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Review Article

ANXIETY DISORDERS: A REVIEW

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ABSTRACT
Anxiety disorders are a highly prevalent and disabling class of psychiatric disorders. Anxiety disorders are highly prevalent and associated with substantial distress, morbidity and mortality. Recent epidemiological studies of anxiety disorders provided evidence of their high frequency in the general population worldwide. Anxiety disorders afflict an estimated 15.7 million people in the United States each year. Anxiety disorders are highly prevalent in adults with females showing higher preponderance of 2:1 as compared to males. Anxiety disorders are a group of mental disorders characterized by various combinations of key features - Irritability, fear, Insomnia, Nervousness, Tachycardia, Inability to concentrate, poor coping skills, Palpitation, Sweating, Agoraphobia and Social Withdrawal. The anxiety disorders, including panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and posttraumatic stress disorder (PTSD), are among the disabling medical disorders. The neurobiology of anxiety disorders is not fully understood, but several different biologic abnormalities have been implicated in their etiology. The GABA, NE and 5HT systems play crucial roles in mediating the affective circuitry underlying the highly related clinical disorders of anxiety. Anxiety is a common psychiatric condition characterized by unnecessary aggression, poor quality of life, fear, worry, avoidance, and compulsive rituals that are associated with significant distress.
KEYWORDS: Anxiety, Stress, GAD.

INTRODUCTION

The term ‘anxiety disorders’ refers to a collection of mental syndromes characterised by abnormally high levels of distress and avoidance associated with scenarios perceived as dangerous[1]. Anxiety disorders are manifested by hyper arousal of the central nervous system and intense feelings of fear, worry or apprehension. These disorders are highly prevalent and associated with substantial distress, morbidity and mortality. Anxiety disorders afflict an estimated 15.7 million people in the United States each year[2]. Anxiety expressed as physical, emotional, and behavioural responses to perceived threats, is a normal part of everyday life. There is substantial overuse of both psychiatric and nonpsychiatric medical services and reduced work productivity among patients with anxiety disorders, compared with the general population[2]. Although, Anxiety disorders form the most common type of psychiatric disorders, yet fewer than 30% of persons with anxiety disorders seek treatment. Anxiety disorder causes a substantial financial burden for patients and their families, as well as a considerable economic burden on society[2,3]. Anxiety disorders are highly prevalent in adults with females showing higher preponderance of 2:1 as compared to males[3]. People with anxiety disorders are incapacitated by chronic and intense feelings of anxiety, so strong that they are unable to function on a day-to-day basis. Because of the difficulty in recognizing and properly diagnosing anxiety disorders, epidemiological prevalence rates may underestimate the true number of people experiencing an anxiety disorder, which is particularly true in the elderly[3]. Anxiety is a common psychiatric condition characterized by unnecessary aggression, poor quality of life, fear, worry, avoidance, and compulsive rituals that are associated with significant distress[2].

CLINICAL SIGNS AND SYMPTOMS

Clinical Signs and Symptoms of Anxiety Disorders are as follows[4-7]:

- Feelings of insecurity, irritability and /restlessness as reflected by worries/ trembling /crying easily tendencies (This parameter covers the emotional condition of uncertainty about the future and ranges from worries, insecurity, irritability and apprehension to overpowering dread, inability to relax, nervousness and trembling), palpitations and tachycardia.
- Fears / Phobia (Fear of the dark, fear of strangers, fear of being alone, fear of animal).

- Insomnia (Difficulty in falling asleep, disturbed sleep, nightmares).
- Intellectual impairment (Difficulties in decision making and judgment).
- Sensory and Somatic symptoms (Muscular weakness, stiffness, increased muscular tone, soreness, increased fatigability, functional disturbances of the senses, including tinnitus, blurring of vision, hot and cold flushes and prickling sensations).
- Gastrointestinal distress (dysphasia, nausea, vomiting, constipation or weight loss).
- Autonomic symptoms (dry mouth, flushing, pallor, sweating or dizziness).

