}	5-HT_{2A}	PLA, BRET	PLA (CA1−CA3 regions of hippocampus)	↑ ipsapirone binding ↑ $G_{i/o}$ coupling	Depression	(Borroto-Escuela et al., 2017)
5-HT_{1A}	5-HT_7	Co-IP, FRET		↓ G_i protein activation ↑ ERK1/2 activation ↑ 5-HT_{1A} receptor internalization		(Renner et al., 2012)
5-HT_{2A}	5-HT_{2C}	LCA, PLA, BRET			Motor impulsivity	(Anastasio et al., 2015; Felsing et al., 2018)
5-$HT_{2A/B}$	5-HT_{2C}	Co-IP, BRET		Blunts 5-HT_{2A} and 5-HT_{2B} receptor-operated signaling		(Moutkine et al., 2017)
5-HT_{1A}	$GalR_1$	FRET		Reciprocal allosteric antagonistic action		(Borroto-Escuela, Narvaez, et al., 2010; Flores-Burgess et al., 2017; Millon et al., 2016)
5-HT_{1A}	GPR39	BRET, Co-IP		↑ ERK1/2 activation and NFκβ-signaling	Depression	(Tena-Campos et al., 2015)
5-HT_{1A}	D_2	BRET, FLIM, FRET, HTRF	PLA (prefrontal cortex)	Cross talk in ERK activation		(Kolasa et al., 2018; Lukasiewicz et al., 2016)
5-HT_{1A}	MOR	Co-IP, BRET, transactivation		5-HT_{1A} receptor transactivation ↓ MOR-operated ERK1/2 activation		(Cussac et al., 2012)
5-$HT_{2A/2C}$	CRFR1		Co-localization interfering peptide (prefrontal cortex)	↑ receptor recycling	Anxiety	(Magalhaes et al., 2010; Narla et al., 2015)
5-HT_{2A}	$mGlu_2$	Genetically encoded photo cross-linkers	Co-IP (cortex)	↓ G_q-PLC signaling, ↑ $G_{i/o}$ signaling	Response to hallucinogens and	(Benvenga et al., 2018; Fribourg et al., 2011;

