Catalytic Factors Associated with Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a complex psychological disorder that develops following exposure to traumatic events. PTSD is influenced by catalytic factors such as dysregulated hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitter imbalances, and oxidative stress. Genetic variations may act as important catalysts, impacting neurochemical signaling, synaptic plasticity, and stress response systems. Understanding the intricate gene networks and their interactions is vital for comprehending the underlying mechanisms of PTSD.

1. Introduction

There are several catalytic factors that can affect PTSD development and progression. These factors include dysregulation of the HPA axis, changes in glucocorticoid levels, imbalances in neurotransmitters, inflammatory markers [1], epigenetic changes [2], and genetic variations [3] in genes related to stress response and resilience. These factors can contribute to the complex interplay of biological processes involved in PTSD. Regarding genetic variations, there is evidence suggesting that they may play a role in the development of PTSD. Genetic variations can contribute to individual differences in vulnerability and resilience to traumatic experiences. Alterations in DNA repair pathways have been proposed as a potential mechanism through which genetic variations can increase susceptibility to mutagenicity and genomic instability [4].

2. Oxidative Stress

Growing evidence indicates that oxidative stress is implicated in the development and persistence of PTSD, highlighting the importance of the imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms [5][6][7]. Several biomarkers of oxidative stress have been identified in association with PTSD, offering insights into its pathophysiology and potential diagnostic and prognostic applications [5][6][7]. One such biomarker is malondialdehyde (MDA), which has shown elevated levels in individuals with PTSD, particularly in relation to hyperarousal symptoms [5]. This suggests that increased MDA may contribute to the severity and persistence of PTSD symptoms. Paraoxonase 1 (PON1), although not a direct marker of oxidative stress, has been found to be inversely correlated with oxidative stress markers, suggesting that reduced PON1 activity may indicate heightened oxidative stress levels [5]. Measuring PON1 activity can serve as an indirect indicator of oxidative stress, potentially aiding in the assessment of PTSD and its associated oxidative burden. Furthermore, studies have demonstrated decreased levels of glutathione (GSH), an essential antioxidant, in individuals with PTSD compared to controls [6]. This reduction in GSH suggests compromised antioxidant defense mechanisms in individuals with PTSD, contributing to increased vulnerability to oxidative damage. Similarly, decreased activity of superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) has been observed in PTSD patients, further supporting the involvement of oxidative stress in the disorder [7]. Taken together, these findings highlight the potential role of oxidative stress in the etiology and persistence of PTSD. Biomarkers such as MDA, PON1, GSH, SOD, GPX, and CAT offer valuable insights into the oxidative imbalance associated with PTSD and hold promise as diagnostic and prognostic tools. Considering, the fact that PTSD is a complex and multifactorial disorder, a panel of biomarkers would work best as such a tool.

3. Genes Variations Related to HPA Axis

The HPA axis is a complex network of interactions between the hypothalamus, pituitary gland, and adrenal gland that is responsible for regulating the body's response to stress. In individuals with PTSD, the HPA axis is often dysregulated. This can lead to changes in the levels of glucocorticoids (GCs), which are hormones that play a role in regulating the immune

system, metabolism, and the body's response to stress. The dysregulation of the HPA axis and changes in glucocorticoid levels may contribute to the development and maintenance of PTSD symptoms, such as hyperarousal, avoidance, and re-experiencing. Additionally, changes in the HPA axis have been linked to alterations in the immune system, inflammation, and changes in neurotransmitter levels, which may also contribute to the development and progression of PTSD [8]. The activity of the HPA axis in individuals with PTSD can vary, and it is not always consistently hyperactive or hypoactive. It is worth noting that individual differences, comorbidities, and the timing of cortisol measurements can influence the observed HPA axis activity in PTSD. Factors like chronicity of symptoms, time since trauma exposure, and the presence of comorbid conditions, such as depression or anxiety, can all contribute to the variability of HPA axis functioning in individuals with PTSD. The case of HPA axis hyperactivation is characterized by increased release of corticotropin-releasing factor (CRF) which is typically associated with acute stress responses. However, the dysregulation of the HPA axis that can occur in PTSD may result in alterations in CRF levels [9]. The HPA axis begins with the release of corticotropin-releasing hormone (CRH) from the hypothalamus in response to various stressors or triggers. CRH stimulates the release of adrenocorticotropic hormone (ACTH). A study showed that ACTH levels were higher in PTSD [10]. This suggests an imbalance in the HPA axis activity, with an elevated release of ACTH in individuals with PTSD.

