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REVIEW

P5-HT$_{1A}$ receptors in mood and anxiety: recent insights into autoreceptor versus heteroreceptor function

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Abstract
Rationale Serotonin (5-HT) neurotransmission is intimately linked to anxiety and depression and a diverse body of evidence supports the involvement of the main inhibitory serotonergic receptor, the serotonin-1A (5-HT$_{1A}$) subtype, in both disorders.
Objectives In this review, we examine the function of 5-HT$_{1A}$ receptor subpopulations and re-interpret our understanding of their role in mental illness in light of new data, separating both spatial (autoreceptor versus heteroreceptor) and the temporal (developmental versus adult) roles of the endogenous 5-HT$_{1A}$ receptors, emphasizing their distinct actions in mediating anxiety and depression-like behaviors.
Results It is difficult to unambiguously distinguish the effects of different populations of the 5-HT$_{1A}$ receptors with traditional genetic animal models and pharmacological approaches. However, with the advent of novel genetic systems and subpopulation-selective pharmacological agents, direct evidence for the distinct roles of these populations in governing emotion-related behavior is emerging.
Conclusions There is strong and growing evidence for a functional dissociation between auto- and heteroreceptor populations in mediating anxiety and depressive-like behaviors, respectively. Furthermore, while it is well established that 5-HT$_{1A}$ receptors act developmentally to establish normal anxiety-like behaviors, the developmental role of 5-HT$_{1A}$ heteroreceptors is less clear, and the specific mechanisms underlying the developmental role of each subpopulation are likely to be key elements determining mood control in adult subjects.

Keywords 5-HT$_{1A}$ · Autoreceptor · Heteroreceptor · Anxiety · Depression · 5-HT · Polymorphism · Development

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Introduction

Depression and anxiety are among the world's leading public health problems today. Indeed, approximately 35 million adults in the US population (16 %) are likely to suffer from depression at some time in their lives (Samuels et al. 2011) and the World Health Organization considers that unipolar depression will be the second highest cause of illness-induced disability by the year 2020 (World Health Organization 2011). Although antidepressants are one of the most commonly used groups of therapeutic agents worldwide, less than half of depressed patients show full symptom remission and at least one quarter show treatment resistance to current antidepressants (Corey-Lisle et al. 2004; Samuels et al. 2011). As concerns anxiety, an authoritative survey in the European Union found that it was the most prevalent of mental health disorders (12-month prevalence, 14 %) affecting over 60 million people each year and entailing a massive economic burden of over 65 billion euros annually (Gustavsson et al. 2010). Despite extensive efforts searching for novel anxiolytic agents, advances have been incremental, notably due to the limitations of classical animal models (Griebel and Holmes 2013).

Such considerations emphasize the need for improved understanding of the mechanisms of action underlying depressive and anxiety states. Thus, while it is known that the serotonergic system plays an important role in the etiology and treatment of mood and anxiety disorders (Charney 1998;

Nemeroff 2002; Rush 2000), the precise means by which this occurs are the subject of an ongoing study.

Direct experimental evidence in humans implicating 5-HT in mood disorders came from studies of tryptophan depletion (Young et al. 1985), reviewed by Ruhe et al. (2007). More recently, multiple lines of evidence implicate dysregulated 5-HT neurotransmission as a primary defect in mood and anxiety disorders (aan het Rot et al. 2009; Durant et al. 2010; Ganasen and Stein 2010; Jans et al. 2007; Ravindran and Stein 2010). Furthermore, complementary data suggesting a role for 5-HT in mood disorders, or at least in the recovery from mood disorders, comes from the use of selective serotonin reuptake inhibitors (SSRIs) and other serotonergic agents as first-line treatments. These drugs are believed to exert their therapeutic action by increasing 5-HT levels and facilitating 5-HT neurotransmission (Gartside et al. 1995). However, evidence from animal models suggests that SSRI treatment during early development increases anxiety or depression later in adulthood, in contrast to the well-known beneficial effects of SSRIs in adults (Ansorge et al. 2008; Caspi et al. 2003; Lira et al. 2003; Oberlander et al. 2009; Olivier et al. 2008). These results suggest that 5-HT may impact immature and mature mood-related circuitry differently. Furthermore, it is important to underscore that 5-HT's effect on mood occurs in the context of multiple other neuromodulatory systems such as noradrenaline, dopamine, and neurotrophins that may have distinct yet related effects on mood regulation and which have their own developmental trajectories (Benes et al. 2000; Blier 2003; Murrin et al. 2007; Covington et al. 2010; Duman 2004; Durant et al. 2010; Nestler 2006; Nikolaus et al. 2010; Skolnick et al. 2009).

Serotonergic neurons are mainly located in the dorsal and median raphe of the brainstem (DRN and MRN, respectively) (Barnes and Sharp 1999). Projections from these neurons release serotonin throughout the entire forebrain and brainstem and modulate a variety of neuronal activities, but there are other raphe nuclei that also provide innervations to the midbrain (Bockaert et al. 2006). The largely neuromodulatory effects of 5-HT are mediated through 14 receptor subtypes that are grouped into subfamilies based on their primary signaling mechanism (Hoyer and Martin 1997). Here we focus on the 5-HT_{1A} receptor, as several lines of evidence from both human and rodent studies suggest that it may play a particularly important role in both the etiology of these disorders and their treatment (Akimova et al. 2009; Gordon and Hen 2004; Hirvonen et al. 2008; Le Francois et al. 2008; Lesch and Gutknecht 2004; Strobel et al. 2003).

The 5-HT_{1A} receptor is a major inhibitory G-protein-coupled receptor subtype that exists in two major populations in the nervous system (autoreceptor and heteroreceptor) and functions by coupling to Gi/Go proteins that control numerous intracellular signaling cascades, including inhibition of cAMP formation, inactivation of calcium channels, and activation of potassium channels (Barnes and Sharp 1999). The 5-HT_{1A} autoreceptor resides on the soma and dendrites of serotonin neurons in the raphe nuclei, where its activation hyperpolarizes and reduces the firing rate of these cells and thereby serotonin extracellular levels in its projection areas (Hjorth and Sharp 1991; Meller et al. 1990; Sprouse and Aghajanian 1986; Verge et al. 1985; Wang and Aghajanian 1977). Studies from several laboratories suggest that the molecular signaling mechanisms of 5-HT_{1A} receptors in the raphe nuclei are distinct from those in other brain regions and may be preferentially mediated by coupling to Gαi3 G-protein subunits leading to partial inhibition of adenylyl cyclase (Liu et al. 1999; Marazziti et al. 2002; Palego et al. 1999; Valdizan et al. 2010). Local release of 5-HT in the raphe nuclei from axonal collaterals or crosstalk between different 5-HT neurons will thus diminish neuronal firing and produce a negative feedback regulation of transmitter release and may add an extra level of topographical specification (Adell et al. 1991; Artigas et al. 1996; Bang et al. 2012). Consistent with their role in regulating serotonergic tone, autoreceptors limit the initial increase of 5-HT extracellular levels induced by SSRIs (Hervas et al. 2000; Hjorth and Auerbach 1994; Hjorth et al. 1996; Rollema et al. 1996), delaying the therapeutic response (Artigas et al. 1996; Blier and De Montigny 1983; Gardier et al. 1996). This effect is gradually overcome by desensitization of 5-HT_{1A} autoreceptors in the raphe nuclei (Dawson and Nguyen 2000), allowing the firing rate of serotonergic neurons to recover (Blier and De Montigny 1983; El Mansari and Blier 2005).

Postsynaptic 5-HT_{1A} heteroreceptors are expressed in target areas receiving serotonergic innervation. These heteroreceptors are mainly located on pyramidal neurons and on GABAergic interneurons (Artigas et al. 2006; Azmitia et al. 1996; Palchaudhuri and Flugge 2005; Santana et al. 2004). They are highly expressed in brain regions implicated in the regulation of mood and anxiety, such as the prefrontal cortex, hippocampus (HP), and amygdala (Beck et al. 1992; Hamon et al. 1990; Pompeiano et al. 1992; Riad et al. 2000). Activation of 5-HT_{1A} heteroreceptors in these areas mediates a hyperpolarizing response to released serotonin on pyramidal neurons (Andrade et al. 1986; Hamon et al. 1990; Riad et al. 2000), an effect that may be mediated by coupling of the receptors mainly to Gαo subunits in the hippocampus, and equally to Gαo and Gαi3 in cerebral cortex (Mannoury la Cour et al. 2001), unlike 5-HT_{1A} autoreceptors that may couple preferentially to Gαi3. Moreover, there is a second indirect mechanism regulating serotonergic neurotransmission that involves 5-HT_{1A} heteroreceptors in the mPFC–raphe pathway (Celada et al. 2001; Hajos et al. 1999). Hence, 5-HT_{1A} receptors are powerful modulators of 5-HT function through their distinct populations, likely exerting differential effects both by their distinct anatomical localizations as well as by distinct Gα subunit coupling that

may account for regional differences in activation versus inhibition of downstream signaling targets. In the present review, we focus on the evidence that demonstrates a distinct role of 5-HT_{1A} autoreceptors versus heteroreceptors in the initial establishment of mood and anxiety homeostasis as well as their developmental requirement in affective illness.

Role of 5-HT_{1A} receptors in depression and anxiety

Human studies

Dysregulation of 5-HT_{1A} receptors occurs in patients suffering from depression and related mood disorders. While there has been considerable discrepancy among postmortem and human imaging studies of 5-HT_{1A} receptor levels in depression, there is growing evidence supporting an increase of 5-HT_{1A} autoreceptors and a decrease of heteroreceptors in major depression (Arranz et al. 1994; Boldrini et al. 2008; Cheetham et al. 1990; Dillon et al. 1991; Joyce et al. 1993; Lowther et al. 1997; Matsubara et al. 1991; Parsey et al. 2010; Stockmeier et al. 1996).

Increases in 5-HT_{1A} autoreceptor density in the midbrain have been demonstrated in depressed suicide patients (Stockmeier et al. 1998). Boldrini et al. (2008) confirmed and extended this observation by using (H^3) 8-OH-DPAT autoradiography and reported an increase in rostral divisions of the dorsal raphe nuclei, which project to the prefrontal cortex, but decreased levels of 5-HT_{1A} autoreceptors in the caudal dorsal raphe nuclei. An increase in autoreceptor levels in rostral divisions might result in a decreased serotonin activity in projection areas by lowering firing rate. However, disagreement exists within the postmortem literature regarding this subpopulation, suggesting that a more complex pattern of 5-HT_{1A} autoreceptor binding abnormalities exists in depression. Indeed, reductions in 5-HT_{1A} autoreceptor binding have also been reported in different PET studies using primary depressives as subjects (Drevets et al. 1999, 2007; Meltzer et al. 2004).

