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## Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease

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### Abstract

The serotonin system is strongly implicated in the pathophysiology and therapeutic alleviation of stress-related disorders such as anxiety and depression. Serotonergic modulation of the acute response to stress and the adaptation to chronic stress is mediated by a myriad of molecules controlling serotonin neuron development (Pet-1), synthesis (tryptophan hydroxylase 1 and 2 isozymes), packaging (vesicular monoamine transporter 2), actions at presynaptic and postsynaptic receptors (5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, 5-HT3A, 5-HT4, 5-HT5A, 5-HT6, 5-HT7), reuptake (serotonin transporter), and degradation (monoamine oxidase A). A growing body of evidence from preclinical rodent models, and especially genetically modified mice and inbred mouse strains, has provided significant insight into how genetic variation in these molecules can affect the development and function of a key neural circuit between the dorsal raphe nucleus, medial prefrontal cortex and amygdala. By extension, such variation is hypothesized to have a major influence on individual differences in the stress response and risk for stress-related disease in humans. The current article provides an update on this rapidly evolving field of research.

### Keywords

Stress; Gene; Strain; Mouse; Inbred; Serotonin; Serotonin transporter; Tryptophan hydroxylase; VMAT2; MAOA; 5-HT1A; 5-HT1B; 5-HT2A; 5-HT2C; 5-HT3; Prefrontal cortex; Hippocampus; Amygdala; Anxiety; Depression; Emergence test; Forced swim test; Restraint

## 1. Introduction

The work of Graeff et al. has contributed greatly to our understanding of the role of serotonin (5-hydroxytryptamine) in orchestrating the behavioral response to psychological stress (Graeff et al., 1996). Their work adds to a large corpus of data compiled over the past couple of decades which has uncovered the major enzymes, transporters and receptors that subserve the serotonergic system's modulation of both the acute response to stress and the adaptation to chronic stress. In concert, a more nascent literature has begun to identify sources of genetic variation within these molecules. These parallel lines of research have led to new ways of thinking about how genetically driven differences in serotonin function might predispose certain individuals to stress-related neuropsychiatric conditions such as depression and anxiety disorders and how we can better identify and therapeutically treat these people.

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The present article provides an update on this rapidly growing field. The focus is studies that have utilized mice with modifications in serotonin genes to assess stress-related phenotypes. These data are placed in the context of salient pharmacological, neurochemical and electrophysiological findings in both rats and mice and, where applicable, findings of genetic influences from studies in humans. The review is also limited in focus to a neural circuit connecting the serotonergic dorsal raphe nucleus to the medial prefrontal cortex (mPFC) and amygdala, given growing evidence implicating this circuit in rodent stress-related responses and human stress-related disease (Drevets, 2001; Ressler and Mayberg, 2007). For a discussion of the mesencephalic tectum system as a site of serotonin's stress-related actions (see Graeff, 2004) and accompanying articles in this Special Issue. There have also been a number of excellent recent reviews dealing with the theme of serotonin genetics and stress, and the reader is referred to these for a complimentary perspective (Ansorge et al., 2007; Gross and Hen, 2004; Joca et al., 2007; Lucki, 1998; Maier et al., 2006; Neumeister et al., 2004a; Southwick et al., 2005). Lastly, for a comprehensive review of the pharmacology of serotonin's stress-related actions see Griebel, 1995; Menard and Treit, 1999; Millan, 2003.

## 2. Serotonin release

Serotonin is a major modulatory neurotransmitter, the actions of which are determined by various synthesizing and catabolizing enzymes, pre- and post-synaptic receptors, and molecules controlling intracellular trafficking and extracellular transport (Fig. 1). Serotonin producing neurons originate in the dorsal and median raphe nuclei located in the midbrain (Dahlstrom and Fuxe, 1964). Despite there being few serotonin neurons relative to total neuron number in brain (Jacobs and Azmitia, 1992), the serotonin system, and particularly the dorsal raphe nucleus (DRN), extensively innervates most of the brain including the key corticolimbic structures involved in the regulation of stress such as the mPFC, septum, extended amygdala, and hippocampus (Ma et al., 1991; Steinbusch, 1981). There is further topographical organization within the DRN itself. Although the possible significance of this organization will not be discussed here, Lowry and colleagues among others have shown that certain DRN subregions appear to be preferentially involved in stress and anxiety (Abrams et al., 2004, 2005; Lowry, 2002; Maier and Watkins, 2005; Silva et al., 2002).

Under most waking states rodent serotonin neurons show slow, regular tonic activity (Jacobs and Azmitia, 1992). Following exposure to stressors such as inescapable shock serotonin neuron activity is increased, as evidenced by increased immediate-early gene expression in the DRN (Amat et al., 2005; Grahn et al., 1999; Takase et al., 2004). A large literature also demonstrates that extracellular fluid concentrations (ECF) of serotonin are increased in both the vicinity of the DRN and the corticolimbic targets of the serotonin system, including the mPFC, amygdala and hippocampus. The stressors shown to cause this increase in ECF, which is almost certainly due to increased serotonin release, range from exposure to a predator, tail pinch, elevated platform exposure, inescapable shock, social defeat, to restraint/immobilization (Adell et al., 1997; Amat et al., 2001; Bland et al., 2003; Funada and Hara, 2001; Grahn et al., 1999; Hajos-Korcsok et al., 2003; Jordan et al., 1994; Kang et al., 2005; Kawahara et al., 1993; Keck et al., 2005; Keeney et al., 2006; Kehr et al., 2001; Kirby et al., 1995, 1997; Kirby and Lucki, 1998; Maswood et al., 1998; Miyata et al., 2007; Mokler et al., 2007; Petty et al., 1994; Price et al., 2002; Renard et al., 2003; Rex et al., 2005; Rueter and Jacobs, 1996; Storey et al., 2006; Takahashi et al., 2000; Thorre et al., 1997; Yoshioka et al., 1995; Yoshitake et al., 2004). It is important to note however that not all studies have found increases in forebrain ECF serotonin in response to stress and there are actually some reports of stress-induced decreases (e.g., Kirby et al., 1997; Rueter and Jacobs, 1996). The reason for these apparent discrepancies is not clear but could be a function of the type of stressor used and other methodological factors, as well as the brain region examined. Another possibility is that the variability reflects genuine biological differences in the capacity for regulating stress-induced

serotonin release that different studies are inadvertently tapping – including genetic diversity between different strains of rat or mouse employed. Whatever the reasons, this issue intimates from the outset the complexity of the serotonergic modulation of the central nervous system's response to stress.

### 3. Serotonin synthesis

The magnitude of stress-induced serotonin release will be dependent in part on the amount of serotonin available in the presynaptic terminal. In rodent, the synthesis of serotonin from L-tryptophan (McGeer and McGeer, 1973) in the brain is controlled by the rate-limiting enzyme tryptophan hydroxylase type 2 (Tph2) (Walther and Bader, 2003). Inhibition of Tph2 activity by chemical agents such as *para*-chlorophenylalanine methyl ester hydrochloride (PCPA) markedly decreases levels of serotonin (Fratta et al., 1973). PCPA-induced depletion of serotonin blocks the antidepressant-like effects of serotonin reuptake inhibitors (SRIs) in rodent assays for these effects, such as the forced swim test (Page et al., 1999) (for a discussion of these tests (see Cryan and Holmes, 2005)). This is consistent with the finding that upregulation of Tph2 mRNA levels in the DRN following chronic SRI treatment correlates with the magnitude of the antidepressant-like response in the forced swim test (Shishkina et al., 2007). Perhaps surprisingly however, serotonin depletion does not seem to affect the behavioral response during exposure to stressful situations – for example, as measured by the level of active swimming relative to passive immobility in the forced swim test. The absence of effects on baseline stress responsivity could be due to compensatory changes within the serotonin system following PCPA insult.

Compensatory adaptations do not however appear capable of mitigating the consequences of genetically driven loss of Tph2 function. In the mouse, a single-nucleotide polymorphism (SNP) has been identified in the mouse *Tph2* gene that leads to a substitution of arginine to proline at position 447 and a significant decrease in brain serotonin levels (Zhang et al., 2004) (for genomic location of this and other mouse genes discussed in this article, see Fig. 2). The BALB/cJ and DBA/2J inbred mouse strains that carry the 1473G allele exhibit significantly lower levels of serotonin in the frontal cortex and striatum relative to the C57BL/6J and 129X1/SvJ strains (with 1473C) (Zhang et al., 2004) (see also Hackler et al., 2006). Interestingly, the BALB/cJ and DBA/2J strains also tend to exhibit higher levels of anxiety-like behavior and stress-reactivity than C57BL/6J, and BALB/cJ also show greater sensitivity to the antidepressant-like effects of SRIs (Anisman et al., 2001; Belzung and Griebel, 2001; Dulawa et al., 2004). The implication here is that the low functioning mouse *Tph2* variant could account for the abnormal anxiety- and stress-related phenotype of these and possibly other mouse strains (Zhang et al., 2004). Further work will be needed to substantiate and extend this hypothesis. For example, because Tph2-mediated serotonin synthesis is known to be regulated by glucocorticoids in C57BL/6J (Clark et al., 2007; Clark et al., 2005) it would be of interest to examine whether this mechanism is impaired in strains with the low-expressing SNP such as DBA/2J and BALB/cJ (Table 1).

Whether genetic control of human *TPH2* might affect human stress-related disease has generated a lot of interest. A loss-of-function SNP (G1463A) in the human *TPH2* gene has been associated with increased incidence of depression; although it is not yet clear whether this association extends beyond a certain subpopulation of patients (Delorme et al., 2006; Zhang et al., 2006; Zill et al., 2004). In addition, using functional magnetic resonance imaging (fMRI) Hariri and colleagues have recently shown that a more common SNP (G(-844)T) in the promoter region of the *TPH2* gene predicts exaggerated amygdala responses to threatening faces (Brown et al., 2005). Finally, there is preliminary evidence that a 218A/C *TPH2* polymorphism is also linked to increased rates of anxiety disorders and depressive illness (Christiansen et al., 2007). Taken together, these data provide encouraging support for the

notion that genetic variation in the control of serotonin synthesis, via Tph2, can affect stress-related behaviors and the neural systems supporting these behaviors, both in mouse and in man.

Although present to some extent in the rodent DRN (Gundlach et al., 2005), the tryptophan hydroxylase isoform Tph1 largely governs peripheral serotonin synthesis. However, even if Tph1 did not act directly in the brain (which is still not certain), the porous blood–brain barrier in developing rodents could render the developing brain highly sensitive to the effects of variation in Tph1 gene function during ontogeny. Intriguingly in this context, mouse dams in which the *Tph1* gene is knocked out produce offspring that exhibit gross abnormalities in brain development, regardless of the offspring's own *Tph1* genotype (Cote et al., 2007). This demonstrates that loss of the maternal supply of peripheral serotonin can have profound consequences for the brain. The question of whether gene variation in the human *TPH1* or mouse *Tph1* gene impacts the development of corticolimbic circuits mediating stress responses has not yet been answered, but represents an important avenue for future work. It also raises the more general issue of how serotonin gene variation can influence stress responses by acting during ontogeny; a critical issue that will be revisited throughout this article.

