



Modulation of the mineralocorticoid receptor as add-on treatment in depression: A randomized, double-blind, placebo-controlled proof-of-concept study

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ABSTRACT

Preclinical and clinical studies have suggested a role of the mineralocorticoid receptor (MR) in the response to antidepressants. We tested in a proof-of-concept study whether adding fludrocortisone (an MR agonist) or spironolactone (an MR antagonist) accelerates onset of action and improves efficacy of escitalopram in patients with major depression.

We included 64 in- and outpatients with major depression (Hamilton Depression Scale-17 score > 18) in a double-blind, randomized, placebo-controlled trial. Patients were randomized in a 2:2:1 fashion to fludrocortisone (0.2 mg/d, $n = 24$) or spironolactone (100 mg/d, $n = 27$) or placebo ($n = 13$) for the first 3 weeks during a 5-week treatment with escitalopram.

No differences in mean HAMD change scores and in time to response emerged between treatments. However, among the responders, patients treated with fludrocortisone responded faster (Breslow test, $p = 0.05$). The mean number of days to response was 16.0 ± 2.6 days vs. placebo 22.2 ± 2.0 vs. spironolactone 22.6 ± 2.3 ($F = 3.78$, $p = 0.03$). In the whole group, plasma cortisol increased during spironolactone and decreased during fludrocortisone treatment ($F = 2.4$, $p = 0.04$). In patients treated with fludrocortisone, non-responders had elevated cortisol values compared to responders throughout the study period ($F = 5.1$, $p = 0.04$).

Stimulation of MR with fludrocortisone as adjunct to escitalopram accelerated the response in the group of responders while no effect emerged in the sample as a whole. A larger randomized controlled trial is warranted.

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1. Introduction

Depression has been identified by the World Health Organization (WHO) as one of the top 10 health problems worldwide in 2007 (WHO, 2007). Despite advances in the treatment of depression, insufficient response to antidepressants and their delayed onset of action still represent major therapeutic obstacles (Nemeroff and Owens, 2002). Therefore, there is an urgent need to develop therapies that act faster and improve response and remission (Insel and Charney, 2003; NIMH, 2003). Accordingly, a recent consensus meeting called for more early-stage, well-designed proof-of-concept studies (Gelenberg et al., 2008).

Most of today's antidepressants elicit their effects through monoaminergic mechanisms. However, evidence suggests that in-

creased activity of the hypothalamus–pituitary–adrenal (HPA) axis leading to elevated cortisol is involved in the pathophysiology of depression rendering the HPA axis a plausible target for novel antidepressive medication (Nemeroff and Owens, 2002; Holsboer and Ising, 2008; Pariante and Lightman, 2008; Schatzberg and Lindley, 2008). Accordingly, several studies have examined whether targeting the HPA axis might exert antidepressive effects. Main strategies involved (1) glucocorticoid receptor (GR) antagonists, such as mifepristone (Belanoff et al., 2002; DeBattista et al., 2006), (2) antagonists of Corticotropin-Releasing Hormone (CRH) (Zobel et al., 2000; Binneman et al., 2008; Holsboer and Ising, 2008), or (3) steroid synthesis inhibitors, such as metyrapone (Jahn et al., 2004) or ketoconazole (Wolkowitz et al., 1999). However, these trials have yielded equivocal results with regard to efficacy. For example, a recent study found that a CRH antagonist was less efficacious than sertraline (Binneman et al., 2008). A recent Cochrane review summarized these findings and concluded that targeting the HPA axis in the treatment of depression is at the proof-of-concept stage and warrants further investigation to establish clinical utility (Gallagher et al., 2008).

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Cortisol, the effector hormone of the HPA axis in humans, exerts its action via two different receptor systems: mineralocorticoid receptors (MR) are restricted in anatomical localization and mainly located in the hippocampus, while GR are expressed throughout the brain (de Kloet et al., 2005). There is preclinical and clinical evidence that MR are involved in the pathophysiology of depression, making them also an interesting target for new antidepressant treatment options (de Kloet et al., 2005; Kellner and Wiedemann, 2008).

