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Review Article

Biomodulators of Anxiety

Preetham Elumalai*, Sreeja Lakshmi

School of Aquatic Food Products and Technology, Kerala University of Fisheries and Ocean Studies, Panangad, Kochi, Kerala, India

Email address:
epreeth@gmail.com (P. Elumalai)

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Abstract: Anxiety is a feeling of unease which everyone feels at some points in their lives. Anxiety becomes a disorder when the symptoms become chronic and interfere daily lives, including behavioral patterns and adaptations. Anxiety disorders come in many forms - Generalized Anxiety Disorder, Panic and Post-traumatic Stress disorders, Obsessive Compulsive Disorders, Social Anxiety Disorders and various Phobias. The state of anxiety is modulated by a multifarious and complex series of biomodulators of the categories, neurotransmitters, peptides and hormones comprising serotonin, norepinephrine, Gamma-Aminobutyric acid (GABA), cortisol, Corticotropin Releasing Factor (CRF), Acetylcholine and many more. The article reviews the anxiogenic and/or anxiolytic functions of selected biomodulators in maintaining anxiety related behaviours.

Keywords: Anxiety, GABA, Serotonin, Norepinephrine, HPA Axis

1. Introduction

Anxiety and depression are strikingly ramping up with today´s life than older times, ranging from students to adults to older people, regardless of gender. Anxiety is a natural human emotion which everyone experiences at times. It is signatured in several psychic problems as one of the behavioural manifestations of stress characterized by an abnormal arousal, hypervigilance, avoidance and fear.[1, 2] A quite nice explanation for anxiety is given by Rachman, that anxiety tends to be pervasive and persistent with uncertain points of onset and offset.[3] Besides, it is a dangerous face, anxiety is often a beneficial behavioural strategy and an adaptive response to meet the demands of any challenging situation. It can be considered as a harmless behavioural pattern of normal day-to-day life. When ´normal´ anxiety becomes chronic, disproportionate and even starts to interfere with the routine of the individual, it will end up in manifesting anxiety disorders.[4] Even if anxiety disorders are prevailing worldwide, they are the most common mental illnesses in the United States[5] and as per a survey of adults conducted by the National Institute of Mental Health, about 40 million adults in the US are suffering from anxiety disorders. Past many decades have seen several fruitful investigations to unveil various strategies for diagnosis and treatment practices for anxiety disorders. This article reviews potential roles of selected biomodulators on different types of anxiety disorders.

2. Characteristics of Clinical Categories of Anxiety

Several recognized anxiety disorders prevail in our society, like Generalized Anxiety Disorder, Panic and Post-traumatic Stress disorders, Obsessive Compulsive Disorders, Social Anxiety Disorders and various Phobias[6] (Figue 1). If chronic worry characterizes generalized anxiety disorders, then overwhelming fear contributes the Panic disorders. Recalling past stressful experiences result in post-traumatic stress disorders. Intrusive and distressing compulsions and obsessions make Obsessive Compulsive Disorder, a chronic psychiatric illness.[7] Persistent fear of public performance/appearance triggers social anxiety disorder. Strong fear for specific things or situations, such as snakes, flying, social encounters, etc. elicits phobias. [6]

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) released by the American Psychiatric Association serves as a reference for providing information regarding the categories of mental disorders with their degree of severity followed by various diagnostic tools.

