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Hanumantharayappa B
Associate Professor,
Department of Pharmacology,
Mallige College of Pharmacy,
Bangalore, Karnataka, India

Priyanka N
Department of Pharmacology,
Mallige College of Pharmacy,
Bangalore, Karnataka, India

Corresponding Author:
Hanumantharayappa B
Associate Professor,
Department of Pharmacology,
Mallige College of Pharmacy,
Bangalore, Karnataka, India

Peripheral and neuroimaging biomarkers of anxiety disorders

Hanumantharayappa B and Priyanka N

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Abstract
Anxiety disorders are complex psychiatric conditions characterized by excessive fear, anxiety, and avoidance behaviours. Despite their high prevalence and burden, anxiety disorders remain poorly understood, and diagnosis relies heavily on clinical interviews. Recent advances in peripheral and neuroimaging biomarkers offer promising avenues for improving diagnosis, treatment, and understanding of anxiety disorders. Peripheral biomarkers, such as cortisol, inflammatory cytokines, and neuropeptides, have been shown to be altered in anxiety disorders. For instance, elevated cortisol levels and altered cortisol awakening responses have been observed in individuals with anxiety disorders. Neuroimaging biomarkers, including functional magnetic resonance imaging and diffusion tensor imaging, have revealed altered neural circuitry and connectivity in anxiety disorders. Studies have implicated the amygdala, hippocampus, and prefrontal cortex in the pathophysiology of anxiety disorders. Abnormalities in these regions, including altered volume, activity, and connectivity, have been linked to symptom severity and treatment response. This comprehensive review aims to summarize the current state of knowledge on peripheral and neuroimaging biomarkers in anxiety disorders.

Keywords: Anxiety, neuropeptides, neurotransmitter, neurotropic factors, neuroimaging biomarker

Introduction
Anxiety disorders are the most commonly reported mental disorders [1]. The prevalence of anxiety disorders, ranges from 3.8% to 25% globally [2]. The autonomic nerve system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis are activated by stress and anxiety, which results in physiological changes that affect hormone levels. These alterations are particularly apparent in symptoms of chronic anxiety [3]. According to research, up to 50% of afflicted individuals do not have their anxiety problems diagnosed by the frequently used questionnaires [1]. It has been shown over the years that these illnesses are significantly under diagnosed and that treating them can be challenging [4]. Finding biomarkers that highlight the pathophysiology of anxiety disorders is one of the contemporary approaches to the problem that will make diagnosis easier and provide a deeper comprehension of the illness [1]. There has been a recent movement to classify mental illnesses using objective criteria, like biological markers [5]. There are different types of anxiety disorder like panic disorder, generalized anxiety disorder, social anxiety disorder, post-traumatic stress etc. [1]. A biomarker is a characteristic that can be precisely tested and evaluated to show the biological response to treatment or to normal biological and pathological processes [6]. In fact, biomarkers have become indispensable tools in a number of clinical domains, particularly cardiovascular and cancer medicine, ensuring greater accuracy and customization of diagnostic procedures and therapeutic interventions [7]. There are certain difficulties with using biomarkers in psychiatry, the first of which is the restricted access to the central nervous system in patients who are still alive [8]. The potential biomarkers are used in anxiety disorders are peripheral biomarkers, neuroimaging, neurochemical studies [9]. These possible biomarkers might also be useful for tracking how well pharmaceutical treatments for anxiety disorders are working [1]. Blood may be one of the most promising peripheral biomarkers since blood is easily accessible and several neurotransmitters, neuropeptides, and neurotrophic factors are transported through the blood-brain barrier and into the peripheral circulation. These biomarkers may reflect the biological mechanisms of the central nervous system [10].

Furthermore, a variety of systems, including the immune system and the hypothalamic-pituitary-adrenal (HPA) axis, are implicated in the pathophysiology of anxiety disorder. Peripheral sampling, such as that of blood, saliva, urine, or hair, can identify possible changes underlying these systems [11, 12]. These review aims to know the knowledge on peripheral and neuroimaging biomarkers in anxiety disorders.