Clinical studies examining MR function in depression revealed equivocal results. Some studies point to a diminished MR function in depression. Depressed patients who committed suicide showed decreased MR expression in hippocampus and prefrontal cortex (Lopez et al., 1998, 2003). Furthermore, preliminary data suggested that adding the MR antagonist spironolactone for the first 10 days of treatment diminished the antidepressive effects of amitriptyline after 3 weeks (Holsboer, 1999). Finally, animal studies demonstrated that antidepressants upregulate central MR (Brady et al., 1991; Seckl and Fink, 1992; Reul et al., 1993; Barden et al., 1995; Yau et al., 1995; Yau et al., 2002). All of these studies would suggest that stimulating MR function might be a promising approach to improve antidepressant treatment.

On the other hand, there are also studies that suggest an increased MR function in depression (Young et al., 2003), up-regulated MR gene expression in the hypothalamus of depressed patients (Wang et al., 2008), down-regulation of hippocampal MR in response to antidepressants (Yau et al., 2001), anxiolytic effects of blocking MR in animals (Korte et al., 1995; Smythe et al., 1997; Bitran et al., 1998), and anxiogenic effects of the MR agonist aldosterone (Hlavacova and Jezova, 2008). Furthermore, spironolactone improved mood in premenstrual syndrome (O'Brien et al., 1979; Wang et al., 1995), in bulimia nervosa (Wernze, 2000), and reduced residual symptoms in euthymic patients with bipolar disorder (Jurueña et al., 2008). These studies suggest that blocking MR might be more promising from a therapeutic perspective.

Given the rationale that derived from previous studies for both stimulating and blocking the MR, we examined in a proof-of-concept study whether adding spironolactone (an MR antagonist) or fludrocortisone (an MR agonist) to escitalopram, a standard selective serotonin reuptake inhibitor, induces a more rapid and efficacious treatment response in patients with major depression.

2. Methods

The aim of this study was to examine whether the adjunctive treatment with an MR agonist (fludrocortisone) or an MR antagonist (spironolactone) accelerates onset of action and improves efficacy of escitalopram. Thus, each patient received escitalopram and was in addition randomized to fludrocortisone, spironolactone, or placebo for the first 3 weeks of treatment. The study was registered at <http://www.clinicaltrials.gov>, reference number NCT00295347 and has been carried out in accordance with the Declaration of Helsinki.

2.1. Participants

A total of 186 patients referred within a 3-year period from January 2005 to May 2008 to a specialized depression clinic at the University Hospital Hamburg met *DSM-IV* diagnostic criteria for major depressive disorder according to assessments by two experienced psychiatrists (CO and KH). A total of 64 patients gave informed consent and were included in the trial (Fig. 1). Inclusion criteria were (1) a diagnosis of major depressive disorder, single or recurrent according to *DSM-IV* criteria 3); (2) a minimum baseline score of 18 points on the Hamilton Rating Scale for Depression,

17-item version (HAMD-17); (3) age from 18 to 70 years; (4) at least 5 days free from antidepressants, antipsychotics, mood stabilizers, and other medications influencing HPA activity, and (5) no treatment with fluoxetine or injectable antipsychotics for at least 30 days. Criteria for exclusion were (1) dementia, schizophrenia or schizoaffective disorder, bipolar disorder, substance dependence < 6 months, (2) serious medical conditions, especially those associated with adrenal insufficiency; steroid use or well-known impact on HPA activity, (3) pregnancy, nursing, or not using a reliable method of birth control, and (4) any contraindication for fludrocortisone, spironolactone, or escitalopram.

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

2.2. Procedures and medication

Following baseline assessments, 64 subjects who met inclusion criteria entered a 3-week, double-blind treatment period with either spironolactone (50 mg given orally two times a day = 100 mg/d) or fludrocortisone (0.1 mg given orally two times a day = 0.2 mg/d), or placebo (two times a day) at 8:00 h and 20:00 h. In addition, standard antidepressant treatment with escitalopram was started in parallel with a fixed dose (10 mg/d) for the first week and could then be increased during the following weeks.

