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SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS (SJ SIEGEL, SECTION EDITOR)

The Role of Cortisol in First Episode of Psychosis: A Systematic Review

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Abstract The stress diathesis hypothesis is currently one of the prevailing models of etiology of psychotic disorders. Cortisol is the most researched stress hormone; yet its role in first episode psychosis (FEP) was only recently investigated. The aim of the present study is to systematically review the evidence on the potential role of cortisol in FEP. Higher cortisol levels in blood samples have been consistently replicated, whereas saliva studies measuring baseline cortisol levels have exhibited divergent results. Moreover, longitudinal studies have revealed a cortisol upregulation in FEP with a subsequent decrease induced by antipsychotic treatment. The evidence suggests a role for cortisol in psychosis, although the association of cortisol with psychopathological symptoms is currently non-specific. Future research should focus on more pure diagnostic entities, clearly defined stages of the disorder and refined methods of hormonal measurement.

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Introduction

Psychosis is considered to be one of the most researched fields in psychiatry. Although research in pathological mechanisms has produced progress, many issues remain obscure. Patients suffering from psychosis are known to exhibit particular vulnerability and intolerance to stressful stimuli. This observation has generated a whole framework through which pathological mechanisms are currently being investigated. The basic pillars of this context include traditional neurodevelopmental models of psychosis, which suggest damage to the hippocampus and, subsequently, heightened vulnerability to psychosis development, due to early life trauma [1].

The hypothalamus pituitary adrenal axis (HPA) is one of the primary mammalian systems moderating the physiological response to psychological and physiological stressors [2, 3]. The latter response, known as adaptive response, incorporates a number of alterations in body organs and systems, thus ensuring psychological and body balance. The HPA axis constitutes one of the two peripheral parts of the stress system, with systemic/adreno-medullary sympathetic nervous system composing the other part. Activation of the HPA axis and Locus Ceruleus (LC)-NorEpinephrinergic (NE) autonomic system results in systemic elevations of glucocorticoids and catecholamines, respectively, which act together to maintain basal and stress related homeostasis [4].

During the past decades much evidence has accumulated concerning the neuroendocrine pathological basis of schizophrenia. Studies have investigated the hormonal status of HPA axis in schizophrenic patients, through evaluation of corticotropin releasing hormone (CRH), adrenocorticotropic

hormone (ACTH) and cortisol levels either in plasma or in saliva, at baseline (that is when no stressor is applied). Fewer studies have looked into the HPA axis reactivity after applying dynamic stressors of neuroendocrine, metabolic or psychosocial nature. The results of the latter studies are currently divergent, probably due to the samples heterogeneity in terms of diagnoses, comorbidity, phase of illness and exposure to medication (for details see review by Bradley et al. 2010 [5]). Additional factors affecting the HPA axis function include stressful life events [6–8], sensitivity to stress [6, 9], childhood trauma [6, 10–12], distress and severity of the psychotic experience [13], heavy tobacco smoking [6, 14], use of cannabis [6, 15], body mass index [16•, 17], night shift work [16•, 18], menstrual cycle phase and use of contraceptive medication in women [16•, 19].

The delineation of the HPA axis status required the elimination of confounding factors, such as medication, illness phase and chronicity. Thus, researchers' attention has recently been shifted to the initial demonstrations of psychotic symptomatology during the first episode of psychosis (FEP).

The aim of this study is to systematically review and summarize current knowledge on cortisol abnormalities and its psychopathological correlates in FEP. We chose to concentrate on research concerning circulating cortisol, which is the most frequently evaluated hormone in HPA axis studies. Up to the time this review was written, only one review [20••] had been conducted on abnormalities of stress system in FEP. The former study did not concentrate on psychopathological correlates, which are extensively investigated in the present review.

Methods

A systematic electronic search of Pubmed (Medline) was conducted in order to identify all relevant scientific articles published between 1990 and 2013. Additionally, the articles reference lists were hand-searched for publications missed during the primary search.

