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# Pharmacology of 5-$HT_2$ Modulation of Amygdala & Hypothalamus in Anxiety Disorders

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## 1. Introduction

"Anxiety disorders" is a blanket term covering several different forms of abnormal and pathological fear and anxiety, and is often comorbid with other mental disorders, particularly clinical depression. These conditions are often related to stressful life experiences, especially when chronic and traumatic. Stress appears to act as a predisposing and precipitating factor in these psychiatric conditions (Strohle and Holsboer, 2003). One particular, extreme case is post traumatic stress disorder (PTSD), a chronic anxiety disorder developed in the aftermath of traumatic stress exposure and persisting long after the removal of the participating stressors.

Advances in cellular and molecular biology and imaging technology have opened several lines of inquiry into the pathogenesis and pharmacotherapy of the anxiety disorders. Dysregulation of neurotransmitter systems, alteration of signal transduction pathways, and reshaping of brain circuitry are all being explored. The availability of animal models of anxiety disorders developed from the "learned helplessness" stress paradigm, in particular, has been a great aid in elucidation of disease etiology and pathophysiology, as well as in the development of more efficacious pharmacological interventions (Drevets, 2003;Maier and Watkins, 2005;Minor and Hunter, 2002). Among several hypotheses for the pathogenesis of anxiety disorders, dysregulation of the serotonergic system has received particular attention in the field since the evidence from both preclinical and animal model studies is substantial and often complementary. In this chapter, we focus on a subset of the serotonergic system, the 5-$HT_2$ receptor system, and review both clinical and preclinical evidence regarding the involvement of this receptor in the pathophysiology of anxiety disorders.

## 2. Neuronal circuitry associated with anxiety disorders

The phenotypic complexity of anxiety disorders indicates that multiple neurotransmitter systems and brain structures are involved in the pathogenesis of such disorders. The

neuronal circuits associated with anxiety disorders appear to involve distributed and interconnected brain structures, including the amygdala, frontal cortex, and amygdala. These structures are also principal recipient regions of the ascending serotonergic pathway originating in the dorsal raphé nucleus (DRN), and with this innervation, form the important DRN-corticolimbic pathway in the brain, a critical component of the neuronal network associated with regulation of stress/emotional response (Graeff et al., 1993;Spannuth et al., 2011;Hale et al., 2010;Kawano et al., 1992). Dysregulation of this pathway has long been recognized in the occurrence of stress-related psychiatric syndromes, including depressive disorders and anxiety disorders (Southwick et al., 1999;van Praag, 2004a). Among various serotonin (5-hydroxytryptamine 5-HT) receptor systems, alterations of the postsynaptic 5-$HT_2$ receptor system in the forebrain may be particularly relevant to the pathophysiology of stress-related psychiatric conditions. There is a general consensus among many PET scan studies that there is decreased forebrain 5-$HT_{2A}$ receptor density in drug-naïve depressed patients (Akin et al., 2004;Malone et al., 2006;Messa et al., 2003;Mintun et al., 2004;Sheline et al., 2004). Several studies also showed that the therapeutic action of antidepressants is associated with an increase and/or normalization in brain 5-$HT_{2A}$ receptor density (Massou et al., 1997;Messa et al., 2003;Sheline et al., 2004;Zanardi et al., 2001). Thus, it is hypothesized that diminished 5-$HT_{2A}$ receptor signaling in the forebrain is associated with the cognitive syndrome observed in PTSD and certain subgroups of depressive illnesses (van Praag, 2004a;van Praag, 2004b).

