Advances in Modern Biomedicine

https://amb.cultechpub.com/amb

Cultech Publishing

Review

Cortisol Signaling in Stress-Induced Pathophysiology: Molecular Mechanism and Therapeutic Implication

Sadiya Gambo Mustapha*, Mujahid Nasir Hussain

Department of Human Physiology, Bayero University Kano, Kano, Nigeria

*Corresponding author: Sadiya Gambo Mustapha, gambomustaphasadiya@gmail.com

Abstract

Cortisol is a glucocorticoid hormone essential for the physiological stress response. Its secretion is controlled by the hypothalamic-pituitary-adrenal (HPA) axis, which coordinates the body's adaptive behaviour to internal and external stressors. Cortisol has extensive effects on metabolic control, the immune system, and the heart. Although brief increases are necessary to sustain homeostasis in response to acute stress, persistent hypercortisolemia impairs normal circadian rhythmicity and also contributes to insulin resistance, visceral adiposity, and increased neuronal degeneration. Together, these perturbations result in a continuum of stress-related pathologies, such as major depressive disorder, anxiety disorders, metabolic syndrome, cardiovascular disease, and neurodegenerative pathologies such as Alzheimer-type dementia. This review incorporates recent molecular understanding of the genomic and non-genomic processes involved in cortisol activity, circadian disruption, and pro-inflammatory pathways, thereby explaining the mechanistic connections between chronic stress and the development of disease. New treatment options, such as selective glucocorticoid receptor modulators (SEGRMs), aim at repairing HPA axis homeostasis with as few adverse effects on the system as possible. Moreover, biosensor platforms, monitoring and detection systems based on proteolytic enzymes, and modern imaging techniques, including functional magnetic resonance imaging and positron emission tomography, can be used to monitor real-time metabolic and neurophysiological changes. Knowledge of the impact of adrenal signalling pathways on systemic physiology underpins personalised intervention measures that have the potential to reduce maladaptive stress responses and prevent the development of chronic pathology.

Keywords

Cortisol, Hypothalamic-pituitary-adrenal axis, Stress pathophysiology, Glucocorticoid receptor, Precision medicine

Article History

Received: 22 September 2025 Revised: 30 October 2025

Accepted: 24 November 2025 Available Online: 22 December 2025

1. Introduction

Cortisol is a type of glucocorticoid hormone that is produced by the adrenal glands and plays a crucial role in the sustenance of various physiological functions, such as balancing metabolism, the immune system, and stabilizing the heart rate. The secretion is closely controlled by the hypothalamic-pituitary-adrenal (HPA) axis, which is the main regulator of stress response [1]. In this axis, the hypothalamus secretes corticotropin-releasing hormone (CRH) that prompts the secretions of adrenocorticotropic hormone (ACTH) by the anterior pituitary. The ACTH then stimulates the adrenal cortex to start cortisol production and secretion [2]. It is assumed that this hormone release is one of the main biomarkers of physiological and psychosocial stress, which are dynamic adjustments of the body in adverse events [3].

In normal physiological situations the HPA axis functions through a negative feedback process that is tightly controlled. Cortisol suppresses the CRH synthesis in the hypothalamus and secretion of the ACTH in the pituitary gland, thus inhibiting cortisol over-accumulation [4]. This homeostatic control mechanism is needed in order to sustain homeostasis, but in pathologies like chronic stress or constant inflammation states, such a balance can be broken. The maladjustment of this negative feedback mechanism is involved in the long-term cortisol levels, and this may cause the disruption of metabolic activities, immune responses, and exposure to stress disorders.

Besides activation by stress, the secretion of cortisol has an excellent circadian rhythm that is controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus, the central circadian pacemaker of the body. The SCN coordinates a stable diurnal rhythm where cortisol levels soar around the beginning of the morning, leading to alertness, energy mobilisation and cognitive preparedness [5]. The levels subsequently decrease mobilization, gradually in the course of the day, and the lowest level is experienced during nocturnal sleep [3]. This day-to-day variation helps the body to balance between the responsiveness to acute stress as well as the metabolic and physiological stability.

Changes in cortisol dynamics can be radically different in cases of disruption of circadian rhythms due to the presence of chronic psychological stress, sleep disorders, shift work, or stress induced by the environment. These may cause a flattened diurnal cortisol slope, increased nocturnal cortisol release, or disrupted morning cortisol peaks, which all are indications of maladaptive activation of the HPA axis [6]. Disturbed cortisol rhythmicity has been linked to numerous undesirable consequences, such as cognitive deficiency, mood swings, and physiological fatigue and damage. An example is that chronic stress often causes a different cortisol rhythm, namely reduced diurnal differences or unsuitable increases, indicating a dysfunctional endocrine resilience [7].

The HPA axis dysregulation in the long run is a key factor in various disease mechanisms. Chronic increase of cortisol may impair immunologic regulation and stimulate the transition of the acute anti-inflammatory effect to counterintuitive pro-inflammatory signalling, especially in the immune-activation conditions. Chronic stress further exacerbates these conditions by significantly contributing to the development of depressive disorders, with the HPA axis playing a central role in mediating stress responses and subsequently altering neurobiological functions in the hippocampus [8]. Research in the recent past has pointed to the fact that long-term stimulation of HPA may worsen the pathophysiology of neurodegenerative diseases by increasing neuroinflammation, oxidative stress, and neuronal susceptibility [6].

The cortisol regulation is also critical to metabolic health. Unregulated cortisol may disrupt glucose metabolism, disrupt lipid homeostasis, and enhance central adiposity, raising the susceptibility of metabolic syndrome and associated cardiometabolic conditions. Such relations help to underline the interrelation between the endocrine, psychological, and metabolic systems. Moreover, issues related to lifestyle, including low quality of sleep, sedentariness, and unhealthy eating habits, are likely to worsen the HPA axis dysfunction, which evidences the impact of behavioral and environmental factors on cortisol physiology [9].

Lastly, the interdependence between the HPA axis and circadian clock events is a very important factor of resilience in stress. It is coordinated communication between these systems that can be effective to provide adaptive release of cortisol at times of acute challenge and proper provision of daily physiological needs at base. Inhibition of this synchronization, as demonstrated in both human and nonhuman primate studies, decreases stress adaptability and predisposes the individual to long-term health threats [10]. The knowledge of such a complex interaction helps to comprehend the role of chronic stress in the multisystem dysfunction and explains the significance of circadian integrity as the key to good health [10,11].

The disregulation of the HPA axis has been directly related to the development of neurodegenerative diseases, especially the development of Alzheimer's disease and Parkinson's diseases, in which the chronic exposures to glucocorticoids stimulate the loss of neurons and cognitive impairment. Cortisol persistence desensitizes glucocorticoid receptors (GR), resulting in cortisol resistance and aggravation of systemic inflammation and neuroimmune imbalance. The dysfunction has long-term implications and involves a variety of organ systems, such as metabolic and cardiovascular pathways, which highlights the significance of hormonal balance in the preservation of physiological integrity [11].

Moreover, cortisol combines with immune mediators via cascades of complex cytokine mediators, which affect acute phase proteins and enhance inflammatory signalling, this intricate interplay can lead to a vicious cycle during chronic stress, where elevated levels of interleukin-1β (IL-1β) convert an inflammatory signal into a nervous one, further exacerbating the stress response [12]. Although short-term HPA activation aids adaptation and survival, chronic

exposure leads to pathological conditions that involve long-term activities of the sympathetic nervous system and extended production of cytokines. Pro-inflammatory cytokines are capable of penetrating the blood-brain barrier and triggering neuroinflammatory events that lead to psychiatric and neurological diseases [13,14]. This type of chronic inflammation initiates a cascade of neurotoxicity and oxidative injury, which worsens the pathogenesis [15]. High glucocorticoids facilitated the growth of amyloid-beta, tau hyperphosphorylation, oxidative stress, and the dysfunction of synapses hallmark signs and symptoms of Alzheimer's disease [16]. These mechanisms interact to perturb neuronal communication, increase the formation of neurofibrillary tangles, and even accelerate the neurodegenerative pathology [16].

