The role of the interaction between the FKBP5 gene and stressful life events in the pathophysiology of schizophrenia: A narrative review

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Summary

Stressful life events have been associated with increased risk for development of schizophrenia and play a pivotal role in its psychopathology. Genes related to stress response, such as *FKBP5* gene associated with hypothalamic–pituitary–adrenal (HPA) axis, modulate brain response to childhood trauma and determine individual susceptibility for development and course of psychosis. It this review we provide an overview of *FKBP5* gene role in human neurophysiology, its association with HPA axis and its role in stress response system in animals and humans. Moreover, we took a closer look on the studies showing the interaction between *FKBP5* gene and stressful life events in the pathophysiology of schizophrenia. We explain how interactions between trauma and *FKBP5* gene polymorphisms contribute to development of the disease, severity of psychotic symptoms and cognitive disturbances. We also discuss epigenetic modifications that may contribute to altered HPA axis reactivity to stress entailing higher risk for development of psychosis. Considering the pivotal role of *FKBP5* gene in physiopathology of schizophrenia we discuss a possible use of new therapeutic agents that may influence HPA axis activity related to the FKBP5 protein especially in individuals exposed to early trauma.

FKBP5, gene-environment interaction, schizophrenia, psychosis, childhood trauma

INTRODUCTION

Schizophrenia is a complex mental disorder with multiple risk factors determining its onset, course and psychopathology. In the recent years, the growing body of research on schizophrenia focuses on gene – environment interactions. This approach differs from the linear gene-phenotype models by positioning an important causal role that is not limited to genetic variability or the environment as isolated factors, but for their synergistic influence on schizophrenia origin and its course (for the review see [1]). There are numerous environmental factors that have been associated with schizophrenia, such as childhood trauma, cannabis use, prenatal maternal infections and obstetric complications [2-4]. Among these factors, early life adversity is one of the most extensively studied social factor associated with the development of psychosis as shown by several meta-analytic studies [5-7]. Traumatic events have been found to be a risk factor for the development of psychosis either in the general population (8,9) or in subjects at familial high risk (10). Moreover, a great body of evidence shows an influence of traumatic life experiences on the psychopathology of psychotic disorders [9,11-15]. It has been repeatedly demonstrated that a history of childhood trauma results in de-

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terioration of cognitive functioning [16-18] exacerbations of the disease and increased intensity of both positive and negative symptoms [16, 19, 20], as well as higher risk of suicide in patients suffering from schizophrenia [21-23].

Due to numerous studies on the impact of stress and trauma on the development and the course of schizophrenia, the role of the hypothalamic–pituitary–adrenal (HPA) axis, a key system in stress response in humans, has also been investigated [24]. It has been shown that early life traumatic experiences may provoke a cascade of biological effects resulting in dysregulation of the HPA axis [25, 26] and thus increasing the risk of psychosis. In this line of research, stress hormones levels have been investigated as well as their association with schizophrenia symptomatology providing mixed results. In the recent years, more attention has also been given to genetic polymorphisms and epigenetic modifications that may contribute to the variability of HPA axis reactivity to stress in hope to find more consistent results linking childhood trauma with the development of psychosis in later life [27]. In this narrative review, we concentrate on one of the genes related to the response to stress associated with the HPA axis – the *FKBP5* gene. Firstly, we provide an overview of the HPA axis alterations observed in schizophrenia and early psychosis. Next, we present the physiological role of *FKBP5* signaling and its relevance to the pathophysiology of psychosis. Finally, we provide a summary of evidence and directions for future studies.

2. CHARACTERISTIC OF FKBP5 GENE ROLE IN HUMAN NEUROPATOPHYSIOLOGY

2.1. HPA axis in schizophrenia

The HPA axis plays an important role in regulating somatic and brain response to day life stressors and controlling correct functioning of circadian rhythm [28, 29]. Corticotropin releasing hormone (CRH) secreted by the hypothalamus stimulates the pituitary to release adrenocorticotropin hormone (ACTH) responsible for adrenal stimulation and secretion of the key glucocorticoid hormone – cortisol, which acts by the negative feedback loop inhibiting CRH and ACTH

release (30). Cortisol acts through its cytoplasmic glucocorticoid receptor (GR) that is translocated to the nucleus after its activation. The GR is acting as a transcription factor which can bind to specific DNA sequences and thus regulate the transcriptional response to stress [31]. Alterations in the HPA axis activation have repeatedly been observed in schizophrenia [32-34]. One of recent meta-analyses in this field found elevated cortisol levels in individuals with FEP [35].

