Journal of Medical and Therapeutical Sciences
Vol.1., No.2: 118-126
Doi: 10.37253/jmts.v1i2.12298

Genetic and Molecular Mechanisms of Emotional Stress: Inflammatory Signaling and Apoptotic Pathways

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Published: 30-06-2026

Abstract
Emotional stress is a psychological and physiological condition associated with inflammation, oxidative stress, and apoptosis. Chronic emotional stress has been linked to psychiatric and neurodegenerative disorders, including depression, anxiety, cognitive impairment, and Alzheimer's disease. This review summarizes the genetic and molecular mechanisms underlying emotional stress, focusing on inflammatory signaling and apoptotic pathways. Literature was obtained from PubMed, Scopus, and ScienceDirect using keywords related to emotional stress, neuroinflammation, oxidative stress, and apoptosis, with studies published between 2021 and 2026 prioritized. Chronic emotional stress activates the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, resulting in increased glucocorticoid secretion and immune dysregulation. Persistent stress exposure promotes the production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β through NF-κB activation. Furthermore, oxidative stress and mitochondrial dysfunction induce apoptotic regulators including Bax, caspases, and p53 while suppressing Bcl-2 expression. Epigenetic modifications and genetic polymorphisms also contribute to individual susceptibility to stress-related disorders. Overall, inflammatory signaling and apoptosis are closely interconnected in the pathophysiology of emotional stress and may represent potential therapeutic targets.
Keywords: Emotional stress, inflammatory signaling, apoptosis, oxidative stress, neuroinflammation.

Abstrak
Stres emosional merupakan kondisi psikologis dan fisiologis yang berkaitan dengan inflamasi, stres oksidatif, dan apoptosis. Stres emosional kronis telah dikaitkan dengan berbagai gangguan psikiatri dan neurodegeneratif, termasuk depresi, kecemasan, gangguan kognitif, dan penyakit Alzheimer's disease. Tinjauan ini merangkum mekanisme genetik dan molekuler yang mendasari stres emosional, dengan fokus pada jalur pensinyalan inflamasi dan jalur apoptosis. Literatur diperoleh dari basis data PubMed, Scopus, dan ScienceDirect menggunakan kata kunci yang berkaitan dengan stres emosional, neuroinflamasi, stres oksidatif, dan apoptosis, dengan memprioritaskan studi yang dipublikasikan antara tahun 2021 hingga 2026. Stres emosional kronis mengaktivasi aksis hipotalamus–hipofisis–adrenal dan sistem saraf simpatis, sehingga meningkatkan sekresi glukokortikoid dan menyebabkan disregulasi sistem imun. Paparan stres yang persisten mendorong produksi sitokin proinflamasi seperti IL-6, TNF-α, dan IL-1β melalui aktivasi NF-κB. Selain itu, stres oksidatif dan disfungsi mitokondria menginduksi regulator apoptosis, termasuk Bax, kaspase, dan p53, serta menekan ekspresi Bcl-2. Modifikasi epigenetik dan polimorfisme genetik juga berkontribusi terhadap kerentanan individu terhadap gangguan yang berhubungan dengan stres. Secara keseluruhan, pensinyalan inflamasi dan apoptosis saling berhubungan erat dalam patofisiologi stres emosional dan berpotensi menjadi target terapeutik di masa depan.
Kata kunci: stres emosional, pensinyalan inflamasi, apoptosis, stres oksidatif, neuroinflamasi.

INTRODUCTION

Emotional stress is a psychological and physiological response to internal or external stressors, including traumatic experiences, social pressure, occupational demands, and environmental challenge(1). In recent decades, the prevalence of emotional stress has increased significantly due to rapid societal and technological changes, making it a major public health concern worldwide(2). Persistent emotional stress has been strongly associated with the development of various psychiatric and neurodegenerative disorders, including depression, anxiety, cognitive impairment, and Alzheimer's disease(3–6). Consequently, understanding the genetic and molecular mechanisms underlying emotional stress has become an important area of biomedical research (7).

At the physiological level, emotional stress primarily activates the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system, resulting in elevated secretion of glucocorticoids such as cortisol and catecholamines (8–10). Although these responses are essential for short-term adaptation and survival, chronic activation of stress pathways can disrupt cellular homeostasis and contribute to pathological alterations in multiple organ systems(8,11). Accumulating evidence indicates that prolonged emotional stress induces dysregulation of immune function and promotes chronic low-grade inflammation (10,12–14).