		Mutants defective for interaction Co-IP, FRET			antipsychotics, schizophrenia	Gonzalez-Maeso et al., 2008; Murat et al., 2018)
5-HT_{2A}	CB_1	BRET	PLA, Interfering peptide (hippocampus, cortex, striatum)	↓ 5-HT_{2A} receptor coupling to G_q ↑ 5-HT_{2A} receptor coupling to Gi	THC-induced memory impairment	(Vinals et al., 2015)
5-HT_{2A}	D_2	BRET, PLA	PLA (ventral and dorsal striatum)	↑ D_2 receptor signaling by hallucinogenic 5-HT_{2A} receptor agonists ↑ 5-HT_{2A}-receptor mediated PLC activation		(Borroto-Escuela et al. 2010, 2014)
5-HT_{2C}	MT_2	Co-IP, BRET	Co-IP (cortex, hippocampus, choroid plexus)	5-HT_{2C} receptor transactivation		(Kamal et al., 2015)
5-HT_{2C}	GHS-R_{1a}	fcFRET	Co-localization (hypothalamic and hippocampal neurons)	↓ Ca^{2+} signaling		(Schellekens et al., 2015)

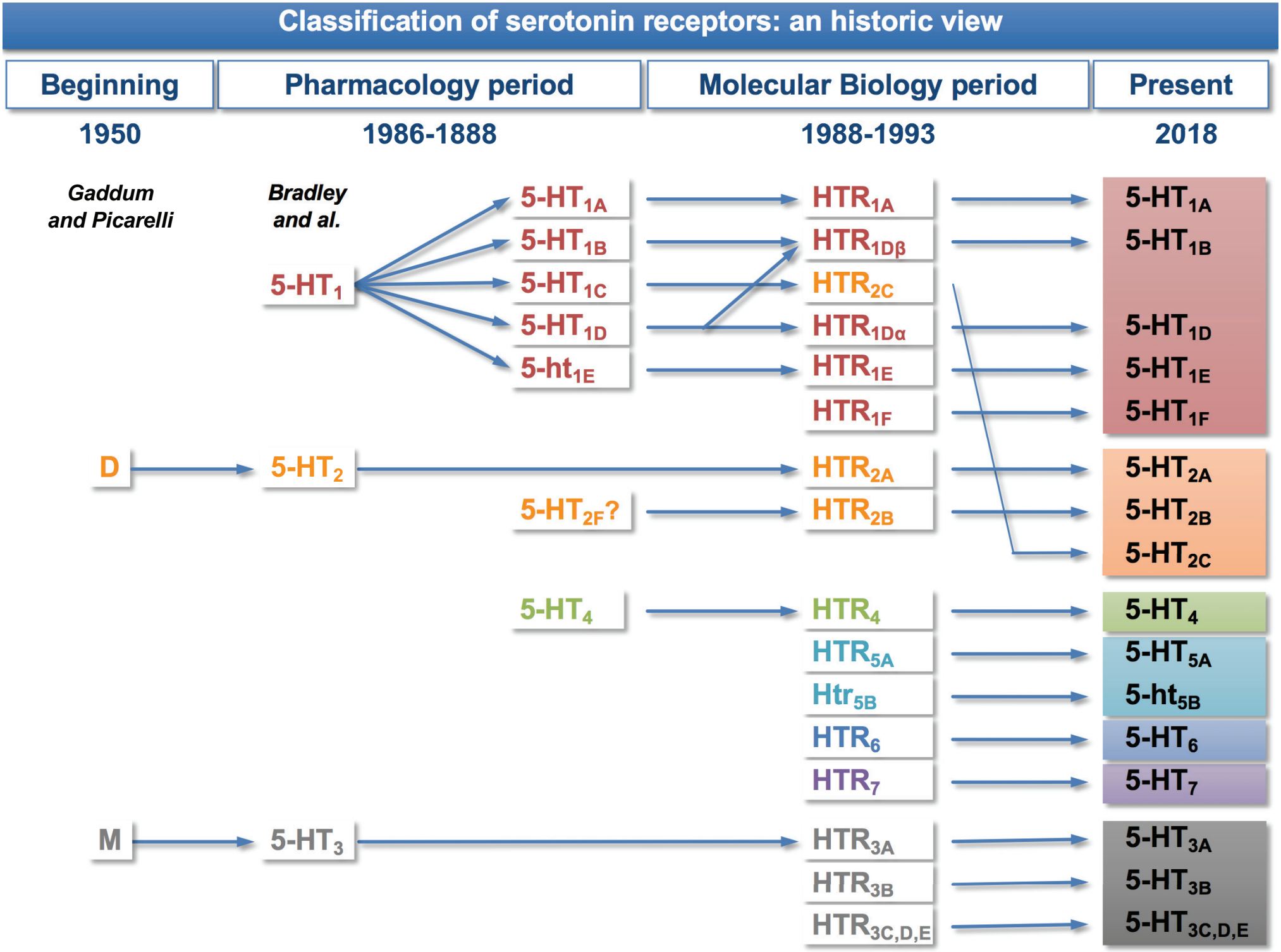
Table 1. 5-HT receptor heteromerization. The name of partner receptors, the methods used to demonstrate heteromerization *in vitro* and *in vivo*, its impact on receptor signal transduction properties and its physiological/pathological consequences are indicated. PLA, proximity ligation assay; LCA, luciferase complementation assay; BRET, bioluminescence resonance energy transfer; fcFRET, flow cytometry fluorescence resonance energy transfer, HTRF, homogeneous time-resolved fluorescence; FLIM, fluorescence-lifetime imaging microscopy.

