

A Scoping Review and Preliminary Illustrative Analysis of Biomarkers in Stress-Related Psychiatric Illness: Diagnostic and Prognostic Implications

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Abstract. Stress is the body's response to any changes that might place it under mental, emotional, or physical strain and could either demand attention or prompt action. A stress reaction can be brought on by both internal and external factors. The conditions, demands, issues, and expectations you deal with every day are all regarded as external influences, as are your physical surroundings, your job, your contacts with others, your family, and all other related factors. The ability of your body to respond to and handle external stimuli depends on internal factors. Your ability to handle stress is influenced internally by your food habits, level of general health and fitness, mental health, and the amount of sleep and rest you get. Such demanding conditions could affect how certain stress hormone levels are regulated. Biomarkers such as mGlu2/3, 5-hydroxyindoleacetic acid (5-HIAA), serum alpha-amylase, amygdala reactivity, neuropeptide Y (NPY), heat shock proteins, cortisol, and catecholamines are used to assess the hormone imbalance. Disease prevention, early detection, and therapy are all possible uses for biomarkers. In this review, we looked at a wide range of stress-related biomarkers that might cause different psychiatric illnesses and how those conditions can, over time, alter a person's lifestyle.

1 Introduction

Stress is the state of being unable to cope with or overwhelmed by unmanageable and intolerant pressures. It may include various situations like the death of a loved one, divorce or separation, loss of employment (figure 1), and unexpected problems with money. Any big change in life can be stressful, even a joyful event like a wedding or a job promotion. When we perceive stress, our body is stimulated to generate stress hormones, and when the stress response is repeatedly triggered or continues over time, the effects can contribute to damage to the body and make the person feel extremely sensitive and react in a 'fight or flight' condition. Lifestyle habits, including body mass index, smoking, alcohol intake, life rhythm, and mental and physical activity, are predictive of stress, anxiety, depression, and life satisfaction. At some point in life or another, most people do come across stressful events, with a prevalence of anxiety disorders of about 29% and that of major depression of 17% [1] [2].



Fig.1 Factors triggering stress

Stress emotions exhibit a major role in the disease, as the body is mobilizing as part of its effort to cope under conditions of harm or danger. There are some mental, behavioral, and physical changes seen as a consequence of stress. Over time, the accumulated effects of chronic stress are related to a number of adverse health outcomes, such as neurodegenerative diseases, osteoporosis, immunosuppression, infertility, psychoneurosis, and metabolic syndromes like diabetes, atherosclerosis, and hypertension [3].

Changes in certain inflammation-related factors (IRFs) have been extensively investigated and reviewed in relation to psychological disorders. Stress also induces our body to release such biomarkers as neuropeptide Y (NPY), cortisol, alpha-amylase, etc., with basic and vital pathways that can be targeted for prevention and interventions. Chronic and repetitive stressors can lead to one or more types of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, altering proper cortisol secretion and affecting the function of the end organ. Especially extreme or chronic stress experienced during the early years of life can be harmful to the patient's mental and physical health. It is expected that dys- and down-regulated HPA axis activity might as well mediate a crucial factor and role in impacting the structure and functions of the brain through life stress (figure 2), constructing its link with depressive disorders and their onset. More and more progressive research has shown a strong correlation between stress, particularly early life and chronic stress, and the development of such conditions. According to a Global Burden of Disease Collaborative Network survey (2017), about 792 million (10.7%) people were affected by mental health disorders, of whom 9.3% were males and 11.9% were females, respectively. Stress (especially early adversity and subsequent traumatic events in life) has been identified as one of the major contributing factors in the precipitation and progression of a vast range of psychiatric conditions, such as schizophrenia and bipolar disorder [4] [5]. Stress-related disorder is a condition characterized by an elevated stress load or diminished adaptability that depletes an individual's reserve capacity and increases their susceptibility to health problems.

However, the role of stressful conditions and the physiology of stress response mechanisms were most closely linked to depressive stress disorders, anxiety, and traumatic stress. The aim of the present review is to illustrate the research findings that evaluate the impact of stress-related psychological disorders.