Abnormalities in cortisol awakening response have been demonstrated in individuals at ultra-high risk of psychosis [36] and schizophrenia patients as summarized by recent review and meta-analysis showing blunted response when compared to healthy controls [37]. One of early HPA axis alterations in psychosis is pituitary enlargement demonstrated in ultra-high risk individuals, especially those who later develop psychosis [38]. Several studies reported the dysregulation in diurnal cortisol levels, showing elevated diurnal and afternoon levels of cortisol in schizophrenia patients [39]. The literature on stress responsivity in schizophrenia is fairly consistent showing a pattern of blunted cortisol levels in response to stressors [40] However, several factors that may account for cortisol alterations in high-risk individuals or those with overt psychosis should be taken into consideration. These include the phase of illness, chronicity, environmental factors, stress vulnerability, medication effects and clinical history (for review see [41]).

Dysregulation of HPA axis plays an important role in the psychopathology of schizophrenia. It has been demonstrated that elevated afternoon cortisol level positively correlates with worse cognitive functioning in patients with FEP, causing an impairment in memory performance across various domains, such as working memory, delayed memory, short-term verbal memory and memory recall [42]. Similar results were obtained in chronic schizophrenia patients, showing a negative correlation between basal cortisol level and cognitive performance [43]. Cortisol level may also impact a symptomatic severity. It has been reported that increased salivary cortisol level positively correlates with negative symptoms severity [44]. Positive and disorganized symptoms have been found to be greater in patients with higher basal cortisol level [43].

2.2 The role of *FKBP5* gene in stress response

The *FKBP5* gene, located on the chromosome 6p21, encodes the FK-506 binding protein, which is a co-chaperone of the hsp90 heat shock protein that regulates GR sensitivity to its ligand – cortisol [45]. The complex formed when the FKBP5 protein is combined with the GR has a lower affinity for cortisol entailing repressed nuclear translocation (Figure 1) [46, 47]. Nonetheless, stress and thus cortisol by itself are responsible for strong upregulation of the *FKBP5* gene, diminishing the GR activity by a FKBP5 protein bounded to the GR complex. Higher levels of FKBP5 protein lead eventually to reduced sensitivity of the GR to cortisol, causing diminished negative feedback regulation of the HPA axis. Hence, the stress response is unusually prolonged because it takes longer to reduce cortisol secretion [45].

There is evidence that the *FKBP5* gene single nucleotide polymorphism (SNP) (rs1360870) is associated with hippocampal structure and function, resulting in greater spatial displacement of hippocampus entailing attention bias for perceived threat for TT/TC vs CC genotypes [48]. Moreover, in the study looking into the interaction between childhood maltreatment and several *FKBP5* SNPs it has been shown that two *FKBP5* variants (rs9470080 and rs9394309) affect threat-related amygdala reactivity in the individuals exposed to childhood emotional neglect [49]. There is also a report showing that the interaction between the *FKBP5* gene SNPs (rs9296158, rs4713016) and trauma has influence on cortisol levels in individuals from the general population [50]. Moreover, a significant interaction between *FKBP5* gene SNP (rs1360780) and childhood maltreatment has been reported to influence cortisol response to stress [51]. Thus, the *FKBP5* gene can be considered as a candidate gene for the studies looking into gene-environment interactions, especially in the context of stressful life experiences, as well as a molecular risk and resilience factor of different psychiatric disorders.
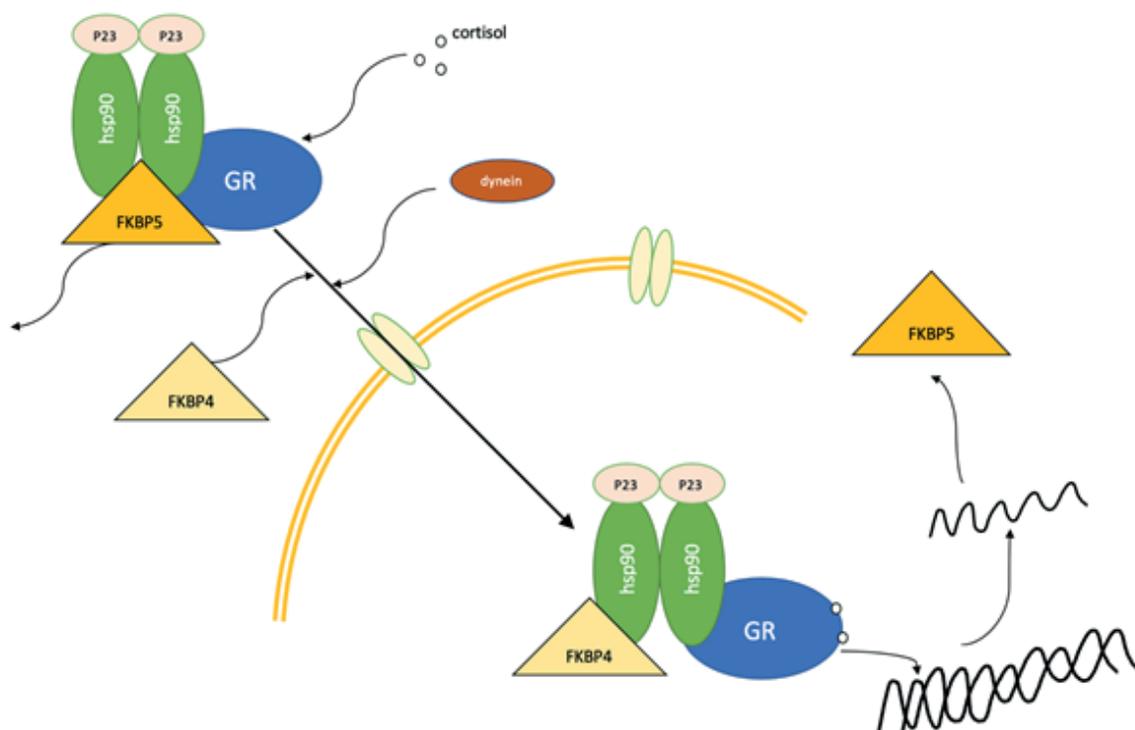
Figure 1 – Functional diagram of the glucocorticoid receptor complex, based on (45) – GR – glucocorticoid receptor, hsp90 – heat shock protein 90. Complex formed by GR and cortisol enhances expression of FKBP5 protein. When cortisol is bound to GR, FKBP5 is exchanged against FKBP4 which binds dynein, what enables nuclear translocation of GR-complex and binding to DNA contributing to increased FKBP5 transcription.

