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ABSTRACT

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NEUROBIOLOGICAL ASPECTS OF PATHOGENETIC MECHANISMS IN THE DEVELOPMENT OF POST-TRAUMATIC STRESS DISORDER (LITERATURE REVIEW)

Post-traumatic stress disorder (PTSD) occurs as a result of exposure to a life-threatening traumatic event or situation involving violence. The main manifestations of PTSD are obsessive re-experiencing of the traumatic event, increased nervous arousal, avoidance of stimuli related to the traumatic event, emotional and cognitive disorders that persist for a long time. This mental disorder is exhausting and causes changes that make it difficult and sometimes impossible for patients with PTSD to function professionally and socially. This results in a significant clinical burden and high socioeconomic costs.

Materials and methods. The authors have reviewed more than 100 scientific papers from the world literature on the problems of diagnosis, symptoms, pathophysiological and neurobiological mechanisms that play an important role in the development of PTSD and can be used as key elements in the choice of treatment measures.

Results. Post-traumatic stress disorder is a multifactorial disease, therefore, numerous pathophysiological mechanisms and factors are involved in its occurrence and progression. The immediate response to stress is the activation of the neuroendocrine and autonomic systems with the release of adrenaline and norepinephrine. The involvement of the hypothalamic-pituitary-adrenal system and subsequent secretion of cortisol may be a trigger for the PTSD development. A link has been found between increased activity of the noradrenergic system, increased glucocorticoid

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exposure, and impaired interaction between neurons in the amygdala and prefrontal cortex. In addition, glucocorticoids are associated with the development of immune response disorders and neuroinflammation. Inflammatory cytokines can regulate and modify the functioning of neurotransmitters such as serotonin and dopamine, which contributes to the onset and progression of PTSD symptoms.

Conclusions. The data from the reviewed literature and the results of a large number of studies allow us to confirm the important role of the following mechanisms in the pathogenesis of PTSD. These include disorders of vegetative regulation, dysfunction of the hypothalamic-pituitary-adrenal system, disorders of immunological regulatory and inflammatory mechanisms, and dysregulation of the monoaminergic transmission system. Further study of the mechanisms of development and pathogenetic pathways will allow for better implementation of the strategy of medical care for patients with PTSD.

Key words: stress, post-traumatic stress disorder (PTSD), pathogenetic mechanisms, neuroinflammation, dysregulation of the hypothalamic-pituitary-adrenal system, monoaminergic disorders, dopamine, serotonin.

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НЕЙРОБІОЛОГІЧНІ АСПЕКТИ ПАТОГЕНЕТИЧНИХ МЕХАНІЗМІВ У РОЗВИТКУ ПОСТТРАВМАТИЧНОГО СТРЕСОВОГО РОЗЛАДУ (ЛІТЕРАТУРНИЙ ОГЛЯД)

Посттравматичний стресовий розлад (ПТСР) виникає внаслідок впливу загрозливої для життя травматичної події чи ситуації, пов'язаної з насиллям. Основними проявами ПТСР є нав'язливе повторне переживання травматичної події, підвищене нервове збудження, уникнення подразників, пов'язаних із травмуючою подією, емоційні та когнітивні розлади, що зберігаються протягом тривалого часу. Цей психічний розлад є виснажливим та викликає зміни, які ускладнюють і навіть іноді унеможливлюють професійне та соціальне функціонування пацієнтів із ПТСР. Це призводить до значного клінічного тягаря і великих соціально-економічних витрат.

Матеріали та методи. Авторами опрацьовано понад 100 наукових праць зі світової літератури, що стосуються проблем діагностики, симптоматики, патофізіологічних та нейробіологічних механізмів, що відіграють важливу роль у розвитку ПТСР і можуть бути ключовими ланками при виборі стратегії лікувальних заходів.

Результати. Посттравматичний стресовий розлад відносять до мультифакторіальних захворювань, тому у його виникненні та прогресуванні залучені численні патофізіологічні механізми та фактори. Негайною відповіддю на стрес є активація нейроендокринної та

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вегетативної систем з вивільненням адреналіну і норадреналіну. Залучення гіпоталамо-гіпофізарно-наднирникової системи і подальша секреція кортизолу може бути пусковим механізмом розвитку ПТСР. Виявлено зв'язок між підвищенням активності норадренергічної системи, посиленням впливу глюкокортикоїдів та порушенням взаємодії між нейронами мигдалевидного тіла і префронтальної кори мозку. Крім того глюкокортикоїди пов'язані з розвитком порушень імунної відповіді та розвитком нейрозапалення. Запальні цитокіни можуть регулювати і змінювати функціонування таких нейромедіаторів як серотонін і дофамін, що сприяє виникненню і прогресуванню симптомів ПТСР.

