

## Review Article

## Anxiety: Insights into Signs, Symptoms, Etiology, Pathophysiology, and Treatment

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**Abstract: Background:** The anxiety disorders are the most common mental disorders. It is manifest by disturbances of mood, as well as of thinking, behaviour, and physiological activity. It includes panic disorder, agoraphobia, generalized anxiety disorder, specific phobia, social phobia, obsessive-compulsive disorder, acute stress disorder, and post-traumatic stress disorder. **Objectives:** The aim of the current review is a high light on the anxiety signs, symptoms, etiology, pathophysiology, treatment. The common symptoms of anxiety are accompanying disturbances of sleep, concentration, social and/or occupational functioning. The anxiety is associated with restlessness, feeling keyed up or on edge, being easily fatigued, difficulty in concentrating or mind going blank, irritability, muscle tension, and irritability. The etiology of anxiety may include stress, physical condition, genetic, and environmental factors. Anxiety symptoms may be due to disrupted modulation within the central nervous system. Many believe that low serotonin system activity and elevated noradrenergic system activity are responsible for its development. Therefore, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors that is the first-line agent for its treatment. Corticosteroids may increase or decrease the activity of certain neural pathways, affecting not only behavior under stress, but also the brain's processing of fear-inducing stimuli. Several studies have found elevated WBC count among anxious individuals there was a negative association between red blood cell and mean corpuscular hemoglobin and symptoms of anxiety. A positive association between anxiety symptoms and levels of hematological inflammatory markers including WBC and RDW. Drugs to reduce anxiety have been used by human beings for thousands of years. **Conclusion:** It can be concluded that anxiety is manifest by disturbances of mood, thinking, behaviour, and physiological activity and accompanying disturbances of sleep, concentration, social and/or occupational functioning. Also, it is associated with restlessness, feeling keyed up or on edge, being easily fatigued, difficulty in concentrating or mind going blank, irritability, muscle tension, and irritability. The etiology of anxiety may include stress, diabetes, depression, genetic, and environmental factors. Anxiety disorders should be treated with psychological therapy, pharmacotherapy, or a combination of both.

**Keywords:** Anxiety, Signs, Symptoms, Etiology, Pathophysiology, Treatment.

### 1. INTRODUCTION

The anxiety disorders are the most common, or frequently occurring, mental disorders (Munir *et al.*, 2019). They encompass a group of conditions that share extreme or pathological anxiety as the principal disturbance of mood or emotional tone. Anxiety, which may be understood as the pathological counterpart of normal fear, is manifest by disturbances of mood, as well as of thinking, behaviour, and physiological activity. The anxiety disorders include panic disorder (with and without a history of agoraphobia), agoraphobia (with and without a history of panic

disorder), generalized anxiety disorder, specific phobia, social phobia, obsessive-compulsive disorder, acute stress disorder, and post-traumatic stress disorder. In addition, there are adjustment disorders with anxiety features, and disorders due to general medical conditions and substance-induced anxiety disorders (Greenberg *et al.*, 1999).

Diagnostic criteria are include excessive anxiety and worry for at least six months, difficulty controlling the worrying. The anxiety is associated with three or more of the following symptoms for at least 6

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months: restlessness, feeling keyed up or on edge, being easily fatigued, difficulty in concentrating or mind going blank, irritability, muscle tension, sleep disturbance, and irritability (Munir *et al.*, 2019).

## 2. Signs and Symptoms

A subjective experience of distress with accompanying disturbances of sleep, concentration, social and/or occupational functioning are common symptoms in many of the anxiety disorders. Despite their similarities, these disorders often differ in presentation, course and treatment. Patients often present with complaints of poor physical health as their primary concern. This may temporarily distract from the underlying anxiety symptoms. This is particularly common in panic disorder, which is characterized by a short period of intense fear and a sense of impending, doom, with accompanying physical symptoms, such as chest pain, dizziness and shortness of breath (Markowitz *et al.*, 1989). When complicated by agoraphobia, the individual fears have a panic attack in a place that prevents escape. This results in the patient avoiding such situations, with subsequent disturbances in functioning (Magee *et al.*, 1996). The ancient term agoraphobia is translated from Greek as fear of an open marketplace. Agoraphobia today describes severe and pervasive anxiety about being in situations from which escape might be difficult or avoidance of situations such as being alone outside of the home, traveling in a car, bus, or airplane, or being in a crowded area (Magee *et al.*, 1996).

Most people who present to mental health specialists develop agoraphobia after the onset of panic disorder. Agoraphobia is best understood as an adverse behavioral outcome of repeated panic attacks and the subsequent worry, preoccupation, and avoidance (Barlow, 1988).

Generalized anxiety disorder (GAD) rarely occurs without a co-morbid psychiatric disorder, with the patient experiencing consistent worry over multiple areas of his or her life for at least 6 months (Schweizer, 1995).