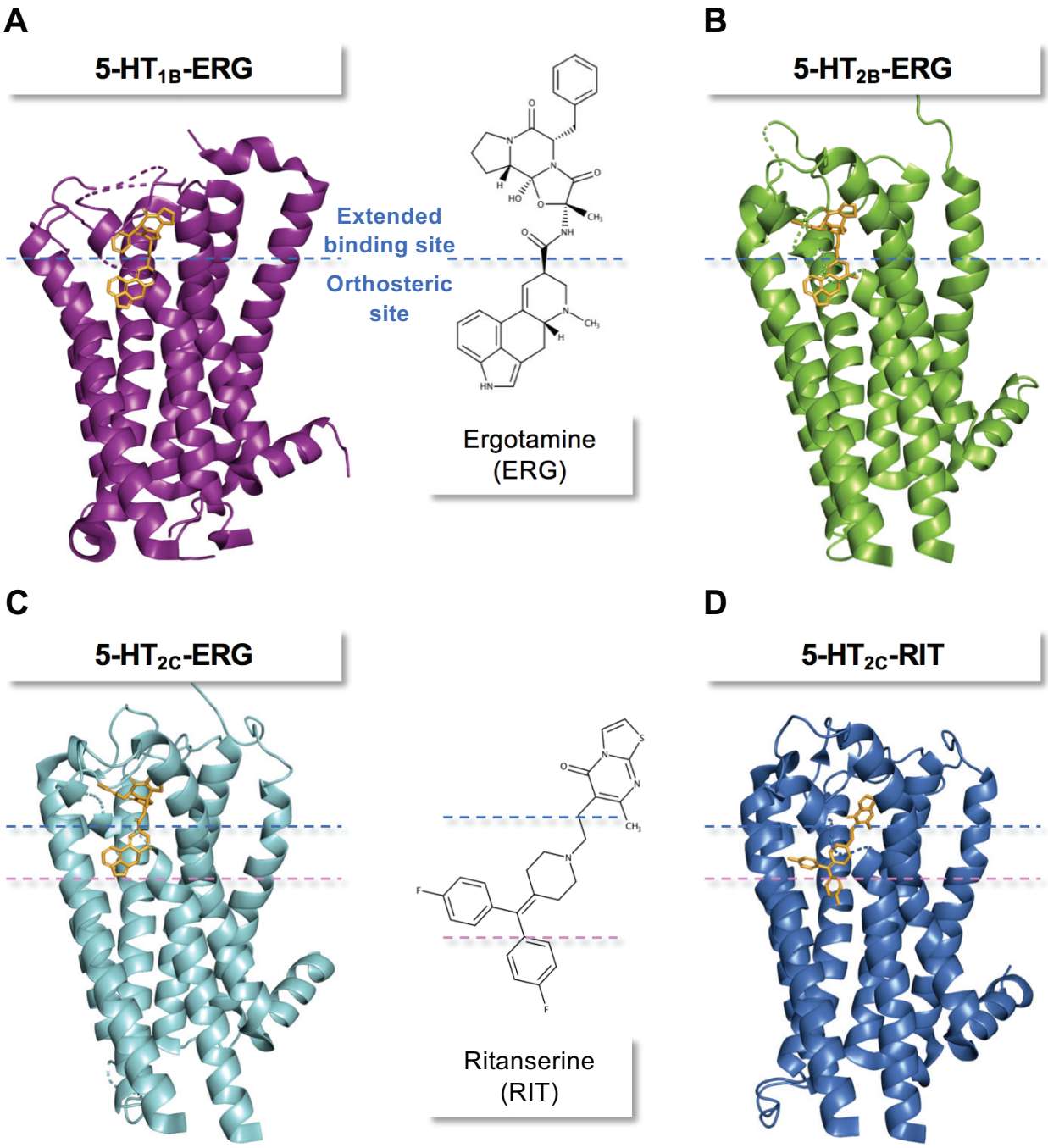
Receptor	Partner	Binding site	Function of the identified interaction	References
5-HT_{1A}	Calmodulin	Intracellular loop	Trafficking, signaling	(Turner et al., 2004)
	Yif1B	C-terminus	Trafficking, dendritic targeting	Carrel et al. 2008; Al Awabdh et al. 2012)
5-HT_{1B}	p11	Intracellular loop	Increases receptor cell surface expression and function, response to L-DOPA treatment, emotional memory	Svenningsson et al., 2006; Zhang et al. 2008; Eriksson et al., 2013)
5-HT_{2A}	PDZ proteins*	C-terminus	Targeting to dendrites	(Xia et al., 2003b)
	PSD-95	C-terminus	Trafficking, signaling, response to antipsychotics, neuropathic pain	(Xia et al., 2003a; Becamel et al. 2002, 2004; Abbas et al. 2009, Pichon et al., 2009, Vogrig et al., 2013)
	MUPP1	C-terminus		(Becamel et al., 2001)
	SAP97	C-terminus	Trafficking, signaling	(Becamel et al., 2004; Dunn et al. 2014)
	MAGI1-3	C-terminus	Internalization, signaling	(Becamel et al., 2004, Hammad et al., 2018)
	MPP3	C-terminus		(Becamel et al., 2004)
	CIPP	C-terminus		(Becamel et al., 2004)
	PDZK1/NHERF3		Trafficking, signaling	(Walther et al., 2015)
	Caveolin	Intracellular loop	Signaling	(Bhatnagar et al., 2004; Cogolludo et al., 2006)
	ARF1-6	Intracellular loop	Signaling	(Robertson et al., 2003)
	PLD1	Intracellular loop	Signaling	(Felder et al., 1999)
