REVIEW ARTICLE

CONTENTS

Dysregulation of immune and stress responses in post-traumatic stress disorder: Increased inflammation and altered stress signalling pathways

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ABSTRACT

Aim: The aim of this review is to summarize current knowledge on the interplay between immune activation and stress-response dysregulation in post-traumatic stress disorder, with particular emphasis on molecular and neurobiological mechanisms.

Materials and Methods: This narrative review was based on a structured search of the PubMed, Scopus, and Web of Science databases, including studies published between 2010 and 2025. Keywords related to post-traumatic stress disorder, inflammation, cytokines, stress response, and neuroendocrine regulation were used. Clinical and experimental studies addressing stress–immune interactions were included.

Post-traumatic stress disorder is increasingly conceptualized as a systemic condition involving persistent dysregulation of neuroendocrine and immune pathways. Disturbances of the hypothalamic–pituitary–adrenal axis, including altered glucocorticoid receptor sensitivity and impaired negative feedback regulation, coexist with increased sympathetic nervous system activity. These abnormalities promote activation of pro-inflammatory transcription factors such as nuclear factor kappa B and increased production of cytokines, including interleukin-1 beta, interleukin-6, tumour necrosis factor alpha, and interleukin-18. Additional mechanisms include activation of the NLR family pyrin domain containing 3 inflammasome, oxidative stress, mitochondrial dysfunction, and microglial activation, which contribute to neuroinflammation and impaired synaptic plasticity. These processes are associated with both psychiatric symptoms and increased risk of cardiovascular and metabolic comorbidities.

Conclusions: Post-traumatic stress disorder may be understood as a disorder of maladaptive stress–immune interaction. Targeting inflammatory pathways and stress-response mechanisms may improve diagnostic approaches and support the development of personalized therapeutic strategies.

KEYWORDS: allostasis, cytokines, glucocorticoid receptors, hypothalamo-hypophyseal system, psychoneuroimmunology

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INTRODUCTION

Post-traumatic stress disorder is a trauma-related psychiatric condition that develops after exposure to a life-threatening or extremely distressing event. It is characterised by intrusive memories, avoidance, negative alterations in mood and cognition, and persistent hyperarousal. Although traditionally conceptualised as a disorder of psychological processing, increasing evidence indicates that post-traumatic stress disorder is also associated with persistent biological alterations involving neuroendocrine and immune systems. These changes may contribute not only to psychiatric symptoms but also to increased risk of somatic diseases [1].

A central mechanism in post-traumatic stress disorder is dysregulation of the hypothalamic–pituitary–adrenal axis, the primary system coordinating the stress response. In healthy individuals, activation of this axis leads to cortisol release, which exerts anti-inflammatory effects and restores homeostasis through negative feedback regulation. In post-traumatic stress disorder, altered glucocorticoid receptor sensitivity and impaired feedback inhibition have been observed. Some patients present with relatively reduced cortisol levels combined with increased receptor responsiveness, which may weaken immunosuppressive control and promote sustained inflammatory activity [2].

Patients with post-traumatic stress disorder also demonstrate increased activity of the sympathetic nervous system. Chronic sympathetic activation elevates catecholamine levels, particularly norepinephrine, contributing to hyperarousal. Immune cells express adrenergic receptors, and prolonged adrenergic stimulation enhances pro-inflammatory signalling. Together, dysregulation of the hypothalamic–pituitary–adrenal axis and sympathetic

overactivity create a state of persistent stress signalling and reduced inflammatory control [3].

At the molecular level, activation of nuclear factor kappa B promotes production of pro-inflammatory cytokines, including interleukin-1 beta, interleukin-6, tumour necrosis factor alpha, and interleukin-18 [4, 5]. Activation of the NLR family pyrin domain containing 3 inflammasome further amplifies inflammation through caspase-1–mediated cytokine maturation. These processes contribute to neuroinflammation, impaired synaptic plasticity, and increased cardiovascular and metabolic risk.

AIM

The aim of this review is to synthesise current evidence on the interplay between stress-response dysregulation and immune activation in post-traumatic stress disorder, with particular emphasis on neuroendocrine, inflammatory, and molecular mechanisms.

MATERIALS AND METHODS

This narrative review was conducted using a structured literature search in PubMed, Scopus, and Web of Science. Publications from 2010 to 2025 were included. The search strategy comprised combinations of the following keywords: post-traumatic stress disorder, hypothalamic–pituitary–adrenal axis, sympathetic nervous system, cytokines, inflammation, nuclear factor kappa B, NLR family pyrin domain containing 3 inflammasome, oxidative stress, mitochondrial dysfunction, microglia, and neuroinflammation.