5-HT_{1A} receptors have been also examined in a number of cerebral cortical and subcortical areas in subjects with a history of mood disorders. PET studies revealed decreased 5-HT_{1A} heteroreceptor levels in the orbitofrontal, anterior cingulate, occipital, and parietal cortex in untreated or treated depressed patients, and it was also decreased in patients with remitted depressive episodes and unmedicated subjects (Bhagwagar et al. 2004; Drevets et al. 2000, 2007; Sargent et al. 2000). Furthermore, reduced 5-HT_{1A} heteroreceptor levels have also been reported in patients with social anxiety disorders (Lanzenberger et al. 2007), as well as in cortical regions from patients suffering from panic disorder (Nash et al. 2008; Neumeister et al. 2004), although not all studies are in agreement (see Meltzer et al. 2004; Parsey et al. 2006; Parsey 2010).

Nevertheless, despite some discrepant findings, overall evidence suggests that 5-HT_{1A} receptor function is altered in clinical populations when compared to controls. Furthermore, it should be underscored that the observed abnormalities in 5-HT_{1A} receptor levels are found in a number of affective and anxiety-related disorders (Neumeister et al. 2004), suggesting that these findings may reflect a general vulnerability factor for psychopathology.

5-HT_{1A} polymorphism

Stress diathesis theories of depression predict that an individual's sensitivity to stressful events depends on their genetic makeup (Costello et al. 2002; Monroe and Simons 1991), and such predictions are now increasingly supported by experimental evidence. Indeed, in the case of 5-HT_{1A} receptors, a functional C(−1019)G single nucleotide polymorphism (SNP) in the transcriptional control region of the HTR1A gene (HTR1A-1019) has been associated with a number of mood-related variables, including depression, risk of suicide, response to antidepressant treatment, and amygdala reactivity (Fakra et al. 2009; Le Francois et al. 2008; Lesch and Gutknecht 2004; Strobel et al. 2003). Lemonde et al. (2003) were the first to report that the G/G genotype is associated with major depression and suicide in two different cohorts. This association has been replicated and extended in most subsequent studies (Anttila et al. 2007; Kraus et al. 2007; Neff et al. 2009; Parsey et al. 2006). The 5-HT_{1A} G(−1019) allele has also been associated with anxiety (Choi et al. 2010; Domschke et al. 2006; Fakra et al. 2009). More recently, it has been suggested that the HTR1A G allele of the polymorphism is associated to the frequent clinical presentation of comorbid major depression and anxiety, suggesting a common genetic background for mixed depression and anxiety state (Molina et al. 2011). Furthermore, the G allele of the polymorphism has also been associated with several mood disorders, such as panic disorder (Rothe et al. 2004; Strobel et al. 2003) and panic attack (Huang et al. 2004). Perhaps not surprisingly for a complex pyschiatric disorder, not all studies have found a clear association of the G allele of the polymorphism with depression (Arias et al. 2002; Hettema et al. 2008; Huang et al. 2004). These discrepancies could be related to different variables such as the frequency of the risk allele, ethnicity, or disease in the population studied. However, the overall message that emerges from literature suggests that the 5-HT_{1A} receptor G(−1019) allele is a risk allele for depression and related mood disorders.

Not only is there evidence for increased risk for mood disorders, but patients homozygous for the G allele consistently have a reduced response to SSRI treatment (Arias et al. 2005; Lemonde et al. 2004; Parsey et al. 2006) compared to

patients with the C/C genotype (Hong et al. 2006; Serretti et al. 2004; Yu et al. 2006) but see (Levin et al. 2007). Overall, these finding suggest that genetic variations in the HTR1A gene may contribute not only to susceptibility to depression but also to individual differences in response to antidepressant treatment.

At the molecular level, the C(−1019)G polymorphism is located in a 26-bp palindrome region within the repressor/enhancer region of the HTR1A promoter (Albert et al. 1996; Albert and Lemonde 2004). This region is recognized by a number of transcription factors including Deaf-1 and Hes5 that act as repressors of the C– but not the G allele of the 5-HT_{1A} polymorphism in the raphe. While Hes5 also appears to function as a repressor of heteroreceptor populations, Deaf-1 may enhance expression of 5-HT_{1A} heteroreceptors in C allele carriers (Lemonde et al. 2003; Czesak et al. 2006). In addition to the effects of Deaf-1 and Hes-5, Hes1 is also a repressor of 5-HT_{1A} autoreceptors, both in vitro and in vivo (Jacobsen et al. 2008). Thus, although initial in vitro reports suggested that this polymorphism could impact autoreceptor levels (Lemonde et al. 2003), a subsequent in vivo study reported that the G allele resulted in increased 5-HT_{1A} expression in both the raphe and other brain regions of antidepressant naive depressed patients (Parsey et al. 2006). Furthermore, a subsequent study showed the opposite regulation of heteroreceptor compared to autoreceptor by the G allele (Czesak et al. 2006) and this was further confirmed in vivo using Deaf1-null mouse model lacking the key transcription factor thought to act at this polymorphism in adults (Czesak et al. 2012). In this model, raphe 5-HT_{1A} receptor RNA and protein were increased by 50 %, while in the prefrontal cortex but not the hippocampus, a smaller 30 % reduction in RNA was observed. However, whether the effects on forebrain levels observed in vivo are primary or secondary to changes in autoreceptor levels remains to be elucidated.

In summary, this model predicts that having relatively higher levels of 5-HT_{1A} autoreceptors results in increased susceptibility to depression and decreased response to treatment. A recent study looking at mice that differed only in their level of autoreceptors supports such a prediction (Richardson-Jones et al. 2010).

Preclinical pharmacological studies

Data from the depression and anxiety literature provide evidence that 5-HT_{1A} receptors are involved in both disorders. Indeed, several clinically approved drugs, including buspirone and tandospirone, likely mediate their anxiolytic properties via prominent 5-HT_{1A} partial agonist activity (Lacivita et al. 2008). Other drugs, such as flesinoxan or flibanserin, exhibit high agonist efficacy at 5-HT_{1A} receptors and have proven active in clinical trials as antidepressants (Pitchot et al. 2005). Further evidence for the involvement of 5-HT_{1A} receptors in the regulation of depressive states comes from co-treatment of depressed subjects with SSRIs and the 5-HT_{1A} weak partial agonist, pindolol. The latter drug (which is also an adrenergic beta-blocker) preferentially occupies 5-HT_{1A} autoreceptors, thus preventing feedback inhibition of serotonin release and accelerating antidepressant response in most though not all studies (Celada et al. 2013; Portella et al. 2011). Consistent with this mechanistic interpretation, co-treatment of depressed patients with buspirone and pindolol elicited an antidepressant effect (McAllister-Williams and Massey 2003), whereas buspirone lacks antidepressant efficacy by itself, likely because of its insufficient partial agonist efficacy at post-synaptic receptors (and full agonist activity at 5-HT_{1A} autoreceptors) (Celada et al. 2013). Furthermore, vilazodone, a combined SSRI and 5-HT_{1A} receptor partial agonist (Sorbera et al. 2001), exhibits anxiolytic and antidepressant-like effects (Bartoszyk et al. 1997; Page et al. 2002).

Taken together, these observations support the importance of 5-HT_{1A} receptors in the control of mood disorders in a clinical context and have spurred investigation of 5-HT_{1A} receptor function using animal models. In particular, efforts have been made to probe 5-HT_{1A} receptor function using pharmacological and genetic approaches.

The existence of specific 5-HT_{1A} ligands has made it possible to study the function of this receptor (Fletcher et al. 1996; Hamon et al. 1990). For example, pharmacological studies demonstrate that 5-HT_{1A} receptor partial agonists such as buspirone exert modest antidepressant and anxiolytic effects in animal studies (Detke et al. 1995; Lucki 1991), and the behavioral effects of imperfectly selective agonists such as 8-OH-DPAT are absent in the 5-HT_{1A} KO mice during the novelty-supressed feeding test (Santarelli et al. 2003). However, these ligands bind to both 5-HT_{1A} autoreceptors and heteroreceptors (Yocca 1990), making it difficult to determine which subpopulation mediates specific behavioral effects. Despite this, behavioral models of stress have consistently shown that activation of 5-HT_{1A} heteroreceptors produce similar changes to conventional antidepressants (Lucki 1991) and several preclinical studies have suggested that 5-HT_{1A} heteroreceptors are particularly important to the antidepressant response (Blier and de Montigny 1994; De Vry 1995).

In order to circumvent the limitation of systemic injections, investigators have used localized infusions of 5-HT_{1A} ligands into restricted brain regions in an attempt to selectively activate 5-HT_{1A} autoreceptors or heteroreceptors. For example, it has been reported that infusion of 5-HT_{1A} agonists into the DRN increased social interaction (SI), suggesting that the drug-induced increases in SI reflected decreases in anxiety (Higgins et al. 1992). Furthermore, the 5-HT_{1A} agonist, 8-OH-DPAT, has been acutely injected into restricted brain areas such as MRN and DRN resulting in an anxiolytic action (Andrews et al. 1994; De Almeida et al. 1998; File et al.

1996; Hogg et al. 1994). On the other hand, acute stimulation of the post-synaptic 5-HT_{1A} receptors in the dorsal HP results in an anxiogenic effect in the same tasks in which the knockouts behave abnormally (Andrews et al. 1994; File and Gonzalez 1996; File et al. 1996; Stefański et al. 1993). Thus, results from localized infusions suggest that stimulating auto- and heteroreceptors may result in opposing phenotypes, a conclusion that would be difficult to reach from systemic administration experiments.

