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CORTISOL AS A KEY FACTOR IN THE DEVELOPMENT OF POST-TRAUMATIC STRESS DISORDER AND THE ROLE OF MELATONIN IN THE NEUROPROTECTION OF THIS CONDITION

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Cortisol is the most important glucocorticoid hormone, the stimulation of which is clearly organized by the hypothalamic-pituitary-adrenal axis, and the secretion itself is provided by the adrenal cortex. It plays a key role in various physiological processes. Cortisol dysfunction due to chronic stress has serious consequences for many body systems and is characterized by hyperactivity of the hypothalamic-pituitary-adrenal axis and disruption of the amygdala-cortico-hippocampal circuit - a trigger for post-traumatic stress disorder. Understanding the multifaceted mechanisms of the constant influence of this hormone is important, as it opens up prospects for mitigating the detrimental effects of traumatic disorders, for example, with the use of melatonin as part of adjuvant therapy. The purpose of the study was to analyze and summarize data from many years of research in the field of disorders arising from post-traumatic stress disorder, to deepen understanding of the importance of further directions and prospects for correcting body dysfunctions in this pathological condition. An analysis of modern publications from the scientometric databases Scopus, Web of Science, PubMed, and Google Scholar was conducted. The following keywords were searched in the PubMed database: “post-traumatic stress disorder”, “cortisol”, “hypothalamic-pituitary-adrenal axis”, “melatonin”, “acute and chronic stress”. Particular attention was paid to publications from the last 5 years to provide an analysis of modern scientific approaches. Additionally, classical studies were taken into account, which laid the foundation for further discoveries in this field. To gain a deeper understanding of the problem, articles were analyzed that included results from double-blind, randomized, placebo-controlled trials, data from meta-analyses and systematic reviews, and studies using biochemical methods to assess cortisol and melatonin levels. After collecting the literature, a critical analysis was conducted using statistical data processing tools. A comparative analysis method was used to evaluate the effectiveness of melatonin in regulating the hypothalamic-pituitary-adrenal axis and reducing symptoms of posttraumatic stress disorder. Particular attention was paid to studies examining the molecular mechanisms underlying cortisol's effects on the hippocampus and amygdala, as well as to works exploring the potential for neuroprotection with melatonin. We suggest that the use of exogenous melatonin can suppress cortisol secretion in patients with posttraumatic stress disorder and, as a result, reduce the frequency of side effects in the form of sleep dysfunction, but this issue requires further research.

Key words: post-traumatic stress disorder, cortisol, hypothalamic-pituitary-adrenal axis, melatonin, acute and chronic stress.

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КОРТИЗОЛ ЯК КЛЮЧОВИЙ ЧИННИК РОЗВИТКУ ПОСТТРАВМАТИЧНОГО СТРЕСОВОГО РОЗЛАДУ І РОЛЬ МЕЛАТОНІНУ В НЕЙРОПРОТЕКЦІЇ ДАНОГО СТАНУ