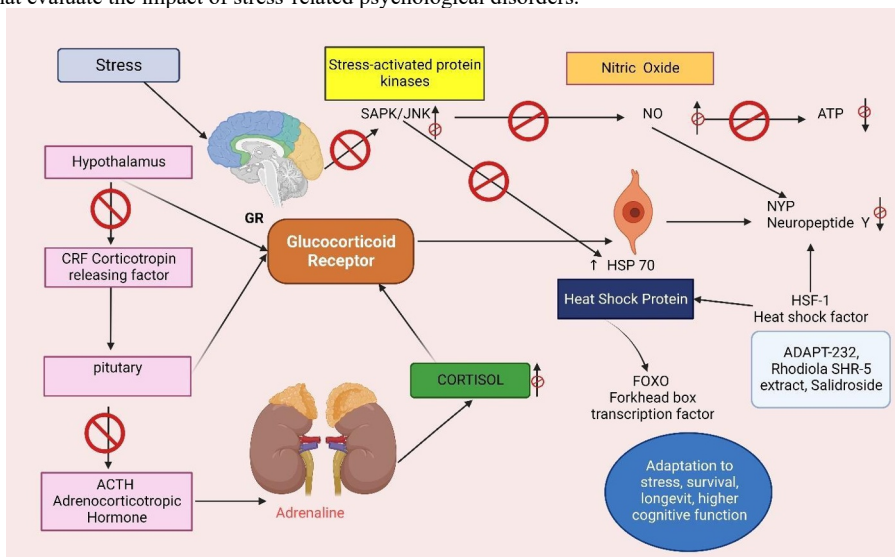


Fig. 2 Hypothetical neuroendocrine mechanism of stress protection

2 Potential Markers Involved in Stress- Related Psychiatric Disorders

2.1 Metabotropic Glutamate Receptors or mGlu2/3

The metabotropic glutamate receptors (mGluRs) play crucial roles in the central nervous system (CNS), particularly in the regulation of mood and cognition. Among the mGluR subtypes, mGlu2 and mGlu3 are of particular interest due to their negative coupling to Gi/Go proteins, which enables them to modulate adenylyl cyclase activity and downstream signaling pathways. The mGlu2 and mGlu3 receptors are members of the G-protein-coupled receptor (GPCR) family, which is one of the largest and most diverse classes of cell surface receptors. GPCRs typically consist of seven transmembrane helices and transmit signals by interacting with intracellular G proteins upon ligand binding. However, the mGluRs possess a larger N-terminal extracellular domain compared to other conventional class A and B GPCRs.

The N-terminal extracellular domain of mGluRs plays multiple important roles. Firstly, it is responsible for the receptor's subtype selectivity, allowing for specific recognition and binding of glutamate, the primary excitatory neurotransmitter in the CNS. Glutamate binding to mGlu2 and mGlu3 receptors activates intracellular signaling cascades and initiates downstream physiological responses. Secondly, the N-terminal domain of mGlu2 and mGlu3 receptors is involved in the activation of the receptor by glutamate receptor agonists. Agonists that specifically bind to mGlu2 and mGlu3 can mimic the effects of glutamate and modulate their activity, thereby influencing neuronal excitability and neurotransmitter release. The negative coupling of mGlu2 and mGlu3 receptors to Gi/Go proteins is another crucial feature. When these receptors are activated by ligands, they initiate signaling pathways that lead to the inhibition of adenylyl cyclase, which in turn reduces the production of cyclic AMP (cAMP). This negative regulation of cAMP levels can have widespread effects on neuronal activity and neurotransmitter release within the CNS [6]. In the anterior cingulate cortex (BA24) of patients with major depressive disorder, lower binding of [3 H] LY341495 to mGlu2/3 was observed, but not in patients with bipolar disorders or schizophrenia [7]. In the visual cortex (BA17) or dorsolateral prefrontal cortex (BA46), there were no variations in radio ligand binding. The results therefore indicate a diagnostic- and regional-specific improvement in mGlu2/3 in major depressive disorder. Considering the function of glutamate in the pathophysiology of the condition [8] [9] [10] and the fact that mammalian targets of rapamycin (MTOR) and mGlu2/3 receptor signaling components are down-regulated in it [11], mGlu2/3 is extensively seen as a potential target for further study. In the brain synapses involved in anxiety and fear responses, agonists of mGlu2/3 reduce presynaptic release of glutamate and also cause postsynaptic hyperpolarization, thereby modulating limbic neuronal excitability [12]. LY354740 inhibits glutamate-evoked synaptic excitatory responses in the amygdala's central and basolateral nuclei, the lateral and medial perifornic routes of the hippocampus, and the medial prefrontal cortex [13]. In animals and humans, these areas have been linked to anxiety and fear control, as well as the development and expression of anxiety and fear responses [14] [15].