Висновки. Дані опрацьованих літературних джерел та результати великої кількості досліджень дозволяють підтвердити важливу роль у патогенезі ПТСР наступних механізмів. До них відносяться порушення вегетативної регуляції, дисфункція регуляції гіпоталамо-гіпофізарно-наднирникової системи, порушення імунологічних регуляторних та запальних механізмів, а також дисрегуляція системи моноамінергічної передачі. Подальше вивчення механізмів розвитку та патогенетичних шляхів дозволить краще реалізовувати стратегію медичної допомоги пацієнтам із ПТСР.

Ключові слова: стрес, посттравматичний стресовий розлад (ПТСР), патогенетичні механізми, нейрозапалення, дисрегуляція гіпоталамо-гіпофізарно-наднирникової системи, моноамінергічні порушення, дофамін, серотонін.

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INTRODUCTION / ВСТУП

A common consequence of exposure to powerful traumatic events is the development of post-traumatic stress disorder (PTSD). The American Psychiatric Association defines PTSD as a debilitating psychiatric condition characterized by the presence of a life-threatening or traumatic event in the anamnesis and the appearance of typical symptoms [1]. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the clinical manifestations of PTSD were grouped into specific symptom clusters. These include obsessive re-experiencing of the traumatic event, the appearance of cognitive and emotional disorders, feelings of anxiety and depression, avoidance of stimuli associated with the traumatic event, repeated and intrusive negative thoughts, distressing memories, abrupt mood swings, symptoms of hyperarousal and reactivity disorders, leading to sleep problems and difficulties with concentration, irritability, and increased alertness, lasting more than one month [2, 3, 4]. PTSD symptoms are characterized by persistence and cause impairment of professional abilities and deterioration of the person's social functions [5]. The clinical manifestations of this disorder are diverse, and in some parts of people who were affected by a traumatic factor, PTSD does not occur. The explanation for this fact may be that the development of the disease depends more on the individual characteristics of the organism of a particular person and the presence of risk factors than on the characteristics of the injury or the injuring agent [3, 6, 7, 8].

The prevalence of post-traumatic stress disorder is approximately 3.9% worldwide, with the rate among women being twice as high (10−12%) as among men (5−6%) [3, 9]. The presence of civilian, military, or combined civilian and combatant or veteran populations in studies significantly influences differences in PTSD

incidence rates. The prevalence of PTSD in the US civilian population has been reported to range from 2.3% to 9.1% over a 1-year period. Calculating indicators throughout the lifetime of the studied individuals allowed to determine the incidence of PTSD ranging from 3.4% to 26.9%. A study of the prevalence of PTSD among military personnel who participated in combat operations and veterans showed significantly higher results, namely from 6.7% to 50.2% and from 7.7% to 17.0%, respectively [10]. Women are believed to be more vulnerable to developing post-traumatic stress disorder. A study by *Davis et al.* showed that the lifetime prevalence of PTSD is higher in females (8–13%) compared to males (4–6%) living in the United States [2, 11]. According to research, the prevalence of PTSD among the population of China was 53.2%, South Korea – 26.8%, Ethiopia – 37.3%, Lebanon – 33.3% and England – 7.8% [12].

Considering the full-scale military invasion of russia on the territory of Ukraine on February 24, 2022, it is difficult to predict the scale and challenges that healthcare services will have to deal with after the end of this war due to the emergence of a huge number of patients with PTSD among the civilian population and especially among military personnel. According to data obtained by the National Health Service of Ukraine (NHSU), the number of patients diagnosed with PTSD in 2023 increased fourfold (12494 patients) compared to 2021 (3167 patients). In 2022, the number of such registered cases was 7051. During the first two months of 2024, almost as many patients (3292 patients) were diagnosed with PTSD as during all of 2021.

MATERIALS AND METHODS

The authors have reviewed more than 100 scientific papers from the world literature on the problems of diagnosis, symptoms, pathophysiological and neurobiological mechanisms that play an important role in the development of PTSD and can be used as key elements in the choice of treatment measures.