After day 21, patients continued to take escitalopram, but fludrocortisone, spironolactone, or placebo medication was stopped. The study period ended after 5 weeks to ensure that possible discontinuation effects would be captured. Fludrocortisone and spironolactone were capsuled, and identical placebo capsules were produced. The concomitant use of lorazepam and/or zolpidem/zopiclone was allowed throughout the study period, whereas any use of antipsychotics or mood stabilizers was not permitted. Allocation codes were provided in sealed envelopes for each patient at the pharmacy of University Hospital Hamburg, where formulation and blinding were conducted. The randomization was organized using the PLAN procedure from the SAS/STAT software (SAS Institute Inc., Cary, NC). Randomization was stratified for sex.

2.3. Scales

We assessed several sociodemographic and illness-related variables at baseline (Table 1). Psychopathology was assessed weekly at days 0, 7, 14, 21, 28, and 35. We used the Hamilton Depression Rating Scale (HAMD-17) and the Beck Depression Inventory (revised 21-item version) to measure severity of depression. Adverse effects were assessed by a German adaptation of the Udvalg for Kliniske Undersøgelser (UKU) side effect scale. All clinical interviews were conducted by two authors (CO and KH).

2.4. Laboratory parameters

Blood samples for clinical chemistry and endocrine parameters (cortisol and aldosterone) were collected on days 0, 7, 14, 21, 28, and 35. All blood samples were taken between 8:00 and 11:00 h. We measured plasma levels of escitalopram during the steady-state phase (day 14). Endocrine parameters were determined by commercial radioimmunoassay with coated tube techniques (DRG-Instruments, Marburg, Germany). For both hormones, the interassay coefficient was <9.0% while the intra-assay coefficient was <4.5%.

Escitalopram was determined after automated extraction via column switching by reverse-phase high performance liquid chromatography using UV detection.

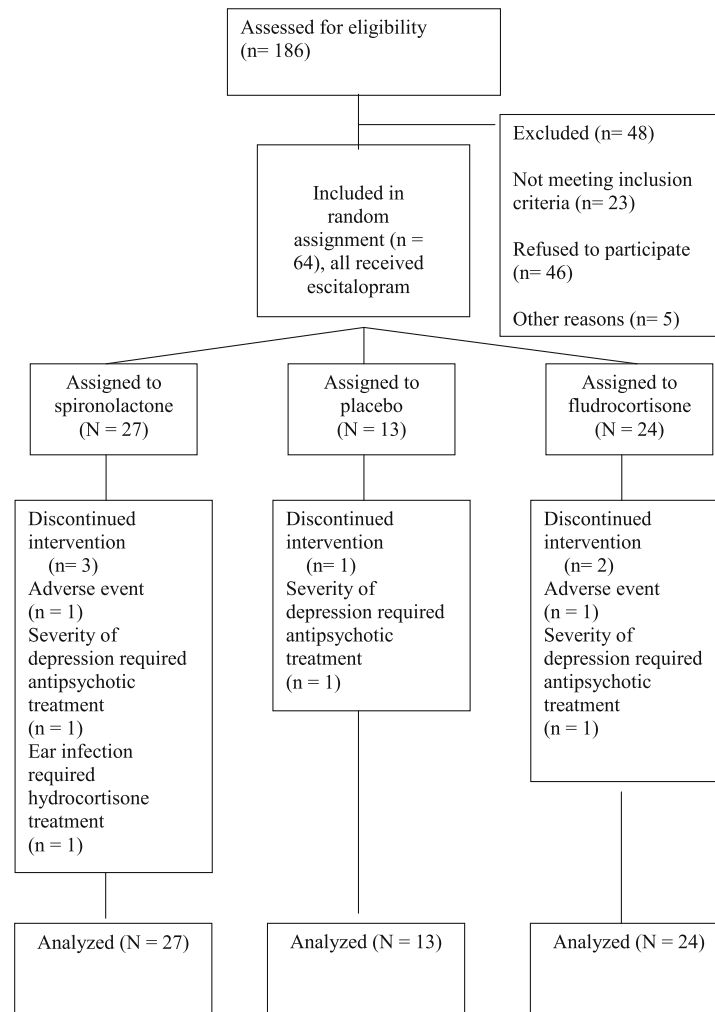


Fig. 1. CONSORT flow chart.

