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INVITED REVIEW

A systematic review of the activity of the hypothalamic–pituitary–adrenal axis in first episode psychosis

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Summary Up to now studies on hypothalamic–pituitary–adrenal (HPA) axis activity in psychosis have shown inconsistent findings. These inconsistencies have been often ascribed to confounding effects of long duration of illness and chronic treatment with psychotropic medications of the subjects studied (chronic psychosis). In the last years, several studies have focused on the study of subjects at their first episode of psychosis to overcome these possible confounders. The aim of this paper was to review the literature investigating HPA axis activity in first episode psychosis. Findings from these studies support the presence of HPA axis hyperactivity and a blunted HPA axis response to stress at the onset of psychosis. Possible biological pathways linking these HPA axis abnormalities to the development of psychosis are discussed.

Contents

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1. Introduction

In the last decades, the vulnerability-stress model has dominated theories on the aetiology and pathogenesis of psychosis (Walker and Diforio, 1997; Walker et al., 2008; Myin-Germeys and van Os, 2007). According to this model, predisposing biological factors increase the sensitivity of some individuals to stress and thus make them more vulnerable to develop psychosis under stressful circumstances (Walker and Diforio, 1997; Walker et al., 2008; Myin-Germeys and van Os, 2007). The study of the hypothalamic–pituitary–adrenal (HPA) axis, the main biological system involved in the stress response, is central to reach a better understanding of the biological mechanisms behind the association between stress and psychosis and leading to the onset of psychosis. HPA axis activity is activated by the release of corticotropin releasing hormone (CRH) and of vasopressin (AVP), synthesized in the hypothalamus, which activate 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 (reviewed by Pariante and Lightman, 2008).

Several previous neuroendocrinological studies have reported that patients in the acute phase of schizophrenia or affective psychosis have an elevated basal HPA axis activity as shown by raised cortisol and ACTH levels, non-suppression of cortisol secretion by dexamethasone in the dexamethasone suppression test, and in the dexamethasone/CRH test (Sachar et al., 1970; Ryan et al., 2003, 2004b; Tandon et al., 1991; Lammers et al., 1995; Herz et al., 1985). However, other studies on patients with chronic schizophrenia have not found elevated basal cortisol levels or an increased rate of suppression at the dexamethasone suppression test, especially if the patients were medicated and clinically stable (Tandon et al., 1991). Indeed, studying first episode psychosis patients gives the opportunity to avoid the possible confounding effects of long duration of illness and chronic treatment with psychotropic medications and allows a better understanding of biological abnormalities at the onset of the disorder. The aim of this paper was to review the main findings on HPA axis activity in first episode psychosis and to discuss the possible implications of HPA axis abnormalities for the etiopathogenesis of psychosis.

2. Methods

We have performed a systematic search of the literature using the following sources: PubMed, PsycINFO, Ovid of Medline and The Cochrane Library. The key words searched in the database were using the following search profile: ''Cortisol AND first episode psychosis'' ''Pituitary AND first episode psychosis'', ''Cortisol And Schizophrenia'', ''Pituitary And Schizophrenia''. The literature search included papers published after 1985 and up to October 2012. Further hand searches were performed to ensure that all relevant papers were included. We selected all original papers that measured cortisol levels or pituitary volumes in patients at first episode of psychosis and schizophrenia. We excluded studies that were reporting cortisol levels of already published samples. Using the titles and abstracts we selected only papers written in English. From a total of 538 papers, 22 reported cortisol levels from already published samples, 10 were conference abstracts and 6 were review articles, and only 16 articles reached the inclusion criteria and were included in this review. From a total of 447 papers reporting findings from studies investigating pituitary volumes in patients with first episode psychosis and schizophrenia and using the same criteria as above we included 11 papers.

3. Results

3.1. Studies on cortisol levels in first episode psychosis

A summary of the studies on cortisol levels in first episode psychosis is shown in Table 1. The first study investigating cortisol levels in first episode schizophrenia date back to 1996 (Abel et al., 1996). In this study the authors showed higher plasma cortisol levels when comparing patients with healthy controls, suggesting a basal HPA axis hyperactivity in these patients. All patients, but one, were drug naïve. Only a few years later, another two studies confirmed higher cortisol levels in first episode psychosis (Ryan et al., 2003, 2004a). In particular, Ryan and colleagues assessed plasma cortisol levels in drug naïve patients with first episode of schizophrenia and age- and sex- matched controls, taking a blood sample at one time-point only during the day (at 8 am after an overnight fasting). Another three later studies also reported baseline higher plasma cortisol levels in patients with first episode psychosis when compared with matched controls (Walsh et al., 2005; Spelman et al., 2007; Kale et al., 2010).

However, not all the studies have confirmed high baseline cortisol levels in first episode psychosis. Indeed, four studies in drug free/drug naïve or minimally treated first episode psychosis patients did not find any difference in serum or plasma cortisol levels collected at one single time point when compared with age- and sex-matched controls (Strous et al., 2004; Garner et al., 2011; van Venrooij et al., 2010; Garcia-Rizo et al., 2012). These inconsistent findings could be partially due to different methodological procedures. Indeed, as suggested by other authors (Ryan et al., 2004b), a procedure based on a single sample for the cortisol

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