2.2 5-hydroxyindoleacetic acid (5-HIAA)

Synthesized in the raphe nuclei, serotonin (5-HT) is a neurotransmitter that is rapidly metabolized in the liver by the mitochondrial enzyme's monoamine oxidase (MAO-A and MAO-B) to 5-hydroxyindole acetic acid (5HIAA) [16] [17]. In several conditions like depression, schizophrenia, Alzheimer's disease, delirium, and cognitive impairment, a prominent decrease in 5-HIAA levels has been spotted. It is now noteworthy that 5-HT is a possible biomarker for various psychological and neurological disorders, indicating a broader scope for its development as an alternative biomarker in future research. The solitary tract nucleus, which includes 5-HT and its subtypes such as 5-HIAA, increases in concentration subsequent to increased "stress" or to a reduction in alcoholic conditions.

Kynurenic acid (KYNA) is a metabolite of tryptophan (amino acid) via the kynurenine pathway. Kynurenic acid is a neuroinhibitory molecule obtained from kynurenine by irreversible enzymatic transamination that exhibits significant pharmacological effects [18] under normal circumstances and is impossible to pass through the blood-brain barrier. KYNA inhibits the action of 7-nicotinic acetylcholine (7nACh) and N-Methyl-D-aspartate (NMDA) receptors, which acts as a ligand for GPR-35, HCAR3, and aryl hydrocarbon (AhR) receptors, and activates M-type K⁺ channels [19]. By interacting with these targets, either directly or indirectly, KYNA possesses its effect on the glutamatergic and cholinergic systems, both of which are essential for healthy cognitive function [20].

Several hypotheses exist that relate changes in serotonin levels to the emergence of new neurological disorders such as depression and schizophrenia [21] [22].

2.3 Serum Alpha-Amylase {SAA}

Serum alpha-amylase (SAA), a member of the endo-amylase family that catalyzes the initial hydrolysis of starch through the cleavage of α -D-(1-4) glycosidic bonds into smaller oligosaccharides, is present in microorganisms, plants, and higher organisms. Chemically, SAA is α -1,4-glucan-4-glucanohydrolase, a calcium-bearing enzyme containing 512 amino acids [23] [24] [25] [26] [27] [28]. Recently, in stress studies, the enzyme has also emerged as a promising biomarker for diagnosing activity in the autonomic nervous system [29]. Due to physical and psychological stress, SAA levels have been found to increase in humans [30] [31] [32] [33]. Their levels have also been reported to have a significant association with the levels of plasma noradrenaline in one of the studies. Concentrations of salivary α -amylase may also contribute to predicting levels of plasma catecholamine in situations involving stress. In order to confer the impact on levels of α -amylase of changes in adrenergic activity, its efficiency as an adrenergic marker can be evaluated through the use of agonists or antagonists of β receptors [31]. In neural astrocytes, pericytes, and dendritic spines, the presence of isotopes of amylase, AMY1A and AMY2A, has also been established. Moreover, increased activity of the enzyme and α -amylase protein levels but downregulated amylase gene expression are seen in patients with Alzheimer's disease. In such patients, periodic Acid-Schiff-positive polyglucan bodies (PGB) in excessive amounts are present in their brains, which is also linked with escalated α -amylase activity. Conclusively, all the findings indicate

the active involvement of α -amylase in human brains. α -amylase gets impaired by AD as well as contributing to its pathology [34].

2.4 Amygdala Reactivity

The amygdala is an ideal potential biomarker for psychological threat to frequent stressors that plays crucial roles in danger stress reactivity, perception, and recall of negative information. [35,36,37]. It has implications for various anger, sleep, and depression-related diseases and is composed of about 13 subnuclei. Elaborately known and identified ones are the basal (BA) nuclei, the central (CeA), and the lateral (LA) nuclei. Various segments of fear response are controlled by the CeA, involving extreme increased response through the midbrain, ANS modulation through the lateral hypothalamus, and control of cortisol release via the paraventricular nucleus of the hypothalamus. While nuclei BA and LA regulate functions of learning and associative functioning [38] [39].

Certain stressors trigger greater and more extreme amygdala reactivity, causing the recollection and avoidance of traumatic experiences and altered stress responses. These characteristics frame important symptoms of anxiety and depression [40]. Moreover, patients with such conditions have increased amygdala reactivity related to threats [41]. Thus, comparatively higher amygdala reactivity to typical stressors may result in a different stress response and a skewed perception and recall of stressful experiences, both of which are key symptoms and characteristics of anxiety and depression disorders. [40] [42] [43] [44]. Not unexpectedly, people with anxiety and depression regularly show increased threat-related amygdala activation [41] [45]. However, it has yet to be confirmed if such increased amygdala activation foretells the future emergence of internalizing symptoms in response to stressful experiences. Amygdala reactivity may serve as a biomarker for predicting psychological susceptibility to severe and uncommon types of trauma.

