ROLE OF DIFFERENT NEUROTRANSMITTERS IN ANXIETY: A SYSTEMIC REVIEW

Sandeep Kaur and Rajmeet Singh *

Department of Pharmacology, G.H.G. Khalsa College of Pharmacy, Gurusar Sadhar, Ludhiana, Punjab - 141104, India.

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ABSTRACT: Anxiety is a persistent feeling of dread, apprehension and impending disaster, or tension and uneasiness. The reported prevalence rates of psychiatric morbidity in the Indian industrial population range from 14-37%. Anxiety disorders may develop from a complex set of risk factors including genetics, brain chemistry, personality and life events. It is a specific class of psychopathology characterized by future-oriented apprehension and elevated threat value associated with physical, social, and mental stimuli. According to multiple-systems, individual shows different types of symptoms i.e. Cognitive, Physiological and Behavioral during anxiety. Abnormal functioning of neurochemicals as well as abnormal chemoreceptor reactivity leads to anxiety. There are various neurotransmitters that are involved in anxiety such as serotonin, glutamate, gamma-amino butyric acid, Cholecystokinin, Adenosine etc. Some are inhibitory and some are excitatory. These neurotransmitters might play role in upregulation or downregulation of anxiety disorders. This review article gives a bird’s eye view of neurotransmitters involved in anxiety.

INTRODUCTION: Anxiety word was derived from the Latin root ‘anxiety’ meaning trouble in the mind about some uncertain event and it has a Greek root ‘anxo’ meaning to squeeze, strangle or press tight. Anxiety is a term used to describe experiences of normal people when they face threat, danger, or when stressed. When people become anxious, they typically feel upset, uncomfortable, and tense. Everyone feels anxious in response to specific events - but individuals who suffer from anxiety disorder have excessive and unrealistic feelings that interfere with their relationships, activities of school and work, social activities and recreation in their lives.

About 40 million adults above age 18 years in America are affected by anxiety which causing them to be filled with fearfulness and uncertainty. Anxiety is considered an analogue of pathological reactions to danger in humans.

The most widely encountered mental disorders in clinical practice are anxiety disorders. Healthcare professionals mistake anxiety disorders by physical illnesses, and only 23% of patients receive appropriate treatment. Individuals with anxiety disorders develop cardiovascular, cerebrovascular, gastrointestinal, and respiratory disorders at a rate significantly higher than the general population. Anxiety disorders are not considered as one disorder but these are a group of disorders characterized by persistent feelings of high anxiety, and extreme discomfort and tension. Other symptoms can include sweating, trembling, feelings of choking, nausea, abdominal distress, dizziness, pins and needles, feelings of losing control and/ or feelings of impending doom.
Many sensations are occurs in human body during anxiety as it prepares for danger. The sensations, which occur in human body, when the natural Alarm System of human body (the “fight-flight-freeze” response) has been activated, are known as “alarm reactions”.  

According to multiple-systems, symptoms of anxiety are (a) Cognitive, (b) Physiological and (c) Behavioral.  

- Cognitive component of anxiety is related to the cognitive distortions in the components of attention, interpretation, and memory for information processing.

- Physiological component of anxiety consists of the autonomic or somatic sensations. It also includes avoidance related to the sleep, insomnia, nightmares, and refusal/reluctance to sleep alone. Accelerated heart rate, heart palpitations, chest pain, shortness of breath, difficulty in swallowing and nausea are other symptoms.

- Behavioral component of anxiety refers to the action that is taken by an individual to prevent feared stimuli exposure. Behavioral symptom associated with the anxiety disorders includes avoidance, in which specific stimuli was avoided by the individual(e.g. bridges) or situations (e.g. public speaking) to prevent anticipated harm. Due to avoidance, there will be impairment in maintaining daily routines or in family, academic and/or social functions by the individual.

Anxiety is a persistent feeling of dread, apprehension and impending disaster, or tension and uneasiness’. It is a specific class of psychopathology characterized by future-oriented apprehension and elevated threat value associated with physical, social, and mental stimuli. Classically, anxiety is distinguished into, the "State" anxiety and the "Trait" anxiety. "State anxiety" is one which is experienced by subject at a particular moment, and it increases by the presence of an anxiogenic stimulus. In contrast, "Trait anxiety" does not vary from moment to moment and everlasting feature of an individual.

