Neurology, Psychiatry and Brain Research 32 (2019) 91–98

Contents lists available at ScienceDirect

Neurology, Psychiatry and Brain Research

journal homepage: www.elsevier.com/locate/npbr

Cortisol and cytokines in early psychosis, do they correlate? A scoping review

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ARTICLE INFO

Keywords:
Cortisol
Cytokines
First episode
Psychosis
Ultra High risk

ABSTRACT

Background: Recently, there has been increasing evidence of the contribution of cortisol and cytokines in the pathophysiology of psychosis that has been accumulated, with a particular focus on the early stages of the disorder. Yet, little is known about their putative interplay.
Objective: The objective was to search the existence of any evidence pertaining to the cortisol-cytokines interaction in early psychosis.
Methods: We implemented the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews guidelines and searched Pubmed, PsychInfo, Embase. This was conducted from inception to September 2018, for the studies involving both measurement of cortisol and cytokines in First Episode Psychosis (FEP) and prodromal stage, with particular focus on the markers' association.
Results: Seven studies fulfilled the selection criteria with six referring to FEP patients and two to Ultra High Risk for Psychosis (UHR-P) subjects. None of the studies either reported or measured significant correlations of cortisol levels/function with cytokines levels. Yet, the majority of the studies provided evidence on cortisol and/or cytokines deviation in the FEP and UHR-P groups.
Conclusion: Apart from a simplistic approach suggesting no interplay between cortisol-cytokines in early psychosis, we suggest that this association, practically, has not been searched hitherto. The minimal findings (when reported) suggested lack of cortisol-cytokines association which appeared to be confounded with research methodologies complexities. The review pinpointed a gap in literature and stresses the need for addressing the endocrine-immune systems interaction as one of the outcomes in future studies on early psychosis.

1. Introduction

According to Hans Selye, one of the main contemporary researchers of stress mechanisms in the 1940s, Glucocorticoids (GCs) enhance the body's defense mechanisms as part of a "general adaptation syndrome". These hormones play critical role in balancing bodily responses to challenges and maintaining homeostasis, by suppressing inflammatory pathways and inhibiting stress related pathways, such as the Hypothalamic-Adrenal-Pituitary (HPA) axis and the Sympathetic Nervous System. Conversely, the absence of GCs, has led to unimpeded inflammatory processes resulting in increased levels of pro-inflammatory cytokines, Nuclear Factor –k Beta (NF-kB), target genes, prolongation of the inflammatory response, neuronal death and mortality (Bellavance & Rivest, 2014). Thus, the equilibrium between GCs signaling on the one hand and immune signaling on the other, will define the overall organism's health outcome. Until now, the evidence supports that HPA axis dysfunction and inflammation may be part of the same pathophysiological process and stress can play a fundamental role in triggering the onset or exacerbations of inflammatory/autoimmune diseases as well as psychiatric disorders (Marques et al., 2009; Silverman & Sternberg, 2012).

So far as the latter ones are concerned, the interplay of the neuro-endocrine-immune factors appears even more complex since it is enriched with the Central Nervous System (CNS) component. There is evidence suggesting a role for cytokines in adult rodents to modulate dopamine turnover (Zalcman et al., 1999); conversely, the dopaminergic system appears to exert a net stimulatory influence on various parameters of the immune system (Masek et al., 2003).

The evidence from the aforementioned novel fields of psycho-neuro-endocrinology and psycho-immunology paved the way for a new understanding of the pathophysiological mechanisms of major psychiatric disorders, with psychosis constituting one of the main conundrums,

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https://doi.org/10.1016/j.npbr.2019.05.002
Received 14 February 2019; Received in revised form 8 April 2019; Accepted 14 May 2019
Available online 22 May 2019

concerning both phenomenology and pathophysiology. During the last decade, evidence from both the psycho-neuro-endocrine and psycho-immunological domains in relation to early stages of psychosis, namely First Episode Psychosis (FEP) and prodrome, has been accumulated. In this way, the effects related to chronicity and treatment, started being eliminated; yet the findings are bewildering in many levels.

