Journal of Affective Disorders 225 (2018) 422–428

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
FKBP5
Systematic review
Gene-environment interaction
Meta-analysis
Risk alleles

ABSTRACT

Background: Gene-environment interaction contributes to the risks of psychiatric disorders. Interactions between FKBP5 gene variants and early-life stress may enhance the risk not only for mood disorder, but also for a number of other behavioral phenotypes. The aim of the present study was to review and conduct a meta-analysis on the results from published studies examining interaction between FKBP5 gene variants and early-life stress and their associations with stress-related disorders such as major depression and PTSD.

Methods: A literature search was conducted using PsychINFO and PubMed databases until May 2017. A total of 14 studies with a pooled total of 15109 participants met the inclusion criteria, the results of which were combined and a meta-analysis was performed using the differences in correlations as the effect measure. Based on literature, rs1360780, rs3800373, and rs9470080 SNPs were selected within the FKBP5 gene and systematic review was conducted.

Results: Based on the Comprehensive Meta-Analysis software, no publication bias was detected. Sensitivity analysis and credibility of meta-analysis results also indicated that the analyses were stable. The meta-analysis showed that individuals who carry T allele of rs1360780, C-allele of rs3800373 or T-allele of rs9470080 exposed to early-life trauma had higher risks for depression or PTSD.

Limitations: The effects of ethnicity, age, sex, and different stress measures were not examined due to limited sample size.

Conclusions: These results provide strong evidence of interactions between FKBP5 genotypes and early-life stress, which could pose a significant risk factor for stress-associated disorders such as major depression and PTSD.

1. Introduction

Early childhood adversity is a major risk factor in the development of a range of psychiatric disorders in adulthood. Several epidemiologic and clinical studies have provided convincing evidence of a strong association between childhood adversity, such as abuse, neglect, parental death, and divorce, and depressive symptoms (Chapman et al., 2004; Kim and Lee, 2016; Lohoff, 2010; Nanni et al., 2012). The experience of multiple childhood adversities increased the risk of major depressive disorder (MDD) and attempted suicide to 4-fold and 2–5-fold, respectively (Bandoli et al., 2017; Dube et al., 2001; Felitti et al., 1998). Twin studies also confirmed that early-life adversity plays a crucial role in the development of MDD (Thapar et al., 1998; Thapar and McGuffin, 1996). Post-traumatic stress disorder (PTSD) is another stress related disorder that has been linked to early-life stress. Individuals who experience early life stress have been shown to develop PTSD in adulthood more often than individuals with no history of early life stress (Anda et al., 2006; Bremner et al., 1993; Breslau et al., 1999; Chapman et al., 2004; Cougle et al., 2010; Dunn et al., 2017; Widom, 1999). Interestingly, not everyone exposed to early life adversity develop such a behavior (Lesch, 2004). The exact mechanisms how early life stress can lead to these disorders is not clearly known, however, several lines of evidence demonstrate that gene x environment interaction contribute significantly to the etiology of these disorders (Alexander et al., 2009; Binder, 2017; Saveanu and Nemeroff, 2012).

Previous studies have found that early-life stress impacts the subsequent risk of depression via effects on the hypothalamic-pituitary-adrenal (HPA) axis system (De Bellis et al., 1994; Heim et al., 2008;

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http://dx.doi.org/10.1016/j.jad.2017.08.066
Received 12 July 2017; Received in revised form 10 August 2017; Accepted 20 August 2017
Available online 24 August 2017

Nemeroff and Owens, 2004; Roy et al., 2012; van Bodegom et al., 2017). Preclinical studies also suggest that early-life stress affects HPA axis function in adulthood (Meaney, 2001; Sanchez et al., 2005; Weaver et al., 2005). Feedback inhibition of the HPA response via the glucocorticoid receptor (GR) signaling is significantly lower in patients with MDD, but specifically those with history of early-life trauma (Heim and Nemeroff, 2001; Heim et al., 2000). GR is a cytosolic receptor whose availability is modulated by a set of chaperone proteins, most significantly FK506-binding protein 51, encoded by FKBP5, which is an hsp90 co-chaperone. Functionally, cytosolic FKBP5 gene expression is induced via GR activation, which leads to translocation of GR into the nucleus and binding to glucocorticoid response elements in the promoter region of FKBP5. FKBP51 binds to and inhibits GR, which is a critical mechanism for GR desensitization (Rein, 2016; Riggs et al., 2003; Wochnik et al., 2005). Therefore, FKBP51 availability and activity is an important moderator for GR sensitivity, a critical element of HPA axis modulation.

In the past, several studies have attempted to examine whether FKBP5 confers a genetic risk factor for PTSD in the event of early life adversity (Binder et al., 2008; Xie et al., 2010). Similarly, gene-environment effects of FKBP5 and early-life stress have also been conducted in relation to MDD, suicide attempts, and aggression (Appel et al., 2011; Bevilacqua et al., 2012; Roy et al., 2010; Zimmermann et al., 2011). However, so far, there is no systematic review and meta-analysis examining whether variants of FKBP5 increase the risk of stress-related disorders such as MDD and PTSD. Therefore, the present study focused on the interaction between FKBP5, early-life stress, and risk for two clinical phenotypes: PTSD and MDD.