Deneris and colleagues have shown that the pheochromocytoma 12 ETS domain transcription factor-1, *Pet-1*, is essential for the generation of serotonin neurons, as evidenced by the ability of gene knockout of mouse *Pet-1* to dramatically disrupt the differentiation of serotonin neurons during embryogenesis (Hendricks et al., 2003). Adult *Pet-1* knockout mice exhibit a 70% loss of serotonin neurons, an 89% decrease in serotonin tissue content in cortex and hippocampus, and significant decrease in Tph2, serotonin transporter and Vmat2 mRNA expression in serotonin neurons that are extant (Hendricks et al., 2003). Preliminary phenotypic analysis of these mice demonstrated an increase in anxiety-like behavior in some of the standard assays such as the novel open field and elevated zero-maze (for description and discussion of these tests, see Cryan and Holmes, 2005), as well as an increase in conspecific aggression (Hendricks et al., 2003). *Pet-1* mice represent a powerful model for studying the stress-related consequences of genetically driven lifelong loss of brain serotonin (see also *Lmx1b* knockout mice (Zhao et al., 2006b)) and further data on these mice is eagerly anticipated.

#### 4. Serotonin vesicular packaging

Following its synthesis, serotonin must be properly packaged into secretory vesicles and transported to the presynaptic terminal prior to release. The vesicular monoamine transporter type 2 (VMAT2) has an important role in this process (Hoffman et al., 1998). An early indication that VMAT2 might contribute to stress-related pathology stemmed from the serendipitous discovery that pharmacological inhibition of VMAT by reserpine treatment produced striking depressive-like symptoms in humans (Freis, 1954). Indeed this was one of the key findings that subsequently led to the monoamine-deficiency hypothesis of depression.

'Reserpinization' of rodents causes a suppression of motor activity that has been likened to a depressive-like state, which probably reflects the combined effects of central depletion of dopamine and norepinephrine as well as serotonin (Bourin, 1990). In addition, repeatedly exposing rats to immobilization or forced swimming has been found to increase or decrease VMAT2 expression (Rusnak et al., 2001; Zucker et al., 2005). Beyond these data there is still surprisingly little investigation of VMAT2's possible role in modulating the stress response until a recent report in a mouse model of loss of Vmat2 (*Slc18a2*) gene function (Fukui et al., 2007).

Complete knockout of *Slc18a2* is lethal, but mice lacking one copy of the gene are viable and develop with significantly reduced brain serotonin (as well as dopamine and norepinephrine) (Fon et al., 1997). Fukui et al. found that Vmat2-deficient mice exhibit normal anxiety-like

behaviors on the standard test assays, but show an exaggerated corticosterone response to forced swim stress and a number of behavioral abnormalities indicative of an increased 'depression-related' phenotype—i.e., poor escape learning in the passive avoidance test and reduced sucrose preference (an assay for anhedonia) (Fukui et al., 2007). These mice also showed an increased 'depression-like' phenotype in the forced swim test and tail suspension tests, in a manner that was reversible by antidepressant treatment (Fukui et al., 2007). This latter observation is noteworthy in the context of recent work by Lucki and colleagues demonstrating that variation in the magnitude of the antidepressant-like response between two inbred mouse strains (BALB/c, A/J) was associated with a quantitative trait locus in the chromosomal region where *Slc18a2* resides (Crowley et al., 2006) (see Fig. 2). Taken together, these rodent data suggest that variation in human *SLC18A2* could influence risk for depression as well as antidepressant efficacy. However, although numerous SNPs have been identified in *SLC18A2* there is not yet any hard evidence linking any specific variants with these phenotypes.

## 5. Serotonin reuptake

Serotonin released as a result of stress will be removed from the extracellular space by the high-affinity serotonin transporter (SERT, 5-HTT). SERT has an important role in determining the magnitude and duration of serotonin's activity on its presynaptic and postsynaptic receptors, because while other monoamine transporters can take up serotonin under certain conditions, SERT is the principal active means of removing substrate from the synaptic space (Blakely et al., 1991) and has a particularly prominent extrasynaptic role in regulating serotonin volume transmission (Torres and Amara, 2007). SERT is best known as the initial molecular target for the SRI class of antidepressants and anxiolytics. Precisely how SERT mediates the effects of these drugs is less certain. The time lag between drug action and clinical efficacy alone demonstrates that SERT blockade is not in and of itself sufficient to alleviate stress-related symptoms and likely represents the initial stage upstream of a complex process eventually leading to therapeutic outcome (Blier and de Montigny, 1994; Duman et al., 1997; Manji et al., 2001).

There is evidence of reduced SERT binding in the PFC and amygdala of depressives (Oquendo et al., 2007; Parsey et al., 2006). However, despite one study reporting no gross alteration in SERT-mediated reuptake in the rat forebrain under acute stress (Martin et al., 2000), and evidence of decreased DRN SERT mRNA in chronically socially stressed rats (McKittrick et al., 2000) (cf. Arborelius et al., 2004; Vazquez et al., 2000) it is not fully clear how SERT function is altered by stress. Notwithstanding, alterations in SERT-mediated reuptake would be predicted to be an important mechanism by which the serotonin system can self-regulate the amount of synaptic serotonin evoked by stress. For example, SERT upregulation could explain why stress-induced increases in extracellular serotonin are sometimes lost with repeated stress (Kirby and Lucki, 1998). Conversely, a failure of SERT-mediated serotonin clearance would significantly limit regulation of ECF serotonin and thereby compromise the dynamic capacity of the system to respond and adapt to stress. This is borne out at the genetic level by a growing body of data from mouse and human studies.

Gene knockout of the mouse SERT gene (*Slc6a4*) produces loss of serotonin clearance and a consequent increase in ECF levels of serotonin in forebrain (Mathews et al., 2004; Montanez et al., 2003). A loss of 5-HT<sub>1A</sub>-R binding and autoreceptor function in these knockout mice further exacerbates ECF levels for the reasons discussed below (Bouali et al., 2003; Fabre et al., 2000; Gobbi et al., 2001; Li et al., 1999, 2000, 2004). These neurochemical changes are associated with an increase in anxiety-like behavior in a battery of the standard test assays (Ansorge et al., 2004; Carroll et al., 2007; Fox et al., 2007; Holmes et al., 2002a, 2003b, 2003c; Kalueff et al., 2007; Lira et al., 2003; Zhao et al., 2006a). Interestingly, transgenic overexpression of the SERT gene produces the opposite phenotype—i.e., reduced anxiety-like

behavior (Jennings et al., 2006). In response to exposure to a variety of stressors such as saline injection and predator odor or low maternal care, SERT knockout or SERT-deficient mice display an exaggerated glucocorticoid catecholamine response and in some cases an enhancement of the anxiety-like phenotype (Adamec et al., 2006; Carola et al., 2007; Li et al., 1999, 2004; Tjurmina et al., 2004). In terms of behavioral responses to stress, these mice exhibit an increased 'depression-related' phenotype on the forced swim test, tail suspension test and passive avoidance task (Ansorge et al., 2004; Holmes et al., 2002b; Lira et al., 2003). Interestingly, SERT knockout mice have been found to show elevated levels of rapid eye movement (or paradoxical) sleep; an abnormality that is also found in human depression (Alexandre et al., 2006; Wisor et al., 2003). Finally and not surprisingly, SERT knockout mice are insensitive to the antidepressant-like effects of drugs that principally target SERT, such as fluoxetine, but not other monoamine transporters, such as desipramine (Holmes et al., 2002b).

A noteworthy extension of these data is that the increased depression-related phenotype seen in SERT knockout mice appears to be exacerbated by repeated stress exposure (Wellman et al., 2007; Zhao et al., 2006a). In fact, in some instances the phenotype is restricted to these repeated stress conditions and this appears to depend upon the genetic background strain onto which the SERT knockout is crossed, as in the case of backcrossing into the relatively stress-resilient C57BL/6 strain (Holmes et al., 2003b; Zhao et al., 2006a). One interpretation of these findings is that consequences of loss of *Slc6a4* in the mouse is determined both by the chronicity of the stressor and by epistatic interactions with other genetic factors that can confer risk or resilience against the effects of *Slc6a4* deletion (Holmes and Hariri, 2003). In support of this hypothesis is recent data demonstrating that stress-related interactions with SERT and brain-derived nerve growth factor (for further discussion, see Carola et al., 2007; Ren-Patterson et al., 2005, 2006).

The mouse *Slc6a4* model finds strong parallels in the human literature. There has been enormous interest in a common variable number tandem repeat (VNTR) polymorphism in the promoter region of human SERT gene (*SLC6A4*). Of all the variants thus far identified in serotonin genes, this polymorphism has undoubtedly been the most widely studied. The short (s) allelic version of the polymorphism is associated with reduced SERT brain expression and lesser serotonin reuptake *in vitro* (Lesch et al., 1996; Little et al., 1999). This variant is considered a loss-of-function variant although functionality is contingent upon additional sources of variation in the *SLC6A4* (Zalsman et al., 2006). Without reiterating a literature that has been exhaustively covered elsewhere (for reviews and meta-analyses (see Anguelova et al., 2003b; Lotrich and Pollock, 2004; Rees et al., 1997; Serretti et al., 2007b), individuals carrying the s allele have been found to be at moderately increased risk for anxiety disorders and depression, and to respond unfavorably to antidepressant drugs. Moreover, reminiscent of the stress-related phenotype observed in the SERT knockout mouse, the risk for major depression in individuals carrying the s allele is particularly pronounced, and perhaps even limited to, cases in which there is a history of exposure to traumatic life events (for discussion, see Caspi and Moffitt, 2006; Hariri and Holmes, 2006; Uher and McGuffin, 2007). Finally, as in SERT knockout mice, human s allele carriers also have significantly reduced 5-HT<sub>1A</sub>-R binding in brain (David et al., 2005) (cf. Lee et al., 2005).

Recent studies, both in rodent and human, provide some insight into the corticolimbic locus of the stress-related phenotype associated with loss of SERT gene function. SERT knockout mice display increased spine density in the basolateral nucleus of the amygdala and elongation of neuronal dendrites in the mPFC (Wellman et al., 2007). In humans, Hariri and colleagues first demonstrated that exposure to threatening faces, a stimulus that reliably engages the amygdala in humans, produces a relatively greater amygdala response in s allele carriers than long (l) allele carriers, as measured by fMRI (Hariri et al., 2002; Munafò et al., 2007).

Subsequent studies found that this amygdala hyperactivity is related to a functional ‘uncoupling’ between the circuit connecting the amygdala with the anterior cingulate region of the PFC (Heinz et al., 2005; Pezawas et al., 2005). These data support a model in which loss of SERT gene function leads to a possible failure of cortical systems to exert sufficient inhibitory control over the amygdala during stressful situations, thereby catalyzing the development of chronic pathological states such as depression (Hariri and Holmes, 2006; Pezawas et al., 2005).

It is worth pointing out at this juncture that the adverse phenotypic consequences of loss of SERT function at the genetic level in human and mouse differ from the therapeutically beneficial (anxiolytic, antidepressant) effects of *chronic* treatment with SRIs (*note bene*—acute SRI treatment can often produce increased anxiety in rodent and human (Griebel, 1995; Holmes and Rodgers, 2003; Millan, 2003; Salchner and Singewald, 2002; Silva and Brandao, 2000)). The reason for this ostensible paradox between genetic and pharmacological inactivation of SERT is not yet understood, but one potentially crucial factor is that loss of SERT gene function may exert its long-term phenotypic effects by acting during brain development (Ansorge et al., 2007; Holmes et al., 2003a). A number of observations support this hypothesis. First, treating non-mutant rats and mice with SERT-blocking SRIs such as fluoxetine during the first weeks of life (corresponding to late pregnancy in humans) mimics the increased anxiety- and depression-like phenotype of *Slc6a4* knockout (Andersen et al., 2002; Ansorge et al., 2004, 2008; Feng et al., 2001b; Hilakivi and Hilakivi, 1987; Maciag et al., 2006a, 2006b). Second, Alexandre and colleagues have shown that either depleting serotonin levels with PCPA or inhibiting 5-HT1A-Rs with WAY 100635 during the first few weeks of life, both of which presumably block some of the actions of excessive neonatal serotonin, is sufficient to rescue some of the depression-related abnormalities in adult SERT knockout mice (Alexandre et al., 2006).