2.3 Animal model studies on *FKBP5* gene and HPA axis

The influence of the *FKBP5* gene on the development of psychiatric symptoms after exposure to trauma has been shown in animal model studies [51]. Corticosterone or dexamethasone supply, restrained stress and food deprivation in mice have been found to result in increased *FKBP5* expression in the hippocampus, paraventricular nucleus and central amygdala [53, 54]. Chronic stress in mice may also result in higher *FKBP5* expression in the dorsal and ventral hippocampus, enhancing dysregulation of the HPA axis activity [55]. This has been further supported by research showing an increase *FKBP5* expression in ventral hippocampus and prefrontal cortex in response to chronic mild stress in rats [56]. Indeed, stress-induced overexpression of the *FKBP5* gene has been associated with a decrease in active stress coping behaviors in mice. Moreover, it has been observed that depletion of the *FKBP5* gene in mice results in reduced HPA axis activity, increase in active coping style strategy and diminished response to acute stress, making *FKBP5*-knockout mice more resilient to acute and chronic stress [57-59]. Repeated unpredictable stress in mice contributes to downregulation of the *FKBP5* in hypothalamus, lower plasma level of ACTH and corticosterone and decreased hippocampal volume [60]. These changes contribute to blunted HPA axis activity and result in increased use of passive coping strategies, anxiety and deficit in weight gain [60]. Stress-induced overexpression of *FKBP5* in the prefrontal cortex, hippocampus and hypothalamus has been demonstrated to result in the development of anxiety-like behaviors in mice exposed to stressful environment in early life [61].

3. FKBP5 AND SCHIZOPHRENIA

3.1. *FKBP5* gene expression in schizophrenia

The *FKBP5* gene expression differs among patients with schizophrenia and healthy individuals. Higher peripheral *FKBP5* mRNA levels have been observed in people with schizophrenia when compared to healthy controls [62]. Interestingly, the same study did not observe analogous differences between patients with schizoaffective disorder and healthy control subjects. Sinclair et al. [63] analyzed 8 SNPs in patients with schizophrenia and revealed increased expression of *FKBP5* mRNA in dorsolateral prefrontal cortex in the brains of patients with schizophrenia when compared to healthy control subjects. Increased *FKBP5* expression in the hippocampus has been reported in brains of patients with schizophrenia [64]. Thus, altered *FKBP5* expression may be associated with the impairment of the HPA axis regulation. It has also been reported that the lowest gene expression of the *FKBP5* mRNA occurs in school-age individuals and rises after adolescence [65]. In turn, the peak of the GR protein levels and the neuronal GR expression coincides with adolescent period [66]. This discrepancy might account for increased sensitivity to stress and greater vulnerability to develop psychosis in response to trauma in young adults. There is however one study that failed to find altered expression of *FKBP5* gene in the brains of patients with schizophrenia [67]. Increased *FKBP5* mRNA expression has also been reported in individuals with major depressive disorder with coexisting psychosis [68].