Animal studies also suggest the involvement of forebrain 5-$HT_2$ receptor signaling in stress-related psychiatric conditions. For example, activation of 5-$HT_{2C}$ receptors in the amygdala during traumatic stress is necessary for the expression of anxiety-like behaviors after traumatic stress exposure (Christianson et al., 2010). Inescapable stress induces a decrease in 5-$HT_{2A}$ receptor expression in the amygdala, and hippocampus (Dwivedi et al., 2005), and hypothalamus (Dwivedi et al., 2005;Petty et al., 1997;Wu et al., 1999), and the decrease in the number of 5-$HT_{2A}$ receptors in the hypothalamus and hippocampus appears to be specifically associated with behavioral depression after exposure to stress (Dwivedi et al., 2005). In addition, alterations of 5-$HT_{2A}$ receptor signaling in the amygdala have been specifically implicated in the initiation of lasting changes in anxiety-like behavior following predator stress and traumatic stress (Adamec et al., 2004;Jiang et al., 2009). Thus stress-related psychiatric syndromes, including various anxiety disorders, may evolve from altered 5-$HT_2$ receptor signaling in the forebrain (Graeff et al., 1996;Menard and Treit, 1999).

## 3. 5-$HT_2$ receptor expression and its neuronal function in the amygdala

The region of the forebrain involved in anxiety disorders that will be focused on herein is the amygdala, a brain region located deep in the anterior temporal lobe. It is believed that abnormal neural excitability and plasticity in the amygdala is an essential feature of multiple types of anxiety disorders and may be directly linked with the expression of the symptoms associated with stress-related psychiatric conditions. 5-$HT_2$ receptors appear to be highly expressed in the amygdala (Morilak et al., 1994;Pompeiano et al., 1994;Wright et al., 1995) and thus may serve an important modulatory role in fear and anxiety response. The 5-$HT_2$ receptor has three subfamilies, including 5-$HT_{2A}$, 5$HT_{2B}$ and 5-$HT_{2C}$. Both 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors have been shown to be highly expressed in the amygdala(Xu and Pandey,

2000;Pompeiano et al., 1994;Jiang et al., 2009). The immunofluorescence data from several laboratories show that the 5-$HT_{2A}$ receptor labeling is primarily localized to the soma and dendrites of interneuron-like cells in the basolateral amydala (BLA), and that the majority of the 5-$HT_{2A}$ signal overlapped with the labeling for the interneuron marker parvalbumin, indicating the 5-$HT_{2A}$ receptor is localized to the interneuron. Interestingly, 5-$HT_{2A}$ receptor immunofluorescence was found to be rarely observed in the pyramidal cells of the BLA, indicating that 5-$HT_{2A}$ receptor expression is restricted to interneurons in the BLA, while the 5-$HT_{2C}$ receptor may be primarily expressed on the pyramidal cells. In addition, the receptors density of various subtypes of 5-$HT_2$ receptor is dynamically regulated by age, gender, hormones and various experimental conditions associated with anxiety (Chen et al., 1995a;Chen et al., 1995b;Jiang et al., 2009).

The specific expression of 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors in different neuronal components of the amygdala may be related to their specific modulation of neuronal functions in the amygdala and of behavioral responses. Indeed, the observations from several laboratories, particularly our own, support this contention, and activation of 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors induce different neuromodulation in the amygdala and different behavioral responses. Restriction of 5-$HT_{2A}$ receptors to interneurons in the amygdala suggests that 5-$HT_{2A}$ receptors participate in inhibitory modulation of the amygdala circuitry. Indeed, a recent publication has shown that the 5-$HT_{2A}$ receptor is the primary receptor responsible for the serotonerigc facilitation of GABA release in the amygdala (Jiang et al., 2009). Activation of this receptor on amygdala interneurons appears to induce the depolarization of the interneurons and facilitate the GABA release from these neurons (Jiang et al., 2009). Since any mediator facilitating GABAergic synaptic transmission in the BLA should induce an anxiolytic effect, it would be expected that the 5-$HT_{2A}$ receptor is anxiolytic. Activation of this receptor has been observed to induce an anxiolytic effect, although that this action is mediated by the amygdala has not been confirmed (Ripoll et al., 2006;Bourin et al., 2005;Nic Dhonnchadha et al., 2003).