More recently, pharmacological investigation of 5-HT_{1A} receptors has advanced with the availability of a new generation of agonists that preferentially target 5-HT_{1A} subpopulations. Indeed, the novel drug, F15599, exhibits a pronounced preference for activation of 5-HT_{1A} heteroreceptors in the frontal cortex, whereas its chemical congener, F13714, has the opposite profile, potently activating 5-HT_{1A} autoreceptors in the raphe. Data supporting this assertion have been generated in models of c-Fos expression in different brain regions, in electrophysiology tests measuring electrical activity of DRN and pyramidal neurons, and in microdialysis experiments, measuring dopamine release as an index of cortical heteroreceptors activation and 5-HT release as an index of autoreceptor activation (Newman-Tancredi 2011). Both F15599 and F13714 drugs are highly selective for 5-HT_{1A} receptors, and their activity in a range of pharmacological models is antagonized by selective 5-HT_{1A} antagonists. The possibility of interactions by F15599 and F13714 at cross-reacting sites can therefore be discounted and the capacity of the drugs to target receptor subpopulations may be attributed to the "biased agonist" profile of these drugs. Indeed, F15599 has a distinctive profile of in vitro signaling in cellular tests of G-protein activation, adenylyl cyclase inhibition, ERK1/2 phosphorylation, and receptor internalization (Newman-Tancredi et al. 2009). F15599 showed a marked potency for ERK1/2 phosphorylation, whereas other 5-HT_{1A} agonists, such as F13714 and 5-HT, did not discriminate (Newman-Tancredi et al. 2009). Interestingly, preferential stimulation of ERK phosphorylation may lead to improved antidepressant efficacy, because ERK phosphorylation deficits are associated with depressed mood. Indeed, deficits in ERK expression and phosphorylation are seen in postmortem brain of depressed suicide victims (Dwivedi et al. 2001, 2009). In rat, chronic stress-induced depression elicits deficits in ERK phosphorylation which are fluoxetine reversible (Qi et al. 2006, 2008). Conversely, chronic administration of a ERK inhibitor elicits anhedonia and anxiety-like behavior (Qi et al. 2009). Consistent with these observations, the potent phosphoryation of ERK1/2 elicited by F15599 in vitro and also demonstrated in ex vivo studies of frontal cortex tissue (Newman-Tancredi et al. 2009) may underlie its antidepressant-like effects of F15599. Indeed, F15599 exhibits antidepressant-like properties in rodent models of mood deficit (FST and ultrasonic vocalization) (Assié et al. 2010) and demonstrates beneficial activity on cognitive function in rats treated with the psychotomimetic drug, phencyclidine (Depoortère et al. 2010). Taken together, the above observations suggest that availability of highly selective biased agonists should facilitate the pharmacological characterization of the role of 5-HT_{1A} receptor subpopulations.

Preclinical genetic approaches

In addition to pharmacologic approaches, genetic strategies have also been used to assess 5-HT_{1A} function, initially with transgenic and KO mice and later with techniques capable of regulating the expression of receptors in a tissue-specific and temporally specific manner. In 1998, three different lines of mice lacking the 5-HT_{1A} receptors were generated (Heisler et al. 1998; Parks et al. 1998; Ramboz et al. 1998). In each of the three studies, 5-HT_{1A} knockout mice exhibited an anxiety-like phenotype in behavioral conflict tests such as open field, elevated plus maze, zero maze, and novelty-suppressed feeding test, a phenotype that is also present in the heterozygote 5-HT_{1A} receptor knockout mice, that expressed approximately one half of the wild-type receptor density, indicating that a partial receptor deficit is sufficient to elicit the anxious behavior (Ramboz et al. 1998). The impaired performance of 5-HT_{1A} knockout mice is likely due to an enhanced fear response to threatening context, but not due to a deficit in exploratory drive (Klemenhagen et al. 2006). Interestingly, despite the association of 5-HT_{1A} function with depression in humans, 5-HT_{1A} knockout mice did not display a prominent depression-like phenotype. Moreover, 5-HT_{1A} KO mice display increased physiological responses to acute stress (Van Bogaert et al. 2006). However, these behavioral alterations are not correlated with 5-HT or 5-HIAA (5-hydroxyindoleacetic acid, the major 5-HT metabolite) brain tissue levels. Furthermore, microdialysis studies have not shown alterations in basal 5-HT extracelullar levels in 5-HT_{1A} KO mice in different brain areas such as the hippocampus, striatum, raphe nuclei, and frontal cortex (Bortolozzi et al. 2004; Guilloux et al. 2006; Knobelman et al. 2001). These results demonstrate that genetic deletion of 5-HT_{1A} receptors leads to an enhanced anxiety phenotype without affecting 5-HT levels (Ramboz et al. 1998), suggesting either a lack of tonic control of 5-HT_{1A} autoreceptors on nerve terminal 5-HT release, or developmental compensation (see below). Indeed, despite findings that serotonin levels are unchanged, there is evidence to suggest increased 5-HT turnover, indicating increased activity of serotonergic neurons or compensatory changes due to the lack of 5-HT_{1A} receptors (Ase et al. 2000).

Pharmacological studies have also provided insight into the role of 5-HT_{1A} receptors in the regulation of 5-HT levels in KO mice. Indeed, SSRIs increase dialysate 5-HT levels in both the frontal cortex and raphe nuclei areas, but this effect is greater in 5-HT_{1A} KO mice (Bortolozzi et al. 2004; Guilloux

et al. 2006; Knobelman et al. 2001), suggesting the absence of an inhibitory feedback control over 5-HT release. Interestingly, 5-HT_{1A} KO mice respond to tricyclic antidepressants (TCAs), but not to the SSRI fluoxetine, in the tail suspension test and the novelty-suppressed feeding test, suggesting that the 5-HT_{1A} receptors are a critical component in the mechanism of action of SSRIs but not TCAs (Mayorga et al. 2001; Santarelli et al. 2003). In contrast to the behavioral changes observed in mice lacking the 5-HT_{1A} receptor, a transgenic line overexpressing the murine 5-HT_{1A} receptor in the central nervous system under control of its endogenous promoter (Kusserow et al. 2004) had reduced anxiety-like behavior, reduced 5-HIAA/5-HT ratio in several brain areas, and elevated serotonin levels in the hippocampus and striatum. The behavioral data from this study suggest the opposite phenotype of 5-HT_{1A} knockout mice and an inverse correlation between 5-HT_{1A} receptor levels and anxiety.

Since 5-HT_{1A} receptors can influence anxiety and depression by impacting either 5-HT levels (as an autoreceptor) or the limbic response to released 5-HT (as a heteroreceptor), it is important to understand the role of these receptor populations in maintaining normal levels of anxiety and depression. Gross et al. (2002), using a gain-of-function approach, ectopically expressed 5-HT_{1A} receptors using a vector driven by CamKII promoter. This results in 5-HT_{1A} overexpression in pyramidal excitatory neurons, but not GABAergic interneurons, in forebrain areas such as the cortex, hippocampus, striatum, and lateral amygdala, in the absence of autoreceptors. They found that this 5-HT_{1A} receptor expression pattern reversed the increased anxiety behavior in 5-HT_{1A} KO mice, leading to the hypothesis that endogenous 5-HT_{1A} heteroreceptors in the forebrain may control the normal establishment of anxiety-like behavior (Akimova et al. 2009; Goodfellow et al. 2009; Gross and Hen 2004; Zhang et al. 2010). However, it is worth noting that this phenotypic reversal occurs in the context of missing autoreceptors (Fig. 1).

More recently, we developed another transgenic system to independently assess the function of 5-HT_{1A} autoreceptors and heteroreceptors (Richardson-Jones et al. 2011). This system provides a number of advances over classic KO and previous transgenic technology. This study demonstrated that supression of endogenous heteroreceptors is not sufficient to impact anxiety-like behavior. However, loss of autoreceptors impacts anxiety in the adult, suggesting that the anxious-like phenotype of the 5-HT_{1A} KO mouse likely results from increased serotonergic neuron excitability during development (reviewed below). Furthermore mice lacking 5-HT_{1A} heteroreceptors throughout life displayed decreased mobility in the FST, or increased behavioral despair, in adulthood. Surprisingly, whole brain knockout mice display higher mobility time in the FST and TST, suggesting that the absence of 5-HT_{1A} receptors could result in an "antidepressant-like" effect. In contrast, loss of 5-HT_{1A} autoreceptors throughout life did not impact behavior in the FST in adulthood.

These results provided the first direct genetic evidence for the distinct roles of the two endogenous receptor populations in mediating anxious or depression-like phenotypes, providing evidence that autoreceptors could impact the establishment of

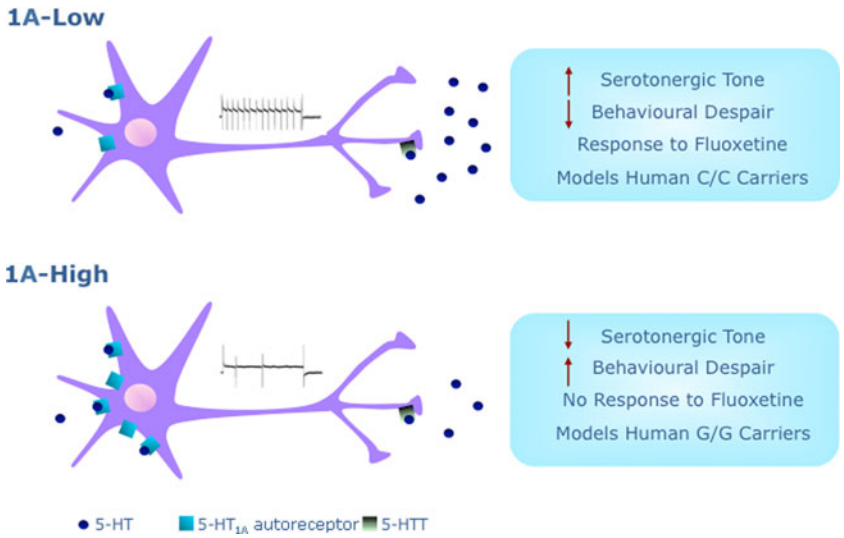

Fig. 1 Model of 5-HT_{1A} autoreceptor effects on the serotonergic raphe nuclei. Schematic depicting representative raphe neurons in 1A-High and 1A-Low animals, emphasizing the differences between the two groups. *Top*, In 1A-Low mice, low levels of somatodendritic 5-HT_{1A} autoreceptors result in a weak negative feedback, resulting in higher firing rates of raphe neurons and concomitant increased release of serotonin. *Bottom*, Conversely, 1A-High mice have lower basal firing rate and high levels of somatodendritic 5-HT_{1A} autoreceptor, which exert robust inhibitory effects on raphe firing. This results in a greater behavioral despair in response to stress, compared to 1A-Low mice. While 1A-High mice do not respond behaviorally to treatment with the antidepressant fluoxetine, 1A-Low mice display a robust behavioral response. 1A-High and 1A-Low mice provide a mechanistic model for humans carrying, respectively, the G/G and C/C alleles of the Htr1aI C(−1019)G polymorphism. Adapted from Richardson-Jones et al. (2010)

anxiety-like behavior, with heteroreceptors affecting behavior in the forced swim test, a depression-related test.