The duality in cortisol functions becomes important towards designing treatment therapeutic measures that would help in the restoration of physiological homeostasis and curbing the progression of the disease. This involves breaking down the confounding interaction between the dysregulation of the HPA axis and neuroinflammation, including how chronic stress contributes to the increase in other conditions such as Alzheimer's disease through the promotion of microglial phenotypic changes to M1 and an increase in the release of pro-inflammatory cytokines [12,17]. It is not only a long-lasting inflammatory condition that impairs neuronal integrity but also predisposes microglia to the pathogenic phenotype, which intensifies neurotoxicity and increases the rate of disease progression [17].

It is important to clarify how chronic stress conditions and dysregulation of the HPA can lead to neurodegenerative pathology to be able to design new therapeutic interventions. The strategies can include the idea of attacking the molecular pathways that connect sustained cortisol increase to oxidative stress, mitochondrial dysfunction, and amyloid-beta buildup interventions to interrupt the vicious circle of neuroinflammation and neuronal decline [15,18]. To tackle the pathophysiology of neurodegenerative diseases, especially Alzheimer's disease, a thorough knowledge of these complicated interactions is therefore necessary [16].

The study aims to assess how cortisol regulates the HPA axis under timing control, gating systems that shift cortisol's functions, and strategies to restore homeostasis in response to systemic influences on neural immune and metabolic functions. The purpose of this study is to demonstrate that chronic dysfunction of the HPA axis links emotional stress with physical disease by investigating the chronic elevation of cortisol, neurodegeneration, immune suppression, and metabolic derangement. In conclusion, this work demonstrated potential therapeutic applications for disorders associated with stress, metabolism, and neuropsychiatric conditions.

2. Methodology

2.1 Literature Search Strategy

A comprehensive literature search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, to ensure broad coverage of peer-reviewed journal articles, reviews, and authoritative reports. The search spanned publications from 2000 to 2025, with particular emphasis on the most recent five years (2020-2025) to capture emerging findings and therapeutic advances.

Search terms combined keywords and Boolean operators, including: “cortisol” OR “glucocorticoid signaling” OR “HPA axis”, “stress-induced pathophysiology”, “cortisol dysregulation”, “neurodegeneration”, “immune suppression”, “metabolic dysfunction,” and “therapeutic interventions.” Reference lists of selected studies were manually screened (snowballing) to identify additional relevant sources not captured by database searches.

2.2 Inclusion and Exclusion Criteria

To maintain relevance and quality, studies were included if they:

(1) Reported on molecular, biochemical, or physiological mechanisms of cortisol in stress-induced pathophysiology.

(2) Examined cortisol’s role in metabolism, immunity, cardiovascular function, or neuropsychiatric disorders.

(3) Discussed therapeutic strategies involving GR modulators, enzyme inhibitors, or non-pharmacological interventions.

(4) Articles were peer-reviewed and published in English.

Exclusion criteria were:

(1) Opinion papers, editorials, or purely theoretical essays without empirical or mechanistic evidence.

(2) Studies unrelated to cortisol or not addressing stress-induced disease pathways.

(3) Non-English language works without reliable translation.

(4) Articles lacking methodological clarity or outcome details.

2.3 Screening and Selection Process

The initial search, conducted across [list databases, e.g., PubMed, Scopus, Web of Science] from January 2020 to December 2025, identified approximately 7.0 articles. After removing duplicates, 410 unique records remained. Title and abstract screening excluded 230 records that did not meet the inclusion criteria. Full-text assessments were conducted for the remaining 180 articles, and high-quality studies were included in the final synthesis. Selection was based on methodological rigor, clinical or experimental relevance, and contribution to understanding cortisol signaling in stress pathophysiology."

2.4 Data Extraction and Synthesis

For each included article, data were extracted on:

The mechanism of cortisol action(genomic vs. non-genomic signaling).

Physiological and pathological roles of cortisol in stress, metabolism, immune regulation, and neurocognitive function.

Links to chronic diseases(e.g., cardiovascular disease, type 2 diabetes, depression, Alzheimer's disease, and Parkinson's disease).

Therapeutic approaches include GR modulators (GR antagonists, SEGRMs), enzyme inhibitors (11β-hydroxysteroid dehydrogenase, 11β-HSD), lifestyle interventions, and novel technologies (biosensors, photobiomodulation).

Extracted data were thematically categorized and synthesized into a narrative discussion, comparative tables, and mechanistic diagrams to highlight emerging patterns, knowledge gaps, and therapeutic implications.

3. Cortisol and Stress-Associated Metabolic Regulation

3.1 Cortisol's Function in the Stress Response

Cortisol is the primary glucocorticoid hormone that enables the body to adapt to stress by coordinating numerous physiological processes. It regulates energy balance, immune function, and brain physiology, thereby providing resilience to both internal and external stressors. The HPA axis regulates cortisol secretion by integrating environmental cues with the body's internal state. The cascade begins when the hypothalamus releases CRH, which stimulates the anterior pituitary to secrete ACTH, which, in turn, prompts the adrenal cortex to synthesize and release cortisol [2,17].

This process under acute stress conditions is adaptive, and cortisol is able to mobilize glucose, increase cardiovascular output, and aid rapid energy expenditure required to bolster the fight-or-flight response. Nevertheless, under chronic stress, in case the HPA axis is constantly stimulated, the cortisol levels do not decrease, and they eliminate the homeostasis of the system. This lifelong hypercortisol condition is a contributing factor to detrimental effects such as insulin resistance, fatty centrality, dyslipidemia, type 2 diabetes, and heart diseases. The chronic exposure to cortisol also affects the proper functioning of the immune system, making a person susceptible to infections. Growth-retarded neuroendocrine dysfunction, at the same time, facilitates neurodegeneration, specifically in the hippocampus, which can cause cognitive impairment and alterations in mood [18,19]. Together, although the cortisol is crucial to the acute stress adaptation, its misregulation turns into a prominent source of disease.

The secretion of circadian melatonin is followed by a slow increase of cortisol in the second part of the night, which eventually leads to the cortisol awakening response. This chronological interaction between the melatonin and cortisol is a physiological necessity. Produced mainly in the pineal gland, the melatonin level has a strong nocturnal rise/peak that controls the onset of sleep and circadian rhythm [20]. It also regulates the activity of the HPA axis, such as the inhibition of nocturnal adrenal cortisol secretions. Melatonin also modulates the effects of GR, including the blockage of GRα nuclear translocation, which demonstrates the important role of melatonin and glucocorticoids in the regulation of neuroprotective and hippocampal cell functions as a central circadian hormone [21]. This prewash effect of melatonin in the regulators of the circadian rhythm determines the downstream effect of cortisol later in the sleep cycle.

There is mounting evidence that cortisol's nighttime interaction with melatonin is necessary in order to have circadian stability, metabolic regulation, and neurological well-being. This well-orchestrated system has been associated with disruptions that cause poor homeostasis as one gets older, or when circadian systems are disrupted, or when sleep disturbances are involved. One of the most critical aspects is the fact that the melatonin secretion will decrease significantly with age; this can reduce almost tenfold during adulthood and deteriorate the circadian robustness and change the dynamics of the neuroendocrine system [22,23].