	Ribosomal S6 kinase	Intracellular loop	Receptor phosphorylation / Signaling	(Sheffler et al., 2006)
	Calmodulin	C-terminus / intracellular loop	Receptor phosphorylation / desensitization	(Turner & Raymond, 2005)
5-HT_{2B}	PDZ proteins*		NO signaling	(Manivet et al. 2000)
	MUPP1			(Becamel et al. 2001)
5-HT_{2C}	MUPP1	C-terminus	Receptor clustering, phosphorylation	(Ulmer et al., 1998; Bécamel et al., 2001; Parker et al. 2003)
	PSD-95	C-terminus	Trafficking	(Becamel et al., 2002, 2004)
	SAP97	C-terminus		(Becamel et al., 2004)

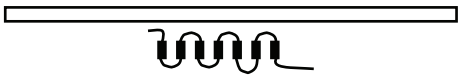
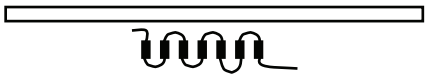
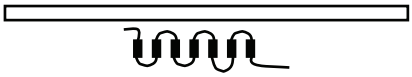
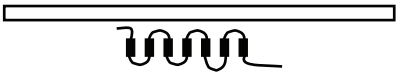
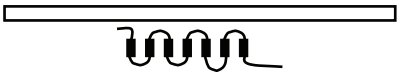
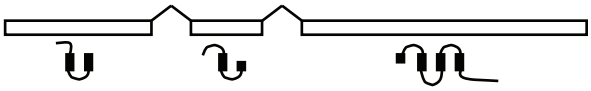
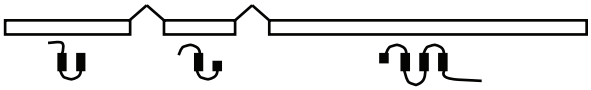
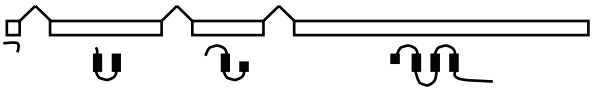
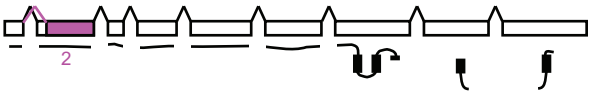
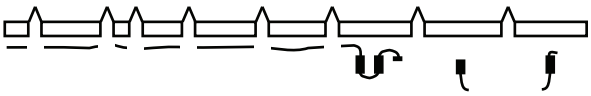
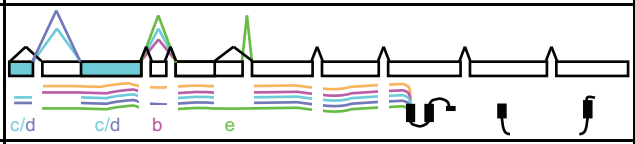
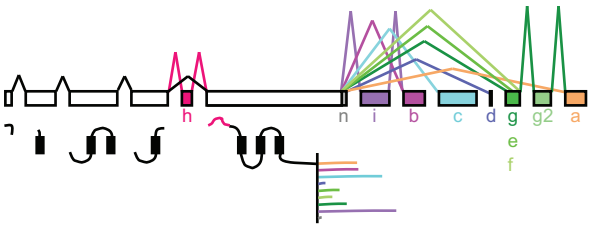
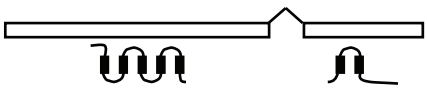
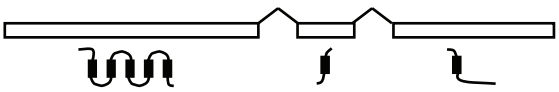
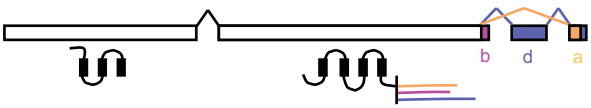
	SAP102	C-terminus		(Becamel et al., 2004)
	MAGI2	C-terminus		(Becamel et al., 2004)
	MPP3	C-terminus	Trafficking	(Becamel et al., 2002, 2004)
	Veli3/CASK/Mint1	C-terminus		(Becamel et al., 2002, 2004)