Studies were included if they addressed neuroendocrine, inflammatory, or molecular mechanisms of post-traumatic stress disorder. Clinical studies in human populations were prioritised, while selected experimental studies, review articles, and meta-analyses were included when relevant. Studies not directly related to post-traumatic stress disorder or not addressing stress–immune mechanisms were excluded.

REVIEW

DYSREGULATION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN POST-TRAUMATIC STRESS DISORDE

The hypothalamic–pituitary–adrenal axis is the main neuroendocrine system coordinating the physiological response to stress. Activation begins with the release of corticotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone. This hormone promotes cortisol release from the adrenal cortex. Cortisol mobilizes energy resources, supports cardiovascular adaptation, and exerts anti-inflammatory effects. Under normal conditions, cortisol binds to glucocorticoid receptors in the brain and peripheral tissues, activating negative feedback mechanisms that suppress further hypothalamic and pituitary stimulation, thereby restoring homeostasis [6, 7].

In PTSD, regulation of the HPA axis is altered. In contrast to major depressive disorder, which is often associated with elevated cortisol levels, PTSD frequently presents with relatively reduced basal cortisol concentrations in some patient groups. At the same time, increased sensitivity of glucocorticoid receptors has been reported. Enhanced receptor responsiveness may strengthen negative feedback inhibition, resulting in lower cortisol secretion despite persistent stress-related activation. This pattern reflects maladaptive regulation rather than simple endocrine hyperactivity [8, 9].

Genetic and epigenetic factors contribute to this dysregulation. Variations and epigenetic modifications in the gene encoding the glucocorticoid receptor and in the gene encoding FK506 binding protein 5 influence receptor sensitivity and stress reactivity. These alterations may arise following trauma exposure and contribute to long-term biological vulnerability by maintaining altered stress responsiveness [10, 11].

Impaired HPA axis function has direct consequences for immune regulation. Cortisol normally suppresses inflammatory gene expression and limits production of pro-inflammatory cytokines. When cortisol secretion is reduced or glucocorticoid signalling is dysregulated, anti-inflammatory control weakens. This may permit increased activation of NF-κB, a transcription factor that promotes expression of inflammatory mediators.

Consequently, elevated levels of IL-1β, IL-6, TNF-α, and IL-18 are observed in many individuals with PTSD [12, 13]. Altered HPA axis activity also affects brain function. Cortisol modulates hippocampal plasticity, amygdala reactivity, and prefrontal cortical regulation of emotional responses. Persistent dysregulation may impair fear extinction and cognitive control. Importantly, HPA axis dysfunction interacts with SNS activation and immune pathways, creating a physiological state characterized by sustained stress signalling and low-grade inflammation. These mechanisms link trauma exposure with chronic immune activation and increased risk of psychiatric and somatic complications in PTSD [14].

SYMPATHETIC NERVOUS SYSTEM HYPERACTIVITY AND IMMUNE MODULATION IN POST-TRAUMATIC STRESS DISORDER

The SNS is a core component of the stress response and functions in coordination with the HPA axis. Activation of the SNS leads to release of catecholamines, primarily

norepinephrine and epinephrine, which increase heart rate, blood pressure, and metabolic activity. Under physiological conditions, this response is transient. In PTSD, persistent sympathetic overactivity is frequently observed [15].

Patients with PTSD often demonstrate elevated resting heart rate, increased blood pressure variability, enhanced startle responses, and increased circulating norepinephrine levels.

Sustained adrenergic activation contributes to hypervigilance, sleep disturbances, and autonomic instability. Importantly, chronic SNS activation has significant effects on immune regulation [16].

Immune cells express adrenergic receptors, particularly beta-adrenergic receptors, which enable catecholamines to modulate immune function. Prolonged adrenergic stimulation enhances intracellular signalling pathways that activate NF-κB, promoting increased production of cytokines such as IL-6 and TNF-α. As a result, sympathetic overactivity contributes directly to a pro-inflammatory state [17].

A bidirectional interaction develops between stress signalling and immune activation. Elevated cytokines influence central nervous system (CNS) function and may further stimulate stress-responsive neural circuits. This interaction occurs through neural and humoral pathways and may sustain heightened arousal and emotional dysregulation [18].