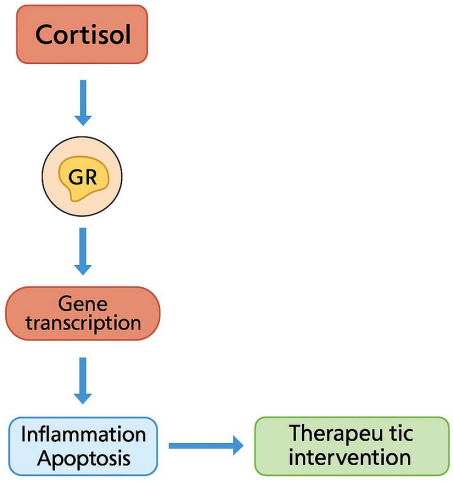

Figure 1. Cortisol signaling in stress-induced pathophysiology.

The Figure 1 above illustrates the cortisol-mediated signaling pathway and its potential points for therapeutic intervention. Cortisol, a glucocorticoid hormone released in response to stress, binds to the GR, forming a hormone-receptor complex. This complex translocates to the nucleus and influences gene transcription, activating or repressing target genes involved in cellular metabolism, immune responses, and stress adaptation. Altered gene transcription can lead to inflammation or apoptosis, depending on the cellular context and duration of cortisol exposure. Chronic or excessive activation of this pathway is often associated with tissue damage, immune dysregulation, and stress-related disorders. Understanding this cascade highlights opportunities for therapeutic intervention, such as drugs targeting GR signaling, modulation of specific gene expression, or anti-inflammatory agents, which can mitigate the detrimental effects of prolonged cortisol exposure while preserving its essential physiological functions.

3.2 Acute Stress Response

The acute stress response is one of the body's most fundamental adaptive responses, enabling one to survive a threat immediately. When stressed for a short period, the HPA axis is activated, leading to a rapid increase in cortisol secretion. When you get a sudden burst of Cortisol, it raises your blood sugar and fat levels. This gives the power-generating organs, like your raw muscles and heart, a boost. Simultaneously, Cortisol works with catecholamines released by the sympathetic nervous system to create the classic "fight or flight" response. Thus, it prepares the organism to respond to potential threats by heightening attention, increasing cardiac output, and sharpening cognitive function [5,24].

The cortisol response has a temporary immunoenhancing effect, another feature. Cortisol mobilizes immune cells into the blood, enhances their surveillance mechanisms, and increases their readiness to fight off pathogens or injuries during stress. This immediate change shows that Cortisol is a short-term protector. It coordinates many systems in the body to help you survive as best as possible under duress. Most importantly, there is a transient, tightly regulated increase in cortisol concentrations due to negative feedback. So negative feedback prevents undue or prolonged exposure, which helps maintain homeostasis after the stressor has been removed.

Even though this system offers a high level of protection, prolonged or frequent activation can cause problems. There is chronic increased activation of the HPA axis, leading to Cortisol not returning to baseline levels. They are now continuously exposed to this stressor, and as a result, Cortisol has been redefined to mean something other than stress. Cortisol does not help you to survive but causes damage to the body. When levels remain elevated for a long time, they disrupt our metabolic, immune, and nervous processes. This sets the stage for disease development like depression, anxiety disorders, and metabolic syndrome. It also leads to neurodegeneration [4]. Thus, the acute stress response reveals Cortisol's dual function: it is essential for short-term adjustment but harmful when it lasts beyond its protective window.

3.3 Chronic Pressure and Prolonged Rise in Cortisol Levels

The HPA system is on long-term when the stress is chronic. The secretion of cortisol continues after the adaptation stage. In the short run, it can save the life of a person when the level of cortisol increases. The body, however, will defer the way it uses its energy when they are in the air over an extended period. There is a growing preference of the system towards short-term survival approaches instead of striking a balance between short-term demands on the needs and long-term sustainability in the growth, repair, and regeneration of the organism. Though beneficial in the scenario of an acute threat, it becomes maladaptive when it lasts weeks, months, or years [25].

Prolonged increases in cortisol are intricate in the metabolism of glucose. Cortisol assists the liver to produce glucose to satisfy the expected energy requirement of the brain. It also avoids the entry of glucose into tissues like the adipose and

muscular ones, and thus it prevents the diversion of energy into storage processes and maintenance. The consequence is a persistent insulin resistance and hyperglycemia, which is very similar to the pathophysiological conditions of Cushing-like syndromes [3]. Such metabolic alterations over the years bring with them the vulnerability to type 2 diabetes, metabolic syndrome, and cardiovascular troubles.

Cortisol dysregulation also has an impact on lipid metabolism in addition to the regulation of glucose. This repeated exposure with the course of time may achieve the improvement of hepatic lipid buildup that would predispose it to steatosis, which preconditions non-alcoholic fatty liver disease (NAFLD). The affected people acquire fatty liver, and this progressively worsens the insulin resistance and leads to inflammation. Moreover, the correlation between the increased level of blood sugar, the increased level of fats in blood, and the inflammatory signalling is difficult to reverse once it is created.

Prolonged maintenance of corticosteroid levels, which is a result of chronic stress, is a necessary adaptive process that may become a pathological engine. The metabolic impacts indicate that stress in the short term may make us adapt, but in the long term, stress is harmful. It plays a major role in causing the chronic disease.

3.4 The Cortisol Signalling and Dysfunction of Metabolism

Cortisol is a very strong metabolic regulator, which majorly regulates the use of energy when a person is stressed. In normal conditions, its signalling is short-lived; that is, it gives a quick adaptive action that mobilizes glucose, lipids, and proteins to survive in that instant. In a case where stress is always present, cortisol becomes balanced, and it is the reverse of what it is supposed to do when there is stress. One of the indications of compromised signalling is that there is more fat in the organs, which is referred to as visceral adiposity. The excessive amounts of cortisol accumulate fat in your belly as it increases the differentiation rate and storing of fats in cells. Visceral adipose tissue is one of the most harmful types of fat. This releases cytokines, which lead to the inflammatory process and increase the level of whole-body inflammation. This connection shows that there is a direct increase of risk [8,26] of cardiometabolic diseases.

Excess insulin resistance may be due to high cortisol levels, which may result in diabetes. Cortisol always increases the level of blood glucose by stimulating the production of hepatic glucose and decreasing the uptake of glucose by muscles. This causes the pancreas to produce even more insulin, but after a certain time, such compensation is no longer possible, which preconditions the development of diabetes. Simultaneously, systemic inflammation, which is aggravated by adipose tissue dysfunction due to cortisol, disrupts metabolic regulation, which creates a feedback mechanism between stress signalling and chronic pathology [8,26].

Not only the level of cortisol but also the rhythm is important. The cortisol level is low during the day and elevated in the early mornings to facilitate the state of being awake. This beat is necessary in order to coordinate metabolism. You do not have much of a peak when you are chronically stressed, when you work shifts, and when you do not get enough sleep. It means that there will be erratic cortisol. Circadian cortisol regulation is destroyed, reducing the stability of the metabolism and outgrowing the inflammatory drift, augmenting the danger of obesity, diabetes, and heart disease [27,28]. In other words, when you are under chronic stress, cortisol increases with time and results in metabolic failure.

3.5 The Obesity and Metabolism Regulation Effect

The fatness and metabolism effect is one of the most significant consequences of chronic low levels of cortisol. To guarantee an immediate supply of energy, cortisol keeps glucose and lipids circulating (i.e., in the blood) at all times. Nevertheless, this condition leads to fat buildup in case it becomes chronic because this state is characterized by the continuous availability of excesses. Fat is deposited viscerally in areas that are most noticeable. These are glucocorticoid-responsive areas that are metabolically active. This enhances belly fat that is closely linked to insulin resistance and cardiometabolic risk in the long run.

Besides the storage of fats, the abnormality in cortisol-based metabolism also increases stress-related pathways in the cell. The consequence of excessive lipolysis is the elevation of the free fatty acids and the absence of the clearance of these fatty acids. They cause endoplasmic reticulum and oxidative stress in adipocytes and peripheral tissues. These stressors initiate signals that enhance inflammation that continue the chain of inflammation and dysfunction. Low-grade chronic inflammation might diminish the insulin sensitivity. In its turn, this may accelerate the onset of type 2 diabetes. In general, it is a contributor to the metabolic disease burden.