Peripheral biomarkers

Peripheral biomarkers are substances that can be measured in the blood, saliva, or other bodily fluids and may reflect the pathophysiology of a condition like anxiety disorder [11]. In accompany these conditions, although no biomarker has yet been fully validated for routine clinical use [8].

- **Salivary:** Saliva appears to be becoming more common in laboratory diagnoses because it is inexpensive and non-invasive [13]. Many chemicals found in saliva can be utilized to quickly and easily identify the main clinical symptoms in people. Their concentration reveals the health of the entire body [14]. Immunological and biochemical methods include spectrophotometry, chromatography, enzyme immunoassay (ELISA), and radioimmunoassay (RIA) are sensitive and specific methods for controlling saliva components [15], correlation between salivary levels of cortisol, immunoglobulin A, lysozyme, melatonin, alpha-amylase, chromogranin A, and fibroblast growth factor 2 in saliva [16].
- **Cortisol:** Prolonged stress and elevated cortisol production also cause a number of alterations in the serotonergic system [17] these endocrine system alterations are linked to the pathophysiology of anxiety [18]. One of the chemical (saliva, blood) that is frequently utilized as a stress indicator is cortisol [19].

According to the meta-analysis, biomarker for acute stress, cortisol in saliva consequently, these studies demonstrated a reduction in morning salivary cortisol levels as well as a reduction in the stressors' relative intensity [20]. The HPA axis is thought to become less sensitive after extended stress, which impacts fatigue and, in turn, lowers the adrenal glands production of cortisol [21]. The findings of a study including individuals with chronic anxiety problems support this idea, showing that their cortisol production was lower than that of healthy controls [22].

Inflammation and immune system: Numerous studies have documented how the defence and inflammatory mechanism contribute to the pathogenesis of anxiety disorder [23]. Possible indicators of inflammation, such as antibodies and cytokines like interleukin (IL) and interferon (IFN), have been studied, indicating their potential use as indicators in the diagnosis of anxiety disorders [24], with the body mass index accounting for the majority of the association behind the existence of a shared pathophysiological mechanism between inflammatory medical diseases and anxiety, lifestyle played a significant impact [25]. Their close ties to the stress response mechanisms controlled by the autonomic nervous system and the HPA axis provide one reason for the elevated inflammation seen in anxiety disorder. Via adrenoceptors on immune cells, norepinephrine and epinephrine directly control inflammation and cytokine release [26]. Another indicator that has been thoroughly studied in psychiatric illnesses is oxidative stress, which is made up of many processes controlling the equilibrium between Reactive Oxygen Species (ROS) [27]. Modified oxidative processes could also account for the pathophysiology of mental illnesses and explain how anxiety disorder and other inflammatory based illnesses overlap [28]. When combined, the evidence from the literature show that inflammation plays a vital role in the evolution to upkeep anxiety disorder. but, elevated inflammation can be observed in other mental illnesses, such as depression, and is not exclusive to these ailments [29].

Oxytocin: It is the neuropeptide that the hypothalamus produces, oxytocin, controls the activity of several different parts of the brain, including the striatum, cingulate cortex, amygdala, hippocampus, and ventrolateral septum [32], OT also plays other significant peripheral roles, such as milk ejection and muscular contraction during delivery [34]. Anxiety, stress modulation, fear learning and extinction are all significantly impacted by OT central activity, which is mediated via the amygdala and the anterior cingulate [35]. Researchers have looked into OT function in several Ads [36]. There has not been much research done on the oxytocinergic system in GAD sufferers [37], but by lowering excessive HPA activity, encouraging relaxation, and inhibiting cortisol release, oxytocin helps GAD patients cope with stress [38]. One of the main symptoms of GAD is serotonin dysregulation. Oxytocin works with the serotonin system to improve mood and lessen overthinking [39]. It has been highlighted that OXT plays a part in panic disorder by impacting dysregulated neural panic networks through enhanced top-down rationalization and threat processing [40]. One possible explanation for this could be that increased OXT secretion is an inadequate compensatory effort to lessen the sensations of social anxiety [39].