	Calmodulin	C-terminus	G protein-independent signaling	(Becamel et al., 2002, Labasque et al., 2006)
	PTEN	Intracellular loop	Receptor dephosphorylation, behavioral responses to drugs of abuse	(Ji et al., 2006)
	Ahi1		Receptor degradation	(Wang et al., 2012)
	CHL1	Intracellular loop	Signaling	(Kleene et al., 2015)
5-HT$_4$	P11	Intracellular loop	Trafficking, signaling, behavioral response to antidepressants	(Meschin et al., 2015; Warner-Schmidt et al., 2009)
	Src		β-arrestin-independent ERK1/2 activation	(Barthet et al., 2009)
	APP/ADAM10		Non-amyloidogenic APP processing	(Cochet et al., 2013)
5-HT$_{4(a)}$	SNX27	C-terminus	Targeting, trafficking	(Joubert et al., 2004)
	NHERF-1 (EBP50)	C-terminus	Targeting	(Joubert et al., 2004)
	MAGI2	C-terminus		(Joubert et al., 2004)
	MPP3	C-terminus		(Joubert et al., 2004)
	Veli1-3	C-terminus		(Joubert et al., 2004)
	CRMP2	C-terminus		(Joubert et al., 2004)
5-HT$_{4(d)}$	GPRIN2		Signaling	(Sokolina et al., 2017)
5-HT$_{4(e)}$	CIPP	C-terminus		(Joubert et al., 2004)
	nNOS	C-terminus		(Joubert et al., 2004)
	Sec23	C-terminus		(Joubert et al., 2004)
5-HT$_6$	Fyn	C-terminus	Signaling	(Yun et al., 2007)
	Jab 1	Intracellular loop / C-terminus	Trafficking, signaling	(Yun et al., 2010)
	mTOR	Intracellular loop / C-terminus	Signaling, cognition, epileptic seizures	(Meffre et al., 2012; Wang et al., 2015)
	Rheb	C-terminus	Signaling	(Meffre et al., 2012)

