REVIEW ARTICLE

CONTENTS

Increased proteasome and inflammasome activity in response to cellular stress and PTSD-induced damage – a narrative review

Ewa Alicja Ogłodek
DR. WŁADYSŁAW BIEGAŃSKI COLLEGIUM MEDICUM, JAN DŁUGOSZ UNIVERSITY IN CZESTOCHOWA, CZESTOCHOWA, POLAND

ABSTRACT

Aim: This review summarizes current evidence regarding increased proteasome and inflammasome activity in response to cellular stress and PTSD-induced neuronal injury.

Materials and Methods: A narrative literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar databases. Studies published between 2015 and 2025 were analyzed using keywords including "PTSD," "proteasome," "inflammasome," "NLRP3," "oxidative stress," and "neuroinflammation." Experimental and clinical studies investigating molecular mechanisms associated with PTSD-related cellular stress were included.

The reviewed studies demonstrated that chronic traumatic stress promotes excessive activation of the NLRP3 inflammasome and dysregulation of proteasome activity. These changes contribute to accumulation of damaged proteins, mitochondrial impairment, increased reactive oxygen species production, and elevated secretion of pro-inflammatory cytokines, including interleukin-1β and interleukin-18. Persistent activation of these pathways is associated with microglial activation, synaptic dysfunction, impaired neuroplasticity, and progressive neuronal degeneration in PTSD.

Conclusions: Proteasome and inflammasome dysregulation play an important role in the neurobiology of PTSD and may contribute to chronic neuroinflammatory and neurodegenerative processes. Targeting these pathways may represent a promising therapeutic strategy for reducing neuronal damage associated with traumatic stress.

KEYWORDS: inflammasome, neuroinflammation, oxidative stress, proteasome, PTSD, synaptic plasticit

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is a chronic and heterogeneous psychiatric disorder that may develop following exposure to traumatic events involving actual or threatened death, serious injury, or sexual violence. It is characterised by intrusive memories, avoidance behaviours, persistent negative alterations in cognition and mood, and hyperarousal, resulting in substantial impairment of social, occupational, and psychological functioning. Epidemiological studies estimate that the lifetime prevalence of PTSD in the general population ranges from approximately 3% to 8%, although considerably higher rates have been reported among military personnel, first responders, survivors of interpersonal violence, and individuals exposed to armed conflict or natural disasters. Owing to its chronic course and frequent psychiatric and somatic comorbidities, PTSD represents a major global public health challenge [1, 2].

The pathogenesis of PTSD is multifactorial and reflects a complex interaction between genetic susceptibility, environmental exposures, neuroendocrine dysregulation, and immune mechanisms. Increasing evidence indicates that PTSD extends beyond a purely psychiatric disorder and is accompanied by persistent biological alterations involving the central nervous system. These include chronic neuroinflammation, oxidative stress, mitochondrial dysfunction, impaired proteostasis, and altered neuroplasticity. Collectively, these abnormalities contribute not only to the persistence of core PTSD symptoms but also to the increased risk of cardiovascular, metabolic, autoimmune, and neurodegenerative disorders observed in affected individuals [3, 4].

Among the biological mechanisms implicated in PTSD, increasing attention has been directed towards disturbances in intracellular protein homeostasis and innate immune signalling. Proteasomes and inflammasomes are recognised as key regulators of cellular adaptation to stress, coordinating protein quality control, inflammatory responses, and neuronal survival. Dysregulation of these systems has been associated with persistent neuroinflammation, impaired synaptic function, and reduced neuronal resilience following chronic or repeated traumatic stress [5, 6].

Growing evidence further suggests that proteasome dysfunction and inflammasome activation represent interconnected components of the cellular stress response rather than independent pathological processes. Their reciprocal interaction may amplify inflammatory signalling, oxidative stress, and neuronal injury, thereby contributing to the long-term neurobiological consequences of PTSD. Understanding these mechanisms may facilitate the identification of novel therapeutic targets aimed at restoring cellular homeostasis and limiting neuroinflammatory damage in trauma-related disorders [7-9].

The aim of this narrative review is to summarise current evidence regarding the role of proteasomes and inflammasomes in the pathophysiology of PTSD, with particular emphasis on their contribution to cellular stress responses, neuroinflammation, and neuronal dysfunction, as well as their potential relevance as therapeutic targets.

The main neurobiological mechanisms linking traumatic stress with neuronal injury in PTSD are summarised in Table 1.