RESULTS AND DISCUSSION

Post-traumatic stress disorder is a multifactorial disease. Therefore, numerous pathophysiological mechanisms and pathways contribute to its occurrence, progression, and duration. In view of this, scientists around the world have worked to investigate possible biological pathways underlying the disorder and to search for hypotheses that would explain the pathogenetic links of the emergence, development of clinical manifestations, and progression processes of PTSD. The reaction of the body to stress is a response to threatening stimuli, indicates a fundamental adaptation, and leads to a redistribution of physiological resources. In addition, the stress response in the human body can be triggered and remain active even in the absence of a stressful or traumatic factor at the moment but is a reaction to a previous stressful experience or the process of expecting a negative event in the future. It has been established that constant activation of the body's stress response system is associated with the occurrence of several diseases. These include cardiovascular pathologies, disorders of immunological reactions, reproductive functions, as well as a number of mental disorders, including PTSD [13]. This is explained by excessive and prolonged activation of the stress response system, which is unnecessary and negatively affects physiological processes.

Recently, thanks to the active work of the scientific community on the study of the mechanisms of PTSD development, numerous pathophysiological pathways involved in its occurrence have been identified. Among them, an important place belongs to vegetative regulation, the hypothalamic-pituitary-adrenal system, inflammatory mechanisms and disorders of immunological regulatory mechanisms, dysregulation of the monoaminergic transmission system, and others. As a result, a spectrum of neuroimmune markers involved in the development of many mental illnesses, and PTSD in particular, was proposed. However, research in this area continues, constantly being supplemented with theories, new facts, and experimental results, and adding to the understanding of the pathogenesis of PTSD [3, 14, 15].

An acute reaction to stress is the active involvement of the mechanisms of the neuroendocrine and autonomic systems, which are aimed at overcoming a threatening condition. Under physiological conditions, this reaction is short-lived and, after the stress factor disappears, contributes to a return to homeostatic norms. As a result of activation of the autonomic system, the adrenal medulla releases adrenaline and noradrenaline, and their action is directed at peripheral adrenergic receptors. Catecholamines are also released in the human brain, where they activate receptors in the central nervous system. The effects of their action are cardiovascular reactions, changes in the redistribution of metabolic resources, and the emergence of behavioral reactions aimed at avoiding threats and increasing attention [16, 17].

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is believed to be an important trigger for the development of PTSD, as it takes place in the body's response to stress through the regulation of glucocorticoid secretion [18, 19]. Neurons of the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone, which increases the production of adrenocorticotropic hormone (ACTH). As a result of the action of ACTH, which was synthesized by the anterior pituitary gland, cortisol is released by the adrenal cortex into the systemic bloodstream. It is known that the biological activity of cortisol is manifested when it is in an unbound state with proteins, such as corticosteroid-

binding globulin [20]. By penetrating the cell membrane and interacting with glucocorticoid receptors in the cytosol, cortisol can exert its biological effects. The cortisol receptor complex can translocate into the cell nucleus and affect transcription processes [18]. Considering the widespread location of glucocorticoid receptors in almost all tissues and organs of the human body, almost all body systems are under its influence. It is known that glucocorticoid receptors localized in the hippocampus and prefrontal cortex of the brain are involved in the processes of regulation of the hypothalamic-pituitary system. However, in patients with PTSD, there is a dysregulation of this system, which is manifested by changes in the number and degree of sensitivity of glucocorticoid receptors, concentrations of ACTH, corticotropin-releasing hormone, and cortisol [21]. It is believed that a decrease in cortisol levels plays a crucial role in the mechanisms of PTSD development. Studies have confirmed that administering cortisol to achieve physiological levels can help curb the onset of symptoms typical of PTSD [22].

The peak of cortisol synthesis is observed within 30-40 minutes after morning awakening, with a subsequent decrease throughout the day. Single determinations of cortisol concentration in saliva or blood samples cannot serve as a reliable indicator of HPA regulation in PTSD precisely because of circadian changes [23, 24]. Therefore, cumulative cortisol levels in urine, nail, and hair samples are determined [25]. It is also possible to investigate the functioning of feedback in the hypothalamic-pituitary-adrenal system using the method of pharmacological blocking of glucocorticoid receptors. For this purpose, low doses of dexamethasone are used. As a result, a decrease in circulating cortisol concentration is expected, which is associated with increased sensitivity of glucocorticoid receptors [26].