The inclusion criteria were:

i. peer reviewed papers written in English from 1990 until May 2013,
ii. studies measuring cortisol levels either in blood or in saliva, regardless if this was the primary aim of the study,
iii. studies including cortisol level measurement in participants on whom stressors had been or had not been imposed,
iv. studies incorporating estimation of salivary cortisol awakening response (CAR),
v. studies which compared cortisol level between patients with schizophrenia and healthy controls (HC), or studies (longitudinal or crossover) aiming to estimate the correlation between cortisol levels and psychiatric symptomatology,
vi. studies including patients with FEP regardless of their medication regime or their being medication naive prior to their initial presentation to psychiatric services,
vii. studies with overlapping samples (clearly stated or confirmed after personal contact with the authors) were excluded,
viii. studies with partially overlapping cohorts which demonstrated contradictory results were included in an attempt to investigate the possible mechanisms accounting for these findings.

Twenty two studies were included [21, 22••, 23, 24•, 25–36, 37•, 38, 39, 40•, 41, 42], according to the above criteria. FEP studies involved in total 911 patients and 697 HC. All but three studies [21, 22••, 23] referring to FEP involved an HC group. Additionally, two of these studies [24•, 25] included a third group with participants at genetic risk for psychosis (AGRP) and at clinical risk for psychosis (ACRP), respectively. The design of the majority of the studies was cross over. As far as diagnosis is concerned, participants were grouped as exhibiting an affective component or not. Patients with an affective component were further subgrouped, according to their receiving a diagnosis of schizoaffective disorder (SCA) (of both manic or depressive type) or bipolar disorder (BPD) with psychotic features or major depressive disorder (MDD) with psychotic features. Similarly, participants with no affective component were subgrouped, depending on their diagnosis of schizophrenia (SCZ), schizophreniform (SCF), delusional (DEL) or psychotic disorder not otherwise specified (NOS). Indeed, 802 of 911 participants were included in the non affective psychotic spectrum. Four of them received diagnosis of substance induced psychotic disorder. It should be noted than one study [29] did not report the exact proportion of diagnoses. As far as the medication status of FEP participants is concerned, 352 (38.6 %) patients were reported as being antipsychotic agents naïve, whereas two studies [21, 30] did not report medication details of participants (despite their large sample sizes of 236 and 56 patients, respectively).

The psychopathological parameters in FEP and their potential connection with cortisol levels were investigated by means of psychometric tools, such as the Positive and Negative Syndrome Scale (PANSS) and its subscales, the Brief Psychiatric Rating Scale (BPRS), the Hamilton Anxiety Rating Scale (HARS), the Hamilton Depression Rating Scale (HDRS), the Perceived Stress Scale, the Childhood Experience of Care and Abuse Questionnaire. The reported features included psychotic symptomatology with its positive and negative features, anxiety, depression, perceived stress, parental bonding, stressful life events and childhood trauma were investigated. Although 14 studies involved the application of

the PANSS scale, only ten of them actually reported the correlation between PANSS findings and cortisol levels. Similarly, the correlation was reported in only half of the eight studies using the BPRS scale.

Results

Results from Blood Examinations

Thirteen studies [25–36, 37•] involved the evaluation of cortisol levels at baseline with a single blood examination, whereas one study [36] included multiple blood examinations every 20 min from 13:00 until 16:00. Additionally, the design of six of the above mentioned studies [26–28, 31, 34, 37•] involved further exposure of the participants to challenging tests, such as oral application of 30 mg of d-fenfluramine [31] or 10 mg of metoclopromide infusion [34]. Furthermore, a low dose (0.25 mg) of Dexamethasone (DEX) was applied during the dexamethasone suppression test (DST) [37•]. The vast majority of the studies (ten out of 13 studies, including the one with consecutive blood tests) reported increased blood cortisol levels in FEP patients. Only two studies [26, 33] reported no difference, whereas one study [37•] reported lower pre-dexamethasone (pre-DEX) values. It should be noted that eight out of the total 13 studies referred to plasma blood samples, whereas the rest referred to serum.

