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Aldosterone and aldosterone/cortisol ratio is higher in serum of long-term compared to first episode schizophrenia patients: A pilot study

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ABSTRACT

We have previously shown that patients with severe depressive episode exhibit higher aldosterone concentrations compared to those with moderate depressive episode. The present study was undertaken to test the hypothesis that circulating concentration of aldosterone reflect the clinical state in patients with schizophrenia. The sample consisted of 36 hospitalized patients (25 men, 11 women) with the first episode or long-term course of schizophrenia. The severity of psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS). Samples for measurement of serum aldosterone were obtained immediately after awakening. The results showed that serum aldosterone concentrations were lower in patients with the first episode compared to those in patients with long-term course of schizophrenia. Importantly, lower aldosterone concentrations observed in patients with the first episode were associated with more severe clinical symptoms as indicated by all subscales of PANSS. Serum cortisol concentrations did not differ between the groups, while the aldosterone/cortisol ratio showed similar pattern as aldosterone concentrations. The present pilot study suggests that circulating aldosterone in patients with schizophrenia may reflect the severity of clinical symptoms but in an opposite direction than in patients with major depressive disorder.

1. Introduction

Adrenocortical steroid aldosterone, which was for a long time considered a mineralocorticoid hormone without any actions in the brain, has lately been shown to induce anxiogenic and depressogenic effects in an animal model (Hlavacova and Jezova, 2008a; Hlavacova et al., 2012). Further preclinical studies showed anxiolytic action of the aldosterone antagonist eplerenone (Hlavacova et al., 2010; Hlavacova and Jezova, 2008b). Moreover, aldosterone was found to be an early marker of the development of depression-like behaviour in a treatment-resistant animal model of depression (Franklin et al., 2015).

Only scarce data on aldosterone concentrations in patients with psychiatric disorders are available. Increased plasma aldosterone was reported on small samples of patients with depressive disorders (Murck et al., 2003; Emanuele et al., 2005). The combination of being depressed and living alone was associated with high concentrations of circulating aldosterone (Häfner et al., 2012). To our knowledge, with the exception of a report on lower plasma aldosterone concentrations in 18 chronic schizophrenic patients during abdominal surgery (Kudoh et al., 1998), nothing is known on aldosterone secretion in patients with schizophrenia.

In our previous studies an association between salivary concentrations of aldosterone and treatment outcome in patients with major depression was shown. In particular, a higher aldosterone/cortisol ratio at baseline predicted poor outcome after 6 weeks of treatment (Büttner et al., 2015). On a larger sample of patients with major depressive disorder, we have obtained intriguing data showing association of salivary aldosterone concentrations with clinical state of the patients. We have demonstrated that aldosterone concentrations are higher at the time of admission compared to those at the time of discharge from the hospital and that salivary aldosterone concentrations reflect the duration and severity of the depressive episode (Segeda et al., 2017). The measurement of aldosterone in saliva is a relatively new experimental approach (Hlavacova et al., 2013). Routinely, aldosterone concentrations are analysed in blood plasma or serum.

The present study was undertaken to test the hypothesis that circulating concentrations of aldosterone reflect the clinical state in patients with schizophrenia in terms of positive correlation between aldosterone concentrations and the severity of symptoms. To respect the usual routes of biological fluid sampling at the hospital and to keep the

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Table 1
Patient characteristics.

Group of patients	PANSS-P (score)	PANSS-N (score)	PANSS-G (score)	PANSS-T (score)	Age (years)	BMI (kg/m^2)	Illness duration (months)
First episode (n = 13)	21.5 ± 1.8 ***	23.0 ± 1.8 **	46.7 ± 3.1 ***	91.2 ± 5.9 ***	23.4 ± 1.6 *	21.8 ± 1.4 **	4.1 ± 1.2**
Long-term (n = 23)	12.2 ± 1.4	16.5 ± 1.3	32.6 ± 2.3	61.3 ± 4.4	31.2 ± 2.2	28.1 ± 1.1	61.3 ± 14.4

PANSS = Positive and Negative Syndrome Scale (P-positive scale, N-negative scale, G-general psychopathology scale, T-total). Data are expressed as mean ± SEM. Statistics: ***p < 0.001, **p < 0.01, *p < 0.05 first episode vs. long-term schizophrenia patients.

consistency and reliability, the serum and not saliva samples were analysed. In addition, serum concentrations of cortisol were measured to calculate the aldosterone/cortisol ratios (Franklin et al., 2012; Varga et al., 2013; Büttner et al., 2015). The second hypothesis to be tested was that aldosterone concentrations are higher in patients with the first episode compared to those in patients with long-term schizophrenia.