In PTSD, there is evidence of dysregulated glucocorticoid signaling, referring to the interactions and effects of GCs on various physiological processes. GCs also play a role in modulating inflammatory processes. In individuals with PTSD, alterations in GC signaling can contribute to dysregulated immune responses and inflammation. Epigenetic modifications, including DNA methylation and histone modifications, can influence GC signaling. In individuals with PTSD, alterations in epigenetic regulation of GR gene expression and GC signaling pathway genes have been reported as analyzed below. These epigenetic changes can impact the sensitivity and functioning of the GR, contributing to GC signaling dysregulation in PTSD. It's important to note that the dysregulation of GC signaling in PTSD is complex and can vary among individuals. Further research is needed to elucidate the precise mechanisms involved in GC signaling dysregulation in PTSD and its implications for the development and maintenance of the disorder [11]. Alterations in glucocorticoid receptors (GR) have also been noted. Research suggests that individuals with PTSD may exhibit enhanced sensitivity of the GR, leading to increased negative feedback inhibition of cortisol release in the HPA axis. This enhanced GR sensitivity could contribute to alterations in stress response regulation observed in PTSD [12]. Cortisol levels in PTSD can also vary depending on specific subtypes of PTSD and the presence of comorbidities. Comorbid conditions such as depression or anxiety may influence cortisol levels in individuals with PTSD. It is important to note that there is considerable variability in cortisol levels among individuals with PTSD, and not all individuals will exhibit the same cortisol patterns. The timing of cortisol measurements, chronicity of symptoms, and other individual factors can contribute to these variations. One hallmark feature of PTSD is an exaggerated or dysregulated cortisol response to stress. Some individuals with PTSD may exhibit an increased cortisol response to stressors, which can indicate hyperactivity of the HPA axis. On the other hand, there are also studies suggesting blunted or reduced cortisol responses to stress in some individuals with PTSD, indicating HPA axis hypoactivity. This dysregulation can be a result of the trauma itself or other factors such as genetics and epigenetics [13]. Overall, the dysregulation of the HPA axis in PTSD is thought to contribute to the persistent and chronic nature of the disorder.

In PTSD, alterations in the HPA axis can impact the effectiveness of standard first-line treatments like trauma-focused cognitive behavioral therapy (TF-CBT) due to the importance of cortisol in memory consolidation and retrieval. The lack of cortisol can hinder the extinction of fear responses associated with traumatic memories, necessitating alternative treatments that target the HPA axis and regulate cortisol levels for non-responsive individuals [14]. The Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) gene plays a role in PTSD as genetic variations have been associated with altered glucocorticoid receptor function, leading to HPA axis dysregulation and impairments in stress response and emotion regulation. Several SNPs in the NR3C1 gene, such as Bcl-1 and ER22/23EK, have been identified as potential risk factors for PTSD. These SNPs are associated with reduced glucocorticoid sensitivity and increased vulnerability to developing PTSD following trauma exposure. Homozygous carriers of the Bcl-1 polymorphism (rs41423247) have been shown to have a higher risk of major depression and PTSD, as well as increased rates of suicide [15][16][17]. The 9β SNP variation in NR3C1 has also been linked to altered glucocorticoid sensitivity and investigated in relation to PTSD [18]. Additionally, the rs258747 SNP in NR3C1 has been associated with PTSD [19].

