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**Review Article**

# NEUROCHEMICAL MODULATION OF ANXIETY DISORDERS

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## ABSTRACT

Anxiety disorders can be considered as "intact" condition, which almost totally disturb the routine life of the person. It creates a condition of unexplained anticipatory fear and apprehension regarding the occurrence of even normal things in life. Drug development for anxiety requires new pharmacological agents acting at specific neurotransmitters and neuropeptides, their reuptake and metabolism. The aim is to bring out treatment(s) that is at least as effective as traditional therapeutic line of benzodiazepines, which have stayed for decades. Apart from GABA, agents with anxiolytic activity have also been found to affect the serotonin and norepinephrine systems. Moreover, neurotransmitter systems of corticotropin-releasing factor and substance P become abnormal in anxious persons, suggesting the potential usefulness of neurotransmitter antagonists for anxiolysis. In addition to these, antistress and antianxiety effects through neurogenesis, decreased glutamate neurotransmission, stimulation of neurotrophic factors (brain-derived neurotrophic factor) also appears to enhance have anxiolytic effects. This paper reviews various neuromodulators affecting biology of brain structures involved in generation of anxiety conditions affecting human population at one stage of life or another.

**Key words:** Anxiety , Neurochemicals

## INTRODUCTION

Anxiety is a state of excessive fear and is characterized by motor sympathetic hyperactivity, apprehension and vigilance syndromes. The most common observation is an acute stress response characterized by a state of abnormal or exaggerated arousal or fear[1]. Generally, anxiety is an adaptive response to supposedly dangerous stimuli, which may perturb homeostasis. However, when it become disproportional in intensity, chronic and/or irreversible, or not genuine, it manifest as debilitating anxious state presenting itself in form of phobia, panic attacks, post-traumatic stress disorder, social anxiety disorder or generalized anxiety disorder. Anxiety states are controlled by both inhibitory and facilitatory mechanisms that either counter or favor anxiety states. These neurochemical and neuropeptide systems have been shown to have effects on distinct cortical and sub cortical brain areas that are relevant to the mediation of the symptoms associated with anxiety disorders[2]. Regional brain networks involved in such stress, anxiety, and anxious behaviors may be appropriate targets for actions of anxiolytics. Drug development in this direction also aim to generate new pharmacological agents with action at specific neurotransmitters and neuropeptides, their reuptake and metabolism. The ultimate objective is to develop substances that are as effective as benzodiazepines, which have been the traditional treatment for anxiety for over 40 years. This search has led to development of unconventional agents, which either are partial benzodiazepine-GABA receptor antagonists or target specific subunits of the $GABA_A$ receptor or manipulate GABA levels, agents that affect the serotonin and nor epinephrine systems, antagonists of neurotransmitter systems such as corticotropin-releasing factor and Substance P, agents that decrease glutamate neurotransmission, such as metabotropic glutamate receptor agonists, stimulation of neurotrophic factors, such as brain-derived neurotrophic factor, which appears to enhance neurogenesis[3].

The neurobiological approach to delineate the pathophysiology of anxiety also come across the fact that anxiety disorders are highly co-morbid with each other and respond to the single or same spectrum of treatments. Therefore, we review both traditional and new molecular targets for treatment of anxiety.

## CLINICAL CATEGORIES OF ANXIETY

- Generalized Anxiety Disorder is an ongoing state of excessive anxiety lacking any clear reason or focus. Essential feature of this class of anxiety is chronic worry[3].
- Panic Disorder is an attack of overwhelming fear occurring in association with marked somatic symptoms such as sweating, unexpected recurrent panic attacks, tachycardia, chest pains, trembling, chocking etc. normally this condition of anxiety has a general component[4].
- Post- traumatic Stress Disorder elaborates an anxiety triggered by insistent recall of past

stressful experiences[5].

- Social Anxiety Disorder is characterized by marked and persistent fear of performance situations when they feel, they will be the center of attention and will do something humiliating or embarrassing. Situation that provokes this fear may be quite specific e.g. public speaking[6].
- Phobia is a strong fear of specific things or situations e.g. snakes, open spaces, flying and social interactions[7].