2. Methods and materials

2.1. Data sources and search strategy

Literature searches were conducted using PubMed and PsychINFO database up until 21 May 2017 for original research studies following the guidelines of 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) (Moher et al., 2009). The search terms included depression, PTSD, childhood adversity, synonyms for depression or PTSD, or early-life stress, and the FKBP5 rs1360780, rs3800373 and rs9470080 polymorphisms. These terms were searched for in the articles' titles, keywords, tests and measures. Moreover, the reference lists of the retrieved articles were also reviewed for the literature that they cited.

2.2. Eligibility criteria

Studies were included if they met the following criteria: (1) PTSD or MDD; (2) FKBP5 rs1360780, rs3800373 or rs9470080 polymorphisms; (3) early-life stress or childhood adversity; (4) an interaction between early-life stress and FKBP5 rs1360780, rs3800373 or rs9470080 polymorphisms; (5) the distribution of the genotypes in Hardy-Weinberg equilibrium; (6) Only papers published in the English language were considered for inclusion. Meeting abstracts, case reports, editorials, and review articles were excluded.

2.3. Data extraction

Two investigators (QZW and YD) independently extracted the relevant p-value from each study. There were no cases of disagreement between the two investigators. When several p values were provided (due to the use of several depression scales), p-value were separated for different subsets of samples. If the test statistic was not reported and the p-value in the source article was indicated as $p < 0.05$ or $p < 0.01$, 0.05 and 0.01 were used as the analyzed p-value, respectively.

2.4. Statistical analyses

The method was based on differences in correlations as the effect measure, which is widely used in meta-analysis for gene x environment interaction studies (Karg et al., 2011; Taylor and Kim-Cohen, 2007). This approach is based on the Fisher Z score transformation of correlations and associated standard error, which is applied using currently available meta-analytic software packages of Comprehensive Meta-Analysis (CMA) and Statistics and Data Analysis (STATA). Generally, the calculation process involves three steps: 1) the p values from the eligible studies are extracted and converted to one-tailed values, with p-values less than 0.50 corresponding to greater rs1360780 T allele stress sensitivity and p-values more than 0.50 corresponding to greater rs1360780C allele stress sensitivity; 2) p values are transformed into z-scores using a standard normal curve; and 3) the z-scores are combined and weighted to take into account the study sample size (Karg et al., 2011; Schmidt and Hunter, 2014).

In this study, the calculation of meta-analysis was carried out with CMA (version 3, Biostat Inc., New Jersey, USA). The statistics data used in the meta-analysis included p-values, tails, sample size, and effect direction. The program displayed each study's effect size, together with Confidential Informant (Cis) and the weight given to each study in the combined estimate.

Between-study heterogeneity was examined with the Chi-square-based Q-test (Cochran's Q statistic) and $p < 0.05$ was considered statistically significant (Cochran, 1954). The I^2 statistic was also calculated to quantify the proportion of the total variation due to heterogeneity and $I^2 > 50\%$ was considered to be statistically significant (Higgins et al., 2003). If the p value of the heterogeneity test was > 0.05, combined analysis were evaluated according to the fixed-effect model.

Publication bias was assessed through Begg's test and classic fail-safe. N and $p < 0.05$ were considered representatives of statistically significant publication bias (Begg and Mazumdar, 1994). Sensitivity analyses were undertaken to determine whether the results were influenced by any single study; the procedure involved systematically excluding each study and recalculating the significance of the results.

3. Results

3.1. Literature search and eligible studies

A flow chart describing the study selection process is shown in Fig. 1. rs1360780, rs3800373, and rs9470080 of the *FKBP5* gene were selected because these three SNPs were most frequently studied for gene-environment interaction. A total of 14 potentially relevant studies on the interactions between rs1360780, rs3800373 or rs9470080 and early-life stress risk for MDD or PTSD were identified and included in the meta-analysis. Detailed characteristics of each study are listed in Table 1. All these studies were confirmed to report the interaction between early-life stress and FKBP5 in MDD and PTSD. No systematic or

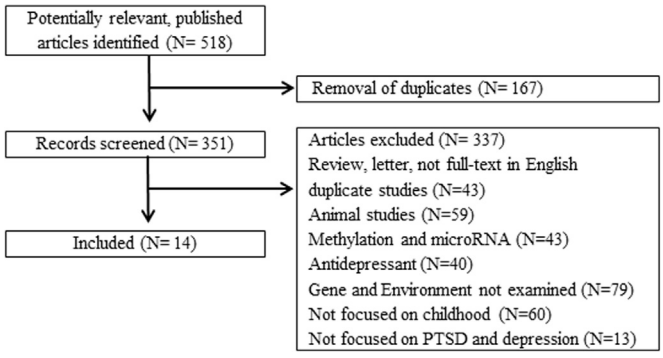

Fig. 1. Flow chart of study selection in meta-analysis.