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Review

Association between FKBP5 and CRHR1 genes with suicidal behavior: A systematic review

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HIGHLIGHTS

- Suicide is a serious public health problem worldwide with an estimated annual mortality rate of 14.5 deaths per 100,000 people.
- FKBP5 and CRHR1 genes have been associated importantly with epigenetic alterations in molecular pathways of the function HPA axis and serotonergic system in patients with suicidal behavior.
- An understanding of the functional consequence of FKBP5 and CRHR1 genes and its polymorphisms from a neuropathological perspective would be convenient to advance our understanding of their role in the HPA axis alterations with suicidal behavior.

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ABSTRACT

Suicide is one of the leading causes of death around the world with approximately one million suicides per year. An increasing number of neurobiological studies implicate HPA system dysfunction in suicide behavior, stimulating genetic research to focus on genes related to this system. This systematic review was focused on searching a correlation between FKBP5 and CRHR1 genes with suicidal behavior. Therefore, an electronic search strategy, using PubMed, EBSCO and Cochrane Library databases, was conducted from the inception of the studies into the databases to July 2016. The inclusion criteria were: use of at least one analysis investigating the relation between either the genetic variants in FKBP5 and/or CRHR1 genes with suicidal behavior. 2) use of a case–control design; 3) investigation about suicidal behavior in the form of suicide completion or history of at least one suicide attempt, as defined by each individual study; 4) inclusion of samples comprising control subjects; and 6) inclusion of reports written only in English language. The PRISMA guidelines were followed and the search strategy ensured that all possible studies were identified to compile the review. Using the keyword combinations, the search strategy provided 3334 articles, of which only 15 case-control studies were included in this systematic review. The included studies comprised 2526 subjects with suicidal behavior. A quantitative synthesis of results from the included studies was not undertaken due to marked methodological heterogeneity. This review showed a significant genetic association in most studies in FKBP5 and CRHR1 genes with a high rate of attempted suicide, pointing out that the expression of these genes and its polymorphisms could be a key predictor of suicide risk. In conclusion, this systematic review supports an association between suicidal behavior and genetic variants in FKBP5 and CRHR1 genes.

Abbreviations: ACTH, adrenocorticotropic hormone; cAMP, cyclic adenosine monophosphate; CRH, corticotropin-releasing hormone; CRHBP, CRH binding protein; CRHR1, type I CRH receptor; ERK, extracellular signal-regulated kinase; FKBP5, FK506-binding protein 51; GRADE, grading of recommendations, assessment, development and evaluation; HPA axis, hypothalamus–pituitary–adrenal axis; HIV, human immunodeficiency virus; HSP-90, heat shock protein 90; MAPK, mitogen-activated protein kinases; NOS, Newcastle-Ottawa scale; NR3C1, nuclear receptor subfamily 3 group C member 1; PKA, Protein kinase A; POMC, pro-opiomelanocortin.

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Contents

1. Introduction

Suicide is a serious public health problem with approximately one million suicides per year worldwide and an estimated annual mortality rate of 14.5 deaths out of every 100,000 people [1]. In this sense, suicidal behavior is classified in three categories: suicidal ideation (refers to thoughts and plans for ending one's life), suicide attempt (engagement in potentially self-injurious behavior with no lethal outcome) and suicide (the person ends with his/her own life) [2]. In clinical perspective, several studies have shown that the majority of suicides are committed by patients with neuropsychiatric disorders, among which include major depressive disorder [3,4], anxiety [5,6], hopelessness [7,8], bipolar disorder [9], schizophrenia [10,11], Alzheimer's disease [12], as well as substance abuse like alcohol and drugs [13–15]. These disorders have been linked with abnormalities in the hypothalamic-pituitary-adrenal system, which regulates the response to stressors, involving the interaction of different molecules such as: receptors, hormones, chaperones, and genetic variants, which could interfere with the function of this system (see Fig. 1) [16,17]. Furthermore, several studies have shown that individuals exposed to life adversities during critical periods of development are more susceptible to suicidal behavior in their adulthood in comparison with individuals without life adversities. [18–20]. In this context, many types of life adversities can increase risk for suicidal behavior, including: physical abuse [21,22], sexual abuse [23,24], childhood neglect [25], parental separation [26,27], domestic violence [28], and physical illness [29,30]. Considering the role of the HPA axis in the physiopathology of neuropsychiatric disorders, the effect of life adversities on suicidal behavior risk could also be mediated by alterations in HPA axis function, which could cause individuals with life adversities to be more vulnerable to suicide behavior [31,32]. In fact, a recent postmortem study in suicide brain samples reported that life adversities decreased glucocorticoid receptor expression by increasing the methylation level of the promoter region [33]. Therefore, the dysregulation of the HPA axis is the most potent biological marker predicting suicidal behavior in combination with others biomarkers of serotonergic activity in individuals with life adversities [34,35]. In this situation, there is evidence showing how the genetic variants at genes involved in the HPA axis may confer predisposition to pathogenesis of suicidal behavior [36–39]. Most of these studies have focused on the analysis about polymorphisms and expression of candidate genes, among which includes: FKBP5 and CRHR1 genes [40–44], which have been associated importantly with epigenetic alterations in molecular pathways of the function HPA axis and serotonergic system in patients with suicidal behavior [39,42,45–47].

FKBP5 (FK506-binding protein 5) gene is located on chromosome 6p21.31 and has 13 exons [48]. The protein encoded by FKBP5 gene has been implicated as a modulator of glucocorticoid receptor function through the association with heat shock protein 90 (hsp90) [39,49]. Upon ligand binding, FKBP5 protein is exchanged with FKBP4, which can promote nuclear translocation of the glucocorticoid receptor, leading to decreased negative feedback regulation of the HPA axis and a slower resolution of the stress response (see Fig. 2) [46,50]. In this sense, several studies have linked the genetic variants in FKBP5 gene with neuropsychiatric and endocrinological alterations, for instance: the frequency of depressive episodes [51,52], suicide attempts in bipolar patients [39,44,48], as well as incomplete normalization of cortisol secretion to stressful events [53,54], as overexpression of FKBP5 gene reduces cortisol binding affinity and nuclear translocation of the glucocorticoid receptor, influencing the transcriptional activity of the genes regulated by the steroid hormone-signaling pathway in HPA axis [55,56].

On the other hand, CRHR1 gene is also an interesting molecule in the context of stress liability in suicidal behavior; it is situated on chromosome 17q21.31, it has 14 exons [57]. CRHR1 gene encodes the G-protein coupled type I CRH receptor (CRHR1), is localized in frontal cortical areas, forebrain, brainstem, anterior pituitary, amygdala, and cerebellum [58–60]. This receptor also plays an important role in the activation of signal transduction pathways that activate HPA axis response to stressful events, through the action of corticotropin-releasing hormone (CRH) on the pituitary to release adrenocorticotropic hormone (ACTH) that stimulates the production of plasmatic cortisol in the adrenal cortex [31,61]. The distinct molecular mechanisms linking the alterations in CRHR1 gene and suicidal behavior have been associated with MAPK activation, which specifically regulate the expression of POMC, the ACTH precursor molecule (see Fig. 3). For a review see Bonfiglio et al. [62]. That is the reason why this review was focused on searching a correlation between FKBP5 and CRHR1 genes with suicidal behavior and to determine if the genetic variants and expression of these genes increase the suicide risk, through a systematic review of case-control studies.