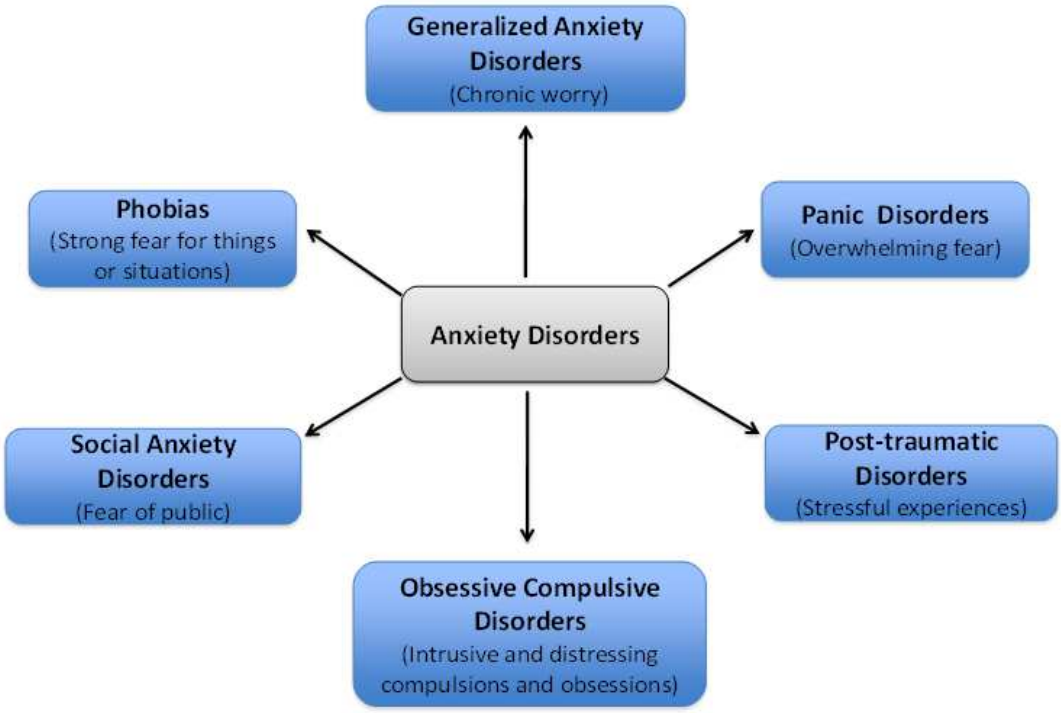

Figure 1. *Six major types of anxiety disorders, Generalized Anxiety Disorders (GAD), Panic Disorders (PD), Post-traumatic Stress Disorders (PSD), Obsessive Compulsive Disorder (OCD), Social Anxiety Disorder (SAD) and Phobias, with highlighted symptoms.*

3. Anxiety Disorders

3.1. Generalized Anxiety Disorder (GAD)

GAD is characterized by chronic worry and lack a clear reason for getting excessively anxious.[6] It is mostly seen in women than men, with the onset around the age of 25. GAD is always accompanied by major depression.[8] DSM-5 criteria for GAD also supports the presence of excessive anxiety and worry, which seems to be highly challenging to control. Along with a heightened state of worry and anxiety, GAD patients also suffer from restlessness, fatigue, muscle aches, sleeping difficulty, making their day-to-day life much harder.[9] GAD is one among the most common anxiety disorder seen in older people of residential aged care centers.[10]

3.2. Panic Disorder (PD)

PD results from overwhelming fear as a consequence of unexpected and spontaneous panic attacks. Other signs may include tachycardia, trembling, chest pains, unexpected panic attacks, intrusive thoughts, fatigue, etc.[6, 9]

3.3. Post-Traumatic Stress Disorder (PTSD)

Insistent recall of threatening or traumatic experiences such as natural disasters, sexual assaults, terrorist attacks, accidents etc., trigger PTSD. Hyperarousal, cognition and mood alterations and avoidance characterize PTSD. Depression, panic disorder, substance or alcohol abuse along with medical conditions like diabetes, dementia and cardiovascular diseases accompany PTSD as well.[11] Unlike the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4), DSM-5 moved PTSD from the group of anxiety disorders and placed under a new section titled ´Trauma and Stressor-Related Disorders´, with the diagnostic criterion being exposure to traumatic or stressful event. Three clusters of DSM-4 symptoms of PTSD are divided into four clusters in DSM-5 - intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity.[9]

3.4. Obsessive Compulsive Disorder (OCD)

OCD is a mental disorder where people are unable to control their intrusive and distressing obsessions or repetitive physical (like handwashing, checking) or mental acts (like praying, counting, silent repetition of words). The condition is even associated with an increased risk of suicide.[6, 9] OCD is comorbid with other psychiatric disorders like body dismorphic disorder, hoarding disorder, trichotillomania and skin excoriation disorder. Eczematous eruptions due to excess handwash, hair loss due to trichotillomania (compulsive hair pulling) and excoriations related to compulsive skin picking are some of the skin lesions associated with OCD.[9]

3.5. Social Anxiety Disorder (SAD)

Extreme fear of public characterizes SAD.[6] It can be a fear of being (negatively) judged by unfamiliar people in social or performance situations. The situation provokes anxiety which may result in panic attacks. DSM states that the fear, anxiety

and avoidance may persist for 6 or more months.[9] SAD is among the most common psychiatric disorders and it begins in the early teenage years.[12]

