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Serotonin 1A and Serotonin 4 Receptors: Essential Mediators of the Neurogenic and Behavioral Actions of Antidepressants

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Abstract

Selective serotonin reuptake inhibitors are the mostly widely used treatment for major depressive disorders and also are prescribed for several anxiety disorders. However, similar to most antidepressants, selective serotonin reuptake inhibitors suffer from two major problems: They only show beneficial effects after 2 to 4 weeks and only about 33% of patients show remission to first-line treatment. Thus, there is a considerable need for development of more effective antidepressants. There is a growing body of evidence supporting critical roles of 5-HT_{1A} and 5-HT_4 receptor subtypes in mediating successful depression treatments. In addition, appropriate activation of these receptors may be associated with a faster onset of the therapeutic response. This review will examine the known roles of 5-HT_{1A} and 5-HT_4 receptors in mediating both the pathophysiology of depression and anxiety and the treatment of these mood disorders. At the end of the review, the role of these receptors in the regulation of adult hippocampal neurogenesis will also be discussed. Ultimately, we propose that novel antidepressant drugs that selectively target these serotonin receptors could be developed to yield improvements over current treatments for major depressive disorders.

Keywords

major depressive disorders; neurogenesis; 5-HT_{1A} receptor; 5-HT_4 receptor; mood disorders; anxiety

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Introduction

Depressive and anxiety disorders are a major burden on society. Major depressive disorder (MDD) affects more than 20 million Americans every year and is currently the second leading cause of disability worldwide (Ferrari and others 2013; Kessler and others 2005). In addition, the World Health Organization predicts that depression will be the leading cause of disease burden globally by 2030 (World Health Organization 2011). MDD also displays high comorbidity with anxiety disorders. A reported 50% to 60% of patients with MDD also have a history of anxiety disorders that usually precede depression (Kaufman and Charney 2000). These findings raise the question of whether mood and anxiety disorders, despite the diagnostic distinctions made clinically, share a common pathophysiology.

Since the discovery and development of these medications, depression has been associated with impairment of serotonergic, noradrenergic, and to a lesser extent dopaminergic neurotransmissions. Most drugs that are currently used to treat MDD, such as selective serotonin reuptake inhibitors (SSRIs; the most commonly prescribed), activate serotonin neurotransmission and also are effective treatments for generalized anxiety (Burghardt and Bauer 2013; Samuels and others 2011; Schatzberg and Nemeroff 2009). SSRIs act as indirect agonists of serotonin receptors, blocking the serotonin transporter (SERT). After chronic SSRI treatment, serotonin (5-HT) is released throughout the forebrain by axons emanating from cell bodies located in the midbrain raphe (Barnes and Sharp 1999) (Figure 1A). The largely neuromodulatory effects of serotonin are mediated through 14 distinct receptor subtypes (heteroreceptors) located postsynaptic to serotonergic nerve terminals (Figure 1B). In addition, 5-HT levels are limited by two inhibitory autoreceptors (5-HT_{1A} and 5-HT_{1B}) expressed in the somatodendritic compartments (5-HT_{1A}) and nerve terminals (5-HT_{1B}) of the serotonergic raphe neurons (Barnes and Sharp 1999). However, it is largely unknown which of the 14 receptor subtypes actually mediate the clinical effects of SSRIs. While there is some evidence that 5-HT_2, 5-HT_3, 5-HT_6, and 5-HT_7 receptor subtypes may play roles in mood disorders and the treatment response (Middlemiss and others 2002), there is a wealth of historical and recent data implicating 5-HT_{1A} and 5-HT_4 receptors. This review summarizes the roles that 5-HT_{1A} and 5-HT_4 receptors play in mood disorders and the mechanisms underlying their antidepressant action. The impact of these receptors on adult hippocampal neurogenesis, a phenomenon that may be required for some of the clinical response to antidepressants, is also addressed.

5-HT_{1A} Receptor Expression Pattern and Signal Transduction

With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel, all serotonin receptors are G-protein coupled receptors containing seven hydrophobic transmembrane helices, three extracellular loops, and three intracellular loops that activate intracellular second messenger cascades to yield either excitatory or inhibitory responses (Hannon and Hoyer 2008) (Figure 2). The first evidence that there were multiple distinct 5-HT receptor types came in the late 1950s, when Gaddum and colleagues found that the effects of 5-HT in guinea pigs could be blocked in part by morphine and in part by dibenzyline (Gaddum and Picarelli 1957). By the late 1970s, radioligand binding studies were beginning to hint at the diversity of the 5-HT receptor family (Hannon and Hoyer 2008). Then, in the late 1980s, advances in molecular biology permitted cloning of the 5-HT_{1A} receptor (Fargin and others 1988; Kobilka and others 1987).

5-HT_{1A} heteroreceptors are expressed in the brain primarily in the septum, hippocampus, amygdala, thalamus, and hypothalamus, and in these areas are mainly located on pyramidal and granule neurons as well as GABAergic interneurons (Albert and others 1996; Garcia-Garcia and others 2014; Tanaka and others 2012) (Figure 3). At these postsynaptic sites, 5-HT_{1A} heteroreceptor activation is thought to primarily exert an inhibitory effect on the neuronal activity induced by various neurotransmitters (Hannon and Hoyer 2008; Li and others 1996). By contrast, 5-HT_{1A} autoreceptors are located on the soma and dendrites of serotonergic neurons in the dorsal and median raphe nuclei where they exert inhibitory control over raphe firing rates and 5-HT release through a negative feedback mechanism (Hannon and Hoyer 2008).

5-HT_{1A} receptors are coupled to G(i/o) type α subunits, which act on downstream effectors to induce inhibition of neuronal firing (Albert and others 1996). Specifically, the G(i/o) subunit inhibits adenylyl cyclase, which results in a reduction in cellular levels of cyclic adenosine monophosphate (cAMP), the closing of calcium channels, and a reduction in the intracellular calcium concentration.

Activation of 5-HT_{1A} receptors in different brain regions can yield at times opposing intracellular effects. This is because of the fact that different cell types express distinct Gα subunits. For example, 5-HT_{1A} autoreceptors in the dorsal raphe nuclei (DRN) primarily couple to Giα3, while heteroreceptors in the hippocampus primarily couple to Goα (Mannoury la Cour and others 2006). Therefore, the differential effects of 5-HT1A receptors are mediated both by distinct anatomical localizations and distinct inhibitory Gαi/o subunit couplings (Garcia-Garcia and others 2014; Polter and Li 2010).

5-HT_4 Receptor Expression Pattern and Signal Transduction

The 5-HT_4 receptor was originally identified by its pharmacology, which was unique among the serotonin receptor subtypes known at the time. In the late 1980s there was speculation that a novel 5-HT receptor subtype was expressed in collicular and hippocampal neurons that stimulated adenylyl cyclase activity and increased cAMP production. However, this receptor subtype was insensitive to known antagonists of the 5-HT_1, 5-HT_2, and 5-HT_3 receptor subtypes (Bockaert and others 1990; Bockaert and others 2004; Dumuis and others 1988). For several years, investigators thought that the 5-HT_3 and 5-HT_4 receptors were closely related because they have similar pharmacological profiles. The first ligands discovered for the 5-HT_4 receptor also had high affinity for the 5-HT_3 receptor (Bockaert and others 2004; Dumuis and others 1988; Eglen and others 1990). The 5-HT_4 receptor was finally recognized as a new serotonergic receptor subtype in 1992 and subsequently several ligands with high affinity and/or selectivity for this receptor subtype were developed. In the late 1990's, the gene encoding the 5-HT_4 receptor, which is exceptionally large and complex (700 kb, 38 exons), was simultaneously cloned in two different species (Bockaert and others 2004; Claeysen and others 1996; Gerald and others 1995). The 5-HT_4 receptor possesses three intracellular loops and three extracellular loops. The amino terminus is in the extracellular space and the carboxyl terminus (C-terminus) is in the cytoplasm (Figure 2).

The large and complex nature of the gene encoding the 5-HT_4 receptor results in several different isoforms, generated through alternative splicing of the gene, with distinct functional properties (Bockaert and others 2004; Claeysen and others 1999; Pindon and others 2002). The sequences of the different isoforms are identical throughout the first 358 residues, but then diverge, which results in differential G protein coupling (Bockaert and others 2004; Claeysen and others 1999). In brain and peripheral tissues, humans have at least six distinct variants of the 5-HT_4 receptor (a, b, c, g, i, and n), whereas mice are currently thought to have only four (a, b, e, and f) (Claeysen and others 1999). In addition to differences in G protein coupling, these distinct splice variants also show differences in the intracellular loops (i3 in particular), and in both phosphorylation and palmitoylation of the C-terminus (Barthet and others 2005). The exact functional roles of these distinct isoforms remain unresolved. However, numerous studies suggest that isoform-specific differences in 5-HT_4 receptors and their distribution impact the overall coupling and regulation of the receptor and, in turn, the potential for 5-HT_4 receptors to be targets for therapeutic intervention (Barthet and others 2005; Bohn and Schmid 2010; Marin and others 2012; Mnie-Filali and Pineyro 2012; Vilaro and others 2005).

