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Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: The role of stress and of antipsychotic treatment

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ABSTRACT

First-episode psychosis (FEP) patients show hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, but the mechanisms leading to this are still unclear. The aim of this study was to investigate the role of stress and antipsychotic treatment on diurnal cortisol levels, and on cortisol awakening response, in FEP. Recent stressful events, perceived stress and childhood trauma were collected in 50 FEP patients and 36 healthy controls using structured instruments. Salivary cortisol was obtained at awakening, at 15, 30, and 60 min after awakening, and at 12 and 8 pm. Patients experienced more recent stressful events, perceived stress and childhood trauma than controls ($p<0.001$). Patients had a trend for higher diurnal cortisol levels ($p=0.055$), with those with less than two weeks of antipsychotics showing significantly higher cortisol levels than both patients with more than two weeks of antipsychotics ($p=0.005$) and controls ($p=0.002$). Moreover, patients showed a blunted cortisol awakening response compared with controls, irrespectively of antipsychotic treatment ($p=0.049$). These abnormalities in patients were not driven by the excess of stressors: diurnal cortisol levels were negatively correlated with the number of recent stressful events ($r=-0.36$, $p=0.014$), and cortisol awakening response was positively correlated with a history of sexual childhood abuse ($r=0.33$, $p=0.033$). No significant correlations were found between perceived stress or severity of symptoms and cortisol levels, either diurnal or in the awakening response. Our study shows that antipsychotics normalize diurnal cortisol hyper-secretion but not the blunted cortisol awakening response in FEP; factors other than the excess of psychosocial stress explain HPA axis abnormalities in FEP.

1. Introduction

Previous studies in patients with psychosis have demonstrated that stress is an important factor in the development of psychosis, but the biological mechanisms by which stress affects psychosis remain unclear. One model of psychosis, the vulnerability-stress model, posits that predisposing biological factors increase the sensitivity of some individuals to stress and thus make them more vulnerable to develop psychosis under stressful circumstances (Myin-Germeys and van Os, 2007; Pariante, 2008). Indeed, an excess of stressful life events has been shown to precede the onset of psychosis and psychotic relapse in patients with schizophrenia (Bebbington et al., 1993; Walker et al., 2008). Moreover, childhood adversities have also been linked to an increased risk for development of psychiatric disorders, and have been reported to be more frequent in patients with psychosis

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than in the general population (Read et al., 2005). Finally, patients with psychosis seem also to perceive daily hassles as more stressful than healthy subjects (Myin-Germeys and van Os, 2007), indicating that they may have a higher sensitivity to stress.

Studies in psychosis have also shown that patients who are in the acute phase of a psychotic disorder, with florid symptoms, newly hospitalized or unmedicated, show hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, the main biological system involved in mediating the effects of stress (Gallagher et al., 2007; Gunduz-Bruce et al., 2007; Herz et al., 1985; Lammers et al., 1995; Sachar et al., 1970; Tandon et al., 1991). HPA axis activity is activated by the release of the corticotropin releasing hormone (CRH) from the hypothalamus, which in turn activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which finally stimulates the secretion of cortisol from the adrenal gland. Cortisol then interacts with its receptors in multiple target tissues including also the HPA axis, where it is responsible for feedback inhibition of the secretion of ACTH from the pituitary and CRH from the hypothalamus (Pariante and Lightman, 2008). Some authors have suggested that HPA axis hyperactivity could contribute to the pathogenesis of psychotic disorders by increasing brain dopaminergic activity (Walker and Diforio, 1997). Indeed, we have recently described that subjects at high risk of developing psychosis, including healthy first degree relatives of patients with schizophrenia (Mondelli et al., 2008) and subjects with prodromal symptoms (Garner et al., 2005), have a larger pituitary volume, again suggesting that hyperactivity of the HPA axis participates to the predisposition to psychosis.