3.6. Phobia

A phobia is a class of anxiety disorder featured by persistent fear for a thing (animals, environment, etc.) or situation (public speaking, crowd). A phobia is found to have a significant impact or interference on affected people with their social or occupational activities.[13]

4. Epidemiology, Causatives and Brain Circuits of Anxiety Disorders

According to epidemiological studies, social anxiety disorders (lifetime prevalence rates ranging 75-12%) are more common of all anxiety disorders where anxiety and depression form the frontline.[14] It has been shown that an approximate of 30% of the total emotional imperfections are associated with anxiety disorders and women are on top rather than men in suffering the same at an age of 20-35 years. During perinatal period, higher occurrence of obsessive compulsive disorder and generalized anxiety disorder are seen in postpartum women.[14, 15]

Various elements take part in anxiety development. Anxiety can be a combination of nature (genetic) and nurture (environment) - heriditability and familial environments contribute to anxiety disorders on an even keel. Stressful life events play a critical role in predisposing anxiety disorders. Childhood browbeat contributes to social phobia which can continue to adulthood.[16] Personality constructs also can be a significant forecaster in developing anxiety disorders, like people with feeling of poor self-esteem and skills, seems to be easily susceptible to anxiety disorders. Post-traumatic stress disorders and generalized anxiety disorders are strongly influenced by personality variations.[17, 18]

In mammalian species, major brain circuits involved in fear and anxiety are, amygdala, hypothalamus and periaqueductal gray (PAG). A circuit from amygdala through hypothalamus down to PAG evokes the execution of fear and anxiety.[19] Amygdala was considered as major site of action of anxiolytes since it has been identified as the centre of events modulating the fear expression.[20] On the other hand, prefrontal cortex (PFC) analyzes the complex situations and modulates the physiological, neuroendocrine and behavioural responses which result in extinction of fear and anxiety related activities.[19, 20] Apart from these findings, a direct correlation between anxiety and hippocampus has been explored. Even though hippocampus is relevant for its coreplay in modulating memory, the synergy of ventral hippocampus, amygdala and hypothalamus is opened up in anxiety related situations. It has been shown that the lesions made in ventral hippocampus result in reduction of anxiety like behaviour in rodents which is unseen in dorsal hippocampus with the similar manipulation.[4, 21]

5. Biological Modulators of Anxiety

Symptoms associated with the anxiety disorders controlled by specific brain areas can be affected by neurochemical and neuropeptide systems. These systems either positively or negatively regulated by facilitatory or inhibitory mechanisms. In accordance, the main targets of anxiolytes will be obviously the brain networks involved, which even promotes the pharmaceutical interventions for curing anxiety disorders through drug therapy. A vast array of multifarious and complex modulators comprising hormones, neurotransmitters, peptides and other neuromodulators are involved in fear and anxiety behavioural patterns. The article brings few representatives of biomodulators and their roles to prevent the maladaptivity of emotional intervenes:

5.1. The Noradrenergic System

Noradrenalin (NA) has roles in vigilance, sleep along with memory and attention. Previous clinical as well as animal studies indicated an increased NA release to hypothalamus, amygdala and the locus ceruleus (LC) following stress and anxiety. A α_2- adrenergic receptor antagonist, yohimbine, is found to increase the NA levels owing to its anxiogenic effects, in animal models and in Post-traumatic stress disorders (PTSD).[22] This shows the link between adrenergic signalling abnormalities with PTSD.[23] Administration of Propranolol, a β-adrenergic receptor antagonist showed combined results in both clinical and animal models. In line with this, one could assume the contradiction existing among the various NA receptors in the mediation of NA action on anxiety behaviors, even though it needs a more cemented disclosure. A recent study has observed changes in extracellular NA levels in mouse models of PTSD, as NA neurotransmission in the forebrain resulted in arousal and contextual fear one month after trauma.[24]

5.2. The Serotonergic System

Serotonins one among the hub of significant neurotransmitters influencing mental health. Mostly being distributed outside the central nervous system (CNS), 2% of serotonin in CNS owe key role in the etiology of mental disorders. Both the receptor and transporter of serotonin functions in synapses, where serotonin neurotransmitters activate 5-hydroxytryptamine (5-HT) receptors and 5-HT transporters uptake serotonin neurotransmitter from the synaptic cleft. Mental disorders like Major Depressive Disorder (MDD), is influenced by the altered serotonin receptor/transporter (SERT) function.[25] A correlation between abnormalities in serotonergic system have found in social anxiety disorders. The Higher level of SERT was reported in patients with social anxiety disorder in response to paroxetine, a selective serotonin re-uptake inhibitor (SSRI).[25] SSRIs are found to improve OCD and PD in pregnant women without any side effects for the babies. Thus SSRI forms the Frontline treatment practice for anxiety disorder in the perinatal period.[26] Reduced serotonin-1A receptor binding is found in amygdala and mesofrontal areas