The 5-HT_4 receptor plays important roles in the heart, gastrointestinal tract, adrenal gland, and urinary bladder, as well as in the central nervous system (Hegde and Eglen 1996). The development in 1993 of two specific radioligands for the 5-HT_4 receptor, the antagonists [^{3}H]-GR 113808 and [^{125}I]-SB 207710, revolutionized the study of this receptor. The usage of these radioligands in biochemical assays and autoradiography experiments permitted accurate determination of the regional distribution of 5-HT_4 receptors in the brain (Grossman and others 1993). The vast majority of 5-HT_4 receptors are expressed in the hypothalamus, hippocampus, nucleus accumbens, the ventral pallidum, amygdala, the basal ganglia, olfactory bulbs, frontal cortex, the septal area, the substantia nigra, and the fundus striatus (Bockaert and others 2004; Eglen and others 1995; Vilaro and others 1996; Vilaro and others 2005; Waeber and others 1993) (Figure 3). More specifically, 5-HT_4 receptors are located in somatodendritic compartments and in axon terminals of striatal spiny efferent neurons containing γ-aminobutyric acid (GABA) (Cai and others 2002; Compan and others 1996; King and others 2008). 5-HT_4 receptors are also expressed in glutamatergic pyramidal neurons in the medial prefrontal cortex and hippocampus (CA1, CA3) and in granule cells of the dentate gyrus (King and others 2008; Roychowdhury and others 1994; Tanaka and others 2012; Vilaro and others 2005). In the cortex, hippocampus, and amygdala, 5-HT_4 receptors are expressed in cholinergic neurons where the binding of selective agonists can stimulate the release of acetylcholine (Waeber and others 1994). Furthermore, recent work demonstrates that 5-HT_4 receptors are also expressed by efferent neurons of the nucleus accumbens that project to the lateral hypothalamus (Jean and others 2012).

Recent work has also used quantitative analyses of mRNA levels and polymerase chain reaction experiments in rat and guinea pig brains to determine the distribution of the 5-HT_4 receptor splice variants. 5-HT_4 receptor isoforms a, b, c, g, and n are highly expressed in the central nervous system (Bockaert and others 2004; Vilaro and others 2002; Vilaro and others

2005). Isoform (a) is highly expressed in the amygdala, hippocampus, nucleus accumbens, and caudate nucleus. Lower levels of expression are found in the small intestine, the atrium, and pituitary gland. Isoform (b) appears to be the most abundant form in the CNS and periphery, and is expressed in the caudate nucleus, putamen, amygdala, pituitary gland, and small intestine. Isoform (g) seems to be highly expressed in the hypothalamus and cortex and isoform (c) is highly expressed in the pituitary gland and small intestine. Lower levels of isoform (c) are found in the caudate nucleus, hippocampus, and putamen. Isoform (d) is not expressed in the CNS, but is found in the small intestine (Bockaert and others 2004; Vilaro and others 2005; Vilaro and others 2002). The 5-$HT_{4(n)}$ variant, which lacks the alternatively spliced C-terminal exon, is widely and abundantly expressed in human peripheral tissues and brain regions including areas involved in mood disorders (frontal cortex, hippocampus) (Vilaro and others 2002).

Roles of 5-HT_{1A} and 5-HT_4 Receptors in Mood Disorders and Treatment Response: Evidence from Clinical Studies

In general, across therapeutic areas, there is often an overall paucity of clinical data that link the pharmacodynamic effects of drugs to the underlying disease or to treatment response. However, several recent complementary studies support important roles of the 5-HT_{1A} and 5-HT_4 receptors in the treatment of anxiety and/or depression (Lucas 2009; Lucas and others 2007; Mendez-David and others 2014; Pascual-Brazo and others 2012). Electrophysiology, behavioral, and binding studies in different brain regions all suggest that 5-HT_{1A} and 5-HT_4 receptors play a role in the pathophysiology of mood disorders and in the treatment response (Licht and others 2009; Lucas 2007; Lucas and others 2009).

For 5-HT_{1A} receptors, human genetic and imaging studies demonstrate that differences in receptor levels and regulation are associated with depression, anxiety, and the response to antidepressants (Le Francois and others 2008; Lesch and Gutknecht 2004; Strobel and others 2003). Postmortem analyses of brainstem samples from depressed suicide patients show a significant increase in levels of 5-HT_{1A} autoreceptors compared wth non-depressed control individuals, especially in the dorsal raphe nuclei (Boldrini and others 2008; Stockmeier and others 1998). Positron emission tomography (PET) studies have yielded some contrasting results when attempting to confirm these data, but this may be due to differences in the characteristics of the populations studied (Descarries and Riad 2012; Drevets and others 2007; Meltzer and others 2004; Parsey and others 2006b; Parsey and others 2010). One of the most recent PET studies, which used a method that made the fewest possible assumptions about nonspecific binding and also used a reference region that did not express 5-HT_{1A} receptors, indeed found that 5-HT_{1A} receptor binding potential was higher in antidepressant-naïve major depressive disorder subjects than in control subjects (Parsey and others 2010). Importantly, these PET findings indicate that 5-HT_{1A} auto- and heteroreceptors are both affected in MDD, but do not decipher whether alterations in binding are causal or a consequence of the disorder.

A C(−1019)G polymorphism in the promoter of the gene encoding the 5-HT_{1A} receptor is associated with several mood-related variables, including trait anxiety, depression, and the response to chronic antidepressant treatment (Fakra and others 2009; Le Francois and others

2008). Depressed patients are more likely to be homozygous for the GG genotype at the C(−1019) allele. They are also more likely to have higher 5-HT$_{1A}$ binding potential (Lemonde and others 2003; Parsey and others 2006b). Furthermore, higher 5-HT$_{1A}$ binding potential and the GG genotype also predict remission failure to antidepressant treatment (Parsey and others 2006a). Taken together, these clinical findings strongly implicate an essential role for 5-HT$_{1A}$ receptors in both the pathophysiology of mood disorders and in the response to antidepressants.

For 5-HT$_4$ receptors, there are two studies suggesting a role in clinical depression. One study reported that polymorphisms in the splice variant region of the gene encoding the 5-HT$_4$ receptor are associated with unipolar depression (Ohtsuki and others 2002). The second study revealed alterations in both 5-HT$_4$ receptor binding and cAMP concentration levels in several brain regions of depressed violent suicide victims (Rosel and others 2004). These results, while more preliminary than the collection of data from the 5-HT$_{1A}$ studies, also implicate a role for 5-HT$_4$ receptors in mood disorders.

Roles of 5-HT$_{1A}$ Receptors in Mood Disorders and Treatment Response: Evidence from Preclinical Studies

In addition to the clinical studies, there is a wealth of preclinical data from rodent studies that indicate a role for 5-HT$_{1A}$ receptors in mood disorders and treatment response. Initial preclinical studies led to the hypothesis that 5-HT$_{1A}$ autoreceptors delay the therapeutic action of SSRIs and other drugs that increase serotonin levels (Blier and others 1998). More specifically, since 5-HT$_{1A}$ autoreceptors exert negative feedback inhibition in response to increased serotonin levels, progressive autoreceptor desensitization may underlie the delayed onset of SSRIs (Blier and others 1998; Gardier and others 1996; Richardson-Jones and others 2010). The functional desensitization of 5-HT$_{1A}$ autoreceptors is because of decreased levels of G(o) proteins following chronic SSRI treatment (Li and others 1996), and not down-regulation of the receptor (Le Poul and others 1995). In rats treated for up to 21 days with SSRIs (either fluoxetine or paroxetine), in vitro recordings show attenuation of the inhibitory effects of 8-OH-DPAT (a 5-HT$_{1A}$ receptor agonist) on firing rates of DRN 5-HT neurons that develops over time (Le Poul and others 1995). Therefore, with sustained SSRI treatment the firing rates of DRN 5-HT neurons initially decreases because of 5-HT$_{1A}$ autoreceptor-mediated inhibition, but then recovers as the receptors desensitize, and is fully restored by 14 days after the initiation of the chronic SSRI treatment (Blier and others 1990; Czachura and Rasmussen 2000). Chronic treatment with 5-HT$_{1A}$ receptor agonists also produces desensitization of somatodendritic 5-HT$_{1A}$ autoreceptors as indicated by electrophysiological and in vivo microdialysis studies (Blier and de Montigny 1987; Kreiss and Lucki 1997). Interestingly, local administration in the dorsal raphe of the 5-HT$_{1A/1B}$ receptor antagonist, WAY-100635, or (±)-pindolol potentiates the effects of paroxetine on mouse cortical extracellular dialysate 5-HT levels ([5-HT]$_{ext}$), which suggests that the onset of action of antidepressant treatment is mediated by somatodendritic 5-HT$_{1A}$ autoreceptors (Guilloux and others 2006). A more recent study suggests that 5-HT$_{1A}$ autoreceptor desensitization alone is not sufficient to induce a SSRI response. Rather, serotonergic tone, governed by intrinsic autoreceptor levels prior to the onset of treatment, is critical for establishing responsiveness and the onset of the SSRI response (Richardson-Jones and others 2010).