Кортизол є найважливішим глюкокортикоїдним гормоном, стимуляція на виділення якого чітко організовується гіпоталамо-гіпофізарно-наднирниковою віссю, а сама секреція забезпечується корою наднирникових залоз. Він відіграє ключову роль у різних фізіологічних процесах. Дисфункції кортизолу внаслідок хронічного стресу мають серйозні наслідки для багатьох систем організму та характеризуються гіперактивність гіпоталамо-гіпофізарно-наднирникової вісі та порушенням мигдале-кортико-гіпокампального контуру – тригера посттравматичного стресового розладу. Розуміння багатогранних механізмів постійного впливу цього гормону має важливе значення, оскільки відкриває перспективи для пом’якшення згубних наслідків травматичного розладу, до прикладу, із застосуванням мелатоніну в складі ад’ювантної терапії. Метою огляду є проаналізувати та узагальнити дані багатьох років досліджень у галузі розладів, що виникають на фоні посттравматичного стресового розладу, поглибити розуміння про важливість подальших напрямків та перспектив корекції дисфункцій організму за даного патологічного стану. Проведено аналіз сучасних публікацій з наукометричних баз даних Scopus, Web of Science, PubMed та Google Scholar. Виконано запити за ключовими словами у базі PubMed: “post-traumatic stress disorder”, “cortisol”, “hypothalamic-pituitary-adrenal axis”, “melatonin”, “acute and chronic stress”. Особливу увагу приділено публікаціям останніх 5 років, щоб забезпечити аналіз сучасних наукових підходів. Додатково було враховано класичні дослідження, що заклали основу для подальших відкриттів у цій галузі. Для більш глибокого розуміння проблеми було проаналізовано статті, що включали результати подвійних сліпих рандомізованих плацебо контрольованих досліджень, дані мета-аналізів та системних оглядів, результати досліджень з використанням біохімічних методів для оцінки рівня кортизолу та мелатоніну. Після збору літератури проводився її критичний аналіз із застосуванням інструментів статистичної обробки даних. Використано метод порівняльного аналізу для оцінки ефективності мелатоніну в регуляції гіпоталамо-гіпофізарно-наднирникової вісі та зменшенні симптомів посттравматичного стресового розладу. Окрему увагу приділено дослідженням, що вивчали молекулярні механізми впливу кортизолу на гіпокамп і мигдалину, а також роботам, які розглядали потенціал нейропротекції за допомогою мелатоніну. Ми припускаємо, що застосування екзогенного мелатоніну здатне пригнічувати виділення кортизолу в пацієнтів з посттравматичним стресовим розладом і, як наслідок, зменшувати частоту прояву побічних ефектів у вигляді дисфунцій сну, проте це питання потребує подальшого дослідження.

Ключові слова: посттравматичний стресовий розлад, кортизол, гіпоталамо-гіпофізарно-наднирникова вісь, мелатонін, гострий та хронічний стрес.

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Post-traumatic stress disorder (PTSD) is a chronic mental state disorder that occurs in response to a traumatic event, accompanied by maladaptation and exhaustion of the central nervous system (CNS). It is often described as a harmful component of the emotional spectrum, re-experiencing traumatic memories and intrusive thoughts. The prevalence of the disorder is about 6–8 % in the general population, but can increase to 25 % among groups that have experienced severe psychological impact, such as wartime activities, veterans, refugees, victims of various forms of violence, or participants and witnesses of road accidents [29].

According to the Ministry of Health of Ukraine, over the past two years, the electronic health system (EHS) has registered a significant increase in the number of patients with a confirmed diagnosis of PTSD. Compared to 2021, the number of cases in 2023 increased almost fourfold, and in the first two months of 2024, the increase in patients was actually equal to the number in 2021 (Fig. 1).

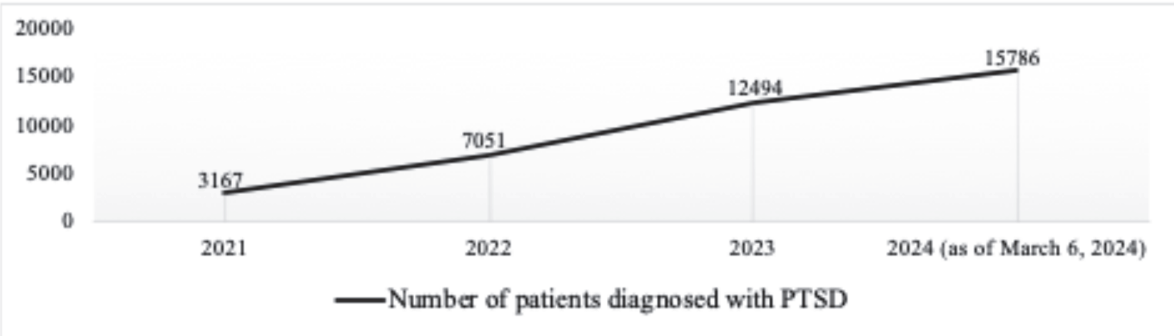

Fig. 1. Increase in PTSD cases by chronology, according to EHS data.