of social anxiety disorders and at the same time, increased serotonin transporter binding is found in psychotropie medication naive patients with generalized social anxiety disorder.[27, 28] In parallel, 5-HT_{1A} receptor knockout mice displays anxiety–related behaviours, but, in contrary, 5-HT_{1B} receptor knockout mice seems to be less anxious and more aggressive.[19] Even though there are many studies which explore the relation between serotonergic system and anxiety disorders, some are totally inconclusive.

5.3. The GABAergic System

γ-Aminobutyric acid (GABA) is the most predominant inhibitory neurotransmitter in the CNS. 2 distinct classes of GABA receptors control neuronal inhibition by GABA. Ionotropic $GABA_A$ receptors exert rapid inhibition and metabotropic $GABA_B$ receptors stand for slow and prolonged inhibitory responses. GABAergic neurons perform a pivotal role in the amygdala in modulating anxiety. GABA agonists have anxiolytic properties and on the flip side, GABA antagonists exert anxiogenic effects.[29] Benzodiazepines, neuroactive steroids, and barbiturates act as allosteric modulators of the $GABA_A$ receptor, β-carboline and the barbiturates function as direct GABA agonists. $GABA_A$-benzodiazepine receptor play key role in anxiety related behaviours and it seems to be the main focus of anxiolytic drugs.[19]

5.4. Hormones of Hypothalamic-Pituitary-Adrenal (HPA) Axis

Older adults at an age of 60 and above are easily vulnerable to the brain defects resulting in cognitive and emotional disruptions. One among the many contributors for this phenomena is the overactivation of HPA axis exerted by the toxic effect of high levels of cortisol (40-70%). As aging progresses, modulation of HPA axis by the prefrontal cortex will get weaker and more cortisol is produced which in turn results in the development of anxiety and negative emotions. The back-up strategies defending the deleterious effects are less functional and the dark side of cortisol is highlighted. Older adults normally face GAD where high levels of cortisol is also seen.[30, 31] It has been studied that cortisol in late-life GAD can be reduced by the SSRI treatment.[30] Aging is prone to neurodegenerative disorders like Alzheimer´s, Parkinson´s and Huntigton´s diseases and if the treatment practices correct the HPA axis dysfunctions, late life anxiety can be reverted to an extent, even though it needs more studies to get cleared.

Corticotropin Releasing Factor (CRF), a 41 amino acid peptide, selectively activate adrenal corticotropin releasing hormone (ACTH) secretion. The role of CRF in anxiety related behaviours and stress has already been studied.[32] CRF is involved in modulating a number of neurotransmitters such as dopamine, serotonin, norepinephrine and hence implicated in anxiety behaviours. Two G-protein coupled receptors, CRF1 and CRF 2 are mediating the actions of CRF. High levels of CRF are often observed in PTSD and panic disorders. CRF 1 antagonist, antalarmin, was found to reduce anxiety like symptoms and thus CRF1 receptor serve as a potent target for pharmaceutical therapy to treat anxiety disorders.[33]

5.5. Acetylcholine

Nicotine facilitates anxiolysis by increasing the level of acetylcholine on intake of acetylcholine esterase inhibitor, physostigmine as well as through GABAergic neurons.[20] Nicotine also modulate specific nicotinic acetylcholine receptors (nAChR) in brain, like the α4β2-nAChR for the extinction of anxiety.[34] A recent study has unveiled the fact that the dopaminergic α4-nAChRs are involved in exerting anxiolytic property of nicotine.[35]

5.6. Atrial Natriuretic Peptide (ANP)

ANP is a 28 aminoacid peptide synthesized and secreted by heart and functions as a key regulator of fluid and electrolyte homeostasis. The impact of ANP on anxiety, stress and craving in alcoholics has been demonstrated. Patients underwent alcohol withdrawal showed decreased levels of ANP and increased craving compared to those with high ANP levels. Plasma ANP concentration and anxiety are inversely proportional. Patients with low ANP level during alcohol withdrawal suffer an increased state of anxiety. It was also suggested that perceived stress mediates the relation between plasma concentration of ANP and craving in alcoholics.[36] The anxiolytic activity of ANP in elevated plus maze test has been studied by the administration of both ANP as well as astriopeptin II, an amino acid residue peptide of ANP.[20]

