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Stress biomarkers as predictors of transition to psychosis in at-risk mental states: Roles for cortisol, prolactin and albumin

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ABSTRACT

Stress and inflammation are thought to play a role in the risk of developing a psychotic disorder. We aimed to identify stress-related biomarkers for psychosis transition in help-seeking individuals with an at-risk mental state (ARMS). We studied 39 ARMS subjects who were attending an Early Intervention Service. We included a control group of 44 healthy subjects (HS) matched by sex and age. Stressful life events and perceived stress were assessed. Stress-related biomarkers were determined in serum (cortisol, prolactin, C-reactive protein and albumin), plasma (fibrinogen) or saliva (morning cortisol, cortisol awakening response). All ARMS were followed-up at our Unit for at least one year. We divided the ARMS group into two subgroups based on the development of a psychotic disorder (ARMS-P, $N = 10$) or not (ARMS-NP, $N = 29$). ARMS-P reported more stressful life events and perceived stress than HS and ARMS-NP groups. In relation to baseline stress biomarkers, ARMS-P subjects had increased prolactin and lower albumin levels in serum, when compared to ARMS-NP and HS groups. These results did not change when repeated in a subsample of antipsychotic-naïve ARMS subjects. We also found significant differences between groups in the cortisol secretion after awakening. In a multinomial logistic regression adjusting for age, sex and life stress, prolactin was a predictor of psychosis transition whereas albumin levels had a protective effect. Our study underscores the role of stress and stress-related biomarkers (cortisol awakening response, prolactin and albumin) in the pathogenesis of psychosis.

1. Introduction

Stress is thought to play a role in the risk of developing a psychotic disorder, as both first episode of psychosis and subjects with prodromal symptoms of psychosis report more stressful life events (Beards et al., 2013; Manzanares et al., 2014) and perceived stress (Pruessner et al., 2011), when compared to healthy subjects. The classical neural diathesis-stress model of schizophrenia suggests that psychosocial stress activates the hypothalamic–pituitary–adrenal (HPA) axis, that induces cortisol release and enhances dopamine transmission, contributing to the emergence of psychosis in vulnerable individuals (Walker and Diforio, 1997). This theoretical hypothesis has been recently demonstrated in a positron emission tomography study reporting stress-induced dopamine release in psychosis (Mizrahi et al., 2012). In first episodes of psychosis, hyperactivation of the HPA axis is a common feature (Borges et al., 2013). Recent studies have also explored HPA axis abnormalities in people suffering from potentially prodromal symptoms, also known as at-risk mental states (ARMS) (Fusar-Poli et al., 2013). Salivary cortisol has been associated with impaired stress tolerance (Corcoran et al., 2012) and a risk of psychosis transition (Walker et al., 2013) in ARMS subjects. A blunted cortisol awakening response (CAR) has been also reported in ARMS individuals, when compared to healthy subjects (HS) (Day et al., 2014). In genetically high risk populations, such as siblings of patients with a non-affective psychotic disorder, unpleasant stressful

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events are associated with psychotic experiences and increased cortisol levels (Collip et al., 2011).

However, although the HPA axis is one of the main biological responses to stress, other stress-related biomarkers may also play a role. Prolactin, an anterior pituitary hormone that increases in response to psychosocial stress (Sobrinho, 2003; Lennartsson and Jonsdottir, 2011), has been demonstrated to be increased in up to 39% of drug-naïve individuals with a first episode of psychosis (Aston et al., 2010; Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013) or with an ARMS diagnosis (Aston et al., 2010). These findings are important, because they underscore that in a substantial proportion of individuals with psychotic disorders at early stages hyperprolactinaemia is not secondary to D2-blockade by antipsychotics. Some authors have suggested that as enhanced prolactin can increase dopamine release through a feedback mechanism, this could contribute to explaining how stress can trigger the outbreak of psychosis (Riecher-Rössler et al., 2013). However, there are no prospective studies exploring whether increased prolactin in ARMS subjects may contribute to the risk of developing a psychotic disorder.

