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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.
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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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Table 1 Summary of findings from studies investigating cortisol levels in patients with first episode psychosis.

Study	FEP patients (*N*)	Healthy controls (*N*)	Measurements details	Information on antipsychotic treatment in FEP patients	Findings
Abel et al. (1996)	13	19	Plasma cortisol between at 08.00 and 09.00	12 drug naïve, 1 on antipsychotic treatment	Higher cortisol levels in patients ($p = 0.0059$)
Ryan et al. (2003)	26	26	Plasma cortisol at 08.00	All drug naïve	Higher cortisol levels in patients ($p < 0.0001$)
Ryan et al. (2004a)	19	19	Plasma cortisol at 08.30	All drug naïve	Higher cortisol levels in patients ($p < 0.003$)
Ryan et al. (2004b)	12	12	Plasma cortisol (multiple time points between 13.00 and 16.00)	All drug naïve	Higher cortisol levels in patients (area under the curve, $p < 0.01$)
Strous et al. (2004)	37	27	Plasma cortisol at 08.00—10.00	All drug free	No significant difference
Walsh et al. (2005)	10	10	Plasma ACTH and cortisol at 13.00	All drug naïve	Higher cortisol levels in patients ($p < 0.02$)
Ceskova et al. (2006)	56	No	Dexamethasone suppression test	N/A	Decrease in non-suppression with treatment
Spelman et al. (2007)	38	38	Plasma cortisol at 08.30	All drug naïve	Higher cortisol levels in patients ($p < 0.001$)
Gunduz-Bruce et al. (2007)	16	No	Salivary cortisol (multiple time-points during the day and awakening response)	10 drug naïve 6 on antipsychotic treatment (range duration of treatment: 3—21 days)	Higher cortisol levels in patients (area under the curve, $p < 0.04$)
Hempel et al. (2010)	27	38	Salivary cortisol (multiple time-points during the day and awakening response)	5 drug free 22 on antipsychotic treatment (mean ± SD duration of treatment: from 1 ± 0 to 4.7 ± 3.1 weeks)	Cortisol concentration decreased more in patients during the day in patients compared with controls ($p < 0.001$)
Kale et al. (2010)	31	48	Plasma cortisol time not stated	All drug naïve	Higher cortisol levels in patients ($p = 0.005$)
Mondelli et al. (2010a)	50	36	Salivary cortisol (multiple time-points during the day and awakening response)	7 drug naïve 43 on antipsychotic treatment (range duration of treatment: 0—119 days)	Higher cortisol levels in patients with less than 2 weeks of treatment ($p = 0.002$). Blunted cortisol awakening response in whole sample of patients ($p = 0.049$)
Garner et al. (2011)	39 (23 f/u)	25	Serum cortisol at 9.00—10.00 (baseline and 12 weeks follow-up)	14 drug naïve 25 on antipsychotic treatment (range duration of treatment: 0—8 days)	No significant difference at baseline. Decrease in cortisol levels over time associated with symptoms improvement
van Venrooij et al. (2010)	10	15	Plasma cortisol time not stated (baseline and response to stress challenge)	All drug free	No significant difference at baseline. Blunted cortisol response to stress challenge ($p = 0.042$)
Garcia-Rizo et al. (2012)	33	33	Serum cortisol at 8.00—9.00	All drug naïve	No significant difference
Pruessner et al. (2012)	56	30	Salivary cortisol (at awakening and 30 and 60 min after awakening)	All on antipsychotic treatment (mean ± SD duration of treatment: Male: 8.58 ± 7.75 months Female: 6.31 ± 4.37 months)	Blunted cortisol awakening in patients compared with controls ($p = 0.023$). Blunted cortisol awakening response in males compared with females patients ($p = 0.001$), but not with controls ($p = 0.38$)

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assessment represents a limitation, since it may not provide an accurate estimate of cortisol levels and of HPA axis activity.