Chronic catecholamine exposure also affects vascular and metabolic systems. Endothelial dysfunction, oxidative stress, and increased platelet activation contribute to elevated cardiovascular risk. Adrenergic effects on glucose metabolism and adipose tissue may increase susceptibility to insulin resistance and metabolic syndrome.

In the brain, excessive noradrenergic signalling alters activity in the amygdala, hippocampus, and prefrontal cortex, impairing fear extinction and cognitive control. Together with HPA axis dysregulation, sympathetic overactivity promotes sustained stress signalling and reduced anti-inflammatory control, contributing to persistent low-grade inflammation and systemic comorbidity in PTSD [19, 20].

PRO-INFLAMMATORY SIGNALLING PATHWAYS AND CYTOKINE DYSREGULATION IN POST-TRAUMATIC STRESS DISORDER

Persistent activation of inflammatory pathways is a central biological feature of PTSD. Trauma exposure and chronic stress are associated with sustained upregulation of pro-inflammatory signalling in both the peripheral immune system and the central nervous system. These alterations are closely linked to dysregulation of stress-response systems and contribute to psychiatric symptoms and systemic complications [21].

A key molecular regulator of inflammation in PTSD is NF-κB. Nuclear factor kappa B is a transcription factor that controls genes involved in immune activation and cytokine production.

In response to stress signals, oxidative stress, or adrenergic stimulation, NF-κB translocates to the nucleus and promotes transcription of pro-inflammatory mediators. Increased NF-κB activity enhances production of IL-1β, IL-6, TNF-α, and IL-18. Elevated circulating levels of these cytokines are frequently observed in individuals with PTSD, reflecting persistent low-grade inflammation [22].

Pro-inflammatory cytokines affect brain function through humoral and neural pathways. They influence neurotransmitter systems and impair synaptic plasticity. Increased IL-1β and TNF-α levels have been associated with reduced long-term potentiation, decreased hippocampal neurogenesis, and altered glutamatergic transmission. These changes may contribute to memory disturbances, heightened fear responses, and emotional dysregulation.

Inflammatory signalling interacts with oxidative stress. Chronic stress increases production of reactive oxygen species, which further activate NF-κB and damage cellular structures. Release of danger-associated molecular patterns sustains immune activation. Microglia respond by adopting a pro-inflammatory phenotype, maintaining neuroinflammation and impairing synaptic integrity [23]. Systemic inflammation also contributes to endothelial dysfunction and metabolic disturbances, increasing cardiovascular risk. Thus, NF-κB activation and cytokine overproduction link psychological trauma with neuroinflammation and somatic disease in PTSD.

THE ROLE OF THE NLRP3 INFLAMMASOME IN POST-TRAUMATIC STRESS DISORDER

The NLRP3 inflammasome is a multiprotein complex central to innate immune activation. It functions as a sensor of cellular stress and promotes maturation of pro-inflammatory cytokines. Evidence indicates that NLRP3 activation links chronic psychological stress with persistent inflammation in PTSD [24].

The complex consists of NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain, and caspase-1. Activation occurs in two stages. The priming stage involves transcriptional upregulation of inflammasome components through pathways such as NF-κB. The activation stage is triggered by intracellular danger signals, leading to assembly of the complex

and caspase-1 activation. Caspase-1 cleaves pro-IL-1β and pro-IL-18 into IL-1β and IL-18 [25, 26].

Chronic stress promotes inflammasome activation through increased reactive oxygen species production, mitochondrial dysfunction, and release of mitochondrial deoxyribonucleic acid (DNA). HPA axis dysregulation and persistent SNS activation enhance priming via NF-κB signalling. In the CNS, microglia expressing NLRP3 produce IL-1β and IL-18, contributing to neuroinflammation and synaptic dysfunction. Inflammasome activation may also induce caspase-1–dependent pyroptosis, increasing neuronal vulnerability [27, 28]. Systemically, elevated IL-1β and IL-18 promote endothelial dysfunction and metabolic disturbances, linking NLRP3 activation with cardiovascular risk in PTSD.

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN POST-TRAUMATIC STRESS DISORDER

Oxidative stress is an important mechanism linking chronic psychological stress with persistent inflammation in PTSD. It reflects an imbalance between the production of reactive oxygen species and the capacity of antioxidant systems to neutralize them. Although reactive oxygen species participate in physiological signalling, their excessive accumulation damages lipids, proteins, and nucleic acids, leading to cellular dysfunction [29].

