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Disturbances of cortisol awakening response in psychotic disorders and at-risk states: a literature review

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Abstract

Background and objective: According to the diathesis-stress model, disturbances of the hypothalamic-pituitary-adrenal (HPA) axis are thought to play a role in the development, onset, and progression of psychosis. The aim of this paper is to present the available body of evidence on the abnormalities of the cortisol awakening response (CAR) in psychotic disorders and at-risk states.

Methods: Review of literature from the years 2011-2022 available across three databases (Scopus, PubMed and Google Scholar) was performed. With an aim to: i) ensure that the review covers a wide range of research related to psychotic presentations as manifested in a broad range of clinical populations (from CHR/UHR to full-blown psychosis), and ii) identify the neurobiological background thereof, the following combination of search terms was applied: "chr" OR "uhr" OR "arms" OR "first-episode schizophrenia" OR "psychosis" AND "cortisol" OR "HPA axis" OR "CAR" OR "cortisol awakening response".

Results and conclusion: Research suggests that abnormalities of the HPA axis (in this case, disturbances of the CAR) appear to be an important factor in the pathogenesis of psychotic disorders. The cortisol awakening response was blunted in patients with first-episode psychosis or schizophrenia. On the other hand, in subjects with at-risk states, the results were inconclusive. These findings, however, are based on a small number of studies; therefore, more research in this area is required

psychosis; cortisol awakening response; first-episode psychosis;clinical high risk; CAR

INTRODUCTION

Psychosis is a serious psychiatric condition that disrupts perceptions of reality. Numerous definitions of psychosis are available in scientific literature to describe impaired reality testing as observed in various conditions, such as schizophrenia [1], clinical high risk (CHR), first-episode psychosis (FEP) [2], or psychosis proneness [3]. Psychotic presentation includes hallucinations, delusions, abnormal motor behavior, disorganized thinking, negative symptoms (i.e., avolition, anhedonia), or cognitive dysfunction. This results in significant functional consequences, including an inability to work, financial problems, homelessness, social isolation, or even suicidal ideation and behavior. Ultimately, psychosis can lead to social exclusion.

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It has been proposed that broadly defined psychosocial stress may lead to the development or exacerbation of psychosis. The diathesis-stress model posits that the interplay of genetic vulnerability and exposure to environmental stressors, which results in abnormal stress function, may underlie the onset of psychosis [4]. The model indicates that, starting at an early age, genetic and environmental factors or stressors increase the risk of psychosis through a cycle of HPA axis dysregulation (hyperactivation) and brain degenerative processes affecting neurons in the hippocampus and prefrontal cortex, and ultimately dopamine and other neurotransmitter function [1,5,6]. Numerous studies on various forms of stress, such as stressful adult life events [7], childhood trauma [8], or stress induced experimentally [9], have shown this association. Likewise, higher odds of psychotic experiences in response to increased stress sensitivity were demonstrated in a large study based on data from 39 countries [10].

However, exposure to psychosocial stress, regardless of its definition, is neither required nor sufficient to develop psychosis. Consequently, it is critical to examine individual mediators of stress reactions. To fully understand the diathesis-stress model, it is essential to explore the biological mechanisms underpinning the stress response. The aim of this article is therefore to review the available body of evidence on the role of cortisol awakening response (CAR) disturbances in psychosis.

THE HPA AXIS AND PSYCHOSIS

One of the primary biological systems in charge of the stress response is the hypothalamic–pituitary–adrenal (HPA) axis [11]. Research on stress and the HPA axis in psychosis has advanced significantly in the last ten years. In response to stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which activates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). The adrenal glands, or more specifically, the adrenal cortex, produce glucocorticoids such as cortisol. An increased level of cortisol inhibits the hypothalamus and pituitary gland from further secretion of CRH and ACTH, which eventually leads to a drop in the blood cortisol level. Such a negative-feedback loop prevents the organism from excessive response.