Developmental requirement of 5-HT$_{1A}$ receptor

The serotonergic system is perfectly poised to play an important role in sculpting the circuitry that subserves anxiety and depression. First, serotonin has clearly been implicated in development at key periods in a number of systems at different developmental timepoints (Benes et al. 2000; Trowbridge et al. 2011; van Kleef et al. 2012). For example, serotonin is known to play a critical role in the development of whisker barrel fields in the somatosensory cortex of the mouse. The critical period for this process appears to be postnatal days 1–6 (Fox 1992). More recently, it has been suggested that the postsynaptic 5-HT$_{1A}$ receptor appears to be critical in the development of the barrel cortex organization (Maya Vetencourt et al. 2008, 2011). At a later stage, Nakamura and colleagues have identified TPH1, an enzyme involved in the rate-limiting step for serotonin synthesis as playing a role in the maturation of sensorimotor gating (Nakamura et al. 2006). TPH1 is specifically required during postnatal days 21–24 for proper maturation of the circuit. Thus, it is clear that serotonin has distinct, clearly defined roles in circuit maturation at different times during development.

In the case of the 5-HT$_{1A}$ receptor, numerous studies have implicated this receptor in the development of normal anxiety-like behavior (Gross et al. 2002; Heisler et al. 1998; Parks et al. 1998; Ramboz et al. 1998). In particular, there is evidence to suggest that normal expression of the 5-HT$_{1A}$ receptor is required in the second and third week of life for the emergence of normal anxiety, with mice lacking functional 5-HT$_{1A}$ receptors during this time developing pathological levels of anxiety (Gross et al. 2002; Leonardo and Hen 2008). Furthermore, the same behavioral phenotype is also seen with pharmacological blockade of 5-HT$_{1A}$ receptors during postnatal development (Lo Iacono and Gross 2008). These studies have also demonstrated that disruption of the 5-HT$_{1A}$ receptor in adulthood does not result in an anxiety phenotype, suggesting that the phenotype of the 5-HT$_{1A}$ knockout mouse is due to its absence during a critical developmental window. Therefore, these data firmly establish the opening of a critical window in the second and third postnatal week.

The requirement for 5-HT$_{1A}$ receptors in the third week of life coincides with the emergence of behaviors that are consistent with conflict-based anxiety. Thus, exploration of and habituation to novel environments emerge at this time (Murrin et al. 2007). In addition, postnatal day 21 is the earliest timepoint in which behavioral differences in anxiety measures can be detected in the 5-HT$_{1A}$ knockout mice (Kristin Klemenhagen, personal communication). As a result, it is reasonable to assume that 5-HT$_{1A}$ receptors during this time period play a role in establishing the circuits that mediate these behaviors. These results also suggest that by the end of the third week of life in the mouse, circuitry capable of mediating anxiety-like behavior is in place. Indeed, genetic attempts to "rescue" normal levels of anxiety after this P21 period have not been successful (Gross et al. 2002). This data leads to the conclusion that if the circuits do not form properly in the first place, they cannot be rescued later. Similarly, the lack of an anxiety phenotype in mice that do not have 5-HT$_{1A}$ receptors in adulthood suggests that once formed, the circuits are either sufficiently stable to withstand the loss of 5-HT$_{1A}$ receptors, or that 5-HT$_{1A}$ receptors play a different role in adulthood than they do in development.

Given the evidence that the 5-HT$_{1A}$ receptor is important for normal development of mood control, it is reasonable to hypothesize that at least some of these effects could be linked to different 5-HT$_{1A}$ receptor subpopulations. Therefore, defining the stage-specific effects of 5-HT$_{1A}$ autoreceptors and heteroreceptors in the establishment and maturation of circuits that subserve anxiety and depression-related behavior in the mouse would form hypotheses concerning mechanisms through which variation in 5-HT$_{1A}$ receptor function leads to related phenotypes in humans.

A few studies have attempted to dissect the developmental requirements of 5-HT$_{1A}$ autoreceptors and heteroreceptors. For example, as mentioned above, overexpression of 5-HT$_{1A}$ heteroreceptors after P21 (in the absence of autoreceptors) using a gain-of-function approach in a knockout background resulted in anxiety levels that are indistiguishable from whole brain knockout animals. Conversely, earlier expression (P15) of the heteroreceptor in the absence of autoreceptors leads to normal anxiety levels in adulthood. These results suggest that normal anxiety-like behavior in the adult requires the proper establishment of circuitry in the early postnatal period and cannot be rescued later (Gross et al. 2002). Likewise, another report showed, using a loss-of-function approach, that supression of endogenous 5-HT$_{1A}$ autoreceptors throughout life is sufficient to increase anxiety-like behavior in the adult (Richardson-Jones et al. 2011). However, modulating 5-HT$_{1A}$ autoreceptors in adulthood does not impact anxiety-like behavior (Richardson-Jones et al. 2010). While seemingly in conflict regarding the population of receptors involved, these data taken together are consistent with a developmental role for 5-HT$_{1A}$ autoreceptors in the establishment of anxiety-related circuitry (Gross et al. 2002; Lo Iacono and Gross 2008). These findings further suggest that serotonin plays a critical role in the maturation and/or development of circuits that influence the processing of anxiety-related cues in adulthood. Furthermore, these results suggest the opening of a critical window in the second and third postnatal week and that this plasticity no longer remains in adult animals. The question of how long these plastic periods last remains to be answered.

The apparent conflict in the population responsible for the anxious phenotype can be resolved by closely examining the different experimental approaches taken in each experiment and the information that each provides. The 5-HT_{1A} autoreceptor knockout mouse was a loss of function model that looked at the effect of disrupting endogenous receptors: absence of 5-HT_{1A} autoreceptors appears to be the dominant element that determines the phenotype of the constitutive knockout mice. In the case of the heteroreceptor overexpression study, a gain-of-function approach was used to demonstrate that ectopic/overexpression of 5-HT_{1A} heteroreceptors in the forebrain can normalize anxious behavior in a knockout mouse. In a loss-of-function approach, another study (Richardson-Jones et al. 2011) demonstrated that suppression of heteroreceptor expression is not sufficient to recapitulate the anxious phenotype of the constitutive 5-HT_{1A} knockout mouse. Thus, the data are most consistent with a loss of autoreceptors resulting in increased anxiety through increased serotonergic signaling from a disinhibited raphe. The gain-of-function experiment suggests that this anxiety can be rescued in these "raphe-disinhibited" mice by increasing signaling through 5-HT_{1A} heteroreceptors which are the major inhibitory serotonin receptor in the forebrain. Thus, there is a fine balance between serotonin levels and inhibitory receptors that seems to be established during this early period.

Regarding 5-HT_{1A} heteroreceptors, there is only one study examining the developmental requirement of this receptor (Richardson-Jones et al. 2011). This study showed that supression of this receptor during development leads to an increased behavioral despair in adulthood. In contrast, this phenotype was not observed when heteroreceptor suppression was initiated in adulthood, suggesting that 5-HT_{1A} heteroreceptors act developmentally to establish the circuitry underlying the behavioral response to forced swim stress without affecting conflict-based anxiety paradigms (Fig. 2). Furthermore, it should be noted that supression of 5-HT_{1A} heteroreceptors results in behavioral despair but not anxiety, while ectopic overexpression in the forebrain of this receptor during development rescues the anxious phenotype of whole brain 5-HT_{1A} KO mice. Future studies should be directed to the suppression of interneuronal versus pyramidal 5-HT_{1A} receptors, potentially elucidating their distinct in the etiology of anxiety and depression.

In humans, it is increasingly accepted that developing circuits are sensitive to environmental insults, with different circuits being sensitive at distinct points in development. In addition, it is increasingly clear that some individuals are more

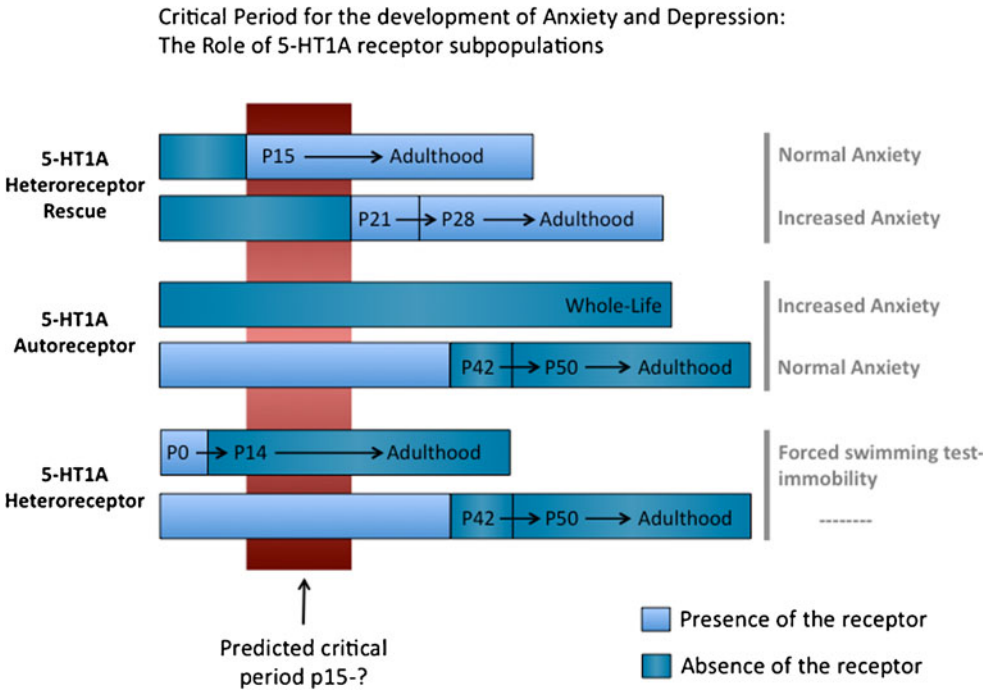

Fig. 2 A summary of data supporting a critical role for 5-HT_{1A} autoreceptors and heteroreceptors in establishing normal anxiety and depressive-like behavior circuits. *Top*, Transgenic forebrain expression of 5-HT_{1A} heteroreceptors in a knockout background beginning at day 15 is sufficient to rescue normal behavior, while graded re-expression of the heteroreceptor beginning at P21 results in an anxious phenotype (Gross et al. 2002). *Middle*, Supression of 5-HT_{1A} autoreceptors throughout life resulted in an increased anxiety-like behavior in the adult. Conversely, loss of endogenous autoreceptors in adulthood is not sufficient to impact anxiety-like behavior (Richardson-Jones et al. 2011). *Bottom*, Supression of 5-HT_{1A} heteroreceptors throughout life resulted in an increased immobility in the forced swim test in the adult. Conversely, loss of endogenous heteroreceptors in adulthood is not sufficient to impact behavior (Richardson-Jones et al. 2011). These results suggest that a critical period exists beginning on the P15. The end of this critical period remains unclear