Compared to catecholamines, glucocorticoids can cause rapid reactions that last within minutes after the appearance of a threatening factor, as well as prolonged ones that can last for several hours. It was found that long-term factors include transcriptional effects implemented by activated glucocorticoid receptors and epigenetic modifications, such as changes in methylation processes [17, 27]. In addition to classical negative feedback mechanisms that play a role in terminating the stress response by reducing the levels of releasing hormones and ACTH, an important regulatory function belongs to ligand-dependent and ligand-independent transcriptional mechanisms and signaling effects mediated by glucocorticoid receptors [28]. As a result of chronic hypersecretion of glucocorticoids under the influence of stress, there is a decrease in the level of expression of glucocorticoid receptors in the human brain. The consequence is a decrease in the ability to regulate through negative feedback and a disruption in the functioning of the hypothalamic-pituitary system [14]. A decrease in the number of glucocorticoid receptors leads to an imbalance between the degree of expression of glucocorticoid and mineralocorticoid receptors, as well as an increase in the level of corticotropin-releasing hormone. These processes are recognized as a possible cause of cognitive changes and emotional disorders in patients with PTSD, as they affect the functions of areas such as the hippocampus and the prefrontal cortex [17].

The main purpose of cortisol functioning is to maintain homeostatic parameters within physiological limits, regardless of changes in the internal and external demands and needs of the body. The processing of physical factors such as noise and pain is carried out mainly by the brainstem (nucleus tracti solitarii) and the dorsomedial nuclei of the hypothalamus. Signals related to the psychological components of stress factors, such as fear and anxiety, are processed by the limbic system, namely the amygdala and the prefrontal cortex, which is accompanied by activation of the paraventricular nucleus of the hypothalamus, the release of corticotropin-releasing hormone, and the activation of the hypothalamic-pituitary-adrenal axis, resulting in the release of cortisol by the zona fasciculata of the adrenal cortex [29]. By stimulating more intensive glucose production, suppressing the functions of the immune system, and influencing the release of hormonal and neurotransmitter factors involved in the processes of concentration of attention, purposeful executive activity, and the formation of the emotional component, cortisol provides enough energy to overcome the impact of the stress factor, perform the necessary tasks under stressful conditions [30]. However, if cortisol secretion occurs over a long period of time, the intensity and frequency of its secretion increases, then negative consequences may occur in the human body, such as impaired immune system functioning, the development of neurotoxicity, and maladaptive neuronal changes [29]. It is believed that such common symptoms that accompany the development of PTSD, such as intrusive memories of a traumatic event or partial amnesia of the traumatic event, increased nervous excitement, and mood swings, can be explained to some extent by changes in the functioning of the hypothalamic-pituitary-adrenal system [31].

Today, it is known that cortisol, with long-term action, can stimulate the processes of extinction of a specific response, to some extent causing the resistance of brain areas that are responsible for the emotional modulation of memory processes [32]. According to research, the activation of brain areas involved in the development of fear, namely the dorsal anterior cingulate gyrus and anterior insular cortex, leads to a late extinction of the cortisol response, which may indicate an

incomplete reduction in fear memory. Increased activity in brain areas associated with fear extinction (dorsolateral and ventromedial areas of the prefrontal cortex) may be a manifestation of regulatory responses to the suppression of fear memory [33, 34]. Individuals diagnosed with PTSD have increased activity in hippocampal neurons and areas of the brain responsible for fear formation, as well as decreased activity in the dorsolateral prefrontal cortex, which corresponds to poorer prognostic indicators regarding subsequent treatment outcomes [35, 36, 37].

The study of the pathogenetic mechanisms of PTSD development has revealed a connection with impaired interaction between neurons in the amygdala and the prefrontal cortex of the brain [38], increased activity of the noradrenergic system, and increased influence of glucocorticoids by the mechanism of negative feedback on the HPA system, due to increased sensitivity. It was reported that the secretion of norepinephrine by the amygdala and adrenal medulla under the influence of a stress factor is associated with better memory of events that are associated with emotional arousal [39]. It was known that the amygdala is involved in the formation of responses to fear and anxiety. Increased amygdala sensitivity has also been noted in individuals with PTSD [40]. Studies of individuals exposed to stress using neuroimaging techniques have revealed an association between increased levels of pro-inflammatory cytokines and increased amygdala activity. The response to social threat in healthy individuals increased amygdala activity and increased levels of IL-6 and TNF-α after endotoxin administration [41]. The hippocampus is also reported to play an important role, as it is involved in fear-processing mechanisms and memory formation. Reduced hippocampal volume found in individuals with post-traumatic stress disorder is associated with the progression of inflammation [42, 43]. Studying the results of modeling on laboratory rats of the influence of inflammation on the functioning of the hippocampus made it possible to obtain the following results. It has been established that the basis of the reduction in the volume and size of the hippocampus in PTSD is the inhibition of neurogenesis and stimulation of apoptosis of neuronal stem cells due to microglial secretion of cytokines [44].