Inflammatory signaling pathways play a critical role in mediating the biological effects of emotional stress. Chronic stress exposure has been associated with increased production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β)(9,10,12,15). These inflammatory mediators can alter neuronal function, impair synaptic plasticity, and disrupt neurotransmitter regulation within the central nervous system. In addition, activation of transcription factors such as nuclear factor-kappa B (NF-κB) has been identified as a key molecular mechanism linking stress responses to inflammatory gene expression. Persistent neuroinflammation has therefore been considered a major contributor to stress-related psychiatric and neurological disorders(15–18).

In addition to inflammation, emotional stress has been closely linked to the activation of apoptotic pathways. Chronic stress conditions can increase oxidative stress and mitochondrial dysfunction, leading to excessive production of reactive oxygen species (ROS) (19–22). Alterations trigger the activation of pro-apoptotic proteins such as Bax, caspases, and p53, while simultaneously suppressing anti-apoptotic regulators including Bcl-2(23–25). Dysregulated apoptosis, particularly in neuronal tissues, may result in neuronal loss, impaired neurogenesis, and cognitive dysfunction. Such mechanisms have been implicated in the pathophysiology of stress-induced neurodegeneration and mood disorders(19).

Recent advances in molecular biology and genomics have further demonstrated that emotional stress can influence gene expression through epigenetic modifications, including DNA methylation, histone modification, and microRNA regulation. These molecular alterations may determine individual susceptibility or resilience to stress-related disorders. Furthermore, genetic polymorphisms in inflammatory and apoptotic signaling genes have been associated with variability in stress responses among individuals (7,26).

Despite substantial progress in this field, the complex interactions between inflammatory signaling and apoptotic pathways under conditions of emotional stress remain incompletely understood. Further investigation is necessary to elucidate the molecular networks involved and to identify potential biomarkers and therapeutic targets for stress-related diseases (22,27). Therefore, studying the genetic and molecular mechanisms of emotional stress, particularly in relation to inflammatory signaling and apoptotic pathways, is essential for advancing the understanding of stress-associated pathophysiology and developing more effective therapeutic strategies.

METHODS

Literature Search Strategy

A systematic literature search was conducted using three major scientific databases: PubMed, Scopus, and ScienceDirect. The search process employed combinations of the following keywords: “emotional stress,” “psychological stress,” “inflammatory signaling,” “neuroinflammation,” “apoptotic pathways,” “oxidative stress,” “cytokines,” “NF-κB,” “caspase activation,” “mitochondrial dysfunction,” and “stress-related disorders.” Articles published in

English between 2021 and 2026 were prioritized to ensure that the review reflected the most recent scientific developments related to the genetic and molecular mechanisms of emotional stress.

Inclusion and Exclusion Criteria

The inclusion criteria comprised original research articles, review articles, and meta-analyses discussing molecular and genetic mechanisms of emotional stress, particularly those involving inflammatory signaling pathways, oxidative stress, and apoptosis. Relevant in vitro studies, in vivo experimental studies, and clinical investigations were also included. Studies focusing on stress-induced alterations in cytokine production, transcription factor activation, mitochondrial dysfunction, neuronal apoptosis, and epigenetic regulation were considered eligible for analysis.

The exclusion criteria included articles unrelated to emotional stress or molecular stress responses, case reports lacking mechanistic discussion, conference abstracts without full-text availability, duplicate publications, and studies published before 2021. Non-English publications were also excluded to maintain consistency in data interpretation.

Literature Selection

The literature selection process was performed in several stages. Initially, titles and abstracts were screened to evaluate their relevance to the topic of emotional stress and its associated inflammatory and apoptotic mechanisms. Articles considered potentially relevant were subsequently reviewed through full-text assessment to determine their eligibility according to the predefined inclusion and exclusion criteria. Only studies meeting all criteria were included in the final synthesis and analysis of this review.

Data Extraction and Analysis

Data extraction and analysis were conducted using a narrative review approach. Each selected study was analyzed comprehensively to identify the molecular pathways associated with emotional stress, including inflammatory cytokine signaling, oxidative stress responses, mitochondrial dysfunction, apoptotic activation, and genetic or epigenetic regulation. Particular attention was given to the involvement of signaling molecules such as NF-κB, IL-6, TNF-α, IL-1β, Bax, Bcl-2, caspases, and p53.

The extracted findings were subsequently synthesized descriptively to establish connections among inflammatory signaling, oxidative stress, and apoptosis in stress-related pathophysiology. This approach enabled a comprehensive interpretation of the molecular interactions underlying emotional stress and their potential clinical implications without the use of quantitative meta-analysis.