The second tissue so much influenced by glucocorticoid signalling is the muscle tissue, which is also abnormally affected by cortisol activity. In case of an abnormally activated glucocorticoid receptor in skeletal muscle, the uptake of glucose is inhibited, glycogen stores are impaired, and insulin sensitivity is lowered. This glucose intolerance abnormality leads to elevated blood sugar and aggravates the obesity complications by interfering with the balance of energy [29].

These mechanisms emphasize the crucial role of cortisol in exposing the body to stress as fat and metabolism imbalances. Obesity and metabolic disease are known to be caused by cortisol signaling, which is out of balance, leading to fat accumulation, inflammation, and inability to metabolize glucose in muscles.

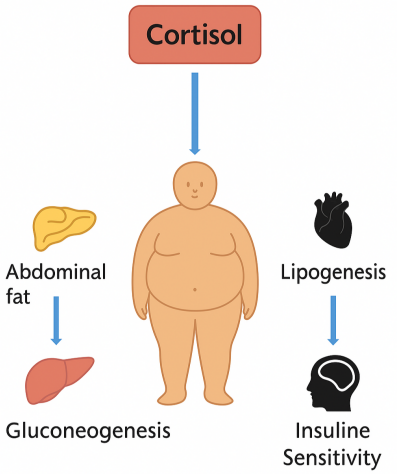

Figure 2. Obesity and metabolism regulation.

The Figure 2 above illustrates the central role of chronically elevated cortisol in driving metabolic dysfunction and obesity, particularly abdominal (visceral) obesity. High cortisol levels directly promote the accumulation of abdominal fat while simultaneously stimulating excessive hepatic gluconeogenesis (the production of new glucose by the liver), which raises blood glucose levels. At the same time, cortisol induces insulin resistance in peripheral tissues (especially muscle and adipose tissue), represented by reduced insulin sensitivity. This combination of increased glucose production and impaired insulin action creates a state of relative hyperinsulinemia and hyperglycemia, further fueling fat storage (lipogenesis), especially in the abdominal region. Thus, chronic hypercortisolemia establishes a vicious cycle that promotes central obesity, insulin resistance, and metabolic syndrome-like features.

3.6 Inflammatory Imbalance

We have traditionally considered cortisol the anti-inflammatory hormone because it suppresses immune activity during acute stress, helping prevent excessive tissue damage. When levels are raised for a long time, the ability to regulate this becomes dysregulated, leading to persistent low-level inflammation. Too much cortisol does not help. It disrupts communication between the immune system and metabolism. It worsens inflammation and reduces the body's ability to self-regulate.

Prolonged exposure to cortisol can lead to the development of a chronic pro-inflammatory state. Increased cortisol levels can alter cytokine profiles. This results in increased levels of inflammatory mediators, meaning insulin's response will not be effective in metabolic tissues. Furthermore, insulin signaling will be prevented in muscle, liver, and adipose tissue. The interruption not only reduces glucose absorption but also increases hepatic glucose release, thereby aggravating hyperglycemia. The pancreas will not be able to keep up with higher insulin demands due to chronic cortisol's effect on pancreatic β-cell activity. The result is insulin resistance and beta cell dysfunction that raise the risk of progression from pre-diabetes to diabetes [8,29].

These processes are interconnected, creating a vicious cycle of pathogen networks. Too much cortisol triggers metabolic changes that worsen inflammation. In turn, signals from inflammation can worsen excess cortisol by interacting with the HPA axis. The two-way relationship boosts insulin resistance and speeds up liver and kidney damage, which worsens without action. Excess cortisol often results in diseases or significant life events, which, in turn, can cause insulin resistance and inflammation.

Cortisol is a big help for the immune system for a short time, but prolonged exposure leads to a smoldering inflammatory state that disrupts metabolic processes. The inflammatory imbalance that occurs from a lengthy exposure to stress is an important maladaptation that leads to chronic disease at a metabolic level.

Table 1 below summarizes how cortisol, the primary stress hormone of the HPA axis, shifts from a beneficial short-term regulator to a driver of metabolic disease when chronically elevated. In acute stress, cortisol rapidly mobilizes energy by stimulating hepatic gluconeogenesis and glycogenolysis, enabling the “fight or flight” response. However, during chronic stress, persistently high cortisol sustains excessive liver glucose production while simultaneously inducing insulin resistance in muscle and fat tissue, resulting in hyperglycemia, compensatory hyperinsulinemia, and a Cushing-like metabolic profile. This prolonged elevation also disrupts normal circadian cortisol rhythms, promotes preferential deposition of visceral (abdominal) fat, increases lipogenesis and free fatty acid release, and contributes to dyslipidemia and NAFLD. Furthermore, chronic hypercortisolemia paradoxically drives low-grade systemic inflammation, impairs immune function, and accelerates hippocampal damage linked to cognitive decline and mood disorders. Collectively, long-term HPA axis overactivation redirects energy allocation toward survival at the expense of metabolic health, significantly elevating the risk of central obesity, type 2 diabetes, cardiovascular disease, and neurodegeneration.

Table 1. Cortisol and stress-associated metabolic regulation.

Physiological/Pathological Aspect	Cortisol's Role	Metabolic/Health Outcome	References
Acute Stress Response	Enhances glucose availability by stimulating gluconeogenesis and glycogenolysis	Short-term adaptation ("fight or flight")	[4,24]
Chronic Stress Response	Prolonged elevation sustains hepatic glucose output and limits peripheral uptake	Insulin resistance, hyperglycemia, and Cushing-like metabolic profile	[3,25]
Circadian Rhythm Regulation	Morning cortisol peaks synchronize metabolism and energy mobilization	Disrupted peaks linked to obesity, diabetes, and cardiovascular risk	[27,28]
Adiposity and Lipid Metabolism	Promotes visceral fat deposition, lipogenesis, and free fatty acid release	Central obesity, NAFLD, and dyslipidemia	[29,30]
Inflammatory Modulation	Excess cortisol drives systemic inflammation through GR dysregulation	Metabolic dysfunction, immune suppression, and higher infection risk	[17,29]
Neurocognitive Effects	Alters hippocampal and synaptic function, linked to metabolic stress	Cognitive decline, neurodegeneration, and mood disorders	[3,4]
Long-Term Systemic Impact	Persistent HPA axis activation alters energy allocation toward survival	Increased risk of type 2 diabetes, cardiovascular diseases, and obesity	[1,6]

Note: HPA axis, hypothalamic-pituitary-adrenal axis; NAFLD, non-alcoholic fatty liver disease.

4. Genomic and Non-Genomic Actions of Cortisol

4.1 Genomic Mechanisms

Cortisol is a significant hormone in humans that helps regulate stress response and metabolism, among other functions. Long-term effects on cellular physiology are primarily mediated through genomic pathways. After secretion due to activation of the HPA axis, cortisol diffuses into target cells and binds to intracellular GRs. The receptor ligand complexes of glucocorticoids are translocated to the nucleus to bind to GCREs present on DNA and affect the transcription of many genes.

Cortisol can change the expression of enzymes, structural proteins, and signalling molecules through this mechanism. Genes that help in gluconeogenesis, lipid metabolism, and immune regulation are often activated, while those regulating anabolic or reparative functions are often repressed. As a result, there will be a synergistic shift in these cellular activities towards catabolism, energy mobilization, and modulation of the immune response [5,6,18].

