Progress in Neuro-Psychopharmacology & Biological Psychiatry 71 (2016) 183–188

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Mineralocorticoid receptor function in depressed patients and healthy individuals

Kim Hinkelmann [a,b,*], Julian Hellmann-Regen [a], Katja Wingenfeld [a], Linn K. Kuehl [a], Marie Mews [a], Juliane Fleischer [a], Isabella Heuser [a], Christian Otte [a]

[a] Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany
[b] Department of Psychosomatic Medicine, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany

ARTICLE INFO

Article history:
Received 28 April 2016
Received in revised form 28 July 2016
Accepted 4 August 2016
Available online 9 August 2016

Keywords:
Depression
Stress
Cortisol
Mineralocorticoid receptor
Spironolactone
HPA

ABSTRACT

Background: Many studies have shown disturbed glucocorticoid receptor (GR) in depressed patients. In contrast, only few studies targeted mineralocorticoid receptor (MR) function with inconclusive results. We examined the effects of the MR antagonist spironolactone on cortisol secretion in depressed patients and healthy individuals.
Methods: Forty-eight unmedicated depressed patients (mean age 41.6 years) and 45 age- and sex-matched healthy participants (40.7 years) received the MR antagonist spironolactone (300 mg) or placebo with three days apart in a randomized, double-blind, within-subject cross-over design. We measured salivary cortisol before ingestion of study medication (baseline) as well as +60 min, +90 min, +120 min, +150 min and 180 min after baseline.
Results: Repeated-measures ANOVA for area under the curve (AUCg) cortisol revealed a treatment effect with higher cortisol after spironolactone and a treatment by group interaction. Post-hoc analyses revealed higher cortisol in depressed patients compared to healthy participants in the placebo condition. In the spironolactone condition, the cortisol levels were not significantly different.
Conclusions: Potentially, impaired MR or GR signaling could be responsible for higher cortisol levels in depressed patients in the placebo condition. However, after MR blockade that increased cortisol secretion across groups leading to higher GR occupation, we found no differences between depressed patients and healthy controls. Thus, our results argue for depression-associated alterations in MR signaling rather than disturbed GR-mediated feedback inhibition.

1. Introduction

Hypercortisolism and glucocorticoid receptor (GR) dysfunction have repeatedly been described in major depression (de Kloet et al., 2005). Cortisol exerts its effects in the brain via two different nuclear receptors, GR and the mineralocorticoid receptor (MR). While GR are distributed throughout the brain and have a low affinity for cortisol, MR have a high cortisol affinity and are expressed primarily in limbic areas. Both receptors are abundantly expressed in the hippocampus and play a crucial role in the fine-tuning of the Hypothalamus-Pituitary-Adrenal axis (HPA). Specifically, MR seem to exhibit a tonic inhibition on the HPA axis (Harris et al., 2013). Lately, animal and human studies have revealed the existence of a membrane bound MR with an intermediate cortisol affinity mediating rapid non-genomic effects (Joels et al., 2013).

While GR have been studied extensively, an increasing number of studies point towards a crucial role for the MR in the pathophysiology of depression (Chen et al., 2016). Human studies in patients with major depression are scarce though.

Young et al. examined MR function in a small pilot study of depressed patients and healthy participants (n = 12 in each group) during high cortisol concentrations in the morning: Treatment with spironolactone, an MR-antagonist, resulted in a significant increase in cortisol secretion across groups. Furthermore, depressed patients showed higher cortisol values compared to controls across conditions. However, the two groups did not show a clearly distinguishable response pattern after spironolactone compared to placebo (Young et al., 2003). Consistent with these results, we found that depressed patients did not exhibit altered MR-mediated feedback inhibition after fludrocortisone, an MR agonist (Otte et al., 2015).

However, two other small studies specifically addressed MR function with regard to HPA axis in subgroups of depressed patients: Juruena et al. demonstrated that patients with treatment resistant depression showed no cortisol response to an MR antagonist (Juruena et al., 2013) compatible with attenuated MR function in these patients. Furthermore, Lembke et al. found a blunted cortisol response to the MR agonist fludrocortisone in depressed patients with psychotic features — but

* Corresponding author at: Department of Psychosomatic Medicine, Charité University Medical Center, Campus Benjamin Franklin, Berlin, Germany.
E-mail address: kim.hinkelmann@charite.de (K. Hinkelmann).

http://dx.doi.org/10.1016/j.pnpbp.2016.08.003
0278-5846/

not in non-psychotically depressed patients — compared to healthy individuals (Lembke et al., 2013).

Both studies suggest impaired MR receptor function in subgroups of depressed patients (namely psychotic depression and treatment resistant depression).

To further clarify MR function in major depression, we investigated the effect of spironolactone, an MR-antagonist, in a larger sample of medication-free depressed patients and carefully matched healthy controls. We hypothesized that spironolactone treatment would lead to an increase of cortisol secretion in healthy participants, but only to a smaller extent — due to attenuated MR function — in depressed patients.