The FK506 Binding Protein 5 (FKBP5) gene has also been implicated in PTSD. Variants of FKBP5 have been found to significantly moderate the effects of early-life stress on PTSD. Several FKBP5 SNPs, including rs3800373, rs9296158, rs1360780, and rs9470080, have been associated with lifetime probable PTSD [19][20]. Another HPA axis-associated genetic variation involves the Corticotropin Releasing Hormone Receptor 1 (CRHR1) gene. CRHR1 has been linked to an increased risk for PTSD symptoms. The rs110402 variation in CRHR1 has been associated with an elevated risk of PTSD symptoms, and other SNPs such as rs12938031, rs12944712, and rs4792887 have been associated with PTSD symptoms and diagnosis [21][22]. In a similar framework, the Corticotropin Releasing Hormone Receptor 2 (CRHR2) gene

encodes a protein involved in coordinating physiological and behavioral responses to stress. In a study of HPA axis genes and their association with PTSD symptoms in Chinese earthquake survivors, a specific SNP in CRHR2, rs2267715, was found to have main effects associated with PTSD severity and most PTSD symptom clusters except dysphoric arousal. This suggests that variations in CRHR2 may contribute to the development and severity of PTSD symptoms [23].

4. Neurotransmitter Imbalances and Related Genes Variations

Neurotransmitter imbalances play a crucial role in the development and progression of PTSD, as evidenced by numerous studies. Serotonin, a neurotransmitter involved in mood regulation, anxiety, and stress, has been associated with PTSD and other anxiety disorders [24]. Similarly, dysregulation in norepinephrine, a neurotransmitter involved in the body's "fight or flight" response, has been linked to hyperarousal symptoms in PTSD [25]. Elevated norepinephrine levels have been observed in individuals with PTSD, contributing to their heightened state of arousal.

Research evidence suggests that low levels of serotonin contribute to the manifestation of PTSD symptoms. More precisely, dysregulation of the brain's serotonergic system is implicated in the pathophysiology of PTSD, with serotonin playing a vital role in regulating emotional responses and overall emotionality [26]. Genetic variations in serotonergic system genes have been identified as potential contributors to the development of PTSD. The solute carrier family 6 member 4 (SLC6A4) gene is of particular interest in the context of PTSD. One polymorphism within its promoter region is the serotonin transporter-linked polymorphic region (5-HTTLPR), where the short (S) allele is associated with reduced expression and function of the transporter compared to the long (L) allele. The S-allele's reduced expression and function lead to decreased serotonin uptake, which can result in emotional instability and increase susceptibility to anxiety and depression. Additionally, the rs25531 single nucleotide polymorphism (SNP) located within the 5-HTTLPR region interacts with these effects. Due to their proximity and potential interaction in influencing serotonin transporter expression and function, these two polymorphisms are often analyzed together as a combined genotype [27]. The 5-hydroxytryptamine receptor 2A (HTR2A) gene is another gene of interest in relation to PTSD. The HTR2A SNP, rs7997012, interacts with PTSD severity to predict reduced connectivity within components of the brain's default mode network (DMN), including the posterior cingulate cortex (PCC), right medial prefrontal cortex, and right middle temporal gyrus. Additionally, two other HTR2A SNPs, rs977003 and rs7322347, have been found to moderate the association between PTSD severity and the PCC-right MTG component of the DMN [28]. The Tryptophan hydroxylase 2 (TPH2) gene encodes the enzyme responsible for the initial and rate-limiting step in serotonin biosynthesis, a neurotransmitter implicated in mood regulation. Notably, the TPH2 rs11178997T allele has shown a significant association with DSM-5-based PTSD severity scores [29]. These findings highlight the involvement of genetic variations in the serotonergic system in the pathogenesis of PTSD.

Imbalances in other neurotransmitters, such as glutamate, GABA, and acetylcholine, have also been implicated in PTSD. Glutamate, an excitatory neurotransmitter, has shown dysregulation in brain regions like the anterior cingulate cortex and hippocampus in individuals with PTSD [30]. The dysregulation of glutamate transmission in these regions may contribute to the cognitive and emotional disturbances observed in PTSD. GABA, the primary inhibitory neurotransmitter involved in anxiety and stress regulation, exhibits reduced tone in individuals with PTSD [31]. This reduction in GABAergic overall activity and functioning in the brain is associated with increased anxiety and fear responses, contributing to the development and maintenance of PTSD symptoms. Studies have found lower levels of GABA in brain regions such as the prefrontal cortex and amygdala, which are involved in emotional processing and regulation. Furthermore, genetic variations in GABA receptor subunit genes have been linked to an increased risk for PTSD, highlighting the role of GABA in the disorder [31]. Dopamine, a neurotransmitter involved in reward processing and motivation, has also been linked to the development of PTSD [32]. The GABA system, which is involved in the regulation of neurotransmission and various physiological and neurological processes, has been implicated in the modulation of anxiety, stress, and fear responses, making it relevant to the study of PTSD. Dysregulation of the GABA system has been observed in individuals with PTSD, suggesting its involvement in the pathophysiology of the disorder. One specific gene that has been studied in relation to PTSD is the GABAA receptor subunit alpha 2 (GABRA2) gene. Polymorphisms in the GABRA2 gene have been investigated for their association with PTSD. A study found that three specific polymorphisms in GABRA2 had significant interactions with childhood trauma in predicting the development of PTSD. This suggests that genetic variations in GABRA2 may contribute to an individual's vulnerability to PTSD, particularly in those who have experienced childhood trauma [33].