Activation of 5-$HT_{2C}$ receptors in the BLA, in contrast, induce anxiety-like effects in animals (Hackler et al., 2006;Campbell and Merchant, 2003;Antonio Pedro de Mello Cruz et al., 2005,Christianson et al., 2010), suggesting that 5-$HT_{2C}$ receptor activation enhances neuronal excitability in the amygdala. The data from our laboratory suggest that the 5-$HT_{2C}$ receptors may play a modulatory role by promoting NMDA function on pyramidal cells in the amygdala. For example, application of the 5$HT_2$ receptor agonist 1-(2,5)-dimethoxy-4-iodophen-2-aminopropane (DOI) enhances NMDA receptor-mediated excitatory postsynaptic potentials and calcium influx, and as a consequence, transforms theta-burst stimulated synaptic plasticity from short-term potentiation (STP) to long-term potentiation (LTP) in the BLA (Chen et al., 2003). The facilitating effects of DOI were blocked by the 5-$HT_2$ receptor antagonist, ketanserin, and by the 5-$HT_{2C}$-receptor selective antagonist, RS102221 (Chen et al., 2003). Therefore, activation of the 5$HT_{2C}$ receptor may induce anxiety-like effects in animals primarily by enhancing NMDA receptor function in the BLA.

In conclusion, 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors appear to be expressed in the different components of the amygdala neuronal circuitry and have opposite functional roles in modulating the amygdala circuitry and the behavioral responses associated with this circuitry. Pharmacotherapy tailored to modulating the effect of 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors in the BLA may have therapeutic implications in anxiety disorders.

## 4. Anxiety disorders and dysregulation of 5-$HT_2$ modulated signaling pathways in the amygdala

Since 5-$HT_2$ receptors in the amygdala play important neuromodulatory roles in fear and stress responses, dysregulation of 5-$HT_2$ receptor signaling in the amygdala may result in the abnormal and pathological fear and stress responses manifested in different forms of anxiety disorders. Specifically, any condition promoting 5-$HT_{2C}$ receptor signaling or decreasing 5-$HT_{2A}$ receptor signaling would predispose the amygdala to over-respond to any sensory input, and anxiety status may ensue. Indeed, overexpression of 5-$HT_{2C}$ receptors in forebrain, particularly in the amygdala, has been observed to lead to elevated anxiety in animals (Kimura et al., 2009). Clinical data and preclinical data also suggest that diminished 5-$HT_{2A}$ receptor signaling in the forebrain, including the amygdala, may contribute to pathogenesis of the cognitive syndrome observed in PTSD and certain subgroups of depressive illnesses (van Praag, 2004a;van Praag, 2004b).