As far as the medication status is concerned, in the study by Strous et al. (2004) all patients were under treatment [33], while in the studies by Garner et al. (2011) [26] and Phassouliotis et al. (2013) [37•] 35,8 % and 52,3 % of patients, respectively, were drug-naive. All studies suggested higher cortisol levels in drug-naive FEP patients. FEP patients with increased cortisol levels were older than 29.5 years of age in all but two studies [25, 34]. On the contrary, the three studies [26, 33, 37•] reporting no difference or decrease in cortisol levels involved patients of significantly lower ages (20.6, 27.2 and 20.6 years of age, respectively).

Results in Saliva of FEP Patients

Three studies [6, 38, 39] assessing baseline cortisol levels in saliva met the inclusion criteria of this review. It should be noted that the first two studies [6, 38] had a partial overlap of cohorts. The study design was similar, involving cortisol measurements just after awakening and at a specific time during the day. Findings on baseline cortisol estimation, corresponding to the total area under the curve (AUC), were reported. The first study [38] (with a primary goal of investigating hippocampal volume in FEP patients) suggested higher cortisol levels in patients, whereas the second study demonstrated a trend for higher cortisol levels in the FEP group [6]. In contrary, Hempel et al. [39] reported no significant differences in basal AUC baseline cortisol between the patient and the control group. However, they detected a more significant decrease during the day in patients, as well as a significantly decreased area under the curve with respect to the increase. The latter finding again indicated a greater decrease in cortisol concentrations of patients during the day. The study by Hempel et al. is so far the only one to have evaluated these parameters.

Results from Salivary Cortisol Awakening Response (CAR)

Two studies [6, 40•] have currently evaluated salivary CAR in FEP patients (by assessment of AUC cortisol) with respect to its increase from awakening and several times thereafter during the next one hour. A variant of this method was used in the study by Hempel et al. [39], who calculated cortisol increase by subtracting morning cortisol level from the level identified 30 min later. Initially the studies evaluating CAR AUC appeared to have similar results. Specifically, cortisol level increase in FEP group was significantly lower compared to the HC group. However, Pruessner et al. [40•] considered the confounding effect of the awakening time and reported that cortisol levels were no longer statistically different. On the other hand, Mondelli et al. [6] clearly stated that the mean awakening time between patients and controls did not differ. Interestingly, Hempel et al. [39] did not identify any difference in the cortisol increase between the under study patient group, whereas Pruessner et al. [40•] demonstrated a sex effect on CAR.

Results from FEP-Active Dynamic Neuroendocrine Tests

Four studies [21, 31, 34, 37•] involved the conduction of dynamic neuroendocrine tests in FEP patients. Two studies [31, 34] implicated iv infusion of 10 mg metoclopramide and oral intake of 30 mg d-fenfluramine, respectively, followed by consequent blood examinations. The other two studies [21, 37•] involved the application of different versions of DST. Walsh et al. [34] reported increased secretion of both ACTH and cortisol in FEP patients, compared to HC. The study by Abel et al. [31] indicated no significant change in cortisol levels regarding the under study groups. Regarding the DST studies, Cesková et al. [21] demonstrated higher rates of DST non suppression in drug free SCZ patients during the acute phase of the illness. In addition, short-term treatment led to a decrease in cortisolaemia and in rates of non suppression. The hypothesis of FEP patients hypersuppressing serum cortisol after 0.25 mg of DEX intake was tested in a recently published study [37•]. The latter study reported no group differences in cortisol decline, although the rate of cortisol hyper-

suppression was significantly higher in the FEP group, when participants were classified as suppressors or not.

Results from Psychosocial Stressors

Two studies [24•, 41] focused on cortisol reactivity after patients' exposure to psychosocial types of stressor. In particular, one study [41] involved cortisol measurement in patients being recorded while speaking in public. The other study [24•] involved three groups of participants: SCZ patients, ACRP participants and HC. All of them were assessed using the Montreal Imaging Stress Test (MIST), while dopamine release was measured with positron emission tomography (PET). Simultaneously saliva samples were collected. The two studies indicated contradictory results. Specifically, in the study by van Venrooij et al. [41] FEP patients exhibited significantly lower cortisol response to the stressor, compared to HC, whereas the other study [24•] demonstrated larger cortisol response to stress in FEP patients, compared with the other study groups.