Post-traumatic stress disorder manifests itself as chronic stress, in which several structures of the neurohumoral system are activated, and a large number of hormones and biologically active substances are released. Of great interest is the influence of cortisol as the primary trigger of PTSD, which plays the role of a trigger mechanism in the processes of neurodestruction [33].

In light of new approaches to PTSD treatment, psychedelic-associated therapy is attracting significant attention. The use of substances such as methylenedioxymethamphetamine (MDMA), ketamine, and psilocybin has shown promising results in reducing PTSD symptoms, especially in cases resistant to standard pharmacotherapy [3, 25, 30]. Psychedelics affect emotional regulation networks, helping to reframe traumatic experiences and reduce the emotional burden associated with them. Although these methods are still the subject of clinical research and ethical debate, their potential opens up a new dimension in the treatment of severe forms of PTSD.

Ketamine is also considered a promising agent in the treatment of PTSD. Studies show that repeated intravenous administration of ketamine can significantly improve PTSD symptoms compared to placebo, although the duration of the effect requires further analysis [13, 31].

In the context of the search for effective but safe remedies, increasing attention is being paid to the role of melatonin as an adjuvant in the treatment of PTSD. Melatonin, as a neuroprotector and regulator of circadian rhythms, can affect sleep quality, reduce anxiety, oxidative stress, and inflammation, which are key links in the pathogenesis of PTSD [35]. Its safety profile and the availability of multiple application sites make melatonin a promising component of multimodal therapy for this disorder.

The purpose of the study was to analyze and summarize data from many years of research in the field of disorders arising from PTSD, to deepen understanding of the importance of further directions and prospects for correcting body dysfunctions in this pathological condition.

As part of the review article, an analysis of modern scientometric databases Scopus, Web of Science, PubMed, The Cochrane Library, EMBASE, and Global Health was conducted. The following keywords were searched in the PubMed database: "post-traumatic stress disorder", "cortisol", "hypothalamic-pituitary-adrenal axis", "melatonin", "acute and chronic stress". To gain a deeper understanding of the problem, articles were analyzed that included the results of double-blind randomized placebo-controlled trials, meta-analyses, and systematic reviews. This approach ensured maximum relevance and scientific reliability of the sources used.

The search was conducted in two stages: an initial electronic search in each database and an additional manual search by analyzing literature lists and articles citing key publications. In total, more than 250 results were analyzed. Of these, 36 sources were selected according to the indexing criteria in

Scopus, Web of Science, and PubMed. Inclusion criteria were: peer-reviewed articles published in journals indexed in Scopus, Web of Science, or PubMed; double-blind randomized placebo-controlled trials, systematic reviews, meta-analyses, clinical and prospective studies; special attention was paid to articles published in the last 5 years; language of publication – English. Exclusion criteria are articles containing data from animal experiments without clinical extrapolation; articles lacking full text; conference abstracts; duplicates; and articles that did not correspond to the topic. Last search performed on August 10, 2025.

For complete transparency, the verbatim search queries used in the PubMed database are provided: “post-traumatic stress disorder” OR “PTSD” AND “cortisol” AND “hypothalamic-pituitary-adrenal axis” OR “HPA axis” AND “melatonin” AND “acute and chronic stress”.

