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5-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 sub-populations and re-interpret our understanding of their role in mental illness in light of new data, separating both spatial (autoreceptor vs heteroreceptor) and the temporal (developmental vs 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 distinct roles of these populations in governing emotion related behavior are 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

1. Introduction

Depression and anxiety are amongst the worlds 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 2nd-highest cause of illness-induced disability by the year 2020 (Organization WH 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-

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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 (Wittchen et al., 2011) and entailing a massive economic burden of over 65 billion euros annually (Gustavsson et al. 2011). 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, whilst it is known that the serotonergic system plays an important role in the etiology and treatment of mood and anxiety disorders (Charney et al. 1998; Nemeroff 2002; Rush et al. 2000), the precise means by which this occurs are the subject of 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 (Ansoerge et al. 2008; Caspi et al. 2003; Lira et al. 2003; Oberlander et al. 2009; Oliver 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 and Carlezon 2006; Nikolaus et al. 2010; Skolnick et al. 2009).

Serotonergic neurons are mainly located in the dorsal and median raphe of 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 sub-families based on their primary signaling mechanism (Hoyer and Martin 1997). Here we focus on the 5-HT_{1A} receptor, as 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 G α i3 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 (Hervás et al. 2000; Hjorth and Auebarch, 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 et al. 2000), allowing the firing rate of serotonergic neurons to recover (Blier and De Montigny 1983; El Mansari et al. 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; Palchadhuri 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 G α o subunits in the hippocampus, and equally to G α o and G α i3 in cerebral cortex (Mannoury la Cour et al. 2001), unlike 5-HT_{1A} autoreceptors that may couple preferentially to G α i3. 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 G α 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.

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

2.1 Human studies

Dysregulation of 5-HT_{1A} receptors occurs in patients suffering from depression and related mood disorders. While there has been considerable discrepancy amongst 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 decrease 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; Drevets et al. 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; Drevets et al. 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. 1998; 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, the 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.

2.2 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 and co-workers (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 psychiatric 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; Serreti et al. 2004; Yu et al. 2006) but see (Levin et al. 2007). Overall, these findings suggest that genetic variations in the HTR1A gene may contribute not only to susceptibility to depression but also to individual differences in responsiveness 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 prefrontal cortex but not 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).

2.3 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 proved active in clinical trials as antidepressants (Pitchot et al., 2005). Further evidence for the involvement of 5-HT_{1A} receptors in 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 and Massey 2003), whereas buspirone lacks antidepressant efficacy by itself, likely because 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 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 suppressed 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 knock-outs behave abnormally (Andrews et al. 1994; File and Gonzalez 1996; File et al. 1996; Stefanski 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 post-mortem brain of depressed suicide victims (Dwivedi et al. 2001; Dwivedi et al. 2009). In rat, chronic stress-induced depression elicits deficits in ERK phosphorylation which are fluoxetine-reversible (Qi et al. 2006; Qi et al. 2008). Conversely, chronic administration of a ERK inhibitor elicits anhedonia and anxiety-like behavior (Qi et al. 2009). Consistent with these observations, the potent phosphorylation 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.

2.4 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 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 behavioural 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 extracellular levels in 5-HT_{1A} KO mice in different brain areas such as hippocampus, striatum, raphe nuclei and frontal cortex (Bortolozzi et al. 2004; Guilloux et al. 2006, Knobelmann 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; Knobelmann 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 behavioural 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.

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 suppression 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 distinct roles of the two endogenous receptor populations in mediating anxious or depression like phenotypes, providing evidence that autoreceptors could impact establishment of anxiety-like behaviour, with heteroreceptors affecting behavior in the forced swim test, a depression related test.