While these effects are adaptive during acute stress, chronic overexposure to cortisol is maladaptive. If a person's genes are regulated for prolonged periods, it contributes to systemic inflammation, insulin resistance, and dyslipidemia. Neurobiological consequences are equally significant. Chronic changes in gene activity in nerve cells disrupt the ability of the brain to form new connections and change old ones, slow the growth of new neurons, and increase susceptibility to psychiatric and neurodegenerative disorders [2,3,4]. So, genomic signaling prepares the organism to cope with a specific stress that interferes with homeostasis. However, if this stress is prolonged, steady activation leads to maladaptation.

4.2 Non-Genomic Mechanisms

Cortisol triggers fast responses without engaging genomic regulation. Immediate responses to acute stress can be mediated by non-genomic actions that occur over minutes. They interact with either membrane-bound GRs or cytoplasmic signaling cascades that modify ion channel activity, kinase pathways, and intracellular calcium flux.

In neurons, non-genomic signalling boosts excitability, alters neurotransmitter release, and induces fast actions that affect cognition, attention, and emotion [1,4]. For instance, cortisol can influence the response of glutamatergic and GABAergic transmission to a stressor. The effects of stress depend on circumstances. It facilitates learning and memory during acute stress. However, when chronic effects are present, stress impairs cognition and increases anxiousness.

Cortisol exerts long-term regulatory effects but, adaptively, triggers short-term responses via genomic and non-genomic pathways. The article emphasizes that therapeutic approaches targeting cortisol signaling must be coordinated in terms of timing, dose, and receptor specificity to avoid inadvertently detrimental effects on everyday physiological actions [1].

5. Cortisol and Circadian Rhythms

Cortisol secretion follows a strong circadian rhythm, regulated by the hypothalamic SCN. Normal cortisol levels are very high early in the morning, peaking just after waking, before falling throughout the day to normal nighttime levels

around midnight. The rhythm is essential for the coordination of metabolic, cardiovascular, immune, and other systemic functions.

Disruption of this rhythm results in a flattened diurnal profile. That may happen with chronic stress, shift work, or psychiatric illness. Rather than having clear-cut peaks and troughs, people can have a persistently elevated baseline or a blunted variation [5,31]. Metabolic regulation is disrupted, which can lead to high blood sugar, high fats and cholesterol, and weight gain.

The immune system is similarly affected. Circadian misalignment alters immune cell trafficking and the timing of cytokine release, thereby increasing susceptibility to infection and autoimmunity. As well, the loss of rhythmic cortisol signaling exacerbates fatigue, mood instability, and the ability to cope with stress, circadian cortisol dynamics form an integral component of physical and psychological health.

6. Cortisol Dysregulation and Stress-Related Disorders

6.1 General Stress Disorders

When cortisol is not properly regulated, it affects almost all the body's systems. Continuous elevation of glucocorticoids causes glucocorticoid resistance, as immune cells become less responsive to cortisol's anti-inflammatory actions. This paradox leads to a chronic, low-grade inflammatory state, which in turn causes metabolic and cardiovascular dysfunction [32,8].

People with high cortisol suffer from insulin resistance, abdominal fatness, high blood pressure, and low immunity. These systemic effects increase the likelihood of infections and psychiatric disorders. Glucocorticoid resistance has been strongly implicated in depression, where inflammation and neuroendocrine dysfunction exist [33,34].

6.2 Depression and Anxiety

The most prevalent biological deviation in depression and anxiety cases is the HPA axis. The sensitivity of GRs to cortisol decreases worsening the situation, moreover, it can lead to inflammation of the brain. One of the vital elements of the stress system is the HPA axis which is often not regulated in patients with mood disorders resulting in excessive release of glucocorticoid and a defective feedback mechanism [35,36]. Some studies have attributed cortisol-mediated neurotoxicity to hippocampal and volumetric loss of prefrontal cortex and hyperactivity of the amygdalar. Cognitive malfunctions, emotional disturbance, sensitivity to stressors in depressed and anxious persons are linked to the changes in the brain structure, which are examined in research [37,38]. It is also interesting to note that clinical research shows that patients with severe depression have high concentrations of cortisol which can serve as a biomarker and a causative agent.

6.3 Post-Traumatic Stress Disorder

In Post-Traumatic Stress Disorder (PTSD), the cortisol profile is different than that seen in depression. Many people with PTSD exhibit reduced basal cortisol levels rather than a consistent rise, along with heightened cortisol reactivity. It is thought this unusual pattern is the result of hypersensitivity of HPA negative feedback mechanisms due to trauma exposure [37].

This contradictory reaction makes the key PTSD symptoms, like disturbing memories, hyperarousal, and sleep issues, even worse. It is interesting to see the difference it can make based on one's gender. Studies on salivary cortisol have not produced consistent evidence for sex differences.

7. Cortisol and Chronic Diseases

7.1 Cardiovascular Disorders

Excessive cortisol leads to negative heart conditions. The effects of cortisol include hypertension and atherosclerosis through causing endothelial dysfunction, increased systemic inflammation, and altering vascular tissue remodelling [39]. High levels of cortisol enhance the rate of sympathetic nervous system activities [40,41]. Over time, such changes accelerate the rigidity of arteries and the formation of plaques, making the patient prone to a heart attack and stroke to a significant extent. This dysbalance of the HPA axis, which is a frequent effect of stressful situations over time, has severe consequences on the cardiovascular system, leading to insulin resistance, dyslipidemia, and visceral adiposity, and, therefore, metabolic syndrome and heart disease. The ability to disrupt the effect of cortisol has made psychosocial stress one of the primary predisposing factors to cardiovascular disease because chronic activation of the HPA axis leads to cardiovascular disease.

7.2 Neurodegenerative Disorders

Cortisol has a key role in the progression of neurodegenerative diseases by engaging neuronal, glial, and immune pathways in the brain. Long-term activation of the HPA axis leads to chronic hypercortisolism, altering the neurochemical balance crucial for neuronal and cognitive function. When cortisol levels are high, it increases pro-inflammatory cytokines, which activate microglial cells, which in turn damage neuronal synapses; as a result, neuroinflammation occurs. Constant exposure to high levels of cortisol reduces the birth of new neurons in the hippocampus and impairs long-term potentiation. Moreover, it causes neuronal apoptosis, particularly in regions involved in learning, memory, and motor control [31,42].

The toxic neurons from the constant addition of stress hormones aggravate the pathological hallmarks of neuromuscular degenerative diseases. Studies show that high levels of cortisol in the body reduce brain size, especially in areas involved in cognition and executive function. The interaction of neuroinflammation, mitochondrial dysfunction, and oxidative stress caused by cortisol may have accelerated the Parkinson's disease and Alzheimer's disease pathology, and identifies cortisol as more than a mere bystander but a causal agent.

7.2.1 Parkinson's Disease

The motor symptoms of tremor, rigidity, bradykinesia, and postural instability in Parkinson's disease are primarily due to degeneration of dopaminergic neurons in the substantia nigra. Research indicates that HPA axis dysregulation aggravates these pathogenic activities. Higher levels of cortisol and ACTH toll the death of neurons in the substantia nigra, hastening dopamine loss [31]. Also, oxidative stress and inflammation due to cortisol impair dopaminergic transmission.

The consequences extend beyond motor dysfunction. There is a strong link between hypercortisolism (high cortisol) and depression, sleep disturbance, and cognitive impairment. Cortisol affects not only dopamine circuits but also circuits from the limbic system and prefrontal cortex, as indicated by these manifestations [43]. Cortisol and the symptoms of Parkinson's disease may affect each other. Moreover, disease-related stressors are known to worsen outcomes. These stressors may accelerate the onset in genetically susceptible individuals. As a result, PD therapy might be enhanced by targeting cortisol dysregulation.

7.2.2 Alzheimer's Disease

Alzheimer's disease is the most common form of dementia. People with Alzheimer's disease suffer from progressive cognitive failure, memory loss, and other aspects of dementia. Typical amyloid-beta plaques and neurofibrillary tangles characterize this condition. Cortisol helps to speed up these actions by promoting tau hyperphosphorylation, amyloid-beta imbalance, and neuroinflammation. High levels of cortisol disrupt glucose metabolism in neurons, increase synaptic vulnerability, and impair the clearance of neurotoxic proteins via the glymphatic system, worsening neurodegeneration.