Table 1

Simplified PRISMA Flow

Stage	Description	Number of Records/Studies
1. Identified	Total number of records identified through database searching and other sources	250
2. Duplicates Removed	Number of records removed before screening (e.g., duplicates)	40
3. Screened (Title/Abstract)	Number of records screened after duplicates were removed	210
4. Assessed for Eligibility (Full-text)	Number of full-text articles assessed for eligibility against the inclusion/exclusion criteria	60
5. Included in Review	Total number of primary studies finally included in the systematic review	36

Post-traumatic stress disorder activates several brain areas, namely the insular cortex, prefrontal cortex, hippocampus, and amygdala [5, 6, 36]. These brain regions work in a consolidated manner to capture and subsequently express fear memories [20]. Most studies of the neuroanatomy of PTSD focus specifically on the role of the amygdala and hippocampus. Maladaptive responses to prolonged stress are associated with profound functional changes in different parts of the amygdala [4, 11, 31]. For example, in contrast to dendritic retraction observed elsewhere in the cortico-limbic system (dorsomedial prefrontal cortex and hippocampus), projection neurons in the basolateral amygdala undergo hypertrophic changes in their dendrites [6, 31]. Researchers using neuroimaging techniques for PTSD almost immediately took note of the hippocampus and reported significantly smaller volumes in individuals exposed to chronic stress compared to controls. To date, this has been confirmed in large-scale meta-analyses [10, 12]. Distorted appraisal of fear is the basis of the etymology of PTSD. The physiological stress response can be triggered by fear or a perceived threat to safety, status, or well-being, and it triggers the secretion of sympathetic catecholamines (adrenaline and noradrenaline) and neuroendocrine hormones (cortisol) to promote survival and motivate success.

Cortisol is a potent anti-inflammatory that mobilizes glucose stores for energy and modulates inflammation. It may also facilitate the consolidation of fear-based memories for future survival and avoidance of danger [23]. As for neural circuits, the most affected is the amygdala. This structure is hyperactivated in response to fear or danger, initiating an immediate sympathetic response, which is soon followed by a neuroendocrine response, instinctively trying to restore homeostasis and promote survival [7, 22]. As a result, the brain is in a constant state of heightened alertness to escape or attack, and the excited amygdala prevents the brain from falling asleep, generating new memories of the traumatic event and nightmares [21, 24, 34].

One of the first symptoms of developing post-traumatic stress disorder is the presence of sleep disorders, such as sleep apnea, insomnia, and nightmares, which disrupt the normal architecture of sleep [11]. Interestingly, sleep disturbances sometimes persist even after other PTSD symptoms have been reduced with appropriate treatment [3]. Sleep dysfunction in post-traumatic stress disorder is individual, but many people with a confirmed diagnosis have trouble falling asleep and waking up easily, often several times a night. Intrusive memories in the form of nightmares are a classic symptom of PTSD, which exacerbates the overall manifestations of the disorder. The memory is often associated with details of past trauma, with many people with PTSD reporting recurring nightmares [3, 24]. Sleep dysfunction is confirmed by data from one of the Dutch studies: compared to healthy control group participants, people with post-traumatic stress disorder had a faster heart rate during sleep, indicating an enhanced response to threat that maintains the body in a state of heightened alertness. Furthermore, compared to controls, patients with signs of the disorder demonstrated a significant increase in the number of awakenings during sleep, which correlated with overnight adrenocorticotropic hormone (ACTH) levels [31].

Cortisol is a vital natural glucocorticoid that is formed during the process of catabolism in the adrenal cortex. It is secreted daily, with peak blood concentrations in the morning to promote awakening, after which the hormone's blood concentration steadily decreases. Throughout the day, cortisol provides energy to the actively functioning brain and neuromuscular system by activating gluconeogenesis enzymes and maintaining glucose levels at a sufficient level. Glucocorticoids are also potent anti-inflammatory hormones: they prevent generalized tissue and nerve damage associated with inflammation [18]. The role of cortisol in the stress response is equally important. In the presence of a physical or psychological trigger, hormone levels increase dramatically to mobilize the energy and substrate needed to combat stress-provoking stimuli or to escape from danger [9]. Increased cortisol concentrations in response to stress are adaptive and short-term, but excessive or prolonged secretion can lead to both physical and psychological paralysis [2, 9, 28]. Depending on duration, stress is divided into acute and chronic, and the cortisol response to each will differ.

