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Cortisol in schizophrenia: No association with tobacco smoking, clinical symptoms or antipsychotic medication

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ABSTRACT

Cigarette smoking is associated with higher cortisol levels in healthy subjects. In schizophrenia this relationship is not clear. There are divergent results on the association between cortisol with smoking, clinical symptoms and medication in schizophrenia. This study evaluated this association in 196 Caucasian inpatients with schizophrenia (51.30 ± 26.68 years old), subdivided into 123 smokers and 73 non-smokers. Basal salivary cortisol levels were measured twice, at 08.00 and 09.00 AM, 90–120 min after awakening. The effect of smoking on cortisol was evaluated according to current smoking status, the number of cigarettes/day and the nicotine addiction intensity. The influence of clinical symptoms and/or antipsychotic medication on cortisol was determined using the Positive and Negative Syndrome Scale (PANSS), and chlorpromazine equivalent doses.

Non-smokers were older, received lower doses of antipsychotics, had higher PANSS scores, and had longer duration of illness than smokers.

Salivary cortisol was similar in schizophrenic patients subdivided according to the smoking status, the number of cigarettes/day and nicotine addiction intensity. No significant correlation was found between salivary cortisol and PANSS scores, chlorpromazine equivalent doses, age of onset or the duration of illness.

The findings revealed no association between salivary cortisol and smoking, nicotine addiction intensity, or clinical symptoms. Our preliminary data showed no correlation between salivary cortisol and chlorpromazine equivalent doses and/or antipsychotic medication. Our findings suggest that smoking does not affect the cortisol response in schizophrenic patients as it has been shown in healthy individuals. Future studies should investigate a possible desensitization of the stress system to smoking.

1. Introduction

Schizophrenia is a severe, heterogeneous chronic mental disorder with diverse clinical manifestations, influenced by various genetic risk factors and complex interplay between environmental risk factors such as stress exposure and gene–environment interactions. It affects about 1% of the population worldwide (Kahn et al., 2015). Patients with schizophrenia have dysregulated major system regulating the stress response, the hypothalamic–pituitary–adrenal (HPA) axis (Bradley and Dinan, 2010; Brenner et al., 2009; Girshkin et al., 2014; Girshkin et al., 2016; Walker et al., 2008), manifested in the form of both hyper- and hypofunction (Bradley and Dinan, 2010). Schizophrenic patients show altered response to stress compared to control subjects (Brenner et al., 2009; Girshkin et al., 2016). The HPA axis abnormalities in schizophrenia are indicated by elevated basal cortisol levels (Girshkin et al., 2014; Jakovljevic et al., 1998; Muck-Seler et al., 1999), non-suppression of cortisol after dexamethasone suppression test (DST) (Hori et al., 2012; Jakovljevic et al., 1998; Muck-Seler et al., 1999), and blunted cortisol awakening response (CAR) (Mondelli et al., 2010). Disrupted 24-h diurnal rhythm of cortisol secretion (Gallagher et al., 2007) and lower cortisol response to psychological stress (Brenner et al., 2009; Gispen-de Wied, 2000) were also reported. However, there are reports showing similar basal cortisol concentration between schizophrenia patients and controls (Bradley and Dinan, 2010). Some variations in the HPA axis are assumed (Murri et al., 2012) to be associated with severity of particular clinical symptoms evaluated by the Positive and Negative

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Syndrome Scale (PANSS) (Kay et al., 1987). However, our previous study did not confirm these findings (Pivac et al., 1997). Cortisol was reported to be associated with positive and depressive symptoms, excitement and disorganization in a small sample of first episode psychosis (Murri et al., 2012). Although schizophrenia is a neurodevelopmental disorder, the neural diathesis-stress model implicates the role of stress and HPA axis, and interaction with disturbed dopaminergic pathways, in the etiology of schizophrenia (Pruessner et al., 2016; Walker et al., 2008).

Smoking has been significantly associated with various neuropsychiatric disorders (Dome et al., 2010) and psychosocial stress (Slopen et al., 2013). The high incidence of tobacco smoking in schizophrenic patients (Sagud et al., 2009; Winterer, 2010) compared to the general population (de Leon and Diaz, 2005; Dome et al., 2010; Manzella et al., 2015) indicates their increased susceptibility to nicotine addiction.

In healthy subjects, elevated cortisol levels are associated with both passive and active tobacco smoking (Soldin et al., 2011). Cortisol levels were significantly higher in smokers than in non-smokers (Steptoe et al., 2004). These findings were confirmed in the large population cohorts of middle-aged (Badrick et al., 2007) and older (Direk et al., 2011) healthy subjects. Salivary cortisol levels were higher in current smokers than in non-smokers, but did not differ between former smokers and never-smokers (Badrick et al., 2007; Direk et al., 2011).

The primary hypothesis of this study was that smoking and/or intensity of nicotine addiction is significantly associated with salivary cortisol levels in patients with schizophrenia. As the effect of smoking on cortisol levels were evaluated in small number of patients with schizophrenia (Brenner et al., 2009; Hori et al., 2012; Iancu et al., 2007; Murri et al., 2012), we included a fairly large group of inpatients with schizophrenia. Given that smoking affects heart rate (Gillum, 1992) and heart rate is regulated by the autonomic nervous system, it was used in our study as an indicator of the cardiovascular system function. The second hypothesis of this study was that salivary cortisol levels are associated with various clinical symptoms of schizophrenia (Girshkin et al., 2014; Murri et al., 2012) and/or with antipsychotic medication (Bradley and Dinan, 2010). Therefore, we assessed the possible associations between salivary cortisol, symptoms of schizophrenia, and different antipsychotic medication.