Social phobia describes fear and anxiety in social situations leading to avoidance of social interaction (Ballenger *et al.*, 1998). Specific phobia is characterized by similar symptoms and behavior, but is triggered by a specific object or situation, such as a fear of certain animals (especially snakes, rodents, and dogs); birds, insects (especially spiders and bees or hornets); heights; elevators; flying; automobile driving; water; storms; and blood or injections (Marks, 1969).

Post-traumatic stress disorder and acute stress disorder occur after a patient experiences a traumatic event with subsequent physiological arousal in the face of stimuli that trigger memories of the event; avoidance of such stimuli; and a sense of re-experiencing the

event. The latter occurs in the short term, while the former describe a more chronic version of the disorder (Kessler *et al.*, 1995).

Obsessive-compulsive disorder (OCD) is characterized by repeated behaviors (compulsions), which serve to reduce anxiety connected to unwanted, intrusive thoughts (obsessions). Commonly seen behaviors are cleaning or washing in response to concerns about contamination, or repeatedly checking to see if a stove is turned off in response to concerns over a fire starting. Some people repeatedly check work or seek excessive reassurance due to obsessive self-doubt (Eddy and Walbroehl, 1998).

## 2. Etiology and psychological basis of anxiety

The etiology of anxiety may include stress, physical condition such as diabetes or other co-morbidities such as depression, genetic, first-degree relatives with generalized anxiety disorder (25%), environmental factors, such as child abuse, and substance abuse (Munir *et al.*, 2019). The anxiety disorders are so heterogeneous that the relative roles of these factors are likely to differ. Some anxiety disorders, like panic disorder, appear to have a stronger genetic basis than others (National Institute of Mental Health [NIMH], 1998), although actual genes have not been identified. Other anxiety disorders are more rooted in stressful life events.

It is not clear why females have higher rates than males of most anxiety disorders, although some theories have suggested a role for the gonadal steroids. Other research on women's responses to stress also suggests that women experience a wider range of life events as stressful as compared with men who react to a more limited range of stressful events, specifically those affecting themselves or close family members (Maciejewski *et al.*, 2001).

What the myriad of anxiety disorders have in common is a state of increased arousal or fear. Anxiety disorders often are conceptualized as an abnormal or exaggerated version of arousal. Much is known about arousal because of decades of study in animals and humans of the so-called "fight-or-flight response," which also is referred to as the acute stress response. The acute stress response is critical to understanding the normal response to stressors and has galvanized research, but its limitations for understanding anxiety have come to the forefront in recent years (Barbee, 1998).

In common parlance, the term "stress" refers either to the external stressor, which can be physical or psychosocial in nature, as well as to the internal response to the stressor. Yet researchers distinguish the two, calling the stressor the stimulus and the body's reaction the stress response. This is an important distinction because in many anxiety states there is no

immediate external stressor. The following paragraphs describe the biology of the acute stress response, as well as its limitations, in understanding human anxiety. Emerging views about the neurobiology of anxiety, attempt to integrate and understand psychosocial views of anxiety and behavior in relation to the structure and function of the central and peripheral nervous system.

There are several major psychological theories of anxiety: psychoanalytic and psychodynamic theory, behavioral theories, and cognitive theories (Thorn *et al.*, 1999). Psychodynamic theories have focused on symptoms as an expression of underlying conflicts (Rush *et al.*, 1998; Thorn *et al.*, 1999). Although there are no empirical studies to support these psychodynamic theories, they are amenable to scientific study (Kandel, 1999) and some therapists find them useful. For example, ritualistic compulsive behavior can be viewed as a result of a specific defense mechanism that serves to channel psychic energy away from conflicted or forbidden impulses. Phobic behaviors similarly have been viewed as a result of the defense mechanism of displacement. From the psychodynamic perspective, anxiety usually reflects more basic, unresolved conflicts in intimate relationships or expression of anger.

More recent behavioral theories have emphasized the importance of two types of learning: classical conditioning and vicarious or observational learning. These theories have some empirical evidence to support them. In classical conditioning, a neutral stimulus acquires the ability to elicit a fear response after repeated pairings with a frightening (unconditioned) stimulus. In vicarious learning, fearful behavior is acquired by observing others' reactions to fear-inducing stimuli (Thorn *et al.*, 1999). With general anxiety disorder, unpredictable positive and negative reinforcement is seen as leading to anxiety, especially because the person is unsure about whether avoidance behaviors are effective.

Cognitive factors, especially the way people interpret or think about stressful events, play a critical role in the etiology of anxiety (Barlow *et al.*, 1996; Thorn *et al.*, 1999). A decisive factor is the individual's perception, which can intensify or dampen the response. One of the most salient negative cognitions in anxiety is the sense of uncontrollability. It is typified by a state of helplessness due to a perceived inability to predict, control, or obtain desired results (Barlow *et al.*, 1996). Negative cognitions are frequently found in individuals with anxiety (Ingram *et al.*, 1998). Many modern psychological models of anxiety incorporate the role of individual vulnerability, which includes both genetic (Smoller & Tsuang, 1998) and acquired (Coplan *et al.*, 1997) predispositions. There is evidence that women may ruminate more about distressing life events compared with men, suggesting that a cognitive risk factor may predispose them to higher rates of anxiety

and depression (Nolen-hoeksema *et al.*, 1999).