1.1. Cytokines levels in early psychosis

1.1.1. Background of cytokines levels in FEP

The first review (Drzyzga et al., 2006) on cytokines in psychosis involved the study of antipsychotics' potential to influence the cytokine networks and suggested that antipsychotic medications predominantly suppress the activity of the Interleukin (IL)-2 system. Later on, Miller et al. (2011) proceeded to the meta-analysis of cytokine alterations in Schizophrenia (SZ) considering both the clinical status and medication effects. The authors suggested a role for IL-1β, IL-6 and Transforming Growth Factor (TGF)-β as state markers and for IL-12, Interferon (IFN)-γ, Tumor Necrosis Factor (TNF)-α and soluble IL-2 Receptor, (sIL-2R), as trait markers in psychosis. Soon afterwards, Upthegrove et al. (2014) systematically reviewed/meta-analyzed 14 studies, including 570 neuroleptic naïve FEP patients of the non-affective psychotic spectrum and suggested increased mobilization of the cytokines of the innate immunity (IL-1β, IL-6, TNF-a) as well as T-cell activation (sIL-2R).

1.1.2. Background of cytokines levels in Ultra High Risk for Psychosis (UHR-P) subjects

Regarding the prodromal phase, the evidence, though recent, comes from two large multisite studies (Cannon et al., 2015; Hayes et al., 2014). The latter study involved a measurement of initially 90 (finally 35) analytes in Cerebrospinal Fluid (CSF) of medication naïve groups of SZ patients, UHR-P subjects as well as Healthy Controls (HC). Out of 15 analytes, the IL-6R, TGF-α and TNFR-2 showed decreased expression in the SZ patients with UHR-P subjects showing the greatest decrease; conversely, IL-8 showed increased expression in the SZ with UHR-P exhibiting the greatest increase. This study spared the prospective design, contrary to the North American Prodrome Longitudinal Study (NAPLS) where UHR-P were followed up monitoring their potential conversion to full psychosis. In this latter project, Cannon et al. (2015) suggested that the rate of prefrontal cortical thinning was significantly associated with higher levels of pro-inflammatory cytokines in the sample overall and this inverse correlation was significantly greater among converters compared to both non-converters and HC.

1.2. Cortisol in early psychosis

The neuro-endocrine component within the context of psychosis has mostly been investigated via measurement of various indexes of the HPA axis. Cortisol's measurement, in various biological liquids with various time patterns and conditions, reflects the most common practice.

1.2.1. Background of cortisol levels/function in FEP

Three recent studies reviewed the baseline cortisol rates in FEP and converged to the conclusion that the patients show a significant increase in cortisol levels compared to HC (Borges et al., 2013; Karanikas et al., 2014; Pruessner et al., 2017). This increase seems to be more profound when cortisol is measured in blood than in saliva and when the patient cohorts consist of medication naïve or minimally treated subjects. It was also concluded that FEP patients show a sharper decrease of diurnal cortisol throughout the day than HC (Karanikas et al., 2014; Pruessner et al., 2017). It was further suggested that multiple sampling constitutes a more reliable method to gauge cortisol levels compared to a single sample. Moreover, longitudinal studies show that, cortisol levels decrease with treatment in the follow-up evaluations (Karanikas et al., 2014).

Cortisol Awakening Response (CAR) is an additional way to gauge HPA axis function since awakening serves as a naturalistic stressor. The CAR studies in FEP suggest that cortisol response to awakening is blunted, yet there is some inconsistency, possibly related to confounding factors such as sex, medication and participants' adherence (Pruessner et al., 2017).

Fewer studies have dealt with the cortisol response to an imposed stressor, of either psychosocial or pharmacological type, the most common of the latter having been the Dexamethasone Suppression Test (DST) (Karanikas et al., 2017; van Venrooij et al., 2012).

1.2.2. Background of cortisol levels/function in UHR-P

When it comes to the HPA axis function at prodrome, three recent reviews favor that baseline cortisol levels are also elevated compared to HC, although the conclusions are less robust here compared to the FEP state (Aiello et al., 2012; Karanikas & Garyfallos, 2015; Pruessner et al., 2017). Even more divergent are the results in relation to baseline cortisol in subjects with Genetic High Risk (GHR) possibly due to the smaller chances -compared to the clinically UHR-P- of conversion to full psychosis (Aiello et al., 2012; Pruessner et al., 2017).

Similarly, to the FEP studies, the HPA axis function research at prodrome involved the measurement of cortisol response to awakening as well as other stressors. Specifically, a recent meta-analysis of the CAR suggested that it is blunted in established SZ and FEP, but normal in UHR-P state (Berger et al., 2016). As for the cortisol response to stressors, the literature is insufficient to extract valid conclusions regarding the UHR-P subjects. There is evidence indicating that it is blunted in antipsychotic-naïve UHR-P adolescents, though inconclusive (Pruessner et al., 2013).