2. Patients and methods

2.1. Participants

We recruited 48 unmedicated patients with major depression from a specialized depression clinic at the Department of Psychiatry and Psychotherapy, Charité University Medical School, Berlin. Inclusion criteria were a diagnosis of major depressive disorder, single, or recurrent according to DSM-IV criteria with a minimum baseline score of 18 points on the Hamilton Rating Scale for Depression, 17-item version (HDRS-17); and a period of at least 5 days free from antidepressants, antipsychotics, mood stabilizers, and other medications influencing HPA activity. Forty-one percent of the patients referred were first-episode patients. Six patients were depressed despite being on antidepressant medication and went through a 5-day wash out for clinical reasons prior to study entry. No patient was withdrawn from medication solely for study purposes. The patients were tapered off from the following antidepressants (single or a combination): SSRI: n = 5, SSNRI: n = 5, tricyclics: n = 2, low dose quetiapine: n = 2. Furthermore, two patients used low dose quetiapine (100 mg) and one patient lorazepam as night medication for 4 days before the washout phase. All patients were started on treatment immediately after the examination.

Criteria for exclusion were dementia, psychotic symptoms, bipolar disorder, substance dependence within the last 6 months according to the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); serious medical conditions, especially those associated with adrenal dysfunctions, steroid use (**except contraceptives**), or well-known impact on HPA activity; pregnancy and nursing; and fluoxetine medication due to long half-life time.

Forty-five healthy participants matched for age, sex, education and, for women also for cycle phase, were recruited via public posting. Criteria for exclusion were former and present DSM-IV axis I disorders according to the MINI-interview and additionally all exclusion criteria that were applied to the patient group.

The study was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

All participants underwent a screening procedure consisting of a medical and psychiatric history questionnaire (evaluating current lifetime psychiatric diagnosis and medical history, use of medication, alcohol, substance abuse, and smoking), and a routine medical examination. Psychopathology was further assessed with the Beck Depression Inventory (BDI) and MINI Interview. The HDRS-17 as clinical interview was only applied in patients.

2.2. Procedures

As the MR has a higher affinity to cortisol than the GR, the MR is mostly occupied in the morning when cortisol levels are high. Therefore we chose the afternoon for the experiment. Participants ingested three spironolactone (100 mg each) pills (Aldactone 100, Roche Vienna, Austria) or three identical looking placebo pills in a randomized order and a double-blind, cross-over design with three days in between test days. The order of spironolactone and placebo administration was balanced. We measured salivary cortisol before ingestion of study medication at baseline (13:50 h and 14:00) as well as +60 min, +90 min, +120 min, +150 min and 180 min after baseline. All participants received oral and written instructions on the correct use of the Salivette salivary collection device (Sarstedt AG, Nümbrecht, Germany). All samples were taken while study personnel were present.

Blood pressure was assessed at baseline, 16:00 h, and 17:00 h by an automatic device (Carescape V100, GE Healthcare).

2.3. Hormonal assessment

Free salivary cortisol was measured using a commercially available competitive immunoassay (IBL, Hamburg, Germany). 0.9 vol of citric-acid-stimulated saliva samples were neutralized by adding 0.1 vol of neutralization buffer consisting of 2-(4-(2-Hydroxyethyl)-1-piperazinyl)-ethanesulfonic acid (Sigma Aldrich, Taufkirchen, Germany), at 1 mol/l, pH 0. For each sample, sufficient neutralization was considered for pH > 6 and confirmed by measuring the pH using paper pH indicator strips. Standard curves were equally prepared in 0.1 vol of neutralization buffer. Intra- and interassay coefficients of variation were below 10%. The limit of detection was 0.5 ng/ml.

2.4. Statistical analyses

Demographic characteristics between depressed patients and healthy participants were compared using univariate analysis of variance (ANOVA) for continuous variables and chi-square tests for dichotomous variables.

For cortisol values, we calculated the area under the curve with respect to ground (AUCg) (Pruessner et al., 2003) and conducted a repeated-measures ANOVA with treatment (spironolactone vs. placebo) as within subjects factor and group (depressed patients vs. healthy participants) as between subject factor.

3. Results

3.1. Demographic and cortisol data

There were no significant differences between groups on any demographic variable except for depression severity (HDRS-17 mean score of 23 indicating moderate depression severity). Information on demographic variables is given in Table 1.

Four depressed women and five healthy women took oral contraceptives. Five depressed women and three healthy control women were postmenopausal. All other women were matched for cycle phase (14 women were in follicular, 16 in luteal phase). The raw cortisol data are shown in Fig. 1.

Table 1
Demographic variables and psychopathology.

	Patients (N = 48) M (SD)	Controls (N = 45) M (SD)	p^*
Age	41.6 (7.0)	40.7 (7.8)	0.49
Female/male	23/25	24/21	0.53
Education (years)	11.3 (1.5)	11.3 (1.5)	0.98
BMI (SD)	26.2 (8.4)	25.9 (3.4)	0.67
Smoking (y/n)	25/23	17/28	0.15
BDI (SD)	33.3 (10.1)	2.3 (2.8)	<0.01
HAMD (SD)	23.2 (5.7)		
First episode (n)	16		
Episode duration (months)	9.0 (7.5)		
Number of episodes	3.8 (10.4)		

Legend: * based on oneway ANOVA for continuous variables and chi-square for dichotomous variables. Abbreviations: BMI: Body Mass Index, BDI: Beck Depression Inventory, HAMD 17-Item Hamilton Depression Scale.