Cholecystokinin: CCK is an important factor in anxiety disorders is the gut hormone. Although it is most recognized for its role in digestion [41], it also functions as a neurotransmitter and neuromodulator in the brain, interacting with the cholecystokinin (CCK) receptors, CCK-A (found primarily in the gut) and CCK-B (found abundantly in the brain) [42]. These CCK-B receptors are involved in fear and anxiety regulation, [43] A powerful panicogenic substance, CCK-4 (a peptide fragment of CCK) can cause panic episodes in anyone, even those without anxiety disorders [44]. Elevated CCK activity in the prefrontal cortex and amygdala is linked to increased anxiety responses [45] the amygdala is a crucial brain area in fear processing and has a high concentration of CCK [46]. The effects of CCK vary depending on the anxiety disorder; in panic disorder, cholecystokinin plays a significant role, as CCK-4 injection can reliably induce panic attack [47] and in GAD-CCK involvement is minimal but increases baseline anxiety [48].

Neuropeptide Y: A 36-amino acid peptide, neuropeptide Y(NPY) is a member of the pancreatic polypeptide family, which also contains pancreatic polypeptide(PP) and peptideYY(PYY) [49]. It is a neurotransmitter that is present in the brain, specifically in the areas that are essential for processing emotions and controlling stress like the amygdala, hippocampus and hypothalamus [50], where it

involved in stress resilience and emotional regulation [51] where these NPY receptors are present in brain up to five (Y1, Y2, Y4, Y5, Y6) of the seven distinct Y receptors (Y1-Y8) that have been identified in vertebrates so far are found in mammals [52]. Although the Y1, Y2, Y4, and Y5 receptors are present in all animals, the Y6 receptor is absent in humans and other mammals, and it has been eliminated in rats [53]. Similar to NPY, the Y1 and Y2 receptors are found in many different parts of the brain, including the lateral septum, ARC, and frontal cortex [54, 55]. The Y5 receptor is expressed in a number of limbic brain regions, although fewer than the Y1 or Y2 receptors, whereas the Y4 receptor is limited to a small number of brain locations, such as the medial preoptic area and PVH [56]. A unique aspect of the stress response is elevated anxiety, with NPY-mediated anxiolysis counteracting the anxiogenic impact of CRH [57]. According to several research, the Y1 receptor is the primary mediator of NPY's anxiolytic action. For example, ICV injection of a selective Y1 receptor agonist is anxiolytic, but intraamygdalar treatment of the Y1 receptor antagonist BIBP3226 is anxiogenic [58, 59]. So, these are the potential therapeutic targets of anxiety disorders. Research indicates that individuals with lower levels of NPY are more susceptible to stress and anxiety-related disorders. Conversely, higher levels of neuropeptide Y are associated with increased resilience to stress and reduced risk of developing Ads [60].

Ghrelin: It is neuropeptide that largely affects food intake but also affects mood, anxiety, and emotions [61] ghrelin has been shown to cause anxiety in a number of investigations [62]. When the HPA axis is activated and anxious behaviours are determined by elevated ghrelin secretion under stressful circumstances [63] and a recent investigation on the levels of ghrelin and leptin in kids with ADs, including GAD, revealed that girls had greater compared to the HCs, but not in boys [64]. Adipose-derived peptide hormone leptin primarily controls energy balance but also affects a number of central nervous system processes, including mood and anxiety management, memory, and learning [65]. There have been conflicting reports on leptin's anxiolytic properties. HCs and children with GAD, SAD, and separation anxiety did not differ in circulating levels, according to Ozmen and colleagues [64] but numerous other research have shown that individuals with psychological stress and anxiety had higher levels of leptin [66].