1.3. Aim of the review

The above mentioned evidence suggests that both the HPA axis and immune system may constitute candidate fields for further investigation of the aetiopathology of psychosis. Cortisol and cytokines represent the most researched biomarkers of the psycho-neuro-endocrine and immune fields, respectively. Despite the exponentially growing bulk of findings regarding the initial phases of psychosis –FEP and prodrome-, we still remain far from synthesizing a holistic psycho-neuro-endocrine-immune model, sufficient to encompass the inconsistent findings. Having said that, the field of the putative psycho-neuro-endocrine and immune systems interplay in early psychosis appears even less investigated if any. Thus, a need for further enlightenment of this emerging scope arises. Based on the identification of this need and gap in literature, the view that a scoping type of review would preferably serve it the most was adopted. Scoping reviews are meant to proceed to a preliminary assessment of the size and scope of the existing literature relating to the available evidence thus highlighting the need for novel research avenues (Grant & Booth, 2009). On this basis, this scoping review was conducted with the aim to search for any evidence, pertaining to cortisol-cytokines interaction in FEP and UHR-P cohorts. Subsequently, commenting on its size, range, nature according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). The hypothesis for this scoping review was that the published evidence on cortisol-cytokines interaction in early psychosis should be fair in size and the preliminary findings should support a substantial cortisol-cytokines interaction.

2. Material and methods

The search was done via the online data bases Pubmed, PsychInfo, Embase using as keywords the following: ["First Episode" OR "Ultra High Risk" OR "At Risk Mental State"] AND "psychosis" AND ["neuroendocrine" OR "HPA axis" OR "cortisol"] AND ["immune" OR "cytokines"] in all possible combinations. The inclusion criteria were: i.

original research articles peer reviewed published in English from inception up to September 2018, ii. publications on either FEP patients and/or UHR-P subjects investigating both cortisol, measured in plasma or serum or saliva and cytokines in blood, no matter what the primary aim of the study was. Due to the scoping nature of the review the inclusion criteria was relaxed and allowed the following: iii. the inclusion of FEP and UHR-P cohorts even if they were not necessarily compared with HC, iv. a partial overlap of the participant cohorts, in case of different protocol studies. The PRISMA-ScR guidelines were applied and implemented the relative checklist. Titles and abstracts, using the eligibility and exclusion criteria, were screened. Potential eligible articles for data extraction were identified after full-text review. Two reviewers [E.K.(see authorship) and E.T.(see Acknowledgment)] independently performed these two stages of screening. Disagreements were resolved by consensus. Forward (Google Scholar) and backward searches (bibliographies of included articles) were conducted to find articles that might have been missed during initial database searches. The two reviewers extracted information independently for each eligible article using a standardized form. The following information was extracted from each study: first author, year of publication, size of cohorts, sex, age, diagnoses, comorbidities, medication, design, techniques of cortisol/cytokines evaluation, psychometric tools used, cortisol-cytokines correlations, controlling for age, sex, BMI, smoking, medication.

3. Results

A flowchart summarizing the study selection process is presented in Fig. 1. During the final step, seven studies fulfilled the selection criteria (Berger et al., 2018; Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2012; Goff et al., 2018; Karanikas et al., 2016; Mondelli et al., 2015; Perkins et al., 2015) (Table 1). A pair of studies (Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2012) despite sharing, at least partly, the patients cohorts were both included due to the different design (FEP vs HC and FEP with deficit symptoms vs FEP non-deficit, respectively). Five studies (Berger et al., 2018; Fernandez-Egea et al., 2009; Garcia-Rizo et al.; Goff et al., 2018; Mondelli et al., 2015) out of the total seven, reporting on early psychosis (FEP and prodromal stage), involved only FEP cohorts, one study only UHR-P cohort (Perkins et al., 2015) and one study both FEP and UHR-P cohorts (Karanikas et al., 2016). Five out of seven studies involved comparisons with the HC group (Berger et al., 2018; Fernandez-Egea et al., 2009; Goff et al., 2018; Mondelli et al., 2015; Perkins et al., 2015).

In total, the reviewed studies included 324 FEP, 84 UHR-P subjects and 226 HC.