3.2. Interaction between trauma and *FKBP5* gene polymorphisms with the risk of schizophrenia

Individual gene variations resulting in different GR sensitivity to cortisol cause different body and brain response to stressful situations entailing different susceptibility to development of schizophrenia [69]. Increased risk of schizophrenia development has been observed in carriers of risk G allele in rs3800373 SNP of *FKBP5* gene after accounting for childhood trauma [69]. Similarly, a high genetic influence of risk A allele of rs9296158 on schizophrenia development has been observed after inclusion the childhood adversity as the confounding factor [69].

3.3 PSYCHOTIC SYMPTOMS

The influence of different SNPs of the *FKBP5* gene on the course and psychopathology of schizophrenia has been widely studied (2,69–

71). The SNP rs1360780 (risk allele C) has been found to be associated with development of psychosis after adjustment for traumatic environmental factor – parental separation in the childhood [70]. Interestingly, the study obtained the same results for cannabis use showing that this common SNP increases the risk of psychosis development in marijuana users [70]. The *FKBP5* polymorphism can influence the severity of psychotic symptoms in patients with schizophrenia previously exposed to traumatic life events. Collip and coauthors have shown that schizophrenia patients who carry a SNP rs9296158 risk A allele are more likely to develop severe psychotic symptoms [50]. Nevertheless, the influence of *FKBP5* on psychotic experiences can also be observed in the general population and the *FKBP5* gene has been shown to impact an intensity of subclinical psychosis [72]. Two studies have shown that healthy individuals who are TT homozygotes of rs1360780 SNP are more vulnerable to the psychosis-inducing effects of childhood trauma when compared to CC homozygotes [50,73]. The T allele of SNP rs1360780 and A alleles for SNPs rs9296158 and rs1043805 interacting with childhood trauma have been indicated as significant risk factors of subclinical psychosis in general twin population [50]. In the group of unaffected siblings of patients with psychotic disorder the positive correlation between level of positive schizotypy and trauma in carriers of SNPs rs1043805/rs992105 (risk C allele) and SNP rs4713916 (risk A allele) has been observed (50). In turn, risk haplotype CATT of the *FKBP5* gene (SNPs rs3800373, rs9296158, rs1360780 and rs4470080) has been found to be responsible for development and intensity of psychotic experiences in an early psychosis individuals exposed to childhood trauma in the past [72].

3.4 Effects of interaction between the *FKB5* gene polymorphisms and trauma on cognitive performance in schizophrenia

It has been demonstrated that a common variation in the *FKBP5* gene (rs1360780) interacts with childhood trauma to negatively affect cognitive performance, especially in the domain of attention in both patients with schizophrenia

and healthy controls [74]. This effect was most significant for the CC homozygotes. In turn, the TT homozygotes showed significantly worse general neuropsychological functioning in the group of patients with schizophrenia, independently from previous trauma exposure. This relationship has also been examined for the *FKBP5* rs3800373 SNP; however, the study did not obtain results supporting its influence on cognitive performance neither in schizophrenia patients nor in healthy controls [75]. Nevertheless, the authors did not record a history of childhood trauma, which could have influenced the relationship between *FKBP5* and cognition. The *FKBP5* rs9296158, rs4713916, rs992105 and rs3800373 SNPs have been found to be irrelevant in the association between childhood trauma and cognitive functioning in patients with psychotic disorder [76]. In turn, it has been observed that the *FKBP5* rs4713902 SNP significantly influences IQ levels in healthy controls, but not in patients with schizophrenia [74]. Interestingly, childhood trauma has been reported to enhance this interaction contributing to lower IQ scores in individuals who experienced maltreatment in early life [74].

4. *FKBP5* METHYLATION STATUS AND PSYCHOSIS.