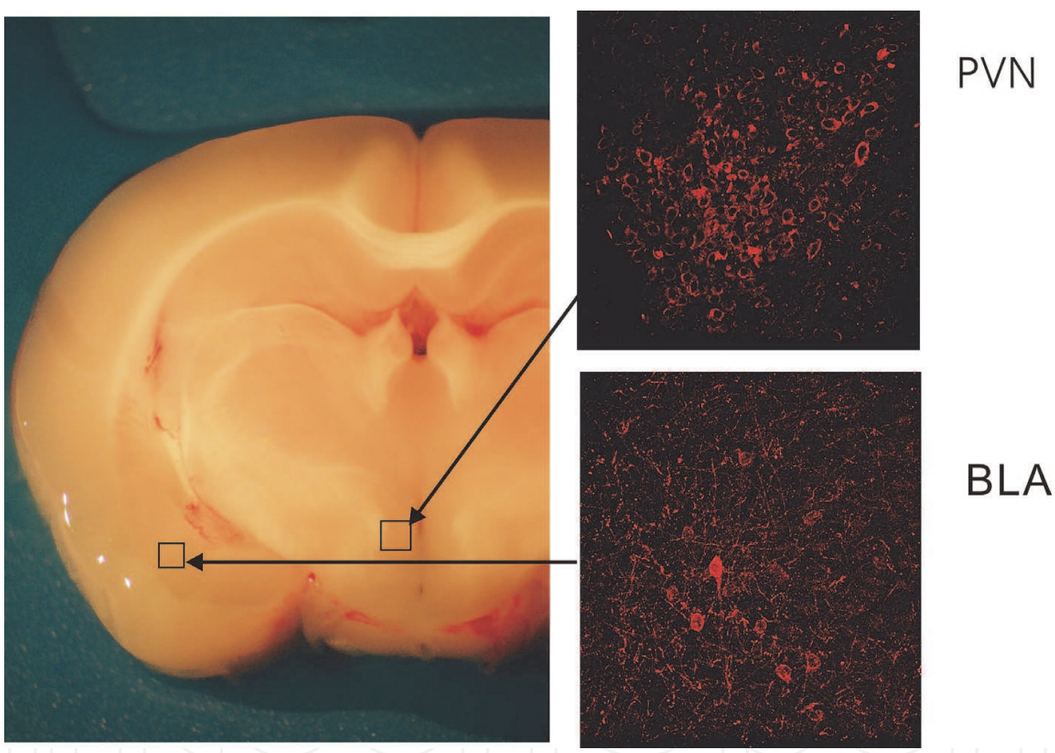


Fig. 1. 5-$HT_2$ receptors in the BLA and in the paraventricular nucleus (PVN) of the hypothalamus: Immunohistochemistry with specific anti-5$HT_2$ receptor antibodies reveals 5$HT_2$ receptors on somata in both the BLA and PVN. In the BLA, 5$HT_2$ receptors appear on dendrites and axons as well (see text for details.)

More convincing data come from animal studies. Chronic or traumatic stress, a primary etiologic factor for anxiety disorder, particularly PTSD, appears to readily impair central 5-$HT_{2A}$ receptor signaling, including in the amygdala (Abi-Saab et al., 1999;Dwivedi et al., 2005;Jiang et al., 2009;Wu et al., 1999), suggesting that stress induces anxiety in animals by impairing 5-$HT_{2A}$ signaling in the forebrain, particularly in the amygdala. If this is true, then it would be expected that 5-$HT_{2A}$ receptor antagonists, administered during stress, would

prevent the subsequent occurrence of abnormalities remisicent of anxiety disorders in animals since the antagonists would prevent the receptors being downregulated and impaired. Indeed, several laboratories have observed that adminstration of 5-$HT_{2A}$ receptor from antagonists during stress averts several behavorial manisfestations of anxiety status in animals, including exaggerated acoustic startle response and open arm avoidance in the plus maze (Adamec et al., 2004;Jiang et al., 2009). In conclusion, alterations of 5-$HT_2$ receptor signaling, particularly 5-$HT_{2A}$ receptor signaling in the amygdala, may be a significant contributor in the pathogenesis of anxiety disorders.

Alterations of 5-$HT_2$ receptor signaling could result from receptor downregulation and degradation, or the disturbance of downstream signal pathways. The 5-$HT_2$ receptor is a G protein-coupled receptor and activation of the receptor leads to activation of phosphoinositide phospholipase C (PLC) and accumulation of D-myo-inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), each of which then leads to its own signaling cascade, mediating a diverse array of physiological responses (Hall et al., 1999;Schmid and Bohn, 2009). Several studies suggest that distubance of downstream signal pathways of 5-$HT_2$ receptor ,including abnormal PLC and

PKC activity, may also be involved in the pathophysiology of stress-related psychiatric conditions (Akin et al., 2004). Other potential candidates involved in stress-related psychiatric syndromes are those molecules associated with receptor desensitization and internalization. Like other similar receptors, 5-$HT_2$ receptors, require the participation of G protein–coupled receptor kinases (GRKs) and β-arrestin in their desensitization and internalization (Schmid et al., 2008;Whalen et al., 2011;Lefkowitz, 1998;Gray et al., 2003; Gray et al., 2001;Bohn and Schmid, 2010), so these molecules could be novel potentially therapeutic targets for anxiety disorders. The most recent finding indeed reveals that β-arrestin-2 is highly expressed in the amygdala and participates in the acquisition and consolidation of fear memories. Manipulation of this molecular signaling pathway thus may be able to regulate the abnormal fear memory associated with certain anxiety disorders (Li et al., 2009).