As far as their design is concerned, the two studies rendered several similarities: they both involved an HC group, the FEP patients' diagnoses were on the non affective psychotic spectrum, the patients had previously been antipsychotic-naive and the assessment of the positive psychotic symptomatology through the PANSS scale did not exhibit significant differences. On the other hand, the studies differed in terms of sampling method (blood vs saliva), applied stressor, as well as sample selection (van Venrooij et al. [41] had excluded female patients, as well as patients with comorbid affective disorders).

Results from Longitudinal Studies

Among the studies investigating cortisol levels in FEP patients, only four [21, 26–28] involved repetition of cortisol measurement within a time framework of three months to one year. Three of the studies [26–28] included an HC group, whereas the remaining one [21] involved the application of DST during baseline, after treatment-remission phase and at one year follow up. Two of the studies demonstrated similar results [27, 28]: higher blood cortisol values in FEP patients at baseline and significant reduction (compared to baseline levels) after three and six months of treatment, respectively. On the contrary, Garner et al. [26] reported no difference in baseline serum cortisol level between FEP and HC groups. Furthermore, cortisol levels were not significantly different, compared to baseline, even after 12-week treatment. On the other hand, Cesková et al. [21] found a significant decrease (without clearly stating figures) in cortisolaemia after treatment, as well as a respective decrease in non suppression rates.

Psychopathology Results

General Psychotic Index

From the 22 studies investigating cortisol levels in FEP patients, only eight [22••, 25, 26, 28, 29, 33, 34, 39] included the total PANSS and BPRS scores. More specifically, four studies [22••, 29, 33, 39] reported total score in the PANSS scale and the other four reported total score in the BPRS scale. As far as the PANSS scale is concerned, results were contradictory. Two studies showed no significant correlation of CAR or AUC (for baseline cortisol during the day) with the total score in the PANSS scale [22••, 39]. Similarly the study by Kale et al. [29] yielded no relation of the total PANSS score with the cortisol level in a single blood sample. On the contrary, Strous et al. [33] found a significant positive association between patients' serum cortisol level (in a single sample) and total PANSS score. As far as the BPRS scale is concerned, three studies [25, 28, 34] failed to identify any significant relation between psychotic features and cortisol levels among FEP patients, whereas one study [26] yielded a positive association between BPRS score and baseline serum cortisol, as well as between BPRS score and the ratio cortisol/Dehydroepiandosterone sulphate (DHEA-S). In addition, the positive relationship persisted throughout the longitudinal part of the study: the cortisol decrease after treatment was significantly correlated with the overall improvement of psychotic symptoms.

Interestingly, the two studies [26, 33] suggesting a positive relation between the overall psychotic symptomatology and the baseline cortisol level, failed to identify a significant difference of cortisol levels between FEP patients and controls during the longitudinal part of the study. On the other hand, the studies reporting no relation between psychotic symptoms and cortisol levels actually demonstrated higher cortisol levels in the patients' group. Another interesting finding included the higher BPRS and PANSS sores in the studies suggesting a positive relation between cortisol levels and psychotic symptoms, compared with the studies reporting no relation (higher BPRS scores: 60 [26] vs 42.9 [34] or 44 [25] or 32.1 [28] and PANSS scores: 75.2 [33] vs 63.3 [22••] and 72 [39]). One of the two studies reporting a relation included a patient group with diagnoses with an affective element (among other heterogeneous diagnoses) [26], as opposed to studies with SCZ patients only [25, 28, 33, 34, 39]. The latter finding is probably in disagreement with the results of the study by Belvederi-Murri et al. [22••]. The latter group further subgrouped patients depending on their diagnoses, but none of the subgroups (including the affective psychotic subgroup) demonstrated a significant correlation of cortisol levels with psychotic symptoms.