In the initial stage of the acute stress response, the amygdala becomes excited and sends nerve impulses to the brainstem, which in turn releases catecholamines (noradrenaline and adrenaline) [7]. Once in the general circulation, neurotransmitters trigger sympathetic adrenergic responses such as tachycardia, tachypnea, and hypertension, stimulate sweating, and cause pupil dilation. It is important to note that this short-term sympathetic dominance is pro-inflammatory [31]. The subsequent response to acute stress is anti-inflammatory and delayed, as it is provided by a neuroendocrine component [6]. When stress is perceived, the amygdala activates the hypothalamic-pituitary-adrenal axis, triggering a cascade that culminates in the release of cortisol from the adrenal cortex. Approximately 15 minutes after the onset of the stressor, the hormone level increases and remains elevated for several hours, after which it gradually decreases [3].

Patients with a confirmed diagnosis of post-traumatic stress disorder are exposed to chronic stress, which leads to more severe consequences, since constant reactivation of stress and, accordingly, the correlation of cortisol levels leads to dysfunction of the latter [3]. Typically, the hormone binds to glucocorticoid receptors and acts as an anti-inflammatory agent. However, prolonged or excessive secretion may lead to compensatory downregulation or receptor resistance, blocking cortisol binding, similar to the mechanism in insulin-resistant diabetes [1, 18]. It has also been suggested that random bursts of glucocorticoid may increase its affinity for the mineralocorticoid receptor, mediating pro-inflammatory activity [36].

Regardless of the etiology, cortisol dysfunction disrupts the negative feedback loop, which suppresses the release of corticotropin-releasing hormone [28]. In turn, the accumulation of the latter leads to the release of norepinephrine from the brainstem's blue spot and increased regulation of glutamate and N-methyl-D-aspartate (NMDA) in the amygdala. Increased excitatory input in the amygdala can hyperpolarize postsynaptic potentials, making it resistant to inhibitory input from the prefrontal cortex [7, 8, 17, 28].

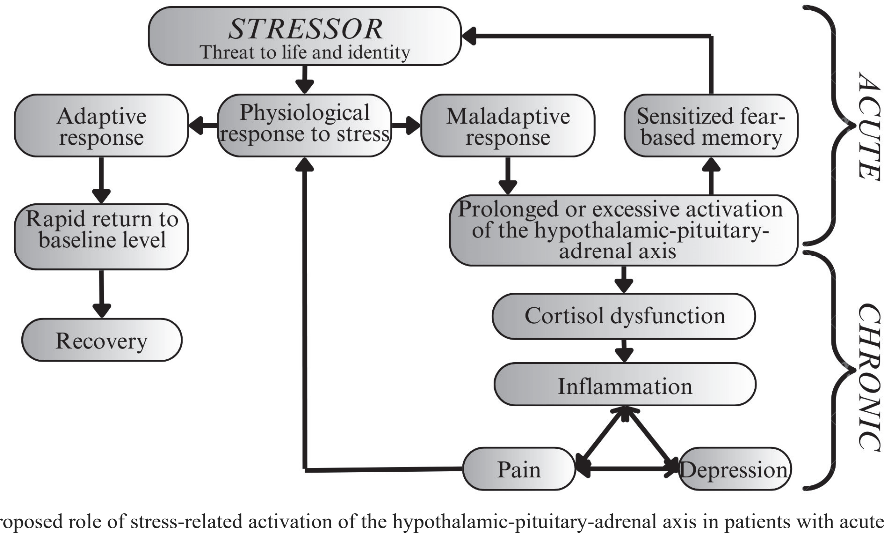

Fig. 2. Proposed role of stress-related activation of the hypothalamic-pituitary-adrenal axis in patients with acute and chronic stress.

This explains the lack of brain deactivation in patients with post-traumatic stress disorder and, as a result, the development of side effects, such as sleep dysfunction. Due to the high frequency of the latter, the issue of using hypnotics as part of adjuvant therapy for PTSD is acute.