## 5. Hypothalamic 5-$HT_2$ receptors, stress, and energy homeostasis

Another forebrain region critically involved in the pathophysiology of stress-related psychiatric conditions is the hypothalamus. The hypothalamus is a center integrating neuronal and endocrine systems for autonomic functions, including those underlying feeding and behavioral arousal (Jo and Role, 2002a;Gerashchenko and Shiromani, 2004). Different neuronal phenotypes and neurotransmitter systems in the hypothalamus play dynamic roles in maintaining homeostasis and neuroendocrine circadian rhythm in the face of acute and chronic internal and external challenges (Harris et al., 2006a). In addition to multiple neuropeptides, monoamines, and cholinergic and purinergic systems, serotonin plays a critical role in the defensive response to stressful environmental stimuli and energy homeostasis (Jo and Role, 2002a;Jo and Role, 2002b;Pyner, 2009).

The paraventricular nucleus (PVN) of the hypothalamus secretes corticotropin releasing factor (CRF), a key mediator in the stress response, and receives heavy innervation from the serotonergic projection. This nucleus expresses both 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors (Kawano et al., 1992;Li et al., 2003) (Figure 1) and secretion of CRF appears to be regulated by both 5-$HT_{2A}$ and 5-$HT_{2C}$ receptor ligands (Heller and Baraban, 1987;Heisler et al., 2007). These receptors in the PVN are also part of the mechanism mediating feeding and body weight

(Leibowitz et al., 1989;Tachibana et al., 2001). Dysregulation of 5-$HT_2$ receptor systems in the PVN is thus implicated in anxiety disorders and several affective disorders associated with loss of energy homeostasis.

Indeed, chronic or traumatic stress, a primary etiologic factor for anxiety disorders, readily decreases central 5-$HT_{2A}$ receptor signaling in the hypothalamus, in addition to other forebrain regions (Dwivedi et al., 2005; Petty et al.,1997; Wu et al., 1999), suggesting that stress induces certain physiological abnormalities associated with anxiety disorders, possibly by impairing 5-$HT_{2A}$ signaling in the hypothalamus. One such physiological abnormality is sustained reduced body weight resulting from stress. Sustained body weight loss is a prominent feature observed in animals exposed to different stress paradigms. Weight loss has also been long regarded as a prominent symptom in certain patients with depression and anxiety disorders (Evers and Marin, 2002;Hirschfeld et al., 2005;Hopkinson, 1981). This includes children with anxiety and stress disorder whose growth is stunted (Richards et al., 2006;Yorbik et al., 2004). Since the hypothalamic 5-$HT_{2A}$ receptor is particularly important in stress-related body weight change (Tao et al., 2002;Bah et al., 2010;Rosmond et al., 1998) and mediation of energy homoeostasis (Halder et al., 2007), reduced hypothalamic 5-$HT_{2A}$ receptors may be a determining factor in the occurrence of severe weight loss (Kaye et al., 2005;Kaye et al., 2001;Bailer et al., 2004;Halder et al., 2007). Therefore, stress-induced decrease of 5-$HT_{2A}$ receptors in the hypothalamus may be the underlying mechanism for the sustained body weight loss in stressed animals.

If this is the case, it would be expected that any condition preventing 5-$HT_{2A}$ receptor down regulaton , such as administration of a 5-$HT_{2A}$ antagonist during stress, would be able to avert the subsequent occurrence of sustained body loss in animals. One recent observation appears to support this contention; administration of the 5-$HT_{2A}$ antagonist MDL 11939 during traumatic stress exposure reverses the sustained body weight loss in stressed subjects (Jiang et al., 2009), suggesting that the mechanisms underlying the long-lasting reduction in body weight involve a disturbance of 5-$HT_{2A}$ receptor signaling in certain brain regions, particularly the hypothalamus.