Inflammatory and oxidative stress biomarkers have been also found to be increased in subjects with a first episode of psychosis (Miller et al., 2011; Flatow et al., 2013). In a previous study by our group we also found increased interleukin-6 levels in ARMS subjects, when compared to healthy subjects (Stojanovic et al., 2014). The inflammatory hypothesis of schizophrenia suggests that peripheral inflammation might cause or reflect brain dysfunction in schizophrenia, as cytokines may directly modulate dopaminergic neurotransmission or indirectly modulate glutamatergic neurotransmission through tryptophan metabolism (Kirkpatrick and Miller, 2013). Albumin, an abundant circulating protein in plasma that may be reduced in severe physical illnesses, could be considered another potential biomarker linked to the risk of psychosis transition as it has antioxidant properties and exerts a favorable influence on redox-signaling processes that regulate inflammation (Roche et al., 2008). Different studies have emphasized the importance of serum albumin in psychiatric disorders. Reduced serum albumin levels have been reported in patients with major depressive disorder (Huang et al., 2005), first episodes of schizophrenia (Reddy et al., 2003; Pae et al., 2004) or chronic schizophrenia (Yao et al., 2000; Huang, 2002). Serum albumin levels correlate with the processing of affective prosody in adult male patients with attention deficit hyperactivity disorder (ADHD) (Grabemann et al., 2014). Additionally, an association between low serum albumin levels and corticosteroid-induced psychosis has been reported in patients with systemic lupus erythematosus (López-Medrano et al., 2002; Chau and Mok, 2003). No studies have addressed whether reduced albumin levels may play a role in the risk of transition to psychosis in individuals at risk for psychosis.

The main aim of our study was to assess whether clinical and biological measures of stress could be predictors of psychosis transition in a sample of help-seeking ARMS subjects attending an Early Intervention Service.

2. Material and methods

2.1. Participants

The initial sample consisted of 40 subjects (30% women, mean age: 23.2 years) fulfilling set criteria for ARMS who had attended the Early Intervention Service from Reus (HU Institut Pere Mata, Spain) for at least one year. Exclusion criteria were: pregnancy, mental retardation, severe head injury or neurological disease, active glucocorticoid treatment, oral contraceptive pill use, active substance dependence (other than tobacco or cannabis) and type 1 diabetes mellitus. Of all 40 subjects, one patient was diagnosed of type 1 diabetes after the initial blood analysis and was therefore excluded, leaving a final sample of 39 ARMS subjects. We included a control group of 44 healthy subjects (HS) matched by sex and age. This group was screened to rule out past or current history of psychiatric disorders. Recruitment of HS included young people from the community who were contacted by advertisements. Ethical approval was obtained from the local Ethics Committee. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Clinical assessments

2.2.1. Baseline visit

ARMS subjects were assessed with the Comprehensive Assessment of At Risk Mental States, to ensure that subjects met criteria for any of the three high-risk groups defined by ARMS criteria (Yung and McGorry, 2007): (1) attenuated psychosis ($n = 24$), (2) brief limited intermittent psychotic symptoms (BLIPS) ($n = 7$), and (3) vulnerability group ($n = 8$), that includes subjects with a family history of psychosis in first degree relative or schizotypal personality disorder in identified patient with a 30% drop in GAF score from premorbid level, sustained for 1 month.

Positive, negative and overall psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Stressful life events in the previous 6 months were assessed with the Holmes–Rahe Social Readjustment Scale (Holmes and Rahe, 1967). This scale was initially developed to explore the relationship between social readjustment, stress and susceptibility to illness. It explores 43 life events and gives a 'stress score' for each item, obtaining a final score by adding the scores of all present life events. This scale has been validated and used in Spanish populations (Roca et al., 2013). Previous studies include the use of this scale to explore the relationship between life events and subclinical psychotic symptoms in the general population (Rössler et al., 2007). Perceived Stress Scale (Cohen et al., 1983) was used to assess psychological perception of stress. This instrument is a 14-item self-report questionnaire that was designed to measure the degree to which situations in ones' life are appraised as stressful. Subjects indicate how often they have found their lives unpredictable, uncontrollable, and overloaded in the last month.

As albumin levels may be affected by protein ingestion (Thalacker-Mercer and Campbell, 2008), we assessed dietary habits by means of a clinical interview conducted by a dietician. Food intake was registered by 24 h recall. Specialized software (CESNID, Barcelona University) was used to calculate the daily calorie and protein intake.

Antipsychotic and antidepressant treatment, and other sociodemographic and clinical variables were obtained by semi-structured interview. In our Early Intervention Service, all psychopharmacological treatments (introduction, changes in dosage and retirement) are registered in an electronic clinical record. We verified antipsychotic treatment at assessment by contrasting information obtained during the clinical interview and data included in the electronic health records. Of all 39 ARMS subjects, 7 (17.9%) were taking antipsychotic drugs at baseline assessment (aripiprazole [$n = 4$], risperidone [$n = 2$] and quetiapine [$n = 1$]). Regarding antidepressant treatment, 16 ARMS subjects (41%) were receiving antidepressants (selective serotonin reuptake inhibitors [$n = 12$], venlafaxine [$n = 2$], duloxetine [$n = 1$] and mirtazapine [$n = 1$]).

2.2.2. Follow-up visits: psychosis transition criteria

ARMS subjects that seek treatment usually attend our unit with frequent visits (every 2–4 weeks). We aimed to include longitudinal data in those ARMS subjects who had a follow-up period of at