#### 4. Pathophysiology

The exact mechanism is not entirely known. Anxiety can be a normal phenomenon in children. Stranger anxiety begins at seven to nine months of life (Munir *et al.*, 2019). Anxiety symptoms and the resulting disorders are thought to be due to disrupted modulation within the central nervous system. Physical and emotional manifestations of this dysregulation are the result of heightened sympathetic arousal of varying degrees (Kaplan and Sadock, 1995).

Several neurotransmitter systems have been implicated to have a role in one or several of the modulatory steps involved. The most commonly considered are the serotonergic and noradrenergic neurotransmitter systems. In very general terms, it is thought that an under activation of the serotonergic system and an over activation of the noradrenergic system are involved (Ressler and Nemeroff, 2000, Munir *et al.*, 2019). These systems regulate and are regulated by other pathways and neuronal circuits in various regions of the brain, resulting in dysregulation of physiological arousal and the emotional experience of this arousal (Ressler and Nemeroff, 2000). Many believe that low serotonin system activity and elevated noradrenergic system activity are responsible for its development. It is, therefore, selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) that are the first-line agent for its treatment (Munir *et al.*, 2019). Disruption of the gamma-aminobutyric acid (GABA) system has also been implicated because of the response of many of the anxiety spectrum disorders to treatment with benzodiazepines (Nutt, 2001). There has been some interest in the role of corticosteroid regulation and its relationship to symptoms of fear and anxiety. Corticosteroids may increase or decrease the activity of certain neural pathways, affecting not only behavior under stress, but also the brain's processing of fear-inducing stimuli (Korte, 2001). Cholecystokinin has long been viewed as a neurotransmitter involved in regulating emotional states (Korte, 2001).

There is such careful orchestration between these neurotransmitters that changes in one neurotransmitter system invariably elicit changes in another, including extensive feedback mechanisms. Serotonin and GABA are inhibitory neurotransmitters that quieten the stress response (Coplan and Lydiard, 1998; Rush *et al.*, 1998). All of these neurotransmitters have become important targets for therapeutic agents.

Many studies indicate that a genetic predisposition to developing an anxiety disorder is likely. However, environmental stressors clearly play a role, in varying degrees. All of the disorders are affected in some way by external cues and how they are processed and reacted to (Kaplan and Sadock, 1995).

Several studies have found elevated WBC count among depressed and anxious individuals (Pitsavos *et al.*, 2006; Kobrosly and van Wijngaarden, 2010; Duivis *et al.*, 2013; Aydin *et al.*, 2016; Shafiee *et al.*, 2017). Shafiee *et al.*, 2017 reported that the mean WBC count increased with increasing severity of symptoms of depression and anxiety among men. Men (but not women) with severe anxiety symptoms had significantly higher values of RDW ( $p < 0.001$ ). Moreover, there was a negative association between red blood cell (RBC) and mean corpuscular hemoglobin (MCH) and symptoms of depression/anxiety. Pitsavos *et al.* (2006) observed that anxiety score is positively correlated with WBC count in women, but not in men. Since WBC count is an independent predictor of atherosclerosis and cardiovascular diseases (Loimaala *et al.*, 2006; Madjid *et al.*, 2004, Shafiee *et al.*, 2017). RDW is a strong predictor of mortality and has association with a variety of cardiovascular and thrombotic disorders (Montagnana *et al.*, 2012; Patel *et al.*, 2009, Shafiee *et al.*, 2017). Therefore, higher levels of RDW among depressed and anxious individuals may predict greater risk of developing cardiovascular diseases in these patients (Shafiee *et al.*, 2017).

Shafiee *et al.*, 2017 concluded that a positive association between depression/anxiety symptoms and levels of hematological inflammatory markers including WBC and RDW, which persisted despite adjustment by potential confounders.

### 5. Biochemical Basis of Anxiety

An exciting new line of research proposes that anxiety engages a wide range of neurocircuits. This line of research catapults to prominence two key regulatory centers found in the cerebral hemispheres of the brain—the hippocampus and the amygdala. These centers, in turn, are thought to activate the hypothalamic-pituitary-adrenocortical (HPA) axis (Goddard & Charney, 1997; Coplan & Lydiard, 1998; Sullivan *et al.*, 1998). Researchers have long established the contribution of the HPA axis to anxiety but have been perplexed by how it is regulated. They are buoyed by new findings about the roles of the hippocampus and the amygdala.