Several studies have used 5-HT_{1A} receptor germline deficient mice to investigate the role of these receptors in anxiety and depression-related behavior. However, these studies are confounded by the fact that they cannot distinguish between the effects of auto- and heteroreceptors. Generally these studies have found a robust anxiety-like phenotype in conflict anxiety paradigms and a decrease in behavioral despair in the forced swim and tail suspension test (Heisler and others 1998; Klemenhagen and others 2006; Mayorga and others 2001; Parks and others 1998; Ramboz and others 1998). In addition, other studies have used mice that are germline deficient for 5-HT_{1A} receptors to determine that 5-HT_{1A} receptors are required for some (Mayorga and others 2001; Santarelli and others 2003), but not all (Holick and others 2008), behavioral effects of antidepressants. More specifically, constitutive 5-HT_{1A} receptor knockout mice do not respond to acute administration of the SSRIs fluoxetine and paroxetine in the tail suspension test (Mayorga and others 2001), or to chronic treatment with fluoxetine in the novelty-suppressed feeding paradigm (Santarelli and others 2003).

More recent studies have used mice engineered to specifically manipulate either auto- or heteroreceptors while preserving the other receptor population. One study used a conditional and inducible transgenic strategy to assess 5-HT_{1A} receptor gain-of-function by conferring temporal and spatial control over receptor expression. This study found that postsynaptic 5-HT_{1A} receptors expressed during a specific developmental window (from postnatal day 5 to 21) are important for establishing normal anxiety-like behavior in the adult mouse (Gross and others 2002). More specifically, spatially selective overexpression of postsynaptic 5-HT_{1A} receptors in the hippocampus and cortex on the knockout mouse background results in mice that perform similarly to wild-type controls in anxiety-related tasks. However, interpretation of these results is slightly confounded by the approach that used ectopic overexpression. More recently, another study developed a genetic system to independently decrease levels of the 5-HT_{1A} auto- and heteroreceptor populations (Richardson-Jones and others 2011). In this study, 5-HT_{1A} autoreceptors affected anxiety-like behavior, while 5-HT_{1A} heteroreceptors affected behavioral despair responses. Ultimately, these lines of work are in their infancy and future studies are necessary to investigate not only autoversus heteroreceptor populations but also subpopulations of heteroreceptors and the temporal roles of all of the different populations.

There are also pharmacological data suggesting a role for 5-HT_{1A} receptors in mood disorders and the response to antidepressant and anxiolytic treatments (Table 1). 5-HT_{1A} receptor agonists induce behavioral effects that are comparable to antidepressant drugs (Blier 2003; Lucki 1991; Santarelli and others 2003). In addition, buspirone and 8-OH-DPAT are 5-HT_{1A} receptor agonists that reduce anxiety (Barrett and Vanover 1993; Griebel 1995; Tunnicliff 1991). Drugs that target 5-HT_{1A} receptors, such as pindolol, have led to somewhat disappointing results in clinical trials (McAskill and others 1998). However, a large-scale clinical study found that buspirone was equally effective as other drugs, such as the dopaminergic agent bupropion, when used as an augmentation therapy for depressed patients that did not remit on initial treatment with a SSRI (Warden and others 2007).

Ultimately, given the differences between auto- and heteroreceptors regarding their distribution and function in the brain, it is now clear that future treatments targeting 5-HT_{1A} receptors will need to specifically target only one of these populations of receptors to improve the antidepressant response.

Roles of 5-HT_4 Receptors in Mood Disorders and Treatment Response: Evidence from Preclinical Studies

The understanding of the roles that 5-HT_4 receptors play in mood disorders also mainly comes from preclinical studies. Animal models of anxiety/depression such as the Flinders sensitive line of rats, olfactory bulbectomy, glucocorticoid receptor heterozygous mice (GR +/−), and maternal prenatal stress, show changes in 5-HT_4 receptor density in limbic areas such as the hippocampus and the caudal portion of the caudate-putamen complex (Chen and others 2012; Licht and others 2010; Licht and others 2009; Ridder and others 2005). Similarly, some chronic monoaminergic antidepressant drugs, such as fluoxetine or venlafaxine, but not reboxetine, decrease 5-HT_4 receptor density in rat brain (Vidal and others 2010).

Further studies investigated whether 5-HT_4 receptor ligands can directly exert antidepressant-like effects or modify the effects of monoaminergic antidepressants (Table 2). In naïve rats, acute fluoxetine-induced decreases in immobility in the forced swim test (FST) are not affected by co-administration of the 5-HT_4 receptor antagonist SB 204070A. In addition, this antagonist has no independent effects in the FST (Cryan and Lucki 2000). Conversely, in a model of anxiety/depression based on chronic elevation of glucocorticoids, a brain penetrant 5-HT_4 receptor antagonist (GR 125487) prevents the effects of the SSRI fluoxetine in Open Field, Tail Suspension Test, Novelty Suppressed Feeding, and the Sucrose Splash test (Mendez-David and others 2014). These results suggest that the antidepressant-like effects of SSRIs are mediated in part through activation of 5-HT_4 receptors. In addition, 5-HT_4 receptor activation with the partial agonist RS 67333 increases the effects of acute SSRI (paroxetine) administration on extracellular 5-HT levels in rat ventral hippocampus (Licht and others, 2010). These increased 5-HT levels are observed both immediately and 3 days after administration (Licht and others 2009; Licht and others 2010). 5-HT_4 receptors are only localized postsynaptic to serotonergic nerve terminals and thus are heteroreceptors. An in vivo electrophysiology study demonstrated that 5-HT_4 receptors exert excitatory influence on central 5-HT neuron activity (Lucas and others 2005). These data suggest that frontocortical 5-HT_4 receptors exert positive feedback on serotoninergic activity by controlling a population of DRN 5-HT neurons.

In addition, administration of 5-HT_4 receptor agonists induces similar molecular and behavioral changes as SSRI antidepressants in rodents (Bockaert and others 2008; Lucas and others 2007; Pascual-Brazo and others 2012). Lucas and colleagues showed that administration of the 5-HT_4 receptor agonists RS 67333 and prucalopride reduce immobility time in rats exposed to the FST by about 50% compared with controls, whereas citalopram only reduces immobility time by about 23%. Additional behavioral experiments also found that the 5-HT_4 receptor agonist RS 67333 is more effective than citalopram in the Rat Forced Swim test and also increases the locomotor activity induced by olfactory bulbectomy

(Lucas and others 2007). Depressed-like behavioral phenotypes observed with olfactory bulbectomy or exposure to chronic mild stress are reversed by 10 to 14 days of RS67333 treatment in rats, suggesting that RS67333 displays a faster antidepressant-like response relative to classical antidepressants (Lucas and others 2007). In addition, short periods of RS 67333 treatment results in antidepressant/anxiolytic-like effects in the sucrose consumption test of anhedonia, in socially defeated mice exposed to the FST, and in the novelty suppressed feeding test in rats (Gomez-Lazaro and others 2012; Pascual-Brazo and others 2012) (Table 2).

In addition, activation of 5-HT_4 receptors mediates several intracellular changes that are associated with the antidepressant drug response. These changes include increases in cAMP levels, protein kinase A activation, phosphorylation of cAMP response element–binding protein (CREB), and transcription of brain-derived neurotrophic factor (BDNF) (Pascual-Brazo and others 2012) (Nibuya and others 1995). Therefore, mechanistic data also suggest that direct activation of 5-HT_4 receptors yield antidepressant-like effects (Lucas and others 2007; Pascual-Brazo and others 2012; Tamburella and others 2009). Furthermore, signaling molecules that interact with the 5-HT_4 receptor, such as P11 (S100A10), in brain regions important for anxiety/depression and cognition such as hippocampal pyramidal cells in CA1 and the hippocampal granule cells in the dentate gyrus (Egeland and others 2011; Warner-Schmidt and others 2009) may provide novel targets for fast-acting anxiolytic/antidepressant treatments. Recent results suggest that cortical neurons expressing both P11 and 5-HT_4 receptors regulate the behavioral effects of SSRIs in mice and that chronic treatment with fluoxetine increases 5-HT_4 receptor expression in these neurons (Schmidt and others 2012). In addition, in behavioral tests such as FST and tail suspension test (TST), the antidepressant-like activity of RS67333 was abolished in P11 knockout mice (Warner-Schmidt and others 2009). Taken together, these studies suggest a link between the 5-HT_4 receptor and depression and provide an encouraging pharmacological strategy to obtain a faster treatment response.