That SERT inactivation during development can have such profound effects is perhaps not surprising considering that serotonin is a major developmental signal (Sodhi and Sanders-Bush, 2004; Whitaker-Azmitia et al., 1996). The rodent neonatal period also corresponds to a time of high transient expression of SERT (but not other monoamine transporters) on non-serotonin neurons (Lebrand et al., 1998). SERT knockout mice exhibit cytoarchitectural malformations and functional deficiencies in various sensory cortical regions that can be rescued by depleting the excess of neonatal serotonin (via PCPA treatment) in these mice (Esaki et al., 2005; Gaspar et al., 2003). This poses the question of whether the PFC-amygdala abnormalities resulting from genetic variation in mouse and human SERT also have their origins in ontogeny. The answer could have important implications for the field.

The VNTR promoter polymorphism is not the only potentially interesting variant in the human *SLC6A4* gene. An intron 2 VNTR polymorphism in *SLC6A4* is also associated, albeit inconclusively, with depression and suicide (Anguelova et al., 2003a, 2003b). Moreover, this variant as well as a rare gain-of-function mutation (I425V), has recently been implicated in various other psychiatric conditions with a major stress component, including autism and obsessive compulsive disorder (Ozaki et al., 2003; Sutcliffe et al., 2005). It is likely that additional sources of variation in *SLC6A4* will be uncovered and these may also prove to influence serotonin regulation of the stress response (Wendland et al., 2008).

## 6. Serotonin degradation

Serotonin cleared from the extracellular space by SERT and returned to the cell undergoes oxidative deamination into inert metabolites by the mitochondrial enzyme monoamine oxidase A (MAOA). The rate at which MAOA degrades serotonin is therefore another determinant of serotonin availability (Shih et al., 1999). MAOA inhibitors were some of the first drugs to exert

demonstrable antidepressant activity in humans (Klein and Fink, 1962). Treatment with these drugs increases serotonin tissue levels in the rodent brain and produces an antidepressant-like response on the forced swim and tail suspension test (Fukui et al., 2007; Holmes et al., 2002b). On the other hand, these drugs increase anxiety-like behavior and cause a resistance to habituation to the effects of chronic mild stress (Griebel, 1995; Holmes and Rodgers, 2003; Menard and Treit, 1999; Millan, 2003; Ward et al., 1998).

The effects of constitutive gene knockout of the mouse *Maoa* gene are in some ways similar to MAOA inhibitors. *Maoa* knockout mice have increased ECF serotonin in the PFC and hippocampus and display exaggerated unconditioned and conditioned fear behaviors, as well as increased conspecific aggression (Cases et al., 1995; Dubrovina et al., 2006; Evrard et al., 1999; Kim et al., 1997; Popova et al., 2000). However, these mice also display an attenuated glucocorticoid response to acute and chronic stressors (Popova et al., 2006) that may relate to the significant reduction in dorsal raphe neuron activity observed in these mice (Evrard et al., 1999).

A very rare point mutation in the human *MAOA* gene causing loss of MAOA function causes impulsive aggression in men within a Dutch family (Brunner et al., 1993). This variant is unlikely to influence stress or emotional traits in the general population, but it does provide a dramatic example of the consequences of loss of *MAOA*. A more common VNTR in the *MAOA* promoter region has been linked to various social and emotional abnormalities. Individuals carrying a lesser expressing form of this variant that were also maltreated as children have been found to be at greater risk of developing an antisocial, violent personality, in some but not all studies (e.g., Caspi et al., 2002; Huizinga et al., 2006; Kim-Cohen et al., 2006). The same variant is coupled with a range of structural and functional abnormalities in the corticolimbic system. Specifically, the low-expressing form of the variant is associated with an augmented amygdala (and hippocampal) response and an attenuated PFC response to threatening faces (Buckholtz et al., 2007; Meyer-Lindenberg et al., 2006). In addition, there is a decrease in anterior cingulate, amygdala, insula, and hypothalamus grey matter volume, and increased orbitofrontal cortex volume in these individuals (Buckholtz et al., 2007; Meyer-Lindenberg et al., 2006).

Both at the neural and behavioral level, the phenotypic consequences of genetically driven loss of MAOA in the mouse and human differ in certain ways to the effects of SERT gene loss. Although both lead to an increased stress-reactivity, there is a tendency for this to manifest as increased aggression in the case of loss of *Maoa/MAOA* but increased harm avoidance in the case of *Slc6a4/SLC6A4* deficiency. The reason for this distinction is likely related to the fact that disruption of *Maoa/MAOA* leads to a significant increase in norepinephrine and dopamine as well as serotonin (as demonstrated in the mouse (Cases et al., 1995))—producing a more complex milieu of neurochemical changes during development and adulthood than would be wrought by an increase in serotonin alone.

## 7. Role of 5-HT1A receptors

Serotonin released into the extracellular space acts at multiple pre-synaptic and post-synaptic located receptors that are organized in a hugely complex pattern of regional and subcellular distribution. For excellent overviews of serotonin receptor pharmacology and signaling mechanisms (see Barnes and Sharp, 1999; Hoyer et al., 2002; Kroeze and Roth, 1998).

The 5-HT1A-R subserves two critical roles within the serotonin system in regards to stress—as an autoreceptor regulating DRN neuron activity and as a postsynaptic receptor mediating serotonin's action on corticolimbic regions including the mPFC and amygdala. Activation of 5-HT1A-R autoreceptors located on the soma and dendrites of serotonin cells (Sotelo et al., 1990; Verge et al., 1986) inhibits DRN neuronal firing and consequent forebrain release



(Clifford et al., 1998; Sprouse and Aghajanian, 1986). This provides an essential mechanism by which the serotonin system can self-regulate its activity under conditions of stimulation, such as stress exposure. This mechanism appears to be compromised by chronic stress. For example, Lanfumey and colleagues have shown that corticosterone or chronic mild stress desensitizes 5-HT<sub>1A</sub>-R autoreceptor control of DRN firing (via a glucocorticoid receptor-dependent mechanism) (Froger et al., 2004; Laaris et al., 1995, 1997; Lanfumey et al., 1999) (see also Gartside et al., 2003). Along similar lines, the loss of 5-HT<sub>1A</sub>-R autoreceptor function caused by gene knockout of the mouse *Htr1a* exacerbates the increase in ECF concentrations in the DRN resulting from mild stress exposure (Amargos-Bosch et al., 2004; Bortolozzi et al., 2004; He et al., 2001).

Genetically driven or stress-induced loss of 5-HT<sub>1A</sub>-R auto-receptor function would prevent some of the plastic changes that occur in the DRN with chronic stress. Maier and colleagues have shown that rats repeatedly exposed to inescapable shock exhibit a passive behavioral response even when escape from shock becomes available in a phenomenon termed ‘learned helplessness’ (Seligman, 1972). Inescapable, but not escapable, stress not only activates DRN neurons (Grahn et al., 1999; Maswood et al., 1998), but ‘sensitizes’ these neurons to subsequent stress (Amat et al., 1998). The development or expression of this sensitization is prevented by pharmacological stimulation of 5-HT<sub>1A</sub>-Rs in the DRN—presumably by inhibiting stress-induced serotonin neuron activation (Maier et al., 1995).

As noted, 5-HT<sub>1A</sub>-R function plays a prominent role in mediating serotonin's postsynaptic actions, and these receptors are densely expressed in the mPFC (Clement et al., 1996; Kia et al., 1996b; Landry and Di Paolo, 2003; Pompeiano et al., 1992; Wright et al., 1995). Application of selective 5-HT<sub>1A</sub>-R agonists such as 8-OH-DPAT directly into the mPFC inhibits the spontaneous and glutamate receptor-mediated firing of the major projection neurons therein (Araneda and Andrade, 1991; Ashby et al., 1994; Borsini et al., 1995; Cai et al., 2002). Likewise, inhibitory actions of serotonin on these neurons is reversed by co-application of selective 5-HT<sub>1A</sub>-R antagonists such as WAY 100635 (Cai et al., 2002; Casanovas et al., 1999; Hajos et al., 2003; Tanaka and North, 1993).

5-HT<sub>1A</sub>-Rs can not only control serotonergic responses to stress via their actions as autoreceptors, but can indirectly influence DRN activity via their postsynaptic actions. There is an important projection from the mPFC back to the DRN (Peyron et al., 1998) (as well as recently identified pathway from the subthalamic nucleus to the DRN (Temel et al., 2007)). The glutamatergic mPFC projection synapses onto GABA interneurons that in turn negatively regulate DRN activity (Hajos et al., 1998). Using the aforementioned learned helplessness paradigm, Maier and colleagues have provided compelling evidence that the mPFC-DRN pathway determines whether stress is ‘perceived’ as uncontrollable and, as a result, the extent to which stress activates the serotonergic system. This is best illustrated by the finding that inactivation of the PFC promotes DRN activation, forebrain serotonin release and learned helplessness behavior in response to stress (for further discussion, see Maier et al., 2006; Maier and Watkins, 2005). By recruiting the mPFC-DRN pathway, activation of 5-HT<sub>1A</sub>-Rs in the mPFC causes a decrease in DRN firing and suppresses forebrain serotonin release (Celada et al., 2001; Gartside et al., 2000; Hajos et al., 1998, 1999, 2001, 2003; Martin-Ruiz et al., 2001; Martin-Ruiz and Ugedo, 2001; Puig et al., 2005). It is not yet certain how the activation of (inhibitory) 5-HT<sub>1A</sub>-Rs in the mPFC can stimulate the projection to the DRN, but may stem from their action at GABA interneurons in mPFC (Aznar et al., 2003; Santana et al., 2004). Whatever the precise mechanism of action, intra-mPFC actions of 5-HT<sub>1A</sub>-Rs (and as described later, other serotonin receptors) is a critical means of system-level regulation of the serotonergic response to stress. In this regard, a loss in mPFC 5-HT<sub>1A</sub>-R binding following stress or glucocorticoid excess (Crayton et al., 1996; Preece et al., 2004) (cf. Arborelius et al., 2004) could significantly impact this form of regulation.

Beyond the mPFC and DRN, 5-HT<sub>1A</sub>-Rs are present in the amygdala (Clement et al., 1996; Pazos and Palacios, 1985). The level of 5-HT<sub>1A</sub>-R binding in basolateral nucleus of the amygdala (BLA) is increased by maternal separation stress in rats (Vicentic et al., 2006) and *Octodon degus* (Ziabreva et al., 2003). Under non-stressed conditions, application of 5-HT<sub>1A</sub>-R agonists (e.g., 8-OH-DPAT) inhibits the excitability of neurons in the BLA, while the inhibitory actions of 5-HT on these neurons can be prevented by 5-HT<sub>1A</sub>-R antagonist co-application (Cheng et al., 1998; Stein et al., 2000; Wang et al., 1999). However 5-HT<sub>1A</sub>-Rs can also suppress GABA interneuron activity in the BLA (Koyama et al., 1999, 2002), which might account for the minimal 5-HT<sub>1A</sub>-R agonist activity in the BLA reported in some studies (Rainnie, 1999). As such, the net effect of stress-induced release in this area of the brain critical for anxiety and fear processing will be determined by the relative balance of 5-HT<sub>1A</sub>-R actions on excitatory and inhibitory neurons. This ambiguity appears to manifest at the behavioral level. Direct administration of 5-HT<sub>1A</sub>-R agonists (ipsapirone, buspirone, 8-OH-DPAT) into the rat BLA amygdala has been shown to reduce anxiety-like behavior in some tests (e.g., shock-induced vocalization), increase anxiety in others (social interaction) and have no or variable activity in others (e.g., elevated plus-maze, shock-punished conflict) (Gonzalez et al., 1996; Griebel, 1995; Hodges et al., 1987; Menard and Treit, 1999; Millan, 2003; Schreiber and De Vry, 1993; Zangrossi Junior and Graeff, 1994).