History of Early Life Stress is related to both hypo-reactivity and hyper-reactivity of the amygdala, making it a particular vulnerability factor for depression [46]. Changes in perception, attitude, and actions are thought to be caused by stress's effects on the amygdala. Individual variations in susceptibility to mood and anxiety disorders, such as emotional reactivity, have been hypothesized to be shaped by these shifts [47].

2.5 Neuropeptide Y (NPY)

Fibers and immune-positive cell bodies of neuropeptide Y are commonly spotted in hypothalamic, limbic, and cortical areas of the brain [48]. NPY effects are controlled by four G-protein-coupled receptor subtypes. The Y1, Y2, Y4, and Y5 subtypes are the major ones. Whereas, primarily, Y6 is found in mice but is absent in rats, while in humans and certain non-human species it is non-functional [49].

In stress-sensitive brain areas such as the locus coeruleus, hypothalamus, amygdala, and cortex, NPY receptors are localized or influence the activity of norepinephrine (NE), glutamate corticotropin-release factor (CRF), and GABA neurons [50].

Recent advances suggest that NPY facilitates stress tolerance by functioning as a defensive neurochemical. Plasma NPY levels in healthy human subjects have been shown to increase in reaction to stress [51]. Clinical studies have found that plasma and CSF in stressed people produce lower amounts of NPY relative to stable controls [52]. Patients with traumatic stress as well as PTSD have been found to have decreased plasma and cerebrospinal NPY levels [53] [54].

Extensive preclinical findings by Eaton K. et al. indicated that NPY is primarily linked to coping with stress and its regulation. NPY maintains emotional homeostasis by counteracting the behavioral consequences of anxiety and stress [55]. Impaired central NPY signaling is also suggested to be directly associated with the neurological pathophysiology of conditions like schizophrenia and trauma-induced disorders like PTSD, alcoholism, anxiety, and depression.

In humans, the involvement of NPY in the behavioral effects of stress was well seen in a study testing plasma NPY with intense interrogation stress in military survival training soldiers. People with lower NPY had dissociation symptoms, while those with better performances and who were more stress-tolerant had higher NPY [56]. According to haplotype-driven NPY expression analysis, greater amygdala activation and better emotional reactivity are found in individuals with lower NPY. NPY expression was found to be inversely linked to trait anxiety. As a result, lower NPY levels in humans can be linked to lower stress resilience [57].

2.6 Heat Shock Proteins

Heat shock proteins (HSPs), also known as stress proteins, are present in all cells of animals [58]. They are highly conserved across species. Some HSPs are also known as chaperones. These play an essential role in the building of multiprotein complexes, the sorting and transport of proteins into subcellular compartments, the unfolding and folding of proteins, the regulation and signaling of the cell cycle, and the protection of cells from stress and cell death.

HSPs have recently been linked to the antigen presentation process, where they chaperone and transmit antigenic peptides to the class I and class II molecules of the major histocompatibility complexes [59]. Additionally, professional immune system antigen-presenting cells like macrophages and dendritic cells can be stimulated by extracellular HSPs [60] [61].

Heat shock proteins (HSPs) form a wide group of evolutionary conserved proteins that protect cells under heat-induced stress from misfolding of denatured proteins. All living organisms react to heat by producing a class of proteins called HSPs, i.e., heat-shock proteins. It has been the most highly preserved genetic system to be known, and it is present in every organism, including plants, mammals, and all classes of bacteria, including eubacteria and archaeobacteria. In response to high temperatures, every living organism analyzed produces proteins that are encoded by the HSP 90 and HSP 70 gene families. The HSP family consists of numerous essential proteins, such as small HSPs, HSP 60, HSP 70, HSP 9, HSP 100, etc. One of the most prominent ones, HSP70, has its main effects in various diverse biological processes and applications in clinical areas. As a result of exposure to short-term stresses like osmotic stress, thermal stress, environmental contamination, and heavy metal toxicity, numerous such proteins get triggered [62]. These mentioned proteins are among the most conserved proteins in existence. Many of the heat-induced proteins are also generically triggered by a range of other stressors. Although the specific combination of efficient inducers varies slightly from organism to organism, ethanol, anoxia, and definite heavy metal ions induce proteins in almost all cells. Moreover, at normal temperatures, all organisms include the HSPs or one of its closely related proteins, which are essential for normal cell activity. Most of the species exhibit extremely rapid HSPs induction, supporting the notion of it being a response in emergency conditions. Additionally, there is a connection between the surroundings of the organism and the induction temperature. The response is elicited in several species at quite different temperatures. The most plausible reason for their immunogenicity is that even at high temperatures, these proteins are abundantly present, given that so many distinct HSPs, which are typically not present on the cell surface, have been described as immunodominant antigens. The close association between the induction of HSPs and the development of thermotolerance is the most convincing proof that they serve a protective function. In healthy cells, the HSPs themselves or their closely related proteins perform essential roles. Important