Abnormal functioning of neurochemicals such as serotonin, norepinephrine, dopamine and gamma-amino butyric acid systems as well as abnormal chemoreceptor reactivity leads to anxiety.

**Different Neurotransmitters Involved In Anxiety**

**Gamma-Amino Butyric Acid:** There are different inhibitory neurotransmitters in the CNS, most of the abundant and important is Gamma-amino butyric acid(GABA). The role of the inhibitory neurotransmitter GABA has long been regarded as Centre for the regulation of anxiety and this neurotransmitter system is the main target of benzodiazepines and other anxiety related drugs used to treat anxiety disorders.

The excitability states in all brain areas are mainly controlled by GABA and the ongoing level of neuronal activity is regulated by the equilibrium between excitatory inputs (mostly glutamatergic) and inhibitory GABAergic activity. If the balance swings towards GABA, then sedation, amnesia and ataxia appear. On the other hand, the mildest attenuation of the GABAergic system results in restlessness, insomnia, arousal, anxiety and exaggerated reactivity.

Historically, the GABA system has been thought to play a role in anxiety disorders largely because of the effectiveness of the benzodiazepines, which are well known to act primarily on GABA receptors, in the management of anxiety.  

When there is binding of GABA with the GABA-A±benzodiazepine receptor complex, it acts as an agonist: inducing conformational changes, with which the permeability of the central pore to chloride ions gets increased. The resulting chloride flux hyperpolarizes the neuron, leads to reduction in its excitability and producing a general inhibitory effect on neuronal activity.

The anxiolytic effects of drugs that act on the GABA receptor provide some of the strongest evidence that GABA dysfunction underlies anxiety states. Agents such as the benzodiazepines, gabapentin, pregabalin, valproate, vigabatrin, tiagabine demonstrate clinically relevant anxiolytic effects.
**Benzodiazepines:** Benzodiazepines have been widely used to manage anxiety disorders, from the short-term relief of anxiety symptoms to specific anxiety syndromes (i.e. GAD, phobia, PD). Benzodiazepines augment the GABAergic inhibition via GABA-A receptors. Benzodiazepine binding allosterically changes the receptor complex to increase the GABA efficiency, which enables the GABAergic circuits to produce a larger inhibitory effect.

There is established efficacy of Benzodiazepines in the treatment of GAD, for which a drug such as Diazepam is suitable. Typical side effects of BZD include drowsiness and impairment of cognitive and motor function.

Benzodiazepines can potentiate the sedative effects of alcohol and other centrally acting drugs. Respiratory depression has been reported in some patients receiving benzodiazepines with clozapine. Drug discontinuation, even with a slow taper, can cause troublesome withdrawal reactions and rebound anxiety, which may necessitate re starting treatment.

**Gabapentin:** Gabapentin was designed as a GABA analog that could penetrate the blood-brain barrier. Although the anxiolytic properties of gabapentin are likely to be linked to its effects on the GABA system, gabapentin has a high affinity for the α2δ subunit of presynaptic P/Q-type, voltage-sensitive Ca^2+ channels modulates certain types of Ca^2+ current, and the release of several monoamine neurotransmitters gets reduced.

In Pre-clinical studies, gabapentin demonstrated anxiolytic effects similar to that of the BZDs. Gabapentin has shown to effectively ameliorate the symptoms of PD and social phobia in placebo-controlled clinical studies. The most commonly reported adverse effects in gabapentin-treated patients with these anxiety disorders are dizziness, dry mouth, headache, nausea and somnolence.

Abrupt discontinuation of augmentative gabapentin treatment has been found to lead to withdrawal symptoms such as rebound anxiety related symptoms of depression and sleep disturbances.