To overcome this possible limitation, Ryan et al. (2004b), investigated 12 drug naïve patients with first episode psychosis and 12 age- and sex-matched controls, measuring plasma cortisol and ACTH levels, collecting blood samples every 20 min (from 1 pm to 4 pm). In agreement with their previous studies, patients with first episode schizophrenia presented higher cortisol and ACTH secretion during the whole sampling period compared with controls, supporting the presence of HPA axis hyperactivity in this condition. In accordance with these findings, two other studies which have compared saliva samples at multiple time points during the day (awakening, noon, mid-afternoon and evening) between drug-naive patients or those with less than three weeks of antipsychotic treatment, and healthy controls, have found higher diurnal cortisol levels in patients (Gunduz-Bruce et al., 2007; Mondelli et al., 2010a). In contrast, the only other study which collected diurnal salivary cortisol levels at multiple time points during the day in first episode patients and controls found that cortisol concentration did not find a difference in cortisol levels at any specific time point but it showed steeper decreases in cortisol levels during the day in patients compared with controls, suggesting a different daytime sensitivity of the HPA axis (Hempel et al., 2010). Most of the patients in the latter study were treated with antipsychotic medication.

Other findings, beyond the ones based on basal cortisol levels, have also supported a role of HPA axis abnormalities in the pathophysiology of psychosis. Indeed, first episode psychosis patients present a higher cortisol response to metoclopramide-induced AVP release than controls, even in presence of an equal AVP increase, suggesting a greater pituitary responsiveness to AVP release in psychosis (Walsh et al., 2005). Moreover, decreases in cortisol levels over time have been shown to be directly related to improvement in depression and psychotic symptoms in first episode psychosis, supporting the involvement of HPA axis activity in the development of psychotic symptoms (Garner et al., 2011).

To further understand the role of HPA axis activity in first episode psychosis, we also conducted a study to test the dynamic activity of the HPA axis showing that first episode psychosis patients have a blunted cortisol awakening response when compared with healthy controls (Mondelli et al., 2010a). Interestingly these findings were confirmed by a more recently published study where, however, an attenuated cortisol awakening response was reported only in male, but not female, first episode psychosis patients (Pruessner et al., 2012).

It is important to stress that this is the first time that a blunted awakening response is described in the context of higher diurnal cortisol levels. Euthymic or acutely ill patients with major depression, a condition usually characterized by elevated cortisol levels during the day (Pariante and Lightman, 2008), tend to show increased cortisol awakening response (Bhagwagar et al., 2003, 2005). In contrast, subjects with chronic fatigue syndrome (Roberts et al., 2004), and post-traumatic stress disorder (Rohleder et al., 2004; Wessa et al., 2006), conditions usually characterized by lower cortisol levels during the day (Cleare, 2003; Yehuda, 2001), also tend to show decreased cortisol awakening responses (Roberts et al., 2004). This suggests that HPA axis dysfunction in psychosis is not simply a correlate of depression or other general psychopathological symptoms but has a specific profile, perhaps linked to a different genetic background or a different developmental trajectory of the stress abnormalities.

The cortisol awakening response is indeed considered a reliable measure for the acute reactivity of the HPA axis, and the finding of blunted cortisol awakening response appears in agreement with a recent study reporting a blunted cortisol response to a psychological stress (public speaking) in first episode psychosis (van Venrooij et al., 2010), further supporting an abnormal HPA axis response to stress in this condition. Interestingly we have also recently shown that a more blunted cortisol awakening response is associated with a worse cognitive functioning in first episode psychosis, and in particular with a more severe deficit in verbal memory and processing speed (Aas et al., 2011). Moreover, the cortisol awakening response has been also found to be associated with clinical symptoms in first episode psychosis (Belvederi et al., 2012). In particular, in patients with first episode of schizophrenia, the cortisol awakening response appeared to be mainly predicted by the severity of positive symptoms. In contrast, in those with depressive psychosis, the cortisol awakening response was instead predicted by excitement, disorganization and depressive symptoms (Belvederi et al., 2012).