Chronic activation of stress-response systems promotes increased generation of reactive oxygen species. Sustained stimulation of the sympathetic nervous system enhances metabolic demand and activates enzymes such as nicotinamide adenine dinucleotide phosphate oxidase, which produces superoxide radicals. Dysregulation of the HPA axis may further impair antioxidant defenses, including reduced activity of superoxide dismutase and glutathione peroxidase. Together, these mechanisms create a pro-oxidative state [30].

Mitochondria are a major source and target of reactive oxygen species. Under chronic stress, impaired oxidative phosphorylation increases electron leakage and reactive oxygen species production. Mitochondrial DNA is particularly vulnerable to oxidative damage due to limited repair capacity. Damage to mitochondrial DNA disrupts respiratory chain function, generating a self-perpetuating cycle of oxidative stress and mitochondrial dysfunction.

Neurons are especially sensitive to mitochondrial impairment because of high energy requirements. Disrupted mitochondrial dynamics may impair long-term potentiation and synaptic stability, particularly in the hippocampus and prefrontal cortex. These alterations may contribute to cognitive dysfunction and impaired emotional regulation [31].

Oxidative stress amplifies inflammation. Reactive oxygen species activate NF-κB, increasing transcription of pro-inflammatory cytokines. Mitochondrial damage promotes activation of the NLRP3 inflammasome, partly through thioredoxin-interacting protein–dependent mechanisms. This interaction sustains immune activation. Systemically, oxidative stress contributes to endothelial dysfunction and impaired insulin signalling, increasing cardiovascular and metabolic risk. Thus, oxidative stress and mitochondrial dysfunction represent central components of stress-related immune dysregulation in PTSD [32].

NEUROINFLAMMATION, MICROGLIAL ACTIVATION, AND IMPAIRED SYNAPTIC PLASTICITY IN POST-TRAUMATIC STRESS DISORDER

Neuroinflammation links stress-related immune dysregulation with brain dysfunction in PTSD. It reflects persistent activation of immune processes within the CNS and results from interactions between peripheral cytokines, glial cells, and neural circuits regulating emotion and cognition.

Microglia play a central role. Under physiological conditions, they support synaptic remodeling and homeostasis. In response to chronic stress, elevated cytokines, and danger-associated molecular patterns, microglia shift toward a pro-inflammatory phenotype characterized by increased production of IL-1β, TNF-α, and IL-6, largely regulated by NF-κB. Sustained microglial activation disrupts synaptic structure and function [33].

Pro-inflammatory cytokines impair long-term potentiation and reduce hippocampal neurogenesis. IL-1β interferes with synaptic plasticity, while TNF-α alters glutamate receptor trafficking, disturbing excitatory and inhibitory balance and promoting heightened reactivity within fear circuits.

The amygdala, hippocampus, and prefrontal cortex are particularly vulnerable. Increased amygdala activity contributes to exaggerated threat perception, whereas reduced hippocampal and prefrontal function impairs contextual processing and fear extinction. Neuroinflammation may underlie these abnormalities by affecting neuronal survival and synaptic connectivity.

Astrocytes further amplify inflammatory signalling. Activated astrocytes release cytokines and regulate glutamate uptake and blood–brain barrier integrity. Their dysfunction may enhance excitotoxicity and facilitate peripheral immune signalling into the brain [34].

Neuroinflammation also reduces proliferation of neural progenitor cells and may alter brain-derived

neurotrophic factor signalling. Interactions between inflammatory pathways, the HPA axis, and the SNS create a self-reinforcing cycle that sustains immune activation. Persistent glial activation therefore impairs neuroplasticity and contributes to cognitive and emotional symptoms in PTSD [35].

SYSTEMIC CONSEQUENCES OF STRESS–IMMUNE DYSREGULATION IN POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder is associated with increased risk of somatic diseases in addition to psychiatric symptoms. Persistent dysregulation of the hypothalamic–pituitary–adrenal axis, chronic activation of the sympathetic nervous system, and sustained inflammatory signalling contribute to systemic alterations. These mechanisms affect cardiovascular, metabolic, and immune function, supporting the concept of PTSD as a multisystem disorder [36].

Elevated cardiovascular risk is one of the most consistent findings. Individuals with PTSD show higher incidence of hypertension, coronary artery disease, and myocardial infarction. Chronic sympathetic activation increases heart rate, vasoconstriction, and blood pressure variability. Concurrently, persistent inflammation marked by elevated interleukin-6 and tumour necrosis factor alpha promotes endothelial dysfunction. Reduced nitric oxide bioavailability and increased oxidative stress impair vascular relaxation and accelerate atherosclerotic processes. Platelet activation further enhances thrombotic risk [37].

