

# **Natural Biological Markers in Anxiety Depression**

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## **Abstract**

Nowadays, the search for biomarkers has attracted attention in medical and psychological sciences. The biomarkers are crucial to prevent diseases, to detect pathologies and to induce quality of life in patients. These disorders are closely related to each other-they occur simultaneously or follow one another. The diagnosis of stress, anxiety and depression is not a perfect procedure currently-it is based on patient observation and an interview with the patient and their family. Such potential salivary biomarkers could also be useful in monitoring the effectiveness of pharmacological treatment prescribed by a psychiatrist. Potential markers are cortisol, immunoglobulin A (sIgA), lysozyme, melatonin,  $\alpha$ -amylase (sAA), chromogranin A (CgA) and fibroblast growth factor 2 (FGF-2). We can include cortisol, lysozyme, sAA and CgA. To differentiate depression from stress, salivary cortisol and melatonin can be helpful.

**Keywords:** anxiety; biological markers; biomarkers; panels; stress.

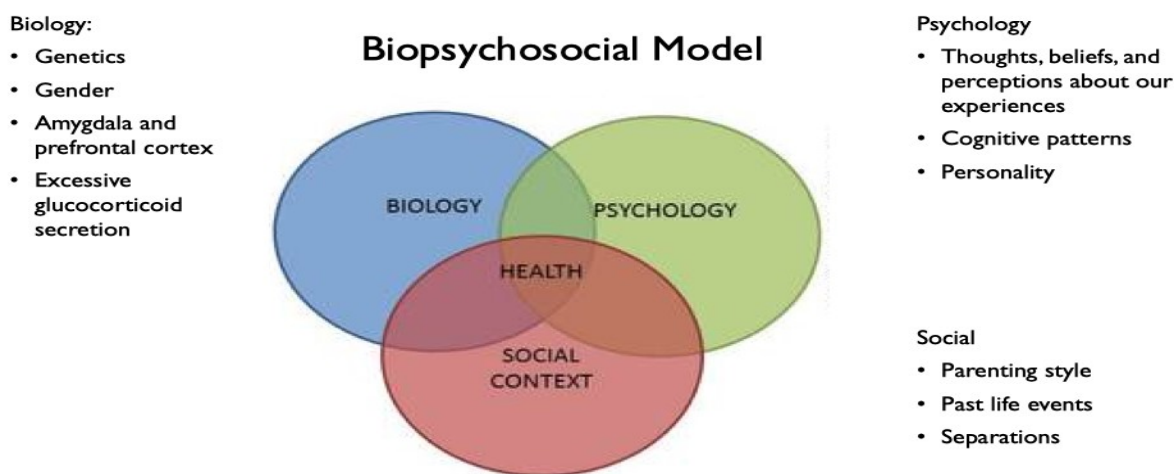
## **Introduction**

Stress and anxiety cause physiological changes, in which hormone levels are altered by the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), which are especially noticeable in chronic anxiety symptoms [6,7]. The moment when the level of stress becomes disturbed is a very individual factor influenced by various circumstances [8]. It is associated with the difficulty in diagnosing and identifying disease thresholds [2]. Research shows that among the commonly conducted questionnaires, anxiety disorders are not identified in up to 50% of affected people [9]. Significant underdiagnosis and difficulties in the

treatment of these disorders have been demonstrated over the years [10]. One of the modern approaches to the issue that will facilitate diagnosis and allow a better understanding of the disease is the identification of biomarkers that underlie the pathogenesis of anxiety disorders [10]. Recently there has been a trend to categorize mental disorders on the basis of objective factors such as biological markers [11,12,13]. Biomarkers are described as a trait that is accurately measured and assessed as an indicator of regular biological processes, pathological processes, or biological responses to therapeutic interventions [12,13]. Researchers have noted that markers could

explain the etiology of mental illness, help to confirm diagnoses, help with the identification of susceptible people, and determine the severity of patient disease [11,14,15]. Some authors also suggested that markers could be used to adjust the treatment method to a specific patient's case and to monitor their clinical response [11,14,15] presented in (Figure 1) Obviously, the markers should have a satisfactory level of sensitivity, specificity, and prognostic value to be used for this purpose [15]. The use of saliva in laboratory diagnostics seems to be more and more popular due to its low cost and non-invasiveness [12].