**EPIDEMIOLOGY**

Anxiety disorder is a chronic, disabling mental illness, characterized by worry and anxiety that are hard to control and that interfere with daily functioning. Anxiety disorders occur in approximately 30% of mood cases[8]. Lifetime prevalence rates for total anxiety disorders are 16.6%. Women are more likely to suffer from anxiety disorders because women experience a wider range of life events including events happening to their close as well as distant relatives and friends, in comparison to men, who react to events limited to themselves or close family members[9]. Anxiety disorders are common during the perinatal period, with reported rates of obsessive-compulsive disorder and generalized anxiety disorder being higher in postpartum women than in the general population[10]. Social anxiety disorder (SAD) is among the most common of all psychiatric disorders with lifetime prevalence estimates ranging from 7% to 13%[8]. Co-morbidity of anxiety and depression is highly prevalent. About 47.5% patients of major depressive disorder also meet criteria for anxiety disorders, whereas 26.1% patients of anxiety disorders meet criteria for major depressive disorder too[11]. About 8% of patients consulting primary care professionals have generalized anxiety disorder. Initial manifestations of anxiety appear at age of 20-35 years and there is predominance in women. Panic disorder commonly coexists with essential hypertension and the postural tachycardia syndrome[12].

**MAJOR CAUSES OF ANXIETY DISORDERS**

**Heredity and anxiety disorders**

Genes represent a significant source of individual variation in the habituation, acquisition, and extinction of fears, and genetic effects specific to fear conditioning are involved. All components of the fear conditioning, a traditional model of acquisition of fear and phobias demonstrate moderate heritability (35% to 45%) in humans[13]. Anxiety disorders run in families. If one identical twin has an anxiety disorder, the second twin is more likely to have an anxiety disorder than non-identical (fraternal) twins. Females are affected double than males. Female specific trait locus on rat chromosome 4 (Ofil-1) influences measures of anxiety and ethanol consumption indicating that Ofil-1 contains linked genes with independent influences on anxiety-related responses[14]. Gene variants has capability to alter specific neuronal activity. Catechol-O-methyltransferase (COMT) gene has a common variant at codon 158. Valine (Val158) alleles have increased greater COMT activity. Its methionine substituted allele; Met158 alleles of catechol-O-methyltransferase (COMT) gene are associated with anxiety[15].

**Personality and Anxiety Disorders**

Generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) are strongly related to personality[16]. Personality constructs such as self-esteem, positive and negative affectivity, age and gender are associated with general well being. Home self esteem is a significant predictor of anxiety. Among various personalities, people having low self-esteem and poor coping skills may be more prone to anxiety disorders [17].

**Life Experiences**

Stress early in life predispose to the development of anxiety disorders. Stressful life events have been documented to play an underlying role in anxiety disorders. The experience of childhood bullying was strongly related to high levels of co-morbid anxiety, both in terms of greater levels of state anxiety and a higher prevalence of both social phobia and agoraphobia. Independent of other childhood risk factors, exposure to bullying was especially predictive of subjects' higher levels of general state anxiety and the tendency to express anxious arousal externally when under stress[18]. Anxiety disorders continue from childhood to adulthood. Separation anxiety in childhood increase the risk of severe anxious-fearful personality disorders in adulthood. Neurotism in specific personality of an individual has a significant relationship with end-of-life sources of distress, including anxiety[19].

**NEUROMODULATORS OF ANXIETY**

**Acetylcholine**

Two different lines of evidence exist regarding cholinergic modulation of anxiety state. Cholinergic input to hippocampus is enhanced in response to anxiogenic and stressful stimuli, wherein, muscarinic $M_1$ receptors mediate induction of anxiety states through noradrenergic pathways[20]. On the other hand, nicotine facilitate GABAergic neurons and induce anxiolysis and anxiolysis is also being observed after by increasing acetylcholine levels on administration of acetylcholinesterase inhibitor physostigmine in dorsal or the ventral hippocampus[21].

**Adenosine**

Adenosine is formed by hydrolysis of 5-adenosine monophosphate and is transformed to inosine, which

is then stored as adenosine triphosphate[22]. Adenosine through $A_1$ and $A_{2A}$ receptors exert anxiolysis through its facilitatory influence on GABA release in the septum and hippocampus[23].

**Arginine vasopressin (AVP)**

This nonapeptide regulates Hypothalamus-pituitary-adrenal system by enhancing the effects of CRH on adrenocorticotropic hormone (ACTH) release. AVP exert its effects through G protein-coupled receptors *viz.* V1A and V1B. SSR149415, selective and orally active non-peptide antagonist of vasopressin V(1B) receptors produced anxiolytic-like activity[24].