3. 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 post-synaptic 5-

HT_{1A} receptor appears to be critical in the development of the barrel cortex organization (Maya-Vetencourt et al. 2008; Maya-Vetencourt et al. 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 2nd and 3rd 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 time-point in which behavioral differences in anxiety measures can be detected in the 5-HT_{1A} knockout mice (Kristin Klemenhausen, 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 sub-serve anxiety and depression-related behavior in the mouse, would inform 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 indistinguishable 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 behaviour 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 suppression 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 signalling from a disinhibited raphe. The gain of function experiment suggests that this anxiety can be rescued in these 'raphe disinhibited' mice by increasing signalling 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 suppression 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 (Figure 2). Furthermore, it should be noted that suppression 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 vs. 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 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 (Lemondé 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 Lemondé 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.

4. 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} receptors 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 requires 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 regulation the plasticity of behavior once circuits mediating anxiety are functional. It is possible that there is a 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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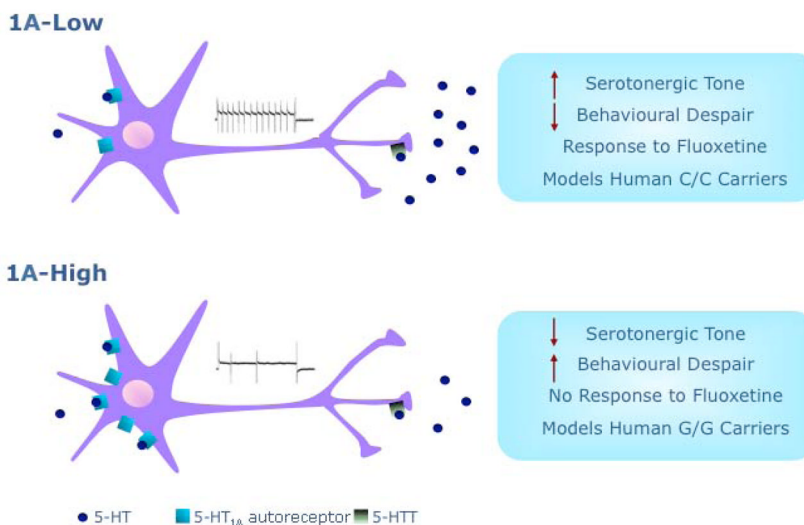


Figure 1. Model of 5-HT_{1A} autoreceptor effects on the serotonergic raphe nuclei. Schematic depicting representative raphe neurons in 1A-High and 1A-Low animals, emphasizing the differences between the two groups. (Top) In 1A-Low mice, low levels of somatodendritic 5-HT_{1A} autoreceptors result in 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.

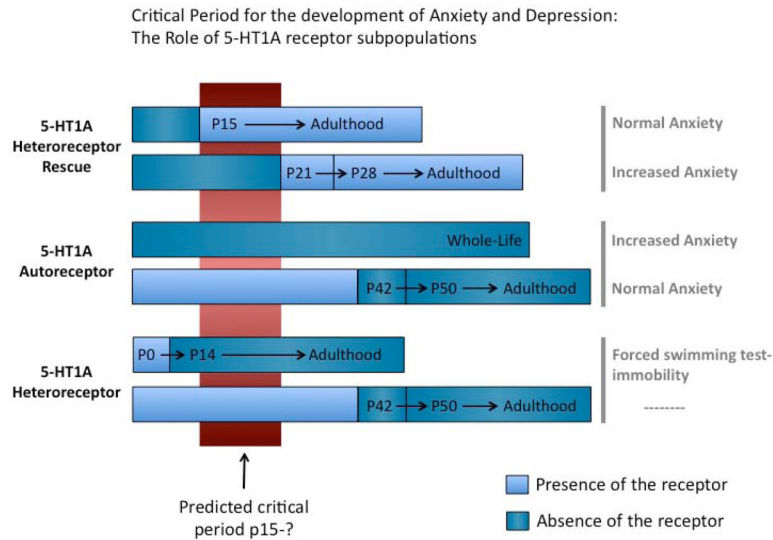


Figure 2.

Figure summarizes 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 a P21 results in an anxious phenotype (Gross et al. 2002). (Middle) Suppression of 5-HT_{1A} autoreceptors throughout life resulted in an increase 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) Suppression of 5-HT_{1A} heteroreceptors throughout life resulted in an increase 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.