AIM

The aim of this review is to summarise current evidence on the role of proteasome and inflammasome dysregulation in the neurobiology of PTSD. Particular attention is given to mechanisms linking traumatic stress with cellular injury, oxidative stress, mitochondrial dysfunction, neuroinflammation, and impaired neuronal plasticity.

The review focuses on the ubiquitin–proteasome system and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome NLRP3 inflammasome as key molecular pathways involved in stress-induced neuronal damage. It discusses how impaired protein degradation and persistent inflammasome activation may contribute to microglial reactivity, synaptic dysfunction, altered neuronal signalling, and increased vulnerability of stress-sensitive brain regions, including the hippocampus, amygdala, and prefrontal cortex.

This review also highlights the therapeutic relevance of targeting proteasome activity and inflammasome signalling in PTSD. Better understanding of these interconnected pathways may support the development of strategies aimed at reducing neuroinflammation, restoring proteostasis, and protecting neuronal integrity after traumatic stress.

MATERIALS AND METHODS

A narrative literature review was conducted to assess current evidence on proteasome activity, inflammasome signalling, and cellular stress mechanisms in PTSD. Relevant publications from January 2015 to February 2025 were identified in PubMed, Scopus, Web of Science, and Google Scholar.

The search strategy used combinations of the following terms: "PTSD", "post-traumatic stress disorder", "proteasome", "ubiquitin–proteasome system", "inflammasome", "NLRP3", "oxidative stress", "neuroinflammation", "microglia", "mitochondrial dysfunction", "neuronal plasticity", and "neurodegeneration". Reference lists of selected articles were also screened manually.

Original experimental, translational, and clinical studies were included when they addressed molecular mechanisms linking traumatic stress with neuronal injury, proteostatic disruption, inflammasome activation, oxidative damage, cytokine signalling, or synaptic dysfunction. Reviews were used to provide additional background and to identify relevant primary studies.

Articles not written in English, conference abstracts, editorials, and publications without clear relevance to neurobiological mechanisms of PTSD or chronic stress were excluded. The selected literature was analysed qualitatively, with particular emphasis on interactions between proteasome dysfunction and inflammasome signalling in stress-related neuronal damage.

REVIEW AND DISCUSSION

PROTEASOME DYSFUNCTION IN PTSD-RELATED NEUROBIOLOGICAL INJURY

The ubiquitin–proteasome system (UPS) constitutes one of the principal intracellular mechanisms responsible for maintaining neuronal proteostasis and regulating degradation of damaged, oxidised, and misfolded proteins. In the central nervous system, proteasomal activity is essential for synaptic remodelling, receptor turnover, axonal transport, mitochondrial quality control, and long-term neuronal survival. Due to their high metabolic demand and limited regenerative capacity, neurons remain particularly susceptible to disturbances in intracellular protein degradation pathways. Increasing evidence suggests that chronic traumatic stress profoundly alters UPS function and contributes to progressive neuronal dysfunction in PTSD [10-12].

Experimental studies have demonstrated that chronic stress exposure induces oxidative modification of proteasome subunits and reduces proteolytic activity within stress-sensitive brain regions. Li et al. observed reduced proteasome activity in the hippocampus of rats exposed to chronic unpredictable stress, accompanied by increased accumulation of ubiquitinated proteins and impaired synaptic plasticity [13]. These

Table 1. Main neurobiological mechanisms involved in PTSD-related neuronal injury

Mechanism	Main molecular components	Neurobiological consequences	Clinical relevance in PTSD
Oxidative stress	Reactive oxygen species (ROS), nitric oxide (NO), mitochondrial dysfunction	Lipid peroxidation, DNA damage, impaired neuronal metabolism	Cognitive impairment, emotional dysregulation
Neuroinflammation	NLRP3 inflammasome, IL-1β, IL-18, TNF-α, IL-6	Microglial activation, cytokine release, synaptic dysfunction	Persistent hyperarousal, impaired fear extinction
Proteasome dysfunction	Ubiquitin–proteasome system (UPS), damaged proteins	Accumulation of oxidised and misfolded proteins, impaired proteostasis	Neuronal vulnerability, impaired synaptic plasticity
Mitochondrial dysfunction	Mitochondrial DNA release, ATP depletion, calcium dysregulation	Apoptotic signalling, increased ROS production	Reduced neuronal resilience and energy metabolism
Impaired neuroplasticity	Reduced BDNF expression, altered glutamate receptor trafficking	Dendritic spine loss, disrupted long-term potentiation	Memory disturbances, emotional instability
Blood–brain barrier disruption	Inflammatory cytokines, endothelial dysfunction	Increased permeability and peripheral immune cell infiltration	Sustained neuroimmune activation