Some historical studies also investigated whether 5-HT_4 receptors mediate the anxiolytic behavioral effects of SSRIs. However, these studies were unable to determine a clear role for 5-HT4 receptors in anxiety. For instance, in the light/dark choice test, diazepam induces dose-dependent anxiolytic-like effects in mice that are inhibited by 5-HT_4 receptor antagonists (GR 113808, SB 204070, and SDZ 205–557) (Costall and Naylor 1997). These data suggest that activation of 5-HT_4 receptors mediate the anxiolytic effects of diazepam. In addition, while this study did not find any effects of 5-HT_4 receptor antagonists alone on anxiety behavior (Costall and Naylor 1997), others report anxiogenic effects of the 5-HT_4 receptor antagonists SB 204070, GR 113808 (Silvestre and others 1996) and SB 207266A (Kennett and others 1997; Silvestre and others 1996) in the elevated plus maze in rats. In these studies, rats acutely treated with SB 204070 or GR 113808 display an increase in the percentage of total time spent in the open arms, which is indicative of anxiety-like behavior. However, while one study did not detect an effect of the antagonists SB 204070 and GR 113808 on the number of open arm entries when a 10 minute pretest injection interval was used (Silvestre and others 1996), another study reported an increase in the percent of open arm entries after SB 204070 or SB 207266A injections when a one hour pretest injection interval was used (Kennett and others 1997). 5-HT_4 receptor knockout mice do not display an anxious or depressed-like phenotype, but they do show an attenuated response to novelty that may be relevant for mood disorders (Compan and others 2004). In a more recent study, chronic treatment with GR125487 did not affect the anxiety-like phenotype induced by chronic corticosterone treatment in mice (Mendez-David and others 2014). Interestingly, this study found that, while a 7-day treatment with fluoxetine or RS67333 induced antidepressant-like activity in the TST and FST, only the 5-HT_4 receptor agonist RS67333 displayed an anxiolytic-like activity in the Open Field paradigm and the Elevated Plus Maze. By contrast, a longer duration of treatment (28 days) was required for fluoxetine to exert anxiolytic-like effects in these tests. These data support the idea that 5-HT_4 receptor agonists may treat anxiety and depression disorders with faster efficacy than traditional antidepressants.

Other investigations have found that 5-HT_4 receptor stimulation inhibits the anxiolytic effects of diazepam (an enhancer of GABA response), particularly under conditions of high serotonergic tone (Costall and others 1993). Since $GABA_A$ receptor-mediated inhibition of synaptic transmission is highly involved in controlling neuronal excitability, and $GABA_A$ receptors are implicated in the pathogenesis of anxiety disorders (Cai and others 2002; Macdonald and Olsen 1994), these data suggest that 5-HT_4 receptors may also act on GABAergic signaling in PFC neurons. Taken together, these studies demonstrate that 5-HT_4 receptors are important mediators of the antidepressant response. Future work, involving spatially restricted deletions of 5-HT_4 receptors or local administration of pharmacological ligands, is necessary to more precisely determine the cellular and circuit-based mechanisms by which 5-HT_4 receptors influence behavior.

Roles of 5-HT_{1A} and 5-HT_4 Receptors in Mediating Adult Hippocampal Neurogenesis

It is well established that new neurons are continuously generated and incorporated into the functional neural network of the mammalian adult brain through a process referred to as adult neurogenesis (Spalding and others 2013). More specifically, neurogenesis occurs in the subventricular zone (SVZ) of the lateral ventricle and in the subgranular zone (SGZ) of the dentate gyrus in most adult mammals (Ming and Song 2005). Adult hippocampal neurogenesis in the SGZ has gained considerable attention over the last decade and a half as a neural substrate potentially underlying the pathophysiology of depression (Figure 4A and B). Most antidepressants, including SSRIs, are potent stimulators of adult hippocampal neurogenesis when administered chronically. Antidepressant treatment increases the proliferation of newborn cells as well as the survival and maturation of the young neurons (Malberg and others 2000; Santarelli and others 2003). The neurogenesis hypothesis originally posited that a decrease in the production of newborn dentate granule cells leads to depression, while enhanced neurogenesis (proliferation, survival, and maturation) is required for treatment of depression (Duman and others 2000; Jacobs and others 2000; Sahay and others 2007; Samuels and Hen 2011). Evidence suggests that this hypothesis is partially correct since adult hippocampal neurogenesis is indeed necessary for some of the behavioral effects of antidepressants (David and others 2009; Santarelli and others 2003; Surget and others 2008; Wang and others 2008). In addition, while no evidence has yet shown that decreasing the production of newborn dentate granule cells leads to depression, a large body of evidence also suggests that mental illness is often marked by diminishments in hippocampal structure and function. For example, patients with depression, posttraumatic stress disorder, schizophrenia, Alzheimer's disease, or stress show decreased hippocampal volume, learning and memory deficits, and mood dysregulation (Nestler and others 2002; Sapolsky 2000). Interestingly, both 5-HT_{1A} and 5-HT_4 receptors are implicated in regulating adult hippocampal neurogenesis.

The Role of 5-HT_{1A} Receptors in Mediating Adult Hippocampal Neurogenesis

Several studies, when taken together, suggest that activation of 5-HT_{1A} receptors increases adult hippocampal neurogenesis (Table 3). The first evidence that 5-HT_{1A} receptors regulated adult hippocampal neurogenesis came from a study assessing the effects of acute administration of antagonists on cell proliferation in the rat dentate gyrus. In this study, three different 5-HT_{1A} antagonists (NAN-190, p-MPPI, and WAY-100635) all resulted in an approximately 30% reduction in the number of BrdU-positive cells (Radley and Jacobs 2002), a marker of cell proliferation. A later study then found that the 5-HT_{1A} and 5-HT_7 receptor agonist 8-OH-DPAT not only increases cell proliferation in the dentate gyrus but can also reverse decreases in cell proliferation induced by a 5-HT synthesis inhibitor, *para*-cholorophenylalanine (Banasr and others 2004). Other 5-HT_{1A} receptors partial agonists, buspirone or tandospirone, increases the number of newborn cells and the number of DCX-positive cells in the DG respectively (Grabiec and others 2009; Mori and others 2014). In addition, an in vitro study found that 5-HT_{1A} receptors regulate self-renewal of precursor cells (Klempin and others 2010).

Another study investigated whether chronic treatment with various antidepressants enhances adult hippocampal neurogenesis in germline 5-HT_{1A} receptor knockout mice (Santarelli and others 2003). Interestingly, while the effects of tricyclic antidepressants remain intact, the effects of the SSRI fluoxetine on both adult hippocampal neurogenesis (newborn cell proliferation) and behavior are abolished in 5-HT_{1A} receptor knockout mice. Taken together, these data suggest that 5-HT_{1A} receptors are critical mediators of the effects of SSRIs on adult hippocampal neurogenesis and behavior. In addition, this study also showed that the effects of the 5-HT_{1A} and 5-HT_7 agonist 8-OH-DPAT are also abolished in 5-HT_{1A} receptor knockout mice, confirming the importance of 5-HT_{1A} receptors in mediating serotonin-induced enhancements in neurogenesis in the adult DG of the hippocampus.

Mice with decreased 5-HT_{1A} autoreceptor levels still show a behavioral and neurogenic response to chronic antidepressants (Richardson-Jones and others 2010), suggesting that 5-HT_{1A} heteroreceptors mediate the effects of increased serotonin neurotransmission on neurogenesis and behavior. Future studies are required to determine the anatomical location of the 5-HT_{1A} heteroreceptor population that mediates these effects.