Saliva contains many substances, the concentration of which exposes the wellness of the whole body, that can be used for easy and rapid detection of primary pathological symptoms in humans [13]. Saliva components can be controlled by specific and sensitive immunological and biochemical techniques, such as radioimmunoassay (RIA), enzyme immunoassay (ELISA), spectrophotometry, or chromatography [4]. On the other hand, the composition of saliva can be affected by many issues, such as circadian rhythm on secretion, age, sex, smoking, diet, and medications [5].



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Cortisol is a hormone that activates metabolism, and activates the bodies “fight or flight” response, and enhances the action of other “stress hormones” such as adrenaline and noradrenaline [7,8]. Therefore, cortisol is one of the substances

that are commonly used as a stress biomarker [2]. Miller et al., in their meta-analysis, confirmed the significance of cortisol in saliva as a biomarker for acute stress.

Immunoglobulins are proteins that are responsible for specific human immune system responses. Anxiety disorders can deteriorate the immune system, and therefore the production of immunoglobulins is reduced [8]. IgA is a class of antibodies that occurs mainly in mucous membranes, including the oral mucosa. These antibodies are often the body’s primary response factor when encountering a pathogen or allergen [8]. Psychological factors can also alter the concentration of IgA in saliva; for example, a positive mood causes an increased level, while negative, stressful stimuli result in a decrease [3]. Studies have shown that there is a potent

association between perceived stress, anxiety, and low levels of salivary immunoglobulin A [10].

Lysozyme provides saliva antibacterial properties and contributes to antiviral defense [4]. Perera et al. found noticeably lower concentrations of lysozyme in saliva samples taken from academics prior to an exam, in contrast to the values after the exam [3], suggesting that salivary lysozyme is useful as a potential stress marker. Other researchers have also shown a negative association between lysozyme concentration and exposure to stress [4]. However, there is a lack of information on the relationship between lysozyme concentration in saliva and anxiety disorders.

Melatonin is a derivative of serotonin that modulates sleep phases and impacts sleep quality [7]. Ito et al. showed that melatonin concentration in saliva during sleep was correlated with anxiety disorders [8]. Interestingly, in the case of depression, this correlation was much stronger.

Salivary alpha-amylase has also been found to be a marker for response to incentives that activate the sympathetic system [5]. In response to stress, there is a rapid increase in the concentration of alpha-amylase in saliva, which could make it a significant biomarker in the future [5].

Chromogranin A (CgA) belongs to the group of acid proteins that contain oligosaccharide chains, which are released from the adrenal medulla and sympathetic nerve endings, which can be detected in saliva samples [5].

Fibroblast Growth Factor 2 (FGF-2) is a mitogen for different kinds of cells found in saliva that is involved in physiological functions related to stress regulation and neuroregeneration [6].

## Peripheral Blood

Measurement of peripheral serotonergic parameters related to 5-hydroxytryptamine (5-HT, serotonin) such as whole blood serotonin, platelet serotonin transporters, and platelets inositol 1,4,5-trisphosphate (IP3) have been identified as clinical predictors of obsessive-compulsive disorder (OCD) [9].

lower levels of brain-derived serum neurotrophic factor (BDNF) occurred in patients with panic disorders, further suggesting that BDNF may contribute to the therapeutic response in panic disorders [7], which was confirmed by research by Suliman et al.,

Platelet markers such as mean platelet volume (MPV) and platelet count (PLT) reflect central serotonergic functions and are thought to reflect the serotonergic functions of the brain [1]. Ransing et al. suggested that platelet and red blood cells (RBC) markers may demonstrate to be useful etiological and predictive markers in patients with panic disorders [7].