Sex-specific differences add further complexity. Women with Alzheimer's disease have higher antedated levels of cortisol compared to men. This could be one explanation for the greater incidence of depression among female Alzheimer's disease patients, as well as the faster cognitive decline in women. Cortisol is not just a biological driver of the disease. It is also a reason why people experience different symptoms. Men and women tend to have different symptoms. When the two are combined, the interaction between cortisol and tau, along with amyloid biology, indicates that it is a biomarker of disease progression and a therapeutic target.

8. Therapeutic Implications

Because of its central role in neurodegenerative and stress-related disorders, many therapeutic strategies aimed at regulating and/or cancelling HPA-axis activities and/or glucocorticoid signalling are under research. Scientists are developing drugs to help people who have too much cortisol in their bodies. GR antagonists block the genomic actions of cortisol, as does mifepristone, which inhibits cortisol synthesis at the adrenal level. Other drugs aim to stabilize and strengthen the circadian rhythm, restoring normal diurnal cortisol fluctuations and limiting sustained hypercortisolism.

Equally important are non-pharmacological interventions. Ways to lower stress, including mindful meditation, exercise, and cognitive therapy, can consistently normalize cortisol rhythms and increase resilience to stress-related disease. Working out decreases baseline cortisol levels and enhances plasticity. Therefore, it is a therapeutic tool in psychiatric and neurodegenerative disorders.

New ways of thinking are coming out in Alzheimer's disease. A 40 Hz flickering light stimulates the glymphatic system, which has been shown to facilitate amyloid clearance and restore neural homeostasis. This approach clears waste products from the brain, and it is one of the main ways in which cortisol disrupts neurobiology [44,45]. Findings like these suggest that regulating cortisol, along with clearing neural waste and reducing inflammation, might lead to novel disease-modifying therapies.

In the end, we do not want to get rid of cortisol, an indispensable hormone that helps us adapt to stress. We want to bring back physiological balance. Treatments that reduce higher-than-normal cortisol while keeping its good functions can improve quality of life and slow disease progression in illnesses like depression, Alzheimer's disease, and maybe even Parkinson's disease.

Table 2. Advantages and disadvantages of glucocorticoid-based therapies.

Therapeutic/Pathological Aspect	Glucocorticoid Role	Clinical/Health Outcome	References
Therapeutic Uses	Provide strong anti-inflammatory and immunosuppressive activity, widely used in asthma, rheumatoid arthritis, autoimmune diseases, and transplant medicine	Effective symptom relief and disease control	[46,47]
Mechanisms of Action	Inhibit NF-κB signaling, cytokine production, and immune cell activation	Suppression of HPA axis, adrenal insufficiency after withdrawal	[48,49]
Clinical Benefits	Rapid reduction of inflammation and effective management of acute and severe disorders	Dose- and duration-dependent adverse effects reduce long-term safety	[50,51]
Adverse Effects	Chronic exposure induces systemic complications across multiple organs	Metabolic: obesity, insulin resistance, diabetes. Cardiovascular: hypertension, atherosclerosis. Neuropsychiatric: depression, anxiety, cognitive decline. Musculoskeletal: osteoporosis, sarcopenia. Immunological: greater susceptibility to infections	[52,53]
Future Directions	Development of SEGRMs and targeted drug delivery systems	Aim to maintain therapeutic benefits while reducing systemic toxicity	[54,55]

Note: NF-κB, nuclear factor Kappa-light-chain-enhancer of activated B cells; HPA axis, hypothalamic-pituitary-adrenal axis. SEGRMs, selective glucocorticoid receptor modulators.

Table 2 above highlights the double-edged nature of glucocorticoid-based therapies, such as prednisone, dexamethasone, or hydrocortisone, which remain cornerstone treatments in medicine due to their potent anti-inflammatory and immunosuppressive effects. By inhibiting NF-κB signaling and cytokine production, glucocorticoids rapidly control life-threatening or debilitating conditions including severe asthma, rheumatoid arthritis, inflammatory bowel disease, autoimmune disorders, and organ transplant rejection, often achieving dramatic clinical improvement. However, prolonged or high-dose use mimics the harmful metabolic profile of endogenous hypercortisolemia: it suppresses the HPA axis (leading to adrenal insufficiency upon withdrawal), promotes central obesity, insulin resistance, and type 2 diabetes, raises blood pressure and atherosclerosis risk, induces mood disorders, cognitive impairment, osteoporosis, muscle wasting, and markedly increases susceptibility to infections. These dose- and duration-dependent adverse effects significantly limit long-term safety. To overcome this limitation, ongoing research focuses on novel selective glucocorticoid receptor agonists/modulators (SEGRMs) and targeted delivery systems that preserve the desired anti-inflammatory benefits while minimizing systemic metabolic, metabolic, and endocrine toxicity.

9. Regulation of Cortisol Synthesis and Breakdown

9.1 Future Outlook and Persistent Concerns

Recent insights further highlight the potential modulatory roles of dietary bioactives in cortisol regulation and glucocorticoid metabolism. The green tea polyphenol epigallocatechin gallate (EGCG) has been shown to bind and inhibit 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1) through protein-protein interactions, thereby influencing local glucocorticoid activation and contributing to tissue-specific cortisol availability--a process known to intensify in metabolic conditions such as obesity and metabolic syndrome [56]. Since 11b-HSD1 amplifies intracellular cortisol generation, its inhibition offers a plausible strategy to mitigate cortisol-driven metabolic and inflammatory dysfunctions. Under conditions of elevated cortisol [57] and/or increased pro-inflammatory cytokine expression that upregulates 11b-HSD1, EGCG may thus provide a non-pharmaceutical means of moderating cortisol activity. Moreover, preclinical data suggest synergistic benefits when EGCG is combined with metformin, enhancing its clinical utility while minimizing the adverse effects associated with synthetic inhibitors [23]. Cortisol, a pivotal glucocorticoid, is synthesized in the zona fasciculata of the adrenal cortex, a process intricately controlled by the HPA axis [58].

Together, these findings reinforce the concept that cortisol homeostasis is not merely a function of endocrine feedback loops, but a broader integrative network influenced by circadian melatonin rhythms, dietary polyphenols, and metabolic

state. Understanding these interconnections offers promising translational potential for the prevention and management of stress-related, metabolic, and neurodegenerative disorders.

9.2 Mitigation of Stress-Induced Cortisol Dysregulation

This involves reducing the cortisol imbalance caused by stress. Drugs such as 11-HSD1 inhibitors and CRH antagonists, which directly aim to reduce cortisol synthesis from producing tissues, provide inhibitory effects. Using cognitive-behavioral therapy, mindfulness-based stress reduction, and exercise has helped lower cortisol levels by affecting the HPA axis. Regular aerobic exercise enhances the expression of GRs, making the effect of cortisol more stable.

It is necessary to alter one's lifestyle when sleep, eating, or social patterns change. Wearable tech and biofeedback systems can monitor cortisol levels in real time for personalized treatment. However, things like how easy these treatments are to get like for folks who do not get much help and how you have to keep doing them make it hard to get lots of people to use them.

10. Conclusion

This review examined the importance of cortisol signalling and HPA axis regulation in the pathophysiology of stress-related conditions. The authors show how important GRs and 11β-HSD enzymes are for feedback corticoids involved in signalling. Cortisol secretion causes many diseases, including metabolic, neuropsychiatric, and inflammatory diseases.