hints about their potential involvement in thermotolerance are provided by their roles in healthy cell activity.

HSP27, one of the small HSPs, regulates canonical functions in response to stress exposure [63]. Earlier, HSP27 was considered a potent thermal stress marker that promoted the successful reorientation of misfolded proteins. Gradually, it is also known to serve as a chemical as well as an oxidative marker, along with a thermal one [64].

In comparison to non-diseased individuals, relatively higher HSP60 and HSP70 levels were observed in patients with bipolar disorder. Patients with an abnormal HPA axis had extremely lower HSP60 levels compared to those with a normal HPA axis. Moreover, an inversely proportional relationship between the levels of HSP60 and adrenocorticotrophic hormone (ACTH) was found [65].

In many studies, it has been shown that HSP70 protects the brain by acting as a chaperone, preventing protein aggregation, and promoting nascent protein folding and aggregation. HSP70 also protects neurons by suppressing inflammation and apoptosis through additional mechanisms.

2.7 HSP70 and Apoptosis

Apoptosis, a vital step in various pathological conditions, can be triggered by mitochondrial injury, resulting in cytosolic cytochrome c release. Apoptosis associated with mitochondria is a component of the apoptosome. On release of cytosolic C into the cytosol from mitochondria, procaspase-9 activates following its attachment to apoptotic protease activating factor-1 (Apaf-1) [66]. The procaspase-9 and Apaf-1 complexes are then activated by cytochrome c (which makes up the so-called apoptosome), resulting in caspase-9 activation. Consequently, CASP9 activates an effector caspase mediating DNA damage through downstream enzymes, CASP3. Second mitochondrial-derived activator of caspase (Smac) or direct inhibitor of apoptosis Binding protein with low pI (DIABLO) and apoptosis inducer factor (AIF) are certain other apoptogenic factors released by mitochondria. Smac works by counteracting inhibitors of apoptosis proteins that are involved in hindering apoptosome activation and promoting apoptosis. whereas AIF advances apoptosis in the absence of caspase activation. After release from the mitochondria, it translocates to the nucleus and begins chromatin condensation. While its mitochondrial release can be restricted by the anti-apoptotic protein Bcl-2 [67]. Furthermore, HSP70 has anti-apoptotic effects, meaning it can inhibit programmed cell death in neurons. Under stressful conditions, such as oxidative stress or the presence of toxic proteins, neurons can undergo apoptosis, leading to cell death. HSP70 can prevent apoptosis by interfering with apoptotic signaling pathways and stabilizing cellular components involved in cell survival. It can inhibit the release of pro-apoptotic factors from mitochondria and block the activation of caspases, which are key players in the apoptotic pathway. Through these mechanisms, HSP70 helps preserve neuronal viability and protects against apoptotic cell death.

2.7.1 HSP70 and Inflammation

HSP70, a vital HSP, exhibits a significant role in inflammatory responses. Nuclear factor kappa B (NFκB), a transcription factor, is now known to play a role in the immunological response [64]. NFκB, attached to IκB, its inhibitory protein, is generally present in the cytosol. It gets triggered by a broad spectrum of conditions, including endotoxin exposure, oxidative stress, and ischemia [68]. This activates the IB kinase, which phosphorylates IB and facilitates its degradation by the proteasome, which in turn frees the transcription factor to translocate to the nucleus. There, it binds to its DNA consensus sequences and upregulates and activates the inflammatory genes [67]. HSP70's overexpression inhibits the activation of NFκB, intervenes in the activity of IB kinase, and gradually inhibits inflammatory responses [69].