Neurotransmitter: It has long been believed that the pathophysiology of ADs is significantly influenced by the monoaminergic system serotonin (5-HT), dopamine (DA), epinephrine (E) and norepinephrine (NE) [67]. The autonomic nerve response directly causes anxiety symptoms, and NE is a crucial neurotransmitter that is typically linked to elevated norepinephrine metabolism and activity [10, 68]. Research has shown that compared to healthy controls, GAD patients have less platel*et al*pha 2 adrenergic receptor binding sites [69], patients with PDA showed abnormal changes in blood pressure, cortisol levels, plasma NE metabolites, anxiety measures, and somatic symptoms, but not those with GAD [70]. In contrast to other ADs, these results demonstrate clear abnormalities in GAD patients NE; these variations may be connected to the previously described functional distinction between anxiety and fear disorders [10]. 5-HT predicts ADs, and it comes from two primary systems and sources: threats mediated by the amygdala, which are likely associated with the feeling "anxiety", which is prominent in OCD and GAD [71], numerous peripheral organs contain 5-HT receptors additionally most 5-HT is generated outside of the central nervous system. 5-HT receptors are easily accessible and show up in blood cells like platelets and lymphocytes and some characteristics of central nervous system mechanisms that can be tracked by assessing peripheral parameters [72]. According to a study, individuals with GAD had lower platelet 5-HT reuptake binding densities than healthy controls (HCs). However, this discrepancy was also noticed in PDA patients, therefore it is not unique to GAD [73]. In contrast, a different study found no changes in the density or affinity of platelet 5-HT reuptake binding sites across GAD, PDA, and HCs [74], a different study that evaluated the HCs and GAD patients did not differ in their 5-HT transporter binding density and affinity expressed on lymphocytes [75]. Additionally, the impacts of neurotransmitter modulations have been studied. Clinically remitted AD patients were studied using an acute tryptophan depletion method that temporarily reduces brain 5-HT [76], Stressors did not cause psychological exacerbations of anxiety symptoms in GAD patients, but they did in PDA and SAD patients [76]. The primary inhibitory neurotransmitter system is GABA [77], experimental research from preclinical and clinical settings confirmed the connection between AD etiology [78]. The positive clinical response to BDZs, which affect the GABA system, further supports this findings [79], Subjects with GAD have been found to have less peripheral BDZ binding sites (translocator protein) on their platelets and lymphocytes than HCs [79-81].

Neurotropic Factors: Particularly, the brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), fibroblast growth factor-2 (FGF2), glial cell-line-derived neurotrophic factor (GDNF), neurotrophin-3, neurotrophin-4, and artemin all showed distinct roles in the pathophysiology of Ads [23].

Brain-derived Neurotropic Factor (BDNF): It is a neurotrophin (NT) that helps neurons in the central and peripheral nervous systems proliferate, survive, and differentiate [82]. BDNF is found in the bloodstream and comes from a variety of sources, including platelets and brain tissue, even though it is more concentrated in brain tissue [83], it has been shown to be able to pass through the blood-brain barrier [84]. It has been believed that BDNF has a role in the development of ADs and depression. Thus, BDNF may control the hypothalamus-pituitary-adrenal (HPA) axis through transmitter systems, which in turn control the response to stress [85]. BDNF protein levels were found to differ between individuals with and without anxiety disorders in six out of the eight included studies, patients with anxiety disorders had lower levels of BDNF (both serum and plasma) than those without the disease, with effect sizes varying from moderate to high [86]. But in PTSD and OCD studies were the only ones that included subgroup analysis of the various anxiety disorders. The OCD studies showed that patients had significantly lower BDNF levels than controls, whereas the PTSD subgroup analysis did not show any group differences in BDNF levels [87, 88]. An Italian study revealed that GAD patients had similar serum BDNF levels as HCs; however, if only females were

examined, the BDNF level was considerably lower [89]. The idea that only females with several forms of ADs have changed serum BDNF is somewhat supported by this gender influence [90] however, the cause of the gender-specific correlation between lower BDNF levels in female GAD patients is still unclear and needs more research [89]. When GAD patients were treated with paroxetine, Shen and colleagues found that their baseline plasma BDNF levels were greater than those of controls, and that these levels returned to normal following GAD remission [91]. Further research is necessary to determine the etiology of the gender-specific association between decreased BDNF levels in female GAD patients [90]. Moreover, compared to HCs, the cord blood of children born to women with GAD had higher levels of BDNF than those of healthy women. GAD patients with MDD had doubled levels of BDNF and artemin, a member of the glial cell line-derived neurotrophic factor family [92, 93]. A meta-analysis revealed that GAD patients had GDNF downregulation, but the difference from HCs was not as great as it was for the BDNF level [94].