In addition to having a major role in controlling fear and anxiety, the amygdala also regulates the hypothalamic–pituitary–adrenal (HPA) axis response to stress via a pathway from the main output nucleus of the amygdala, the central nucleus, to the paraventricular nucleus of the hypothalamus (PVN) (Swanson and Petrovich, 1998). Serotonin can influence the HPA axis response to stress not only via the amygdala, but also via the mPFC, the hippocampus and direct innervation from the raphe (for review, see Herman et al., 2005). Intra-amygdala (and in some cases systemic) administration of 5-HT<sub>1A</sub>-R agonists can attenuate both the behavioral and neuroendocrine responses to various stressors, including restraint, forced swim and conditioned fear stimuli (Krysiak et al., 2000; Li et al., 2006; Rittenhouse et al., 1992). Conversely, although mRNA for the receptor is not abundant in the paraventricular nucleus of the hypothalamus (Heisler et al., 2007b), 5-HT<sub>1A</sub>-R agonists such as 8-OH-DPAT injected directly into this structure stimulates the HPA-axis (Calogero et al., 1990, 1993; Gilbert et al., 1988; Pan and Gilbert, 1992). A pro-HPA-axis action of 5-HT<sub>1A</sub>-Rs would be consistent with the observation that systemic administration of the 5-HT<sub>1A</sub>-R agonist flesinoxan increased c-Fos expression in corticotropin-releasing hormone (CRH)-labeled cells in the PVN of the hypothalamus (as well as the central nucleus of the amygdala) (Compaan et al., 1996, 1997).

The complex and sometimes opposing actions of serotonin at 5-HT<sub>1A</sub>-R on different cell types and multiple nodes within the DRN-mPFC-amygdala circuit might explain why 5-HT<sub>1A</sub>-R agonists never reached their full potential as clinical anxiolytics and antidepressants (Blier and Ward, 2003; Holmes, 2008). This complexity also suggests that genetically driven loss of 5-HT<sub>1A</sub>-R function should have pleiotropic consequences for stress-related phenotypes. This is indeed so in the case of gene knockout of mouse *Htr1a*. Adrien and colleagues have shown that 5-HT<sub>1A</sub>-R knockout mice display a profile of increased paradoxical sleep and insensitivity to stress-induced changes in sleep patterns (Boutrel et al., 2002) that is similar to that seen in other mouse models of depression (Popa et al., 2006). On the other hand, 5-HT<sub>1A</sub>-R knockout mice display a profile in the tail suspension test that is more consistent with an antidepressant-like response, and a normal profile on the ‘differential-reinforcement-of-low-rate 36-seconds’ test for depression-related behavior (Heisler et al., 1998; Jones and Lucki, 2005; Mayorga et al., 2001; Pattij et al., 2003). These mice are also insensitive to the antidepressant-like effects of SRIs in the tail suspension test implying the receptor may be an important mechanism in these effects (Knobelman et al., 2001a, 2001b; Mayorga et al., 2001).

In terms of anxiety, 5-HT1A-R knockout mice exhibit increased spontaneous anxiety-like behaviors on the standard exploration-based tests (Bailey and Toth, 2004; Gross et al., 2000; Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998; Zhuang et al., 1999). In addition, Olivier and colleagues have demonstrated exaggerated autonomic (e.g., hyperthermia, tachycardia) responses to acute stress exposure in these mice (Pattij et al., 2001, 2002a, 2002b) (see also Gross et al., 2000). Finally, consistent with a loss of the inhibitory actions at 5-HT1A-R's in the mPFC and the excitatory effects of 5-HT1A-Rs on the HPA-axis, respectively, both effects are diminished by knockout of the receptor (Bruening et al., 2006; Gross et al., 2000).

Further extending the phenotypic profile of the 5-HT1A-R knockout mouse, Gross and colleagues have recently demonstrated that these mice have a fear bias towards environmental cues that are ambiguous predictors of trauma and which produce little fear in non-mutant mice (Klemenhagen et al., 2006; Tsetsenis et al., 2007). 5-HT1A-Rs are expressed on pyramidal neurons in the hippocampus (Chalmers and Watson, 1991; Clement et al., 1996; Khawaja, 1995; Kia et al., 1996a, 1996b; Pazos and Palacios, 1985; Raurich et al., 1999; Wright et al., 1995) where they exert an inhibitory action (Corradetti et al., 1998). 5-HT1A-R knockout mice display signs of hippocampal hyperexcitability (Sibille et al., 2000) and Tsetsenis et al. found that inhibition of cells within the dentate gyrus subregion of the hippocampus was sufficient to normalize the abnormal fear bias in the knockouts (Tsetsenis et al., 2007). While the hippocampus is not a focus of the current review, these findings are consonant with the idea that the hippocampus works in concert with the PFC and amygdala to gate environmental information regarding the precise stimulus features of threatening stimuli (Maren and Quirk, 2004; McHugh et al., 2007) (see also Gray and McNaughton, 1996). The data in knockout mice identify hippocampal 5-HT1A-Rs as a mechanism subserving this process. It is worth pointing out, therefore, that stress exposure likely impacts this mechanism via changes in 5-HT1A-R expression and function in the hippocampus. An increase in hippocampal 5-HT1A-R binding or mRNA is seen in rodents exposed to glucocorticoids, unpredictable stress, amygdala-kindling, and, in some studies at least, maternal separation (Arborelius et al., 2004; Harvey et al., 2003; Kalynchuk et al., 2006; Lopez et al., 1999; Neumaier et al., 2002; Vazquez et al., 2000, 2002).

Both the fear-related and anxiety-like phenotypes in 5-HT1A-R knockout mice appear to have their origins in development. The most compelling evidence of this comes from the finding that restricting genetic loss of 5-HT1A-R to the second and third postnatal weeks was sufficient to recapitulate the pro-anxiety-like effects of constitutive gene knockout (Gross et al., 2002). Contrariwise, deleting the 5-HT1A-R only in adulthood had no effect on anxiety-like behavior. Using a simple pharmacological approach, the fear-bias to ambiguity was mimicked in non-mutant mice by treatment with a 5-HT1A-R antagonist (WAY 100635) during the third and fourth postnatal weeks (Tsetsenis et al., 2007). These data again speak to the importance of serotonin as a factor driving the development of the corticolimbic systems subserving the stress response later in life (for further discussion, see Ansorge et al., 2007; Gross and Hen, 2004; Hariri and Holmes, 2006).

The rodent data strongly support variation in the human *HTR1A* gene as a candidate for stress-related disorders. A SNP (-1019C/G) in the promoter region of the human *HTR1A* gene is associated with depression, suicide and panic (Huang et al., 2004; Lemonde et al., 2003). There is also an interesting fMRI report that relatively low levels of 5-HT1A-R autoreceptor binding in the midbrain predict increased amygdala reactivity to threatening faces (Fisher et al., 2006), which extends positron emission tomography studies indicating lesser PFC 5-HT1A-R binding and blunted neuroendocrine responses to the 5-HT1A-R partial agonist ipsapirone in patients with panic disorder and depression (Lesch et al., 1992; Lopez-Figueroa et al., 2004; Neumeister et al., 2004b; Sullivan et al., 2005). However, it was not clear in these cases whether

this apparent loss of 5-HT<sub>1A</sub>-R was genetic in origin or a consequence of a stress phenotype. We still await real insight into this genetic contribution of this receptor in human stress-related disease.

## 8. 5-HT<sub>1B</sub> receptors

5-HT<sub>1B</sub>-Rs serve as terminal presynaptic autoreceptors regulating serotonin release and as heteroreceptors on non-serotonin neurons (Moret and Briley, 1997; Morikawa et al., 2000). The autoreceptor function of 5-HT<sub>1B</sub>-Rs is exemplified by the augmentation of stimulated-increases in ECF serotonin levels in forebrain regions by pharmacological antagonism or gene knockout of the receptor (Ase et al., 2000; de Groote et al., 2002a, 2002b; Knobelman et al., 2001a, 2001b; Malagie et al., 2001; Trillat et al., 1997). Virus-induced overexpression of 5-HT<sub>1B</sub>-R autoreceptors has been shown to increase basal, but attenuate stress-induced, anxiety-like behavior in rats (Clark et al., 2002, 2004); which is generally consistent with the pro-anxiety effects of 5-HT<sub>1B</sub>-R agonist such as CP 94,253 (Lin and Parsons, 2002; Moret and Briley, 2000). On the other hand, normal variation in levels of 5-HT<sub>1B</sub>-R mRNA in the DRN of the rat has also been correlated with differences in anxiety-like behaviors, such that higher 5-HT<sub>1B</sub>-R levels were associated with relatively low levels of anxiety-like behavior in various tests (Clark et al., 2004; Kaiyala et al., 2003; Neumaier et al., 2002) (cf. Edwards et al., 1991). However, this relationship was lost in rats that were exposed to forced swim, restraint or shock stress, possibly due to the downregulation of 5-HT<sub>1B</sub>-Rs caused by the stress exposure (Bolanos-Jimenez et al., 1995).

Gene knockout of mouse *Htr1b* is notable for the hyper-aggressive, locomotor hyperactivity and impaired impulse control phenotype that results (Bouwknicht et al., 2001; Malleret et al., 1999; Saudou et al., 1994; Zhuang et al., 1999). This, in and of itself, is pertinent to stress in view of the high incidence of suicide, a form of self-directed impulsive aggression, in stress-related disorders such as depression. 5-HT<sub>1B</sub>-R knockout mice do not exhibit any clear change in anxiety-like behavior. However, these mice do show an exaggerated autonomic reaction to acute stress and depressive-like enhancement of paradoxical sleep and an antidepressant-like response in forced swim and tail suspension test that is normalized by SRI treatment or PCPA depletion of central serotonin (Boutrel et al., 1999; Brunner et al., 1999; de Boer and Koolhaas, 2005; Dirks et al., 2001; Groenink et al., 2003; Jones and Lucki, 2005; Lopez-Rubalcava et al., 2000; Mayorga et al., 2001; Olivier and van Oorschot, 2005; Pattij et al., 2003; Ramboz et al., 1996; Sibille et al., 2007). On the face of it the antidepressant-like phenotype is congruent with the antidepressant-like activity of the selective 5-HT<sub>1B</sub>-R antagonist SB-616234-A (Dawson et al., 2006).

Providing insight into the signaling mechanisms underlying the 5-HT<sub>1B</sub>-Rs role in stress, Svenningsson et al. recently found that the activity of p11 (also known as S100A10), an intracellular signaling molecule which localizes 5-HT<sub>1B</sub>-R to the cell surface, is increased in mouse brain following antidepressant treatment, and is downregulated in postmortem brain samples from human depressives (Svenningsson et al., 2006). These authors were also able to demonstrate that gene knockout of p11 (causing loss of 5-HT<sub>1B</sub>-R function) caused increased 'depression-related' behavior in mouse tail suspension and sucrose preference tests, while transgenic overexpression of p11 produced the opposite phenotype. The 'pro-depressive' phenotype of p11 knockout contrasts from the 'antidepressant-like' phenotype of knockout of 5-HT<sub>1B</sub>-R itself, but the reason for this is not clear.

