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Salivary cortisol in early psychosis: New findings and meta-analysis

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ABSTRACT

Background: Schizophrenia is a multifactorial disorder and environmental risk factors for it might contribute to hypothalamo–pituitary–adrenal axis (HPA) dysregulation. While increased cortisol levels have been reported in schizophrenia, as well as in early psychosis (compared to healthy controls), a crucial unresolved issue is whether elevated cortisol levels could be related to the distress of an emerging illness, rather than being specific to psychosis. Here, we report new findings from the first French cohort of young help-seekers (ICAAR) including ultra-high risk subjects (UHR), first-episode of psychosis (FEP) and non at-risk help seekers controls (HSC), followed by a meta-analysis of all available reports on salivary basal cortisol levels in early psychosis (UHR and FEP).
Methods: In the ICAAR study, 169 individuals (15–30 years old) had their basal cortisol levels sampled and they were categorized (at baseline) as either UHR, FEP, or HSC using the criteria of the Comprehensive Assessment of At-Risk Mental States (CAARMS). The three groups were compared at baseline, and the UHR and HSC individuals were also included in a one-year longitudinal follow-up. UHRs who converted to psychosis at the follow up (UHR-P) were compared to non-converters (UHR-NP). We also performed a meta-analysis from case-control studies with basal salivary measures of cortisol, drawing from a systematic bibliographic search using the keywords 'cortisol', 'glucocorticoid', 'HPA' with 'UHR', 'CHR', 'at-risk mental state', 'schizotypal', 'prodromal schizophrenia', 'first-episode psychosis', 'first episode schizophrenia', 'newly diagnosed schizophrenia', 'recent onset schizophrenia' [in Medline, Web of Knowledge (WOS), EBSCO], followed by a systematic screening of the resulting articles.
Results: Basal cortisol levels were not significantly different between UHR, FEP, and HSC controls in the ICAAR cohort. Interestingly, initial cortisol levels were correlated with positive symptoms at the one year follow-up in the ICAAR cohort. The meta-analysis revealed a significant elevation of the salivary basal cortisol levels in UHR individuals compared to controls (8 studies—1060 individuals), but not between FEP and controls (6 studies—441 individuals). Indirect comparison of salivary basal cortisol levels between UHR and FEP did not yield significant differences. Finally, no differences were detected between the baseline cortisol of UHR-P and UHR-NP (4 studies—301 individuals).
Conclusion: The meta-analysis (including new data) indicates that basal cortisol levels were increased in UHR compared to controls, but FEP levels were not different from UHR or controls. Many confounding factors could decrease the effect size in FEP especially medication intake. Taken together with our new results (which made use of help-seeker controls, and not merely healthy controls), the findings indicate that basal cortisol levels may not be a reliable biomarker for early psychosis. Further studies are needed to clarify the precise role of the HPA axis in psychotic conversion.

1. Introduction

Schizophrenia is a complex multifactorial disorder (Modinos et al., 2013). In conjunction with genetic predisposition, several environmental factors, such as childhood adversity, urbanicity,

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daily hassles, and minority group position increase the risk for schizophrenia (Van Os et al., 2010), and they also appear to impact hypothalamo–pituitary–adrenal (HPA) axis regulation. Childhood adversities have been linked to flattened morning cortisol secretion in adulthood (Power et al., 2012), urban upbringing has been correlated with increased HPA axis reactivity in response to acute stress (Steinheuser et al., 2014), and low perceived social support has been associated with higher cortisol levels (Lederbogen et al., 2010). Thus, cortisol dysregulation could be a converging consequence of these environmental factors that contributes to the precipitation of psychosis.

Various evidence supports the view that the stress hormone cortisol has cerebral effects pertinent to the etiology of schizophrenia. For instance, acute and prolonged cortisol exposure can lead to the dysregulation of neurotransmission (Popoli et al., 2012) and stressors can precipitate psychosis (Trotman et al., 2014). The neurotransmitter dopamine is also strongly implicated in schizophrenia (Howes and Murray, 2014), and centrally-acting antipsychotics (which antagonize dopamine receptors) lead to cortisol level decreases (Walker et al., 2008). Likewise, in a positron emission tomography study, cortisol levels correlated with striatal dopamine release in patients with schizophrenia and in high-risk individuals (Mizrahi et al., 2012). There has also been case report describing individuals with hypercorticism syndrome who manifested psychotic symptoms (Zielasek et al., 2002), which have also been observed after glucocorticoids use. Altogether, these results suggest cortisol dysregulation may be germane to understanding the etiology of schizophrenia, and that cortisol levels may be a relevant biomarker for the emergence of psychosis.