MAJOR CAUSES OF 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[8]. 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. People having low self-esteem and poor coping skills may be more prone to anxiety disorders[9]. Stressful life events have been documented to play an underlying role in anxiety disorders[10]. Low levels of GABA, a neurotransmitter that reduces activity in the central nervous system, contribute to anxiety[11]. Severe anxiety can be induced by sustained alcohol abuse which in most cases abates with prolonged abstinence. Caffeine, alcohol and benzodiazepine dependence can worsen or cause anxiety and panic attacks. In the same way that behavioural traits are passed from parent to child, anxiety disorders tend to run through family structures. Studies comparing the risk of psychiatric illness in identical twins (who share 100% of their DNA) have found that in general, if one identical twin has a psychiatric condition, the risk that the other twin will have the same condition is approximately 50%. It therefore appears that non-genetic factors, including environmental influences occurring throughout the lifespan, must also contribute to the risk of developing an anxiety disorder[8].

DIAGNOSIS OF ANXIETY DISORDERS

Anxiety disorders are very common, affecting as many as one fourth of all adults in the United States over the course of their lifetimes. The diagnosis of chronic anxiety disorders can be difficult, because nonspecific or vague symptoms can be masked by other co-morbid conditions or may be inadequately described or expressed by the patient[3]. Co-morbidity with psychiatric disorders is common, especially in major depressive disorder, but others include multiple anxiety disorders (panic disorder, social anxiety disorder, post-traumatic stress disorder, generalized anxiety disorder)[1,12,7]. Because of the difficulty in recognizing and properly diagnosing anxiety disorders, epidemiological prevalence rates may underestimate the true number of people experiencing an anxiety disorder[1].

CLASSIFICATION OF ANXIETY DISORDERS

The anxiety disorders, including panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and posttraumatic stress disorder (PTSD), are among the disabling medical disorders. They frequently begin early in life, are characterized by repeated episodes and chronicity, and can have serious medical and psychological consequences leading to functional disability in many patients. These disorders are diagnosed using standardized diagnostic criteria [DSM-IV, 2000] and International Classification of Diseases [ICD-10][4,6]. A brief description of the 5 major anxiety disorders is provided as below:

Social Anxiety Disorder

A fear of negative evaluation in social or performance situations, resulting in distress of functional impairment; distress may be generalized or specific[7,4]. Fear and anxiety associated with social or performance situations, resulting in functional impairment or distress, are characteristic of social anxiety disorder[7].

Post-traumatic Stress Disorder

Persistent symptoms of anxiety which occur after an extremely traumatic or life-threatening event, persisting for at least 4 weeks; patients often relive the triggering event[3,4,7].

Generalized Anxiety Disorder

Pervasive and uncontrollable worrying and anxious feelings that persist for at least 6 months, accompanied by at least 3 of the following: restlessness, difficulty concentrating, easy fatigability, irritability, muscle tension, disturbed sleep[3,4,6,7].

Panic Disorder

Recurring panic attacks (sudden and unprovoked episodes of fear and discomfort), which may be accompanied by somatic symptoms, such as palpitations, increased heart rate, chest pain, nausea, trembling, shortness of breath, or sweating[3,4,7]. Panic disorder is marked by recurrent, unexpected panic attacks with persistent concern about future panic attacks or worries about their implications or consequences[7].

Obsessive-compulsive Disorder

Presence of obsessions; recurrent, unwanted, and intrusive thoughts, images, or urges that cause marked anxiety (for example, thoughts about contamination, doubts about actions, distressing religious, aggressive, or

sexual thoughts) and Compulsions; repetitive behaviours or mental acts that are performed to reduce the anxiety generated by the obsessions (for example, checking, washing, counting, or repeating)[13,4,7].

PATHOPHYSIOLOGY OF ANXIETY DISORDERS

Dysfunctions of various neurotransmitters and receptors in the brain have been implicated in anxiety disorders. The 3 neurotransmitters primarily implicated in anxiety are GABA, serotonin (5-HT) and noradrenaline[10,11,14]. Dysregulations in the noradrenergic systems are hypothesized to occur in anxiety disorders. Noradrenaline modulates autonomic arousal mechanisms, including increased heart rate and respiration. This leads to a physiological cascade resulting in panic symptoms such as paraesthesia, numbness and tightness in the chest. GAD is associated with noradrenergic overactivity, serotonin receptor (5-HT1A, 5-HT2C) dysregulation and a decrease in the number of benzodiazepine sites on the GABAA - benzodiazepine receptor complex[15].