Cortisol is secreted by the HPA axis in circadian rhythm, which is controlled by the hypothalamus [12]. Cortisol levels start to gradually increase two to three hours after the initial part of sleep, peaking at around nine in the morning, and then gradually decreasing during the day until they reach their lowest point around midnight, when the HPA axis activity is also the lowest [12–14]. The morning rise of cortisol levels is called the cortisol awakening response (CAR)

Cortisol affects the brain via two types of receptors: high-affinity mineralocorticoid receptors (MR) and lower-affinity glucocorticoid receptors (GR). MR are activated at the basal hormone level, whereas GR are only activated during stress and the circadian peak of glucocorticoid secretion [15]. While MR are mostly expressed in the limbic regions such as the hippocampus, amygdala, and prefrontal cortex, GR are found in the majority of brain regions and cell types [16]. Glucocorticoid effects on psychopathology are a reflection of the different actions of GR and MR in the brain. Accordingly, overstimulation of GR is believed to increase the likelihood of developing mood disorders [17]. And so, patients with Cushing syndrome have been found to develop psychological symptoms such as anxiety, irritability, and depression in response to exposure to extremely high cortisol levels [18]. In turn, low MR activity was observed in schizophrenia, depression, and bipolar disorder [19]. Additionally, a decreased MR activity has been suggested to result in a loss of the tonic regulation of the HPA axis, which could manifest itself via persistently high cortisol levels. Eventually, such high cortisol levels are reported to lead to reduced overall stress resilience [18,19].

The connection between psychosocial stress and psychosis may lie in the cross-talk between dopaminergic neurotransmission and the HPA axis. There is growing evidence that the pathophysiology of psychosis may be influenced by aberrant HPA axis activity [5]. In fact, studies suggest that cortisol may increase dopaminergic activity in a number of areas of the brain, particularly in the mesolimbic system [1]. An ele-

vated stress-induced release of dopamine was demonstrated in subjects with early psychosis, indicating a substantial correlation between the striatal dopaminergic activity and the salivary cortisol response to stress [9]. In a recent meta-analysis of post-mortem research, it was found that schizophrenia patients had reduced volume and neuron counts in numerous areas of the left hippocampus [20]. All these observations raise questions about the role of CAR disturbances in the pathogenesis of psychosis.

SEARCH STRATEGY

The aim of this research is to discuss the neurobiological role of cortisol in psychotic disorders or UHR/CHR states, focusing on cortisol awakening response. For this purpose, a review of literature from the years 2011-2022 available across three databases (Scopus, PubMed and Google Scholar) was performed. With an aim to: i) ensure that the review covers a wide range of research related to psychotic presentations as manifested in a broad range of clinical populations (from CHR/UHR to full-blown psychosis), and ii) identify the neurobiological background thereof, the following combination of search terms was applied: "chr" OR "uhr" OR "arms" OR "first-episode schizophrenia" OR "psychosis" AND "cortisol" OR "HPA axis" OR "CAR" OR "cortisol awakening response". This search strategy resulted in identification of 82 records. Search results were screened for eligibility (i.e. relating to a broad spectrum of psychotic disorders and the CAR) based on title and abstract, then by full-text review. Ultimately, 12 papers reporting on experimental evidence were included and analyzed in this narrative review.

The cortisol awakening response

The cortisol awakening response is a rapid increase in cortisol levels that takes place within the first 15–40 minutes of awakening [21,22]. The optimal cortisol circadian rhythm relies heavily on the CAR [23,24]. It is assumed to be a dynamic, separate activity brought on by awakening as distinct from a continuation of the typical diurnal cortisol profile [25]. Studies show the cortisol cycle is regular and repeatable under physiologically normal circumstances [27]. What makes the CAR a useful biomarker of the HPA axis activity is that: 1) response patterns might be measured from saliva collected by patients themselves (no need for blood sampling) [14], 2) it is a relatively basic parameter of the HPA axis function, which does not require special conditions to be measured [25], 3) the CAR is regulated differently from the diurnal cortisol profile, which reduces the correlation between the CAR and cortisol sampled later in the day [23]. It has been shown that abnormalities of the CAR are associated with a variety of health problems, ranging from troubles with sleeping [12] to cardiovascular disease [28].