sensitive to these environmental insults than are others. As described above, there is a growing body of literature describing the effects of a functional polymorphism in the promoter of the human 5-HT_{1A} receptor (Lemonde et al. 2003). The polymorphism C(−1019)G is thought to result in altered levels of 5-HT_{1A} receptor expression and is thought to moderate susceptibility to stress (Albert and Lemonde 2004). The time course of susceptibility has not been mapped out for this polymorphism. Given the evidence that 5-HT_{1A} receptors are important during normal development in the mouse, at least some of the effects seen from this polymorphism in human populations may be due to alterations in circuit formation that occurred during critical developmental periods.

Conclusions

The elucidation of the role of 5-HT_{1A} receptors in the development and/or stabilization of circuitry that mediates emotional behaviors has been complicated by the fact that the receptor exists as two distinct populations, having the dual ability to modulate both global serotonin levels, and local responses to released serotonin. However, various approaches are being used to cast light on the role of 5-HT_{1A} auto- and heteroreceptors in mood disorders. Experimental strategies include pharmacological approaches, using local administration by microinjection or using novel biased agonists targeting receptor subpopulations, and new transgenic approaches that allow independent manipulation of endogenous autoreceptors and heteroreceptors. Results from these new experimental strategies, in conjunction with results from more classic approaches, have provided new perspectives on how 5-HT_{1A} receptor subpopulations differentially influence anxiety and depression.

However, although it is well established that 5-HT_{1A} receptors act developmentally to establish normal anxiety and depressive-like behaviors, the specific mechanisms underlying the developmental role of each subpopulation require further investigation. In addition, although disruption of 5-HT_{1A} receptor functioning during adulthood does not result in a prolonged anxious or depressive phenotype, the 5-HT_{1A} receptor may still play a role in the regulation of the plasticity of behavior once circuits mediating anxiety are functional. It is possible that there is time after the circuits are developed when the system remains plastic and enduring, even permanent changes to be effected by alterations in 5-HT_{1A} receptor function. This may be true for the development of pathological states but also for therapeutic interventions, potentially opening new avenues for improved treatment of debilitating mood deficit disorders

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References

Aan het Rot M, Mathew SJ, Charney DS (2009) Neurobiological mechanisms in major depressive disorder. CMAJ 180(3):305–313

Adell A, Carceller A, Artigas F (1991) Regional distribution of extracellular 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in the brain of freely moving rats. J Neurochem 56:709–712

Akimova E, Lanzenberger R, Kasper S (2009) The serotonin-1A receptor in anxiety disorders. Biol Psychiatry 66:627–635

Albert PR, Lemonde S (2004) 5-HT1A receptors, gene repression, and depression: guilt by association. Neuroscientist 10:575–593

Albert PR, Lembo P, Storring JM, Charest A, Saucier C (1996) The 5-HT1A receptor: signaling, desensitization, and gene transcription. Neuropsychopharmacology 1:19–25

Andrade R, Malenka RC, Nicoll RA (1986) A G protein couples serotonin and GABAB receptors to the same channels in hippocampus. Science 234(4781):1261–1265

Andrews N, Hogg S, Gonzalez LE, File SE (1994) 5-HT1A receptors in the median raphe nucleus and dorsal hippocampus may mediate anxiolytic and anxiogenic behaviours respectively. Eur J Pharmacol 264(3):259–264

Ansorge MS, Morelli E, Gingrich JA (2008) Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. J Neurosci 28(1):199–207

Anttila S, Huuhka K, Huuhka M, Rontu R, Hurme M, Leinonen E, Lehtimaki T (2007) Interaction between 5-HT1A and BDNF genotypes increases the risk of treatment-resistant depression. J Neural Transm 114:1065–1068

Arias B, Arranz MJ, Gasto C, Catalan R, Pintor L, Gutierrez B, Kerwin RW, Fananas L (2002) Analysis of structural polymorphisms and C-1018G promoter variant of the 5-HT(1A) receptor gene as putative risk factors in major depression. Mol Psychiatry 7:930–932

Arias B, Catalan R, Gasto C, Gutierrez B, Fananas L (2005) Evidence for a combined genetic effect of the 5-HT1A receptor and serotonin transporter genes in the clinical outcome of major depressive patients treated with citalopram. J Psychopharmacol 19:166–172

Arranz B, Eriksson A, Mellerup E, Plenge P, Marcusson J (1994) Brain 5-HT1A, 5-HT1D, and 5-HT2 receptors in suicide victims. Biol Psychiatry 35:457–463

Artigas F, Bel N, Casanovas JM, Romero L (1996) Adaptative changes of the serotonergic system after antidepressant treatments. Adv Exp Med Biol 398:51–59

Artigas F, Adell A, Celada P (2006) Pindolol augmentation of antidepressant response. Curr Drug Targets 7:139–147

Ase AR, Reader TA, Hen R, Riad M, Descarries L (2000) Altered serotonin and dopamine metabolism in the CNS of serotonin 5-HT(1A) or 5-HT(1B) receptor knockout mice. J Neurochem 75(6): 2415–2426

Assié MB, Bardin L, Auclair AL, Carilla-Durand E, Depoortère R, Koek W, Kleven MS, Colpaert F, Vacher B, Newman-Tancredi A (2010) F15599, a highly selective post-synaptic 5-HT(1A) receptor agonist: in-vivo profile in behavioural models of antidepressant and serotonergic activity. Int J Neuropsychopharmacol 13(10):1285–1298

Azmitia EC, Gannon PJ, Kheck NM, Whitaker-Azmitia PM (1996) Cellular localization of the 5-HT1A receptor in primate brain neurons and glial cells. Neuropsychopharmacology 14:35–46

Bang SJ, Jensen P, Dymecki SM, Commons KG (2012) Projections and interconnections of genetically defined serotonin neurons in mice. Eur J Neurosci 35(1):85–96

Barnes NM, Sharp T (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38:1083–1152

Bartoszyk GD, Hegenbart R, Ziegler H (1997) EMD 68843, a serotonin reuptake inhibitor with selective presynaptic 5-HT1A receptor agonistic properties. Eur J Pharmacol 322(2–3):147–153

Beck SG, Choi KC, List TJ (1992) Comparison of 5-hydroxytryptamine1A-mediated hyperpolarization in CA1 and CA3 hippocampal pyramidal cells. J Pharmacol Exp Ther 263: 350–359

Benes FM, Taylor JB, Cunningham MC (2000) Convergence and plasticity of monoaminergic systems in the medial prefrontal cortex during the postnatal period: implications for the development of psychopathology. Cereb Cortex 10(10):1014–1027

Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ (2004) Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635. Mol Psychiatry 9:386–392

Blier P (2003) The pharmacology of putative early-onset antidepressant strategies. Eur Neuropsychopharmacol 13(2):57–66

Blier P, De Montigny C (1983) Electrophysiological investigations on the effect of repeated zimelidine administration on serotonergic neurotransmission in the rat. J Neurosci 3:1270–1278

Blier P, de Montigny C (1994) Current advances and trends in the treatment of depression. Trends Pharmacol Sci 15:220–226

Bockaert J, Claeysen S, Becamel C, Dumuis A, Marin P (2006) Neuronal 5-HT metabotropic receptors: fine-tuning of their structure, signaling, and roles in synaptic modulation. Cell Tissue Res 326:553–572

Boldrini M, Underwood MD, Mann JJ, Arango V (2008) Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides. J Psychiatr Res 42:433–442

Bortolozzi A, Amargos-Bosch M, Toth M, Artigas F, Adell A (2004) In vivo efflux of serotonin in the dorsal raphe nucleus of 5-HT1A receptor knockout mice. J Neurochem 88:1373–1379

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389

Celada P, Puig MV, Casanovas JM, Guillazo G, Artigas F (2001) Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: involvement of serotonin-1A, GABA(A), and glutamate receptors. J Neurosci 21:9917–9929

Celada P, Bortolozzi A, Artigas F (2013) Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs 27(9):703–716

Charney DS (1998) Monoamine dysfunction and the pathophysiology and treatment of depression. J Clin Psychiatry 59(Suppl 14):11–14

Cheetham SC, Crompton MR, Katona CL, Horton RW (1990) Brain 5-HT1 binding sites in depressed suicides. Psychopharmacol (Berl) 102:544–548

Choi WS, Lee BH, Yang JC, Kim YK (2010) Association study between 5-HT1A receptor gene C(−1019)G polymorphism and panic disorder in a Korean population. Psychiatry Investig 7:141–146

Corey-Lisle PK, Nash R, Stang P, Swindle R (2004) Response, partial response, and nonresponse in primary care treatment of depression. Arch Int Med 164:1197–1204

Costello EJ, Pine DS, Hammen C, March JS, Plotsky PM, Weissman MM, Biederman J, Goldsmith HH, Kaufman J, Lewinsohn PM, Hellander M, Hoagwood K, Koretz DS, Nelson CA, Leckman JF (2002) Development and natural history of mood disorders. Biol Psychiatry 52(6):529–542

Covington HE 3rd, Vialou V, Nestler EJ (2010) From synapse to nucleus: novel targets for treating depression. Neuropharmacology 58(4–5): 683–693

Czesak M, Lemonde S, Peterson EA, Rogaeva A, Albert PR (2006) Cell-specific repressor or enhancer activities of Deaf-1 at a serotonin 1A receptor gene polymorphism. J Neurosci 26:1864–1871