To better elucidate context-specific cortisol signalling pathways, future studies should use omics technologies, conduct longitudinal human studies, and employ integrative stress models. Alongside this, there is an urgent need to study inter-individual differences, sexual dimorphism, and environmental and epigenetic factors that affect cortisol metabolism. The findings may reveal novel biomarkers and sharpen treatment targets for stress diseases.

The results of the study could lead to better therapies, such as drugs that block 11β-HSD, modulate the GR, and personalised stress management approaches combining drugs and behavioural interventions. In the end, integrating molecular discoveries into holistic, fair health care systems will be essential for alleviating the burden of cortisol dysregulation and optimising outcomes in stress-related disorders.

Acknowledgements

The authors acknowledge the contributions of Sadiya Gambo Mustapha and Mujahid Nasir Hussain for their valuable input and support in the preparation of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

References

[1] Antomagesh F, Vijayan MM. Stable-isotope tracing reveals the role of corticosteroid receptors in driving cortisol-mediated central and peripheral glucose regulation in zebrafish. Frontiers in Endocrinology, 2025, 16, 1670637. DOI: 10.3389/fendo.2025.1670637

[2] Naeem AN, Guldin S, Ghoreishizadeh SS. Electrochemical sensors for cortisol: A review. IEEE Sensors Journal, 2024, 24(5), 5746. DOI: 10.1109/jsen.2023.3349293

[3] James K, Stromin JI, Steenkamp N, Combrinck M. Understanding the relationships between physiological and psychosocial stress, cortisol and cognition. Frontiers in Endocrinology, 2023, 14, 1085950. DOI: 10.3389/fendo.2023.1085950

[4] Porta M, Maier JAM, Cazzola R. Effects of *Withania somnifera* on cortisol levels in stressed human subjects: A systematic review. Nutrients. 2023, 15(24), 5015. DOI: 10.3390/nu15245015

[5] Rusch J, Layden BT, Dugas LR. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. Frontiers in Endocrinology. 2023, 14, 1130689. DOI: 10.3389/fendo.2023.1130689

[6] Knezevic E, Nenic K, Milanovic V, Knezevic NN. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. Cells, 2023, 12(23), 2726. DOI: 10.3390/cells12232726

[7] Molendijk AJ, Koenderman L. Glucocorticoid-driven gene expression in circulating monocytes and neutrophils in health and severe inflammation. bioRxiv, 2023. DOI: 10.1101/2023.05.10.23289779

[8] Lei A, Phang VWX, Lee Y, Kow ASF, Tham CL, Ho Y, et al. Chronic stress-associated depressive disorders: the impact of HPA axis dysregulation and neuroinflammation on the hippocampus A mini review. International Journal of Molecular Sciences, 2025, 26(7), 2940. DOI: 10.3390/ijms26072940.

[9] Martire VL, Berteotti C, Zoccoli G, Bastianini S. Improving sleep to improve stress resilience. Current Sleep Medicine Reports, 2024, 10(1), 23-33. DOI: 10.1007/s40675-024-00274-z

[10] Goncharova ND, Chigarova OA, Oganyan TE. Age-related and individual features of the HPA axis stress responsiveness under constant light in nonhuman primates. Frontiers in Endocrinology, 2023, 13, 1051882. DOI: 10.3389/fendo.2022.1051882
[11] Ailioaie LM, Ailioaie C, Litscher G. Photobiomodulation in Alzheimer's disease--a complementary method to state-of-the-art pharmaceutical formulations and nanomedicine? Pharmaceutics, 2023, 15(3), 916. DOI: 10.3390/pharmaceutics15030916
[12] Zefferino R, Di Gioia S, Conese M. Molecular links between endocrine, nervous and immune system during chronic stress. Brain and Behavior, 2021, 11(2), e01960. DOI: 10.1002/brb3.1960
[13] Warren A. The relationship between perceived stigma and perceived stress in cognitive decline: a survey of persons with mild cognitive impairment and their caregivers. Frontiers in Psychology, 2023, 14, 1293284. DOI: 10.3389/fpsyg.2023.1293284
[14] Numakawa T, Kajihara R. Involvement of brain-derived neurotrophic factor signaling in the pathogenesis of stress-related brain diseases. Frontiers in Molecular Neuroscience, 2023, 16, 1247422. DOI: 10.3389/fnmol.2023.1247422
[15] Dmytriv TR, Tsiumpala SA, Semchyshyn H, Storey KB, Lushchak VI. Mitochondrial dysfunction as a possible trigger of neuroinflammation in PTSD. Frontiers in Physiology, 2023, 14, 1222826. DOI: 10.3389/fphys.2023.1222826
[16] Huang Z, Hamblin MR, Zhang Q. Photobiomodulation in experimental models of Alzheimer's disease: state-of-the-art and translational perspectives. Alzheimer's Research & Therapy, 2024, 16(1), 114. DOI: 10.1186/s13195-024-01484-x
[17] Su MP, Nizamutdinov D, Liu H, Huang JH. Recent Mechanisms of Neurodegeneration and Photobiomodulation in Alzheimer's Disease. International Journal of Molecular Sciences, 2023, 24(11), 9272. DOI: 10.3390/ijms24119272
[18] Behnke A, Shire D, Leonard SJ, Park A, Chu LE, Goyal A, et al. Diurnal dynamics and psychobiological regulation of cell-free mitochondrial and nuclear DNA in human saliva. bioRxiv. 2025, 10.13.25337887. DOI: 10.1101/2025.10.13.25337887
[19] Hwang E, Kim H, Lee H, Nam H, Lee J. Effects of Melanopic Equivalent Daylight Illuminance on Sleep Regulation and Chronotype-Specific Responses in Young Adults. bioRxiv. 2025. DOI: 10.1101/2025.10.21.25338466
[20] Mok H, Ostendorf E, Ganninger A, Adler AJ, Hazan G, Haspel JA. Circadian immunity from bench to bedside: a practical guide. Journal of Clinical Investigation, 2024, 134(3), e175706. DOI: 10.1172/jci175706
[21] Stalder T, Oster H, Abelson JL, Huthsteiner K, Klucken T, Clow A. The Cortisol Awakening Response: Regulation and Functional Significance. Endocrine Reviews, 2025, 46(1), 43-59. DOI: 10.1210/endrev/bnae024
[22] Zhang J, Zhou H, Cai Y, Yoshida S, Li Y, Zhou Y. Melatonin: Unveiling the functions and implications in ocular health. Pharmacological Research, 2024, 205, 107253. DOI: 10.1016/j.phrs.2024.107253
[23] Ding J, Chen P, Qi C. Circadian rhythm regulation in the immune system. Immunology, 2023, 171(4), 525-533. DOI: 10.1111/imm.13747
[24] Capri M, Montano N, Piccirillo S, Narici M, Ferranti F, Maccarrone M. Spaceflight exposome/microgravity effects on the psychoimmunoneuroendocrine system. Npj Microgravity, 2025, 11, 66. DOI: 10.1038/s41526-025-00487-8
[25] He X, Gao Y, Ng D, Michalopoulou E, George S, Adrover JM, et al. Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment. Cancer Cell, 2024, 42(3), 474-486. DOI: 10.1016/j.ccell.2024.01.013
[26] Yan J, Chen Y, Luo M, Hu X, Li H, Liu Q, et al. Chronic stress in solid tumor development: from mechanisms to interventions. Journal of Biomedical Science, 2023, 30(1), 8. DOI: 10.1186/s12929-023-00903-9
[27] Yamazaki H, Uehara M, Yoshikawa N, Kuribara-Souta A, Yamamoto M, Hirakawa Y, et al. The crucial role of muscle glucocorticoid signaling in accelerating obesity and glucose intolerance via hyperinsulinemia. JCI Insight, 2023, 8(8), e162382. DOI: 10.1172/jci.insight.162382
[28] Pofi R, Caratti G, Ray D, Tomlinson J. Treating the side effects of exogenous glucocorticoids; can we separate the good from the bad? Endocrine Reviews, 2023, 44(6), 975-1011. DOI: 10.1210/endrev/bnad016
[29] Yan F, Chen X, Quan X, Wang L, Wei X, Zhu J. Association between stress hyperglycemia ratio and 28-day all-cause mortality in critically ill patients with sepsis. Cardiovascular Diabetology, 2024, 23(1), 163. DOI: 10.1186/s12933-024-02265-4
[30] Dal O, Demirkol ME. Stres ve beyin: psikiyatrik hastaliklarda kortizolun yeri. DergiPark (Istanbul University). 2024, 4(2), 44 - 51.
[31] Fahim M, Yao Y, Tipparaju SM, Xuan W. The heart-brain crosstalk in age related cardiovascular and neurodegenerative diseases. Fluids and Barriers of the CNS, 2025, 22(1), 89. DOI: 10.1186/s12987-025-00700-6
[32] Ross IL, Husebye ES, Henry M. Editorial: Glucocorticoids and cognition: recent advances in understanding their interaction, with a particular focus on clinical applicability for the treating endocrinologist. Frontiers in Endocrinology, 2023, 14, 1339165. DOI: 10.3389/fendo.2023.1339165
[33] Linnemann C, Lang UE. Pathways connecting late-life depression and dementia. Frontiers in Pharmacology, 2020, 11, 279. DOI: 10.3389/fphar.2020.00279
[34] Yang X. Grey Matters: The unique landscape of depression treatment in older adults. Psychology, 2023, 14(7), 1164. DOI: 10.4236/psych.2023.147064
[35] Tong RL, Kahn UN, Grafe LA, Hitti FL, Fried NT, Corbett BF. Stress circuitry: mechanisms behind nervous and immune system communication that influence behavior. Frontiers in Psychiatry, 2023, 14, 1240783. DOI: 10.3389/fpsyt.2023.1240783
[36] George MY, Mageed SSA, Mansour DE, Fawzi SF. The cortisol axis and psychiatric disorders: an updated review. Pharmacological Reports, 2025, 77(6), 1573-1599. DOI: 10.1007/s43440-025-00782-x
[37] Mantovani A, Garlanda C. Humoral Innate Immunity and Acute-Phase Proteins. New England Journal of Medicine, 2023, 388(5), 439-452. DOI: 10.1056/nejmra2206346;
[38] Fu X, Wang Y, Zhao F, Cui R, Xie W, Liu Q, et al. Shared biological mechanisms of depression and obesity: focus on adipokines and lipokines. Aging, 2023, 15(12), 5917-5950. DOI: 10.18632/aging.204847
[39] Bezerra TPT, Santos RM, Minervino AJ, Dejani NN. Impact of obesity on immune function and depressive disorder: integrative review. Debates Em Psiquiatria, 2023, 13, 1-18. DOI: 10.25118/2763-9037.2023.v13.631
[40] Sharan P, Vellapandian C. Hypothalamic-Pituitary-Adrenal (HPA) Axis: Unveiling the Potential Mechanisms Involved in Stress-Induced Alzheimer's Disease and Depression. Cureus, 2024, 16(8), e67595. DOI: 10.7759/cureus.67595
[41] Arino-Brana P, Zareba MR, Montolio MI, Visser M, Pico-Perez M. Influence of the HPA Axis on Anxiety-Related Processes: An RDoC Overview Considering Their Neural Correlates. Current Psychiatry Reports, 2025, 27(10), 593-611. DOI: 10.1007/s11920-025-01633-5
[42] Bertollo AG, Santos CF, Bagatini MD, Ignacio ZM. Hypothalamus-pituitary-adrenal and gut-brain axes in biological interaction pathway of the depression. Frontiers in Neuroscience, 2025, 19, 1541075. DOI: 10.3389/fnins.2025.1541075