**Atrial natriuretic peptide (ANP*)***

Atrial natriuretic factor is produced by heart and released into the circulation. Intracerebroventricular (i.c.v.) administration of ANP elicit anxiolytic activity in the open field, the social interaction, and the elevated plus maze tests[25]. Central and peripheral administration of atriopeptin II, an amino acid residue peptide of ANP also produce anxiolysis in elevated plus maze test[26].

**Cannabinoids**

They suppress flow of glutamate, norepinephrine and dopamine in hippocampus and cortex and interfere with GABAergic transmission in the amygdale and hippocampus and frontal cortex[27]. Due to complex pattern of influence of cannabinoids on release of neurotransmitters, both anxiolytic as well as anxiogenic profile has been observed[28].

**Cholecystokinin (CCK)**

CCK is one of the most abundant brain neuropeptides. CCK-immunoreactive fibers and CCK (2) receptors are rich in anatomical locations like periaqueductal gray (PAG), which mediate anxiety. Neuronal expression of CCK-2 receptor result in manifestation of anxiety-like behaviors, attenuated by diazepam[29].

**Corticotropin-releasing Factor (CRH)**

Corticotropin-releasing factor mediates endocrine, autonomic, and behavioral responses to stress[30]. Administration of antisense oligodeoxynucleotides corresponding to the start-coding region of CRH mRNA to stressed rats decreased CRH biosynthesis and reduced anxiety-related behavior[31].

**Gamma-aminobutyric acid (GABA)**

GABA is the central nervous system's most abundant inhibitory neurotransmitter. The presence of GABA in neural tissue tends to hyperpolarize neurons. This hyperpolarization occurs when GABA neurotransmitter binds to GABA-A receptors on neurons. Negatively charged chloride ions are allowed to flow down chemical gradient and into the neuron's cell body. This electrochemical negativity inhibits the neuron and decreases the likelihood of its firing further electrical impulses. As GABA levels and GABA activity rises, neuronal firing and activity lowers[32]. Physiologically, GABA is a sedative and muscle relaxant. Preclinical and clinical evidence exist for dysregulation of the central GABA-ergic tone in anxiety disorders. Tiagabine, a selective GABA reuptake inhibitor exert anxiolytic effect via GAT-1 transporter blockade thus facilitating GABA neurotransmission[33]. Herbal anxiolytics like valerian roots are found to contain appreciable amounts of GABA and possess GABAergic activities.

**Galanin**

Galanin suppress the noradrenergic, serotonergic and dopaminergic neurons[34]. Endogenous galanin exert anxiolysis in amygdale in response to stressful conditions[35]. However, exogenous galanin has produced variable effects in anxiety states. Intracerebroventricular administration of galanin reduced anxiety-like behavior, whereas, injection into amygdala produced an anxiogenic effect[36].

**Glutamatergic transmission**

Glutamate levels are profoundly increased upon exposure to aversive stimuli and stress.[37] Antagonism of endogenous excitatory amino acid neurotransmission in the DLPAG reverse behavioral suppression. Glutamate antagonists show an anxiolytic-like profile in the elevated plus maze[38].

**Glucagon-like peptide-1**

Glucagon-like peptide-1 is widely present in brain stem neurons, which innervate locus cerulus, hippocampus and amygdala. Injection of Glucagon-like peptide-1 into amygdala produced anxiogenic effect[39].

**Melanin-concentrating hormone** (MCH)

MCH (1) receptor mediate the regulation of emotion and stress responses. Blockade of MCH(1) receptors results in antidepressant and anxiolytic effects. The effects of MCH(1) receptor antagonists in animal models, together with their rapid onset of effect and lack of adverse CNS effects advocate their investigation as potential treatments for depression and anxiety disorders[40].

**Melatonin**

Melatonin controls sleep and rhythm, which are generally disturbed in anxiety. Melatonin produce anxiolysis, which is blocked by Flumazenil, a $GABA_A$ receptor antagonist[41].

**Norepinephrine (NE)**

Majority of noradrenergic neurons are found in the locus ceruleus. Altered noradrenergic signaling is linked to anxiety disorders. Sustained stimulation of locus ceruleus result in manifestation of anxiety symptoms. Stress-induced release of NE facilitates a number of anxiety-like behavioral responses too

including stress-induced reduction of open-arm exploration on the elevated plus-maze, stress-induced reduction of social interaction behavior[42]. Norepinephrine transporter-deficient mice have increased circulating catecholamines and elevated heart rate and blood pressure[43]. Blockers of adrenergic β receptors have also been utilized clinically for treatment of performance anxiety[44].