Any link between genetic variation in the human *HT1BR* gene and stress is unlikely to be any less straightforward, but the available data are meager. Perhaps most notable is that a G816C SNP in the human *HT1BR* gene, which could encode for lesser 5-HT<sub>1B</sub>-R binding (Duan et

al., 2003; Huang et al., 1999), is significantly more frequent in depression (Huang et al., 2003).

## 9. 5-HT<sub>2A</sub> receptors

Although distributed in various corticolimbic regions, there is accumulating evidence that 5-HT<sub>2A</sub>-Rs play a particularly important role in mediating serotonin's action in the mPFC during stress. 5-HT<sub>2A</sub>-R are located on the dendrites of glutamatergic pyramidal neurons and interneurons in the rodent mPFC (Aghajanian and Marek, 1997; Cornea-Hebert et al., 1999; Hamada et al., 1998; Jansson et al., 2001; Miner et al., 2003; Willins et al., 1997; Xu and Pandey, 2000). Electrophysiological studies have demonstrated that selectively stimulating 5-HT<sub>2A</sub>-Rs (typically by co-applying a mixed 5-HT<sub>2A</sub>-R/5-HT<sub>2C</sub>-R agonist and a 5-HT<sub>2C</sub>-R antagonist to isolate 5-HT<sub>2A</sub>-Rs) can either excite or inhibit the activity of neurons in the rat mPFC, although an excitatory action appears to predominate under most conditions (Aghajanian and Marek, 1997, 1999; Amargos-Bosch et al., 2007; Araneda and Andrade, 1991; Arvanov et al., 1999; Ashby et al., 1990, 1994; Liu and Aghajanian, 2008; Marek et al., 2006; Puig et al., 2003; Zhou and Hablitz, 1999). On the basis of what appears to be an extrasynaptic localization of 5-HT<sub>2A</sub>-Rs on mPFC neurons (Jansson et al., 2001), some authors have proposed that the excitatory action of this receptor may be particularly prominent under conditions of high serotonin release (Sharp et al., 2007).

There is strong evidence that 5-HT<sub>2A</sub>-Rs work in close concert with the glutamate system to modulate mPFC activity (for reviews, see Beique et al., 2007; Celada et al., 2004). 5-HT<sub>2A</sub>-R activation augments glutamatergic thalamic input to the mPFC, and synergizes with AMPA and metabotropic mGluR2/3 glutamate receptors to excite mPFC neurons (Aghajanian and Marek, 1999; Ashby et al., 1990; Beique et al., 2007; Lambe and Aghajanian, 2001; Lopez-Gil et al., 2007; Marek et al., 2001, 2006; Martin-Ruiz et al., 2001; Muschamp et al., 2004; Puig et al., 2003; Scruggs et al., 2000, 2003). In addition, 5-HT<sub>2A</sub>-Rs positively modulate stress-induced release of dopamine in the mPFC (Pehek et al., 2006). As such, changes in 5-HT<sub>2A</sub>-R function in mPFC would be expected to have a broad impact on the overall activation of the mPFC following stress. In this context, exposure to chronic unpredictable stress, isolation rearing or chronic corticosterone treatment have been found to increase 5-HT<sub>2A</sub>-R binding in the mPFC (and amygdala) and alter 5-HT<sub>2</sub>-mediated head shakes (Chaouloff et al., 1994; Izumi et al., 2002; Katagiri et al., 2001; Ossowska et al., 2001; Preece et al., 2004; Schiller et al., 2003; Takao et al., 1997). It is difficult to posit whether this upregulation is the result of either stress-induced elevation or diminution of serotonin in the mPFC. 5-HT<sub>2A</sub>-Rs are atypical amongst 5-HT receptors in exhibiting desensitization and downregulation not only following chronic agonism but also in response to chronic antagonism and serotonin depletion; thus upregulation could potentially occur through various stress-related changes in serotonergic neurotransmission (Blackshear et al., 1986; Blackshear and Sanders-Bush, 1982; Buckholtz et al., 1985; Conn and Sanders-Bush, 1986; Gray and Roth, 2001; Marek et al., 2001; McKenna et al., 1989).

As already noted, pharmacological studies indicate that 5-HT<sub>2A</sub>-Rs can sometimes exert inhibitory actions in the mPFC. This likely occurs via local  $\gamma$ -aminobutyric acid (GABA)ergic interneurons that synapse onto projection neurons (Abi-Saab et al., 1999; Amargos-Bosch et al., 2004; Blue et al., 1988; Feng et al., 2001a; Jansson et al., 2001; Martin-Ruiz et al., 2001; Pompeiano et al., 1994; Roth et al., 1998; Santana et al., 2004; Willins et al., 1997; Zhou and Hablitz, 1999). These inhibitory actions provide an additional mechanism by which 5-HT<sub>2A</sub>-Rs can modulate mPFC activity and speak to the highly nuanced nature of 5-HT<sub>2A</sub>-R function in this key brain region. Defining the physiological conditions under which inhibitory versus excitatory actions of 5-HT<sub>2A</sub>-Rs in mPFC predominate, and how this balance is shifted by stress and genetic variation, are major issues that are not yet answered. This balance will not

only determine the intrinsic functionality of the mPFC but also the level of negative feedback control over the DRN.

We discussed earlier how 5-HT1A-Rs in the mPFC control DRN activity via a subcortical projection. Selective stimulation of PFC 5-HT2A-Rs decreases (but in some cases increases) the activity of DRN neurons to affect a consequent change in ECF serotonin concentrations in mPFC and other forebrain targets (Boothman et al., 2003; Bortolozzi et al., 2003; Celada et al., 2001; Martin-Ruiz et al., 2001). As in the aforementioned 5-HT1A-R model of DRN regulation, 5-HT2A-R-mediated excitation of the mPFC likely inhibits DRN neuronal activity via stimulation of local GABAergic interneurons (Boothman et al., 2006; Boothman and Sharp, 2005; Liu et al., 2000). Although activation of 5-HT1A-Rs and 5-HT2A-Rs in the mPFC can both exert an inhibitory influence on the DRN, there is evidence that co-application of agonists for the two subtypes can nullify these subcortical effects (Amargos-Bosch et al., 2004; Araneda and Andrade, 1991; Martin-Ruiz et al., 2001). Notwithstanding the complexity of these interactions, the functional localization of 5-HT2A-Rs in the mPFC positions this receptor subtype to exert a profound influence over the serotonergic response to stress.

Beyond the PFC, most amygdala nuclei show low to moderate levels of 5-HT2A-R binding and mRNA (Pazos et al., 1985; Pompeiano et al., 1994; Wright et al., 1995). (Tangentially, 5-HT2A-R-immunoreactive neurons in the BLA project to the mediodorsal thalamus; thereby providing another link to the mPFC (McDonald and Mascagni, 2007).) Immunocytochemical analyses indicate 5-HT2A-R expression on the dendrites of pyramidal neurons in the BLA, and more intense staining on parvalbumin-containing interneurons in this area (Cornea-Hebert et al., 1999; McDonald and Mascagni, 2007; Morilak and Ciaranello, 1993; Xu and Pandey, 2000). The presence of 5-HT2A-Rs on these GABAergic interneurons likely accounts for the inhibitory actions of the receptor in the amygdala. These effects are inferred from the observation that serotonin or mixed 5-HT2A-R/5-HT2C-R agonists such as DOI inhibit BLA neuronal firing in a manner that can be mimicked by 5-HT2A-R (not 5-HT1A-R) agonists and be blocked by GABA receptor antagonists (Rainnie, 1999; Stein et al., 2000; Stutzmann and LeDoux, 1999).

For a number of years, a lack of agonists with specificity for 5-HT2A-Rs over 5-HT2C-Rs meant that pharmacological dissociation of the role of these subtypes in stress-related behaviors had to be inferred from the ability of subtype-selective antagonists to block the behavioral effects of mixed 5-HT2A-R/5-HT2C-R agonists (e.g., DOI). This approach has shown that systemic antagonism of 5-HT2A-Rs, but not 5-HT2C-Rs, is sufficient to block the anxiolytic-like effects of DOI or SRIs, even though selective 5-HT2A-R antagonists such as MDL 100,907 have weak inherent anxiolytic-like activity (Griebel, 1995; Griebel et al., 1997; Kehne et al., 1996; Millan, 2003; Mora et al., 1997; Nic Dhonnchadha et al., 2003; Ripoll et al., 2006; Schreiber et al., 1998). Systemic treatment with selective 5-HT2A-R antagonists such as MDL 100,907 is also capable of blunting the corticosterone release and activation of CRH-positive PVN hypothalamic neurons produced by mixed 5-HT2A-R/5-HT2C-R agonists like DOI (e.g., Hemrick-Luecke and Evans, 2002; Van de Kar et al., 2001).

The pharmacological data are extended by the finding that gene knockout of the mouse *Htr2a* causes a decrease in anxiety-like behavior in various tasks (Weisstaub et al., 2006). Weisstaub et al. were able to demonstrate that expressing 5-HT2A-Rs in the cortex of these knockout mice was sufficient to normalize the anxiety-like behavior, suggesting that cortical 5-HT2A-Rs normally serve to promote anxiety-like behavior. Precisely how this relates to the regulation of mPFC neuronal activity by 5-HT2A-Rs is not yet clear. Furthermore, although 5-HT2A-R knockout mice showed normal 'depression-related' behavior in the forced swim test, and a normal HPA-axis response to this stressor (Weisstaub et al., 2006) further examination of these mice for other stress-related behaviors would be informative. Such studies

are encouraged by the increased PFC 5-HT<sub>2A</sub>-R binding found in depression (Meyer et al., 1999; Yatham et al., 2000), and the antidepressant efficacy of drugs with 5-HT<sub>2A</sub>-R antagonist properties (e.g., nefazodone, trazodone, mirtazapine) (Celada et al., 2004; Millan, 2003).

Genetic associations between stress-related disorders and variants in the human *HTR2A* gene, including the more well-studied 102 T/C and Tyr452 variants, remain preliminary (Norton and Owen, 2005; Serretti et al., 2007a). There has in fact been more interest in *HTR2A* gene variation as a risk factor for psychosis given the role of the 5-HT<sub>2A</sub>-R subtype in mechanism of action of both psychotomimetics and antipsychotics (Kroeze and Roth, 1998; Meltzer, 1999; Sanders-Bush et al., 2003). This is nonetheless potentially very salient to stress. First, executive dysfunction is not limited to schizophrenia, and is prominent in affective disorders such as major depression (Taylor Tavares et al., 2007). Second, 5-HT<sub>2A</sub>-Rs localized in the mPFC have been found to be important modulators of executive functions that are known to be impaired in affective as well as psychotic illness, such as working memory, cognitive flexibility and impulse control (Clarke et al., 2004; Stein et al., 2007; Williams et al., 2002; Winstanley et al., 2004). Third, exposure to stress causes dendritic retraction of mPFC pyramidal neurons and blunts 5-HT<sub>2A</sub>-R-mediated modulation of these neurons (Liu and Aghajanian, 2008), and produces associated deficits in PFC-mediated behaviors such as fear extinction and attentional set-shifting (Izquierdo et al., 2006; Liston et al., 2006). Thus, loss of 5-HT<sub>2A</sub>-R function in the mPFC could be a mechanism linking stress with some of the cognitive and executive symptoms found in stress-related disease.