FIG. 1: SHOWING DIFFERENT NEUROTRANSMITTERS INVOLVED IN ANXIETY

Case reports have suggested the potential use of gabapentin in the management of symptoms of PTSD, GAD, refractory PD and GAD and schizophrenia/ mood disorders with comorbid PD and OCD. The most common side effects noted in these reports were drowsiness and dizziness.
**Pregabalin:** Pregabalin is another GABA analog with similarities to gabapentin; it is functionally similar to gabapentin. Pregabalin is thought to act by increasing total GABA content in the brain via an undetermined mechanism.  

Pregabalin was found to induce anxiolytic-like effects in a dose dependent manner in a preclinical murine model of anxiety and reduces the GAD symptoms and social phobia in randomized, placebo-controlled clinical trials. The most commonly reports adverse events in pregabalin clinical trials were dizziness, somnolence, dry mouth, nausea and ataxia.

**Glutamate:** The excitatory action of amino acid L-glutamate in the mammalian brain and spinal cord has been known since the 1950s. Glutamate is the main excitatory neurotransmitter in the human Central Nervous System (CNS). Glutamate is ubiquitous within the central nervous system and has been shown to play important roles in different brain functions, including neurodevelopment (e.g., differentiation, migration and survival), learning (e.g., long-term potentiation and depression), acute neurodegeneration (e.g., cerebral ischemia, traumatic brain injury) chronic neurodegeneration (e.g., Huntington’s disease, Alzheimer’s disease) and, more recently, the stress response and anxiety disorders.

Glutamate controls the synaptic release by a wide range of presynaptic receptors. These include not only the Group II and Group III glutamate metabotropic receptors but also cholinergic (nicotinic and muscarinic) receptors, adenosine (A1), kappa opioid, γ-amino butyric acid (GABA B), cholecystokinin and neuropeptide Y (Y2) receptors.

Glutamate mainly show its actions through ligand-gated ion channel (ionotropic) receptors, including the N-methyl-d-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtypes, and G protein-coupled metabotropic receptors (mGlur1-8). Each NMDAR complex consists of four (occasionally five) subunits: two NR1 subunits (generated by alternative splicing of a single gene, NR1), and two or three NR2 subunits (coded by four related genes, NR2 A–D).

Recently, a third type of NMDA receptor subunit (NR3), which dramatically reduces ion permeability, has been described. This situation leads to an enormous heterogeneity in terms of modulation of neurochemical profiles.

A major role is played by Glutamatergic system in the pathogenesis of anxiety and fear conditioning. Many studies suggest that glutamatergic neurotransmission of limbic system plays a pivotal role in the pathogenesis of anxiety disorders. Severe stress exposure directly leads to glutamate excitotoxicity, which can cause neuronal damage and/or death. By decreasing the level of endogenously released glutamate, the anxiolysis could be induced. NMDA receptor would be activated by diminished glutamate release but to less extent and CNS excitation would remain at a stable stage. Such an effect can be achieved by switching on the regulatory machinery of presynaptic glutamate release.

Monosodium glutamate (MSG) [C₅H₈NO₄NaH₂O] a sodium salt of naturally occurring (non-essential) L-form of glutamic acid, is one of the flavor enhancers, which is mainly used as an ingredient in various food products. Glutamate Consumption has been linked to obesity and metabolic syndrome independent of physical activity and calorie intake. Some researchers have also reported neurotoxic effects of glutamate.

MSG is an excitotoxic which excites the neurons and may cause their death. Moreover, it has been reported that MSG is a neurotoxic substance, which is capable of producing degeneration of population of neurons, accompanied by pathological conditions, such as stroke, epilepsy, schizophrenia, anxiety, depression, Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, and amyotrophic lateral sclerosis. This could be due to its well known excitotoxic effect, as MSG can cause overexcitotoxicity of neuronal cells to damage or death point, resulting in brain injury, mostly accompanied by oxidative stress. Spermidine, spermine and putrescine, which are polyamines, are found in green vegetables, milk products, and meat. Polyamines are naturally occurring, ubiquitous, low molecular weight aliphatic polycations with nucleophilic centers, which are found at elevated levels in the brain.
The polyamines are a group of aliphatic amines with a polycationic structure, carrying a positive charge on each nitrogen atom at physiological pH. Polyamines can interact with several intracellular targets, including nucleic acids and enzymes, and exert several selective and complex actions on a variety of ion channels. Among them, especially remarkable is the dual modulation of a-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and N-methyl-D-aspartate (NMDA) receptors, which have been implicated in important plasticity events, such as learning and memory.