**Neuropeptide Y**

Activation of Y1 and Y5 receptors of NPY in the basolateral amygdala produces dose-dependent anxiolytic-like effects, which is reversed by $\alpha_2$-adrenergic receptor antagonists. Moreover, mutant mice lacking NPY show increased anxiety-related behavior[45].

**Neuroactive steroids (Neurosteroids)**

They are steroids synthesized from cholesterol in glial cells and neurons and has capability to alter neuronal excitability. They exert anxiolysis through $GABA_A$ receptors[46]. Deoxycorticosteroid derivatives like 3á, 5á-tetrahydroprogesterone (3á,5á-THP) and 3á,5á-tetrahydrodeoxycorticosterone (3á,5á-THDOC) bind at GABA-A receptors to enhance GABA-induced chloride currents, similar to benzodiazepines. Neurosteroids may be tested as therapeutic target for the treatment anxiety disorders with improved efficacy without motor and cognitive side effects[47].

**Serotonin (5-HT)**

Serotonergic neurons are implicated in the alteration of appetite, energy, sleep, mood and cognitive function in anxiety. Its role in anxiety is supported by its modulating effect on the locus ceruleus and its projections to the amygdale; anatomical structure almost conclusively implicated in anxiety. Fear and stress activate serotonergic pathways[48].

**Tachykinins and Substance P**

Tachykinins throughout the brain, spinal cord, and peripheral nervous system are implicated in the pathophysiology of anxiety. Pre-clinical studies suggest anxiolytic effects of NK1 receptor antagonists[49]. Further, disruption of the NK1 receptor by knockout techniques results in reduced anxiety in response to stress[50].

**Table1: Neuromodulators, their action on respective receptors and their possible role in anxiety modulation.**

| Neuromodulator | Anxiety modulation | Proposed mode of action |
|---|---|---|
| Acetylcholine | (1) Anxiogenic<br>(2) Anxiolytic | (1) through $M_1$ receptors<br>(2) through facilitation of GABAergic influence |
| Adenosine | Anxiolysis | $A_1$ and $A_{2A}$ receptors (through GABA release) |
| Arginine Vasopressin | Anxiogenic | V (1B) receptors |
| Atrial Natriuretic Peptide | Anxiolytic activity | direct i.c.v. injection |
| Cannabinoid | Mixed profile | non-selective influence on glutamate, norepinephrine and dopamine in hippocampus and cortex and interfere with GABAergic transmission in the amygdala, hippocampus |
| Cholecystokinin | Anxiogenic | CCK-2 receptors |
| Corticotropin - releasing Factor (CRH) | Anxiogenic | CRH-1 receptors |
| GABA | Anxiolysis | Enhancement of GABAergic transmission |
| Galanin | Anxiolysis | Direct action in amygdala |
| Glucagon-like peptide – 1 | Anxiogenic | Direct action in amygdala |
| Glutamate | Anxiogenic | Enhanced excitatory neurotransmission |
| Melanin – Concentrating Hormone | Anxiogenic | MCH-1 receptor stimulation |
| Melatonin | Anxiolysis | GABA-A receptor stimulation |
| Neuroactive steroids | Anxiolysis | GABA-A receptor stimulation |
| Neuropeptide Y | Anxiolysis | Activation of Y1 and Y5 receptors |
| Noradrenaline | Anxiogenic | Stimulation of β receptors |
| Serotonin | Anxiogenesis | Activation of serotonergic neurons |
| Substance P and Tachykinin | Anxiolysis | NK1 receptor antagonism |

**CONCLUSION**

The authors have attempted to piece together various neurochemicals involved in a way or other in pathology of anxiety. Pharmacological studies using receptor antagonists and receptor knock-out techniques indicate that anxiety disorders are result of underlying changes in a diversity of neurotransmitter

systems. The presently existing reports on majority of these chemicals comprise their physiological implications, receptor expression analysis and pharmacological reversal of anxiety states induced by these modulators. Further, biochemical estimations of neurotransmitters, measurement of activity of enzymes involved in their synthesis, their involvement in differential anxiety states i.e. generalized or panic, phobic, post-traumatic stress disorders and their pharmacological modulation in these pathological states using appropriate animal models will serve to highlight more convincing profile of the above mentioned neurochemicals.

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