Source: Compiled by the author of this study

Table 2. Interactions between proteasome dysfunction and NLRP3 inflammasome activation in PTSD

Pathophysiological process	Proteasome dysfunction	NLRP3 inflammasome activation	Resulting eaffect
Oxidative stress	Reduced degradation of oxidised proteins	ROS-mediated inflammasome activation	Amplification of neuronal injury
Mitochondrial damage	Impaired mitochondrial quality control	Release of mitochondrial DNA and ROS	Sustained neuroinflammation
Cytokine signalling	Proteasome impairment induced by inflammatory mediators	Increased IL-1β and IL-18 maturation	Chronic inflammatory state
Synaptic dysfunction	Altered receptor turnover and protein trafficking	Microglial-mediated synaptic pruning	Impaired fear extinction and cognition
Neuronal survival	Accumulation of toxic protein aggregates	Caspase-1 activation and pyroptotic signalling	Increased neuronal apoptosis
Neuroplasticity	Reduced BDNF-related adaptive mechanisms	Persistent inflammatory signalling	Impaired stress adaptation

Source: Compiled by the authors of this study

changes were associated with elevated concentrations of reactive oxygen species and reduced expression of brain-derived neurotrophic factor (BDNF), suggesting that oxidative stress-induced impairment of proteostasis contributes directly to neuronal vulnerability and cognitive dysfunction. Similar findings were reported by Madrigal and colleagues, who demonstrated that prolonged glucocorticoid exposure impaired proteasomal degradation and promoted accumulation of oxidatively damaged proteins within hippocampal neurons [13-15].

Recent evidence indicates that proteasome dysfunction may also influence mitochondrial integrity. Under physiological conditions, damaged mitochondrial proteins are eliminated through coordinated interactions between the UPS and mitophagic pathways [16]. However, chronic stress disrupts mitochondrial turnover and promotes persistence of dysfunctional organelles. Kaufmann FN et al. demonstrated that chronic restraint stress increased mitochondrial fragmentation and reduced expression of proteasome-related proteins within the prefrontal cortex, resulting in impaired neuronal metabolism and increased apoptotic signalling. These findings support the hypothesis that traumatic stress induces widespread disturbances in intracellular quality-control systems, thereby amplifying oxidative injury and neuronal degeneration [17].

Proteasome impairment has additionally been associated with abnormalities in glutamatergic neurotransmission and dendritic remodelling. Several studies have reported that chronic stress reduces expression of synaptic proteins involved in long-term potentiation and disrupts trafficking of glutamate receptors. Because synaptic plasticity requires tightly regulated degradation of structural and signalling proteins, disturbances in UPS activity may directly interfere with fear extinction and adaptive memory processing. Such mechanisms may contribute

to persistent hyperarousal, intrusive recollections, and emotional dysregulation characteristic of PTSD [18, 19].

Clinical observations further support the relevance of proteostatic dysregulation in trauma-related disorders. Peripheral biomarkers associated with oxidative protein damage and impaired protein degradation have been identified in patients with PTSD, including elevated concentrations of ubiquitinated proteins and oxidative stress markers. Although the majority of available studies remain experimental, these findings suggest that chronic traumatic stress may induce systemic alterations in cellular degradation pathways extending beyond the central nervous system [20-23].

INFLAMMASOME ACTIVATION AND NEUROINFLAMMATION IN PTSD

Neuroinflammation has emerged as a central mechanism underlying the pathophysiology of PTSD. Increasing evidence indicates that chronic traumatic stress activates innate immune pathways within the brain and promotes persistent inflammatory signalling in regions involved in emotional regulation and fear processing. Among the molecular complexes associated with these responses, the NLRP3 inflammasome appears particularly important due to its ability to integrate signals associated with oxidative stress, mitochondrial dysfunction, and cellular injury [24-27].

The NLRP3 inflammasome is a cytosolic multiprotein complex composed of the NLRP3 receptor, the adaptor protein - apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and procaspase-1. Following activation, caspase-1 promotes maturation of interleukin-1β (IL-1β), and interleukin-18 (IL-18), leading to amplification of inflammatory cascades and microglial activation. Under physiological conditions, inflammasome activity contributes to host defence and regulation of immune homeostasis. However, excessive or persistent activation may promote neuronal dysfunction and neurodegeneration [28].

