REVIEW ARTICLE

CONTENTS

The role of genetic predictors in PTSD development

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ABSTRACT

Aim: To analyse the role of polymorphic sites in genes encoding key regulators of the hypothalamic-pituitary-adrenal axis and the neurotrophic system, which play an important role in determining genetic susceptibility to the development of post-traumatic stress disorder.

Materials and Methods: To prepare this review, a systematic search was conducted in the Scopus, PubMed and ResearchGate databases using keywords relating to the genetic aspects of PTSD development. The analysis included publications from the last ten years that examined molecular-genetic mechanisms, the role of polymorphisms in shaping individual vulnerability to stress, and their impact on the regulation of the hormonal response.

Conclusions: Genetic variability is an important factor determining individual differences in susceptibility to PTSD. Studying polymorphisms in investigated genes helps to explain the difference between resilience and susceptibility to mental disorders following traumatic events. This will help to improve the development of personalised approaches to the diagnosis, prognosis and treatment of PTSD, and opens up prospects for the creation of new therapeutic strategies that take into account patients' individual genetic characteristics.

KEYWORDS: stress, post-traumatic stress disorder, hypothalamic-pituitary-adrenal axis

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is an exhausting mental health disorder that develops following exposure to extremely stressful or traumatic events, such as war, accidents, natural disasters or sexual violence. It is characterised by persistent symptoms that go beyond a normal adaptive response to stress and significantly impair the patient's quality of life. The most common symptoms fall into several categories: recurrent experiences related to the traumatic event (flashbacks, nightmares, intrusive thoughts about the event), avoidance (consciously avoiding places, people or situations that remind one of the trauma), hyperarousal (increased anxiety, irritability, sleep disturbances, difficulty concentrating), and negative changes in cognition and mood (feelings of detachment, guilt, and a loss of interest in activities that were previously enjoyed) [1].

PTSD is a complex, multifactorial condition in which numerous pathogenic mechanisms and factors play a role. The involvement of the hypothalamic-pituitary-adrenal axis, as well as dopaminergic, serotonergic, adrenergic, neurotrophic and other systems, has been confirmed [2, 3, 4]. Considering that the pathogenesis of PTSD is quite complex and involves a large number of systems, it was decided in this review to focus on disorders relating to the hypothalamic-pituitary-adrenal axis and the neurotrophic system.

Given that the functional properties of proteins are determined by the structural characteristics of their genes, changes of the DNA nucleotide sequence – such as single-nucleotide polymorphisms – may disrupt regulatory mechanisms and the body's response to stress, ultimately leading to the development of mental health disorders. Sensitivity to stressors depends to a large extent on an individual's personal characteristics. Under similar conditions, when exposed to identical stressors, differences in the body's responses become apparent: some individuals adapt, developing resilience, whilst others are unable to cope with such stress. Disruption occurs in the fine line between physiologically protective compensatory responses to prolonged stressful conditions and the development of persistent pathological changes, which are the cause of mental disorders such as anxiety disorders, depression, aggressive behaviour and PTSD. It is therefore very interesting from a scientific point of view and highly relevant from a medical and so-

cial perspective – given the growing number of patients with such disorders – to investigate the role of genetic variability in susceptibility to the development of mental disorders under the influence of stress.

The study of the genetic mechanisms underlying the development of PTSD, particularly the role of single nucleotide polymorphisms (SNPs), is a promising area of modern psychiatry and neurobiology. The influence of genetic factors may explain individual differences in susceptibility to PTSD and opens up the possibility of personalised treatment.

AIM

The aim was to conduct a systematic analysis of the role of single-nucleotide polymorphisms in genes that regulate the functioning of the hypothalamic-pituitary-adrenal axis and the neurotrophic system in the genetic predisposition to post-traumatic stress disorder development. The study focused on summarising current data on the relationship between gene variants in this system and characteristics of stress reactivity, determining their contribution to the pathogenesis of PTSD, as well as identifying promising areas for further molecular-genetic and clinical research that may contribute to the search for risk biomarkers and the development of personalised strategies for prevention and treatment.

MATERIALS AND METHODS

To prepare this review, a systematic search of scientific sources was conducted in the Scopus, PubMed and ResearchGate databases, which are a leading resources for medical and biological research. The search strategy used keywords related to the genetic aspects of the development of post-traumatic stress disorder, in particular SNPs of genes associated with the functioning of the hypothalamic-pituitary-adrenal axis and neurotrophic system. The focus was on publications released over the past ten years to ensure relevance and alignment with current research directions. The analysis included studies that examined the molecular and genetic mechanisms of PTSD, the role of genetic variations in determining individual vulnerability to stress, and their impact on the regulation of the hormonal response.