Positive Psychotic Symptomatology

Six studies [22••, 27, 29, 35, 39, 40•] investigated the correlation between cortisol baseline levels/cortisol total secretion/cortisol total change with the score in the PANSS positive scale in FEP patients. Five of them [22••, 27, 35, 39, 40•] indicated no significant relation. Specifically, the six studies investigated saliva CAR with respect to morning cortisol increase [22••, 39, 40•], basal total AUC cortisol with respect to baseline measurement during daytime [22••, 39], AUC of cortisol increase during day [39], changes in cortisol levels after treatment [27] and single plasma cortisol at baseline [35]. On the contrary, further subgrouping according to diagnoses [22••] yielded a positive association of CAR with the score in the PANSS positive subscale, as well as a negative correlation of the same score with AUC cortisol during daytime in the SCZ subgroup. Similarly, in the study by Kale et al. [29] increased plasma cortisol levels were negatively correlated with the positive symptom scores, particularly in female patients.

In terms of diagnoses in the FEP groups, only three studies [27, 35, 39] included pure SCZ patients, whereas the remaining ones included mixed affective and non affective psychotic spectrum disorders. It is important to notify that Belvederi Murri et al. [22••] dealt with this limitation by further subgrouping the participants, as already mentioned. Furthermore, the studies involved participants with variable exposure to treatment, whereas they did not use psychometric tools to evaluate depressive features. The only exception was the study by Pruessner et al. [40•], which included Calgary Depression Scale (CDS) use, although scores were not clearly stated. Similarly, comorbidity factors were taken into consideration in only two studies [35, 39].

Negative Symptomatology

Studies investigating the potential correlation of cortisol levels with negative psychotic symptomatology have so far exhibited contradictory results. Specifically, seven studies [22••, 27, 29, 34, 35, 39, 40•] suggested no significant association between the negative PANSS subscale and cortisol levels, four studies [21, 22••, 26, 33] indicated a positive association and two studies [22••, 39] reported a negative one. In particular, the correlations of negative symptoms referred to single basal blood cortisol measurements [27, 29, 33–35], saliva CAR [22••, 40•], morning cortisol increase [39], total AUC cortisol with respect to baseline measurement during daytime [22••, 39], AUC of cortisol increase [39], post DEX cortisol levels after treatment [21], cortisol change after treatment [26] and post stimulation (metoclopramide infusion) plasma levels [34]. Of note, a recent study [23] on FEP patients in the non affective psychotic spectrum (divided into deficit/non deficit subgroups, based on the existence of primary, enduring negative symptoms without distress) showed no correlation between negative symptoms and cortisol. Apart from the variations in their design, the studies [22••, 27, 29, 34, 35, 40•] reporting no association shared similar finding in the area of cortisol hypersecretion and aberrant function, as indicated by higher basal cortisol levels [27, 29, 34, 35] and lower CAR saliva [40•] in FEP patients compared to controls. It is crucial to underline that three [22••, 29, 40•] of the above mentioned studies, at least prior to their subgrouping, comprised mixed diagnoses, whereas the rest [27, 34, 35] of them referred exclusively to SCZ patients. The obscurity remained even after the participants had been subgrouped (according to diagnoses) [22••] in one of the studies. It can be, thus, concluded that only the affective psychosis subgroups exhibited no association between negative symptoms and cortisol levels. That particular study [22••] did not use an HC group, so we cannot draw conclusions on the role of cortisol, in general.

Similarly, only half of the studies with a positive association [21, 22••, 24•, 26, 33] included an HC group and only one [33] of them suggested cortisol dysregulation (higher serum cortisol) in FEP patients. Thus, the notion of a direct involvement of cortisol in psychotic pathology has been only partly supported so far.

Affective Symptomatology

Results from correlation analyses between patients' anxiety/depressive features and cortisol levels have been reported in four studies [21, 22••, 26, 40•]. Specifically, anxiety was measured in three studies [21, 22••, 26], which used the HARS or the respective item G2 of the general scale of PANSS or the five symptom dimension evaluation based on factor analysis of the PANSS. The depressive feature was estimated through the CDS, the HDRS, the respective item G6 of the general PANSS [21] and the five symptom dimension evaluation [21, 22••, 26, 40•].