3.1. Diagnoses within and design of the FEP studies

The majority of the studies reporting on FEP cohorts, involved patients of the non-affective psychotic spectrum (Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2012; Goff et al., 2018; Karanikas et al., 2016). The Berger et al. (2018) study included patients with SZ (N = 26) as well as Schizoaffective Disorder (SAD) (N = 2). Similarly, to the latter, the Mondelli et al. study (2015) involved patients from both the affective (ie SAD and affective psychosis) and non-affective psychotic spectra. Regarding the medication status, the majority of the studies involved naïve patients with the prerequisite of lifetime exposure less than seven (Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2012) and three (Karanikas et al., 2016) days prior to blood sampling. Similarly, the 86% of the FEP patients in the Berger et al. (2018) study were antipsychotic naïve and the rest were off medication for at least six weeks. On the contrary, in the Mondelli et al. (2015) study, 90% of the patients were on medication for a mean of 355 and 463 days for the Responders and Non Responders respectively.

The design of the studies regarding the HPA axis parameters involved measurement of cortisol at rest (baseline) in blood samples in all but two studies where saliva samples were collected (Goff et al., 2018; Mondelli et al., 2015). All studies measuring one cortisol sample incorporated the same design of a morning sampling (08.00 − 09.00) without further control for awakening effect. Furthermore, two studies involved evaluation of day time cortisol secretion through multiple sampling (Area Under Curve ground, AUCg) (Karanikas et al., 2016; Mondelli et al., 2015), whereas one study gauged the median value of multiple saliva cortisol samples (Goff et al., 2018). Moreover, in the Karanikas et al. (2016) study an extra measurement of the cortisol change throughout the day (AUC increase, AUCi) plus DST were

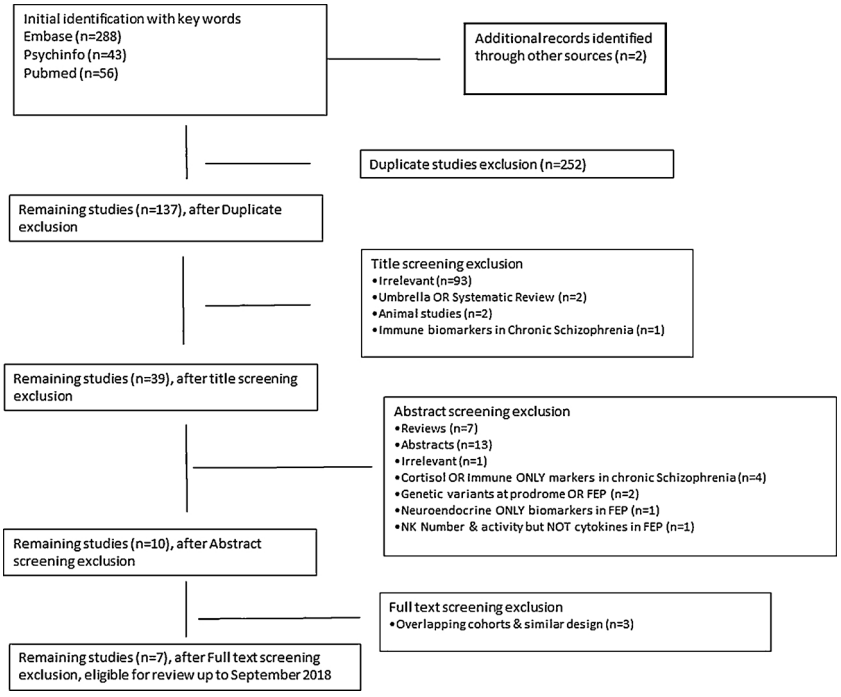

Fig. 1. Flowchart of the study selection process.

Table 1
Characteristics of the reviewed studies.