This study is linked to the Sustainable Development Goals of Organization of United Nations, in particular Goal 3 – 'Good Health and Well-being'. Its significance lies in helping to create a society where everyone has access to high-quality healthcare, opportunities to maintain their physical and mental health, and the conditions for a long and active life [5].

ETHICS

All sources used in this literature review are publicly available.

REVIEW AND DISCUSSION

Recent research has confirmed that post-traumatic stress disorder is a complex psychoneurobiological condition involving numerous regulatory systems within the body. Among the most intensively studied are genetic variants relating to the functioning of the hypothalamic-pituitary-adrenal axis. Particular attention has been focused on genes encoding neurotrophic factors, which influence the plasticity of the nervous system and its ability for adaptation. The following sections provide an overview of the main findings from studies investigating associations between single-nucleotide polymorphisms of these systems and the risk of developing PTSD.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Hypothalamic-pituitary-adrenal (HPA) axis is one of the body's key integrative systems, ensuring coordination between the central nervous and endocrine systems in response to stressful factors. It functions as a complex, multi-level mechanism that regulates adaptation to environmental changes, maintains homeostasis and determines behavioural responses. The HPA axis is a central component of the stress response, enabling the body to mobilise energy resources, modify metabolic processes and modulate the immune response. Its activation enables rapid adaptation to adverse conditions, but prolonged or excessive activation can lead to pathological changes. It is crucial for mental health, as hormonal signals from cortisol influence the functioning of the hippocampus, the amygdala and the prefrontal cortex – structures responsible for memory, emotions and behavioural regulation. According to the conclusion of *Russell et al*., the HPA axis plays a fundamental role in the development of the stress response, as evidenced by the increase in symptoms of depression and anxiety resulting from disturbances in the physiological mechanisms of the hypothalamic-pituitary-adrenal axis [6].

The heritability of post-traumatic stress disorder is estimated to range from 30% to 70%, indicating that genetic factors play a significant role in its development [7]. Much attention has been devoted to genes that encode components of the hypothalamic-pituitary-adrenal axis—a key system regulating the stress response. Polymorphisms of these genes can modify glucocorticoid receptor activity and influence cortisol

secretion, which, in turn, accounts for individual differences in sensitivity to traumatic events and the risk of developing PTSD [8].

Under stress, plasma glucocorticoid (GC) levels rise, leading to the activation of glucocorticoid receptors (GR). This, in turn, triggers specific transcriptional processes that determine functional changes in various tissues and cells. Some scientists suggest that single-nucleotide polymorphisms of the *NR3C1* gene, which encodes glucocorticoid receptors, play a key role in regulating their functional activity and expression levels. Changes in this gene may modulate receptor sensitivity to glucocorticoids, alter transcriptional processes, and account for individual differences in the body's response to stress [9]**.** Another factor that plays a significant role in regulating the action of glucocorticoids is FKBP5. This protein acts as a co-chaperone for HSP90 and regulates glucocorticoid receptor signalling, in particular the process of their translocation from the cytoplasm to the nucleus. When cortisol binds to the glucocorticoid receptor, FKBP5 dissociates, allowing the receptor complex to be transported to the nucleus, where it can influence the transcriptional activity and expression of genes involved in the stress response. Furthermore, FKBP5 provides a negative feedback mechanism in the regulation of glucocorticoid-receptor interaction, as elevated levels of the FKBP5 protein can bind to GR and inhibit its translocation to the nucleus; therefore, polymorphic variants of the *FKBP5* gene may be responsible for the development of PTSD [10, 11].

According to *Carvalho et al*., the BclI polymorphism (rs41423247) of the *NR3C1* gene and four polymorphisms of the *FKBP5* gene (rs1360780, rs3800373, rs9296158, rs9470080) are considered the most significant genetic risk factors for the development of post-traumatic stress disorder, associated with the functioning of the hypothalamic-pituitary-adrenal axis [12]. The results of the studies revealed an association between the BclI polymorphism of the *NR3C1* gene and experiences of childhood trauma in relation to GR levels measured prior to conscription into military service [*13*]. In another study, the Bcll polymorphic site of the GR (*NR3C1*) gene has been linked to hypersensitivity to glucocorticoids and the development of PTSD symptoms. Furthermore, a history of traumatic events in childhood and a high GR score, as determined prior, to military conscription, were considered predictors of a more severe course of PTSD. Among patients with PTSD, GR levels remained high during follow-up assessments at one and six months [14].