5.7. Cholecystokinin (CCK)

CCK is one of the most abundant neuropeptide in the brain. Two types of receptors of CCK are present- CCK- A (CCK-1) and CCK-B (CCK-2). CCK–A receptors are more abundant in the periphery than in the brain, on the other hand CCK-B is richly localized in the brain. It has been shown that upon activation, CCK-B receptors in basolateral amygdala are capable of eliciting anxiety and CCK-B antagonists reverse the situation.[37]

5.8. Cannabinoids

Cannabinoids are a class of plant (*Cannabis sativa*) derived compounds, acting via Cannabinoid type 1 receptors (CB1), targeting endogenous ligands, endocannabinoids. They cause interference in the transmission of GABA in the amygdala, hippocampus and frontal cortex as well as reduce the circuit of glutamate, NA and dopamine in hippocampus.[6] Low dose of cannabinoids is anxiolytic whereas high doses generate anxiogenic like behaviours. Anxiogenic effects are observed in the case when CB1 receptors are deleted.[38] More studies are needed to understand the dual role of cannabinoids towards anxiety and to highlight endocannabinoids as targets of drug therapy.

Apart from the above mentioned mainstream neurobiomodulators of anxiety, several other peptides, neurotransmitters and hormones play roles in fear and anxiety

related behaviours - like Neuropeptide Y, galanin, melatonin and melanin concentrating hormone, Tachykinins, substance P, etc. Decreased secretion of Leutinizing hormone and testosterone is observed in males following anxiety. Injection of inhibitors of Nitric oxide synthase (NOS) in PAG exerts anxiolytic effects bringing the role of nitric oxide out in defense mechanisms.[6, 19]

6. Synergy Amongst Gut Flora and Anxiety

Recent researches came up with an interesting correlation revealing the role of the intestinal microbiota as the key players in the gut - brain axis. Living organisms contributing to the health of the host by inhabiting the gut are termed probiotic bacteria. Clinical trials have already suggested the role of probiotics in improving mood and anxiety symptoms in patients with bowel syndrome.[39] A related study has shown that *Lactobacillus rhamnosus* reduce the level of stress induced corticosterone and anxiety related behaviours through GABA receptor expression. The study also identifies vagus as the communicative pathway between gut bacteria and brain.[40] In parallel, anxiolytic effect of the probiotic, *Bifidobacterium longum* NCC3001 was also studied in mice with colitis. The probiotic was found to normalize anxiety-like behaviour and the level of hippocampal brain derived neurotrophic factor (BDNF).[41] In another mice experiment *Bifidobacterium* was found to reduce the stress hormones and increase the perseverance of the animal.[42] The studies show the profound influence of intestinal health on brain health; that our diet is so close to maintain the brain health. Diet rich in n-3 polyunsaturated fatty acids (Eicosa pentanoic acid and docosa hexanoic acid) reduce anxiety like behaviours and provide new hope for psychic disorders.[43] The potential candidature of natural products is also supported by the identification of Lavendula Angustifolia as a source of anxiolytic drugs which have been proved clinically.[44] It carries extreme interest and importance to know that Yoga is included as a treatment strategy for PTSD, GAD, depression and substance abuse.[45]

7. Conclusion

Mental health problems, a growing issue in modern society, makes one´s life quite dissatisfactory in all respects. Each one of us will experience one or other types of mental stress in different forms and intensities. Some consider these as personal failures and remain reluctant to face proper diagnosis followed by medications. It is important to follow clinical strategies and pharmacological interventions in order to drive away long held doubts and dogma. Anxiety is a normal response to potential threats, regardless of age. Anxiety puts one´s own personality to a heightened state of awareness. When felt inappropriate or uncontrolled, the stage will end up to anxiety disorders, with high prevalence in our society and has an increased risk of self-injurious behavious, even suicide. Neuroimaging, genetic, psychopharmacologic and psychotherapeutic studies are heading to increase the efficasy of treatment practices for anxiety disorders. Several biomodulators perform key roles in modulating anxiety and related behaviours comprising neurotransmitters, hormones and peptides. As current stressy day-to day life compell us to rely mostly on remedies from natural resources, practising lifestyle factors like diet and regular exercise will enable us to keep distance from anxiety disorders and to build an abode of positivity.

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