## 6. Pharmacotherapy for anxiety disorders

Since 5-$HT_{2A}$ receptor and 5-$HT_{2C}$ receptor signaling in the amygdala and hypothalamus may be critically involved in the pathophysiology of anxiety disorders, any agent which is able to specifically modulate 5-$HT_{2A}$ or 5-$HT_{2C}$ receptor signaling in the amygdala and hypothalamus has the potential to treat symptoms associated with various forms of anxiety disorders, including PTSD. Indeed, several clinical studies have shown that the 5-$HT_2$ receptor antagonist, nefazodone, is effective in improving symptoms of intrusion, avoidance and hyperarousal in a group of Vietnam veterans with chronic-refractory, combat-related PTSD (Neylan et al., 2003;Hertzberg et al., 2002;Garfield et al., 2001;Domon and Andersen, 2000;Zisook et al., 2000;Davis et al., 2000;Mellman et al., 1999;Hidalgo et al., 1999;Davidson et al., 1998). In particular, substantial evidence supports 5-$HT_{2A}$ receptor antagonists for preventing the development of behavioral and physiological changes associated with anxiety disorders , suggesting that these antagonists are promising preventive agents in the fight against stress-associated disorders. Several novel, more selective 5-$HT_{2A}$ antagonists have recently been developed (Bartoszyk et al., 2003) and have been entered into clinical trials for treatments of schizophrenia and insomnia (de Paulis, 2001;Fish et al., 2005). These

drugs appear to be well tolerated by all study participants (David et al., 2004) and thus should also be entered into trials for anxiety disorders, especially PTSD. Among these antagonists, R-96544, a drug metabolized from an orally administrated predrug, R-102444, should be paid particular attention (Ogawa et al., 2005;Ogawa et al., 2004;Ogawa et al., 2002;Tanaka et al., 2008). The pharmacological profile of R-96544 suggests this 5-$HT_{2A}$ receptor antagonist for easy oral administration in the battle field and on site of traumatic events, thus potentially making it an ideal drug for preventing the psychiatric consequences of trauma.

## 7. Conclusion

Evidence from different disciplines suggests that alterations of 5-$HT_2$ receptor signaling may be a critical link in the pathogenesis of anxiety disorders. 5-$HT_2$ receptor signaling in the amygdala and hypothalamus is particularly important in this respect since alterations of receptor signaling in these areas may be directly related to certain symptoms associated with anxiety disorders. Pharmacotherapy tailored to modulating the effect of 5-$HT_{2A}$ and $HT_{2C}$ receptors in the these areas thus represents an important future direction in developing novel, more efficacious pharmacological agents for the symptoms associated with anxiety disorders, including PTSD.

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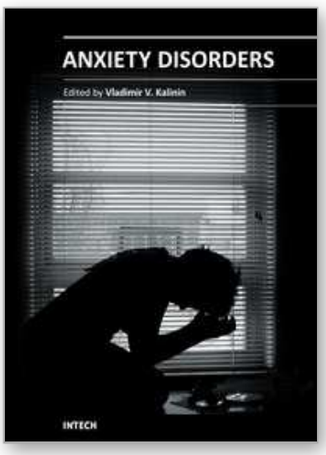


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During the last 2-3 decades drastic research progress in anxiety issues has been achieved. It concerns mostly the study of different subtypes of anxiety and their treatment. Nevertheless, the data on anxiety pathogenesis is less elaborated, although here a multidimensional approach exists. It includes neurochemistry, pathophysiology, endocrinology and psychopharmacology. Again, we are able to recognize the multifarious sense of anxiety, and the present collective monograph composed of 16 separate chapters depicting the different aspects of anxiety. Moreover, a great part of book includes chapters on neurochemistry, physiology and pharmacology of anxiety. The novel data on psychopathology and clinical signs of anxiety and its relationship with other psychopathological phenomena is also presented. The current monograph may represent an interest and be of practical use not only for clinicians but for a broad range of specialists, including biochemists, physiologists, pharmacologists and specialists in veterinary.



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