Furthermore, some studies are now extending the findings of an attenuated cortisol awakening response with first episode of psychosis to possible links with exposure to early adversity (Pruessner et al., 2012), and thus indicating a possible neurobiological mechanism in support of the growing and robust findings that childhood adversity leads to an increased risk of developing psychosis (Varese et al., 2012).

Only one study investigated the cortisol response to the dexamethasone suppression test in patients with first episode schizophrenia; the authors studied patients at the time of admission to hospital (before starting antipsychotic treatment), at the time of discharge, and again after 1 year and did not have a comparison group of healthy controls (Ceskova et al., 2006). The rate of non-suppression was 17.9% at baseline before starting the treatment, 5.3% at the time of discharge, and 16% after one year (Ceskova et al., 2006). In agreement with the literature in chronic schizophrenia, rates of dexamethasone non-suppression are higher in drug-free and unmedicated patients. The increase in the rate of non-suppression after 1 year is explained as a possible consequence of clinical deterioration and of non compliance with treatment (Ceskova et al., 2006).

3.2. Studies on pituitary volume in first episode psychosis

The pituitary gland plays an important role in the regulation of the HPA axis. The volume of the pituitary gland can change in size as a consequence of both physiological and pathological alterations in the patterns of hormone secretion. Interestingly, in major depression, HPA axis hyperactivity has been linked to an increased volume of the pituitary gland (Axelson et al., 1992).

A summary of the studies on pituitary volume in first episode psychosis is shown in Table 2. Four of the studies

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Table 2 Summary of findings from studies investigating pituitary volumes in patients with first episode psychosis compared with healthy controls.

Study	FEP patients (*N*)	Healthy controls (*N*)	Findings
Pariante et al. (2004)	24	51	Patients > controls
Pariante et al. (2005)	78	78	Patients > controls
MacMaster et al. (2007)	16	12	Increase in pituitary volume at 12 months follow-up: Patients > controls
Upadhyaya et al. (2007)	51	55	Patients < controls
Garner et al. (2009)	42	No	Larger pituitary volume associated with less improvement in overall psychotic symptoms at 12 weeks follow-up
Nicolo et al. (2010)	73	48	No difference between patients and controls
Buschlen et al. (2011)	23	20	Patients > controls
Takahashi et al. (2011)	18	20	Patients > controls at baseline and follow-up. Pituitary enlargement over time: patients > controls
Gruner et al. (2012)	55	59	No difference between patients and controls
Habets et al. (2012)	10	32	Though not significant, patient group had larger pituitary volumes than controls
Klomp et al. (2012)	26	156	No difference between patients and controls

reviewed assessing pituitary volume in patients with first episode psychosis report a larger pituitary volume in patients when compared with healthy controls, further supporting the presence of HPA axis hyperactivity at the onset of psychosis (Pariante et al., 2004, 2005; Buschlen et al., 2011; Takahashi et al., 2011). However, other studies reported smaller or no significant difference in pituitary volume between first episode psychosis and healthy controls (MacMaster et al., 2007; Nicolo et al., 2010; Gruner et al., 2012; Klomp et al., 2012; Habets et al., 2012).

A possible explanation for these inconsistent findings (with the exception of Nicolo et al., 2010; Habets et al., 2012), is that in contrast to the studies above, these studies assessed patients with first episode of schizophrenia (MacMaster et al., 2007; Gruner et al., 2012; Klomp et al., 2012), whom by definition are likely to have a longer duration of illness. Habets et al. (2012) compared pituitary volume between those with an illness duration of less than five years (FEP), those with an established psychosis, and healthy controls, and found that first episode patients had increased pituitary volumes compared with controls, whom in turn had increased pituitary volumes compared with those with an established illness, though these differences were not statistically significant, which may have been due to the small sample size employed ($N = 10$ in both patient groups). Indeed, a longer duration of illness has been suggested to be associated with a reduction in pituitary volume possibly due to an exhaustion of the HPA axis activation (Upadhyaya et al., 2007; Pariante et al., 2004).