The findings indicated no association between the anxiety factor with either cortisol levels at baseline (except for one study reporting a positive association with pre DEX cortisol [21]), or with cortisol alterations after treatment [26]. Moreover, the multidimensional regression analysis of symptoms in PANSS [22••] yielded no significant predictive value of the anxiety-depressive component with the AUC during daytime and with the CAR in the total population of the study. On the contrary, the anxiety-depressive component was predictive of the CAR in the depressive psychosis subgroup.

When it comes to the depressive component, the evidence, though limited, pointed towards no association with cortisol levels. Four studies [21, 22••, 26, 40•] were suggestive of a

non significant relation between depressive mood state and cortisol levels. Specifically, the aforementioned studies referred to the CAR [40•], the cortisol levels at baseline before treatment [26], both the CAR and AUC during daytime [22••] and the pre- and post- DEX cortisol values at baseline and after treatment [21]. On the other hand, one study [26] suggested a positive relation between depressive moods and cortisol level alterations longitudinally after treatment.

It should be noted that three [22••, 26, 40•] of the four studies involved participants with diagnoses on both the affective and non affective psychotic spectrums. In addition, comorbid psychiatric entities had not been excluded, thus adding to the studies heterogeneity. Moreover, two of the four studies [21, 22••] involved no HC group, whereas the remaining two [26, 40•] reported no difference in cortisol basal levels or reactivity between groups. Thus, it may be suggested that cortisol dysregulation is not the principal pathological mechanism in psychosis.

Conclusions

A higher blood cortisol level in patients with FEP is a relatively consistent finding in the majority of studies. The latter finding was replicated in nearly all studies involving drug naive SCZ patients of an older age (well older than adolescents), contrary to studies of patients with heterogenous diagnoses, under treatment or not. Thus, a role for diagnosis, medication and age in the neuroendocrine profile of FEP patients may be suggested. The studies failing to replicate aberrant cortisol levels were characterized by minimal duration of medication exposure, thus discrediting the importance of the medication factor. On the other hand, the regulatory effect of age on the pattern of cortisol secretion has been previously suggested [2, 42–44]. As far as the affective component is concerned, it has not yet been evaluated, thus its possible role cannot be currently excluded. Similarly, comorbitity has not been taken into consideration by the majority of studies.

In contrast, studies involving baseline saliva measurement failed to replicate the finding of the increased cortisol. The divergence of the results might be explained by the limited number of studies, the small proportion of participants being drug naive and the varied duration of the applied medication. On the other hand, diversity of diagnoses was not identified and, thus, does not seem to be involved in the divergence.

Moreover, evidence from longitudinal studies favours the notion of cortisol upregulation in FEP patients and subsequent decrease after antipsychotic treatment. Again, the more homogenous in terms of diagnoses, matched for age and less exposed to medication effects the groups were, the more the pattern of cortisol upregulation seemed to prevail.

To summarize, the majority of the evidence suggests that cortisol levels are upregulated when a full blown psychotic episode occurs. The evidence appears to be in line with the existing pathological models of psychosis. According to a model appearing in two studies [2, 42], a prolonged overproduction of glucocorticoids during adolescence, possibly exacerbated by an altered set point of HPA-axis activity, can negatively affect the already damaged hippocampus. In turn, the hippocampal damage may have a negative impact on the HPA axis regulation, leading to a feed-forward circuit that overdrives glucocorticoid production. Prolonged heightened cortisol levels continue to damage the hippocampus, thus further reducing negative feedback. This vicious cycle of events is often referred to as the "glucocorticoid cascade" [2, 45]. Heightened HPA axis activity has also been associated with enhanced dopamine activity in subcortical brain regions [2, 46]. These hormonal and neuronal modifications are thought to unmask the underlying vulnerability to psychosis, paving the way for the development of psychotic symptoms.