Due to their immunosuppressive effect, influence on the intensity of metabolic reactions, and participation in the regulation of the hypothalamic-pituitary system (HPS), suppressing negative feedback, glucocorticoids act as a link that combines the mechanisms of functioning of neuroendocrine regulation with the immune response and inflammatory changes [45]. By interacting with specific receptors located on the surface of immune cells, cortisol is able to weaken the immune response [22, 46]. It is known that cortisol can stimulate the expression of lipocortin-1, which is an anti-inflammatory factor with the ability to reduce the activity of enzymes that play a key role in the synthesis of inflammatory mediators such as prostaglandins and leukotrienes [19]. According to the results of a meta-analysis of data on the level of pro-inflammatory cytokines, a significant increase in the concentration of interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a) was found in individuals with diagnosed PTSD, compared to individuals in the control group without PTSD [9]. Under the influence of inflammatory mediators, physiological and pathological processes are implemented, and complex regulatory networks are formed [47]. Pro-inflammatory mechanisms triggered by dysfunction of hypothalamic–pituitary–adrenal system (HPAS) regulation cause the development of chronic inflammation and damage to brain cells, leading to the occurrence of PTSD. Under physiological conditions, glucocorticoids, in particular cortisol, are secreted in response to the stressor effects of HPAS. The result is inhibition of lymphocyte proliferation and a decrease in the level of pro-inflammatory cytokines. However, during the development of PTSD, a decrease in cortisol levels is observed. In this regard, dysregulation of the functioning of the HPAS, on the contrary, can cause the excessive formation of pro-inflammatory cytokines IL-1β, IL-6, IL-12, and TNF-α with the subsequent formation of neuroinflammation, which occurs due to excessive stimulation of the adaptive immune system in the brain [19, 41, 48]. Microglial cells may play a role as agents stimulating neuroinflammatory responses, being activated by cytokines and other inflammatory mediators. The role of pro-inflammatory cytokines IL-6, IL-8, and TNF-α in promoting inflammation and migration of immune cells to the site of inflammation has been confirmed [49]. The role of another pro-inflammatory cytokine in the activation of inflammatory mechanisms and regulation of the immune response, namely IL-18, has been proven by studies [50]. Chronic inflammation resulting from the action of cytokines over a long period of time can contribute to tissue damage and influence the pathogenetic links in the development of many chronic diseases [47, 49]. The development of neuroinflammation is a protective mechanism aimed at overcoming the effects of infection or damage and restoring hemostasis of the central nervous system. However, along with this, neuroinflammatory reactions are one of the key links in the development of neurodegenerative diseases [47, 51]. Also, as a result of inflammatory mechanisms, an excessive amount of reactive oxygen species is formed, which leads to oxidative stress and the progression of inflammatory reactions [19].

Given that peripheral inflammatory reactions can exert their influence on brain functioning, there is a need

to better study the pathogenetic links of neuroinflammation development and the combination of influences and interactions between the brain and the immune system. Therefore, several such mechanisms have recently been discovered. Peripheral cytokines can cross the blood-brain barrier (BBB) at sites of reduced permeability. Also, some of the cytokines (IL-1α, IL-1β, IL-6, TNF-α) can be actively transported by specific cytokine transporters and thus have a direct effect on the development of inflammation. Due to the activation of cytokine receptors on afferent nerve fibers, for example, the vagus nerve, signals from cytokines are transmitted to the corresponding areas of the brain, thus realizing an indirect effect. In response to signals from peripheral cytokines, microglia cells synthesize monocyte chemoattractant protein (MCP-1), which attracts activated peripheral cells to the brain, including monocytes, macrophages, and T-cells. In addition, cytokines are also synthesized in the brain by activated microglia and astrocytes, which contribute to the progression of neuroinflammatory processes [40, 52]. Another negative consequence of increased inflammatory manifestations is the impact on neurotransmitter systems associated with emotional and behavioral symptoms characteristic of PTSD. It is about serotonin, norepinephrine, dopamine, and glutamate [53]. Due to the possibility of influencing the processes of synthesis, reuptake, and secretion mechanisms, inflammatory cytokines regulate and change the functions of these neurotransmitters [41, 54].