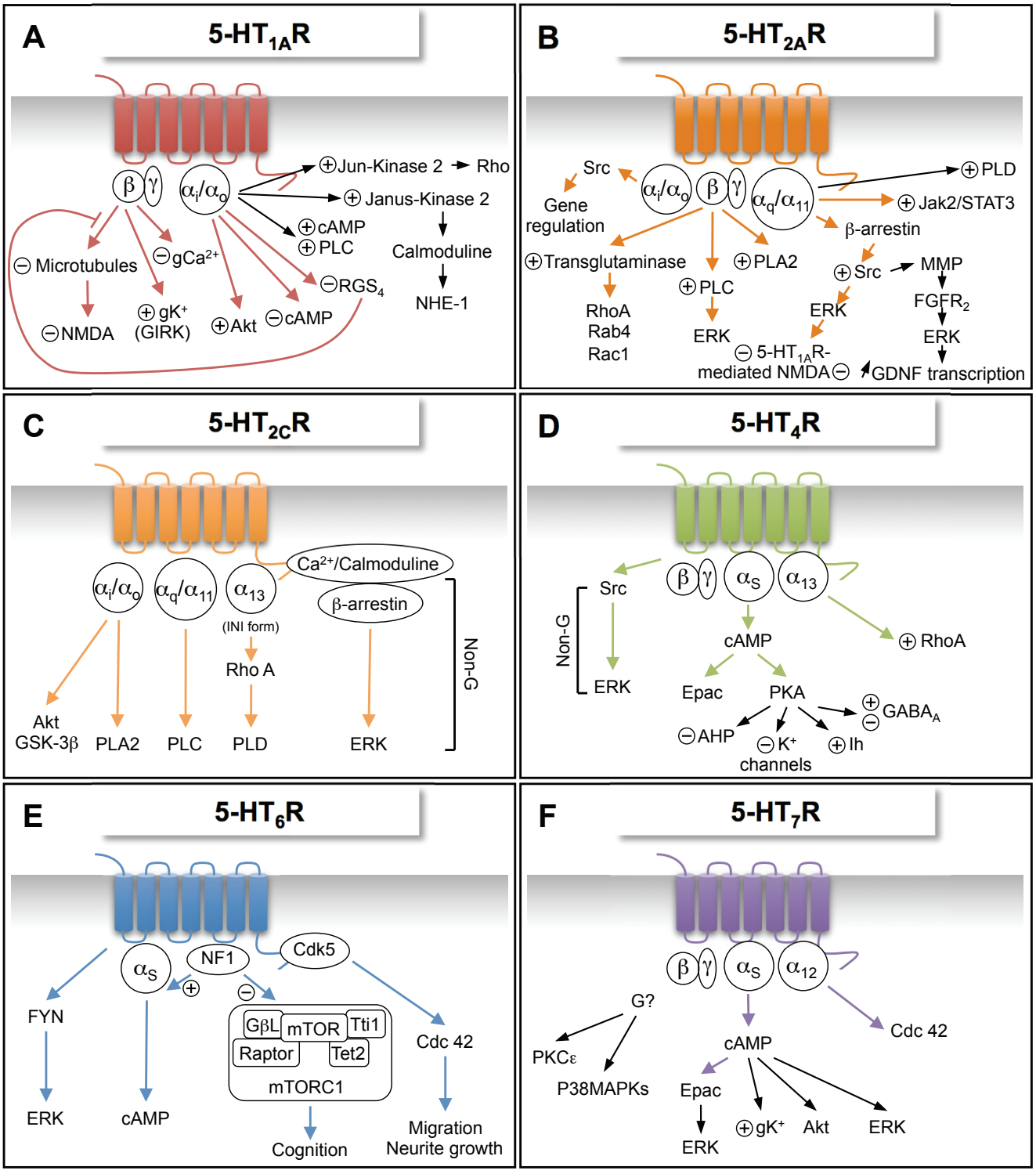
	Raptor		Signaling, cognition	(Meffre et al., 2012)
	Tti1			(Meffre et al., 2012)
	Tel2			(Meffre et al., 2012)
	Cdk5	C-terminus	Neuronal migration, neurite growth	(Duhr et al., 2014; Jacobshagen et al., 2014)
	Map1b	C-terminus	Trafficking, signaling	(Kim et al., 2014)
	Neurofibromin	C-terminus	Agonist-independent Gs signaling	(Deraredj-Nadim et al., 2016)
	SNX14	Intracellular loop	Receptor internalization/degradation	(Ha et al., 2015)
5-HT_7	RhoBTB3	C-terminus	Receptor stability	(Matthys et al., 2010)
	S100B	Intracellular loop	Behavioral response to fluoxetine	(Stroth & Svenningsson, 2015)
	CD44		Dendritic spine remodeling, synaptic pruning and impairment of LTP	(Bijata et al., 2017)

Table 2. **5-HT receptor interacting proteins and their impact upon receptor signal transduction and functions**. Only receptor subtypes for which interacting proteins have been unambiguously identified are mentioned. * Refers to experiments in which the receptor PDZ binding motif has been deleted.


Classification of serotonin receptors: an historic view
Beginning
Pharmacology period
Molecular Biology period
Present
1950
1986-1888
1988-1993
2018
Gaddum and Picarelli
Bradley and al.
5-HT1
5-HT1A
5-HT1B
5-HT1C
5-HT1D
5-ht1E
HTR1A
HTR1Dβ
HTR2C
HTR1Dα
HTR1E
HTR1F
5-HT1A
5-HT1B
5-HT1D
5-HT1E
5-HT1F
D
5-HT2
HTR2A
5-HT2F?