The hippocampus and the amygdala govern memory storage and emotions, respectively, among their other functions. The hippocampus is considered important in verbal memory, especially of time and place for events with strong emotional overtones (McEwen, 1998). The hippocampus and amygdala are major nuclei of the limbic system, a pathway known to underlie emotions. There are anatomical projections between the hippocampus, amygdala, and hypothalamus (Jacobson & Sapolsky, 1991; Charney & Deutch, 1996; Coplan & Lydiard, 1998).

Studies of emotional processing in rodents (Rogan & LeDoux, 1996) and in humans with brain lesions (Adolphs *et al.*, 1998) have identified the

amygdala as critical to fear responses. Sensory information enters the lateral amygdala, from which processed information is passed to the central nucleus, the major output nucleus of the amygdala. The central nucleus projects, in turn, to multiple brain systems involved in the physiologic and behavioral responses to fear. Projections to different regions of the hypothalamus activate the sympathetic nervous system and induce the release of stress hormones, such as CRH. The production of CRH in the paraventricular nucleus of the hypothalamus activates a cascade leading to release of glucocorticoids from the adrenal cortex. Projections from the central nucleus innervate different parts of the periaqueductal gray matter, which initiates descending analgesic responses (involving the body's endogenous opioids) that can suppress pain in an emergency, and which also activates species-typical defensive responses (e.g., many animals freeze when fearful) (Davis, 1997).

Anxiety differs from fear in that the fear-producing stimulus is either not present or not immediately threatening, but in anticipation of danger, the same arousal, vigilance, physiologic preparedness, and negative affects and cognitions occur (LeDoux, 1996). Different types of internal or external factors or triggers act to produce the anxiety symptoms of panic disorder, agoraphobia, post-traumatic stress disorder, specific phobias, and generalized anxiety disorder, and the prominent anxiety that commonly occurs in major depression. It is currently a matter of research to determine whether dysregulation of these fear pathways leads to the symptoms of anxiety disorders. It has now been established, using noninvasive neuroimaging, that the human amygdala is also involved in fear responses (Breiter *et al.*, 1996). Fearful facial expressions have been shown to activate the amygdala in MRI studies of normal human subjects (Breiter *et al.*, 1996). Functional imaging studies in anxiety disorders, such as PET studies of brain activation in phobias (Rauch *et al.*, 1995), are also beginning to investigate the precise neural circuits involved in the anxiety disorders.

What is especially exciting is that neuroimaging has furnished direct evidence in humans of the damaging effects of glucocorticoids. In people with post-traumatic stress disorder, neuroimaging studies have found a reduction in the size of the hippocampus. The reduced volume appears to reflect the atrophy of dendrites—the receptive portion of nerve cells—in a select region of the hippocampus. Similarly, animals exposed to chronic psychosocial stress display atrophy in the same hippocampal region (McEwen & Magarinos, 1997). Stress-induced increases in glucocorticoids specially corticosterone are thought to be responsible for the atrophy (McEwen, 1998). If the hippocampus is impaired, the individual is thought to be less able to draw on memory to evaluate the nature of the stressor (McEwen, 1998).

## 6. Treatment of anxiety

Drugs to reduce anxiety have been used by human beings for thousands of years. One of the first anxiolytics and one that continues to be used by humans is ethanol. A number of other drugs including the barbiturates and the carbamates (meprobamate) were used in the first half of the 20<sup>th</sup> century and some continue to be used today.

### 6.1. Serotonin Receptor Modulators and Reuptake Inhibitors

Serotonin has long been viewed as a neurotransmitter involved in regulating emotional states. Of the 14 or so mammalian serotonin receptor subtypes that have been described in the literature, at least four have been implicated in anxiety in various animal models (Lucki, 1996). As reported by Lucki, 1996 the original hypothesis implicating serotonin in anxiety surfaced from observations that reduced levels of serotonin can produce anxiolytic effects. One of the receptor subtypes implicated in anxiety is the serotonin 1A receptor subtype (5HT1A), which is an auto receptor located presynaptically on serotonin neurons. When stimulated, this receptor inhibits the synthesis and secretion of serotonin. The 5-HT1A receptor agonist buspirone exhibits anxiolytic effects in animals and was approved by the Food and Drug Administration (FDA) in 1986 for human generalized anxiety disorder. Other serotonin receptors potentially involved in anxiety include the 5-HT2A, 5-HT2C and 5-HT3 receptors. Antagonists for the 5-HT2A receptor, like ritanserin, exhibit anxiolytic effects in some animal models (Critchley and Handley, 1987; Gleeson *et al.*, 1989). Likewise, blockade of the 5-HT2C receptor produces anxiolytic effects in animals and prevents the anxiogenic effects of m-CPP (Kennett *et al.*, 1989). Finally, the 5-HT3 receptor antagonist ondansetron was reported to be anxiolytic in some animal models (Costall and Naylor, 1991).