A study of the immune system in civilians diagnosed with PTSD revealed an impaired ratio of T-cells $CD4^+$ to $CD8^+$, as well as an increase in the number of effector forms of $CD8^+$ T-cells, compared to immature ones [55]. Since elderly people experience a decrease in $CD4^+$ cells and an increase in $CD8^+$ T-cells, which are recognized as signs of physiological aging of the immune system, the data obtained in studies of individuals with PTSD confirm the development of premature aging of their immune system [56]. According to many studies, individuals with PTSD have changes in laboratory parameters that indicate the state of the immune system. Changes in peripheral cytokine levels were detected, including γ-interferon [57], interleukin-1β (IL-1β) [9], interleukin-6 (IL-6) [58, 59, 60], tumor necrosis factor-alpha (TNF-α) [61], as well as C-reactive protein (CRP) [58, 62, 63, 64].

There is an increasing number of studies indicating that, in addition to neuroinflammation, processes associated with mitochondrial dysfunction are involved in the development of PTSD [65, 66, 67]. In particular, it was reported that mitochondrial dysfunction, which is observed in individuals with PTSD, may be the cause of oxidative stress and the development of inflammatory reactions [48]. The reason for the increased production of reactive oxygen species by peripheral organs and immune cells, which plays an important role in the development of peripheral inflammation, may be the disruption of mitochondrial functions [68]. There is a theory that mitochondrial dysfunction is the link between the development of inflammation, oxidative stress, and metabolic disorders [69]. Another group of scientists formulated a model of “mitochondrial allostatic load” to explain the interactions between the formation of inflammatory reactions, adverse metabolic disorders, and the occurrence of post-traumatic stress disorder. According to this model, the primary disorder in patients diagnosed with PTSD is metabolic dysregulation, which negatively affects mitochondrial activity, resulting in hyperproduction of reactive oxygen species and inflammation [41]. On the other hand, mitochondrial dysfunction can regulate the levels of neurotransmitters that play a leading role in shaping mood, such as dopamine and serotonin. As a result, typical symptoms of depression and anxiety develop, which are observed in individuals with PTSD [70]. In addition, mitochondrial dysfunction may be associated with other factors that underlie the development of PTSD, such as genetic predisposition. As a result, pathogenetic mechanisms lead to a vicious cycle in which mitochondrial dysfunction stimulates the development of PTSD and vice versa [19].

Research results indicate that the development of post-traumatic stress disorder may be caused by dysfunction of many neuroendocrine systems. Hormones, neuropeptides, and neurotransmitters are involved in the body's response to stress. The important role of monoamines such as dopamine and serotonin in the formation of behavioral reactions and rapid response to stress factors has been confirmed [39]. Neurotransmitter imbalance plays a crucial role in the development and progression of the pathogenetic mechanisms of PTSD [71]. Serotonin and dopamine are endogenous chemicals by nature that provide signal transmission between two nerve cells across the synapse [72].

Serotonin is a neurotransmitter associated with the regulation of mood, emotional component, development of anxiety and stress, which is associated with many anxiety disorders as well as PTSD [73, 74]. According to research results, a decrease in serotonin concentration may act as a trigger for the development of PTSD symptoms, and dysregulation of the brain's serotonin system is involved in the pathophysiological links of its pathogenesis [75]. The precursor to serotonin is 5-hydroxytryptophan (5-HTP), which is synthesized from the amino acid tryptophan [76]. The next stage involves the formation of serotonin with the participation of vitamin B6, so there must be a sufficient amount of it in the body. It is known that melatonin, a hormone that