Gamma Aminobutyric Acid (GABA)

GABA is the main inhibitory neurotransmitter in the CNS. There are 2 subtypes of GABA receptors GABAA and GABAB. Benzodiazepines bind to the benzodiazepine receptor complex located on the postsynaptic neuron. Such binding augments the effect of GABA leading to the opening of chloride ion channels, causing influx of the chloride ions into the cell resulting in neuronal membrane stabilization[14]. GABA may also influence anxiety levels by mediating the release of other neurotransmitters such as cholecystokinin and suppressing neuronal activity in the serotonergic and noradrenergic systems. Although it is likely that differing pathophysiologies underlie various anxiety disorders, it is widely believed that the gamma -aminobutyric- acid (GABA) circuits are one of the systems integrally involved in anxiety disorders[16]. Neuroimaging studies have reported reductions in GABA levels and GABAA-benzodiazepine receptor binding in patients with anxiety disorders[14,16,17]. The Glutamate is the main excitatory central nervous system neurotransmitter and is the counterpart of GABA in this respect[16]. GABA-benzodiazepine receptors are widely distributed in the brain and spinal cord. They are particularly concentrated in portions of the brain thought to be involved in anxiety, including the medial PFC, amygdala, and hippocampus, and results from several studies have indicated abnormalities in this system in patients with anxiety disorders[14].

Serotonin

The central and peripheral norepinephrine system, because of its role in the adaptive response to acute physiologic and psychologic stressors, has been a natural focus of investigation concerning the pathophysiology of anxiety disorders[16]. The role of 5-HT and its receptor subtypes in mediating the symptoms of anxiety, panic and obsessions is complex. Specific attention has been drawn to the 5-HT1A and 5-HT2C receptor subtypes. 5-HT released from the nerve terminal binds to the postsynaptic 5-HT2C receptor subtype, which mediates anxiety[14,18]. 5-HT1A is an auto- receptor on the presynaptic neuron which, when stimulated, inhibits the release of 5-HT from the presynaptic neuron into the synapse[19]. Serotonergic neurons are implicated in the alteration of appetite, energy, sleep, mood and cognitive function in anxiety[18]. 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[14].

The 5-HT system is significant for its established role in the treatment of anxiety disorders[16]. Serotonergic pathways arising from the raphé nuclei in the brainstem innervate a wide range of structures thought to be involved in anxiety, including the frontal cortex, amygdala, hypothalamus, and hippocampus[16,19,20]. In addition, serotonergic mechanisms are believed to underlie the biologic activity of a wide range of medications used to treat mood disorders, including its anxiety symptoms. Any of a large number of abnormalities in the serotonergic system, including hypo- or hyper-innervations of key brain structures and/or cellular mechanisms resulting in aberrant neurotransmission may be involved in the etiology of anxiety disorders[14]. Cellular pathology that may contribute to the development of anxiety disorders includes abnormal regulation of 5-HT release and/or reuptake or abnormal responsiveness to 5-HT signalling[21]. The 5-HT1A receptor is thought to play a particularly important role in anxiety. Activation of 5-HT1A receptors enhances potassium currents and inhibits the activity of adenylate cyclise[17]. These receptors are localized as inhibitory autoreceptors on the dendrites of serotonergic cell bodies in the raphé nuclei and are also present on non–5-HT neurons in the hippocampus, entorhinal cortex, septum, amygdala, periaqueductal gray and frontal cortex. Long-term stress desensitizes presynaptic 5-HT1A receptors, an action that potentiates serotonergic neurotransmission. Activation of 5-HT1A receptors is also involved in the induction of adrenocortical trophic hormone and corticosteroid secretion in response to stress[15]. The 5-HT1A receptor is also involved in panic disorder. A specific polymorphism in the gene encoding the 5-HT1A

receptor has been shown to have significant associations with both agoraphobia and panic disorder[21].