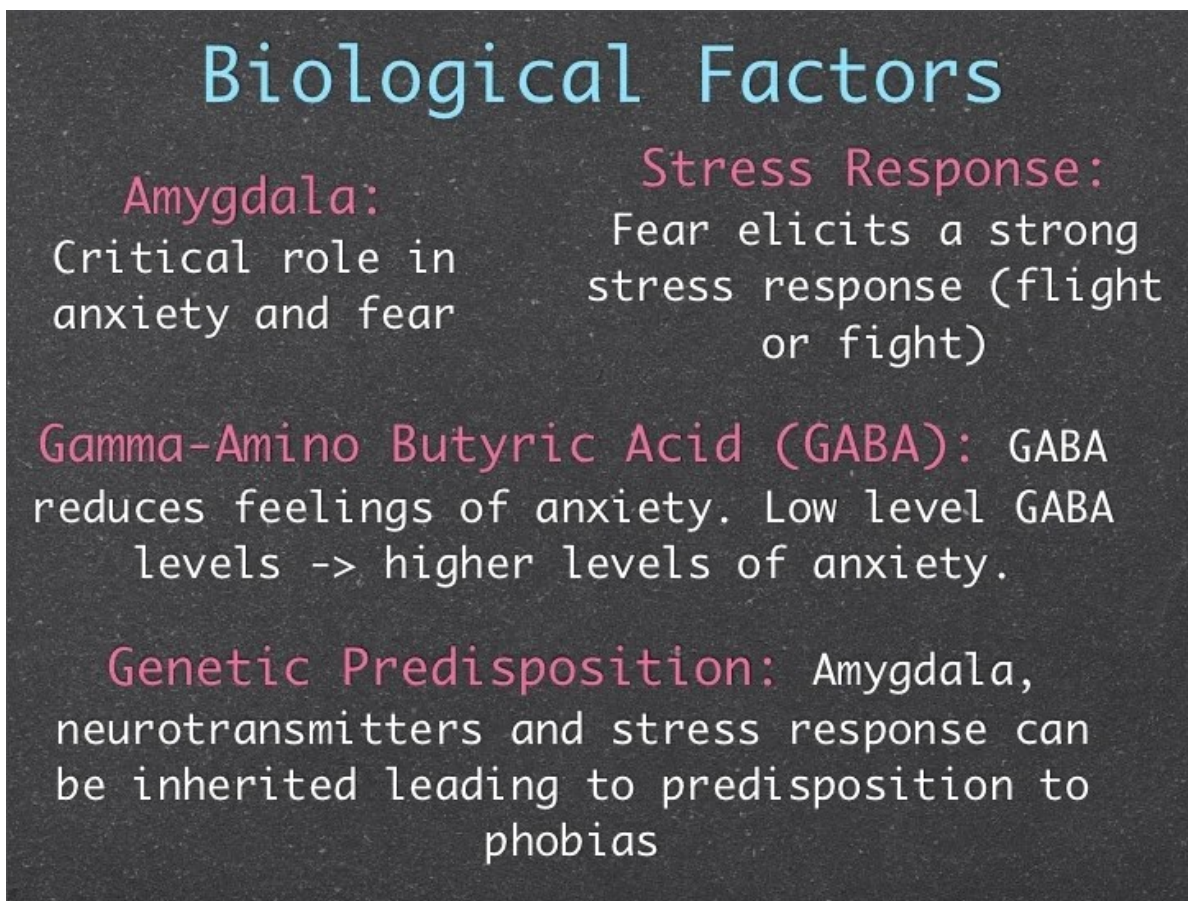
Neuropeptide S (NPS) is involved in states related to fear and stress and the accompanying neuroendocrine processes [9]. HPA axis activation studies of panic disorders have used cortisol secretion as an indicator of HPA function through panic attacks and compared patients with panic disorders (PDs) to a control group [8]. Studies report inconsistent results, although some evidence points to higher cortisol secretion in people being tested with a PD compared to controls.

Persistent anxiety and the associated chronic stress cause proinflammatory changes that are directly related to the hypothalamic-pituitary (HPA) axis, thus, increasing the risk of excessive systemic inflammation [9]. Cross-sectional analyses have shown some indications for higher levels of IL-6 and TNF- $\alpha$  in people with GAD compared to those without GAD, although most studies had small sample sizes and did not sufficiently take into account confounding factors.