Melatonin is the main pineal hormone that regulates the body's sleep-wake cycle. The synthesis and secretion of the bioregulator is controlled by the suprachiasmatic nucleus of the hypothalamus and depends on the time of day, and the possibility of oral administration has sparked interest in its use for the treatment of insomnia. The hormone's mechanism of action is mediated by two types of membrane-specific receptors: high-affinity ML1 sites and low-affinity ML2 sites. ML1 is localized in the anterior pituitary and the suprachiasmatic nucleus of the hypothalamus, which is the anatomical site of the circadian clock, as well as in the cerebral cortex, hippocampus, and amygdala [15, 16, 19, 26]. Exogenous melatonin supplementation is well tolerated and has no apparent short- or long-term side effects. Melatonin synchronizes circadian rhythms and improves the onset, duration, and quality of sleep [27, 31]. Since the endocrine response to acute and chronic stress is regulated by two major peptidergic activators of the hypothalamic-pituitary-adrenal axis: corticotropin-releasing hormone and arginine vasopressin, researchers have become interested in the effects of melatonin on these biologically active substances. The secretory activity of the latter was determined in an experiment in which rats received daily melatonin injections. 7 days after the hormone was administered to rats in the experimental group, a decrease in blood glucocorticoids was observed in response to acute and chronic stress. Indeed, chronic melatonin treatment prevented the decrease in adrenocorticotropic hormone secretion induced by chronic stress. Hypothalamic corticotropin-releasing hormone levels were significantly lower in treated rats, while arginine vasopressin remained largely unchanged, but melatonin administration counteracted the chronic stress-induced decrease in hypothalamic arginine vasopressin levels and release in vitro [14]. Thus, it can be argued that the positive effect of chronic melatonin treatment is provided by its simultaneous action in several areas of the brain:

a) suprachiasmatic nucleus of the hypothalamus: modulation of endogenous hormone secretion due to afferent impulses to the pineal gland;

b) anterior pituitary: inhibition of adrenocorticotropic hormone secretion;

c) hippocampus and amygdala.

Despite the significant amount of available data, interpretation of the results was limited in part by heterogeneity in study designs, different methods of measuring cortisol levels and sleep parameters, and a paucity of studies directly comparing acute and chronic stress in the context of PTSD. In addition, some studies relied on small samples or animal model data, limiting the generalizability of their findings to the broader population.

Conclusions

1. PTSD is a debilitating neuropsychiatric disorder described as the re-experiencing of traumatic memories, negative thoughts, and emotions, and the key area of the brain responsible for the manifestation of PTSD symptoms is the amygdala-cortico-hippocampal circuit. Excessive activation of this network's structures causes severe dysfunctions in the body.

2. There is a difference between the body's responses to acute and chronic stress: in the first case, an increased level of cortisol contributes to the consolidation of the main mechanisms that determine the physiological response to stress, in the second case, chronic reactivation of the HPA axis leads to the development of cortisol dysfunctions, which has a detrimental effect on the body as a whole.

3. Long-term melatonin administration reduced cortisol levels by activating structures previously inhibited by glucocorticoids. Thus, these two hormones of the endocrine system enter into an antagonistic relationship.

4. Further progress in the study of the neurobiology and biomarkers of PTSD will contribute to the development of basic strategies and approaches to the treatment of traumatic disorders aimed at increasing neuronal plasticity, and the integration of already known neural circuits and large-scale research will open great prospects for transformative progress in the prediction and prevention of this debilitating condition.

Summarizing the above, it can be argued that cortisol, being a key hormone of the stress response, has a pathogenetic role in the development of PTSD through activation of the amygdala-cortico-parahippocampal circuit and inhibition of the prefrontal cortex. Melatonin shows potential to reduce PTSD symptoms by normalizing circadian rhythms and reducing hypothalamic-pituitary-adrenal axis hyperactivity. Promising directions for solving the problem include developing multimodal therapy combining melatonin with cortisol antagonists, using biomarkers for early diagnosis, and conducting multicenter clinical trials to optimize the dosage and duration of therapy.

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