Endothelial dysfunction represents a central link between inflammation and vascular pathology. Pro-inflammatory cytokines increase adhesion molecule expression, facilitating leukocyte recruitment and vascular inflammation. Oxidative stress promotes lipid oxidation and structural vascular changes, impairing tissue perfusion over time.

Metabolic disturbances are also common. Chronic inflammation and altered stress hormone dynamics interfere with insulin receptor signalling, increasing the risk of insulin resistance and type 2 diabetes. Changes in cortisol regulation may promote visceral adiposity, which further amplifies inflammatory activity. This interaction between metabolic and inflammatory pathways sustains systemic dysfunction [38].

Chronic immune activation may also contribute to accelerated biological aging and increased susceptibility to autoimmune and neurodegenerative disorders. Sleep disturbances frequently observed in PTSD further enhance sympathetic activity and inflammatory signalling, increasing cardiovascular and metabolic risk.

Overall, persistent stress–immune dysregulation extends beyond the central nervous system. Chronic inflammation, autonomic imbalance, and metabolic alterations collectively increase somatic disease burden and may contribute to reduced life expectancy in PTSD [39].

POTENTIAL BIOMARKERS AND THERAPEUTIC IMPLICATIONS IN POST-TRAUMATIC STRESS DISORDER

Identification of biological markers in post-traumatic stress disorder (PTSD) may improve diagnostic precision and support individualized treatment. Persistent dysregulation of stress-response and immune pathways provides several candidate biomarkers reflecting underlying mechanisms [40].

Markers related to the HPA axis include basal cortisol levels, diurnal cortisol rhythm, and glucocorticoid receptor sensitivity. Altered cortisol dynamics and enhanced negative feedback responses have been described in subgroups of patients. Epigenetic modifications in genes regulating glucocorticoid signalling may indicate long-term stress vulnerability.

Pro-inflammatory cytokines are among the most studied biomarkers. Elevated concentrations of IL-1β, IL-6, TNF-α, and IL-18 have been reported in many patients with PTSD. C-reactive protein has also been associated with symptom severity. Despite variability across studies, a pattern of low-grade systemic inflammation is frequently observed [5].

Components of the NLRP3 inflammasome may represent more specific indicators of innate immune activation. Increased expression of inflammasome-related genes, elevated caspase-1 activity, and higher levels of mature IL-1β and IL-18 suggest enhanced inflammasome signalling. Markers of oxidative stress, including reduced antioxidant capacity and mitochondrial DNA alterations, further reflect cumulative cellular stress [7, 12].

These biological findings have therapeutic implications. Standard treatment includes psychotherapy and pharmacotherapy targeting neurotransmitter systems. However, persistent inflammation may reduce treatment responsiveness in some individuals. Anti-inflammatory agents, inhibitors of IL-1 signalling, and compounds targeting oxidative stress are being investigated. Modulation of SNS activity and lifestyle interventions improving sleep and metabolic health may also reduce inflammatory burden. Stratification of patients based on biological profiles may enable more targeted therapeutic approaches. Integration of neuroendocrine, inflammatory, and oxidative markers could

Table 1. Integrative stress–immune axis in post-traumatic stress disorder

Pathophysiological Level	Mechanism	Mediators	Functional Consequences
Stress exposure	Severe psychological trauma	Acute stress signaling	Activation of HPA axis and SNS
Neuroendocrine regulation	HPA axis dysregulation	Cortisol, glucocorticoid receptor	Impaired anti-inflammatory feedback
Autonomic activation	SNS hyperactivity	Norepinephrine, adrenergic receptors	NF-κB activation, cytokine production
Transcriptional control	NF-κB activation	IL-1β, IL-6, TNF-α, IL-18	Persistent low-grade inflammation
Innate immune activation	NLRP3 inflammasome	Caspase-1, IL-1β, IL-18	Amplified inflammatory signaling
Oxidative mechanisms	Mitochondrial dysfunction	Reactive oxygen species	Inflammasome activation, cellular damage
Central nervous system effects	Neuroinflammation	Microglia, astrocytes	Impaired synaptic plasticity
Systemic consequences	Endothelial dysfunction, metabolic alterations	Cytokines, oxidative stress	Cardiovascular and metabolic risk

Source: Compiled by the authors of this study

Table 2. Comparative neuroendocrine and inflammatory features across stress-related conditions