Advances in molecular biology has led to the development of serotonin receptor gene knockout methodology, which generates mice lacking the 5-HT1A receptor, allowing for the evaluation of this receptor subtype in a variety of measurable behaviors. Ramboz *et al.*, 1998 reported results consistent with the 5-HT1A agonist's data cited above. Mice lacking this receptor displayed less exploratory activity in an open field and more anxious behavior than the wild types in the elevated plus maze. According to the serotonin hypothesis of anxiety (Johnson and file, 1986), removing the negative feedback control of 5-HT with the 5-HT1A receptor knockout animals should result in increased levels of 5-HT in the synaptic cleft, which would be expected to lead to the anxiogenic behavior. However, Ramboz *et al.* 1998, reported normal levels of 5-HT, which confuses the issues related to anxiety modulation and serotonin levels.

In 1986, the FDA approved the 5-HT1A partial agonist, buspirone for generalized anxiety disorder. This drug was the first to challenge the benzodiazepines for this patient group and was generally perceived as an improvement because of the lack of benzodiazepine side effects. The efficacy of buspirone, however, was not the same as that of the benzodiazepines in terms of its delayed onset of action, and it is generally accepted that when buspirone offers clinical benefit to GAD patients, it takes 3 to 4 weeks to match the efficacy of benzodiazepines such as diazepam and alprazolam (Coplan *et al.*, 1995). The 5-HT1A partial agonist properties of buspirone are believed to account for its clinical effects, but it should be noted that the drug is also a D2 antagonist and is extensively metabolized. One of the major metabolites, 1-pyrimidinylpiperazine (1-PP), may contribute to the pharmacologic activity of buspirone (Mahmood and Sahajwalla, 1999). In a double-blind, placebo-controlled study of buspirone in GAD patients (Laakmann *et al.*, 1998), the drug was reported to be as efficacious as lorazepam at the end of a 4-week treatment period. After the drugs were discontinued, however, the lorazepam-treated patients worsened whereas the buspirone-treated subjects maintained clinical improvement. Thus, there continues to be evidence that buspirone is effective in GAD.

The development of selective serotonin reuptake inhibitors (SSRIs) in the 1980s and 1990s widely expanded the treatment for depressive disorders, and these drugs (fluoxetine, sertraline, venlafaxin, paroxetine) have recently made inroads in treating anxiety disorders such as panic, obsessivecompulsive disorder, social phobia, and GAD. Successful treatment of GAD with a class of drugs working through the serotonergic system will come from the SSRIs (Rocca *et al.*, 1997).

OCD is a chronic, disabling anxiety disorder. In a review of the diagnosis and treatment of OCD, Goodman, 1999 states that the backbone of pharmacologic treatment for OCD is a 10- to 12-week trial with an SSRIs in adequate doses. It is clear from a review of the role of the 5-HT1A receptor (Coplan *et al.*, 1995) in OCD that partial agonists such as buspirone are generally ineffective in treating OCD. The authors also note that in studying the potential to augment efficacy of the standard OCD medication, buspirone was not different from placebo as an augmenting agent. Drugs that work through other serotonin receptor subtypes also appear to be ineffective in treating OCD. Thus, drugs modifying the 5-HT1A, 5-HT1D and 5-HT3 receptors appear ineffective in treating OCD symptoms and rule out a critical involvement of these receptor subtypes in OCD (Broocks *et al.*, 1998; Pian *et al.*, 1998).

In the past, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, as well as high potency benzodiazepines, have been used to treat patients with panic disorder. The SSRIs have also been added to the list of effective agents for the disorder. In reviewing the pharmacotherapy of panic disorder, den Boer, 1998 notes that antidepressants are more effective than benzodiazepines in reducing associated depressive symptomatology and are at least as effective for improving anxiety, agoraphobia, and overall impairment. Bell and Nutt, 1998 remark that SSRIs improve 60% to 70% of panic patients, a similar percentage to those seen with the TCAs.

Like OCD, panic disorder is well treated by SSRIs but does not appear to be effectively treated by receptor specific compounds. Coplan *et al.*, 1995 reviewed the role of 5HT 1A drugs such as buspirone in panic disorder and reported that buspirone does not significantly treat panic in several well-controlled studies. Using the 5-HT<sub>1A</sub> receptor agonist flesinoxan, ikvan Vliet *et al.*, 1996 reported a worsening of symptoms in panic patients treated with high doses of the drug. It has also been reported that the 5-HT<sub>2A/2C</sub> antagonist ritanserin had no effects on panic attacks or phobic avoidance, and a similar negative finding has been reported with the 5-HT<sub>3</sub> antagonist ondansetron.

