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Research report

Genetic variability at HPA axis in major depression and clinical response to antidepressant treatment

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Abstract

Background: Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in major depression. Normalization of HPA axis has been suggested to play a role in the mechanisms of action of antidepressants. Our aim was to investigate the influence of genetic variants in CRHR1, CRHR2, CRH-BP and FKBP5 genes on both the vulnerability for depression and the response to antidepressant treatment.

Methods: The sample consisted of 159 depressive outpatients and 96 healthy controls of Spanish origin. Patients were assessed for clinical features including, among others, age of onset, seasonality or suicidal behavior. The episode was treated with citalopram and followed along 12 weeks. Severity of symptoms was evaluated at the inclusion and then monthly along the follow-up using a 21-item Hamilton Depression Rating Score (HDRS). SNPs were assayed using Applied Biosystems SNaP-Shot and TaqMan technology.

Results: rs110402, in CRHR1 gene, was associated with an increased risk to present a seasonal pattern and an early age of onset of the first depressive episode. Allele G carriers of rs2270007 of CRHR2 gene, showed a worse overall response to citalopram along time of follow-up (Genotype effect $F=7.45$, $P=0.007$). G allele carriers showed 2.93 increased risk (95% CI [1.24–6.90]) for non-responding at 4th week to citalopram treatment ($\chi^2=7.59$, $df=1$, $P=0.006$).

Limitations: On the light of the moderate sample size, associations based on the mentioned polymorphisms need to be considered with caution and require further replication studies in other samples.

Conclusions: Variability at genes encoding proteins with a pivotal role in HPA axis regulation seems to influence i) the expression of severity variables of the depressive spectrum including early age of onset or a seasonal pattern and ii) the interindividual variation in clinical response to SSRI antidepressants.

Keywords: Major depression; Follow-up study; SSRIs; Clinical response; HPA axis; CRHR1; CRHR2; CRH-BP; FKBP5

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1. Introduction

Major depressive disorder has been described as a common and severe psychiatric disorder with prevalence estimates ranging 5% to 20% (Bierut et al., 1999; Hamet and Tremblay, 2005) with woman almost twice as likely to be affected as men. Twin studies suggest polygenic inheritance with evidence of major locus effects and an overall heritability likely to be in the range of 31%–42% (Sullivan et al., 2000). Then, major depression is a clinically heterogeneous disorder thought to result from interplay of multiple genes interacting with environmental factors such as early stressful life events (Caspi et al., 2003). Although serotonergic system has been classically involved in the aetiology of major depression, the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has also been widely reported in depressive patients (Holsboer, 1999; Holsboer, 2000) pointing towards an altered neuroendocrine activity (Heuser et al., 1994; Nemeroff, 1996; Owens and Nemeroff, 1993; Stokes et al., 1984; Van Den Eede et al., 2006). Some authors have reported evidences of HPA axis dysregulation as a trait genetically determined which contributes to an increased risk for depression. The fact that this trait is found both in affected subjects and in healthy relatives with a high familial risk, added to its stability over time, has made HPA axis an interesting candidate endophenotype for affective disorders (Holsboer et al., 1995; Modell et al., 1998).

Studies investigating the hypothetical causes of an impaired regulation of HPA axis in depression have mainly focused on two elements: i) glucocorticoid receptor (GR) feedback mechanisms and ii) CRH signaling system.

Reduced GR function has been pointed out as the responsible of diminished sensitivity to cortisol which would lead to an inefficient feedback mechanism (Pariante and Miller, 2001). On the other hand, CRH peptide mediates the regulation of HPA axis as well as autonomic and behavioral responses in front of acute and chronic stress (Arborelius et al., 1999).

Several CRH receptor subtypes have been described: two membrane-bound receptors, CRH-R1 and CRH-R2, and a secreted glycoprotein that binds free CRH, CRH binding protein (CRH-BP). Knock-out mice studies have reported a central role of CRHR1 and 2 (Reul and Holsboer, 2002) and CRH-BP (Karolyi et al., 1999) in the modulation of stress response and anxiety-like behavior, highlighting the interest of CRH-related molecules in the understanding of anxious-depressive disorders.

Corroborating these data, so far two genes involved in CRH system, CRHR2 and CRH-BP (Claes et al., 2003; Villafuerte et al., 2002), and one gene involved in cortisol feedback mechanisms, the glucocorticoid receptor (GR) gene (van Rossum et al., 2006; van West et al., 2006), have been associated with an increased risk to suffer major depression.

Moreover, dysregulation of HPA axis has also been suggested to play a central role in the mechanisms of action of antidepressants (Holsboer, 2000; Nemeroff and Owens, 2002). Normalization of disturbances at HPA axis has been considered a prerequisite of a proper clinical response to antidepressant treatment (Holsboer and Barden, 1996; Nemeroff, 1988). A previous pharmacogenetic study has shown the influence of genetic variability at CRHR1 gene on a better response to antidepressant treatment (Licinio et al., 2004).

In vitro studies have shown that structurally different antidepressant compounds induce a rapid translocation of GR to the nucleus, the first step of the activation of GR, maybe facilitating GR-mediated feedback inhibition of HPA axis (Okuyama-Tamura et al., 2003; Pariante et al., 1997). This close relationship between antidepressants and GR has been reinforced by pharmacogenetic studies based on GR (van Rossum et al., 2006) and cochaperone FKBP5 (Binder et al., 2004), which modulates GR sensitivity.

On the light of this huge body of evidence, the aim of this study was to investigate the influence of genetic variants in CRHR1 (17q21.31), CRHR2 (7p14.3), CRH-BP (5q13.3) and FKBP5 (6p21.31) genes on the vulnerability, clinical expression and response to citalopram, a Selective Serotonin Reuptake Inhibitor (SSRI), in major depression.

2. Materials and methods

2.1. Sample

Our sample consisted of 159 depressive outpatients (124 females and 35 males; mean age 39.5 ± 12.2 years) from the Centre de Salut Mental Esquerre de l'Eixample (Hospital Clínic i Provincial de Barcelona, Spain). All depressive patients fulfilled DSM-IV criteria (APA 1994) for a current episode of major depression at recruitment and diagnosed using the Spanish version of Structured Clinical Interview (SCID-I) (Spitzer et al., 1990). No bipolar I or II diagnosed subjects were included in this sample.

The 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) was used to evaluate clinical severity of the index depressive episode. Patients were