The Role of 5-HT$_4$ Receptors in Mediating Adult Hippocampal Neurogenesis

5-HT$_4$ receptor agonists also can induce neurogenesis in the hippocampus as well as in the enteric system in adult rodents (Ishizuka and others 2014; Liu and others 2009; Lucas and others 2007; Pascual-Brazo and others 2012). Interestingly, the beneficial effects of 5-HT$_4$ receptor agonists seem to appear faster than traditional antidepressants not only on behavior but also on adult hippocampal neurogenesis (Table 4). A recent study performed in naive, non-stressed rats confirmed that 3 days of treatment with the 5-HT$_4$ receptor agonist (RS67333) significantly enhanced neurogenesis in the subgranular zone of the dentate gyrus of the hippocampus, an effect that requires at least 2 weeks of treatment with classical antidepressants such as SSRIs (Pascual-Brazo and others 2012). However, no direct evidence currently links the antidepressant-like behavioral effects of 5-HT$_4$ receptor activation to increased adult hippocampal neurogenesis. A recent study found that the 5-HT$_4$ receptor agonist RS67333 increases neurogenesis (proliferation and maturation) to a lesser extent than fluoxetine and that the 5-HT$_4$ antagonist GR125487 partially blocks the neurogenic effects of chronic fluoxetine treatment (Mendez-David and others 2014). Taken together, these results suggest that while 5-HT$_4$ receptors contribute to the effects of fluoxetine on proliferation and maturation of newborn neurons other 5-HT receptors, such as the 5-HT$_{1A}$ receptor, are also important.

Recent work also indicates that 5-HT$_4$ receptor activation may result in antidepressant-induced dematuration of mature dentate granule cells (Kobayashi and others 2010). This study found that upregulation of 5-HT$_4$ receptor induced cAMP signaling may play an instructive role in the reversal of neuronal maturation induced by chronic antidepressant treatment (Kobayashi and others 2010). However, the exact mechanisms underlying this phenomenon will require further investigation using spatially restricted 5-HT$_4$ receptor knockout mice.

Analysis of 5-HT$_4$ receptor-mediated intracellular signaling further suggests that targeting this receptor yields antidepressant-like effects. More specifically, 5-HT$_4$ receptors are G(s)-coupled G-protein coupled receptors that activate adenylyl cyclase, and thus increase production of cAMP (Dumuis and others 1989; Torres and others 1995). Increased production of cAMP activates protein kinase A, which in turn phosphorylates the transcription factor CREB. Interestingly, chronic antidepressant drug treatment activates the same signal transduction machinery (Nibuya and others 1996). Phosphorylation of CREB is thought to constitute a key step in the facilitation of adult hippocampal neurogenesis as it results in increased BDNF levels (Castren 2014; Duman and others 2001; Malberg and others 2000). Increased BDNF levels can modulate behavior, promote neurite outgrowth and synaptic plasticity, and enhance survival of new neurons (Duman and Monteggia 2006). Therefore, since activation of 5-HT$_4$ receptors ultimately increases BDNF expression, it is a reasonable target to achieve antidepressant-like effects. Interestingly, BDNF levels are increased in the rat hippocampus after only 3 days of treatment with the 5-HT$_4$ receptor agonist RS67333 (Pascual-Brazo and others 2012). Another study found that acute administration of the 5-HT$_4$ partial receptor agonist SL65.0155 also increases BDNF levels in rats (Tamburella and others 2009). These preclinical studies, when combined with behavioral test results, indicate that 5-HT_4 receptors provide a putative target for faster acting antidepressants.

Conclusions

Taken together, much evidence indicates that SSRIs mediate some of their effects through both 5-HT_{1A} and 5-HT_4 receptors, thus being reasonable targets for future antidepressant drug development. However, 5-HT_{1A} receptors in different anatomical locations show distinct brain functions, and therefore it may be necessary to selectively target subpopulations of these receptors to attain the optimal therapeutic outcome. In addition, the localization of 5-HT_4 receptors may also be a critical consideration for drug targeting since these receptors also play important roles outside the central nervous system. More specifically, 5-HT_4 receptors are also expressed in cardiac and intestinal tissues and administration of 5-HT_4 receptor agonists can lead to arrhythmia (Ferrari and others 2013). Thus, future antidepressants should target either specific anatomical populations of 5-HT_{1A} and 5-HT_4 receptors or downstream effectors. To this end, recently developed 5-HT_{1A} receptor agonists seem to preferentially target 5-HT_{1A} receptor subpopulations (Garcia-Garcia and others 2014). If the appropriate 5-HT_{1A} heteroreceptor population can be targeted, then these agonists may be faster acting antidepressants that avoid the delays caused by autoreceptor-mediated feedback inhibition of serotonergic tone observed following chronic administration of SSRIs. In addition, signaling molecules that interact with the 5-HT_4 receptor, such as P11, may also represent novel targets for faster-acting antidepressant activity (Egeland and others 2011; Warner-Schmidt and others 2009). Perhaps novel multitarget-directed ligands with both 5-HT_{1A} and 5-HT_4 agonistic properties could also yield more effective antidepressants.

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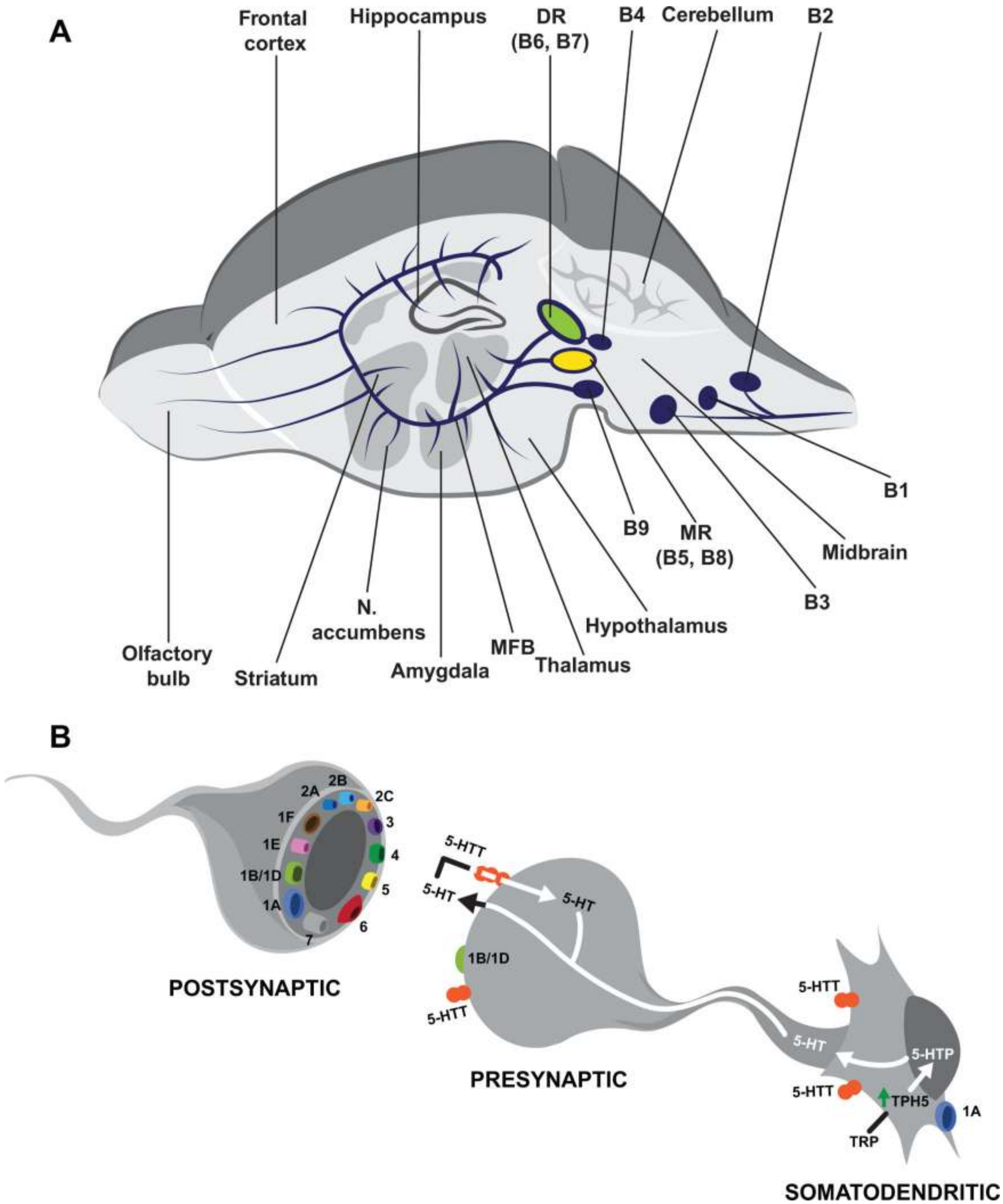

Figure 1.