The Spindle and Kinetochore-associated Complex Subunit 2 (SKA2) gene and its rs7208505 polymorphism have been implicated in the development of PTSD. The SKA2 gene is involved in regulating the stress response and has been associated with an increased risk for depression and suicide. Individuals with PTSD have been found to exhibit lower levels of SKA2 gene expression compared to those without PTSD. Additionally, the rs7208505 polymorphism has been associated with lower SKA2 gene expression and higher PTSD symptoms, particularly in individuals with a history of

childhood trauma [34]. While the Cannabinoid-1 receptor (CNR1) gene is not typically considered a candidate gene for the hypothalamic-pituitary-adrenal (HPA) axis, it is part of the endocannabinoid system, which may interact with the HPA axis and play a role in stress response and related disorders such as PTSD. Some evidence suggests that CNR1 genetic variations may be associated with HPA axis dysregulation and increased risk for PTSD. Another study investigated the effects of the G1359A genetic variant (rs1049353) in the CNR1 gene and childhood abuse on the development and expression of PTSD symptoms [35]. Another CNR1 variation associated with PTSD is the rs806371 [36]. The study found a trending association between the genotype at rs806371 in CNR1 and PTSD symptom severity at follow-up. It is important to note that further research is needed to fully understand the mechanisms by which the SKA2 and CNR1 genes contribute to PTSD and the specific roles of their genetic variations in the development and progression of the disorder.

Dysregulation of dopamine signaling pathways may contribute to the emotional dysregulation and altered reward processing observed in individuals with PTSD. These findings collectively highlight the significance of neurotransmitter imbalances in the development and maintenance of PTSD symptoms. Dopaminergic dysregulation in PTSD appears to involve alterations in the brain's reward system, which is modulated by dopamine. Studies have demonstrated that individuals with PTSD exhibit reduced reward processing compared to healthy controls, indicating potential dysregulation of the mesolimbic dopaminergic pathway responsible for reward processing and motivation [37]. Furthermore, the dopaminergic system has been found to interact with the dysregulated HPA axis, as discussed earlier [38]. The dopamine receptor D2 gene (DRD2) is of particular interest in the context of PTSD. Within this gene, a specific SNP known as rs1800497 has been identified, which has two alleles: T (A1) and C (A2). The DRD2/ANKK1-Taq1A variant (rs1800497) is located in the ANKK1 gene, adjacent to the dopamine D2 receptor gene (DRD2) on chromosome 11. This polymorphism has been associated with the regulation of dopamine synthesis and reduced D2 receptor expression in the brain, which forms the pathophysiological basis for various PTSD symptoms. The rs1800497 polymorphism has been shown to contribute to the severity of PTSD symptoms, and individuals with the A1 allele are more likely to develop PTSD following trauma exposure [39].

An additional genetic variation of interest is associated with the dopamine D3 receptor (DRD3) gene. A study showed several SNPs within the DRD3 gene to be associated with PTSD. These SNPs, including rs2134655, rs201252087, rs4646996, and rs9868039, were found to be linked with reduced risk for PTSD. The minor alleles of these SNPs were linked to a decreased likelihood of developing PTSD. In the replication sample of trauma-exposed African American participants, another SNP, rs2251177, showed a nominal association with PTSD in men. The minor allele of this SNP was associated with a lower risk of PTSD [40].