Study	Subjects	Design	Methods	Findings		
				Cortisol	Cytokines	Associations
Fernandez-Egea et al., 2009	FEP N = 50,HC = 50	cross sectional	Serum, Base Cort,IL-6	↔	FEP IL-6 > HC	NS(IL-6 increase NOT confounded by cortisol)
Garzia- Rizo et al., 2012	FEP/D,N = 20 vsND,N = 42	cross sectional	Serum, Base Cort,IL-6	↔	FEP/D IL-6 > ND	NR
Perkins et al., 2014	UHR-P,N = 32 vs UHR-NP,N = 40 vs HC,N = 40	prospective (2yFU) (symptoms,cortisol,cytokines at Base & conversion FU)	Plasma 185 multi-analytes	Conversion prediction	Conversion prediction:IL-1b,IL-7,IL-8	NR
Mondelli et al., 2015	FEP-R, N = 30vsFEP-NR,N = 38,vs HC,N = 33	prospective (3mFU) (symptoms,cortisol,cytokines at Base & FU)	Base Sal CortAUC,CAR & serum IL-6,IFN-γ,IL-4,IL-10 & 3mFU	BaseCAR: FEP-NR < R < HC,CortAUC:↔, 3mFUCAR:FEPNR < R	BaseIL-6,IFN-γ:FEPNR > R > HC, IL-4 & IL-10: NR > HC, 3mFUIL-6,IFN-γ:NR > R	NR
Karanikas et al., 2016	FEP N = 25vsUHR-P N = 12	cross sectional	Base serum CortAUC,DST,TNF-a, TNF-b, IL-4,IL-2,IL-10,IL-12,IFN-γ	Base AUCg UHR > FEP	BaseTNF-a,IL-2,IL-10,IL-12,IFN-γ:FEP > UHR	NS
Berger et al., 2018	SCZ,N = 28 vsFEP,N = 28,vsHC,N = 53	prospective (6&12wFU) (symptoms,cortisol,cytokines at Base & symptoms FU)	Base serum Cort, IL-6, TNF-a	FEP > HC(Base)	↔(Base)	NR
Goff et al., 2018	FEP,N = 71 vs HC,N = 73	prospective (8wFU) (HV,cortisol,cytokines at Base& their change FU)	Base Sal median Cort & plasmaIL-1b,IL-8,IFN-γ,TNF-a & 8wFU	BaseTotal FEP > HC,Base Med-free FEP↔HC,Base Med-Free FEP↔post8w MedFEP	↔(Base &FU)	NR

Abbreviations (alphabetical order): AUCArea Under Curve;AUCgAUC ground;BaseBaseline value;CARCortisol Awakening Response;CortCortisol;DSTDexamethasone Suppression Test;FEPFirst Episode Psychosis;FEP/D;FEP/Deficit; FEP/NDFEP/Non Deficit;FEP/NRFEP/Non responders;FEP/RFEP/Responders;FUFollow Up;HCHealthy Controls;HVHippocampal Volume;IFNInterferon;ILInterleukin;mmonths;MedMedication;NRNon reported;NSNon Significant;SalSaliva;TNFTumor Necrosis Factor;UHR-PUltra High Risk for Psychosis ;UHR-NPUHR-Non converted to Psychosis;wweeks;↔no difference.

applied, whereas only in one study was CAR estimated (Mondelli et al., 2015). All studies involving multiple cortisol sampling adopted similar design procedure which involved sampling in three time points -morning, noon, evening- throughout the day.

Regarding the immune field in the FEP studies, CRP and IL-6 were the most studied parameters. It is worthwhile mentioning that none of the reviewed studies utilized the high sensitivity CRP methodology. Furthermore, in three studies, the research groups utilized multiple analyte kits measuring cytokines of both the innate and adaptive immune arms as well as neurotrophic factors (Goff et al., 2018; Karanikas et al., 2016; Mondelli et al., 2015). Relative to the participating groups design, four studies involved comparisons of FEP with HC (Berger et al., 2018; Fernandez-Egea et al., 2009; Goff et al., 2018; Mondelli et al., 2015). Two other studies involved the division of the FEP group into subgroups depending on their deficits symptoms (Garcia-Rizo et al., 2012) and the comparison of FEP directly with UHR-P without a HC group (Karanikas et al., 2016).

Half of the FEP studies followed cross sectional design while the other half involved longitudinal designs which differed in both their intervals (from baseline to follow up) duration and the assessed (pertaining to this review) variables. Specifically, Mondelli et al. (2015) re-assessed symptoms, cortisol and cytokines levels in three months, Berger et al. (2018) re-evaluated symptoms only in six and 12 weeks and Goff et al. (2018) symptoms, cortisol and cytokines change in their two months follow up.·

3.2. Diagnoses within and design of the UHR-P studies

Relative to the research investigating both cortisol and cytokines in UHR-P populations, two studies were deemed as eligible for inclusion (Karanikas et al., 2016; Perkins et al., 2015). The studies totally involved 84 UHR subjects, 72 of whom were evaluated with the Structured Interview for Prodromal Syndromes (SIPS), followed up longitudinally and evaluated for conversion to psychosis in the context of the NAPLS study (Perkins et al., 2015). In addition, another 12 UHR-P subjects were involved (Karanikas et al., 2016), who were classified with the Personal Assessment and Crisis Evaluation (PACE) criteria in the context of the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2005). Regarding the inclusion of HC group in the study design, only the NAPLS study did incorporate 32 HC. In the NAPLS study the aim was to develop a “greedy” algorithm of analytes -involved in neuro-endocrine responses, inflammation, growth, oxidative stress and metabolism- sufficient to predict conversion of prodromal subjects to full psychosis. On the other hand, the Karanikas et al. (2016) group utilized kits for measurement of 10 cytokines as well as cortisol (AUCg, AUCi and post-Dexamethasone).