Zhang et al. demonstrated significantly increased expression of NLRP3, caspase-1, and Il-1β within the hippocampus of rodents exposed to chronic stress paradigms resembling PTSD. These alterations were accompanied by impaired spatial memory, increased anxiety-like behaviour, and enhanced microglial activation [29]. Importantly, pharmacological inhibition of NLRP3 signalling attenuated behavioural abnormalities and reduced inflammatory cytokine production, suggesting a direct contribution of inflammasome activity to stress-induced neuronal dysfunction [30].

Additional evidence has been provided by studies investigating mitochondrial mechanisms involved in inflammasome activation. Iwata et al. reported that chronic stress increased mitochondrial reactive oxygen species production and induced release of oxidised mitochondrial DNA, both of which acted as potent triggers of NLRP3 activation. Mitochondrial injury additionally promoted calcium dysregulation and activation of apoptotic pathways within hippocampal neurons. These findings indicate that oxidative stress and mitochondrial dysfunction represent critical upstream mechanisms linking traumatic stress with neuroinflammatory injury [31].

Microglial activation constitutes another important feature of inflammasome-mediated neuroinflammation in PTSD. Under chronic stress conditions, microglia adopt a pro-inflammatory phenotype characterised by increased secretion of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), nitric oxide (NO), and reactive oxygen species (ROS).

Excessive microglial activation contributes to synaptic pruning, dendritic spine loss, and disruption of neuronal communication. In imaging studies, individuals with PTSD demonstrated increased neuroinflammatory markers within limbic structures, supporting the translational relevance of experimental findings [32].

Recent investigations have also implicated inflammasome activation in disruption of blood–brain barrier integrity. Elevated concentrations of inflammatory cytokines increase endothelial permeability and facilitate infiltration of peripheral immune cells into the central nervous system. This process may amplify local inflammatory responses and sustain chronic neuroimmune dysregulation. Several clinical studies have demonstrated elevated peripheral concentrations of IL-1β, IL-18, and C-reactive protein (CRP) in patients with PTSD, suggesting persistent activation of inflammatory pathways at both central and systemic levels [33, 34].

INTERACTIONS BETWEEN PROTEASOME DYSFUNCTION AND INFLAMMASOME SIGNALLING

Current evidence suggests that proteasome dysfunction and inflammasome activation are closely interconnected processes contributing to neuronal injury in PTSD. Oxidative stress appears to represent a major link between these mechanisms. Excessive production of reactive oxygen species damages proteins and mitochondrial structures, overwhelming intracellular degradation systems and promoting accumulation of damage-associated molecular patterns capable of activating innate immune signalling [35].

Impaired proteasomal degradation facilitates persistence of oxidised proteins and dysfunctional mitochondria, thereby enhancing inflammasome activation. Conversely, inflammatory cytokines generated during inflammasome signalling may further impair proteasome function through oxidative modification of proteasome subunits and disruption of mitochondrial metabolism. This reciprocal interaction creates a self-perpetuating cycle of oxidative injury, neuroinflammation, and neuronal dysfunction [36, 37].

Research conducted by Bansal Y et al. demonstrated that inhibition of proteasome activity enhanced NLRP3 inflammasome activation in microglial cultures exposed to oxidative stress [38]. Increased accumulation of damaged mitochondrial proteins promoted release of mitochondrial DNA and amplified secretion of interleukin-1β. Similar observations were reported in animal models of chronic stress, where reduced proteasome activity was associated with enhanced inflammatory signalling and increased neuronal apoptosis within the hippocampus.

Disturbances in these interconnected pathways may have profound consequences for synaptic plasticity and neuronal resilience. Both proteasome activity and inflammasome signalling regulate turnover of synaptic proteins, glutamate receptor trafficking, dendritic spine formation, and neurotrophic signalling. Chronic dysregulation of these processes may therefore contribute to impaired fear extinction, maladaptive memory consolidation, and persistent behavioural abnormalities observed in PTSD [39].

Recent studies additionally suggest that chronic neuroinflammation and impaired proteostasis may accelerate biological ageing within the brain. Increased oxidative stress, mitochondrial dysfunction, and persistent inflammatory activation resemble molecular alterations observed in neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. Several epidemiological studies have demonstrated increased risk of cognitive decline and dementia among individuals with chronic PTSD, supporting the hypothesis that traumatic stress may induce progressive neurodegenerative vulnerability.

The reciprocal interactions between proteasome dysfunction and NLRP3 inflammasome activation in PTSD-related neuronal injury are presented in Table 2.