5. Inflammatory System Candidate Gene Variations

Inflammatory system candidate genes are genes that play a role in the body's inflammatory response. The C-reactive protein (CRP) gene, which encodes the CRP protein involved in the immune system's response to inflammation, has been associated with PTSD symptoms. Specifically, the SNP rs1130864 within the CRP gene has been significantly linked to increased PTSD symptoms, including hyperarousal symptoms. The genotype of CRP was also associated with the likelihood of a PTSD diagnosis. This SNP was further associated with elevated CRP levels, a protein produced by the liver in response to inflammation. The study found that higher CRP levels were positively correlated with PTSD symptoms and fear-related psychophysiology. These findings suggest that genetic variability in the CRP gene may contribute to the development of PTSD, potentially through an increased pro-inflammatory state [41]. The Interleukin 1 Beta (IL1B) gene, responsible for encoding the interleukin-1 beta protein involved in the immune response, has also been investigated in relation to PTSD. A study found that the minor allele frequencies of IL1B SNPs, rs1143633C, and rs16944A, were significantly lower in patients with PTSD compared to controls. This suggests that these alleles may have a protective effect against PTSD, indicating that the IL1B gene could be involved in the pathogenesis of the disorder [42]. Polymorphisms in the promoter region of the Tumor Necrosis Factor α (TNFα) gene, which encodes the pro-inflammatory cytokine TNFα, have been associated with an increased susceptibility to PTSD. In particular, the SNP rs1800629 in TNFα has been linked to PTSD severity, with the GG genotype identified as a risk genotype for psychiatric disorders. The study also observed significant differences in serum TNFα levels between cases and controls, as well as significant correlations between elevated TNFα levels and PTSD severity [43].

6. G Protein-Coupled Receptor (GPCR) System Candiate Gene Variations

The Regulator of G-protein signaling-2 (RGS2) gene has been associated with cognitive functioning, particularly in memory and learning processes. Studies have also found an association between RGS2 gene variation and PTSD. For example, one study linked the RGS2 rs4606 allele with PTSD in individuals who experienced a traumatic hurricane under conditions of high stress and low social support [44]. However, further research is needed to understand the specific

prosses through which RGS2 gene variations contribute to PTSD. The ADCYAP receptor type I (ADCYAP1R1) gene encodes a G protein-coupled receptor that binds the neuropeptide adenylate cyclase-activating polypeptide (PACAP) and is involved in various physiological processes, including stress response. The ADCYAP1R1 gene has been implicated in stress response, and previous studies have investigated its potential link to PTSD with mixed results. A meta-analysis focusing on the rs2267735 variant in the ADCYAP1R1 gene found that the C allele of this variant was associated with an increased risk for PTSD in the combined sex sample and in the subsample of women and girls, but not in the subsample of men and boys. These findings suggest that the ADCYAP1R1 gene may play a role in PTSD, and there may be sex differences in this association [45]. The Adrenoceptor Beta 2 (ADRB2) gene encodes the beta-2 adrenergic receptor, which is involved in responding to the neurotransmitter norepinephrine and the hormone epinephrine. A study identified an association between a single nucleotide polymorphism (SNP) within the promoter region of the ADRB2 gene, specifically rs2400707, and PTSD symptoms, particularly in interaction with childhood trauma. The rs2400707 polymorphism has been linked to the function of the adrenergic system and was found to be associated with relative resilience to childhood adversity [46]. Further research is necessary to fully uncover the underlying dynamics through which variations in the RGS2, ADCYAP1R1, and ADRB2 genes contribute to PTSD susceptibility and the specific roles of these genetic variations in the development and progression of the disorder.

7. Other Genes Variations

The brain-derived neurotrophic factor (BDNF) gene, which codes for the BDNF protein, has been extensively studied in relation to PTSD. BDNF is believed to play a role in the development and maintenance of PTSD, and several studies have reported lower levels of BDNF in individuals with PTSD compared to healthy controls. Additionally, lower BDNF levels have been associated with more severe PTSD symptoms. One specific SNP within the BDNF gene that has been investigated is the val66met polymorphism. This SNP leads to a valine (val) to methionine (met) substitution at codon 66 of the BDNF protein. The Met allele of the BDNF Val66Met polymorphism (rs6265) has been associated with reduced levels of BDNF release, heightened HPA axis reactivity, and impaired fear extinction. These factors may contribute to an increased risk for more severe PTSD symptoms [47]. It is important to note that while there is evidence supporting the involvement of the BDNF gene in PTSD, further research is needed to fully understand the mechanisms and implications of these genetic variations in the development and progression of the disorder.