Over the last 10 years, there has been numerous research on the links between disturbances of the CAR and psychosis (or at-risk states). Pruessner et al. [28] found lower CAR in male patients with FEP (n=38) compared to female patients (n=20). Saliva samples were obtained immediately, at 30 and 60 minutes after awakening, in order to evaluate the CAR. The authors also observed a decreased CAR in the entire FEP group (n=58) compared to the controls (n=33), although this difference did not reach statistical significance after correcting for awakening time. Incidentally, by revealing lower CAR in men compared to women in both groups, the authors managed to replicate their previous findings [29]. The researchers also investigated the possibility of a connection between a blunted CAR and early adversity, as indicated by parental attachment (measured with the use of the Parental Bonding Inventory). A considerably smaller percentage of patients reported optimal maternal parenting compared to controls. Quite remarkably, unfavorable paternal parenting was associated with diminished CAR only in FEP patients [28].

In another study on the CAR in FEP, Pruessner et al. [30] yet again reported its reduced levels in the clinical group relative to controls. The authors recruited 58 patients with FEP (39 men and 19 women) and 27 healthy community controls (15 men and 12 women). Saliva samples were collected in the same way as in the previous study [28]. Apart from CAR measurement, magnetic resonance imaging (MRI) on a 1.5 T scanner was performed on every study partic-

ipant in order to investigate differences in hippocampal volume (HV) between the two groups and on an intra-group level. The authors found that male patients had considerably lower left and right HVs than female patients and the control group.

In their next study, Pruessner et al. [5] focused on UHR patients (n = 42, 24 men) in comparison to 46 healthy controls (HC=23 men). Saliva samples were collected three times (at awakening, 30, 60 min after). Every subject underwent an MRI scan to evaluate hippocampal volume. Results showed no significant difference between UHR and HC subjects in terms of CAR. MRI scans showed smaller HV in male UHR patients.

Cullen et al. [31] focused on children aged 9–12 divided into three groups: 33 children with an increased risk of psychosis due to several schizophrenia risk factors (ASz) defined as 1) speech and/or motor development lags/problems; 2) internalizing, externalizing, and/or peer-relationship problems in the clinical range; and 3) psychotic-like experiences; a control group of 40 typical developing children (TD); and 22 high-risk children with a family history of illness (FHx) (to find proper subjects, the authors used a caregiver screening questionnaire; they also reviewed South London and Maudsley National Health Service (NHS) Foundation Trust). Saliva samples were collected four times (at awakening, at 15, 30, and 60 minutes after). The authors found a significant decrease in CAR in FHx children relative to the TD group. At the same time, no abnormalities were noted in ASz children in comparison to the TD group.

Blunted CAR was also observed in subjects with FEP by Mondelli et al. [32] The authors gathered a group of 68 patients with FEP and 57 controls. Saliva samples were collected on two separate time points (five times per day at baseline and after 12 weeks of observation) to analyze CAR and diurnal cortisol levels. In addition, on day one and after 12 weeks serum samples were collected to measure interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-α, and interferon-γ (IFN-γ) levels. During these 12 weeks, patients were taking antipsychotic medications. Later on, the FEP group was divided into 2 subgroups: responders (n=30) and non-responders (n=38) based on the remission symptom criteria of the Schizophrenia Working Group Consensus. Results showed significantly lower CAR and higher IL-6 and IFN-γ in non-responders group in comparison to responders at baseline. After 12 weeks non-responders had even lower CAR and higher IL-6 and IFN-γ in comparison to responders. Both responders and non-responders had abnormalities in terms of CAR when compared to the control group, but in the non-responders group the difference proved more significant.