[43] Gulyaeva NV. Augmented Cortisol and Antiglucocorticoid Therapy in Mood Disorders: the Hippocampus as a Potential Drug Target. Journal of Evolutionary Biochemistry and Physiology, 2024, 60(4), 1516-1530. DOI: 10.1134/s0022093024040203
[44] Hassamal S. Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. Frontiers in Psychiatry, 2023, 14, 1130989. DOI: 10.3389/fpsyt.2023.1130989
[45] Chu C, Pan W, Ren Y, Mao P, Yang C, Liu C, et al. Executive function deficits and medial temporal lobe atrophy in late-life depression and Alzheimer's disease: a comparative study. Frontiers in Psychiatry, 2023, 14, 1243894. DOI: 10.3389/fpsyt.2023.1243894
[46] Quatrini L, Ugolini S. New insights into the cell- and tissue-specificity of glucocorticoid actions. Cellular & Molecular Immunology, 2021, 18(2), 269-278. 10.1038/s41423-020-00526-2
[47] Schaaf MJM, Meijer OC. Immune modulations by glucocorticoids: from molecular biology to clinical research. Cells, 2022, 11(24), 4032. DOI: 10.3390/cells11244032
[48] Shimba A, Ejima A, Ikuta K. Pleiotropic effects of glucocorticoids on the immune system in circadian rhythm and stress. Frontiers in Immunology, 2021, 12, 706951. DOI: 10.3389/fimmu.2021.706951
[49] Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduction and Targeted Therapy, 2024, 9(1), 53. DOI: 10.1038/s41392-024-01757-9
[50] Smith LC, Ramar M, Riley G, Mathias CB, Lee JY. Steroid hormone regulation of immunometabolism and inflammation. Frontiers in Immunology, 2025, 16, 1654034. DOI: 10.3389/fimmu.2025.1654034
[51] Moortel LV, Gevaert K, Bosscher KD. Improved Glucocorticoid Receptor Ligands: Fantastic Beasts, but How to Find Them? Frontiers in Endocrinology, 2020, 11, 559673. DOI: 10.3389/fendo.2020.559673
[52] Saag KG. Glucocorticoids in chronic disease: the good, the bad, the bone. Transactions of the American Clinical and Climatological Association, 2023, 133, 69-80.
[53] Beuschlein F, Else T, Bancos I, Hahner S, Hamidi O, van Hulsteijn L, et al. European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency. European Journal of Endocrinology, 2024, 109(7), 1657-1683. DOI: 10.1210/clinem/dgae250
[54] Butz H, Patocs A. Mechanisms behind context-dependent role of glucocorticoids in breast cancer progression. Cancer and Metastasis Reviews, 2022, 41(4), 803-832. DOI: 10.1007/s10555-022-10047-1
[55] Zhu J, Chen W, Sun Y, Huang X, Chu R, Wang R, et al. Recent advances on drug delivery nanoplatforms for the treatment of autoimmune inflammatory diseases. Materials Advances, 2022, 3(21), 7687. DOI: 10.1039/d2ma00814a
[56] Hernandez-Bustamante A, Bini EI, Torre-Villalvazo I, Tovar AR, Barrios-Payan J, Marquina-Castillo B, et al. Structural homology between 11b-hydroxysteroid dehydrogenase and Mycobacterium tuberculosis Inh-A enzyme: Dehydroepiandrosterone as a potential co-adjuvant treatment in diabetes-tuberculosis comorbidity. Frontiers in Endocrinology, 2023, 13, 1055430. DOI: 10.3389/fendo.2022.1055430
[57] Han R, Han G, Yan Y, Han L, Li L, Zhang H. Protective effects and mechanisms of the Erzhi formula on glucocorticoid induced primary cortical neuron injury. Frontiers in Pharmacology, 2023, 14, 1038492. DOI: 10.3389/fphar.2023.1038492
[58] Kiebzak W, Żurawski A, Głuszek S, Kosztołowicz M, Białek WA. Cortisol levels in infants with central coordination disorders during VOJTA therapy. Children (Basel), 2021, 8(12), 1113. DOI: 10.3390/children8121113