CAR investigation in saliva samples of FEP patients has shown divergent results. The majority of the studies (though their total number is limited) tended to demonstrate no significant variation of AUC CAR cortisol in FEP patients compared with HC, after controlling for time of awakening. Controversial results have arisen as to the role of medication in CAR. The diversity may be due to heterogeneity in diagnoses and comorbidity, as well as obscurity regarding affective and psychotic psychopathology. It seems that these particular associations should be further investigated.

The more dynamic methods of evaluating HPA axis function in FEP patients include DST and other stressors of neuroendocrine and psychosocial type. DST constitutes a common approach to investigate HPA axis reactivity and furthermore about glucocorticoid signaling effect to the extent the latter is dependent on the levels of circulating glucocorticoids and glucocorticoid receptor numbers (GR) or the binding affinity or functional capacity of GRs [2, 47]. The existing findings are limited and divergent: neuroendocrine response ranges from increased rate of cortisol non suppression congruent with blunted sensitivity of GRs [21] to enhanced glucocorticoid-mediated negative feedback inhibition of the HPA axis congruent with low basal cortisol [37•]. The latter suggestion referred to at least a subgroup of FEP patients with a possible association between traumatic events and enhanced GR functional capacity. The findings are reminiscent of the known HPA hypo-function pattern, which has been described in patients with PTSD and low basal cortisol, as well as enhanced GR activity [37•, 48–50].

Questions arise concerning the suitability of the applied stressors for the activation of the HPA axis. According to the literature, metabolic stressors seem to be less likely to evoke

HPA axis activation [51–54]. An already hypothesized dissociation of catecholaminergic mediated response to metabolic stress, as opposed to HPA/cortisol response [51, 53], should be taken into consideration in the design of future studies.

Studies investigating the HPA axis function/reactivity in FEP, within a context of more dynamic methods than basal sampling, have produced divergent results. The latter are probably associated with various factors interfering with HPA axis sensitivity. Altered numbers and/or sensitivity of GRs and prolonged cortisol secretion in response to stress may constitute the pathological pillars of the HPA axis aberrant function.

In turn, these mechanisms may be subjected to alterations, depending on the pre-onset exposure of prone-to-psychosis subjects to stressful life events [6–8]. Such events include increased rate of childhood trauma [6, 10–12], distress and severity of the psychotic experience [13], heavy tobacco smoking [6, 14] and increased use of cannabis [6, 15]. In addition, even healthy individuals with a history of adverse events [16•, 55], childhood physical abuse [16•, 56], childhood parental divorce [16•, 57], bullying [16•, 58] and unresolved trauma due to sexual abuse [16•, 59] can exhibit alteration in HPA reactivity function.

It is important to emphasize that dysregulations in reactive cortisol levels are not necessarily related to changes in basal cortisol levels [16•, 60–62]. The variety of cortisol assessment methods could partly explain contradictory findings, such as cortisol hypersecretion at baseline in schizophrenia patients [16•, 36, 63, 64] or hypocortisolism in reactive measures [6, 16•, 40•, 51, 65–70].

The aforementioned data are indicative of the complexity of the pathological mechanisms, which underlie the multifaceted phenomenon of psychosis. Genetic liability, combined with personal history incorporating traumatic experience, chronic stress and personality traits, could lead to different neuroendocrinological patterns. These versatile patterns could in turn fuel the differential endophenotypes of psychosis. These assumptions may be taken into consideration in future study planning and design.

The role of cortisol in psychotic psychopathology does not seem to be justified by the current preliminary evidence. Findings on the correlation of cortisol levels and psychotic symptoms were highly contradictory, with the majority of evidence pointing towards the lack of an association. Of note, the studies showing positive association tended to report higher PANSS and BPRS scores in general. The aforementioned findings favour only an indirect participation of cortisol in the pathophysiology of psychosis and suggest that the intensity of psychopathology along with other parameters (HPA axis dysregulation included) interact to define the psychotic endophenotype. This suggestion is in line with the assumption by Belvederi Murri et al. [22••] that cortisol levels may be associated with the severity of a wide array of symptoms altogether, rather than with a specific clinical dimension.