In a study whose main purpose was to investigate the association between dysregulation of the HPA axis and cognitive dysfunction in FEP patients (n=30), Ass et al. [33] found significantly poorer cognitive functioning in FEP patients in comparison to the control group. In addition, a further link between a more blunted CAR, slower processing speed and a significantly larger loss of verbal memory was only found in the patient population.

Day et al. [34] compared CAR and diurnal cortisol levels in UHR patients (n = 52) and a control group (n = 42). In addition, they were investigating a potential correlation between cortisol measures and symptom severity. Of note, 11 UHR subjects were taking psychiatric medications (3 – antipsychotic,6 – antidepressant, 1 – anxiolytic, 1 – mood stabiliser) on the day of measurement (saliva samples were collected at awakening, 30 and 60 minutes after awakening, at 12 and 8 p.m.). Results showed blunted CAR in UHR patients, with a more significant difference in medication-naïve UHR patients compared to those taking psychotropic medications. There was no evidence of a link between current symptoms and cortisol levels.

In a slightly larger study (FEP: 34, ARMS: 21, and healthy subjects: 34), Labad et al. [35] found a link between FEP diagnosis and blunted CAR. Furthermore, the authors discovered that excited PANSS symptoms were associated with blunted CAR. In addition, the manifestation of excited symptoms was reported to differ between ARMS and FEP groups (blunted CAR in ARMS patients vs. greater CAR in FEP patients).

Nordholm et al. [36] compared a group of 41 UHR subjects, 40 antipsychotic-naïve FES patients and 47 matched controls. All participants were instructed to collect saliva five times per day (at awakening, 15, 30, and 60 minutes after awakening, as well as at 12 and 8 p.m.). They

were requested to not eat, smoke, or brush their teeth 30 minutes before collecting the sample. Every participant underwent an MRI scan. The authors were not able to demonstrate blunted CAR in FES and UHR patients. Also, the authors did not find any significant abnormalities in pituitary gland volume.

Ciufolini et al. [37] studied the impact of childhood maltreatment severity on HPA axis activity in first-episode psychosis and healthy controls. The authors compared a group of 169 FEP patients with 133 controls who experienced different levels of physical and sexual abuse throughout childhood (from no exposure to abuse, through non-severe exposure to abuse, to severe exposure to abuse). The study found that individuals with a history of childhood abuse had a blunted CAR and a less reactive HPA.

Ilen et al. [38] focused on subjects with 22q11.2 deletion syndrome (22q11DS), which is associated with a higher risk of psychiatric disorders (including psychosis). Patients suffering from this syndrome are assumed to have higher levels of chronic stress, which may lead to changes in the functioning of the hypothalamic-pituitary-adrenocortical (HPA)-axis. The authors observed that cortisol levels were not related to the severity of psychotic symptoms but elevated CAR was found in subjects with 22q11DS alongside higher levels of general psychopathology.

DISCUSSION

The purpose of this narrative review was to analyze the current state of knowledge on the relationship between psychotic disorders or at-risk states and abnormalities in CAR. This study identified 12 papers that focus on this problem. Several interesting conclusions stem from the analysis of the collected data. First and foremost, blunted CAR was observed in patients with FEP in all selected studies except for the one conducted by Nordholm et al. [36]. This discrepancy may be explained, at least in part, by a significant difference observed in terms of the baseline characteristics of the control groups. Namely, it turns out that when compared to previous studies, the healthy controls recruited by Nordholm et al. [36] had lower cortisol response levels to awakening. Hence, it may have been due to the low awakening response in HCs, that the cortisol response in UHR and FES patients could be overestimated, failing to show the expected blunted response in the clinical groups. Of note, although not demonstrated in the other experimental studies selected for this narrative review, the lack of blunted CAR in FEP patients is consistent with previous findings [39,41] and the blunted response may be explained in part by the acute psychotic symptoms.