Polyamines (125–250 nmol, i.c.v.) cause damage of hippocampus and learning impairment in rats at high doses and also increases dizocilpine-induced impairment of a learning task in rats. These studies show that high cerebral levels of polyamines are neurotoxic and impair learning and memory.

Different studies suggest that antidepressant drugs (SSRIs, SNRIs, TCAs, and MAOIs) decreases glutamatergic activity in some regions (like hippocampus) on chronic administration and that NMDA receptor antagonists on acute administration have antianxiety and antidepressant properties in preclinical and clinical models. Glutamate release is inhibited by Lamotrigine and is currently used as an anticonvulsant as well as a treatment for bipolar depression. A clinical study has shown lamotrigine to be effective in certain PTSD symptoms (re-experiencing and avoidance/numbing). Similarly, topiramate, an AMPA/kainate blocker among other actions, was found in an open-label study to reduce re-experiencing symptoms in PTSD.

**FIG. 2: SHOWING ROLE OF DIFFERENT NEUROTRANSMITTERS IN ANXIETY**
Serotonin: 5-HT plays a vital role in the development and the persistence of anxiety disorders in addition to GABA. Different studies have shown that 5-HT concentration when increased in the brain also increases anxiety and a reduction of 5-HT level reduces anxiety.  

Serotonergic neurons are involved 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 coeruleus and its projections to the amygdala. Fear and stress activate serotonergic pathways.

Several studies show that anxiety disorders patients may have genetic polymorphisms in the 5-HT transporter or in the 5-HT2A receptor and the 5-HT1A receptor. Panic disorder patients show reduction in the number of 5-HT1A receptors in the limbic system. There is an involvement of 5-HT3 receptors in the regulation of anxiety but clinical efficacy is still uncertain.

SNRIs (Serotonin-Norepinephrine reuptake inhibitors) results in 5-HT and NA transporters binding to selectively inhibit the reuptake of these neurotransmitters from the synaptic clefts. SNRIs show “dual mode of action”. SNRIs block the reuptake of both 5-HT and NA with differing selectivity. Whereas milnacipran blocks reuptake of 5-HT and NA with equal affinity, duloxetine has a 10-fold greater selectivity for 5-HT, and venlafaxine show 30-fold greater selectivity for 5-HT.

Venlafaxine was the first SNRI that comes in market. Venlafaxine inhibits neuronal uptake of 5-HT (most potent, present at low doses), NA (moderate potency, present at high doses) and dopamine (DA) in order of decreasing potency. Venlafaxine has no affinity for α2- or β-adrenoceptors, benzodiazepine or opiate receptors. It has a much greater affinity for the 5-HT transporter than for the norepinephrine (NE) transporter. At low doses, it inhibits the 5-HT transporter almost exclusively, acting like a selective serotonin reuptake inhibitor (SSRI), with significant NE reuptake inhibition only occurring at higher doses.

Cholecystokinin: CCK, a neuropeptide, was, like 5-HT, discovered originally in the digestive tract and found in the CNS later. CCK-immunoreactive fibers and CCK (2) receptors are most abundantly present in anatomical locations like periaqueductal gray (PAG), which mediate anxiety. The CCK2 receptor regulates the fear-related behaviours in humans and animals CCK-4 injection triggers the panic attacks in patients with a history of panic disorder.

Adenosine: Adenosine results due to hydrolysis of 5-adenosine monophosphate and is transformed to inosine, which is then stored as adenosine triphosphate. Adenosine is also involved in the regulation of anxiety-related behavior. High doses of caffeine, which is the nonselective adenosine receptor antagonist, induce fear in healthy people and trigger panic attacks in anxiety disorder patients. Adenosine through A1 and A2A receptors exert anxiolytic effect through its facilitatory influence on release of GABA in the septum and hippocampus. On treatment with caffeine, rats were more anxious in the elevated plus-maze test (X-maze) and a free exploratory paradigm, while an adenosine-1 receptor agonist had an anxiolytic effect in the X-maze.