Corticotropin-releasing Factor

Some abnormalities in the- hypothalamic-pituitary-adrenal axis and central corticotropin-releasing factor (CRF) neuronal functioning have been identified in several anxiety disorders. Patients with combat-related posttraumatic stress disorder have a pattern of central overproduction of CRF, with low plasma cortisol and up-regulation of lymphocyte corticosteroid receptors[15,20,22]. Corticotropin-releasing factor, a 41 amino acid peptide, is a neurotransmitter within the central nervous system (CNS) that acts as a key mediator of autonomic, behavioral, immune, and endocrine stress responses. The peptide appears to be anxiogenic, depressogenic, and proinflammatory and leads to increased pain perception. Gama-Aminobutyric acid (GABA) inhibits CRF release[14,23].

Corticotropin-releasing Hormone

CRH is important mediator of the stress response, as reflected by the stress-induced release of CRH from the hypothalamus into the hypthalamo-pituitary portal circulation resulting in activation of HPA axis and the increased release of cortisol and DHEA[23,19]. The following brain regions have neurons that contain CRH: the PFC, the cingulate cortex (CeA), the bed nucleus of the stria terminalis (BNST), the nucleus accumbens (NAc), the periaqueductal gray (PAG), and brain stem nuclei, such as the major norepinephrine (NE)–containing nucleus, the locus ceruleus (LC) and the serotonin nuclei in the dorsal and median raphe[20]. Amygdala CRH neuronal hyperactivity may mediate fearrelated behaviors, while excessive cortical CRH may reduce reward expectation. Early life stress results in chronic elevation of brain CRH activity and the individual response to heightened CRH function may depend upon the social environment, past trauma history, and behavioral dominance[24]. In contrast, preliminary data suggest that stimulation of the CRH-2 receptor results in reduced anxiety-related behaviors. Research into the role of CRH in the pathophysiology of anxiety disorders has been limited by the lack of CRH receptor ligands useful for brain imaging in human subjects. Increased cerebrospinal fluid (CSF) levels of CRH have been linked to PTSD by several studies[24].

Cortisol

Psychological stress has been demonstrated to increase the synthesis and release of cortisol. Cortisol has many different functions including mobilization of energy stores, increased arousal, vigilance, focused attention, and memory formation, inhibition of the growth and reproductive system, and containment of the immune response. The behavioral effects of cortisol are due, in part, to regulatory effects on the hippocampus, amygdala, and prefrontal cortex (PFC)[10]. Cortisol increases the effects of CRH on conditioned fear, and facilitates the encoding of emotion-related memory[19]. Many of the effects of cortisol, particularly those outside the hypothalamo- pituitary-adrenal (HPA) axis, are mediated via an interaction with the glucocorticoid receptor (GR). Another adrenal steroid that is intimately involved in the stress response is dehydroepiandrosterone (DHEA). DHEA is secreted with cortisol in response to fluctuating adrenocorticotropic hormone (ACTH) levels. There is evidence that DHEA possesses antiglucocorticoid and antiglutamatergic properties in the brain. Since peripherally produced DHEA is thought to be a major source of brain DHEA, it is likely that within the brain regionally specific metabolism of DHEA may ultimately control the nature of DHEA's effects on cognition and behaviour[19]. Dysregulations in cortisol secretion and in the hypothalamic pituitary axis, which modulate stress responses, have been observed in anxiety disorders such as GAD and PTSD[24].

Other substances implicated in anxiety include neuropeptide Y, tachykinins and glutamate. Neuropeptide Y (NPY**)** is among the most abundant neuropeptides in mammalian brain with high concentrations in the LC; paraventricular nucleus of the hypothalamus; septohippocampal neurons; nucleus of soli- tray tract; and ventrolateral medulla[19,25]. Moderate levels are found in the amygdala, hippocampus, cerebral cortex, basal ganglia, and the thalamus. NPY has been shown to have anxiolytic activity and to impair the consolidation of memories. 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[9].