regulates sleep metabolism, is produced from serotonin. Accordingly, impaired functioning or decreased levels of serotonin synthesis may be the cause of serious sleep disorders associated with melatonin deficiency [77, 78]. In addition to sleep disorders, serotonin deficiency leads to eating disorders, which often cause weight gain, concentration problems, irritability, exhaustion, migraines, anxiety, and depression. Serotonin deficiency can be caused by insufficient intake of tryptophan and vitamin B6, impaired intestinal absorption, viral infections, and chronic inflammation [79, 80]. It was found that serotonin, through specific receptors, modulates the functioning of the hippocampus and the medial prefrontal cortex [81, 82, 83, 84]. The cell bodies of serotonin-containing neurons are located in the dorsal and medial nuclei of the brainstem, and their processes are directed to such areas of the forebrain as the amygdala, hippocampus, hypothalamus, and prefrontal cortex [85, 86, 87]. Serotonin plays an important role in regulating sleep, appetite, impulsive or aggressive behavior, motor functions, pain relief, and neuroendocrine functions. By influencing the neurohormonal homeostasis of the brain, serotonin is able to exercise control over stress responses during traumatic events [88, 89, 90]. The data obtained as a result of research indicate that the development of stress is associated with disturbances in the metabolism and functions of serotonin in areas of the brain involved in the body's stress response system, namely in the medial prefrontal cortex. A connection between changes in the functioning of serotonin and the development of depression and PTSD has been established [73]. Serotonin has been shown to play an important role during traumatic stress. Serotonin is released into the frontal cortex in the event of moderate stress to reduce anxiety and dysphoria and to calm the mind. However, during severe stress or trauma, serotonin hyperactivation occurs in many areas of the brain. Chronic or ongoing trauma with high serotonin levels results in the depletion of serotonin reserves [74, 81]. Intrusive memories of a traumatic event, re-experiencing trauma or stress leads to chronic activation of serotonin. The hyperarousal seen in individuals with PTSD may be triggered by serotonin depletion, and is manifested by impulsivity, increased alertness, and irritability [91, 92]. According to studies, the presence of symptoms such as alertness, hostility towards others, emotional instability, aggression, the development of depressive states, and the appearance of suicidal thoughts in patients with PTSD are associated with serotonin deficiency [93]. Other findings suggest that impaired serotonin neurotransmitter function during PTSD is confirmed by decreased serum serotonin concentrations, decreased platelet serotonin reuptake site density, and altered response to a serotonergic CNS challenge test [94, 95], accompanied by the development of PTSD symptoms such as increased alertness, aggression, emotional impulsivity, and intrusive memories [74].

Another important neurotransmitter in the brain is dopamine. The midbrain region is the site of primary dopamine synthesis, with subsequent spread along axons to other areas of the brain, influencing key physiological processes, including synaptic plasticity and stabilization of neural circuits [96]. According to research, the presence of symptoms such as psychomotor inhibition, decreased interest in previously loved things, a sense of isolation from others, and loss of pleasure in PTSD is associated with changes in the functioning of the mesocortical and mesolimbic dopamine pathways [97]. High levels of dopamine release in the projection of axons of the medial prefrontal cortex under the influence of stress factors have been detected. Also, increased dopamine release by the prefrontal cortex of the brain was associated with the development of cognitive impairments that were a consequence of the body's response to stress. This confirms the significant contribution of the dopamine system to the development of pathogenetic links and mechanisms of stress-related disorders, including PTSD [98]. The precursor for dopamine synthesis is l-3,4-dihydroxyphenylalanine (L-DOPA), and its conversion reactions are catalyzed by monoamine oxidase, catechol-O-methyltransferase (COMT), and aldehyde dehydrogenase. Dopamine participates in the cycle of metabolic transformations of adrenaline and noradrenaline; therefore, together, they participate in the mechanisms of the body's response to stress and, accordingly, play an important role in the etiology of PTSD [99]. The results of the conducted studies demonstrated a decrease in dopamine levels because of chronic stress, which affects the characteristics of working memory and executive functions of the cerebral cortex. These findings suggest that increasing dopamine levels may help improve working memory performance in individuals suffering from PTSD symptoms [100]. There is a high concentration of dopamine neurons in the ventral tegmental area, substantia nigra, olfactory bulbs, and hypothalamus [101]. The role of dopamine in the development of habitual and procedural behavior through implicit learning that occurs in the nucleus accumbens and dorsal striatum has been confirmed, as well as its role in the mechanisms of working memory and long-term plasticity in neurons of the prefrontal cortex [99]. Because dopamine in the prefrontal cortex plays a key role in the functioning of working memory processes, it can be argued that changes related to memory in individuals with PTSD are associated with dopaminergic neurotransmitter dysfunction [102, 103]. It is known that

