Psychoneuroendocrinology 93 (2018) 20–28

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Hypothalamic-pituitary-adrenal axis activity in the comorbidity between obsessive-compulsive disorder and major depression

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ARTICLE INFO

Keywords:
HPA axis
Cortisol
Cortisol awakening response
OCD
Major depression
Trait anxiety

ABSTRACT

Major depressive disorder (MDD) is the most common psychiatric comorbidity in patients with obsessive–compulsive disorder (OCD). Hypothalamic-pituitary-adrenal (HPA) axis abnormalities have been described in both disorders and might play a role in the association between them. We aimed to study the role of HPA axis activity in the comorbidity between OCD and MDD, while controlling for psychopathological dimensions such as anxiety and depressive symptoms. We studied 324 participants belonging to four diagnostic groups: 1) MDD (n = 101), 2) OCD with comorbid MDD (n = 33), 3) OCD without MDD (n = 52), and 4) healthy subjects (n = 138). State anxiety, trait anxiety and depressive symptoms were assessed. Three HPA axis measures were analyzed in saliva: cortisol awakening response (CAR), diurnal cortisol slope (calculated using two formulas: [1] awakening to 11 p.m. [AWE diurnal slope]; [2] considering fixed time points [FTP diurnal slope] from 10 a.m. to 11 p.m.), and dexamethasone suppression test ratio after 0.25 mg of dexamethasone (DSTR). Multiple linear regression analyses were conducted to explore the contribution of clinical diagnosis and symptom dimensions to each HPA axis measure. A more flattened FTP diurnal cortisol slope was observed for OCD patients with comorbid MDD. Regarding the CAR and DSTR, a significant interaction was found between trait anxiety and OCD, as OCD patients with greater trait anxiety showed an increased CAR and reduced cortisol suppression after dexamethasone administration. Our results suggest that trait anxiety plays an important role in the relationship between HPA axis measures and OCD/MDD comorbidity.

1. Introduction

Symptoms of major depression often appear in the context of other psychiatric diagnoses such as obsessive–compulsive disorder (OCD), where the lifetime diagnosis of major depressive disorder (MDD) is about 50% (Hofmeijer-Sevink et al., 2013; Torres et al., 2016). The high comorbidity between MDD and OCD suggests a pathogenic overlap between the two disorders, with shared psychological determinants, including dimensions of distress or negative affectivity, as well as a shared genetic predisposition and common neurobiology (Goodwin, 2015). Trait anxiety, which is closely related to neuroticism and refers to the stable tendency to experience negative emotions, is a risk factor for both MDD and OCD (Grupe and Nitschke, 2013).

However, mechanistic pathways that might account for the differences and similarities between MDD and OCD are poorly understood. Studying the hypothalamic-pituitary-adrenal (HPA) axis could help to elucidate this issue, since abnormalities in the HPA axis have been described in both MDD and OCD. In MDD, the most consistent findings involve hyperactivation of the HPA axis (e.g., increased serum, urinary, or cerebrospinal fluid cortisol levels), lack of cortisol suppression in the dexamethasone suppression test (DST) (Wolkowitz et al., 2009), and an increased cortisol awakening response (CAR) (Vreeburg et al., 2009). Although comparatively fewer studies have explored the role of the HPA axis in the pathogenesis of OCD, hyperactivity of the HPA axis has

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https://doi.org/10.1016/j.psyneuen.2018.04.008
Received 5 June 2017; Received in revised form 4 March 2018; Accepted 10 April 2018

also been demonstrated in patients suffering from this condition, with elevated levels of corticotrophin releasing hormone (CRH) in cerebrospinal fluid (Altemus et al., 1992), higher plasma cortisol levels in the early morning (Gustafsson et al., 2008), and increased nocturnal secretion of adrenocorticotropic hormone (ACTH) (Kluge et al., 2007). However, previous studies in OCD samples have not assessed the putative modulatory effects of comorbid depression on HPA axis measures. Moreover, to date, no previous studies have explored the CAR in patients with OCD.

There are bidirectional interactions between the HPA and hypothalamic-pituitary-gonadal (HPG) axes: the HPA has an inhibitory effect on the female reproductive system, and oestrogens stimulate the HPA axis (Chrousos et al., 1998). In women with MDD or OCD, symptom severity appears to fluctuate over the reproductive life cycle, as some women experience a worsening of symptoms at reproductive events that are associated with lower oestrogen levels including the premenstrual, postpartum and perimenopause periods (Labad et al., 2005; Soares and Zitek, 2008). The functional cross-talk between the HPA and HPG axes is particularly important during pregnancy and early postpartum. Placental CRH drives the pituitary-adrenal axis to secrete high levels of cortisol during the latter part of pregnancy. The withdrawal of placental CRH after delivery induces a secondary hypothalamic CRH deficiency with psychopathological consequences (increased risk for mood disorders or OCD) and autoimmune phenomena (Chrousos et al., 1998). An exaggerated cortisol-placental CRH feed-forward loop has been suggested to be apparent among women who develop postpartum depression (Glynn et al., 2013). In postpartum OCD, greater cortisol responses to the cold pressor test have been reported compared to those in healthy controls (Lord et al., 2011). In another study by our group that included 132 healthy pregnant women (Labad et al., 2011), increased plasma ACTH levels at 48 h postpartum were found in women who would later experience postpartum intrusive thoughts of harming the infant, symptoms that are phenomenologically similar to aggressive obsessions experienced by OCD patients. In relation to premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD), there is no consistent evidence that women with and without PMS/PMDD demonstrate mean-level differences in cortisol or differences in cortisol reactivity (Kiesner and Granger, 2016). Perimenopausal depression does not seem to be associated with alterations in basal HPA axis hormone concentrations, although studies examining HPA axis activation in response to stress in women with perimenopausal depression are lacking (Gordon et al., 2015).