Some studies have shown that people with depression have higher-than-normal levels of the proinflammatory cytokines IL-1, IL-6, IL-8, IL-12, interferon- γ (IFN- γ), and TNF- α in their blood [70]. As well as being found to have elevated plasma levels of IL-1b, IL-1 receptor antagonist, IL-5, IL-6, IL-7, IL-8, IL-10, granulocyte colony-stimulating factor (G-CSF), and IFN- γ [71]. It's interesting to note that postmortem dorsal anterior cingulate tissue from MDD patients had higher levels of macrophage recruitment and microglial activation [72]. Furthermore, among people who died by suicide, there was a significant increase in microglial activity in the ventral prefrontal white matter [73] [74]. Microglia are the first line of defense in the CNS's innate immune system, which actively regulates micro-environmental changes in both healthy and diseased brains. Inflammation, synaptic refinement, synaptic pruning, and neural connection are all controlled by microglial activation [75].

DAMPs (damage-associated molecular patterns) are endogenous signals produced by cells in response to stress, injury, or death. They have the ability to activate the immune system and cause systemic toxicity, as seen in mental illnesses. Extracellular DAMPs, like HSP70, have been found to be linked to the activation of NF- κ B, which causes sterile inflammatory signaling in response to both physical and psychological stress [76] [77]. A meta-analysis found that nonsteroidal anti-inflammatory medicines, specifically the selective COX-2 inhibitor celecoxib, reduced depression symptoms when compared to placebo. Moreover, people with major depressive disorder (MDD) who had greater levels of inflammatory markers seemed to gain the most from this treatment strategy.

Additionally, it has been shown that HSPs interact with proinflammatory substances, including NFκB, MMPs, and reactive oxygen species, to produce an anti-inflammatory state. It has been discovered that heat and stress could induce intracellular overexpression or stimulation of Hsp70, lower inflammatory cell levels like nitric oxide and iNOS, and reduce the activation of NF-κB in astrocytes [78]. Moreover, heat stress is also connected with reducing ROS generation and TNF- α production. Tumor necrosis factor- α (TNF) and interleukin-1 (IL-1) are two inflammatory cytokine responses that Hsp70 can suppress [79], whereas Hsp70 overexpression in macrophages prevents the LPS (lipopolysaccharides) increases in the levels of TNF, IL-1, IL-10, and IL-12 [80]. MMPs are proteases that are capable of causing damage to the extracellular matrix and can cross the blood-brain barrier (BBB), permitting circulating immune cells, serum proteins, and hemorrhage to enter deeper [81]. Overexpression of Hsp70 decreased TNF- α expression as well as prevented the rupturing of the BBB, which could lead to edema development and neurological damage in an intracerebral hemorrhage model [82] [83].

2.8 Cortisol

The hypothalamic-pituitary-adrenocortical (HPA) system regulates the secretion of cortisol, while the secretion of catecholamines is regulated by the sympathetic adrenomedullary (SAM) system [84]. In conditions of stress, a significant correlation has been spotted between blood and salivary cortisol concentrations [85]. The HPA system gets triggered by exposure to various stresses that cause cortisol secretion in the blood. In such cases, a reliable measure of the stress-induced activity of HPA could be salivary cortisol levels [86].

A diurnal pattern also governs the release of cortisol, which increases in the morning and progressively drops throughout the night. There is a noticeable acute increase in cortisol release at waking in addition to this circadian variation [87]. According to a study, it is believed that persistent or repeated activation of the HPA axis both initiates and sustains mental diseases [88]. Following that, cortisol levels are evaluated in hair to determine long-term systemic cortisol levels [89]. Hair cortisol concentrations (HCC) are a reliable and dependable retrospective evaluation of average cortisol and can offer details regarding chronic stress [90]. Although comorbid anxiety and depression are commonly associated with a rising value of cortisol [91] [92], the findings regarding hair cortisol concentration in the context of anxiety disorders tend to be more inconsistent (i.e., greater, shorter, or no influence on HCC), with effects on the cerebrum (frontal, parietal, occipital, and temporal lobes), limbic system (hypothalamus, thalamus, amygdala, and hippocampus), and ventral tegmental area (midbrain that sends dopaminergic neural projections to both the cortical and limbic areas), not only that, but it can also increase the potential for obesity [92]. Those patients with mental diseases show dramatically fluctuating amounts of endocannabinoids and sex hormones as compared to healthy individuals [93]. To assess average cortisol levels over specific periods of time, researchers have utilized cortisol concentrations in