Czesak M, Le François B, Millar AM, Deria M, Daigle M, Visvader JE, Anisman H, Albert PR (2012) Increased serotonin-1A (5-HT1A) autoreceptor expression and reduced raphe serotonin levels in deformed epidermal autoregulatory factor-1 (Deaf-1) gene knock-out mice. J Biol Chem 287(9):6615–6627

Dawson LA, Nguyen HQ (2000) The role of 5-HT(1A) and 5-HT(1B/1D) receptors on the modulation of acute fluoxetine-induced changes in extracellular 5-HT: the mechanism of action of (+/−)pindolol. Neuropharmacology 39:1044–1052

De Almeida RM, Giovenardi M, Charchat H, Lucion AB (1998) 8-OH-DPAT in the median raphe nucleus decreases while in the medial septal area it may increase anxiety in female rats. Neurosci Biobehav Rev 23(2):259–264

De Vry J (1995) 5-HT1A receptor agonists: recent developments and controversial issues. Psychopharmacology (Berlin) 121(1):1–26, Review

Depoortère R, Auclair AL, Bardin L, Colpaert FC, Vacher B, Newman-Tancredi A (2010) F15599, a preferential post-synaptic 5-HT1A receptor agonist: activity in models of cognition in comparison with reference 5-HT1A receptor agonists. Eur Neuropsychopharmacol 20(9):641–654. doi:10.1016/j.euroneuro.2010.04.005

Detke MJ, Wieland S, Lucki I (1995) Blockade of the antidepressant-like effects of 8-OH-DPAT, buspirone and desipramine in the rat forced swim test by 5HT1A receptor antagonists. Psychopharmacology (Berlin) 119:47–54

Dillon KA, Gross-Isseroff R, Israeli M, Biegon A (1991) Autoradiographic analysis of serotonin 5-HT1A receptor binding in the human brain postmortem: effects of age and alcohol. Brain Res 554:56–64

Domschke K, Braun M, Ohrmann P, Suslow T, Kugel H, Bauer J, Hohoff C, Kersting A, Engelien A, Arolt V, Heindel W, Deckert J (2006) Association of the functional −1019C/G 5-HT1A polymorphism with prefrontal cortex and amygdala activation measured with 3 T fMRI in panic disorder. Int J Neuropsychopharmacol 9:349–355

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C (1999) PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 46:1375–1387

Drevets WC, Frank E, Price JC, Kupfer DJ, Greer PJ, Mathis C (2000) Serotonin type-1A receptor imaging in depression. Nucl Med Biol 27:499–507

Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, Mathis C (2007) Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nucl Med Biol 34:865–877

Duman RS (2004) Depression: a case of neuronal life and death? Biol Psychiatry 56(3):140–145

Durant C, Christmas D, Nutt D (2010) The pharmacology of anxiety. Curr Top Behav Neurosci 2:303–330

Dwivedi Y, Rizavi HS, Roberts RC, Conley RC, Tamminga CA, Pandey GN (2001) Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. J Neurochem 77(3):916–928

Dwivedi Y, Rizavi HS, Zhang H, Roberts RC, Conley RR, Pandey GN (2009) Aberrant extracellular signal-regulated kinase (ERK)1/2 signalling in suicide brain: role of ERK kinase 1 (MEK1). Int J Neuropsychopharmacol 12(10):1337–1354

El Mansari M, Blier P (2005) Responsiveness of 5-HT(1A) and 5-HT2 receptors in the rat orbitofrontal cortex after long-term serotonin reuptake inhibition. J Psychiatry Neurosci 30:268–274

Fakra E, Hyde LW, Gorka A, Fisher PM, Munoz KE, Kimak M, Halder I, Ferrell RE, Manuck SB, Hariri AR (2009) Effects of HTR1A C(−1019)G on amygdala reactivity and trait anxiety. Arch Gen Psychiatry 66:33–40

File SE, Gonzalez LE (1996) Anxiolytic effects in the plus-maze of 5-HT1A-receptor ligands in dorsal raphe and ventral hippocampus. Pharmacol Biochem Behav 54(1):123–128

File SE, Gonzalez LE, Andrews N (1996) Comparative study of pre- and postsynaptic 5-HT1A receptor modulation of anxiety in two ethological animal tests. J Neurosci 16(15):4810–4815

Fletcher A, Forster EA, Bill DJ, Brown G, Cliffe IA, Hartley JE, Jones DE, McLenachan A, Stanhope KJ, Critchley DJ, Childs KJ,

Middlefell VC, Lanfumey L, Corradetti R, Laporte AM, Gozlan H, Hamon M, Dourish CT (1996) Electrophysiological, biochemical, neurohormonal and behavioural studies with WAY-100635, a potent, selective and silent 5-HT1A receptor antagonist. Behav Brain Res 73:337–353

Fox K (1992) A critical period for experience-dependent synaptic plasticity in rat barrel cortex. J Neurosci 12:1826–1838

Ganasen KA, Stein DJ (2010) Pharmacotherapy of social anxiety disorder. Curr Top Behav Neurosci 2:487–503

Gardier AM, Malagie I, Trillat AC, Jacquot C, Artigas F (1996) Role of 5-HT1A autoreceptors in the mechanism of action of serotoninergic antidepressant drugs: recent findings from in vivo microdialysis studies. Fundam Clin Pharmacol 10:16–27

Gartside SE, Umbers V, Hajós M, Sharp T (1995) Interaction between a selective 5-HT1A receptor antagonist and an SSRI in vivo: effects on 5-HT cell firing and extracellular 5-HT. Br J Pharmacol 115(6): 1064–1070

Goodfellow NM, Benekareddy M, Vaidya VA, Lambe EK (2009) Layer II/III of the prefrontal cortex: inhibition by the serotonin 5-HT1A receptor in development and stress. J Neurosci 29:10094–10103

Gordon JA, Hen R (2004) The serotonergic system and anxiety. Neuromol Med 5:27–40

Griebel G, Holmes A (2013) 50 years of hurdles and hope in anxiolytic drug discovery. Nat Rev Drug Discov 12(9):667–687. doi:10.1038/nrd4075

Gross C, Hen R (2004) The developmental origins of anxiety. Nat Rev Neurosci 5:545–552

Gross C, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R (2002) Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. Nature 416:396–400

Guilloux JP, David DJ, Guiard BP, Chenu F, Reperant C, Toth M, Bourin M, Gardier AM (2006) Blockade of 5-HT1A receptors by (+/−)-pindolol potentiates cortical 5-HT outflow, but not antidepressant-like activity of paroxetine: microdialysis and behavioral approaches in 5-HT1A receptor knockout mice. Neuropsychopharmacology 31: 2162–2172

Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, Dodel R, Ekman M, Faravelli C, Fratiglioni L, Gannon B, Jones DH, Jennum P, Jordanova A, Jönsson L, Karampampa K, Knapp M, Kobelt G, Kurth T, Lieb R, Linde M, Ljungcrantz C, Maercker A, Melin B, Moscarelli M, Musayev A, Norwood F, Preisig M, Pugliatti M, Rehm J, Salvador-Carulla L, Schlehofer B, Simon R, Steinhausen HC, Stovner LJ, Vallat JM, Van den Bergh P, van Os J, Vos P, Xu W, Wittchen HU, Jönsson B, Olesen J; CDBE2010Study Group. Cost of disorders of the brain in Europe 2010. (2011) Eur Neuropsychopharmacol. 21(10):718–79. doi: 10.1016/j.euroneuro.2011.08.008. Epub 2011 Sep 15. Erratum in: Eur Neuropsychopharmacol. 2012 Mar;22(3):237–8. den Bergh, Peter Van [corrected to Van den Bergh, Peter].

Hajos M, Hajos-Korcsok E, Sharp T (1999) Role of the medial prefrontal cortex in 5-HT1A receptor-induced inhibition of 5-HT neuronal activity in the rat. Br J Pharmacol 126:1741–1750

Hamon M, Gozlan H, el Mestikawy S, Emerit MB, Bolanos F, Schechter L (1990) The central 5-HT1A receptors: pharmacological, biochemical, functional, and regulatory properties. Ann N Y Acad Sci 600: 114–129, discussion 129–31

Heisler LK, Chu HM, Brennan TJ, Danao JA, Bajwa P, Parsons LH, Tecott LH (1998) Elevated anxiety and antidepressant-like responses in serotonin 5-HT1A receptor mutant mice. Proc Natl Acad Sci U S A 95:15049–15054

Hervas I, Queiroz CM, Adell A, Artigas F (2000) Role of uptake inhibition and autoreceptor activation in the control of 5-HT release in the frontal cortex and dorsal hippocampus of the rat. Br J Pharmacol 130:160–166

Hettema JM, An SS, van den Oord EJ, Neale MC, Kendler KS, Chen X (2008) Association study between the serotonin 1A receptor (HTR1A) gene and neuroticism, major depression, and anxiety disorders. Am J Med Genet B Neuropsychiatr Genet 147B:661–666

Higgins GA, Jones BJ, Oakley NR (1992) Effect of 5-HT1A receptor agonists in two models of anxiety after dorsal raphe injection. Psychopharmacology (Berlin) 106(2):261–267

Hirvonen J, Karlsson H, Kajander J, Lepola A, Markkula J, Rasi-Hakala H, Nagren K, Salminen JK, Hietala J (2008) Decreased brain serotonin 5-HT1A receptor availability in medication-naive patients with major depressive disorder: an in-vivo imaging study using PET and [carbonyl-11C]WAY-100635. Int J Neuropsychopharmacol 11: 465–476

Hjorth S, Auerbach SB (1994) Further evidence for the importance of 5-HT1A autoreceptors in the action of selective serotonin reuptake inhibitors. Eur J Pharmacol 260(2–3):251–255

Hjorth S, Sharp T (1991) Effect of the 5-HT1A receptor agonist 8-OH-DPAT on the release of 5-HT in dorsal and median raphe-innervated rat brain regions as measured by in vivo microdialysis. Life Sci 48: 1779–1786

Hjorth S, Bengtsson HJ, Milano S (1996) Raphe 5-HT1A autoreceptors, but not postsynaptic 5-HT1A receptors or beta-adrenoceptors, restrain the citalopram-induced increase in extracellular 5-hydroxytryptamine in vivo. Eur J Pharmacol 316(1):43–47