Inflammatory biomarkers, such as inflammatory cytokines and acute-phase proteins, are substantially elevated in a significant proportion of patients with anxiety disorders and PTSD and may be a causative agent of behavioral symptoms [9]. It could be explained by the existence of specific biological mediators between stress and inflammation, including corticotrophin-releasing factor [2]. Another inflammatory marker, C-reactive protein, has been shown to be significantly higher in men with anxiety disorders

than in men without, even taking into account other disease factors and lifestyle [9]. In addition, stress and anxiety can cause physiological changes that are especially strong in chronic anxiety symptoms [100]. Thus, the presence of anxiety, especially in the long term, can cause a cascade of physiological changes, putting the individual at risk for general health conditions.

MicroRNAs (miRNAs) are regulators of gene expression that play an important role in neuronal development, in particular in the formation and shaping of synapses. Gene expression, in turn, is directly related to the neurobiological system that underlies stress and anxiety management [11]. Incorrect expression of microRNAs has been implicated in a wide variety of fear and anxiety disorders.



## Cerebrospinal Fluid

Due to the relatively simple method of sampling, blood seems to be a rational source of metabolic measurements. However, because of the existence of the blood-brain barrier, drawing conclusions from the neurochemical composition of plasma about the processes taking place in the brain is not always straightforward. The most important neuropeptides that play a role in modulating stress and anxiety-related behavior are cholecystinin (CCK) [12], oxytocin (OXT). CCK-B receptors could be located in high density in the hypothalamus, limbic system, basal ganglia, hippocampus, cortex, and brainstem. Numerous

studies have investigated the role of CCK in moderating anxiety and the stress response in humans. Ghrelin is a neuropeptide involved mainly in food intake, which additionally influences the regulation of emotions, mood, and anxiety.

## Neuroimaging

There is currently a growing interest in measuring microglia activation, which occurs in patients with anxiety disorders, by using neuroimaging strategies such as positron emission tomography (PET) or magnetic resonance imaging (MRI). We can use MRI and PET imaging to assess the

effects of inflammation on neurotransmitters and neurological circuits related to the reward and anxiety pathways in the central nervous system (CNS). The effect of systemic inflammation on the brain involves glutamatergic and dopaminergic pathways that can lead to psychiatric disorders, including anxiety disorders. Among patients with anxiety disorders, there is an accumulation of peripheral immune cells in the perivascular and meningeal compartments, which is associated with local specific activation of microglia. Peripheral inflammatory cytokines can enter the CNS to initiate a local immune response

## Discussion

Anxiety disorders are a multi-dimensional topic, as they have multifactorial origins [15], and it is unlikely that a single biomarker could explain the dynamic nature of the psychiatric illness [15]. Biomarkers can be used for early detection of mental states, especially those requiring urgent medical intervention, known as trait markers [1]. The most promising biological trait markers included in this article are sAA, CgA, FGF-2, NPS, and ghrelin. Biomarkers mentioned in this review as melatonin, BDNF, 5-HIAA, microRNAs, and neuroimaging biomarkers. Numerous biomarkers, such as serotonin, cortisol, lysozyme, and inflammatory biomarkers, can perform both functions. Cortisol in the initial stage is elevated, which makes it possible to treat it as a trait biomarker, then its concentration decreases; therefore, we can monitor it to assess the progress of the disease. Due to the existence of the blood-brain barrier, the neurochemical composition of plasma may be different from that of the CSF, and therefore it is difficult to draw direct conclusions. For example, concentration of OXT in the cerebrospinal fluid is definitely higher than in the blood. In contrast, the identified microRNAs are associated with the characteristic expression of BDNF. The saliva biomarkers described in this review only show their potential application in practice.


## Conclusion

Overall, it is highly unlikely that a single common biomarker for anxiety disorders can be established. However, even though the diagnosis of anxiety disorders is still largely based on clinical symptoms, biomarkers could be a valuable tool to help identify individual patients with the disorder, improve treatment fit, and predict treatment responses. Identifying beneficial biomarkers can help diagnose and classify a group of psychiatric disorders.

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