Nerve growth factor (NGF): Neuropeptide that controls whether certain target neurons develop, maintain, proliferate, and survive [95]. A genetic variant of NGF was shown to be associated with trait anxiety in a sample of healthy individuals [96], though its function in AD patients has not been well studied, a decrease in NGF has been regularly observed in depressed participants [97] according to a study, patients' and controls' baseline NGF serum levels were comparable. But following a successful course of CBT, (the patients' NGF serum concentrations increased significantly after treatment, from 22.23±4.19 before treatment to 9.41±6.87 (p<0.0001) after treatment), which may indicate a changed stress reaction and potentially contribute to a positive therapeutic response with CBT [98]. Salles and colleagues looked into the potential link between NGF and mental illnesses, however they found no discernible variations in PDA patients' serum NGF levels [99].

Neuroimaging biomarker

The discovery of the structural and functional neuroanatomy of anxiety disorders has been made possible in large part by neuroimaging techniques [100], such as single photon emission tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and high-resolution magnetic resonance imaging (MRI) [101]. The area of the brain where anxiety disorders are pathophysiologically linked (e.g., amygdala, anterior cingulate cortex (ACC), insula, hippocampus etc.) [102] these days, there is a wealth of evidence linking the volumetric changes of various brain structures to mental illnesses [103]. For example, PTSD is linked to a smaller hippocampus, and obsessive-compulsive disorder (OCD) is linked to abnormalities in the orbitofrontal-striatal-thalamic circuitry [104]. There are numerous studies on neuroimaging biomarkers of anxiety disorders, including connectivity, structural, and functional modalities (MRI, fMRI, etc.) [105].

Structural neuroimaging studies: Involvement in threat evaluation and the fear response, the amygdala is most prominently linked to Ads [106], methodological variations hamper research on amygdala size in relation to social anxiety that yields conflicting results. For instance, it appears to matter if they use an a priori region of interest (ROI) method or a whole-brain approach. Regarding amygdala volumes, the majority of research has shown non-significant results [107] to check brain size have used voxel-based morphometry, or VBM, a whole-brain technique, to compare the anatomical differences between people who are socially anxious and those who are not [103]. In SAD: reduced amygdala volume has been observed in individuals with social anxiety disorder, particularly in the left amygdala[108] and abnormal shape has been observed in individuals with SAD, particularly in the anterior and posterior region of the amygdala [107]. But in one studies shown differently, those who were socially apprehensive had larger bilateral amygdalae than controls. Participants with sub threshold social anxiety had an increased right hippocampal volume in comparison to controls. The overall brain volume did not differ across the groups [109]. In GAD: the volume amygdala reduced which is observed in generalized anxiety disorder patient especially left side and even abnormal shape of amygdala can be observed [110]. In addition to the amygdala the hippocampal volume associated with the disorder, reduction in the volume has been consistently observed in post-traumatic stress disorder and generalized anxiety disorder [111], SAD [107]. While some research on recent or new-onset PTSD has found no changes in hippocampus volume, other investigations have observed decreases [112]. Using data from all published research, recently conducted a meta-analysis and discovered that toddlers showed no change and that adult men and women with persistent PTSD had decreased volumes on both the left and right sides, equally [113]. A decrease in hippocampus volume was not observed in more recent research on Holocaust survivors with PTSD [114]. Cortical thickness: It refers to the thickness of the cerebral cortex, which is the outer layer of the brain [115]. Reduced cortical thickness has been observed in PTSD and GAD, particularly in the prefrontal cortex and anterior cingulate cortex [116, 117] but in SAD abnormal cortical thickness take place at temporal lobes [118].