Sheerin et al. conducted a meta-analysis, the results of which revealed a significant association between polymorphic sites of the *NR3C1* (rs258747) and *FKBP5* (rs9296158) genes and an increased risk of developing PTSD. At the genetic level, significant associations have been identified between post-traumatic stress disorder and the *NR3C1* and *FKBP5* genes. These associations remained significant even after sensitivity analysis, confirming their reliability and potential role in the pathogenesis of PTSD [15]. Given that the *NR3C1* gene is responsible for the synthesis of glucocorticoid receptors, and *FKBP5* encodes a protein that regulates their function, a clear link can be established between these genetic factors and the pathophysiological mechanisms underlying post-traumatic stress disorder. This is consistent with increased sensitivity to glucocorticoids, which is a characteristic feature of PTSD. In this context, it has been shown that the Bcl1 polymorphism of the *NR3C1* gene is associated not only with the severity of PTSD symptoms but also with reduced cortisol levels, confirming its potential role in the dysregulation of the stress response [16, 17].

Lian et al. investigated the association between single-nucleotide polymorphisms of the glucocorticoid receptor gene and the development of PTSD, as well as the combined effect of genetic factors, traumatic events and levels of social support on the risk of developing this condition among the Chinese population. A significant association was found between the rs258747 and rs41423247 variants of the *NR3C1* gene and the risk of developing PTSD. A study of "gene-environment" interactions has confirmed a 3.26-fold increased risk of developing PTSD among individuals in the high-risk group (carriers of the minor allele for the rs258747 and rs41423247 polymorphisms, a high number of traumatic and stressful life events, and a low level of social support). This finding remained statistically significant even after stratification into subgroups based on the presence or absence of traumatic events in childhood [18]. Other studies have also confirmed that the rs41423247 (C/G) polimorphic variant of the *NR3C1* gene is associated with the development of depression and PTSD symptoms [19, 20].

Several research teams have investigated the impact of genetic polymorphisms in the FKBP5 gene on the severity of PTSD, depending on the traumatic experiences endured during childhood and adolescence. It has been found that the polymorphisms rs9296158, rs3800373, rs1360780 and rs9470080 are associated with higher levels of FKBP5 protein expression, leading to glucocorticoid receptor resistance and disruption of negative feedback. An association has been confirmed between polymorphic sites in the *FKBP5* gene and the development of PTSD symptoms over the course of a lifetime in individuals who experienced childhood

abuse [21, 22]. Other researchers have identified a link between the rs1360780 and rs3800373 polymorphisms of the FKBP5 gene and the onset of anxiety, depression, anger and dissociation, which are early predictors of mental disorders, and PTSD in particular [23]. According to *Yeo et al.*, these same polymorphisms of the *FKBP5* gene were studied in relation to the combined influence of genetic factors and a history of childhood trauma on the development of PTSD, and significant findings were obtained confirming this influence [24]. It has been found that the severity of childhood maltreatment is significantly associated with reduced cortisol levels among carriers of the CC genotype of the rs1360780 polymorphism, whereas no such association is observed in individuals with the T allele. The findings suggest that FKBP5 plays a functional role in the development of long-term changes in neuroendocrine stress regulation induced by childhood trauma, which may act as a premorbid risk factor or, conversely, a factor contributing to resilience against the development of stress-related mental disorders [25]. The results of the meta-analysis indicate that carriage of the indicated alleles of the *FKBP5* gene (T – rs1360780, C – rs3800373, T – rs9470080) in combination with traumatic experiences in early childhood is a significant predictor of an increased risk of developing depressive disorders and post-traumatic stress disorder [26].

Other important HPA genes, single nucleotide polymorphisms of which have been studied in relation to the development of PTSD, include the corticotropin-releasing hormone receptor genes (*CRHR1* and *CRHR2*) [27]. A study was conducted among children with accident-related injuries, revealing an association between the rs12944712 polymorphism of the CRHR1 gene and an increased susceptibility to developing PTSD, as well as more severe symptoms in the future [28]. *White et al. investigated the role of other polymorphisms in the same gene among individuals who had experienced trauma as a result of a hurricane. A link was confirmed between the rs12938031 and rs4792887 polymorphisms of the CRHR1 gene and the development of PTSD* [*29*]. Other researchers analysed the impact of polymorphisms of the *CRHR1* (rs110402, rs242924 and rs16940665) and *CRHR2* (rs2190242, rs2284217 and rs2014663) genes on the course and outcomes of childhood trauma. The significant importance of these genetic factors was confirmed, and their association with an increased risk of suicide attempts was identified. In addition, the study examines the interaction between polymorphic loci and environmental factors (G × E) in individuals with childhood trauma [30]. There is evidence that the rs8192496 and rs2190242 polymorphisms of the *CRHR2* gene have a protective effect, as they reduce the risk of developing PTSD in female veterans who have experienced trauma. The presence of a minor allele for these polymorphisms in the genotype is significantly associated with a lower risk and a milder severity of PTSD [31].