Feature	PTSD	Major Depressive Disorder	Chronic Stress
Basal cortisol	Often reduced	Often elevated	Variable
Glucocorticoid receptor sensitivity	Increased	Decreased	Mild alteration
SNS activity	Markedly increased	Moderately increased	Transient
NF-κB activation	Increased	Increased	Mild–moderate
NLRP3 inflammasome activation	Present	Partial evidence	Limited evidence
IL-1β / IL-6 / TNF-α	Elevated	Elevated	Slight increase
Neuroplasticity	Impaired	Impaired	Reversible changes
Cardiovascular risk	Increased	Increased	Usually low

Source: Compiled by the authors of this study

support development of precision strategies aimed at reducing both psychiatric symptoms and systemic risk in PTSD [18].

INTEGRATIVE MODEL, LIMITATIONS, AND FUTURE DIRECTIONS

PTSD can be conceptualized as a disorder of persistent interaction between stress-response systems and immune regulation. Severe stress activates the HPA axis and the SNS. In PTSD, altered glucocorticoid receptor sensitivity and sustained sympathetic overactivity reduce anti-inflammatory control and enhance immune activation [12–16].

Chronic stress promotes NF-κB activation, increasing transcription of pro-inflammatory cytokines and inflammasome components. Subsequent activation of the NLRP3 inflammasome, driven by oxidative stress and mitochondrial dysfunction, leads to maturation of IL-1β and IL-18, amplifying systemic and central inflammation [7, 8].

Neuroinflammation mediated by microglia and astrocytes disrupts synaptic plasticity and connectivity in the amygdala, hippocampus, and prefrontal cortex. Impaired neuroplasticity links molecular inflammation with hyperarousal, intrusive memories, and cognitive dysfunction. Persistent inflammation and endothelial dysfunction increase cardiovascular and metabolic risk [10, 15, 17–20].

To provide a structured summary of the sequential and interacting mechanisms linking stress exposure with immune activation and systemic consequences in PTSD, the principal components of the stress–immune axis are presented below (Table 1).

Current evidence is limited by population heterogeneity, methodological variability, and predominance of cross-sectional studies. Lack of standardized biomarker panels restricts translation. Future research should include longitudinal designs integrating molecular and neuroimaging data. Identification of inflammatory phenotypes may support development of biologically informed therapeutic strategies in PTSD [23].

For comparative context and to distinguish shared and disorder-specific patterns of neuroendocrine and inflammatory dysregulation, selected features of PTSD, major depressive disorder, and chronic stress are summarized below (Table 2).

DISCUSSION

Post-traumatic stress disorder may be conceptualised as a condition involving persistent interaction between stress-response systems and immune regulation. Available evidence suggests that dysregulation of the hypothalamic–pituitary–adrenal axis and sustained sympathetic nervous system activation are associated with increased inflammatory activity; however, it remains unclear whether these alterations represent primary mechanisms or secondary consequences of chronic stress exposure.

Activation of nuclear factor kappa B and increased cytokine production have been reported across multiple studies, although findings are not entirely consistent. Variability may reflect differences in study design, patient populations, comorbidities, and timing of biomarker assessment.

Similarly, activation of the NLR family pyrin domain containing 3 inflammasome has been proposed as a link between stress signalling and innate immune activation. While several studies indicate increased inflammasome activity, its causal role in disease progression remains to be fully established.

Evidence regarding cortisol dynamics is also heterogeneous. Some studies report reduced basal levels, whereas others show normal or variable concentrations. These discrepancies may be related to trauma type, chronicity, or methodological differences.

From a clinical perspective, integration of neuroendocrine and inflammatory markers may support identification of biologically distinct subgroups. However, current evidence is insufficient for routine clinical application.

LIMITATIONS

Current evidence is limited by the predominance of cross-sectional studies, heterogeneity of study populations, and lack of standardised biomarker assessment. Comorbid conditions may further influence neuroendocrine and inflammatory markers, complicating interpretation.

CONCLUSIONS

Post-traumatic stress disorder may be understood as a condition involving dysregulated interaction between stress-response systems and immune pathways. Although increasing evidence supports the involvement of neuroendocrine and inflammatory mechanisms, their exact contribution to disease onset and progression remains incompletely defined.

Future research should focus on longitudinal study designs, standardisation of biomarker assessment, and integration of molecular and clinical data. Identification of biologically defined subgroups may improve diagnostic precision and support the development of targeted therapeutic strategies.

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CONFLICT OF INTEREST
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