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Attenuated cortisol response to acute psychosocial stress in individuals at ultra-high risk for psychosis

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ABSTRACT

We recently reported that individuals at ultra-high risk for the development of psychosis (UHR) have elevated levels of chronic stress and deficits in the putative protective factors self-esteem, social support and coping skills. The aim of the present study was to assess endocrine and autonomic responses to acute psychosocial stress and their associations with self-ratings of stress and protective factors in individuals at UHR.

Twenty-one patients diagnosed with an "at risk mental state" (12 male, 9 female; mean age 20.8 ± 3.27) and 21 healthy age and gender matched community controls were exposed to the Trier Social Stress Test (TSST). Saliva samples for cortisol assessment and measurements of heart rate and blood pressure were taken throughout the testing period. Levels of perceived chronic stress, protective factors and depression were assessed with reference to the preceding month and year (stress only).

Compared to healthy controls, individuals at UHR reported significantly higher levels of depression, deficits in protective factors, and a trend for higher chronic stress levels. Cortisol levels and systolic blood pressure during the TSST were significantly lower in the UHR group, while heart rate changes were comparable to controls. Lower cortisol levels in the UHR group were associated with higher self-ratings of stress in the past year and a lower level of education. Attenuated cortisol responses to acute psychosocial stress in the presence of high chronic stress could indicate a desensitization of the HPA axis. Associated poor metabolic and psychological adjustment to stress might increase vulnerability for the development of psychosis.

1. Introduction

Chronic or cumulative exposure to psychosocial stress is considered an important factor implicated in the pathophysiology of schizophrenia (Phillips et al., 2007; van Winkel et al., 2008). In a recent study, we reported elevated levels of perceived chronic stress in individuals at ultra-high risk for the development of psychosis (UHR) (Pruessner et al., 2011). In accordance with this finding, two other recent studies reported greater distress and negative emotions in response to life events and daily hassles in people at UHR compared to healthy controls (Palmier-Claus et al., 2011; Phillips et al., 2011). These findings supplement previous reports of high emotional reactivity to daily events in first-degree relatives of patients with psychosis (Myin-Germeys et al., 2001) and of more undesirable life events and more distress in response to daily hassles in adolescents with schizotypal personality disorder (SPD) (Tessner et al., 2011). In general, rather than being exposed to a higher number of stressful events, high-risk individuals might perceive events as more stressful than healthy controls (Phillips et al., 2007), a conclusion that has also been drawn for patients with established psychosis (Norman and Malla, 1993a,b). Such vulnerability to stress is probably determined largely by the interaction of a person's genetic make-up and the consequences of previous life stressors (Zubin and Spring, 1977). In addition, the subjective experience of stress and its long-term health impact are likely to be influenced by the availability of certain protective factors. For example, patients at high risk for psychosis exhibit deficits in coping skills, social support and self-esteem (Phillips et al., 2011; Pruessner et al., 2011), and both high stress levels and deficits in protective factors can predict symptom severity in the high risk phase (Tessner et al., 2011; Palmier-Claus et al., 2011; Pruessner et al., 2011).

The two major physiological systems responding to stress are the sympathetic nervous system (SNS) and the hypothalamus–pituitary–adrenal (HPA) axis, which set into motion various processes to ensure adaptation to metabolic and behavioral needs in stressful

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situations (de Kloet et al., 2005; Chrousos, 2009). Neural diathesis stress models propose the endocrine stress system as a likely mediator between the experience of stress and the onset or exacerbation of psychotic symptoms (Walker and Diforio, 1997; Corcoran et al., 2003). Acute stress normally leads to cortisol increase, but animal and human studies have shown that cumulative or chronic exposure to stress can cause pathological alterations in the regulation of the hypothalamus–pituitary–adrenal (HPA) axis with various consequences for subsequent function of the axis and related health outcomes (Heim et al., 2000; McEwen, 2008). In psychosis, elevated cortisol levels are believed to cause alterations in dopamine regulation resulting in psychotic symptoms (Walker and Diforio, 1997). Evidence for a dysregulation of the HPA axis in patients with established psychosis comes from studies reporting elevated baseline cortisol levels (Ryan et al., 2004; Gallagher et al., 2007) and non-suppression to dexamethasone challenge (Muck-Seler et al., 1999). In contrast to these reports of hypercortisolism at baseline, evidence points to lower than normal cortisol levels in patients when the reactivity of the HPA axis is tested, with an attenuated cortisol response to awakening (Pruessner et al., 2008; Mondelli et al., 2009; Pruessner et al., 2013) and in response to acute psychosocial stress (Jansen et al., 1998, 2000; Brenner et al., 2009; Steen et al., 2011).