2. Materials and methods

2.1. Participants

The study included 196 inpatients with schizophrenia (51.30 ± 26.68 years old), diagnosed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) and recruited from the Psychiatric Hospital Vrapce, Zagreb, Croatia from January 2014 to December 2015. Schizophrenic patients were subdivided into 123 smokers (i.e. current smokers) and 73 non-smokers (i.e. never smokers and former smokers). All patients were Caucasians of Croatian origin. Besides the SCID, all patients were assessed for the presence or the severity of particular clinical symptoms of schizophrenia using the scores in the total PANSS and PANSS subscales. Inclusion criterion was a diagnosis of schizophrenia in subjects older than 18 years. All participants were screened for potential medical issues that may influence the HPA axis activity. Subjects were excluded if they had diabetes, significant alcohol or substance use, were pregnant, in lactation or breast-feeding, received Phenytoin, Ventolin, CRH, ACTH, dexamethasone, metyrapone or were treated for arthritis or multiple sclerosis. They were asked to restrain from physical activity before the protocol started. Besides nicotine dependence, no other co-morbid substance abuse or dependence was present.

All patients were treated with different antipsychotic medication: olanzapine (5–20 mg/day), clozapine (300–800 mg/day), risperidone (2–6 mg/day), fluphenazine (5–15 mg/day), haloperidol (4–15 mg/day), promazine (400–500 mg/day), alone or combined with benzodiazepines, i.e. diazepam (2–10 mg/day). Mean dose of antipsychotic medication, calculated into chlorpromazine equivalent doses, was 309.5 ± 263.5 mg/day (range 50–1600 mg/day).

This study was conducted with the approval of the Ethics Committee of the Psychiatric Hospital Vrapce, Zagreb, Croatia, and in accordance with the ethical standards established by the 1975 Declaration of Helsinki. The procedures were discussed with all patients in detail. Patients were included in the study after they agreed to participate and provide written informed consent.

2.2. Assessment of smoking habits/nicotine exposure

Current smokers were asked to be overnight nicotine abstinent before the sample collection. Nicotine dependence was assessed by the medical charts, psychiatric interview and the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Patients were subdivided according to the FTND scores into those with mild (< 5 scores), moderate (5–7 scores) and severe (> 7 scores) addiction.

Patients who regularly smoke 10 or more cigarettes per day (N = 123) were asked to smoke their own first cigarette with average nicotine amount (containing at least 1 mg of nicotine), in a “smoking” protocol, immediately after the first salivary cortisol sampling. Eight days later, a part of smokers (N = 28) who were included in the previous “smoking” protocol, were asked to refrain from smoking their first cigarette, in another “nonsmoking” protocol, between the first and the second salivary cortisol sampling.

2.3. Symptom assessment

Based on previous factor analyses of PANSS (Citrome et al., 2011; Emsley et al., 2003; Murri et al., 2012), symptoms were assessed using the PANSS total and PANSS subscale scores.

2.4. Cortisol assessment

Since cortisol levels depend on the time of sampling and cortisol has its peak, i.e. CAR, 30–40 min after awakening (Girshkin et al., 2016; Stalder et al., 2016), morning salivary cortisol levels (μmol/l) were determined in schizophrenic inpatients 90–120 min after awakening. Awakening time for all inpatients was between 06.00 and 06.15 AM. To avoid CAR, saliva sampling started at 08.00 AM after fasting overnight. Patients were asked to refrain from breakfast, coffee, tea, smoking, brushing their teeth, taking medication, or doing exercises before collecting salivary samples. Subjects were allowed to drink only plain water during the protocol, but not just before the salivary cortisol collections. Procedure started by measuring the patients' heart rate and taking the first saliva sample at 08.00 AM using Salimetrics oral swab storage tubes (Salimetrics Europe Ltd.) according to manufacturer's instructions (2 min under the tongue). Samples were immediately refrigerated at 4 °C and later stored at − 20 °C. Second saliva sample (at about 09.00 AM) was scheduled 45–50 min after smoking, or 55–60 min after the first salivary sample for non-smokers. During this period smokers completed the FTND. Non-smokers rested between the first and the second saliva sampling.

Salivary cortisol levels were measured using Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics Europe Ltd.), according to the manufacturer's instructions. Detection was based on a reaction between cortisol conjugated horseradish peroxidase enzyme and tetramethylbenzidine as a substrate. The optical density was read on a standard plate reader at 450 nm. All samples were run in duplicates. Samples from an individual patient (sampled at 08.00 and 09.00 AM) were analyzed within the same run. Coefficient of variation (CV) was 7.7%, and an inter-assay CV was 13.6%.

Salivary cortisol data were divided according to treatment with typical vs. atypical antipsychotics alone or in combination with benzodiazepines, or according to chlorpromazine equivalent doses.