Secondly, all studies selected for this review which investigated gender differences in terms of cortisol response to awakening report its blunted levels in male but not in female psychosis-spectrum patients [29,30,39].

Observed tendency in male patients may be explained by reported neurobiological abnormalities, such as smaller temporal lobes [42, 43], smaller lateral ventricles [42, 42], and lower hippocampal volume [5, 30]. All of these factors may lead to an increased risk of psychosis and a more severe course of illness in men. Furthermore, the preliminary information gathered from two studies regarding the effect of antipsychotic medications on the CAR [32,34] may suggest a possible positive impact of pharmacological psychiatric treatment on general resilience to stress. Walker et al. [1] postulated that psychotropic drugs such as antipsychotics and antidepressants could stabilize the HPA axis in psychosis. Notwithstanding, due to limited evidence, this requires further investigation.

Cullen et al. [31] demonstrated a blunted CAR in children who were related to individuals with schizophrenia, suggesting that disturbances of CAR may be associated with familial proneness to psychosis. These findings lend credence to the notion that at least some HPA axis abnormalities described in psychosis may in fact precede illness onset rather than constitute a subsequent phenomenon. A blunted CAR may therefore be construed and likely used as an early marker of psychosis vulnerability, which, if confirmed, could constitute the answer to the widely researched problem of biomarkers of schizophrenia and other psychoses.

Interestingly, one significant source of stress which may potentially determine the CAR in psychosis is childhood trauma. And so, the findings in [37] reveal that severe childhood abuse has a differential effect on HPA axis activity in

individuals with first-episode psychosis and in controls. In the presence of severe childhood maltreatment, a blunted CAR and a less reactive HPA axis may be one of the biological elements involved in the development of psychosis. However, these aspects were not always considered when the study and control groups were formed, and they could have had a significant impact on the presented results.

Despite the fact that several significant outcomes emerge from the analysis of the above research, there are a number of issues, which preclude further or more definitive conclusions. There are a few possible explanations. The literature is highly diverse, with a wide range of methodologies and outcomes. A number of key methodological challenges add to the difficulty of investigating the link between psychosis or ARMS and CAR abnormalities in the natural environment. Presently, cortisol levels are measured primarily by saliva, allowing patients to perform the test on their own. It is crucial to provide clear instructions on how to do the test (how much time should elapse between tooth cleaning, eating, smoking, etc.) in order to obtain reliable results. Individual study limitations and inconsistencies in methodology, including sample sizes and quantities, laboratory measurement procedures, and consideration of covariates such as quality of sleep, hours of exercise/activity, age differences, taken medications, preferred time of awakening, or hours of exposure to daylight, daily stressors which are potential confounders of the results, may explain discrepancies in results across studies. The experience sampling methodology (ESM) implementation could solve at least some of these problems. Because of technology improvements, the chances for gathering intensive time series data in mental health research have significantly increased. ESM has incredible potential for digital monitoring and personalized feedback on service users' experiences and behaviors on daily basis, which can be used usefully by both service users and clinicians [40].

CONCLUSIONS

To conclude, a full understanding of the pathogenesis of psychosis is still ahead. A review of the selected studies showed blunted CAR in patients with FEP, but at the same time raised a number of questions (impact of medications on CAR, correlation between symptom severity and cortisol level, impact of daily stressors, gender, and family history on results). Further analysis of its association with disturbances of the HPA axis is therefore timely and valid, especially taking into account the new technological possibilities. With that being said, what needs to be remembered is that apart from analyzing the neuroendocrine system, other biological markers (such as inflammatory, anatomical or metabolic ones) which also play a role in the pathogenesis of psychosis cannot be neglected. In addition, it is important to bear in mind that not only psychotic-related symptoms may cause abnormalities of the CAR. To provide reliable information about the links between the CAR and psychotic disorders or at-risk states, it is of utmost importance to think not only about what to study but also how to go about it; otherwise, our results will be incomplete.

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