THERAPEUTIC PERSPECTIVES

Growing understanding of the interaction between proteasome dysfunction and inflammasome activation has generated interest in novel therapeutic strategies targeting neuroinflammatory and proteostatic pathways. Experimental studies suggest that selective inhibition of NLRP3 signalling may reduce neuronal injury and improve behavioural outcomes in chronic stress models.

MCC950, a selective NLRP3 inhibitor, has demonstrated significant neuroprotective effects in experimental studies. Administration of MCC950 reduced interleukin-1β production, attenuated microglial activation, and improved synaptic plasticity within the hippocampus. Similar effects were observed following administration of antioxidant compounds targeting mitochondrial oxidative stress, indicating that reduction of reactive oxygen species may indirectly suppress inflammasome activation [40].

Modulation of proteasomal activity may represent another potential therapeutic strategy. Experimental studies suggest that restoration of intracellular protein degradation pathways improves neuronal survival and reduces oxidative injury. Although pharmacological targeting of the UPS in psychiatric disorders remains insufficiently explored, regulation of proteostasis may become increasingly relevant in future neurobiological treatment approaches [24, 27].

Non-pharmacological interventions may additionally influence neuroinflammatory and proteostatic pathways. Physical exercise, sleep regulation, stress reduction, and dietary interventions have been associated with reduced inflammatory activity, improved mitochondrial function, and enhanced neuroplasticity. Such approaches may complement pharmacological strategies aimed at restoring neuronal homeostasis following traumatic stress exposure.

Further investigation is required to clarify the precise molecular interactions between proteasome dysfunction, inflammasome activation, mitochondrial injury, and synaptic abnormalities in PTSD. Improved understanding of these mechanisms may facilitate identification of novel biomarkers and support development of targeted neuroprotective therapies for trauma-related disorders [14, 18, 26].

LIMITATIONS

Several limitations should be considered when interpreting the evidence presented in this review. First, a large proportion of available data derives from experimental animal models and in vitro studies, which do not fully reproduce the clinical heterogeneity of PTSD. Although chronic stress paradigms mimic selected behavioural and molecular features of trauma-related pathology, their translational validity remains limited.

Second, most clinical studies are cross-sectional, which restricts conclusions regarding causality and temporal relationships between proteasome dysfunction, inflammasome activation, oxidative stress, mitochondrial impairment, and PTSD progression. The sequence in which these processes emerge after trauma exposure remains insufficiently defined.

Third, methodological heterogeneity across studies may affect interpretation of results. Differences in stress models, biological samples, brain regions, inflammatory biomarkers, and techniques used to assess proteasome activity or NLRP3 inflammasome signalling limit direct comparison between studies.

Clinical investigations are also frequently constrained by small sample sizes and confounding factors, including comorbid depression, anxiety disorders, sleep disturbance, substance use, metabolic abnormalities, and pharmacological treatment. These variables may independently influence neuroinflammatory, oxidative, and proteostatic pathways. Further longitudinal and translational studies are therefore required to clarify the mechanistic contribution of proteasome and inflammasome dysregulation to PTSD-related neuronal injury.

CONCLUSIONS

Current evidence indicates that proteasome dysfunction and inflammasome activation are important, interconnected mechanisms in the neurobiology of PTSD. Chronic traumatic stress promotes oxidative damage, mitochondrial dysfunction, impaired proteostasis, and persistent neuroinflammatory signalling within stress-sensitive brain regions, particularly the hippocampus, amygdala, and prefrontal cortex.

The interaction between the ubiquitin–proteasome system and the NLRP3 inflammasome may create a self-perpetuating cycle of cellular stress, microglial activation, cytokine release, synaptic dysfunction, and reduced neuronal plasticity. These mechanisms may contribute to impaired fear extinction, emotional dysregulation, cognitive disturbances, and increased neuronal vulnerability observed in PTSD.

Targeting proteasome activity, mitochondrial homeostasis, oxidative stress, and inflammasome signalling may represent a promising direction for future therapeutic development. Further studies are needed to identify reliable biomarkers and neuroprotective strategies capable of limiting chronic neuroinflammation and preserving neuronal integrity after traumatic stress

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CONFLICT OF INTEREST

The Author declares no conflict of interest

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CORRESPONDING AUTHOR

Ewa Alicja Ogłodek

Dr. Władysław Biegański Collegium Medicum,
Jan Długosz University in Czestochowa,
Częstochowa, Poland
e-mail: eoglodek@gmail.com

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