Hogg S, Andrews N, File SE (1994) Contrasting behavioural effects of 8-OH DPAT in the dorsal raphé nucleus and ventral hippocampus. Neuropharmacology 33(3–4):343–348

Hong CJ, Chen TJ, Yu YW, Tsai SJ (2006) Response to fluoxetine and serotonin 1A receptor (C-1019G) polymorphism in Taiwan Chinese major depressive disorder. Pharmacogenomics J 6:27–33

Hoyer D, Martin G (1997) 5-HT receptor classification and nomenclature: towards a harmonization with the human genome. Neuropharmacology 36:419–428

Huang YY, Battistuzzi C, Oquendo MA, Harkavy-Friedman J, Greenhill L, Zalsman G, Brodsky B, Arango V, Brent DA, Mann JJ (2004) Human 5-HT1A receptor C(−1019)G polymorphism and psychopathology. Int J Neuropsychopharmacol 7:441–451

Jacobsen KX, Vanderluit JL, Slack RS, Albert PR (2008) HES1 regulates 5-HT1A receptor gene transcription at a functional polymorphism: essential role in developmental expression. Mol Cell Neurosci 38(3):349–358

Jans LA, Riedel WJ, Markus CR, Blokland A (2007) Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. Mol Psychiatry 12(6):522–543, Epub 2006 Dec 12

Joyce JN, Shane A, Lexow N, Winokur A, Casanova MF, Kleinman JE (1993) Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics. Neuropsychopharmacology 8: 315–336

Klemenhagen KC, Gordon JA, David DJ, Hen R, Gross CT (2006) Increased fear response to contextual cues in mice lacking the 5-HT1A receptor. Neuropsychopharmacology 31:101–111

Knobelman DA, Hen R, Blendy JA, Lucki I (2001) Regional patterns of compensation following genetic deletion of either 5-hydroxytryptamine(1A) or 5-hydroxytryptamine(1B) receptor in the mouse. J Pharmacol Exp Ther 298(3):1092–1100

Kraus MR, Al-Taie O, Schafer A, Pfersdorff M, Lesch KP, Scheurlen M (2007) Serotonin-1A receptor gene HTR1A variation predicts interferon-induced depression in chronic hepatitis C. Gastroenterology 132:1279–1286

Kusserow H, Davies B, Hortnagl H, Voigt I, Stroh T, Bert B, Deng DR, Fink H, Veh RW, Theuring F (2004) Reduced anxiety-related behaviour in transgenic mice overexpressing serotonin 1A receptors. Brain Res Mol Brain Res 129:104–116

Lacivita E, Leopoldo M, Berardi F, Perrone R (2008) 5-HT1A receptor, an old target for new therapeutic agents. Curr Top Med Chem 8(12): 1024–1034

Lanzenberger RR, Mitterhauser M, Spindelegger C, Wadsak W, Klein N, Mien LK, Holik A, Attarbaschi T, Mossaheb N, Sacher J, Geiss-Granadia T, Kletter K, Kasper S, Tauscher J (2007) Reduced serotonin-1A receptor binding in social anxiety disorder. Biol Psychiatry 61(9):1081–1089

Le Francois B, Czesak M, Steubl D, Albert PR (2008) Transcriptional regulation at a HTR1A polymorphism associated with mental illness. Neuropharmacology 55:977–985

Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou XM, Albert PR (2003) Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci 23:8788–8799

Lemonde S, Du L, Bakish D, Hrdina P, Albert PR (2004) Association of the C(−1019)G 5-HT1A functional promoter polymorphism with antidepressant response. Int J Neuropsychopharmacol 7:501–506

Leonardo ED, Hen R (2008) Anxiety as a developmental disorder. Neuropsychopharmacology 33:134–140

Lesch KP, Gutknecht L (2004) Focus on The 5-HT1A receptor: emerging role of a gene regulatory variant in psychopathology and pharmacogenetics. Int J Neuropsychopharmacol 7:381–385

Levin GM, Bowles TM, Ehret MJ, Langaee T, Tan JY, Johnson JA, Millard WJ (2007) Assessment of human serotonin 1A receptor polymorphisms and SSRI responsiveness. Mol Diagn Ther 11: 155–160

Lira A, Zhou M, Castanon N, Ansorge MS, Gordon JA, Francis JH, Bradley-Moore M, Lira J, Underwood MD, Arango V, Kung HF, Hofer MA, Hen R, Gingrich JA (2003) Altered depression-related behaviors and functional changes in the dorsal raphe nucleus of serotonin transporter-deficient mice. Biol Psychiatry 54:960–971

Liu YF, Ghahremani MH, Rasenick MM, Jakobs KH, Albert PR (1999) Stimulation of cAMP synthesis by Gi-coupled receptors upon ablation of distinct Galphai protein expression. Gi subtype specificity of the 5-HT1A receptor. J Biol Chem 274:16444–16450

Lo Iacono L, Gross C (2008) Alpha-Ca2+/calmodulin-dependent protein kinase II contributes to the developmental programming of anxiety in serotonin receptor 1A knock-out mice. J Neurosci 28:6250–6257

Lowther S, De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW (1997) 5-HT1A receptor binding sites in post-mortem brain samples from depressed suicides and controls. J Affect Disord 42:199–207

Lucki I (1991) Behavioral studies of serotonin receptor agonists as antidepressant drugs. J Clin Psychiatry 52(Suppl):24–31

Mannoury la Cour C, Boni C, Hanoun N, Lesch KP, Hamon M, Lanfumey L (2001) Functional consequences of 5-HT transporter gene disruption on 5-HT(1a) receptor-mediated regulation of dorsal raphe and hippocampal cell activity. J Neurosci 21:2178–2185

Marazziti D, Palego L, Giromella A, Mazzoni MR, Borsini F, Mayer N, Naccarato AG, Lucacchini A, Cassano GB (2002) Region-dependent effects of flibanserin and buspirone on adenylyl cyclase activity in the human brain. Int J Neuro Psychopharmacol 5:131–140

Matsubara S, Arora RC, Meltzer HY (1991) Serotonergic measures in suicide brain: 5-HT1A binding sites in frontal cortex of suicide victims. J Neural Transm Gen Sect 85:181–194

Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, Castren E, Maffei L (2008) The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science 320:385–388

Maya Vetencourt JF, Tiraboschi E, Spolidoro M, Castren E, Maffei L (2011) Serotonin triggers a transient epigenetic mechanism that reinstates adult visual cortex plasticity in rats. Eur J Neurosci 33: 49–57

Mayorga AJ, Dalvi A, Page ME, Zimov-Levinson S, Hen R, Lucki I (2001) Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. J Pharmacol Exp Ther 298(3):1101–1107

McAllister-Williams RH, Massey AE (2003) EEG effects of buspirone and pindolol: a method of examining 5-HT1A receptor function in humans. Psychopharmacology (Berlin) 166(3):284–293, Epub 2003 Feb 13

Meller E, Goldstein M, Bohmaker K (1990) Receptor reserve for 5-hydroxytryptamine1A-mediated inhibition of serotonin synthesis: possible relationship to anxiolytic properties of 5-hydroxytryptamine1A agonists. Mol Pharmacol 37:231–237

Meltzer CC, Price JC, Mathis CA, Butters MA, Ziolko SK, Moses-Kolko E, Mazumdar S, Mulsant BH, Houck PR, Lopresti BJ, Weissfeld LA, Reynolds CF (2004) Serotonin 1A receptor binding and treatment response in late-life depression. Neuropsychopharmacology 29:2258–2265

Molina E, Cervilla J, Rivera M, Torres F, Bellon JA, Moreno B, King M, Nazareth I, Gutierrez B (2011) Polymorphic variation at the serotonin 1-A receptor gene is associated with comorbid depression and generalized anxiety. Psychiatr Genet 21:195–201

Monroe SM, Simons AD (1991) Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychol Bull 110(3):406–425

Murrin LC, Sanders JD, Bylund DB (2007) Comparison of the maturation of the adrenergic and serotonergic neurotransmitter systems in the brain: implications for differential drug effects on juveniles and adults. Biochem Pharmacol 73:1225–1236

Nakamura K, Sugawara Y, Sawabe K, Ohashi A, Tsurui H, Xiu Y, Ohtsuji M, Lin QS, Nishimura H, Hasegawa H, Hirose S (2006) Late developmental stage-specific role of tryptophan hydroxylase 1 in brain serotonin levels. J Neurosci 26:530–534

Nash JR, Sargent PA, Rabiner EA, Hood SD, Argyropoulos SV, Potokar JP, Grasby PM, Nutt DJ (2008) Serotonin 5-HT1A receptor binding in people with panic disorder: positron emission tomography study. Br J Psychiatry 193(3):229–234

Neff CD, Abkevich V, Packer JC, Chen Y, Potter J, Riley R, Davenport C, DeGrado WJ, Jammulapati S, Bhathena A, Choi WS, Kroeger PE, Metzger RE, Gutin A, Skolnick MH, Shattuck D, Katz DA (2009) Evidence for HTR1A and LHPP as interacting genetic risk factors in major depression. Mol Psychiatry 14:621–630

Nemeroff CB (2002) Comorbidity of mood and anxiety disorders: the rule, not the exception? Am J Psychiatry 159:3–4

Nestler EJ (2006) Carlezon WA Jr (2006) The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 59(12):1151–1159

Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, Eckelman W, Herscovitch P, Charney DS, Drevets WC (2004) Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci 24:589–591

Newman-Tancredi A (2011) Biased agonism at serotonin 5-HT1A receptors: preferential postsynaptic activity for improved therapy of CNS disorders. Neuropsychiatry 1(2):149–164

Newman-Tancredi A, Martel JC, Assié MB, Buritova J, Lauressergues E, Cosi C, Heusler P, Bruins Slot L, Colpaert FC, Vacher B (2009) Cussac D (2009) Signal transduction and functional selectivity of F15599, a preferential post-synaptic 5-HT1A receptor agonist. Br J Pharmacol 156(2):338–353

Nikolaus S, Antke C, Beu M, Müller HW (2010) Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders—results from in vivo imaging studies. Rev Neurosci 21(2):119–139, Review

Oberlander TF, Gingrich JA, Ansorge MS (2009) Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. Clin Pharmacol Ther 86:672–677