## 6.2. $\Gamma$ -Aminobutyric Acid Receptor Modulators (Benzodiazepines and Related Drugs)

A majority of the synapses in the mammalian CNS use the amino acids I-glutamic acid, glycine, or  $\gamma$ -aminobutyric acid (GABA) for signaling. GABA is formed by the decarboxylation of I-glutamate, stored in neurons, and released, and its action is terminated by reuptake; GABA's action mimics the naturally occurring inhibitory transmission in the mammalian nervous system. Because of these findings, it has been accepted for over 20 years that GABA fulfills the characteristics of a neurotransmitter (Paul, 1995). Along with I-glutamate, acetylcholine, and serotonin, GABA possesses two different types of receptor conserved across different species and phyla that control both excitation and inhibition. Molecular biological studies of the receptors causing these effects have indicated that GABA's effects on ionic transmission (ionotropic) and metabolism (metabotropic) are mediated by proteins in two different superfamilies. The first superfamily (GABA<sub>A</sub> receptors) is a set of ligand-gated ion channels (ligand-gated superfamily) that convey GABA's effects on fast synaptic transmission (Siegharr, 1995). When a GABA<sub>A</sub> receptor is activated, an ion channel is opened (gated) and this allows chloride to enter the cell; the usual result of chloride entry is a slowing of neuronal activity through hyperpolarization of the cell membrane potential. The second superfamily (GABA<sub>B</sub>) is slower, mediating GABA's action on intracellular effectors through a seven transmembrane spanning receptor (serpentine superfamily) that modulates the action of

certain guanine nucleotide binding proteins (G proteins) (Kaupmann *et al.*, 1997). Through their activity on other effector systems, G proteins can change second messenger levels, altering signal transduction and gene expression, or open ion channels that are dependent on the G-protein subunit activities (Wess, 1997). Both excitatory and inhibitory activities are possible on a time scale that is longer than GABA<sub>A</sub> receptor mediated events. There is extensive heterogeneity in the structure of the GABA<sub>A</sub> receptor members of the ligand-gated superfamily. These receptors are the targets of a number of widely used and prescribed drugs for sleep, anxiety, seizure disorders, and cognitive enhancement; they may also contribute to mediating the effects of ethanol on the body.

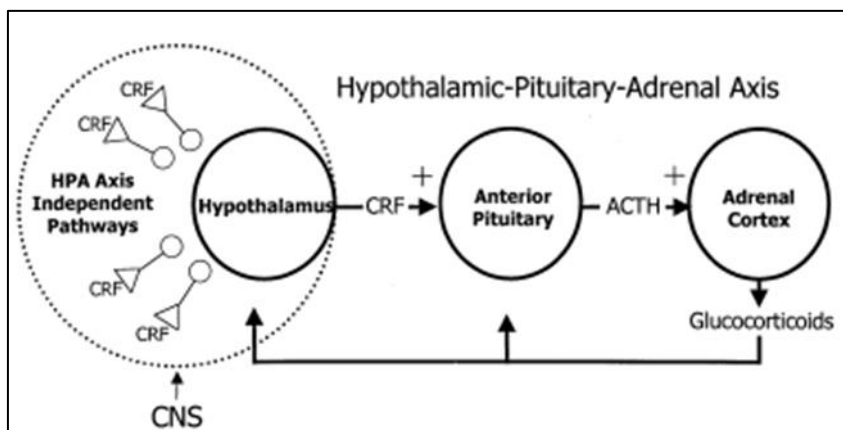
It is well established that the GABA<sub>A</sub> receptors possess binding sites for the neurotransmitter GABA, as well as allosteric modulatory sites for benzodiazepines, barbiturates, neurosteroids, anesthetics, and convulsants (Tallman *et al.*, 1980; Tallman and Gallager, 1985).

## 6.3. Corticotrophin-Releasing Factor Modulators

Corticotrophin-releasing factor (CRF) is a 41 amino acid peptide that plays an important role in mediating the body's physiologic and behavioral responses to stress (Koob *et al.*, 1993). Figure (1) illustrates that this role of CRF may be mediated by multiple sites of action. As a secretagogue, CRF stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary. In addition, CRF plays a neurotransmitter or neuromodulatory role through neurons and receptors distributed in diverse brain regions (DeSouza and Grigoriadis, 1995). CRF neurons, localized in the hypothalamic periventricular nucleus, are a major mediator of stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis, whereas pathways innervating limbic and cortical areas are thought to mediate the behavioral effects of CRF. There is a large body of both preclinical and clinical literature implicating a key role of CRF in affective disorders such as anxiety and depression. A significant clinical literature suggests that dysfunctions of CRF in its role as a hormone in the HPA axis or as a neurotransmitter in the brain may contribute to the etiology of a variety of psychiatric conditions, including anxiety and depression (Gold *et al.*, 1995). The link between CRF and depression is particularly strong, as numerous clinical studies have demonstrated that depressed patients show elevated cerebrospinal fluid (CSF) levels of CRF, elevated plasma cortisol, and a blunted ACTH response following intravenous CRF. Successful antidepressant treatment was shown to have a normalizing effect on CRF levels. A role of CRF in anxiety disorders has also been postulated, though the clinical evidence is not as strong as it is for depression (Arborelius *et al.*, 1999). Preclinical studies have demonstrated that CRF administered exogenously into the central nervous system (CNS) can produce