Acetylcholine: Acetylcholine plays a pivotal role in learning and memory processes. Acetylcholine levels can be modulated by stress in several brain regions. Acetylcholinesterase present in the CNS catalyzes the hydrolysis of acetylcholine to choline. Acetylcholine is released in the synaptic cleft where it activates both presynaptic and postsynaptic cholinergic receptors namely nicotine and muscarinic leading to an increase of cholinergic transmission which results in cognitive impairment. Cholinergic input to hippocampus is enhancing in response to anxiogenic and stressful stimuli. Muscarinic M1 receptors induce anxiety through noradrenergic pathway. Nicotine facilitates GABAergic neuron that induces anxiety.

Cannabinoids: Cannabinoid receptor is widely distributed in the CNS present in the brain areas related to stress responses such as the central amygdala and the paraventricular nucleus of the hypothalamus and in the limbic system. Cannabinoid-1 agonist can induce both anxiolytic
and anxiogenic responses in animal studies. Low doses of the cannabinoid produce anxiolytic effects, whereas higher doses result in anxiety. Acute administration of the selective CB1 receptor antagonist SR141716A induced anxiety-like responses in the elevated plus maze and the defensive withdrawal tests. CB1 knockout mice showed anxiogenic-like response in the light/dark box.

**Corticotrophin-Releasing Factor:** Corticotrophin-Releasing Factor is made up of peptide containing 41 amino acids. This neurotransmitter in CNS acts as a key mediator of autonomic, immune, behavioral and endocrine stress responses. The peptide appears to be anxiogenic, proinflammatory and leads to increase pain perception. Corticotrophin-Releasing Factor is an essential component, which mediates endocrine and behavioral anxiety-like responses, and stimulation of CRF2 may produce anxiolytic-like effects.

**Melatonin:** Melatonin is synthesized by the pineal gland during night and acts through G-protein coupled receptors (GPCRs), MT1 (MEL1a) and MT2 (MEL1b). Melatonin is involved in numerous physiologic processes including circadian rhythms, mood regulation, anxiety, sleep, appetite, immune responses and cardiac functions. Preoperative anxiolytic effects of melatonin found a significant reduction in anxiety. MT2 receptors modulate anxiety levels and consequently this receptor may become a novel target for the treatment of anxiety.

**Substance P:** Substance P neurotransmission has been associated with aversion and anxiety behavioral model. Substance P act primarily at the neurokinin-1 (NK1) receptor. NK-1 antagonists are mediated by the dorsal raphe nucleus. NK-1 receptor exhibit anxiolytic effects in several models including elevated plus maze and social interaction tests. Disruption of NK-1 receptor results in 5-HT1A-receptor desensitization and anxiolytic behavior and the effect of substance P play a role in anxiogenic behavior.

**Neuroactive Steroids (NAS):** GABA-A receptor is a direct binding site for the neuroactive steroids. Enzymes involved in the biosynthesis of these NASs, such as 5α-reductase and 3α-hydroxysteroid oxidoreductase are found in key neuroanatomic structures involved in the anxiety such as the amygdala and the hippocampus. Positive modulation of the GABA-A receptor has been associated with anxiolytic activity whereas anxiogenic activity in animals models of anxiety in association with negative modulation. The potential role of NAS analogues is in the treatment of anxiety disorders.

**CONCLUSION:** A variety of neurotransmitters modulates the neuroanatomic circuits that provide support to fear and anxiety behavior. Neurotransmitters like GABA, Adenosine, Melatonin and neuroactive steroids are anxiolytics. Glutamate, Serotonin, Acetylcholine, Cholecystokinin and Corticotrophin releasing hormone are anxiogenic. Whereas Cannabinoids and Substance P show dual action i.e. they are anxiolytic as well as anxiogenic. This detailed knowledge about role of different neurotransmitters in anxiety will help in reducing the morbidity of anxiety disorders.

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