Several studies also provide evidence for abnormal HPA regulation in people at elevated risk for psychosis. Compared to healthy controls, patients with schizotypal personality disorder showed higher salivary cortisol levels at baseline (average of three samples taken between 9 and 11 am) (Walker et al., 2001; Mittal et al., 2007), and individuals who subsequently converted to psychosis displayed increased cortisol secretion at initial assessment (Walker et al., 2010). Furthermore, in individuals at high risk for psychosis, the experience of more hassles was associated with a higher cortisol response at 8 am. Similarly, siblings of patients with psychosis presented with higher diurnal cortisol levels and higher cortisol reactivity to negative daily events (Collip et al., 2011). Whereas increased cortisol levels were related to the severity of psychotic like experiences in some studies (Walker et al., 2001; Collip et al., 2011), another study did not find such an association (Thompson et al., 2007b).

No study to date has assessed the cortisol response to acute psychosocial stress in individuals at UHR for psychosis. Our aims for the present study were (1) to compare the cortisol response to an established psychosocial stress task in individuals at clinically high risk for psychosis and healthy controls and (2) to assess the relationship of this endocrine measure with subjective measures of acute and chronic stress and with protective factors. Based on our previous findings in UHR patients and literature regarding patients with clinically confirmed psychosis, we hypothesized higher stress levels, lower ratings on protective factors, and an attenuated cortisol response to a psychosocial stress task in the UHR group compared to healthy controls.

2. Materials and methods

2.1. Subjects

Twenty-one patients who met criteria for 'ultra-high risk' for psychosis (12 male, 9 female, mean age 20.8, range 16.4–27.2) and 21 healthy, age and gender matched controls (mean age 20.8, range 15.9–27.4) participated in the study. Patients were recruited from the Clinic for Assessment for Youth at Risk (CAYR) and had been identified as presenting with an 'at risk mental state' with the Comprehensive Assessment for At Risk Mental States (CAARMS; Yung et al., 2005). Eighteen patients met criteria for attenuated psychosis and three patients had been accepted on the basis of family history of psychosis plus decline in functioning. Six patients were treated with antidepressant medication at the time of testing, and none of the patients had been exposed to antipsychotic medication. Age and gender matched control subjects were recruited through advertisements in a local free journal in the Montreal area. Absence of any history of mental illness, history of psychosis in first-degree relatives, and use of antipsychotic and/or antidepressant medication was assured through a telephone screening and a follow-up SCID NP interview (First et al., 2002). For both groups, participants who suffered from neuroendocrine disorders and/or took steroid based medication, were excluded from the study. Table 1 provides details on demographic variables, smoking and drug use.

2.2. Assessment

2.2.1. The Trier Social Stress Test

The Trier Social Stress Test (TSST) is a well known standardized laboratory protocol to evaluate endocrine and other physiological responses to a moderate psychosocial stressor (Kirschbaum et al., 1993). It consists of a 10 min anticipation period and a 10 min testing period, during which the participant delivers a speech and performs mental arithmetic (5 min each) in front of an audience and a camera. The combination of a public speaking and a cognitive task produces a robust cortisol increase (Kirschbaum et al., 1993), probably determined by their association with social evaluative threat and uncontrollability, two important characteristics of psychological stressors to induce strong cortisol responses (Dickerson and Kemeny, 2004). For our study, subjects made the required presentation in front of a one-way mirror and a camera while the experimenter and confederate were seated behind the one-way mirror. In order to minimize the impact of diurnal rhythm on the cortisol responses, all participants were seen in the afternoon between 13:00 and 16:00 h. Participants were informed about the nature of the task after two baseline saliva samples had been collected. Cortisol analysis of the saliva samples was performed using a time-resolved immunoassay with fluorescence detection which possesses adequate reliability and validity (Dressendorfer et al., 1992).

2.2.2. Physiological measurements

Blood pressure and heart rate changes to the TSST were assessed at the time of cortisol assessment with an automatic blood pressure monitor (Omron IntelliSense HEM-711). Physiological measures could not be obtained for one patient and two controls.

2.2.3. Stress measurement

Chronic stress during the past month was assessed with the Trier Inventory for the Assessment of Chronic Stress (TICS) (Schulz and Schlotz, 1999). Additionally, perceived stress in the past year was assessed with a single item measure "How stressed did you feel in

Table 1
Differences in socio-demographic variables and substance use between patients and controls.

	UHR	Controls	Statistic (df)	p-Value
Age, mean (SD)	20.8 (3.27)	20.8 (3.10)	$t(40) = -0.03$	.980
Years of education, mean (SD)	11.9 (2.01)	13.29 (1.93)	$t(40) = -2.35$	.024
Relationship status, single, N (%)	3 (14.3)	5 (23.8)	$\chi^2(1) = 0.62$	.432
Ethnicity, white, N (%)	14 (66.7)	16 (76.2)	$\chi^2(1) = 0.47$	.459
Tobacco smoking, >5 cigarettes/day, N (%)	3 (14.3)	3 (14.3)	$\chi^2(1) = 0.00$	1.0
Cannabis use in past 3 months, N (%)	8 (38.1)	5 (23.8)	$\chi^2(1) = 1.00$	.317
Past stimulant[a] and hallucinogen[b] use[c]	3 (14.3)	1 (4.8)	$\chi^2(1) = 1.11$	.293

[a] Amphetamines, cocaine.
[b] Magic mushrooms.
[c] Not used since one month or longer.