3.3. Results on cortisol-cytokines in FEP

With regard to the results of the studies concerning FEP populations, the evidence favors alterations in both the immune and neuro-endocrine fields. In relation to the former, half of the studies involving comparisons with HC group, suggested significant deviations in the FEP–these having been increased IL-6 at baseline (Fernandez-Egea et al., 2009), increased IL-6, IFN-γ at baseline for both Responders and Non Responders and increased IL-4, IL-10 for the Non Responders (Mondelli et al., 2015). When it comes to the HPA axis function in FEP, three studies out of five suggested deviations from normality, such as decreased CAR (Mondelli et al., 2015), increased cortisol levels at baseline both in single blood sample (Berger et al., 2018) and in multiple saliva samples (Goff et al., 2018). Interestingly, in the latter study, the free medication sub-group (65 out of total 69) failed to show cortisol deviation compared with both the HC at baseline and the FEP after 8 weeks follow up. Thus, the number of studies suggesting HPA axis function alteration decreased to two out of five. As far as the main outcome (cortisol/cytokines associations) of the present scoping review is concerned, one FEP study reported no significant ones (Karanikas et al., 2016), whereas another four studies appeared with no reports whatsoever (Berger et al., 2018; Garcia-Rizo et al., 2012; Goff et al., 2018; Mondelli et al., 2015). The Fernandez-Egea et al. (2009) study implied indirectly no significant associations, based on the finding, in multiple regression analyses, that IL-6 increase in the FEP was not confounded by cortisol levels.

3.4. Results on cortisol-cytokines in UHR-P

Regarding the studies on UHR-P subjects, the evidence is obscure since only the one (out of the total 2) did involve HC group (NAPLS project) (Perkins et al., 2015). The analytes used included IL-1b, IL-7, IL-8 as well as cortisol. Yet, no report was identified relative to cortisol-cytokines correlations. On the contrary, the Karanikas et al. (2016) study suggested that the UHR-P group showed increased baseline cortisol AUCg but decreased TNF-a, IFN-γ, IL-2, IL-10, IL-12 levels compared to FEP patients; it also reported on cortisol-cytokines correlation suggesting no significant associations both within the FEP and UHR-P groups separately.

4. Discussion

With regard to the main query (cortisol/cytokines interaction in early psychosis) of this scoping review, either the findings were negative or non-reported. A first interpretation could be that there is no interplay between the two systems; yet this would contrast the ever increasing evidence of dysregulation of each one of the immune and neuro-endocrine systems in early psychosis. Besides, knowledge from basic neuroscience favors a close interaction between inflammatory and stress mechanisms (Horowitz et al., 2013). A second interpretation could be that the immune and HPA axis mechanisms, despite appearing to deviate from normality even from the prodromal psychotic stage, are not as closely interconnected for the studies to capture this interconnectivity; this could be due to other mechanisms playing mediating role. Results from another study (van Venrooij et al., 2012) failed to provide evidence for a significant association between the neuro-endocrine (cortisol, ACTH) and immune (NK numbers and activity) parameters on FEP patients, further supporting the aforementioned presumption. A third factor that could have accounted for the absence of reports on cortisol-cytokines association, might simply be the lack of incorporation of cortisol-cytokines correlation measurement into the studies’ protocols. This could be due to the fact that the main outcomes of the studies focused on other variables, such as Diabetes related factors (Fernandez-Egea et al., 2009), Allostatic Load (AL) (Berger et al., 2018), Hippocampal Volume Integrity (HVI) instead of the cortisol-cytokines correlation (Goff et al., 2018).