Serotoninergic system in rodent brain. (A) The serotoninergic system is organized in nine raphe nuclei (from B1 to B9). B1 to B3 nuclei project axons to the spinal cord and the periphery, Dorsal raphe nuclei (DR, B6–B7), Medial Raphe nuclei (MR, B5, B8), and the B9 nucleus project throughout the brain. (B) Steps involved in the synthesis and release of serotonin. Serotonin (5-HT) synthesis depends on the uptake of tryptophan (Trp) into the presynaptic cells localized in the raphe nuclei. The conversion of Trp to 5-hydroxytryptophan (5-HTP) is catalyzed by tryptophan hydroxylase (TPH). 5-HTP is converted to 5-HT by aromatic amino acid decarboxylase (AADC) before being stored in vesicles. The release of 5-HT into the synapse is calcium-dependent. Once released, 5-HT binds to postsynaptic receptors (e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7), pre-synaptic autoreceptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}), or is transported back into the serotonergic cell by the 5-HT transporter (SERT).

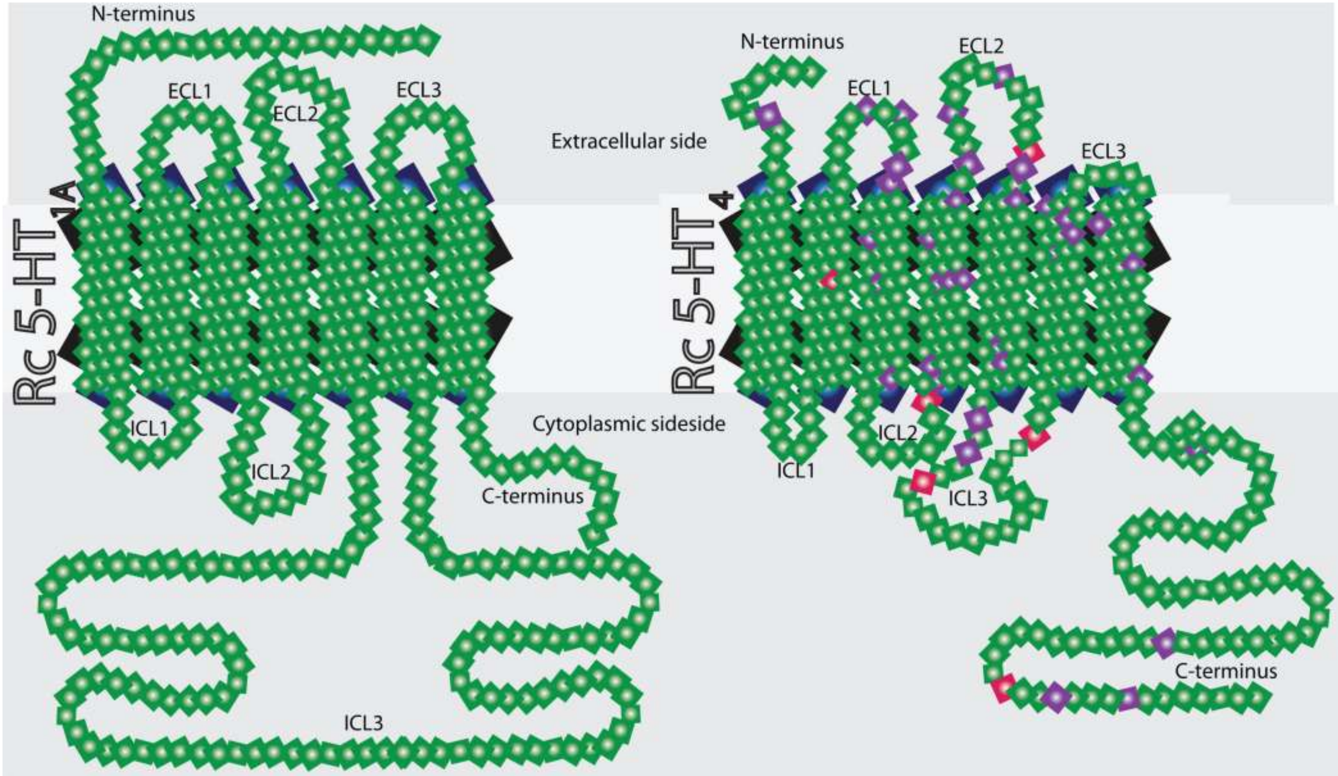

Figure 2.

Two-dimensional representation of the 5-HT_{1A} and the 5-HT_4 receptor sequences. The 5-HT_{1A} and the 5-HT_4 receptors are metabotropic receptors that are coupled to G proteins and contain a seven-transmembrane domain structure. The 5-HT_{1A} and 5-HT_4 receptors possess three intracellular loops and three extracellular loops. The amino terminus is oriented toward the extracellular space, whereas the carboxyl terminus (C-terminus) is oriented toward the cytoplasm. Primary sequences of the different isoforms are identical throughout the first 358 residues but diverge at their C-terminal end resulting in differential G protein coupling.

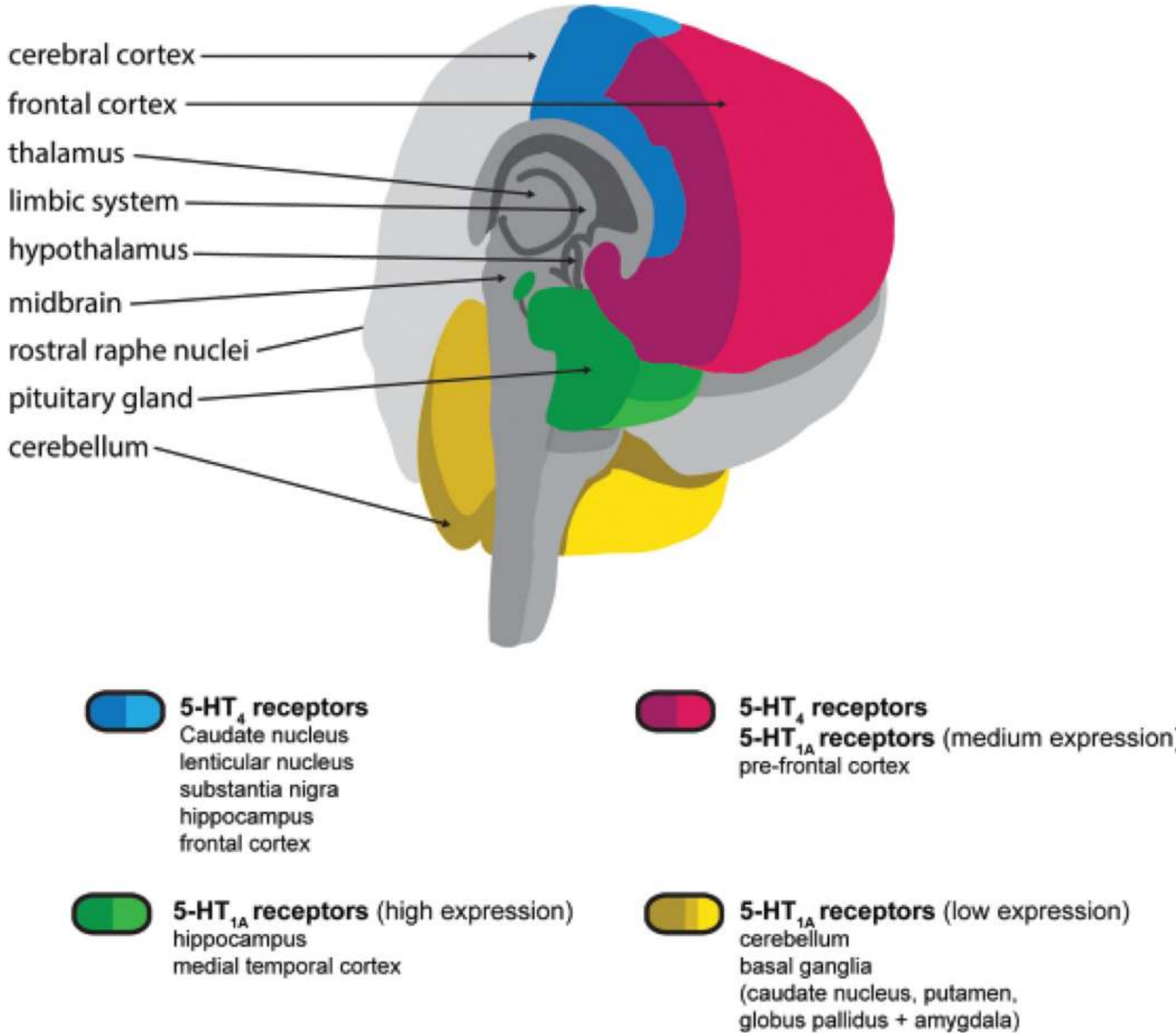

Figure 3.