The hyperactivity of the HPA axis in psychosis is particularly evident at the illness onset, which is often described as the most distressing time. Indeed, studies in subjects experiencing their first psychotic episode have shown increased circulating levels of cortisol and ACTH (Broome et al., 2005; Gunduz-Bruce et al., 2007; Pariante et al., 2004, 2005; Ryan et al., 2003; Ryan et al., 2004; Sachar et al., 1970) and higher rate of dexamethasone non-suppression (Ceskova et al., 2006). Our own work has shown a larger pituitary volume in patients with a first-episode psychosis (Pariante et al., 2004, 2005). This increased volume has been interpreted as indirect evidence of HPA axis hyperactivity as it is present in antipsychotic free patients as well as in patients receiving non-prolactin elevating atypicals, although clearly the volume of the pituitary is even larger in subjects taking prolactin-raising antipsychotics (Pariante et al., 2004, 2005; Pariante, 2008). Moreover, one study has recently described a blunted cortisol awakening response – a marker of dynamic HPA responsivity to a naturalistic stressor (Clow et al., 2004; Roberts et al., 2004) – in a small group of patients with recent onset of psychosis (Pruessner et al., 2008). In contrast, data in patients with established psychosis show that long-term antipsychotic treatment normalizes HPA axis hyperactivity (Tandon et al., 1991). Indeed, previous studies have shown that treatment with atypical antipsychotics, such as olanzapine, clozapine or risperidone, causes reduction in cortisol levels in patients with schizophrenia as well as in healthy controls (Cohrs et al., 2006; Hatzimanolis et al., 1998; Mann et al., 2006; Markianos et al., 1999; Meltzer, 1989; Scheepers et al., 2001; Zhang et al., 2005); interestingly studies investigating typical antipsychotics like haloperidol, pimozide or sulpiride, reported that cortisol levels are unaffected by these drugs in healthy volunteers (Cohrs et al., 2006). Therefore, studies in first episode are particularly relevant to understand the role of stress and HPA axis hyperactivity in psychosis, while avoiding confounders such as the long-term antipsychotic treatment and chronicity of the illness.

Several factors have been hypothesized to explain the HPA axis hyperactivity at the onset of psychosis: an increased level of stressful life events preceding the onset (Bebbington et al., 1993; Garner et al., 2005); an increased sensitivity to stress (Myin-Germeys and van Os, 2007); an increased rate of childhood trauma (Fisher et al., 2009; Nemeroff, 2004; Read et al., 2005); the distress and severity of the psychotic experience (Dinan, 2005); heavy tobacco smoking (De Leon and Diaz, 2005); and an increased use of cannabis (Di Forti et al., 2007), which in turn increases cortisol levels in humans (D'Souza et al., 2004, 2005). Surprisingly, however, these factors have not been yet studied together with HPA axis activity in first-episode psychosis. Therefore, in our study we investigate HPA axis activity (salivary cortisol during the day and in response to awakening) together with all of the putative mechanisms described above as well as the effects of antipsychotic treatment, in a sample of patients at their first-episode psychosis, and in healthy controls from the same geographical area.

2. Methods

2.1. Subjects

First-episode psychosis patients were recruited in London (UK) from the Lambeth, Southwark and Croydon inpatient and outpatient units, part of the South London and Maudsley (SLAM) NHS Foundation Trust, as part of the Genetic and Psychosis (GAP) study. The recruitment strategy was based on contacting inpatients and outpatients services regularly, interviewing staff and reviewing clinical notes, and approaching all subjects aged 18–65 who presented for the first time to these services for a functional psychotic illness (ICD10 F10–19, excluding coding F1x.0 for Acute intoxication; F20–29 and F30–39, psychotic codings) (World Health Organisation, 1992). Patients with organic psychosis, learning disabilities or requiring a translator because of lack of English fluency were excluded from the study. Controls were recruited from the same catchment's area as the patients through advertisement in local newspapers, hospitals and job centers, as well as from existing volunteer databases. Controls were screened using the Psychosis Screening Questionnaire (PSQ) (Bebbington and Nayani, 1995), and excluded if they met criteria for a present or past psychotic disorder. Both patients and controls were excluded if taking any kind of hormonal treatment. The study was approved by the local Ethical Committee, in accordance with the code of ethics of the World Medical Association, and written informed consent was obtained by all participants.

We recruited and assessed 50 patients with first-episode psychosis and 36 healthy controls. None of the controls was clinically depressed or treated with antidepressants at the time of the study. Seventeen patients received a DSM-IV diagnosis of schizophrenia, nine of schizophreniform disorder, thirteen of