## 10. 5-HT<sub>2C</sub> receptors

5-HT<sub>2C</sub>-Rs are highly expressed in the mPFC and amygdala (Abramowski et al., 1995; Clemett et al., 2000; Li et al., 2003; Lopez-Gimenez et al., 2002; Molineaux et al., 1989; Pompeiano et al., 1994; Sharma et al., 1997; Wright et al., 1995). Pharmacological studies point to a role for this receptor subtype in mediating serotonin's pro-anxiety effects at the level of the amygdala. Treatment with the non-specific serotonin receptor agonist *m*-chlorophenylpiperazine (mCPP) has potent anxiogenic effects in rodent and man alike (Griebel, 1995; Menard and Treit, 1999; Millan, 2003; Murphy et al., 1986). Selective blockade of 5-HT<sub>2C</sub>-Rs with compounds such as SB 242084, either systemically or in the amygdala, is sufficient to prevent mCPP-induced (and in some cases, spontaneous or stress-induced) rodent anxiety-like behavior (Campbell and Merchant, 2003; Cornelio and Nunes-de-Souza, 2007; Graeff et al., 1996; Griebel, 1995; Hackler et al., 2007; Harada et al., 2006, 2007; Kennett et al., 1996; Martin et al., 2002; Millan, 2003). Systemic treatment with SB 242084 also blocks the enhancement of conditioned fear produced by acute SRI treatment (Burghardt et al., 2004, 2007) (cf. Santos et al., 2006). The ability of SB 242084 to antagonize the anxiogenic-like effects of mCPP were associated with a significant attenuation of neural activation in the amygdala (as well as the hippocampus and hypothalamus, but not mPFC) (Hackler et al., 2007). Finally, the aforementioned anxiety-like phenotype in SERT knockout mice is associated with a significant increase in 5-HT<sub>2C</sub>-R binding density in the amygdala (Li et al., 2003). Collectively, these findings indicate that serotonin's ability to promote anxiety is mediated in part by actions at 5-HT<sub>2C</sub>-Rs in the amygdala. This presumably occurs by exciting projection neurons therein, although there is surprisingly little electrophysiological verification of such an action.

The pharmacological literature on 5-HT<sub>2C</sub>-R and stress-related behaviors has been extended by a mouse model of gene knockout of the X-linked *Htr2c* gene. Gene knockout of 5-HT<sub>2C</sub>-R leads to a decrease in anxiety-like behavior on a variety of assays (Heisler et al., 2007a). These mice also exhibit significantly lesser DOI- or mCPP-induced activation of CRH-positive cells in the central nucleus of the amygdala and bed nucleus of the stria terminalis, and signs of CRH downregulation in the PVN of the hypothalamus (Heisler et al., 2007a, 2007b).

Serotonin normally stimulates glucocorticoid release in part via an action on CRH neurons in the PVN (Calogero et al., 1990, 1993; Fuller and Snoddy, 1980; Heisler et al., 2007b; Jorgensen et al., 1998, 2002), but Heisler et al. showed that this effect is lost in the 5-HT<sub>2C</sub>-R knockout mice and ablated in non-mutant mice systemically treated with the selective 5-HT<sub>2C</sub>-R antagonist RS 102221. Whether 5-HT<sub>2C</sub>-R inactivation would also inhibit stress-induced HPA-axis activation has not been reported; although one study showed a greater decrease in body weight in response to acute restraint stress in aged 5-HT<sub>2C</sub>-R knockout mice (Chou-Green et al., 2003).

5-HT<sub>2C</sub>-R knockout mice do not show abnormalities in tests for 'depression-related' behaviors such as the tail suspension test. However, either 5-HT<sub>2C</sub>-R gene knockout or systemic treatment with the selective 5-HT<sub>2C</sub>-R antagonists SB 242084 or RS 102221 has been shown to both potentiate the antidepressant-related effects of SRIs in the tail suspension test and augment the increases in cortical and hippocampal ECF serotonin levels produced by SRI treatment (Cremers et al., 2004, 2007). On the other hand, systemic treatment with the novel 5-HT<sub>2C</sub>-R agonists WAY 163909, RO 600175 also exert antidepressant-like effects in a range of rodent assays (Cryan and Lucki, 2000; Martin et al., 1998; Rosenzweig-Lipson et al., 2007). These data have not been reconciled but they imply that the influence of genetically driven variation in human *HTR2C* function on risk for depression in humans may be complex.

An interesting feature of both the rodent and human 5-HT<sub>2C</sub>-R is that the receptor undergoes post-transcriptional RNA editing to an isoform with reduced constitutive and agonist-stimulated signaling activity (Burns et al., 1997; Sanders-Bush et al., 2003). The BALB/cJ and DBA/2J inbred mouse strains have been found to exhibit differences in basal rates of 5-HT<sub>2C</sub>-R editing in the mPFC and amygdala relative to other strains such as C57BL/6J (Englander et al., 2005; Hackler et al., 2006). Schmauss and colleagues have shown that either exposure to swim stress in adulthood or chronic maternal separation early in development increases 5-HT<sub>2C</sub>-R editing in the PFC of the stress-reactive BALB/cJ strain but not stress-resilient C57BL/6J strain, and that the increase in BALB/cJ can be normalized by SRI treatment (Bhansali et al., 2007; Englander et al., 2005). This has led to the idea that trait variation in 5-HT<sub>2C</sub>-R editing could contribute to differences in stress reactivity in the mouse and, by extension, increase risk for stress-related disorders in the human (Schmauss, 2003). Intriguingly, a number of studies have found increased 5-HT<sub>2C</sub>-R editing in the mPFC of schizophrenics and depressive suicides (Gurevich et al., 2002; Sodhi et al., 2001). There is also preliminary evidence that structural variants in the human *HTR2C* gene, including a Cys23Ser SNP, are associated with bipolar disorder and major depression (Lappalainen et al., 1999; Lerer et al., 2001; Massat et al., 2007).

## 11. 5-HT<sub>3</sub> receptors

The 5-HT<sub>3</sub>-R distinguishes itself from other members of the 5-HT receptor family by being a ligand-gated ion channel (as opposed to a G-protein-coupled receptor) (Derkach et al., 1989) and by being largely expressed in the rodent brain as a presynaptic heteroreceptor on non-serotonergic neurons, including GABA interneurons in the mPFC and amygdala (Kilpatrick et al., 1987; Morales et al., 1998; Morales and Bloom, 1997; Tecott et al., 1993). Systemic administration of 5-HT<sub>3</sub>-R antagonists such ondansetron and tropisetron have anxiolytic-like effects in rodent assays, although this is not always consistently seen (reviewed in Costall and Naylor, 2004; Griebel, 1995; Millan, 2003). There are 5-HT<sub>3A</sub>-R and 5-HT<sub>3B</sub>-R subtypes of this receptor, but despite its presence in the human amygdala (Davies et al., 1999) little is known about the contribution of 5-HT<sub>3B</sub>-R to corticolimbic function and stress. By contrast, the contribution of 5-HT<sub>3A</sub>-R has been demonstrated by the finding that gene knockout of *Htr3A* in mouse is associated with a reduction in anxiety-like behavior on various tasks (Bhatnagar et al., 2004b; Kelley et al., 2003). 5-HT<sub>3A</sub>-R knockout mice also show exaggerated



amygdala-mediated conditioned fear (Bhatnagar et al., 2004b), which might reflect the reported pro-cognitive effects of 5-HT<sub>3</sub>-R antagonists in rats (Costall and Naylor, 2004).

5-HT<sub>3A</sub>-Rs are located in the PVN of the hypothalamus (Tecott et al., 1993). 5-HT<sub>3A</sub>-R knockout mice show an attenuated adrenocorticotropin-releasing hormone response to restraint stress (Bhatnagar et al., 2004b; Bhatnagar and Vining, 2004) similar to the attenuated restraint stress-induced prolactin response produced by the 5-HT<sub>3</sub>-R antagonist ondansetron in rats (Jorgensen et al., 1992; Nonaka, 1999) (but see Jorgensen et al., 1998). By extension the elevated levels of CRH mRNA in the central nucleus of the amygdala of 5-HT<sub>3A</sub>-R knockout mice may be an upstream compensation for a chronically depressed HPA-axis (Bhatnagar et al., 2004b), although it could also reflect a loss of normal GABAergic facilitation mediated by this receptor in the amygdala (Koyama et al., 2002; Turner et al., 2004). Systemic treatment with 5-HT<sub>3</sub>-R antagonists including ondansetron and ramosetron also inhibit CRH and restraint stress-induced colonic propulsion (Hirata et al., 2007; Miyata et al., 1993, 1998; Yamamoto et al., 1998). This is one reason why 5-HT<sub>3</sub>-R antagonists have garnered interest as potential treatments for Irritable Bowel Syndrome, a condition frequently found in stress-related conditions (Gershon, 2005).

Recent evidence indicates that SRIs and other antidepressants have 5-HT<sub>3</sub>-R antagonist properties (Eisensamer et al., 2003, 2005). Systemic treatment with the 5-HT<sub>3</sub>-R antagonist ondansetron can augment the antidepressant-like actions of SRIs in the forced swim and tail suspension tests, while the 5-HT<sub>3</sub>-R agonist 1-(*m*-chlorophenyl)-biguanide (mCPBG) has the opposite effect (Nakagawa et al., 1998; Redrobe and Bourin, 1997) (cf. Akagawa et al., 1999; Millan et al., 2003). 5-HT<sub>3A</sub>-R knockout mice do not display changes in baseline behaviors in these tests with the exception of increased 'depression-related' behavior in female knockouts with repeated forced swim exposure (Bhatnagar et al., 2004a). Whether these mice respond abnormally to antidepressants is not known.

There is emerging evidence of a link between 5-HT<sub>3</sub>-R, stress and alcohol abuse. There is a high degree of comorbidity between stress-related disorders and alcohol abuse and ondansetron has efficacy in the treatment of certain types of alcoholism (Johnson, 2004). In the rodent, systemic treatment with 5-HT<sub>3</sub> antagonists including ondansetron, tropisetron and LY-278,584 reduces stress-induced reinstatement of alcohol self-administration and reward-related place learning (Le et al., 2006; Matsuzawa et al., 1999). 5-HT<sub>3A</sub>-R knockout mice fail to show the normal reduction in voluntary ethanol consumption produced by 5-HT<sub>3</sub>-R antagonist LY-278,584, but otherwise show normal baseline consumption and sensitivity to the acute behavioral effects of ethanol (Hodge et al., 2004). A different phenotype is produced by post-developmental transgenic overexpression of 5-HT<sub>3</sub>-R in forebrain regions including the mPFC and amygdala (Engel et al., 1998; Harrell and Allan, 2003). These transgenic mice show increased sensitivity to the locomotor stimulant effects of ethanol and reduced voluntary ethanol self-administration (but normal ethanol discriminative stimulus capabilities) (Engel and Allan, 1999; Engel et al., 1998; Shelton et al., 2004). Interestingly, this phenotype is mimicked by exposure to chronic swim stress in certain inbred strains of mice (Boyce-Rustay et al., 2007a, 2007b). It is also similar to the ethanol-related phenotype found in SERT knockout mice (Boyce-Rustay et al., 2006; Daws et al., 2006), which display increased 5-HT<sub>3</sub>-R binding and mRNA levels in various brain regions, including a near 50% increase in the mPFC (Mossner et al., 2004). Collectively, these data suggest that the 5-HT<sub>3</sub>-R might be an important link between stress and alcohol-related behaviors, including the propensity to abuse alcohol.