Localization of the 5-HT_{1A} and 5-HT_4 receptor in the human brain. Both 5-HT_{1A} and 5-HT_4 are heteroreceptors, but only the 5-HT_{1A} is also an autoreceptor localized in the raphe nuclei. 5-HT_{1A} and 5-HT_4 heteroreceptors are both expressed in the brain primarily in the hippocampus, the cortex, the globus pallidus, and the caudate nucleus.

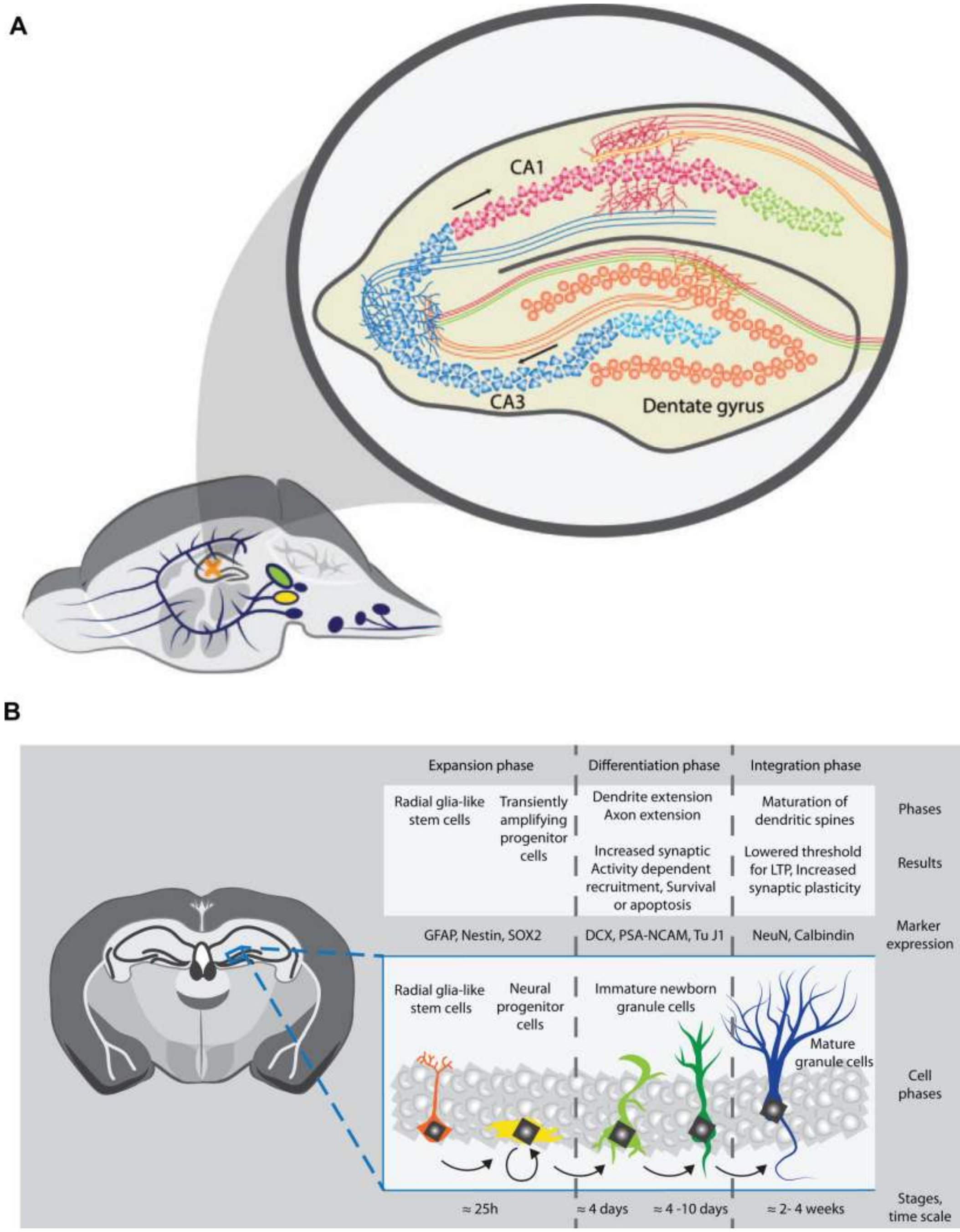

Figure 4.

Production of new neurons in the adult dentate gyrus. (A) The hippocampal trisynaptic circuit in mouse brain. Neurons of the enthorinal cortex project to the dentate gyrus, with additional collaterals projecting to the CA3 subfield (perforant pathway). Granule cells in the dentate gyrus project to the CA3 field of the hippocampus via the mossy fiber pathway. The CA3 pyramidal cells project onto themselves and also to the CA1 through Schaffer collaterals. (B) Hippocampal neurogenesis is possible in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus because of the presence of stem cells. These stem cells evolve into neural progenitor cells that can produce multiple cell types in the central nervous system such as neurons, astrocytes, oligodendrocytes, or microglial cells. In rodents, the duration of the mitotic cycle of proliferating precursors is approximately 12 to 24 hours, leading to the production of about 8,000 to 10,000 new neurons per day.

Table 1

Effects of 5-HT_{1A} Receptor Ligands on Anxiety/Depression-Like Phenotypes.

References	Name	Pharmacologica Properties	Doses	Species	Paradigms	Effects	Importance
Lucki (1991)	8-OH-DPAT: 8-hydroxy-2-dipropylaminotetralin	Agonist	Varied	Varied (mostly rats)	FST, LH, OF and Feeding after Restraint	Review assessing outcomes found that most studies showed antidepressant-like effects	Most studies suggest that the behavioral effects of 5-HT_{1A} receptor agonists mimic those of antidepressants
	Buspirone; gepirone; ipsapirone	Partial agonists					
	Pindolol	Partial agonist/antagonist				Review assessing outcomes found that most studies showed no effects when administered alone, but reversed antidepressant-like effects of 8-OH-DPAT	
	NAN 190: 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl] piperazine hydrobromide	Antagonist					
Griebel (1995)	Buspirone	Partial agonist	Varied	Varied	Varied	Review assessing outcomes found that 71% of 210 studies show an anxiolytic-like profile	Most studies suggest that the behavioral effects of 5-HT_{1A} receptor agonists are anxiolytic
	8-OH-DPAT: 8-hydroxy-2-dipropylaminotetralin	Agonist	Varied			Review assessing outcomes found that 61% of 112 studies show an anxiolytic-like profile	
Santarelli and others (2003)	8-OH-DPAT: 8-Hydroxy-2-dipropylaminotetralin	Agonist	1 mg/kg/d for 28 days	Mice	NSF	Decreased latency to feed	Chronic administration of a 5-HT_{1A} receptor agonist mimics the behavioral effects of chronic antidepressant treatment

FST = forced swim test; LH = learned helplessness; NSF = novelty suppressed feeding; OF = open field.

Table 2

Effects of 5-HT_4 Receptor Ligands on Anxiety/Depression-Like Phenotypes.