Olivier JD, Van Der Hart MG, Van Swelm RP, Dederen PJ, Homberg JR, Cremers T, Deen PM, Cuppen E, Cools AR, Ellenbroek BA (2008) A study in male and female 5-HT transporter knockout rats: an animal model for anxiety and depression disorders. Neuroscience 152:573–584

Page ME, Cryan JF, Sullivan A, Dalvi A, Saucy B, Manning DR, Lucki I (2002) Behavioral and neurochemical effects of 5-(4-[4-(5-Cyano-3-indolyl)-butyl)-butyl]-1-piperazinyl)-benzofuran-2-carboxamide (EMD 68843): a combined selective inhibitor of serotonin reuptake and 5-hydroxytryptamine(1A) receptor partial agonist. J Pharmacol Exp Ther 302(3):1220–1227

Palchaudhuri M, Flugge G (2005) 5-HT1A receptor expression in pyramidal neurons of cortical and limbic brain regions. Cell Tissue Res 321:159–172

Palego L, Giromella A, Marazziti D, Borsini F, Naccarato AG, Giannaccini G, Lucacchini A, Cassano GB, Mazzoni MR (1999) Effects of postmortem delay on serotonin and (+)8-OH-DPAT-mediated inhibition of adenylyl cyclase activity in rat and human brain tissues. Brain Res 816:165–174

Parks CL, Robinson PS, Sibille E, Shenk T, Toth M (1998) Increased anxiety of mice lacking the serotonin1A receptor. Proc Natl Acad Sci U S A 95:10734–10739

Parsey RV (2010) Serotonin receptor imaging: clinically useful? J Nucl Med 51(10):1495–1498

Parsey RV, Olvet DM, Oquendo MA, Huang YY, Ogden RT, Mann JJ (2006) Higher 5-HT1A receptor binding potential during a major depressive episode predicts poor treatment response: preliminary data from a naturalistic study. Neuropsychopharmacology 31: 1745–1749

Parsey RV, Ogden RT, Miller JM, Tin A, Hesselgrave N, Goldstein E, Mikhno A, Milak M, Zanderigo F, Sullivan GM, Oquendo MA, Mann JJ (2010) Higher serotonin 1A binding in a second major depression cohort: modeling and reference region considerations. Biol Psychiatry 68:170–178

Pitchot W, Hansenne M, Pinto E, Reggers J, Fuchs S, Ansseau M (2005) 5-Hydroxytryptamine 1A receptors, major depression, and suicidal behavior. Biol Psychiatry 58(11):854–858

Pompeiano M, Palacios JM, Mengod G (1992) Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. J Neurosci 12(2):440–453

Portella MJ, de Diego-Adeliño J, Ballesteros J, Puigdemont D, Oller S, Santos B, Álvarez E, Artigas F, Pérez V (2011) Can we really accelerate and enhance the selective serotonin reuptake inhibitor antidepressant effect? A randomized clinical trial and a meta-analysis of pindolol in nonresistant depression. J Clin Psychiatry 72(7):962–969. doi:10.4088/JCP.09m05827blu

Qi X, Lin W, Li J, Pan Y, Wang W (2006) The depressive-like behaviors are correlated with decreased phosphorylation of mitogen-activated protein kinases in rat brain following chronic forced swim stress. Behav Brain Res 175(2):233–240

Qi X, Lin W, Li J, Li H, Wang W, Wang D, Sun M (2008) Fluoxetine increases the activity of the ERK-CREB signal system and alleviates the depressive-like behavior in rats exposed to chronic forced swim stress. Neurobiol Dis 31(2):278–285

Qi X, Lin W, Wang D, Pan Y, Wang W, Sun M (2009) A role for the extracellular signal-regulated kinase signal pathway in depressive-like behavior. Behav Brain Res 199(2):203–209

Ramboz S, Oosting R, Amara DA, Kung HF, Blier P, Mendelsohn M, Mann JJ, Brunner D, Hen R (1998) Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. Proc Natl Acad Sci U S A 95:14476–14481

Ravindran LN, Stein MB (2010) The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry 71(7):839–854, Review

Riad M, Garcia S, Watkins KC, Jodoin N, Doucet E, Langlois X, el Mestikawy S, Hamon M, Descarries L (2000) Somatodendritic localization of 5-HT1A and preterminal axonal localization of 5-HT1B serotonin receptors in adult rat brain. J Comp Neurol 417: 181–194

Richardson-Jones JW, Craige CP, Guiard BP, Stephen A, Metzger KL, Kung HF, Gardier AM, Dranovsky A, David DJ, Beck SG, Hen R, Leonardo ED (2010) 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. Neuron 65:40–52

Richardson-Jones JW, Craige CP, Nguyen TH, Kung HF, Gardier AM, Dranovsky A, David DJ, Guiard BP, Beck SG, Hen R, Leonardo ED (2011) Serotonin-1A autoreceptors are necessary and sufficient for the normal formation of circuits underlying innate anxiety. J Neurosci 31:6008–6018

Rollema H, Clarke T, Sprouse JS, Schulz DW (1996) Combined administration of a 5-hydroxytryptamine 5-HT1D antagonist and a 5-HT reuptake inhibitor synergistically increases 5-HT release in guinea pig hypothalamus in vivo. J Neurochem 67:2204–2207

Rothe C, Gutknecht L, Freitag C, Tauber R, Mossner R, Franke P, Fritze J, Wagner G, Peikert G, Wenda B, Sand P, Jacob C, Rietschel M, Nothen MM, Garritsen H, Fimmers R, Deckert J, Lesch KP (2004) Association of a functional 1019C>G 5-HT1A receptor gene polymorphism with panic disorder with agoraphobia. Int J Neuropsychopharmacol 7:189–192

Ruhe HG, Mason NS, Schene AH (2007) Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry 12:331–359

Rush AJ (2000) The use of placebos in unipolar major depression: the current status. Biol Psychiatry 47:745–747

Samuels BA, Leonardo ED, Gadient R, Williams A, Zhou J, David DJ, Gardier AM, Wong EH, Hen R (2011) Modeling treatment-resistant depression. Neuropharmacology 61(3):408–413

Santana N, Bortolozzi A, Serrats J, Mengod G, Artigas F (2004) Expression of serotonin1A and serotonin2A receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. Cereb Cortex 14:1100–1109

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301(5634):805–809

Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ (2000) Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry 57:174–180

Serretti A, Artioli P, Lorenzi C, Pirovano A, Tubazio V, Zanardi R (2004) The C(−1019)G polymorphism of the 5-HT1A gene promoter and antidepressant response in mood disorders: preliminary findings. Int J Neuropsychopharmacol 7:453–460

Skolnick P, Popik P, Trullas R (2009) Glutamate-based antidepressants: 20 years on. Trends Pharmacol Sci 30(11):563–569, Review

Sorbera LA, Rabasseda X, Silvestre J, Castaner J (2001) Vilazodone hydrochloride–antidepressant–5-HT1A partial agonist–5-HT reuptake inhibitor. Drugs Future 26:247–252

Sprouse JS, Aghajanian GK (1986) (−)-Propranolol blocks the inhibition of serotonergic dorsal raphe cell firing by 5-HT1A selective agonists. Eur J Pharmacol 128:295–298

Stefański R, Pałejko W, Bidziński A, Kostowski W, Płaźnik A (1993) Serotonergic innervation of the hippocampus and nucleus accumbens septi and the anxiolytic-like action of midazolam and 5-HT1A receptor agonists. Neuropharmacology 32(10):977–985

Stockmeier CA, Shapiro LA, Haycock JW, Thompson PA, Lowy MT (1996) Quantitative subregional distribution of serotonin1A receptors and serotonin transporters in the human dorsal raphe. Brain Res 727:1–12

Stockmeier CA, Shapiro LA, Dilley GE, Kolli TN, Friedman L, Rajkowska G (1998) Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression—postmortem evidence for decreased serotonin activity. J Neurosci 18(18):7394–7401

Strobel A, Gutknecht L, Rothe C, Reif A, Mossner R, Zeng Y, Brocke B, Lesch KP (2003) Allelic variation in 5-HT1A receptor expression is

associated with anxiety- and depression-related personality traits. J Neural Transm 110:1445–1453

Trowbridge S, Narboux-Neme N, Gaspar P (2011) Genetic models of serotonin (5-HT) depletion: what do they tell us about the developmental role of 5-HT? Anat Rec 294:1615–1623

Valdizan EM, Castro E, Pazos A (2010) Agonist-dependent modulation of G-protein coupling and transduction of 5-HT1A receptors in rat dorsal raphe nucleus. Int J Neuro Psychopharmacol 13:835–843

Van Bogaert M, Oosting R, Toth M, Groenink L, van Oorschot R, Olivier B (2006) Effects of genetic background and null mutation of 5-HT1A receptors on basal and stress-induced body temperature: modulation by serotonergic and GABAA-ergic drugs. Eur J Pharmacol 550:84–90

van Kleef ES, Gaspar P, Bonnin A (2012) Insights into the complex influence of 5-HT signaling on thalamocortical axonal system development Eur. J Neurosci 35:1563–1572

Verge D, Daval G, Patey A, Gozlan H, el Mestikawy S, Hamon M (1985) Presynaptic 5-HT autoreceptors on serotonergic cell bodies and/or dendrites but not terminals are of the 5-HT1A subtype. Eur J Pharmacol 113:463–464

Wang RY, Aghajanian GK (1977) Inhibition of neurons in the amygdala by dorsal raphe stimulation: mediation through a direct serotonergic pathway. Brain Res 120:85–102

World Health Organization (2011) Mental health disorders management: depression. http://www.who.int/mental_health/management/depression/definition/en/

Yocca FD (1990) Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT1A receptors. J Clin Psychopharmacol 10:6S–12S

Young SN, Smith SE, Pihl RO, Ervin FR (1985) Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology (Berlin) 87:173–177

Yu YW, Tsai SJ, Liou YJ, Hong CJ, Chen TJ (2006) Association study of two serotonin 1A receptor gene polymorphisms and fluoxetine treatment response in Chinese major depressive disorders. Eur Neuropsychopharmacol 16:498–503

Zhang J, Huang XY, Ye ML, Luo CX, Wu HY, Hu Y, Zhou QG, Wu DL, Zhu LJ, Zhu DY (2010) Neuronal nitric oxide synthase alteration accounts for the role of 5-HT1A receptor in modulating anxiety-related behaviors. J Neurosci 30:2433–2441