different lengths of hair segments. Specifically, 1 cm of hair segments can provide a retrospective assessment of cortisol levels over the previous 4 weeks, while 3 cm of hair strands can reflect cortisol levels over the previous 3 months. This approach takes into account the average hair growth rate of 1 centimeter per month [94] [95]. Cortisol levels were significantly higher in the group of persons who had tried suicide as compared to baseline cortisol levels in the healthy group, according to prior research [96]. Our findings imply that cortisol levels may be a phenotype of suicide attempters due to a change in the HPA axis, and that this may get enhanced in the presence of depression or the frequency of suicide attempts [97]. Children with anorexia nervosa, a disorder characterized by severe weight loss and distorted body image, show increased activity in the hypothalamic-pituitary-adrenocortical (HPA) axis, which is involved in the regulation of cortisol production. In this context, cortisol concentration is positively correlated with the severity of illness in children with anorexia nervosa. This means that as the severity of the disorder increases, cortisol levels tend to rise. Additionally, changes in cortisol levels over time can provide insights into the prognosis of the disease, indicating how the condition may progress or improve [98]. It has been found that long-term cortisol increases may harm hippocampus neurons and alter the glucocorticoid feedback regulation of CRH production, leading to increased CRH and cortisol concentrations [99]. Depression is a risk factor for type 2 diabetes mellitus, and it has been shown that it increases with the likelihood. In women, central obesity, which refers to the accumulation of fat around the abdominal area, has been associated with a specific cortisol secretor response to meals. This means that the release of cortisol in response to food intake differs in women with central obesity compared to those without central obesity. On the other hand, in males who have central fat distribution, the hypothalamic-pituitary-adrenocortical (HPA) axis, which is involved in the regulation of cortisol production, tends to be more active. This suggests that males with central obesity may exhibit heightened activity in the HPA axis, leading to increased cortisol levels [100]. Various studies on conditions of stress-related anxiety have reported the identification of illness by cortisol levels [101]. Moreover, severe depression is also linked with a long-term attenuation of cortisol secretion [102].

2.9 Catecholamines

Neurotransmitters of catecholamines include epinephrine, norepinephrine, and dopamine. The initiator for all three in biochemical synthesis is the amino acid tyrosine. Tyrosine is converted by tyrosine hydroxylase to dopa (TH), an intermediate compound [103]. Noradrenergic neurons have the neurotransmitter noradrenaline (or norepinephrine), which, using dopamine β -hydroxylase Spector, transforms dopamine into noradrenaline [104]. Eventually, in adrenergic neurons, norepinephrine, with the help of the phenolamine N-methyltransferase enzyme, gets transformed into epinephrine. Only adrenergic and noradrenergic neurons contain synthetic enzymes necessary for epinephrine and norepinephrine generation, respectively, while all catecholamine synthesizing neurons contain tyrosine hydroxylase and DOPA decarboxylase [105]. Pharmacologic modulations in concentrations of synaptic catecholamines play a major role in the management of attention deficit hyperactivity disorder (ADHD) and depression-like conditions.

The constant activation of the sympathetic-adreno-medullary axis, which is part of the stress response system, results in an increased circulation of catecholamines (hormones like adrenaline and noradrenaline). These hormones, in turn, cause adaptive changes such as the expression of beta-2-adrenoceptors.

The purpose of these physiological changes is to prepare the body for a "fight or flight" response. This includes increased blood pressure, elevated heart rate, mobilization of energy reserves, heightened mental activity, and enhanced cellular metabolism. At the same time, blood flow to non-essential organs decreases as resources are redirected towards supporting rapid physical activity. However, if these modifications caused by chronic stress persist or occur repeatedly over a person's lifetime, they may contribute to the development of cardiovascular and other degenerative illnesses [106]. This suggests that prolonged exposure to stress-induced physiological changes can potentially have detrimental effects on health. Not only that, catecholamine also maintains homeostasis in various conditions, like cold [107] [108] [109]; heat [109]; and high-altitude hypoxia [110] [111], which can all increase catecholamine levels.

Subsequently, catecholamine-neuropeptide systems that are "sandwiched" between the arousal response transmitted from the sensorium to the brain primarily through the noradrenergic system of the LC and the final effector system, a hybrid catecholamine/corticosteroid hormone release, form an overall image of catecholamine-neuropeptide systems that are "sandwiched" between the arousal responses conveyed.