References	Name	Pharmacological Properties	Doses	Species	Paradigms	Effects
Silvestre and others (1996)	SB204070: 8-amino-7-chloro-(*N*-butyl-4-piperidyl)-methylbenzo-1,4-dioxan-5-carboxylate hydrochloride	Antagonist	0.3–3 mg/kg, s.c., acutely	Rat	EPM	Exhibits an anxiolytic-like profile
	GR 113808: 1-[2-methylsulphonylamino)ethyl]-4-piperidinyl]methyl-1-methyl-1H-indole-3-carboxylate maleate	Antagonist	0.3–3 mg/kg, s.c., acutely			Exhibits an anxiolytic-like profile
Kennett and others (1997)	SB204070: 8-amino-7-chloro-(*N*-butyl-4-piperidyl)-methylbenzo-1,4-dioxan-5-carboxylate hydrochloride	Antagonist	0.01 and 10 mg/kg p.o. 0.01 and 1 mg/kg s.c., acutely	Rat	Social interaction/ EPM	Increased time spent in social interaction / induced anxiolysis
	SB 207266A: 2H-(1,3)oxazino(3,2-a)indole-10-carboxamide, *N*-((1-butyl-4-piperidinyl)methyl)-3,4-dihydro-, monohydrochloride	Antagonist	0.001 and 0.1 mg/kg s.c. 0.01 and 1 mg/kg s.c., acutely		Social interaction /elevated x-maze	Increased time spent in social interaction / induced anxiolysis
Costall and Naylor (1997)	SDZ205–557: 2-methoxy-4-amino-5-chloro-benzoic acid 2-(diethylamino ester)	Antagonist	0.001–100 μg/kg, i.p., acutely	Mice	Light/dark	No effect by itself, but reduced the disinhibitory effect of diazepam
	GR113808: 1-[2-methylsulphonylamino)ethyl]-4-piperidinyl]methyl-1-methyl-1H-indole-3-carboxylate maleate	Antagonist	0.001–10 μg/kg, i.p., acutely			No effect by itself, but reduced the disinhibitory effect of diazepam
	SB204070: 8-amino-7-chloro-(*N*-butyl-4-piperidyl)-methylbenzo-1,4-dioxan-5-carboxylate hydrochloride	Antagonist	0.001–10 μg/kg, i.p., acutely			No effect by itself, but reduced the disinhibitory effect of diazepam
Schreiber and others (1998)	GR 125487: [1-[2-[(methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate	Antagonist	3 mg/kg, s.c., acutely	Rat	ultrasonic vocalization	No effect
Cryan and Lucki (2000)	SB204070: 8-amino-7-chloro-(*N*-butyl-4-piperidyl)-methylbenzo-1,4-dioxan-5-carboxylate hydrochloride	Antagonist	3 mg/kg, s.c., acutely	rat	FST	No effect
Lucas and others (2007)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone)	Agonist	1.5 mg/kg, i.p. during 3 days	Rat	FST	Antidepressant-like profile: decrease immobility duration and increase climbing duration
			1.5 mg/kg, i.p. during 3 and 14 days	OBX rat	Locomotor activity	Reversed OBX-induced increase in locomotor activity after 14 days
				CMS rat	Sucrose consumption	Reversed CMS-induced decrease in sucrose consumption after 14 days
Tamburella and others (2009)	SL 65.0155: [5-(8-amino-7-chloro-2,3-dihydro-1,4-benzo-dioxin-5-yl)-3-[1-(2-phenylethyl)-4-piperidinyl]-1,3,4-oxadiazol-2 (3H)-one-monohydrochloride]	Partal agonist	0.1, 0.5, and 1 mg/kg, i.p. during 1 day	Rat	FST	Antidepressant-like profile: increase swimming and climbing and reduce immobility duration
Pascual-Brazo and others (2012)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone)	Agonist	1.5 mg/kg, i.p. during 3/7 days	Rat	FST/NSF	Anxiolytic/Antidepressant-like profile: decrease immobility duration at 3/7 days,

References	Name	Pharmacological Properties	Doses	Species	Paradigms	Effects
			1.5 mg/kg, i.p. during 3/7 days			decrease latency to feed after 7 days
				Cort-treated rat	Sucrose intake	Antidepressant-like profile: increase sucrose intake at 3/7 days
Gomez-Lazaro and others (2012)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone)	Agonist	1.5 mg/kg, i.p. during 5 days	Social stress in rat	FST	Antidepressant-like profile: increase swimming behavior
Mendez-David and others (2014)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone)	Agonist	1.5 mg/kg, osmotic mini-pumps during 7 days	Cort-treated mice	OF/EPM/ST/TST/NSF	Anxiolytic/Antidepressant-like profile: increase time spent in the center and ratio of ambulatory distance in the center divided by total distance in the OF, increase time and entries in EPM, increase grooming duration and decrease immobility duration, the latency to feed in ST and TST, and NSF, respectively
	GR 125487: [1-[2-[(methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate	Antagonist	1 mg/kg, osmotic mini-pumps during 7 days	Cort-treated mice	OF/EPM/NSF/ST/TST	No effect[a]

CMS = chronic mild stress; EPM = elevated plus maze; FST = forced swim test; i.p. = intrapetoneally; NSF, novelty suppresses feeding; OBX = olfactory bulbectomy; OF = open field; s.c. = subcutaneously; ST = splash test; TST = tail suspension test.

[a]GR125487 partially prevents fluoxetine-induced increase in time spent in the center in OF, prevents fluoxetine-induced increase in grooming duration in ST and decrease immobility duration in TST, prevents fluoxetine-induced decrease in latency to feed in NSF.

Table 3

Effects of 5-HT_{1A} Receptor Ligands on Proliferation and Maturation of Newborn Neurons in the Adult Hippocampus.

References	Name	Pharmacological Properties	Doses	Species	Steps	Effects
Radley and Jacobs (2002)	NAN-190: 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl] piperazine hydrobromide	Antagonists	2.5 mg/kg 2.5 hours before sacrifice	Rats	Proliferation	Decreases the number of newborn cells in the SGZ of DG
	p-MPPI: 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylbenzamide		10 mg/kg 2.5 hours before sacrifice			
	WAY-100635: (*N*-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride		5 mg/kg 2.5 hours before sacrifice			
Santarelli and others (2003)	8-OH-DPAT: 8-Hydroxy-2-dipropylaminotetralin	Agonist	1 mg/kg/day for 28 days	Mice	Proliferation	Increases the number of newborn cells in the SGZ of DG
Banasr and others (2004)	8-OH-DPAT: 8-hydroxy-2-dipropylaminotetralin	Agonist	1 mg/kg 2.5 hours before sacrifice	Rats	Proliferation	Increases the number of newborn cells in the SGZ of DG
Grabiec and others (2009)	Buspirone	Partial agonist	3 mg/kg 3 hours before sacrifice	Opossums	Proliferation	Increases the number of newborn cells in the SGZ of DG
Klempin and others (2010)	8-OH-DPAT: 8-hydroxy-2-dipropylaminotetralin	Agonist	1 mg/kg 1 day before sacrifice	Mice	Proliferation	Increases the number of newborn cells in the SGZ of DG
			1 mg/kg for 7 days			No effect
	WAY-100635: (*N*-(2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl)-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride	Antagonist	10 mg/kg 1 day before sacrifice			No effect
			10 mg/kg for 7 days			Decreases the number of newborn cells in the SGZ of DG
Mori and others (2014)	Tandospirone	Partial agonist	1 or 10 mg/kg for 10 days	Rats	Maturation	Increases the number of DCX-positive cells in the DG

DCX = doublecortin; DG = dentate gyrus; SGZ = subgranular zone.

Table 4

Effects of 5-HT$_4$ Receptor Ligands on Proliferation, Maturation, and Survival of Newborn Neurons in the Adult Hippocampus.

References	Name	Pharmacological Properties	Doses	Species	Steps	Effects
Lucas and others (2007)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone) versus citalopram (77–300 μg/kg i.v.)	Agonist	1.5 mg/kg, osmotic mini-pumps during 3 days	Rats	Proliferation	Increases the number of newborn cells in the SGZ of DG
Tamburella and others (2009)	SL 65.0155: [5-(8-amino-7-chloro-2,3-dihydro-1,4-benzo-dioxin-5-yl)-3-[1-(2-phenylethyl)-4-piperidinyl]-1,3,4-oxadiazol-2(3H)-one-monohydrochloride]	Partial agon	0.1, 0.5 and 1 mg/kg, i.p. during 1 day	Rats	Survival	Increases Bcl-2 expression after acute administration
Pascual-Brazo and others (2012)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone)versus fluoxetine (10 mg/kg/d)	Agonist	1.5 mg/kg, i.p. during 3/7 days	Rats	Proliferation	Increases the number of newborn cells in the SGZ of DG at 3/7 days and up-regulate some neuroplasticity-related markers as BDNF, CREB, and AKT
Ishizuka and others (2014)	GR 113808: 1-(2-methylsulfonylaminoethyl-4-piperidinyl)methyl-1-methyl-1H-indole-3-carboxylate	Antagonist	1 μM during 30 min and 40 hours later during 30 minutes for 2 days	Mouse induced pluripotent stem cells	Differentiation	Blocks all-trans retinoic acid-induced neural differentiation of mouse iPS cells into NPC
Mendez-David and others (2014)	RS 67333: (1-[4-amino-5-chloro-2-methoxyphenyl]-3-[1-butyl-4-piperidinyl]-1-propanone) versus fluoxetine (18 mg/kg/d)	Agonist	1.5 mg/kg, osmotic mini-pumps during 7 days	Cort-treated mice	Proliferation	Increases by 51% the number of newborn cells in the SGZ of DG
					Maturation	Increases by 44% the maturation index
					Morphology	Increases the dendritic length and the number of dendritic intersections
	GR 125487: [1-[2-[(methylsulfonyl)amino] ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate	Antagonist	1 mg/kg, osmotic mini-pumps during 7 days	Cort-treated mice	Proliferation/ maturation/ morphology	No effect[a]

Bcl-2 = B-cell lymphoma 2; BDNF = brain-derived neurotrophic factor; CREB = cAMP response element–binding protein; DG = dentate gyrus; i.p. = intraperitoneally; iPS = induced pluripotent stem; i.v. = intravenously; SGZ = subgranular zone.

[a]Partially blocks the effects of chronic fluoxetine-induced increase in proliferation of newborn cells and increase in maturation.