Similarly, the indirect only role of cortisol in psychotic symptomatology emerged, when positive and negative symptoms were separately investigated. Of note, heterogeneity of the diagnosis and treatment exposure, as well as the omission of depressive features or other psychiatric comorbidity, should prompt cautiousness in the interpretation of the results.

Collectively, the field of negative psychotic symptomatology and its relation to cortisol levels seems to be currently unclear. Nevertheless, a subtle portion of the reviewed literature, furthering an indirect or no role for cortisol in negative symptoms, seems to outweigh the studies supporting a larger role.

The affective parameters do not seem to clearly relate to cortisol dysregulation, as well. In particular, current evidence suggests that neither the anxiety parameter, nor the depressive component, are directly connected to cortisol function in FEP.

Conclusively, despite the well established knowledge of cortisol involvement in the pathological mechanisms of affective disorders [16•, 71–74], the current review does not support the hypothesis of a dysregulated HPA axis. The latter hypothesis could possibly stem from comorbid depression symptoms which are commonly anticipated while psychosis emerges [16•, 75]. The divergence may be associated with the limited data, the heterogeneous study design and subjects' diagnoses, the comorbid psychiatric entities, the absence of HC groups in many studies etc. Belvederi Murri et al. [22••] have suggested that cortisol association with a particular dimension of symptoms lacks specificity. The multifaceted clinical and neuroendocrine patterns of psychotic disorders have been previously recognized [22••, 76], thus prompting future researchers to more targeted (in terms of diagnostic entities, phase of illness, medication status, comorbitity) studies.

The present review incorporates a basic advantage; its systematic nature: to the best of our knowledge, this is the first attempt to systematically investigate cortisol patterns along with psychopathological parameters in FEP. Moreover, it has concentrated on psychosis first stage, thus providing insight into this particular phase, while excluding confounding factors. Importantly, the current review underlines the necessity for consensus in the applied methods to evaluate both cortisol levels and its function. The former should involve multiple samples along time, instead of single sampling, whereas the latter should incorporate the evaluation of cortisol fluctuation along time, rather than its total secretion in respect to baseline. Currently, total secretion measurement constitutes the common practice, thus minimizing the comprehension of the stress system sensitivity. On the other hand, our findings must be interpreted in the light of the shortcomings of systematic reviews (publication bias in particular). Furthermore, the present study lacks a meta-analytical orientation, which theoretically could help quantitatively delineate cortisol aberrant function. Additionally, it has not taken into account other components of the HPA axis, such as ACTH, CRH or

volumetric studies of secretory/target organs, e.g. hippocampus and pituitary, which all hold a role in the coordination of stress response.

In conclusion, the literature related to the investigation of cortisol level alteration at the first stage of psychosis is at a preliminary stage. Studies evaluating cortisol reactivity/fluctuation are even more limited. Findings converge towards an elevation of cortisol secretion during FEP. While cortisol seems to participate in the pathological mechanism of psychosis, the exact cause effect sequence remains to be elucidated. It should be noted that CAR, DST and other neuroendocrine tests render different neuroendocrine patterns, possibly associated with heterogeneity in diagnoses, medication effect, comorbitity, childhood trauma and other types of psychopathological burden. Metabolic and psychosocial types of stressors were related with contradictory results, as well.

The current evidence suggests a role of cortisol in psychosis, but the relation of cortisol with psychopathological symptoms is not specific. The pattern of an only subtle, indirect connection of psychopathology with aberrant cortisol level and/or function implies the involvement of confounding factors, such as genetic load, environmental stressors, neuroendocrine alterations and psychotic-affective-cognitive symptoms. For these mechanisms to be further elucidated, research should further focus on more pure diagnostic entities, clearly defined stages of the disorder and refined methods (multiple as opposed to single sampling, estimation of cortisol reactivity rather than basal secretion).

Compliance with Ethics Guidelines

Conflict of Interest Evangelos Karanikas, Diomidis Antoniadis, and George D. Garyfallos declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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