Another consideration that should be made, and possible explanation for the inconsistent findings is that the use of antipsychotic medications has been found to influence pituitary volume, possibly by the stimulation of prolactin secreting cells. Prolactin-enhancing antipsychotics have been shown to be associated with a larger pituitary volume (Pariante et al., 2005; MacMaster et al., 2007; Pariante, 2008), whilst a longitudinal study has demonstrated that prolactin-sparing medications reduced pituitary volume over time in a dose-response manner (Nicolo et al., 2010). Therefore, pituitary volume increases associated with long duration of illness may become undetectable if combined with the use of prolactin-enhancing medication.

Studies conducted so far in psychosis, clearly suggest that pituitary is a dynamic organ, which changes according to different stages of the psychotic disorder, in response to both the disorder itself, and the treatment with antipsychotics. Specifically, as previously suggested (Pariante, 2008) the pituitary volume increases during the prodromal phase leading to psychosis onset (Garner et al., 2005), and it is larger (by 10–20% compared to controls) if assessed during the first 12 months after the psychosis onset (Pariante et al., 2004, 2005; Takahashi et al., 2011). This effect is not due to antipsychotic treatment, as it is present in antipsychotic-naïve prodromal subjects (Garner et al., 2005) as well as in neuroleptic-free patients with first episode psychosis (Pariante et al., 2005; Buschlen et al., 2011), and it is likely to reflect HPA axis hyperactivity.

Interestingly, the pituitary volume is larger in people at high risk of developing psychosis closer to the psychosis onset, suggesting not only that HPA axis hyperactivity is present already before the onset of psychosis, but that this can also predict subjects who will make the transition to psychosis (Garner et al., 2005). These findings have been recently supported by another study, which showed larger pituitary volume in first episode psychosis patients and in subjects at high risk of developing psychosis, who later on developed psychosis, when compared with healthy controls or with high-risk subjects who did not make transition to psychosis (Buschlen et al., 2011). Moreover, a more recent study in drug naïve first episode psychosis patients found that a larger pituitary volume at onset is associated with less improvement in psychotic symptoms after 12 weeks of antipsychotic treatment (Garner et al., 2009), whilst greater pituitary enlargement over three years has been associated with less improvement of psychotic symptoms at follow-up (Takahashi et al., 2011), further supporting the role of HPA axis hyperactivity in clinical outcome of these patients.

In summary, preliminary evidence would suggest that enlarged volumes of the pituitary gland is associated with increased vulnerability of psychosis, and an enlarged

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pituitary compared to control samples is exhibited in individuals shortly after psychosis onset. However, the pituitary gland is evidently a highly dynamic organ, and the reported inconsistencies in the findings of pituitary volume in first episode psychosis samples may be related to the heterogeneity of the samples in terms of illness duration, the type of antipsychotic drug prescribed, and state-related impairments.

4. Discussion

This systematic review highlights that converging evidence exists to suggest that individuals with a first episode of psychosis show a specific pattern of HPA axis hyperactivity, demonstrated by higher baseline cortisol levels compared with controls, and a blunted cortisol awakening response. Moreover, MRI studies demonstrate that these individuals also exhibit an enlarged pituitary in comparison to healthy controls shortly after psychosis onset, supporting HPA axis hyperactivity in this sample.

4.1. HPA axis hyperactivity: a consequence of illness onset, or a vulnerability marker?

The question remains however whether the abnormal HPA axis response to stress in first episode psychosis samples is caused by the onset of the disorder, due to the stressful nature of the psychotic experiences or an effect of the stressful experience of being hospitalised, or alternatively, whether the enhanced stress response exists prior to illness onset, and represents a marker of biological vulnerability. Several lines of preliminary evidence point to the latter hypothesis.