The Monoamine oxidase B (MAOB) gene encodes the MAOB enzyme, which is an isozyme of the MAOA gene and involved in the breakdown of dopamine. The rs1799836 variant in the MAOB gene has been linked to negative emotional personality traits and depression. There is also evidence of a marginally significant association between the MAOB rs1799836 polymorphism and the severity of PTSD symptoms [48]. In addition, the rs1799836 polymorphism has been associated with the severity of PTSD symptoms in male war veterans [49]. The Neuropeptide Y (NPY) gene has been implicated as a potential risk factor for anxiety disorders, including PTSD. A pilot prospective study found that individuals expressing a combination of genetic variants, including the NPY rs16147 polymorphism, were more susceptible to developing PTSD in the absence of early intervention in a high-risk group [50]. The Apolipoprotein E (ApoE) gene has been primarily studied in the context of its association with Alzheimer's disease.

The Oxytocin Receptor (OXTR) gene has been investigated for its role in stress and social behavior, including its potential involvement in PTSD. The rs53576 variant in the OXTR gene has been associated with probable lifetime PTSD [51]. The Fatty Acid Amide Hydrolase (FAAH) gene, which is involved in the regulation of the endocannabinoid system, has been studied in relation to fear learning and PTSD. The FAAH rs324420 polymorphism has been shown to influence physiological, cognitive, and neural signatures of fear learning in women with PTSD [52]. Additionally, the A/A genotype at rs324420 in the FAAH gene was associated with higher PTSD symptom severity and was found exclusively in Black participants [36]. The Protein Phosphatase, Mg^{2+}/Mn^{2+} Dependent 1F (PPM1F) gene has been investigated for its involvement in stress response pathways and serotonergic signaling. Variations in the PPM1F gene have been found to moderate the association between PTSD symptom severity and cortical thickness in specific brain regions, including bilateral superior frontal and orbitofrontal regions, as well as the right pars triangularis [53].

A study investigated the role of the opioid receptor–like 1 (OPRL1) gene in PTSD and fear learning in humans. In particular, the SNP rs6010719, was associated with increased PTSD symptoms in individuals who had experienced moderate to severe child abuse. This association remained significant even after controlling for factors such as age, sex, and substance abuse, which are known to be related to PTSD. The study also found that the association between the G allele carriers of rs6010719 and PTSD risk increased with the degree of trauma exposure. These findings suggest that genetic variations in the OPRL1 gene may contribute to the development and severity of PTSD symptoms [54].

The variant rs4790904 in the protein kinase C alpha (PRKCA) gene has been also associated with PTSD. A study showed that in the Caucasian population, there was a significant correlation between rs4790904 and PTSD symptom clusters (re-experiencing, avoidance and numbing, and hyperarousal). In the African American veterans, a significant association was found between rs4790904 and a current diagnosis of PTSD [55].

8. GWAS Studies

Genome-Wide Association Studies (GWAS) are powerful research approaches used to identify genetic variations associated with complex traits or diseases. These studies involve analyzing the entire genome of individuals to detect genetic markers or variants that are more common in individuals with a particular trait or disease compared to those without it. In the case of PTSD, a variety of associated genes were identified in GWAS. The Retinoid-related Orphan Receptor Alpha (RORA) gene encodes a nuclear hormone receptor that is involved in circadian rhythm regulation and has been implicated in various psychiatric disorders. The association between the rs8042149 variant in the RORA gene and PTSD as shown in GWAS, suggests a potential role of RORA in the development or maintenance of PTSD [56]. Further research is needed to elucidate the specific mechanisms by which RORA may contribute to the development of PTSD. In a similar manner, the Phosphoribosyl Transferase Domain Containing 1 (PRTFDC1) gene has been associated with PTSD. Specifically, the rs6482463 variant in the PRTFDC1 gene has been linked to PTSD [57]. The exact function of PRTFDC1 in relation to PTSD is not well understood, and further studies are required to explore its role and potential mechanisms.

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