behaviors indicative of anxiety and depression, for example, heightened startle responses, anxiogenic behaviors on the elevated plus maze, decreased food consumption, and altered sleep patterns. The anxiogenic effects of CRF are not blocked by adrenalectomy, suggesting that they are centrally mediated effects occurring independently of the HPA axis (Berridge and Dunn, 1989a). Other studies strengthening the link between CRF and anxiety include recent work by Kalin *et al.* (2000) demonstrating that a “fearful” phenotype in monkeys is associated with increased pituitary-adrenal activity and increased brain CRF levels. Other

studies have shown that exposure to early postnatal separation stress in rat pups results in elevated levels of CRF messenger RNA (mRNA) in brain regions including the paraventricular nucleus (PVN) and the central nucleus of the amygdala (Heim *et al.*, 1997; Plotsky and Meaney, 1993). CRF acts through two Gs-protein coupled receptors, the CRF-1 and CRF-2 receptor subtypes (Perrin and Vale, 2000; Dieterich *et al.*, 1997). CRF-1 receptors show homology to a number of other neuropeptide receptors, including vasointestinal peptide (VIP) and calcitonin (Perrin and Vale, 2000).



**Figure1. The role of corticotrophin-releasing factor (DeSouza and Grigoriadis, 1995)**

CRF-1 and CRF-2 receptors have different pharmacology and different localizations in the brain and periphery. In situ hybridization and receptor autoradiography techniques have been used to map the relative distributions of CRF-1 and CRF-2 receptors in the rat brain (Chalmers *et al.*, 1995; Primus *et al.*, 1997). High expression of CRF-1 receptors was seen in the pituitary, and in a number of brain regions including the PVN of the hypothalamus, cerebral cortex, olfactory bulb, cerebellar cortex, and basolateral and medial amygdala. In contrast, high densities of CRF-2 are found in more circumscribed regions, including the lateral septum, ventromedial nucleus of the thalamus, and choroid plexus. Moderate densities of CRF-2 receptors were reported for the medial amygdala and dorsal raphe nucleus (Sanchez and Young, 1999). CRF receptors utilize 3',5'-cyclic adenosine monophosphate (cAMP) as a second messenger in the pituitary and brain and can be regulated by chronic activation. Thus, desensitization following exposure to CRF has been demonstrated both in vitro (Dieterich *et al.*, 1966) and in vivo (Hauger and Aguilera, 1993). Furthermore, chronic stress can down-regulate CRF receptors and decrease CRF-stimulated cAMP production in multiple brain areas (Aguilera *et al.*, 1987; Anderson and Kant, 1993). Down-regulation of pituitary CRF receptors following adrenalectomy presumably results from decreased ACTH mediated inhibitory feedback, which produces excess CRF stimulation. There are a number of pharmacologic agents available for dissecting the functional significance of CRF-1 and CRF-2 receptors.

Much work has been carried out using the peptide antagonists  $\alpha$ -helical-CRF and D-Phe CRF. However, these compounds have shortcomings in that they do not penetrate the CNS and therefore have to be administered intracerebro-ventricular (icv). Furthermore, they do not discriminate between CRF receptor subtypes and therefore do not allow a determination of their relative contributions to behavior. More recently, the development of selective, nonpeptidic antagonists of the CRF-1 receptor such as CP 154,526 (Schulz *et al.*, 1996) have provided important pharmacologic tools for the analysis of CRF-1 receptor function. Mutation studies have demonstrated that peptide and nonpeptide antagonists bind to different domains of the CRF-1 receptor (Perrin and Vale, 2000). To date, selective CRF-2 antagonists have not been described, though recently, non peptide dual antagonists of the CRF-1 and CRF-2 receptors have been described (Luthin and Rabinovich, 1999). Studies utilizing transgenic and knockout mouse models have provided important information with regard to the contribution of CRF and CRF receptor subtypes to processes including energy balance, emotionality, cognition, and drug dependence (Contarino *et al.*, 1999). Over expression of CRF in transgenic mice produced anxiogenic effects using either the black-white box test (Heinrichs, *et al.*, 1997) or the elevated plus maze (Stenzel-Poore *et al.*, 1994). The latter effect was reversed by central administration of the CRF receptor antagonist  $\alpha$ -helical CRF, but not by adrenalectomy, supporting the role of central CRF pathways

independent of the HPA axis (Stenzel-Poore and Heinrichs, 1994). Studies using antisense directed against CRF in rats have produced evidence of anxiolytic activity (Skutella *et al.*, 1998). Finally, over expression of CRF-BP is anxiolytic, whereas binding protein knockout mice (in which free CRF levels are elevated) display an anxiogenic phenotype in the elevated plus maze (Ramesh *et al.*, 1998). These data generally support the link between CRF and anxiety.