NEUROTROPHIC SYSTEM

Neurotrophins are a group of proteins that perform key functions in maintaining neuronal viability, regulating synaptic activity and plasticity, and are also involved in shaping the nervous system's adaptive responses to stressors [32]. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that acts as a key regulator of neuronal growth and plasticity in the brain, ensuring that these processes are maintained throughout a person's lifetime [33]. BDNF is initially synthesised as a 32 kDa precursor – proBDNF – which is capable of interacting with the p75 receptor and the sortilin receptor complex, thereby triggering a cascade of apoptotic reactions. The main part of proBDNF undergoes intracellular and extracellular cleavage involving plasmin, furin and protein convertases, resulting in the formation of the mature form of BDNF with a molecular weight of 14 kDa. The functional role of the mature form of BDNF remained largely unclear for a long time, but there is now evidence that it is involved in modulating physiological processes in neurons [34]. The BDNF protein plays a key role in ensuring the differentiation and maturation of neuronal cells. Its highest level of activity is observed in neurons involved in the cellular signalling required for the transmission of information that determines the mechanisms of synaptic plasticity [35]. People with post-traumatic stress disorder have been found to have lower levels of BDNF both in peripheral blood and in key areas of the brain, particularly the hippocampus and the prefrontal cortex [36, 37]. Reduced levels of BDNF are considered a critical factor that may limit the brain's ability to effectively regulate fear-related memories, hinder the fading of traumatic associations, and disrupt memory consolidation mechanisms. Such neurobiological disturbances, in turn, are associated with the development of persistent nightmares and a deterioration in sleep quality, which has significant clinical implications for individuals with post-traumatic stress disorder [38, 39].

Brain-derived neurotrophic factor is encoded by the *BDNF* gene, which is located on the short arm of chromosome 11p14.1. One of the most widely studied polymorphisms of the *BDNF* gene is Val66Met (rs6265). Its essence lies in the single-nucleotide substitution of guanine for adenine at position 196 of exon 5, which leads to the replacement of the amino acid valine (Val)

for methionine (Met) in codon 66 of the protein [3, 40]. It is known that carriers of the Met allele have a violation of the extracellular level of BDNF, since this polymorphism is able to affect the transition of pro-BDNF from the Golgi apparatus to secretory vesicles with subsequent release into the synaptic cleft. Individuals with the Met allele in the genotype had episodic memory deficits and decreased cognitive function [41, 42]. According to the results of some studies, carriers of the minor allele at the Val66Met polymorphic site of the *BDNF* gene had slower information processing speed and poorer memory than homozygotes for the major allele [43]. Some researchers have concluded that the combination of carrying the Met allele with chronic stress leads to an increase in the formation of fear-related reactions, which makes them more vulnerable to the development of anxiety conditions and disorders such as PTSD [44, 45]. Another study found that the simultaneous carriage of the Met allele at the rs6265 polymorphism with the presence of additional factors, such as reduced prefrontal cortex volume, may cause increased vulnerability to anxiety disorders and exacerbate negative consequences after traumatic events due to increased sensitivity to threats. It is known that the presence of the minor allele in the Val66Met polymorphism of the *BDNF* gene among USA military veterans was associated with a more severe course of PTSD symptoms throughout life [46]. *Nedic Erjavec et al.* investigated the role of polymorphic loci of the *BDNF* gene (rs6265 and rs56164415) and the impact of smoking on the cognitive function properties of military veterans with a diagnosis of PTSD. The study included over six hundred military men with symptoms of PTSD resulting from combat exposure and 120 healthy controls without PTSD. It was found that the rs56164415 polymorphism of the *BDNF* gene was significantly associated with cognitive impairment in individuals with PTSD ($P = 0.011$). The essence of this polymorphism is the replacement of C by T in the 5'-untranslated region of the *BDNF* gene, which affects the transcription of this gene, and therefore, the expression of brain-derived neurotrophic factor. According to the data obtained, in individuals with PTSD who were carriers of the minor allele, a decrease in cognitive functions was observed. The division of patients with PTSD into two subgroups depending on the presence or absence of smoking revealed that carriers of the T-allele had pronounced cognitive impairment and significantly worse short-term visual memory performance, which was confirmed for both subgroups. Thus, the significant role of rs56164415 of the *BDNF* gene in the development of PTSD was confirmed [42].

CONCLUSIONS

Post-traumatic stress disorder is a complex psycho-neurobiological condition in the development of which numerous regulatory systems of the body are involved. According to an analysis of current research, disturbances in the functioning of the hypothalamic-pituitary-adrenal axis and the neurotrophic system play an important role in the pathogenesis of PTSD. It has been established that single-nucleotide polymorphisms in the genes encoding receptors and proteins of these systems can modify the hormonal response, influence neurotransmitter levels and determine individual differences in susceptibility to stress.

Genetic variability is therefore an important factor determining individual differences in the course of PTSD. It explains why some people demonstrate resilience to traumatic events, whilst others develop persistent mental health disorders. Studying these mechanisms opens up prospects for the creation of biomarkers to predict risk and the development of personalised treatment strategies that take into account the patient's genetic profile.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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