Schizophrenia involves a progression from vulnerability to disease that is likely under the influence of gene–environment interactions (EU-GEI et al., 2014). In their pioneering work Yung and McGorry (1996) advocated for improving methods for detecting prodromes of psychosis in order to facilitate early intervention strategies that seek to avoid disease progression. This objective prompted the development of the *clinical staging model* (Wood et al., 2011; McGorry et al., 2014), which orders schizophrenic disease progression into 5 stages: genetic high risk patients (stage 0); patients with mild or nonspecific symptoms (stage 1a); ultra-high risk subjects (UHR) who experience attenuated, or time-limited psychotic episodes, or who have a familial history of psychosis, or who have a schizotypal personality disorder associated with significant functional decline (stage 1b); patients who reach the criteria for first-episode of psychosis (FEP; stage 2) (Fusar-Poli et al., 2013); patients with full-blown psychosis (stage 3: remitting illness with or without relapse and stage 4: chronic enduring illness).

Considering this framework, a meta-analysis revealed a moderate increase in morning cortisol levels in the plasma of patients with full-blown schizophrenia compared to controls (Girshkin et al., 2014), but studies of HPA axis activation in such patients have yielded mixed results (Bradley and Dinan, 2010). Most previous reports suggest hypercorticism in UHR, as well (Carol and Mittal, 2015; Manzanares et al., 2014; Sugranyes et al., 2012; Thompson et al., 2007a,b; Walker et al., 2013) but see Day et al. (2014), Pruessner et al. (2013a) and Aiello et al. (2012) for a review. In the case of FEP, eleven of fifteen studies have suggested these individuals show elevated cortisol levels (reviewed by Borges et al., 2013). In view of these results, dysregulation of the HPA axis could manifest very early in psychosis and it may be a candidate biomarker for disease progression (McGorry, 2013). The precise relation between psychotic symptomatology and cortisol levels, however, is still debated, with some evidence suggesting that increased cortisol levels in schizophrenia may be more tightly linked to anxiety and stress-intolerance parameters than to psychosis itself (Karanikas and Garyfallos, 2015). Consequently, a major unresolved issue is whether cortisol plays a specific causal role in the onset of psychosis, or if it might only reflect the distress associated with an emerging illness.

Evidence supporting this "distress" hypothesis includes the observation that adolescents with early symptoms of psychosis, but who are not yet help-seeking, have normal cortisol levels (Cullen et al., 2014). There are also discrepant results concerning individuals with a family history of psychosis (i.e., at genetic high-risk for the disorder, GHR) whereby the majority of studies have reported no differences in cortisol between GHR and healthy controls (Brunelin et al., 2008; Collip et al., 2011; Cullen et al., 2014; Marcelis et al., 2004; Yang et al., 2012; Yıldırım et al., 2011). In this regard, it may be important that previous studies have used healthy individuals as the control group. Such individuals may tend to exhibit less cortisol secretion (compared to help-seeking individuals who are not at risk for psychosis) because they are less likely to experience distress related to a perception that they might be ill. That is, the use of help-seeker controls (instead of healthy individuals) might provide a more stringent evaluation of cortisol levels in UHR because HSC individuals are more likely to share the same level of distress.

Along with measurements of cortisol that directly estimate the activation of the HPA axis (via salivary samples, plasmatic cortisol dosage, or with the dexamethasone response test), indirect measures, such as the measurement of pituitary or hippocampal volume, have also been used to examine the HPA's relationship with psychosis. The results of a meta-analysis suggest that UHR individuals with higher pituitary volume are more likely to convert to psychosis (UHR-P) compared to controls, and that FEP individuals display a similar tendency (Nordholm et al., 2013). This conclusion is not supported by two more recent studies, however (Takahashi et al., 2013; Walter et al., 2015). To our knowledge, there has been no meta-analysis exploring the basal cortisol level in early psychosis.

Consistent with the clinical staging model, we postulated that UHR individuals, FEP individuals, and controls would have differences in cortisol levels with more abnormal measures emerging in the more severe stages. Specifically, we hypothesized that cortisol levels would be greater in FEP than in UHR, and greater in UHR than in controls. To test these hypotheses, we directly compared basal salivary cortisol levels in UHRs, FEPs and controls in an original prospective longitudinal study. Controls consisted of non-UHR help-seekers, rather than healthy individuals, in order to test the predictive value of cortisol level in a more naturalistic condition and to directly address the question of whether high cortisol levels could stem from the distress associated with an emerging illness (or from other psychological difficulties linked to help-seeking), or whether it is more specifically associated to psychosis, with a possible causal role. Along with our new findings, we also performed a systematic review and a comprehensive meta-analysis of the available data that was restricted to salivary cortisol data. This analysis defined the basal cortisol level as cortisol measured at rest, which enabled us to compare most of the available studies.

2. Methods

2.1. Original study of basal cortisol in early psychosis (ICAAR cohort)

2.1.1. Description of the clinical cohort

We conducted a prospective longitudinal one-year study (ICAAR study—Influence du Cannabis sur l'émergence de symptômes psychopathologiques des Adolescents et jeunes Adultes présentant un état mental à Risque—PHRC AOM 07-118) sponsored by Sainte-Anne Hospital (Paris, France). Individuals (15–30 years old) were consecutively referred to a specialized outpatient clinic: Adolescent and Young Adults Assessment Centre ('Centre d'évaluation