HPA Axis and Anxiety

The HPA axis is an interactive system of hormones released in response to stress. The release of CRF by the hypothalamus prompts the pituitary to disperse adrenocorticotropin-releasing hormone (ACTH) into the bloodstream. ACTH is detected by the adrenal cortex, facilitating the release of glucocorticoids such as cortisol[24,19]. Negative feedback occurs when cortisol binds to glucocorticoid receptors on the hypothalamus and pituitary, suppressing the subsequent release of CRF and ACTH[10,16,19].

High levels of anxiety result in negative physiological manifestations, such as elevated blood cortisol levels and increased blood pressure and heart rate, leading to slower

wound healing, diminished immune response, and increased risk of infection[26]. The stress response in humans involves a cascade of hormonal events, including the release of corticotropin-releasing factor (CRF), which, in turn, stimulates the release of corticotropin, leading to release of the stress hormones (glucocorticoids and epinephrine) from the adrenal cortex[20]. The glucocorticoids typically exert negative feedback to the hypothalamus, thus decreasing the release of CRF [26]. As a result, when humans chronically and erroneously believe that a homeostatic challenge is about to occur, they enter the realm of neurosis, anxiety, and paranoia. The amygdala is the primary modulator of the response to fear- or anxiety-inducing stimuli. It is central to registering the emotional significance of stressful stimuli and creating emotional memories. Thus, the stress response involves activation of the hypothalamic-pituitary-adrenal axis. This axis is hyperactive in depression and in anxiety disorders[27].

Neural Circuits Involved in Anxiety

The neurobiology of anxiety disorders is not fully understood, but several different biologic abnormalities have been implicated in their etiology. Results from both animal and human studies have suggested that a number of specific brain structures, including the amygdala and prefrontal cortex (PFC), are involved in the mediation of fear and anxiety[10, 23]. The amygdala is central to the processing of fear and anxiety, and its function may be disrupted in anxiety disorders (Davis, 1992). Sensory information enters the amgydala through the nuclei of the basolateral complex (consisting of lateral, basal, and accessory basal nuclei). The basolateral complex processes sensory-related fear memories and communicates their threat importance to memory and sensory processing elsewhere in the brain, such as the medial prefrontal cortex and sensory cortices[20]. Another important area is the adjacent central nucleus of the amygdala, which controls species-specific fear responses, via connections to the brainstem, hypothalamus, and cerebellum areas. In those with general anxiety disorder, these connections functionally seem to be less distinct, with greater gray matter in the central nucleus. Another difference is that the amygdala areas have decreased connectivity with the insula and cingulate areas that control general stimulus salience, while having greater connectivity with the parietal cortex and prefrontal cortex circuits that underlie executive functions. More recently, functional brain imaging studies have been particularly useful in delineating the neurocircuitry of the anxiety disorders. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) scanning studies have identified several areas of increased activity when patients with SAD are presented with anxiety-provoking situations, including the amygdale and prefrontal regions, although a range of other regions may also play a role[27,28]. Functional brain imaging studies have also demonstrated changes in the activity of the amygdala and medial PFC in patients with PTSD, and a meta-analysis of results from scanning studies has indicated that activity is altered in both the orbitofrontal cortex and head of the caudate nucleus of patients with OCD[28]. Recent advances in brain neuroimaging techniques have significantly contributed to ongoing research aimed at understanding the possible anatomical sites of dysfunction in the brain in relation to anxiety disorders. Neuroimaging studies of GAD have suggested that there are dysregulations in parts of the brain such as the basal ganglia, several areas of the cortex and parts of the limbic system and thalamus[29]. Two major nuclei, the locus caerulus and raphe nuclei in the brain stem are major mediators of noradrenergic and serotonergic systems respectively. The aforementioned neurotransmitters are abundant in these brain structures and hence involved in the pathophysiology of anxiety states[20,23].

CONCLUSION

Anxiety expressed as physical, emotional, and behavioural responses to perceived threats, is a normal part of everyday life. There is substantial overuse of both psychiatric and nonpsychiatric medical services and reduced work productivity among patients with anxiety disorders, compared with the general population. Anxiety disorders cause a substantial financial burden for patients and their families, as well as a considerable economic burden on society.

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