Clinical correlates of hypothalamic-pituitary-adrenal axis measures in individuals at risk for psychosis and with first-episode psychosis

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ABSTRACT

Hypothalamic-pituitary-adrenal (HPA) axis alterations in at-risk mental states (ARMS) resemble those observed in established psychosis but are less consistent. We aimed to explore HPA axis abnormalities in both first-episode psychosis (FEP) and ARMS patients, while controlling for psychopathological symptoms. We studied 21 ARMS, 34 FEP patients and 34 healthy subjects. Clinical assessment included psychopathological symptoms (positive, negative, disorganized, excited and depressive symptoms) and stress measures. Saliva cortisol levels were determined at awakening, 30′ and 60′ post-awakening, 10:00 h, 23:00 h and 10:00 h on the day after the administration of 0.25 mg of dexamethasone, which occurred at 23:00 h. Three HPA axis measures were calculated: cortisol awakening response (CAR), cortisol diurnal slope and cortisol suppression ratio of the dexamethasone suppression test (DST). There were no significant differences between groups in HPA axis measures. However, when exploring the relationship between HPA axis measures and psychopathological symptoms, in ARMS subjects (but not FEP patients), a flatter cortisol slope was associated with more prominent negative symptoms, whereas a blunted CAR was associated with excited symptoms. Although no significant differences in HPA axis measures were found between diagnostic groups, subtle abnormalities in the CAR or circadian cortisol rhythmicity might be important for the phenotype of ARMS individuals.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is a stress response system that has been suggested to be involved in the risk of developing a psychotic disorder (Walker et al., 2008). The diathesis-stress model has dominated theories about the pathophysiology of psychosis, suggesting a link between psychosocial stressors, glucocorticoid secretion and dopamine synthesis (Pruessner et al., 2017). For many years, several studies have reported HPA axis hyperactivity and a blunted HPA axis response to psychological stress in chronic patients with schizophrenia (Bradley and Dinan, 2010) or with first-episode psychosis (FEP) (Borges et al., 2013). In the last decade, along with the study of the clinical staging model of psychosis (Fusar-Poli et al., 2017, 2014), several works (Labad et al., 2015; Sugranyes et al., 2012; Walker et al., 2013) have aimed to detect significant HPA axis abnormalities in early phases of the psychotic illness by including people who are at clinical high risk for psychosis (also known as at-risk mental states [ARMS]).

Assessment of HPA axis indices may include baseline cortisol measures (initial measurement without experimental manipulation or exposure) and cortisol dynamic tests in response to either a physiological condition (e.g., cortisol awakening response [CAR]), stressful situation (e.g., Trier Social Stress Test [TSST]) or a pharmacological challenge (e.g., dexamethasone [DEX] suppression test [DST]). When comparing ARMS, FEP and healthy subjects (HS) in terms of HPA axis activity, there are some conflicting results in the literature. A recent meta-analysis (Chaumette et al., 2016) suggests that baseline cortisol levels might be increased in ARMS but not FEP patients. In line with this view, longitudinal studies of ARMS individuals have also reported that elevated baseline cortisol is a predictor of psychosis transition (Walker et al., 2013). In contrast to basal levels, a blunted response to an acute psychosocial stressor (TSST) has been described in both psychotic patients and ARMS individuals (Ciufolini et al., 2014; Pruessner

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et al., 2013). In relation to the CAR, a meta-analysis suggests that a blunted response to awakening is present in FEP but not ARMS patients (Berger et al., 2016). However, one study (Day et al., 2014) found that medication-free ARMS participants show a blunted CAR when compared to healthy controls. Another prospective study by our group found an increased CAR in those ARMS individuals who developed a psychotic disorder when compared to HS and ARMS without a psychosis transition (Labad et al., 2015). Classical studies using the standard (1 mg) DST (Tandon et al., 1991) or the DEX/CRH test (Lammers et al., 1995) in patients with schizophrenia have reported high rates of non-suppression, suggesting an impaired glucocorticoid receptor-mediated negative feedback of the HPA axis. However, other studies using the same DEX dose have failed to detect a greater proportion of non-suppression in patients with schizophrenia (Ismail et al., 1998). An increased suppression to a low dose (0.25 mg) of DEX has been reported in FEP patients, when compared to healthy controls (Phassouliotis et al., 2013). In ARMS individuals, higher cortisol during the latter stages of the DEX/CRH test have been described in those ARMS without a psychosis transition when compared with those who developed a psychotic disorder (Thompson et al., 2007).