dopaminergic influences of the nucleus accumbens and the mesolimbic pathway affect the formation of a sense of pleasure; therefore, dysfunction of the dopamine system may be the cause of the lack of pleasure and the development of anhedonia in patients with PTSD [73]. It was found that the dysfunction of the dopamine system is associated with an increased risk of developing stress-related mental illnesses, such as PTSD [104]. The emergence of emotional dysregulation and changes in the reward processing system, a common symptom in individuals with PTSD, is associated with the dysregulation of dopaminergic mechanisms. A comparison of individuals with PTSD and healthy control individuals confirmed the impairment of the reward system in the study group, indicating dysregulation of the mesolimbic dopaminergic pathway responsible for reward processing and motivation. The interaction of the dopaminergic system and the hypothalamic-pituitary-adrenal system has also been identified, the dysfunction of which plays a significant role in the mechanisms of the emergence and progression of PTSD symptoms [105]. It has been confirmed that dopamine plays a leading role in the implementation of neuropsychological processes, such as motivation regulation, executive functions, the reward system, and the body's response to stress [106]. Dysfunction of the dopaminergic system has been associated with several mental illnesses, such as attention deficit hyperactivity disorder (ADHD), drug and alcohol addiction, schizophrenia, and post-traumatic stress disorder [72, 107].

CONCLUSIONS

The global problem of the growing incidence of PTSD has prompted the international community to study in detail the mechanisms of occurrence, factors involved in the development and play an important role in the progression of the disease and PTSD symptoms development.

According to the DSM-5, the main cluster symptoms of PTSD are cognitive and emotional disturbances, intrusive experiences related to the traumatic event, anxiety, depression, repeated intrusive negative thoughts, avoidance of trauma-related stimuli, disturbing memories, mood swings, sleep disorders, impaired concentration, irritability, and others. PTSD is a fairly common disease worldwide among civilians and especially among military combatants and veterans. It is known that women are more susceptible to the development of stress-related disorders.

Numerous pathophysiological mechanisms and factors underlying the onset and progression of post-traumatic stress disorder have been identified. Under the influence of stress, the autonomic vegetative system is immediately activated, which stimulates the release of adrenaline and norepinephrine by the adrenal medulla. The cardiovascular reactions and changes in the use of metabolic resources that develop as a result are aimed at increasing concentration and avoiding threats. Dysregulation of the hypothalamic-pituitary-adrenal axis plays an important role in the development of PTSD, which is manifested by changes in the number of active glucocorticoid receptors and their sensitivity, changes in the concentration of ACTH, corticotropic releasing hormone and cortisol. These processes can affect the functioning of hippocampal and prefrontal cortex neurons and cause the development of cognitive changes, emotional disturbances that are typical for PTSD. It has been established that there is a link between increased activity of the noradrenergic system, stronger effects of glucocorticoids and disruption of the interaction between neurons of the amygdala and prefrontal cortex. Glucocorticoids are associated with the development of immune response disorders. Specifically, cortisol, as a result of interaction with specific receptors localised on the surface of immune cells, can weaken the immune response. Under the influence of stress factors, the HPA system stimulates the secretion of glucocorticoids, which leads to a decrease in the proliferation of lymphocytes and proinflammatory cytokines. However, cortisol synthesis is deficient in individuals with PTSD. As a result, a large number of proinflammatory cytokines may be produced and neuroinflammation may develop. According to the results of scientific studies, patients with PTSD diagnosed demonstrate changes in indicators characterising the state of the immune system, and the development of its premature aging has been confirmed. The imbalance of mediators, including serotonin and dopamine, plays an important role in the development of pathogenetic mechanisms of PTSD. Serotonin is involved in the regulation of sleep, appetite, impulsive or aggressive behaviour, motor functions, and neuroendocrine functions. By influencing the neurohormonal homeostasis of the human brain, serotonin controls stress responses to traumatic events, and a decrease in its concentration can initiate the mechanisms of development of PTSD specific symptoms. It has been revealed that dopamine plays a key role in the formation of a lack of pleasure, anhedonia development, dysregulation of motivation, executive functions, and the organism's reactions to stress.

Despite significant progress in understanding the neurobiological principles of PTSD development in recent years, further study of pathophysiological mechanisms and biological markers is a necessary direction to improve diagnostic and treatment measures for stress-related diseases and PTSD in particular.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Today, a lot is known about the pathogenesis of PTSD, but the prospects for further research lie in deepening the understanding of neurobiological processes and pathophysiological mechanisms of this disorder. The influence of genetic factors on the occurrence of disorders associated with stress and traumatic events is undeniable and requires serious study. Investigating the role of epigenetic changes in the development of PTSD will allow for a broader understanding of pathogenetic factors and the identification of specific markers.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

ARTIFICIAL INTELLIGENCE DISCLOSURE / ВИКОРИСТАННЯ ШТУЧНОГО ІНТЕЛЕКТУ

The authors confirm that no artificial intelligence-based technologies were utilized in the writing or editing of the manuscript.

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