Functional neuroimaging biomarkers: It alludes to quantifiable markers of brain activity that can be utilized to identify, track, and forecast how well an anxiety disorder treatment would work [119]. The amygdala's hyperactivity in reaction to emotional stimuli has been regularly noted.

Neuroimaging modalities: it helps to measures the concentration of specific neurotransmitters and metabolites and also know about the blood flow in brain [100]. Different imaging modalities, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), Single Photon Emission Computed Tomography (SPECT) [101], have been employed to investigate these conditions. Social anxiety disorder is distinguished by extreme social anxiety or performance-related situations, as well as a noticeable fear of embarrassment and a poor appraisal, which causes severe suffering and functional impairment. The neuroimaging modalities are useful instruments for studying how the brain works [120]. Nuclear imaging experiments are the main source of current understanding about resting regional neural activity in SAD, Specifically when assessed in conjunction with fMRI blood oxygen level-dependent resting state data (which computes the division between regions in the resting state activity) [121]

because it creates the standards by which task-based research must be evaluated, this type of study is crucial [122]. The thalamus and middle frontal gyrus were more connected and amygdala-frontal and posterior cingulate/precuneus-cerebellar connectivity were among the significant disruptions (in SAD participants compared with healthy controls) reported by a single nuclear imaging study that conducted such analyses. These findings were generally consistent with findings from fMRI work [123], fMRI-based studies consistently show increased amygdalar (and periamygdalar) response in SAD during symptom provocation [124]. Therefore, it can come as a surprise that the outcomes of comparable investigations with [15] O-water PET vary in this regard [121]. Despite not finding any difference in amygdalar reactivity between the SAD and healthy control groups, the largest of these studies the only one that used a strict statistical threshold found a link between amygdalar reactivity and the allelic status of serotonergic polymorphism [125], studies using nuclear imaging show no signs of amygdalar activation while at res [121].

Generalized Anxiety Disorder (GAD): fMRI studies have consistently identified hyperactivity in the amygdala of individuals with patients, suggesting heightened sensitivity to emotional stimuli. Additionally, altered connectivity between the amygdala and prefrontal cortex has been observed, indicating potential disruptions in emotion regulation processes [126]. In PET scan have been employed to assess neurotransmitter activity in generalized anxiety disorder patients. These studies have revealed alternations in GABA (Gamma Aminobutyric Acid), suggesting a potential imbalance between excitatory and inhibitory signaling in the brain [127].

Panic disorder: Basal cerebral blood flow in PD patients was examined in three research. In one (18 FDG)-PET study, a lower metabolic rate in the left inferior parietal lobe was discovered in comparison to controls [128]. While one study revealed increased cerebral blood flow in the hippocampus, bilateral CBF decreases were observed in the posterior temporal lobe, inferior parietal lobe, and cerebellar cortex [105].

Conclusion

The quest for biomarkers in anxiety disorders has yielded significant advancements. Peripheral biomarkers, including inflammatory, and neurotransmitter biomarkers, have shown promise in detecting anxiety disorders. Neuroimaging biomarkers, including structural, functional and connectivity biomarkers, have provided valuable insights into the neural mechanisms underlying anxiety disorders. The integration of peripheral and neuroimaging biomarkers holds great promise for developing more accurate diagnostic tools and personalized treatment approaches. Abnormalities in cortisol, IL-6, and serotonin levels, as well as altered activity patterns in the amygdala, prefrontal cortex, and default mode network, have been implicated in anxiety disorders. Future research should focus on integrating these biomarkers, developing personalized biomarkers, and conducting longitudinal studies. This may lead to the development of more effective treatment approaches and improved patient outcomes. The identification of reliable biomarkers for anxiety disorders has the potential to revolutionize our understanding and treatment of these conditions, ultimately improving the lives of millions of individuals worldwide. By continuing to advance our knowledge of biomarkers in anxiety disorders, we can work towards a future where these conditions are more accurately diagnosed and effectively treated.

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