The picture of the putative cortisol-cytokines interaction becomes even more obscure should someone take into consideration the complexity, the multiple hypotheses and the deviating results characterizing each of the immune and stress systems in psychosis. Thus, a number of aetio-immuno-pathological theories (Drexhage et al., 2011; Müller & Schwarz, 2010; Smith & Maes, 1995), implicating different arms of immunity, have been postulated. Similarly, various neuro-endocrine modes of the HPA axis function –baseline cortisol secretion vs response to dynamic stress vs CAR- have been suggested functioning independently (Pruessner et al., 2017). The lack of a definitive aetiopathological model regarding psychosis, increases the difficulty to encompass the hitherto findings from both the neuro-endocrine and immune scopes. In addition, the range of published studies researching both the fields in psychosis is limited. Moreover, the cohorts are relatively small and the designs tend to vary, [ranging from utilization of different immune analyte kits to evaluating different aspects of the HPA axis function (a cortisol sample of baseline secretion, AUC from multiple samples, CAR, DST, responses to psychosocial test) in different biological liquids (serum, plasma, saliva)]. The aforementioned may

explain the non-significant (in case they were searched) and/or the non-reported (consequent to them either having been evaluated and found insignificant or not having been searched whatsoever) cortisol-cytokines correlations of this review. Another factor that could have played a role in the studies' heterogeneity and consequently the decreased likelihood for capturing significant cortisol/cytokines correlations, is the medication effect. Indeed, the authors of the majority of the present review studies classified their FEP participants as antipsychotic medication naïve. A careful reading shows that all of them, allowed their FEP subjects to have been on medication for a number of days/doses prior to blood sampling. Even this subtle exposure in medication could have accounted for the failure to capture a hint of cortisol-cytokines associations, since the medication effect is a known moderator of both the HPA and immune systems (Baumeister et al., 2016).

A general finding of the review is that the majority of the studies suggested evidence for deviation of either the cytokines or the cortisol levels/function when psychosis emerges at its full blown intensity and even prior to that. Conversely viewing, two of the reviewed studies were suggestive of a simultaneous deviation of both the neuro-endocrine and immune parameters in the same cohort, despite the fact that no significant associations in between those fields were identified or reported (Mondelli et al., 2015; Perkins et al., 2015). These findings are partially in line with the presumption of an interplay between the neuro-endocrine and immune systems (Horowitz & Zunszain, 2015), yet remain inconclusive regarding causality and sequence. Specifically, the HPA axis has been shown to exert profound effects on the innate immune system, largely understood to be inhibitory, by preventing the transcriptional activity of one of the key inflammatory transcription factors, NF-kB and suppressing the production and secretion of pro-inflammatory cytokines (Silverman & Sternberg, 2012); on the other hand, pro-inflammatory cytokines may both act as stimulants of the HPA axis (Mastorakos et al., 1993) and interfere with GR function (Raison et al., 2006). Thus, a state known as GR resistance is induced, through mechanisms like disruption of GR translocation, GR–DNA binding and GR phosphorylation status (Pace & Miller, 2009). To make matters more complex, recently a hypothesis of GCs, exerting both pro- and anti-inflammatory action, has been posited to explain the coexistence of high levels of inflammation and GCs in pathological states (Frank et al., 2013).

Another interesting finding is that, despite the fact that, arithmetically speaking, the number of the reviewed studies (Fernandez-Egea et al., 2009; Mondelli et al., 2015; Perkins et al., 2015), suggesting aberrant cytokine levels within the FEP and/or the UHR-P cohorts, do not differ significantly (three studies vs four) from the ones indicating cortisol levels/function variance (Berger et al., 2018; Goff et al., 2018; Mondelli et al., 2015; Perkins et al., 2015). But, qualitatively speaking, the cytokines' trend for deviation tend to subtly outweigh cortisol malfunction. Specifically, in the Goff et al. (2018) study, the free medication FEP subgroup, which constituted the vast majority of the FEP participants, failed to show cortisol deviation in relation to both the HC group at baseline and to the FEP after eight weeks follow up. Furthermore, only two of the reviewed studies failed to find immune deviations of the FEP subjects relative to HC at baseline (Berger et al., 2018; Goff et al., 2018). Nevertheless, the cytokines were significantly associated with the AL index and the decrease of HVI -main outcomes of the studies- respectively. In addition, the FEP and UHR-P cohorts of the Karanikas et al. (2016) study, when compared to a HC group in a subsequent study, presented deviations from normality in the cytokines component but not in cortisol (Karanikas et al., 2017). This subtle supremacy of the immune parameter compared to cortisol, in relation to the psychosis pathophysiology, is also suggested by a genetic study (Fillman et al., 2014) as well as two recent meta-reviews (Belbasis et al., 2018; Pillinger et al., 2018). The former study, via a recursive two-step clustering analyses of both inflammatory-related genes and GR-related mRNA, showed that inflammation has greater association with SZ while GR stress signaling with Bipolar Disorder. Pillinger et al. (2018) observed a significant effect size ($g = 1.19$) for the immune parameters in FEP patients and less for the HPA axis parameters ($g = 0.68$), though not in direct comparison. Similarly, Belbasis et al. (2018) classified the evidence (P-value < 0.001) for psychosis's association with IL-6 and CRP as suggestive, thus outweighing the weak evidence showed by cortisol, (P-value < 0.05). The hypothesis of a principally immune-driven aetiopathology in psychosis is also furthered by the under review Perkins et al. (2015) study on UHR-P subjects, suggesting that most of the analytes, putatively sufficient to predict conversion to psychosis, are immunomodulatory. The majority of the reviewed studies lack prospective design. Thus, any safe presumption of the etiological sequence between the immune and neuro-endocrine dysregulation in psychosis cannot be extracted and lies beyond the objectives of this exploratory review.