Epigenetic mechanisms have been shown to underlie the effects of environmental exposures on DNA expression, being possibly responsible for the relationship between childhood trauma and the development of psychosis [77]. Lower methylation status has been observed in patients with first-episode psychosis reporting traumatic experiences [78]. Considering the relationship between trauma and the *FKBP5* gene, the level of methylation of this gene in the population of patients with childhood trauma experience has also been examined. Is has been observed that the level of physical and emotional abuse is negatively correlated with the methylation level of the *FKBP5* gene [79]. Interestingly, the correlation has been observed in the risk A allele carries of the rs1360780 polymorphism but not in the protective G allele, independently of heterozygosity of the allele [79]. Similar results have been obtained in the animal model study, showing

that increased and chronic corticosterone supply is positively correlated with decreased methylation of the *FKBP5* gene in the hippocampus and the hypothalamus in mice (54). Moreover, it has been demonstrated that childhood trauma-induced hypo-methylation in the promoter region of the *FKBP5* gene results in increased gene transcription entailing down-regulation of the GR complex [79 80]. Decrease in DNA methylation status has been found in children exposed to trauma, especially to physical and or sexual abuse [79, 80]. This epigenetic mechanism may provoke dysregulation of the stress hormone system leading to psychosis development [81].

5. CONCLUSIONS

Epidemiological studies show that both genetic and environmental factors, particularly exposure to stressful life events, contribute to the development of psychiatric disorders. Of special interest for future studies are genes that have been shown to modulate stress response through the influence on the HPA axis reactivity. One of such genes is the *FKBP5* gene encoding protein that is stress responsive [82]. Numerous studies have shown that *FKBP5* gene affects the susceptibility and symptomatology of many psychiatric disorders by interacting with life adversities and stressful life events, mainly post-traumatic stress disorder (PTSD), anxiety disorders, substance abuse disorders and depression [83]. There have been 31 independent studies comprising over thirty thousand individuals investigating interaction of *FKBP5* with life adversities with the majority of these studies showing significant interactive effect of early trauma and higher risk of psychopathology (for the review see [84]).

It has been demonstrated that particular *FKBP5* gene polymorphisms have significant influence on the development of psychosis, severity of symptoms and the level of cognitive impairment in patients with schizophrenia [50, 69, 85]. Moreover, genetic polymorphisms of the *FKBP5* have also been reported to affect the level of psychotic-like experiences in non-clinical population [72]. Bullying, neglect and abuse in childhood have been associated with the development of psychotic-like, negative-like and par-

anoid symptoms in young adults [86], which is in line with still growing body of research examining the impact of early life traumatic experiences on the development of psychosis. The *FKBP5* gene plays an important role in development of psychosis and the course of schizophrenia in response to chronic and acute stress by altering the structure or activity of brain regions related to stress hormone system [10, 69, 79]. Thus, several variants of this gene may both enhance or diminish the risk of illness and be responsible for possible exacerbations of psychosis and response to treatment in schizophrenia. Knowing the level of the risk could provide grounds for personalized care and prevention in subjects at risk of psychosis.

Taking into the consideration the body of studies supporting the pivotal role of the *FKBP5* in the pathophysiology of psychotic disorders, especially in individuals exposed to early trauma, future studies could focus on possible pharmacotherapeutic agents that may influence GR activity related to the FKBP5 protein. Several studies proposed that compounds with the activity of interacting with the FKBP506-binding protein could be helpful in the treatment of stress-related disorders [83, 87, 88]. Animal model studies show that administration of selective inhibitor of the FKBP506-binding protein via microinjections to adrenal gland or intraperitoneal injections results in both reduction of anxiety-related behaviors and increase in active coping behaviors in mice [89, 90]. In turn, intra-amygdala injection of neuropsin, which is a serine protease involved in the regulation of the *FKBP5* gene expression, results in enhanced resilience to stress exposure in mice [91]. To date, no similar research has been performed on humans, and no study has examined the influence of above-mentioned novel agents on the severity of psychotic symptoms. However, considering the strong association of the *FKBP5* gene with stress-related disorders, this field should remain open for future experimental studies. According to relatively low number of studies examining the relationship between the *FKBP5* gene, trauma experience and their influence on the development of preclinical psychotic experiences more studies are needed to verify current findings and empower possible therapeutic strategies. However, several

limitations of previous studies need to be taken into account. These include low sample size and a lack of considering timing of exposure. Indeed, it has been recommended that sample size required to detect interactions should be at least four times higher compared to sample sizes of studies that aim to detect main effects of comparable magnitude [2, 92]. Timing of exposure might be of great importance for a history of childhood trauma, which is recorded under the age of 17-18 years by the majority of self-reports. At least theoretically, this broad definition may create latent confounding related to attribution of silent stressful experiences to psychotic outcomes [93]. Moreover, there is evidence that simple models might be insufficient to address gene x environment interactions in psychosis [94]. Indeed, early-life stress might also be a pre-requisite for various psychological processes, such as ineffective stress coping, cognitive biases and self-disturbances that make individuals more prone to develop psychotic-like experience or overt psychotic symptoms. Finally, longitudinal studies are also required to understand causal associations between the *FKBP5* gene, early-life stress and psychosis.

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