RESULTS

1. Inflammatory Signaling Pathways in Emotional Stress

Current evidence demonstrates that emotional stress induces significant activation of inflammatory signaling pathways at both systemic and cellular levels. Chronic emotional stress has consistently been associated with elevated production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) (10,15,18). Increased cytokine expression contributes to persistent neuroinflammation and dysregulation of neuronal communication within the central nervous system. In addition, activation of the nuclear factor-kappa B (NF-κB) pathway has been identified as a central molecular mechanism linking stress exposure to inflammatory gene expression(15,28,29).

Stress-induced inflammatory responses were also found to promote oxidative stress through excessive generation of reactive oxygen species (ROS). Elevated ROS levels contribute to mitochondrial dysfunction, lipid peroxidation, and cellular damage, particularly in neuronal tissues. Persistent inflammatory activation may therefore impair synaptic plasticity, neurogenesis,

and cognitive function, ultimately increasing susceptibility to psychiatric and neurodegenerative disorders(15,20,22).

2. Apoptotic Pathways Activated by Emotional Stress

Multiple studies indicate that chronic emotional stress activates apoptotic signaling pathways through both intrinsic and extrinsic mechanisms. Mitochondrial dysfunction caused by oxidative stress promotes the release of cytochrome c and subsequent activation of caspase-dependent apoptosis. Increased expression of pro-apoptotic proteins such as Bax, caspase-3, caspase-9, and p53 has been observed under prolonged stress conditions, whereas anti-apoptotic proteins including Bcl-2 are frequently downregulated(23,24,30–32).

Excessive neuronal apoptosis resulting from chronic stress has been associated with structural and functional alterations in brain regions involved in emotional regulation, including the hippocampus, amygdala, and prefrontal cortex. These alterations may contribute to impaired memory, emotional instability, anxiety disorders, and depressive symptoms. Furthermore, stress-induced apoptosis has also been implicated in accelerated neurodegenerative processes through progressive neuronal loss(15,19,22).

3. Genetic and Epigenetic Regulation of Stress Responses

Recent molecular studies have demonstrated that emotional stress can alter gene expression through both genetic and epigenetic mechanisms. Several genes involved in inflammatory signaling and apoptosis exhibit dysregulated expression following chronic stress exposure. Transcription factors such as NF-κB and p53 play major roles in regulating inflammatory mediators and apoptotic proteins during stress responses(7,28,33).

In addition, epigenetic modifications including DNA methylation, histone modification, and microRNA dysregulation have been reported to influence stress susceptibility and resilience. These molecular alterations may affect long-term neuronal adaptation and contribute to the progression of stress-related disorders. Certain genetic polymorphisms in cytokine-related and apoptosis-related genes have also been associated with interindividual variability in stress responses(7,26,34).

4. Clinical Implications and Potential Therapeutic Targets

The findings from recent literature suggest that inflammatory and apoptotic biomarkers may have important clinical applications in stress-related disorders. Biomarkers such as IL-6, TNF-α, ROS levels, caspase activation, and Bcl-2 expression have been proposed as potential indicators for disease progression and therapeutic monitoring(22,35–37).

Several therapeutic strategies targeting inflammatory signaling and apoptotic pathways have shown promising results in experimental studies. Anti-inflammatory agents, antioxidants, and neuroprotective compounds may reduce oxidative damage and suppress excessive inflammatory activation. Furthermore, therapies targeting mitochondrial protection and epigenetic regulation are increasingly being explored as potential approaches for preventing stress-induced neuronal damage. However, further clinical studies are still required to evaluate the long-term efficacy and safety of these interventions(38–41).

DISCUSSION

This review demonstrates that emotional stress plays a significant role in the activation of inflammatory signaling and apoptotic pathways, both of which contribute to the pathophysiology of stress-related disorders. Chronic emotional stress disrupts physiological homeostasis through persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, leading to prolonged exposure to glucocorticoids and inflammatory mediators. These alterations trigger molecular and cellular responses that may ultimately impair neuronal integrity and systemic health(10,15,42).