The scoping nature of this review, ie the author's question "What is known about the cortisol-cytokines association in early psychosis?", which consequently incorporated studies with different designs and main objectives, could potentially explain the counterintuitive minimal reports or lack of associations (when reported). Simultaneously this scoping nature constitutes a limitation on its own. Other factors acting both as limitations and exploratory objectives of this scoping review could be: the small cohorts number, medication effect, lack of control for childhood trauma, comorbidities, adherence to sampling, awakening effect on morning cortisol levels, menstrual cycle phase, level and type of psychopathology, illicit substance use as well as statistical complexities. The latter relate either to the lack of correction for multiple comparisons or the hitherto non reinforcement of Miller et al. (2013) recommendation to index cortisol responsivity via auto-regressive latent trajectory mixture models. Last but not least, the provisional status of FEP diagnosis as well as the heterogeneity of the UHR-P sample in relation to their selection criteria which appear to provide with subgroups differing in terms of transition risk and prognosis (Fusar-Poli et al., 2016; Fusar-Poli et al., 2017), plus the restricted range of scores on the positive symptom ratings in SIPS (Woods et al., 2009) and the CAARMS (Yung et al., 2005), but not on the other symptom domains, fuel the participant cohorts with heterogeneity and potentially act as confounders in future studies on similar scope.

On the contrary, the main strengths of the present review are the scoping nature by itself and the application of the recently suggested PRISMA guidelines for scoping reviews. Moreover, the majority of the reviewed studies involved medication naïve or free patients of the non-affective psychotic spectrum in active phase.

5. Conclusions

To summarize, this current review aimed to search, via the PRISMA-ScR principles, the existence/report of any evidence pertaining to cortisol-cytokines (as major representatives of the psycho-neuro-endocrine and immunology fields respectively) interaction, within the context of early psychosis and subsequently to filter and comment on its extent, range and nature. Surprisingly, none of the reviewed studies had incorporated in any of their outcomes the exploration of the cortisol-cytokines association. The findings indicated that there were either non-reports or non-significant results (when reported), relative to the under exploration scope of cortisol-cytokines interaction, thus opposing our initial hypothesis. Yet, the majority of the reviewed studies suggested deviation of cortisol levels/function and/or cytokines levels. Apart from a simplistic approach that there is no constitutional relationship between stress and immune mechanisms in early psychosis, the chances are that either the cortisol-cytokines association has not practically been searched and/or multiple confounding factors, interfering with the HPA axis function and/or cytokines' secretion, may have accounted for the non-significant correlation (when reported). Thus, our scoping review hopes to stress the gap in literature and hopefully to instigate researchers to embark on the study of the putative interplay between neuro-endocrine and immunological parameters within the wider

context of psychosis' aetiopathology. For this effort to be proven fruitful, a design of multisite, well controlled, longitudinal studies, focusing on the early stages of psychosis appears imperative. Only in this way will the complex and multidimensional conundrum of psychosis unravel.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

The author E.K. was involved in the conception and design of the study; acquisition and analysis of data; drafting the manuscript, figure and table.

Disclosure statement

The author declares no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

No animal or human studies were performed.

Declarations of interest

None.

Acknowledgements

The Author wishes to thank senior investigator Eleni Tsalkitzi, MSc, for her contribution to the screening of articles for eligibility at all stages of search (medical data bases, abstract, full text screening) as well as data extraction, independently from the author.

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