Differences found between ARMS, FEP and chronic psychotic patients may be influenced by different variables. Confounding factors such as antipsychotic treatment may explain some inconsistencies, because antipsychotic treatment is thought to normalize HPA axis hyperactivity (Mondelli et al., 2010; Sugranyes et al., 2012). However, a recent study failed to confirm the significant effect of antipsychotic medication on cortisol secretion in patients with schizophrenia (Nedic Erjavec et al., 2017). Differences between chronic patients, FEP patients and ARMS individuals also highlight the importance of the stage of the illness in the study of HPA axis activity. As proposed by some authors (Pruessner et al., 2017), attenuated cortisol responses to stress and awakening might be the consequence of a prolonged hyperactivity of the HPA axis. As suggested by these authors (Pruessner et al., 2017), a lesson that can be learned from the incongruent findings is that differences in various indices of HPA axis activation must be taken into consideration and incorporated into models when conceptualizing the role of stress and the HPA axis in the etiology of psychosis. Inconsistencies in previous studies of early psychosis might be due to the potential contribution of symptoms to some HPA axis indices. Some studies conducted in patients with psychotic disorders suggest that the CAR is associated with positive, disorganized and excitement symptoms (Belvederi Murri et al., 2012) and that diurnal cortisol patterns (a flattened cortisol slope) is associated with positive and negative symptoms (Ho et al., 2016). Two systematic reviews that included ARMS (Karanikas and Garyfallos, 2015) and FEP (Karanikas et al., 2014) samples, have noted that the relationship between cortisol measures and psychopathological symptoms is not specific, and positive associations between psychotic symptoms and cortisol measures do not seem to be well replicated. Another explanation for inconsistencies between studies could rely on the heterogeneity of samples in terms of socio-demographic or other clinical variables (Karanikas et al., 2014; Karanikas and Garyfallos, 2015).

The cortisol diurnal slope is one HPA axis measure less investigated in FEP patients and ARMS individuals. The HPA axis follows a marked circadian variation, with greater cortisol secretion in the morning than the evening (Posener et al., 1996). Altered circadian cortisol rhythms are one sign of HPA axis dysregulation (Rosmond et al., 1998), and a flattened diurnal cortisol slope has been identified in patients suffering from major depression (Jarcho et al., 2013). It is important to explore whether there are differences in cortisol diurnal secretion patterns between ARMS and FEP patients because circadian disturbances (fragmented rhythms and low daily activity) have been associated with increased psychotic symptom severity among ARMS participants and predict psychosocial impairment at 1-year follow-up (Lunsford-Avery et al., 2017). In a study that compared adolescents with schizotypal personality disorder with other two groups (other personality

disorders or no disorders), a significantly greater linear decline in cortisol release was observed in the schizotypal personality disorder group, when compared to the normal comparison group (Weinstein et al., 1999). In another study that included siblings of patients with a psychotic disorder and a healthy comparison group, there were no significant differences in the diurnal cortisol slope between the two groups (Collip et al., 2011).

The main aim of our work was to conduct an exploratory study to assess whether there are differences in several HPA axis indices between patients with an ARMS or FEP diagnosis, in comparison to HS. As a secondary aim, we wanted to ascertain whether HPA axis measures are moderated by the severity of clinical symptoms (positive, negative, excited, disorganized, and depressive).

2. Methods

2.1. Participants

We studied 21 ARMS and 34 FEP patients aged between 18 and 35 years from the Early Intervention Service of the Hospital Universitari Institut Pere Mata (Reus, Spain). An age- and sex-matched control group of 34 HS were recruited from the community using advertisements. The sample partially overlaps with the sample of previous studies that explored different hypotheses (Labad et al., 2016, 2015). Participants were excluded from the study if they were pregnant or had severe neurological disease or mental retardation; language difficulties; visual impairment; alcohol, heroin or cocaine dependence; or undergone treatment with glucocorticoids or hormonal contraceptive treatment. In patients with acute inflammatory processes (e.g. active infection), recruitment was conducted after the recovery from the inflammatory condition. Ethical approval was obtained from the local Ethics Committee. After a complete description of the study was provided to all participants, written informed consent was obtained.

2.2. Clinical assessment

2.2.1. Clinical assessment of all participants (patients and HS)

Sociodemographic, smoking and cannabis use data were obtained via semistructured interviews. Stressful life events occurring during the previous 6 months were assessed using the Holmes—Rahe Social Readjustment Scale (HRSRS) (Holmes and Rahe, 1967). This scale explores 43 life events and gives a 'stress score' for each item; then, a final score is obtained by adding the scores of all reported life events. The 14-item Perceived Stress Scale (PSS) (Cohen et al., 1983) was used to explore the psychological repercussions of stress during the previous month.

Weight and height were assessed by physical examination. Body mass index (BMI) was calculated using the following formula: weight/height^2.

2.2.2. Clinical assessment of patients

All patients were interviewed by a psychiatrist using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). The Operational Criteria Checklist for Psychotic Illness (OPCRIT, version 4.0, available at http://sgdp.iop.kcl.ac.uk/opcrit/) was used to assign DSM-IV diagnoses of psychotic disorders (schizphreniphorm disorder [N = 5], schizophrenia [N = 2], schizoaffective disorder [N = 2], bipolar disorder [N = 7] and psychotic disorder not otherwise specified [N = 18]) in the FEP group. The Comprehensive Assessment of At-Risk Mental States (Yung et al., 2005) was administered to ensure that ARMS individuals met the criteria for any of the three high-risk groups falling under the ARMS category (attenuated psychosis [N = 12], brief limited intermittent psychotic symptoms [N = 3] or vulnerability group [N = 6; family history of psychosis, or schizotypal personality disorder, with a reduction in functionality]). Psychotic symptoms were assessed in both ARMS and FEP patients using the Positive and Negative