Since trait anxiety and neuroticism have been associated with both MDD and OCD, as well as HPA axis abnormalities, including higher morning cortisol levels (Polk et al., 2005; Portella et al., 2005) and a more flattened diurnal cortisol slope (Doane et al., 2011; Hauner et al., 2008; Hilt et al., 2017); it is also important to investigate whether the association between HPA axis measures and these two mental disorders might be moderated by trait anxiety. Here we aimed to study the role of HPA axis activity in the comorbidity between OCD and MDD, while controlling for psychopathological dimensions of anxiety and depressive symptoms. This approach is in line with previous studies that have illustrated the added value of using symptom dimensions when investigating neuroendocrine mechanisms underlying psychiatric disease (Wardenaar et al., 2011). Phenotypic dimensional and categorical approaches can also be validated by using indices of HPA axis function, as some authors have suggested (Veen et al., 2011). In the study by Veen et al. (2011), the authors assessed several HPA axis measures (CAR, diurnal cortisol slope) and compared the categorical DSM-IV diagnoses of a sample of patients with depressive, anxiety and comorbid depressive and anxiety disorders with a dimensional approach using three clinical dimensions (anhedonic depression, anxious arousal, and general distress) of the Mood and Anxiety Symptom Questionnaire. Interestingly, anhedonic depression and anxious arousal were associated with both an increased CAR and higher cortisol concentrations during the diurnal decline, whereas for depressive patients defined by DSM-IV categories, only a steeper diurnal cortisol slope was found. In another study (Harris et al., 2015) that also considered categories and dimensions of anxiety and depression, no associations were found for the main diagnostic categories, but a reduced CAR and a more flattened cortisol diurnal slope were associated with the somatization scale of the Hopkins Symptom Checklist-25 (HSCL-25). These studies are also in agreement with the Research Domain Criteria (RDoC) initiative, which seeks dimensional constructs that integrate psychological and biological phenomena in order to complement the classical approach of studying biological processes using the empirical categories of diagnostic manuals (Yee et al., 2015).

We hypothesize that trait anxiety and depressive symptoms are associated with HPA axis abnormalities in a transdiagnostic way, that is, independently of an MDD or OCD categorical diagnosis. Regarding different HPA axis measures (CAR, diurnal cortisol slope, DST) and specific hypotheses, we expect trait anxiety and depressive symptoms rather than OCD or MDD diagnoses to be associated with an increased CAR and a more flattened cortisol slope. Moreover, depressive symptoms are expected to be associated with higher cortisol levels after the DST (lower suppression after dexamethasone administration).

2. Material and methods

2.1. Study sample

The sample consisted of 324 participants distributed across four diagnostic groups: 1) MDD (n = 101), 2) OCD with comorbid lifetime MDD (n = 33), 3) OCD without MDD (n = 52), and 4) healthy subjects (HS) (n = 138). All patients were diagnosed according to DSM-IV-TR criteria and were consecutively recruited through the Psychiatry Department of Bellvitge University Hospital (Hospitalet de Llobregat, Barcelona). HS from the same geographic area were recruited through advertisements. The sample partially overlaps that used in a previous study, which included 97 MDD patients and 97 HS and explored a different hypothesis (Salvat-Pujol et al., 2017).

Exclusion criteria were: age less than 18 years, non-Caucasian ethnicity, a diagnosis of other psychiatric disorders including substance abuse or dependence (except nicotine), mental retardation, neurological disorders, severe medical conditions, pregnancy or puerperium, electroconvulsive therapy in the previous year, and corticosteroid treatment in the previous three months. All participants were Caucasian because the original study protocol aimed to include participants with a homogeneous genetic pedigree, as DNA was also obtained to test other genetic-based hypotheses in future analyses. Of the 431 subjects who initially fulfilled the criteria for participating in the study, 107 were excluded after the screening for several reasons described in the supplementary material (Table S1). Thus, the final study sample consisted of 324 participants.

The research protocol was approved by the Ethics Committee of Bellvitge University Hospital (*Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge*), and all participants provided written informed consent after having received a full explanation of the study. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975 (revised in 2013).

2.2. Clinical assessment

Patients were diagnosed by an experienced psychiatrist using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and met DSM-IV-TR criteria for MDD and/or OCD.

HS had no past or current history of psychiatric disorders (assessed in a semi-structured interview by an experienced psychiatrist) and scored below 7 on the 28-item Spanish adaptation of the Goldberg General Health Questionnaire (GHQ-28) (Lobo et al., 1986).

Sociodemographic and clinical variables, substance use, and treatment were assessed using a semi-structured interview administered by