HTR2B
5-HT2A
5-HT2B
5-HT2C
5-HT4
HTR4
5-HT4
HTR5A
5-HT5A
Htr5B
5-ht5B
HTR6
5-HT6
HTR7
5-HT7
M
5-HT3
HTR3A
HTR3B
HTR3C,D,E
5-HT3A
5-HT3B
5-HT3C,D,E


A
5-HT1B-ERG
Extended binding site
Orthosteric site
Ergotamine (ERG)
B
5-HT2B-ERG
C
5-HT2C-ERG
Ritanserine (RIT)
D
5-HT2C-RIT

Gene	Gene structure	Gene products	Cds
HTR1A 5q12.3		5-HT$_{1A}$: 422aa	1269b
HTR1B 6q14.1		5-HT$_{1B}$: 390aa	1173b
HTR1D 1p36.12		5-HT$_{1D}$: 377aa	1134b
HTR1E 6q14.3		5-HT$_{1E}$: 365aa	1098b
HTR1F 3p11.2-p11.1		5-HT$_{1F}$: 366aa	1101b
HTR2A 13q14.2		5-HT$_{2A}$: 471aa	>65kb
HTR2B 2q37.1		5-HT$_{2B}$: 481aa	>17kb
HTR2C Xq23		5-HT$_{2C}$: 458aa	>325kb
HTR3A 11q23.2		5-HT$_{3A(a)}$: 510aa $_{(b)}$: 478aa, $_{(c)}$: 463aa	>15kb
HTR3B 11q23.2		5-HT$_{3B(1)}$: 441aa 5-HT$_{3B(2)}$: 430aa	>50kb
HTR3C 3q27.1		5-HT$_{3C}$: 447aa	>7kb
HTR3D 3q27.1		5-HT$_{3D(1)}$: 404aa $_{(2)}$: 279aa, $_{(3)}$: 454aa	>7kb
HTR3E 3q27.1		5-HT$_{3E(a)}$: 471aa $_{(b)}$: 456aa, $_{(c)}$: 441aa $_{(d)}$: 456aa, $_{(e)}$: 482aa	>6kb
HTR4 5q32		5-HT$_{4(a)}$: 387aa $_{(b)}$: 388aa, $_{(c)}$: 411aa, $_{(d)}$: 360aa, $_{(e)}$: 371aa, $_{(f)}$: 363aa, $_{(g)}$: 378aa, $_{(hb)}$: 402aa, $_{(i)}$: 428aa, $_{(n)}$:359aa	>203kb
HTR5A 7q36.2		5-HT$_{5A}$: 357aa	>17kb
Htr5b 2q14.1		Pseudogene	none
HTR6 1p36.13		5-HT$_{6}$: 440aa	>15kb
HTR7 10q23.31		5-HT$_{7(a)}$: 445aa 5-HT$_{7(b)}$: 432aa 5-HT$_{7(d)}$: 479aa	>119kb


A
5-HT1AR
β
γ
αi/αo
⊕Jun-Kinase 2
Rho
⊕Janus-Kinase 2
⊕cAMP
⊕PLC
Calmoduline
NHE-1
⊖Microtubules
⊖gCa2+
⊖RGS4
⊖NMDA
⊕gK+ (GIRK)
⊕Akt
⊖cAMP
B
5-HT2AR
Src
Gene regulation
αi/αo
β
γ
αq/α11
⊕PLD
⊕Jak2/STAT3
β-arrestin
⊕Transglutaminase
⊕PLA2
⊕Src
MMP
FGFR2
RhoA
Rab4
Rac1
⊕PLC
ERK
ERK
ERK
⊖5-HT1AR-mediated NMDA⊖
GDNF transcription
C
5-HT2CR
αi/αo
αq/α11
α13
(INI form)
Ca2+/Calmoduline
β-arrestin
Rho A
Non-G
Akt
GSK-3β
PLA2
PLC
PLD
ERK
D
5-HT4R
β
γ
αS
α13
Src
Non-G
ERK
cAMP
⊕RhoA
Epac
PKA
⊕⊖GABAA
⊖AHP
⊖K+ channels
⊕Ih
E
5-HT6R
αS
NF1
Cdk5
FYN
GβL
mTOR
Tti1
Raptor
Tet2
mTORC1
Cdc 42
ERK
cAMP
Cognition
Migration
Neurite growth
F
5-HT7R
β
γ
αS
α12
G?
Cdc 42
PKCε
P38MAPKs
cAMP
Epac
⊕gK+
Akt
ERK
ERK