Studies of the biological response in individuals at Ultra High Risk for psychosis allow for an investigation of whether abnormal HPA axis response to stress exists prior to illness onset whilst reducing the confounds associated with hospitalisation. Increasing evidence suggests that within those at risk for psychosis, higher levels of cortisol is associated with prodromal and/or psychotic symptoms (Mittal and Walker, 2011; Corcoran et al., 2012), and as already highlighted, a larger pituitary at baseline in those at risk is predictive of later transition to illness (Garner et al., 2005; Buschlen et al., 2011). Moreover, in support of findings from first episode psychosis samples, research has found alterations in HPA axis function in those with Schizotypal Personality Disorder (SPQ; Mitropolou et al., 2004; Mittal et al., 2007) and in healthy individuals rating highly on schizotypal traits (e.g. Hori et al., 2011), thereby reducing the confounds associated with hospitalisation, medication, and the psychosocial consequences of psychiatric diagnoses (Mednick and McNeil, 1968).

Lastly, as reviewed by Aiello et al. (2012), within individuals at genetically high risk of psychosis (i.e. in unaffected relatives of patients with psychosis), studies have shown increased ACTH blood levels in response to stress (Brunelin et al., 2008), as well as increased cortisol levels at baseline and in response to negative daily stress (Collip et al., 2011). Interestingly, we have found that also first-degree relatives of patients with schizophrenia present larger pituitary volume compared with controls (Mondelli et al., 2008). Though studies of HPA axis activity are limited in number, these results suggest a familial, possibly genetic, vulnerability to hyper-activity of the HPA axis in schizophrenia.

4.2. The link between HPA axis and onset of psychosis

To understand how abnormalities in the HPA axis might be involved in the onset of psychosis, we will discuss some of the main relevant biological pathways influenced by HPA axis activity and how these might play a role in the development of psychotic symptoms. One of the most relevant mechanisms to understand the link between HPA axis activity and onset of psychosis is the synergistic relation between glucocorticoids and dopamine. Indeed, the notion that the dopaminergic system is involved in the development of psychotic symptoms is well established. Interestingly, previous studies have showed that glucocorticoid secretion augments dopamine activity in certain brain regions, especially the mesolimbic system (reviewed by Walker et al., 2008). The molecular mechanisms behind this effect are still unclear, and are currently a focus of research, especially in animal models.

Another possible mechanism involved in the association between HPA axis abnormalities and onset of psychosis involves the studies finding a blunted HPA axis response to stress (Mondelli et al., 2010a; van Venrooij et al., 2010). Even in the presence of HPA axis hyperactivity during the day, the impaired activation of HPA axis in critical stressful situations could represent one of the mechanisms leading to the development of psychopathology. According to Roelofs et al. (2007), a blunted cortisol response to acute stress may compromise optimal cognitive performance and approach-avoidance behaviour in situations where it may be important to function maximally. Moreover, cortisol has been reported to blunt sympathetic nervous system responses activated by stress in humans (Raison and Miller, 2003). Interestingly, although cortisol response to psychological stress was blunted in first episode psychosis, the sympathetic nervous system response to stress has been shown to be preserved in the same subjects (van Venrooij et al., 2010). Therefore, it is possible to suggest that, in presence of a stressful condition, the lack of cortisol response cannot restrain the activation of the sympathetic nervous system, resulting in a persistent increased arousal and a consequent exacerbation of psychotic symptoms.

Glucocorticoids can also influence neuroplasticity (decreasing neurogenesis and remodelling neuronal dendrites), affecting neurotrophins levels, such as BDNF, and through their interaction with pro-inflammatory cytokines, excitatory amino acid neurotransmitters and NMDA receptors (reviewed by McEwen, 2000). This is particularly important since a number of studies have shown brain volume changes at the onset of psychosis, or during the transition to psychosis, suggesting a critical role for neuroplasticity, especially in specific brain areas, in the development of psychosis (Takahashi et al., 2009; Cahn et al., 2009). Indeed, we have recently shown that high cortisol levels are associated with smaller hippocampal volume in first episode psychosis, further supporting also this possible biological pathway to explain the link between HPA axis hyperactivity and onset of psychosis (Mondelli et al., 2010b, 2011).