Variation in the human *HTR3A* thus represents an attractive candidate for affective illness and alcoholism. An allelic variant of a SNP in the human *HTR3A* gene, C178T, is associated with increased 5-HT<sub>3</sub>-R expression *in vitro* (Niesler et al., 2001). Individuals carrying this variant exhibit lower scores for anxiety-related traits such as harm avoidance (Melke et al., 2003) and

reduced amygdala and PFC activity in response to threatening stimuli as measured by fMRI (Iidaka et al., 2005). This interesting source of gene variation in the serotonin system warrants further study.

## 12. 5-HT4, 5-HT5A, 5-HT6, and 5-HT7 receptors

This review has largely focused on the 5-HT1, 5-HT2 and 5-HT3 receptor classes because other receptor subtypes have been relatively less well studied due to their recent cloning or a lack of well-defined research tools such as subtype-selective ligands or gene mutant mice. Of course, this does not necessarily imply that these subtypes play any less of a role in modulating serotonin's stress-related actions. In fact there are promising leads for a number of subtypes expressed in the DRN-mPFC-amygdala circuit.

Both 5-HT4-Rs and 5-HT5A-Rs have been shown to exert negative feedback control over the DRN, probably via an indirect, mPFC-mediated, and a direct, autoreceptor-mediated, mechanism respectively (Lucas et al., 2005; Lucas and Debonnel, 2002; Thomas et al., 2006). Genetic deletion of the mouse *Htr5a* has minimal effect on anxiety-like behavior (Grailhe et al., 1999). Systemic treatment with 5-HT4-R-selective doses of the agonists RS 67333 and prucalopride has demonstrated an antidepressant-like profile across a range of assays (forced swim test, olfactory bulbectomy, chronic mild stress) in rats (Lucas et al., 2007). Pharmacological antagonism or gene knockout of 5-HT4-R in the mouse reduces anxiety-like behaviors, and also attenuates certain stress-induced changes in gut motility and feeding (Compan et al., 2004; Conductier et al., 2006; Kennett et al., 1997; Smriga and Torii, 2003). These data hint at a contribution of 5-HT4-Rs to the gastrointestinal and eating-related symptoms that are prominent in stress-related disorders.

Pharmacological antagonism of 5-HT6-R produces cognitive improvement in conjunction with anxiolytic-like and antidepressant-like activity, and a blockade of certain neural, molecular and behavioral effects of SRIs (Mitchell and Neumaier, 2005; Svenningsson et al., 2007; Wesolowska, 2008; Wesolowska and Nikiforuk, 2007, 2008; Woolley et al., 2004). This contrasts with the pro-anxiety effects of antisense knockdown of 5-HT6-R (Hamon et al., 1999) and a report in abstract form that mouse *Htr6* knockout leads to increased anxiety-like behavior (Tecott et al., 1998). Finally, antagonism of 5-HT7-R, via systemic SB-258719 or SB-269970 treatment, also produces antidepressant-like effects, and there is preliminary evidence that this receptor is upregulated by stress (Guscott et al., 2005; Hedlund et al., 2005; Wesolowska et al., 2006; Yau et al., 2001). Along similar lines, *Htr7* knockout gene knockout produces an antidepressant-like (and in some studies anxiolytic-like) phenotype and decreased paradoxical sleep (Guscott et al., 2005; Hedlund et al., 2005; Hedlund and Sutcliffe, 2007).

These emerging preclinical data encourage further investigation of these various serotonin receptor subtypes. Not surprisingly however, we still know very little about how genetic variation in any of these receptors might affect risk for stress-related psychiatric disorders in man.

## 13. Summary and concluding remarks

The large literature from preclinical studies in rodents indicates that genetically driven functional disruption at all levels of the serotonin system – from prenatal development to neurotransmission in the adult brain – can influence the behavioral, physiological and neuroendocrinological response to stress. While the field is still at an early stage and there is much yet to be clarified, advances have been made in defining the contributions of key molecules within the serotonin system. At the risk of oversimplifying a hugely complex literature, some of the main findings and avenues for future work can be summarized.

It is increasingly evident that the influence of serotonin gene variation begins during ontogeny with the developmental formation of the neural systems mediating the stress response including, but certainly not limited to, the pathway interconnecting the DRN, mPFC and amygdala. By acting during development, functional alterations of *Pet-1*, *Tph1*, *MAOA*, *SERT*, and *5-HT1A-R* function have all been found to produce lasting changes in rodent stress-related phenotypes and/or the corticolimbic systems subserving the stress response. Defining the putative developmental influence of natural gene variation in these molecules is critical for future work. There are also good grounds for predicting that genetically driven loss of the key molecules controlling serotonin synthesis (*Tph2*), packaging (*VMAT2*), reuptake (*SERT*) and degradation (*MAOA*) would cause an imbalance in serotonin availability and, in doing so, significantly limit the plasticity of the adult serotonin system's adaptation to stress.

Serotonergic neurotransmission in the DRN-mPFC-DRN pathway occurs through a myriad of receptors with complimentary and opposing actions (see Fig. 3). Pharmacological and electrophysiological studies in the adult brain imply that variation in *5-HT1A-R* function in the mPFC and amygdala will determine the extent of serotonin's inhibitory postsynaptic actions in these regions, as well as mPFC-mediated negative feedback to serotonin neurons. *5-HT1A-Rs* as well as *5-HT1B-Rs*, also directly regulate serotonergic neuronal firing or *5-HT* release in their capacity as presynaptic autoreceptors. Variation in *5-HT2A-R* is expected to have a major influence on serotonin's actions in the mPFC with implications not only for stress-responsivity but also stress-induced cognitive-executive dysfunction. *5-HT2C-Rs* are a critical component of the amygdala and HPA-axis response to stress and there is already evidence that genetic and epigenetic (e.g., mRNA editing) variation in this receptor impacts stress-related phenotypes. The *5-HT3A-R* is also distributed in the mPFC and amygdala, and this subtype appears to have a distinct role in linking stress and alcohol-related behaviors. Of the other 14-plus serotonin receptor subtypes, there is already data encouraging the further exploration of the role of *5-HT4-R*, *5-HT5A-R*, *5-HT6-R*, and *5-HT7-R* in mediating serotonergic modulation of the response to stress.

This impressive corpus of data supports the contribution of molecular nodes throughout the serotonin system to the stress response. It is unlikely, however, that a gene variant in any one node within this complex system would in and of itself act in isolation to promote risk for stress-related disease. The serotonin system is by its nature modulatory and extremely plastic. A genetic variant in one component would be expected to lead to compensatory changes at both the molecular and system level. For example, a loss of function variant in *TPH2*-mediated synthesis could be mitigated by a compensatory downregulation in *SERT*-mediated reuptake, or a genetically driven increase in *5-HT2A-R* drive of PFC neurons could be balanced by a parallel increase in *5-HT1A-R* inhibition on the same neurons. Likewise, the reciprocal nature of interconnected regions within the DRN-mPFC-amygdala circuit allows for a functional alteration in one brain region in response to an abnormal level of activity in another.

From this perspective, stress-related pathology would be expected to manifest only when the net effect of multiple gene variants causes a system-level failure to maintain homeostasis in the face of persistent environmental challenge (Caspi and Moffitt, 2006; Holmes and Hariri, 2003; Jabbi et al., 2007; Murphy et al., 2003). Disentangling these epistatic interactions will be an enormous task, but there is every reason to be optimistic that major advances toward this goal can be made in the coming years.