More recently, several studies have highlighted the importance of the CRF-1 receptor subtype in anxiety. CRF1 knockout mice demonstrated a diminished anxiogenic response on the elevated plus maze and decreased ACTH and corticosterone responses to restraint stress (Smith *et al.*, 1999). Similar findings were reported, using the blackwhite box anxiety paradigm (Timpl *et al.*, 1998). Furthermore, inactivation of the CRF-1 receptor with an antisense oligonucleotide was shown to reduce the anxiogenic effect of intraventricularly administered CRF (Skutella *et al.*, 1998). Liebsch *et al.*, 1995 provided evidence of anatomic localization by showing anxiolytic activity from CRF-1 antisense that was chronically infused into the central nucleus of the amygdala, an area of the limbic system shown by Davis M, 1997; LeDoux J, 1996, and others to be important in mediating fear and anxiety processes. Finally, CRF-2 knockout mice show anxiety-like behavior and are hypersensitive to stress (Bale *et al.*, 2000), indicating that the CRF-2 receptor has an opposite functional role to that of the CRF-1 receptor. Thus, it could be argued that CRF-2 agonists, rather than antagonists, might be potentially useful as anxiolytic agents.

Another potential use for CRF antagonists is in the treatment of drug abuse. Several lines of evidence suggest that during the period of withdrawal from drugs of abuse such as ethanol, morphine, and cocaine, there is an activation of central CRF pathways. Anxiety is among the many physical symptoms of drug withdrawal, and given the link that has been made between CRF and anxiety, it is not surprising that CRF-1 receptor knockout mice demonstrated decreased anxiety responses during withdrawal from alcohol (Timpl *et al.*, 1998).

#### 6.4. Neurokinin Receptor Antagonists

There is an extensive literature demonstrating that the peptide tachykinins such as substance P and their associated receptors have a widespread distribution in the brain, spinal cord, and periphery, and may play important roles in chronic pain and inflammation processes (Otsuka and Yoshioka, 1993; Khawaja and Rogers, 1996; Longmore *et al.*, 1997; Mantyh *et al.*, 1989; Tooney *et al.*, 2000). In addition, anatomic and physiologic evidence has also indicated that these peptides limbic structures that are involved in the regulation of mood, such as the amygdala, hypothalamus, and periaqueductal gray (Culman and

Unger, 1995). This notion is supported by early positive clinical findings using a selective neurokinin-1 (NK-1) antagonist for the treatment of depression and anxiety (Kramer *et al.*, 1998). Tachykinins collectively refer to small peptides that include substance P (SP), neurokinin A (NK-A), and neurokinin B (NK-B). These peptides show preferential affinity for three receptors, designated NK-1, NK-2, and NK-3, respectively, which are members of the seven-transmembrane, G-protein-coupled family. Of these three receptors, NK-1 and NK-3 are found in the brain, whereas NK-2 is primarily localized peripherally in smooth muscle of the respiratory, urinary, and gastrointestinal tracts. Neurokinin receptors are localized in a number of different brain areas that are implicated in anxiety, including the amygdala, hypothalamus, and locus coeruleus.

Studies assessing the effects of direct administration of neurokinin agonists such as substance P into the nervous system are complicated by the findings that, depending on factors such as the site and dose, opposite effects on behavior may be achieved (Kramer *et al.*, 1998).

#### 6.5. Cholecystokinin B antagonists

Cholecystokinin (CCK) is a peptide found extensively both in the gut (where it was originally identified) and in the brain (Mutt and Jorpes, 1971). CCK exists in multiple forms, the most predominant of which is CCK octapeptide (CCK8) and, to a lesser extent, CCK tetrapeptide (CCK4) (Hokfel *et al.*, 1985). CCK is colocalized with a number of different neurotransmitters, including serotonin, dopamine, GABA, substance P, neuropeptide Y, and VIP. CCK-like immunoreactivity has been demonstrated in anatomic regions that include the amygdala, cerebral cortex, hippocampus, striatum, hypothalamus, and spinal cord (Emson *et al.*, 1982). There are two subtypes of CCK receptor, CCKA (sulfated CCK) and CCKB (unsulfated CCK) (Moran *et al.*, 1986). CCKA receptors are localized in the nucleus accumbens, posterior hypothalamus, and area postrema. CCKB receptors are localized in cortex, olfactory bulb, nucleus accumbens, and other brain areas (Pisegna *et al.*, 1992).

### 7. CONCLUSION

It can be concluded that anxiety is manifest by disturbances of mood, thinking, behaviour, and physiological activity and accompanying disturbances of sleep, concentration, social and/or occupational functioning. Also, it is associated with restlessness, feeling keyed up or on edge, being easily fatigued, difficulty in concentrating or mind going blank, irritability, muscle tension, and irritability. The etiology of anxiety may include stress, diabetes, depression, genetic, and environmental factors. Drugs to reduce anxiety have been used by human beings for thousands of years. The drugs were used to reduce anxiety, including the barbiturates and the carbamates



(meprobamate) drugs were used for treatment of anxiety in the first half of the 20<sup>th</sup> century and some continue to be used today. Anxiety disorders should be treated with psychological therapy, pharmacotherapy, or a combination of both.

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