2. Material and methods

2.1. Participants

The sample included patients that were admitted for schizophrenia (both patients with first episode and other/multiple episode(s) or in partial remission) to the Department of Psychiatry of the Faculty of Medicine of Masaryk University and the University Hospital Brno, Czech Republic. Only those patients that fulfilled the criteria for schizophrenia (F20) according to the International Classification of Diseases, revision 10 (ICD-10) and without other psychiatric comorbidities, such as mood, anxiety and personality disorders, or substance abuse (except of nicotine) were included in the study. Diagnosis was confirmed by two independent experienced psychiatrists from the medical chart review and with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). A total of thirty-six patients of both sexes (n = 25 males, n = 11 females) with mean age of 28.4 ± 1.6 years and BMI 25.8 ± 1.0 kg/m^2 participated in the study. The sample was too small to consider the menstrual cycle phase. Only those patients who were able to sign an informed consent form were admitted to the study. The study was approved by the local ethics committee of the University Hospital Brno, Czech Republic and complies with the requirements of the Declaration of Helsinki.

2.2. Study procedures

The severity of psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS has three subscales including seven-item positive (PANSS-P), a seven-item negative (PANSS-N), and sixteen-item general psychopathology (PANSS-G) subscale for a total of thirty items. The PANSS total (PANSS-T) score is computed by taking the sum of all thirty items.

Samples for measurement of serum aldosterone were taken after at least 8 h of sleep immediately after awakening (around 6 a.m.). Blood was collected from patients in supine position. After centrifugation of blood at 4 °C, the aliquots of serum were stored at −18 °C until analysed. Serum aldosterone concentrations were measured using radioimmunoassay with commercial kit (RIA Aldosterone, Beckman Coulter, Prague, Czech Republic). The analytical sensitivity of the method was 14.8 pg/ml with an intra- and inter-assay coefficient of variation of 5.4% and 7.5%, respectively. Serum cortisol concentrations were measured using chemiluminescent microparticle immunoassay (ARCHITECT Cortisol Reagent Kit, Abbot Diagnostics, Prague, Czech Republic). The analytical sensitivity of the method was ≤0.8 μg/dl with an intra- and inter-assay coefficient of variation of 2.1% and 4.1%, respectively. For technical reasons, 7 values of cortisol concentration were not available.

2.3. Statistics

The values were checked for the normality of distribution using the Shapiro-Wilks test. The statistical analysis of data was performed by two-tailed *t*-test for independent groups with Welch's correction for unequal variance if appropriate (aldosterone concentrations, aldosterone/cortisol ratio). Pearson's correlation was computed to determine relationships between hormone concentr ations and scores in PANSS. Values are expressed as means ± SEM. The overall level of statistical significance was defined as $p < 0.05$.

3. Results

Pearson correlation analysis did not find any significant relationships between aldosterone or cortisol concentrations and clinical symptoms measured by all subscales of PANSS in the whole sample (data not shown). No association between aldosterone concentration and the duration of illness was found. The stratification of patients by sex did not reveal any effect of sex on the relationships between aldosterone concentrations and all subscales of PANSS (data not shown).

Next, the sample was divided, according to the duration of the disorder to the group of first episode patients (n = 13; 9 men, 4 women) and the group of patients with long-term course of schizophrenia (n = 23; 16 men, 7 women). The scores in all PANSS subscales were significantly lower ($p < 0.01$) in long-term schizophrenia patients compared to those in patients with first episode (Table 1). The group of patients differed in the age and BMI with higher age ($t_{34} = -2.44$, $p < 0.05$) and lower BMI ($t_{34} = -3.30$, $p < 0.01$) in long-term than in first episode patients (see Table 2).

Statistical analysis of serum aldosterone showed significantly higher concentrations in long-term schizophrenia patients compared to those in first episode patients ($t_{33} = 2.37$; $p < 0.05$, Fig. 1a). No differences in serum cortisol concentrations were detected between long-term and first episode patients (Fig. 1b). The ratio of aldosterone to cortisol concentrations was significantly higher ($t_{22} = 2.56$; $p < 0.05$, Fig. 1c) in long-term schizophrenia patients than in patients with first episode

Table 2
Antipsychotic medication use in patients with schizophrenia investigated (n = 36).

Medication	Number of patients	
	First-episode	Long-term
Monotherapy antipsychotic		
Aripiprazole		1
Clozapine	1	3
Zuclopentixol		1
Risperidone	7	2
Olanzapine	3	5
Paliperidone		1
Combination of antipsychotics		
Clozapine + Amilsupride		3
Olanzapine + Paliperidone		4
Clozapine + Aripiprazole	1	
Risperidone + Quetiapine	1	
Risperidone + Clozapine		2
Risperidone + Aripiprazole		1