4.3. Methodological considerations

4.3.1. Cortisol collection

Cortisol levels vary during the day, reaching the zenith at the awakening time in the morning, and decreasing in the late

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afternoon and evening. Unfortunately most of the studies reviewed in this paper measured cortisol levels using a single sample of plasma, which does not take in account the circadian variability of cortisol and might have also been confounded by an increase in cortisol due to the pain/distress of the injection (Kirschbaum and Hellhammer, 1994). Measuring cortisol from saliva has been proposed as the method of choice in stress research as it avoids potential variations due to the stress of blood drawing procedures, and it allows collection at multiple time points during the day without an invasive procedure (Hellhammer et al., 2009).

Only few studies have until now assessed cortisol levels at multiple time points during the day in first episode of psychosis (Ryan et al., 2004b; Gunduz-Bruce et al., 2007; Hempel et al., 2010; Mondelli et al., 2010a; Pruessner et al., 2012). One of these studies have shown a steeper decrease in cortisol levels during the day in first episode psychosis, further highlighting the importance of studying cortisol diurnal rhythm in these patients (Hempel et al., 2010). Recent studies have also suggested that time of awakening could affect the extent of the cortisol awakening response, and therefore this should be taken into account in future studies assessing cortisol awakening response (Pruessner et al., 2012).

4.3.2. Effect of medication on cortisol levels

Most of the studies assessing cortisol levels in first episode psychosis were conducted in drug naïve or medication free patients (Abel et al., 1996; Ryan et al., 2003, 2004a,b; Strous et al., 2004; Walsh et al., 2005; Spelman et al., 2007; Kale et al., 2010; van Venrooij et al., 2010; Garcia-Rizo et al., 2012). However, five of the reviewed studies included patients treated with antipsychotic medications. Since the duration of antipsychotic treatment and the type of antipsychotic differed across the subjects in the same study as well as across the different studies, it is difficult to draw any definitive conclusion on the effect of antipsychotic treatment on cortisol levels in first episode psychosis.

Indeed, previous studies in patients with chronic schizophrenia have shown that both first and second generation antipsychotics affect cortisol levels, and increasing evidence suggests that second generation antipsychotics reduce cortisol to a greater extent than first generation ones (Zhang et al., 2005; Popovic et al., 2007; Jakoveljevic et al., 2007; Tanaka et al., 2008). Interestingly, second generation, but not first generation, antipsychotics have also been shown to significantly reduce cortisol levels in healthy controls, suggesting that this effect may precede, or be independent from, the effect of the antipsychotic medication on the psychotic symptoms (Cohrs et al., 2006). Future longitudinal studies are needed to clarify the effect of antipsychotic treatment, as well as possible effect of hospitalization, on HPA axis activity in first episode psychosis, and its possible relationship with the clinical outcome.

5. Conclusions

In summary, the onset of psychosis is characterized by HPA axis hyperactivity, as supported by findings of high cortisol levels and larger pituitary volume. Our and other authors' findings also suggest a blunted HPA axis response to stress in first episode psychosis. Both these abnormalities could play a relevant role not only in the development of psychosis, through their effect on the neurotransmitter systems as well as on neurogenesis. Further study of HPA axis activity in first episode psychosis is needed not only to help us in getting a clearer understanding of ethiopathogenesis of this serious condition, but, more importantly, to facilitate, in the future, the design of prevention strategies as well as the development of novel treatment strategies for individuals affected by psychosis.

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Conflict of interest

None.

Role of contributors

All authors contributed to the collection, analysis and interpretation of the data and in writing the manuscript.

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