One of the major findings highlighted in this review is the strong association between emotional stress and inflammatory signaling. Prolonged stress exposure increases the production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, which contribute to chronic neuroinflammation and immune dysregulation. Activation of NF-κB signaling appears to be a central mechanism underlying this process, as it regulates the transcription of numerous inflammatory genes (10,15,29,43). Persistent inflammatory activation may impair synaptic plasticity, neurotransmitter balance, and neuronal communication, thereby increasing vulnerability to psychiatric disorders including depression and anxiety. These findings are consistent with previous studies demonstrating that chronic inflammation contributes significantly to stress-related neurological dysfunction(15,27).

Oxidative stress also represents an important mediator linking inflammation to cellular injury during emotional stress. Excessive production of reactive oxygen species (ROS) promotes mitochondrial dysfunction, lipid peroxidation, and DNA damage. Mitochondria are particularly vulnerable to oxidative injury due to their central role in cellular energy metabolism. Under chronic stress conditions, mitochondrial impairment may reduce neuronal energy production and increase susceptibility to apoptosis. This mechanism supports the hypothesis that oxidative stress is a critical factor in the progression of neurodegenerative and psychiatric disorders associated with chronic emotional stress(22,44,45).

The present review further demonstrates that apoptotic pathways are strongly influenced by prolonged emotional stress. Increased expression of pro-apoptotic proteins such as Bax, caspase-3, caspase-9, and p53, combined with decreased expression of anti-apoptotic proteins including Bcl-2, promotes neuronal apoptosis and tissue degeneration. Activation of mitochondrial-mediated apoptosis has been particularly associated with structural changes in the hippocampus and prefrontal cortex, which are brain regions involved in memory, cognition, and emotional regulation. Excessive neuronal apoptosis may therefore explain the cognitive impairment and emotional dysregulation commonly observed in individuals experiencing chronic stress(15,16,19,24).

Another important aspect discussed in this review is the role of genetic and epigenetic regulation in stress responses. Emotional stress can alter gene expression through DNA methylation, histone modification, and microRNA regulation, resulting in long-term changes in neuronal function and stress adaptation. These epigenetic modifications may contribute to individual variability in stress susceptibility and resilience. In addition, genetic polymorphisms involving inflammatory cytokines and apoptotic regulators may influence the severity of stress-induced cellular damage. Such findings suggest that both environmental and genetic factors interact dynamically in determining stress-related disease outcomes(7,46).

The reviewed literature also highlights several potential clinical implications. Biomarkers associated with inflammation and apoptosis, including IL-6, TNF-α, ROS, caspase activation, and Bcl-2 expression, may serve as valuable indicators for diagnosis, prognosis, and therapeutic monitoring in stress-related disorders. Furthermore, therapeutic strategies targeting inflammatory signaling, oxidative stress, and mitochondrial dysfunction have shown promising potential in experimental studies. Anti-inflammatory agents, antioxidants, neuroprotective compounds, and epigenetic modulators may help reduce cellular injury and improve neuronal survival under chronic stress conditions(20,22,39,41).

Nevertheless, several limitations remain within the current literature. Many studies are still based on experimental animal models or in vitro systems, which may not fully represent the complexity of human emotional stress responses. Variability in study design, stress models, and biomarker assessment also contributes to inconsistent findings across studies. In addition, the molecular interactions between inflammatory signaling and apoptosis remain incompletely

understood, particularly regarding their temporal regulation and tissue-specific effects (7,15,22,27).

Overall, this review emphasizes that emotional stress is closely associated with inflammatory activation, oxidative stress, mitochondrial dysfunction, and apoptosis at the molecular level. The interaction among these pathways contributes substantially to the development and progression of stress-related psychiatric and neurodegenerative disorders. A deeper understanding of these mechanisms may facilitate the development of more effective diagnostic tools and targeted therapeutic interventions for emotional stress-associated diseases (15,19,20,22,27).

CONCLUSION

Emotional stress contributes significantly to the activation of inflammatory signaling and apoptotic pathways involved in stress-related disorders. Chronic stress induces HPA axis activation, excessive production of pro-inflammatory cytokines, oxidative stress, and mitochondrial dysfunction, leading to neuronal damage and impaired cellular homeostasis. Activation of NF-κB signaling and apoptotic regulators such as Bax, caspases, and p53, along with suppression of Bcl-2, plays a major role in stress-induced inflammation and apoptosis. In addition, genetic and epigenetic mechanisms influence individual susceptibility to stress-related diseases. Biomarkers and therapeutic approaches targeting inflammation, oxidative stress, and apoptosis may provide promising strategies for the diagnosis and treatment of stress-associated disorders. However, further studies are required to clarify the molecular mechanisms and evaluate the effectiveness of targeted therapies.

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