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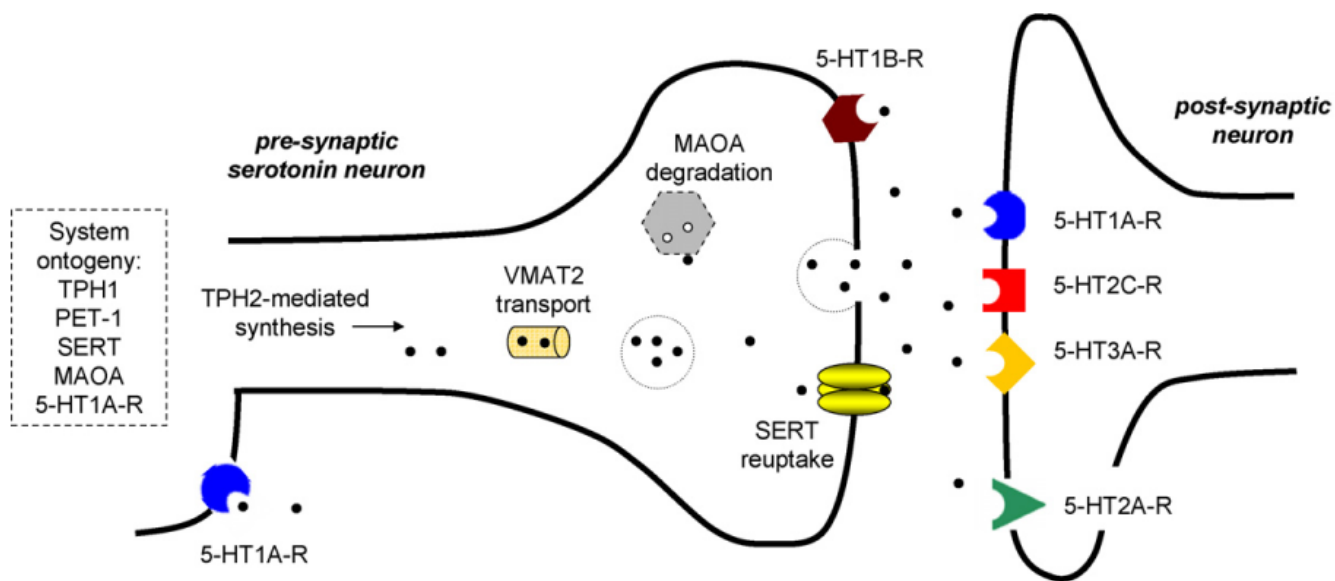
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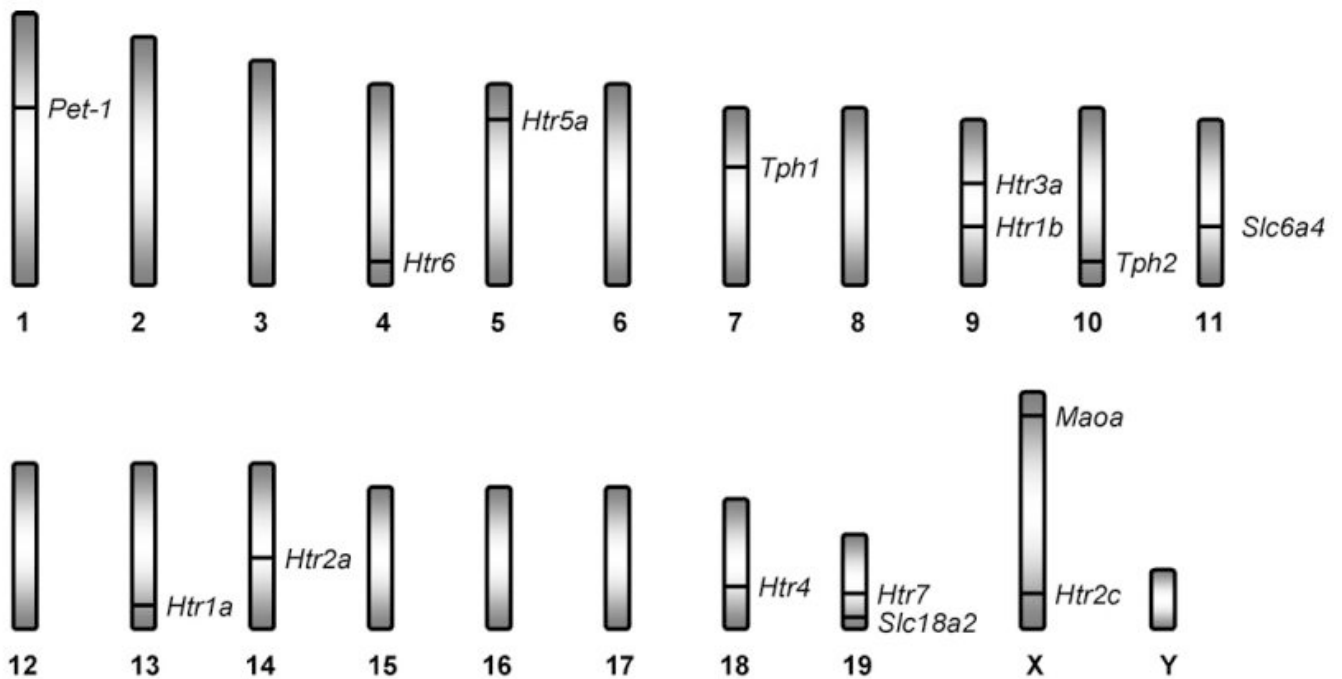
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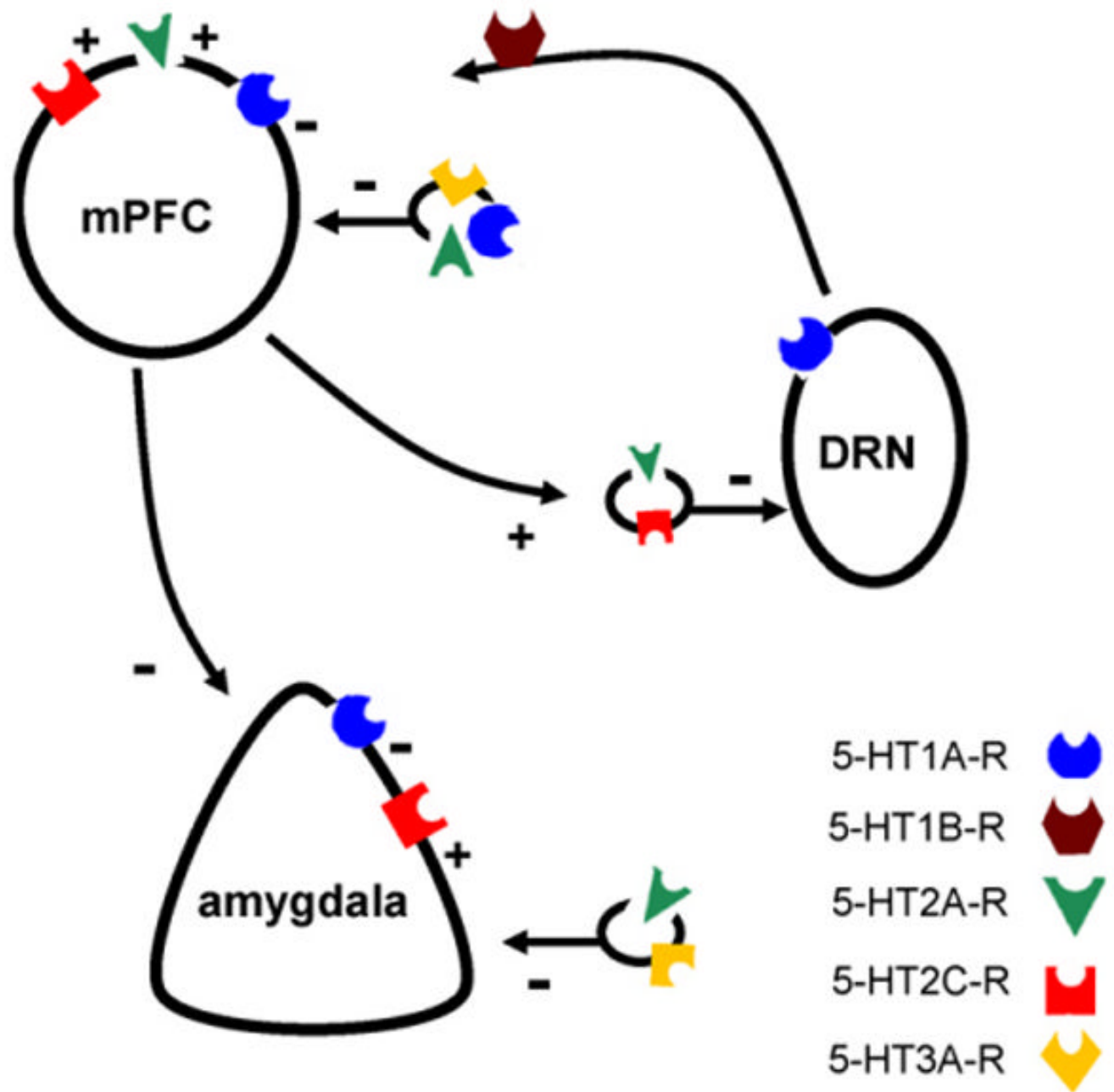


**Fig. 1.** Major molecular components of the serotonin system. The serotonin system is shaped during ontogeny by various molecules including the peripheral synthesizing enzyme tryptophan hydroxylase 1 (TPH1), the serotonin neuron precursor PET-1, the serotonin transporter (SERT) and serotonin degrading enzyme monoamine oxidase A (MAOA), and the 5-HT1A-R receptor subtype. Within the adult pre-synaptic neuron, serotonin is synthesized by the rate-limiting enzyme tryptophan hydroxylase 2 (TPH2) and packaged and transported via vesicular monoamine transporter 2 (VMAT2) to the synapse for release. Following release, extracellular concentrations of serotonin are regulated by SERT-mediated reuptake and by pre-synaptic autoreceptors at both terminals (5-HT1B-R) and soma (5-HT1A-R). Internalized serotonin is deaminated by MAOA. Extracellular serotonin acts on multiple post-synaptic receptor subtypes located synaptically, as in 5-HT1A-R, 5-HT2C-R, and 5-HT3A-R, as well as extra-synaptically, as may be the case for 5-HT2A-R. The 5-HT4-R, 5-HT5A-R, 5-HT6-R, and 5-HT7-R receptor subtypes are also important functional components of the system these are not depicted here for the sake of clarity.



**Fig. 2.**

Approximate genomic location of serotonin system genes implicated in stress-related phenotypes in the murine genome. *Htr1a* = 5-HT1A receptor (13 58.0 centimorgans (cM)), *Htr1b* = 5-HT1B receptor (9 46.0 cM), *Htr2a* = 5-HT2A receptor (14 41.5 cM), *Htr2c* = 5-HT2C receptor (X 66.15 cM), *Htr3a* = 5-HT3A receptor (19 A5.3), *Htr4* = 5-HT4 receptor (18 D3), *Htr5a* = 5-HT5A receptor (5 15.0 cM), *Htr6* = 5-HT6 receptor (4 64.9 cM), *Htr7* = 5-HT7 receptor (19 33.0 cM), *Maoa* = monoamine oxidase A (X 5.2 cM), *Slc6a4* = serotonin transporter (11 42.0 cM), *Slc18a2* = vesicular monoamine transporter 2 (19 D3), *Tph1* = tryptophan hydroxylase 1 (7 23.5 cM), *Tph2* = tryptophan hydroxylase 2 (10 D2).



**Fig. 3.** Localization of 5-HT1A-R, 5-HT1B-R, 5-HT2A-R, 5-HT2C-R, and 5-HT3A-R serotonin receptor subunits in the DRN-mPFC-amygdala circuit. These receptor subtypes exhibit a complex and often overlapping pattern of localization within the circuit. DRN = dorsal raphe nucleus, mPFC = medial prefrontal cortex.



**Table 1**

Summary of stress-related phenotypes associated with experimentally induced mouse gene mutations and naturally occurring variation in mouse and man

Gene	Mouse gene mutation	Mouse gene variant	Human gene variant
<i>Htr1a</i>	KO: increased anxiety-like behavior, autonomic response to stress, fear bias to ambiguity, decreased 'depression-like' behavior (postnatal KO mimics anxiety-related phenotype)	—	–1019C/G SNP associated with depression and panic
<i>Htr1b</i>	KO: locomotor hyperactivity, impulsivity p11 KO: increased 'depression-like' behavior p11 overexpression: decreased 'depression-like' behavior	—	G816C SNP associated with depression
<i>Htr2a</i>	KO: decreased anxiety-like behavior (rescued by expressing 5-HT2A-R in cortex)	—	102 T/C SNP, Tyr452 SNP preliminary association with anxiety and depression
<i>Htr2c</i>	KO: decreased anxiety-like behavior, HPA-axis response to serotonin, increased antidepressant-like response	Lesser RNA splicing in strains with increased anxiety-like behavior and stress reactivity	
<i>Htr3a</i>	KO: decreased anxiety-like behavior, HPA-axis stress response, increased conditioned fear, depression-like behavior (females)	—	C178T SNP associated with trait anxiety, reduced prefrontal-amygdala response to threatening faces
<i>Htr4</i>	KO: decreased anxiety-like behavior, attenuated gut motility and feeding response to stress	—	—
<i>Htr5a</i>	KO: no change in anxiety-like behavior	—	—
<i>Htr6</i>	KO: increased anxiety-like behavior	—	—
<i>Htr7</i>	KO: decreased anxiety-like behavior, 'depression-like' behavior	—	—
<i>Maoa</i>	KO: increased anxiety-like behavior, conditioned fear, aggression	—	Rare loss-of-function variant associated with impulsive aggression in Dutch family Loss-expressing VNTR associated with antisocial personality in maltreated children, abnormal prefrontal-amygdala function and structure
<i>Pet-1</i>	KO: increased anxiety-like behavior, aggression	—	—
<i>Slc6a4</i>	KO: increased anxiety-like behavior, HPA-axis stress response, 'depression-like' behavior, impaired fear extinction, reduced aggression, abnormal prefrontal-amygdala neuronal morphology	—	Low-expressing 's allele' associated with increases harm avoidance, depression after trauma, lesser antidepressant efficacy, abnormal prefrontal-amygdala function and structure
	Overexpression: decreased anxiety-like behavior		Rare I425V associated with obsessive compulsive disorder
<i>Slc18a2</i>	KO: increased 'depression-like' behavior	<i>Slc18a2</i> in QTL associated with antidepressant efficacy	—
<i>Tph1</i>	KO dams bear offspring with gross brain abnormality	—	—
<i>Tph2</i>	—	Low functioning C1473G SNP present in strains with increased anxiety-like behavior and stress reactivity	Uncommon G1463A SNP associated with increased depression
			G(-844)T SNP associated with increased amygdala reactivity to threatening faces 218A/C SNP

Gene	Mouse gene mutation	Mouse gene variant	Human gene variant
			associated with increased anxiety and depression

*Htr1a* = 5-HT1A receptor; *Htr2a* = 5-HT2A receptor; *Htr2c* = 5-HT2C receptor; *Htr3a* = 5-HT3A receptor; *Htr4* = 5-HT4 receptor; *Htr5a* = 5-HT5A receptor; *Htr6* = 5-HT6 receptor; *Htr7* = 5-HT7 receptor; KO = knockout; *Maoa* = monoamine oxidase A; QTL = quantitative trait locus; *Slc6a4* = serotonin transporter; *Slc18a2* = vesicular monoamine transporter 2 (Vmat2); *Tph1* = tryptophan hydroxylase 1; *Tph2* = tryptophan hydroxylase 2.