To enable catecholamine release during acute or chronic psychogenic/psychological (social defeat, immobilization) or systemic/physical (sepsis, cold, hypoglycemia) stress from the splanchnic nerve, pituitary adenylate cyclase-activating polypeptide (PACAP) is released (figure 3). Furthermore, activation of the HPA axis at a central stage is regulated by PACAP; however, apparently, this regulation is not functional for systemic stress but active for psychogenic type stress only [105] [112].

The striatum, amygdalae, hippocampus, and associative cortex are brain regions that express the post-synaptic protein neurogranin. Different studies show that neurogranin has emerged as a biomarker of synaptic impairment associated with Alzheimer's disease (AD) in the cerebrospinal fluid [113] [114].

In relation to anxiety, individuals with low levels of the enzyme Catechol-O-methyltransferase (COMT) may have a higher tendency for anxiety.[115,116] COMT is responsible for metabolizing and degrading catecholamines, such as adrenaline and noradrenaline.[117] Reduced COMT activity can lead to increased levels of these catecholamines in the bloodstream, which have been linked to anxiety.[118] Study show that individuals with genetically low COMT enzyme activity may be more susceptible to experiencing excessive and prolonged anxiety responses when exposed to emotional stress [119] [120,121].

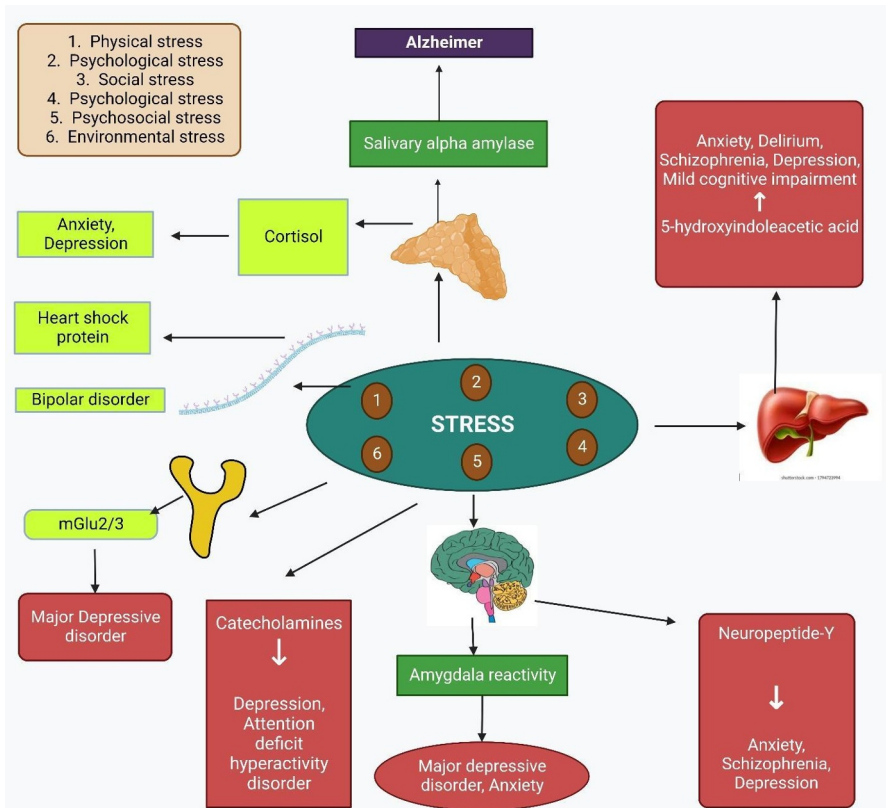


Fig. 3 Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP): A Master Regulator in Central and Peripheral Stress Responses

3 Conclusion

Homeostasis is greatly affected by metabolic disturbances and molecular disruptions induced by multiple stressors. Successful study attempts are in the process of establishing the relative utility of numerous biomarkers in identifying and classifying several conditions involving stress. There is a strong demand to recognize the different stress signs that can help us detect stress at an early level. Biomarkers found so far have been shown to be an important way to detect stress status. Certain precise markers to measure stress responses are crucial in determining them in tears, saliva, urine, and feces. Integration of this molecular, epidemiological, zoonotic, and ecological evidence is important in identifying suitable metrics for perceiving the risk, prognosis, diagnosis, and efficacy of drugs. In the present review, various potent regulators and mediators of the CNS and stress-like conditions are accounted for. Progress in scientific strategies for exploring different, critical stages and their fundamental, underlying pathways is required to elucidate better, potent, and powerful biomarkers and benefit treatments and outcomes.

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