Table 1

Characteristics of participants according to treatment group.

Variable	Fludrocortisone n = 24	Spironolactone n = 27	Placebo n = 13	p-Value
Age, years	36.5 ± 12.7	36.7 ± 10.6	34.5 ± 12.7	.85
Women, %	63	61	64	.99
Smokers, %	68	50	35	.13
Inpatients, %	67	63	75	.95
First episode, %	23	52	50	.07
Previous episodes, mean No.	1.5 ± 1.4	0.6 ± 0.9	0.8 ± 1.2	.03
Positive family history, %	65	63	50	.67
Duration of current episode, months	7.4 ± 5.4	8.0 ± 9.9	5.2 ± 3.3	.50
HAMD	26.0 ± 4.4	27.1 ± 5.2	27.3 ± 4.2	.90
BDI	31.1 ± 9.9	31.2 ± 9.7	30.1 ± 10.4	.86
Escitalopram dosage (mean mg/day 35)	16.4 ± 4.1	14.7 ± 4.5	15.0 ± 4.1	.39
Lorazepam dosage (mean mg/d)	0.18 ± 0.4	0.21 ± 0.2	0.15 ± 0.3	.92
Zolpidem/zopiclon dosage (mean No. tablets/day)	0.33 ± 0.4	0.33 ± 0.3	0.22 ± 0.3	.78

All values given as mean ± SD except otherwise stated. HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, BDI = Beck Depression Inventory.

2.5. Statistical analyses

The sample of 64 patients was estimated to be sufficient to detect equally large effect sizes that we found in our previous study with metyrapone (Jahn et al., 2004) with a power of 80% at an α level of .05. For statistical evaluation of outcome criteria, we used the intention-to-treat sample of 64 patients with the last observation carried forward approach. Differences between treatment groups

in demographic baseline variables or adverse effects were tested by univariate ANOVA or nonparametric tests (Fisher's exact test or median test).

Our a priori primary outcome criteria were the change of mean HAMD scores from baseline to day 21. Multivariate mixed analyses of variance (MANOVA) were applied to test the effects of treatment (between-subject factor) and time (within-subject factor with six levels) on HAMD scores as dependent variables. The time to re-

sponse was our secondary outcome criteria and was analyzed by a Kaplan–Meier survival analysis and embedded Breslow test considering dropouts as censored cases. Time to response was determined in the whole group and in the responders only.

ANCOVA with a repeated measures design was applied to test the effects of treatment (between-subject factor) and time (within-subject factor with six levels) on cortisol and aldosterone as dependent variables. We adjusted our analyses for covariates known to influence HPA activity (sex, age, smoking, and body mass index). In case of significant treatment $\times$ time interactions, we used paired *t*-tests to determine endocrine changes within each treatment group. As a nominal level of significance, $\alpha = .05$ was accepted. Measures are given in mean $\pm$ SD unless otherwise stated.

3. Results

3.1. Study sample

Demographic variables for the three treatment groups are shown in Table 1. Participants receiving fludrocortisone were less likely to have a first depressive episode and had a greater number of previous episodes. No other differences in demographic or baseline variables emerged between groups including inpatient vs. outpatient status (Table 1).

Of the 64 patients randomized, 58 patients completed the trial and six patients dropped out (Fig. 1).

3.2. Psychopathology

There were no significant baseline differences in severity of depression between treatment groups (Table 1).

In the whole group, MANOVA revealed a significant effect of time ($F = 21.3$, $p < 0.01$) indicating improvement across treatment groups. However, no significant main effect of treatment or time $\times$ treatment interaction emerged on HAMD or BDI values (Table 2).

Survival analysis (Fig. 2a) revealed no differences between treatment groups in the whole sample. However, among the responders ($n = 41$), survival analysis demonstrated that patients treated with fludrocortisone responded faster (Breslow test, $p = 0.05$, Fig. 2b). Patients treated with fludrocortisone responded 6 days earlier than patients treated with placebo or spironolactone ($F = 3.8$, $p = 0.03$, Fig. 3).

Because participants randomized to fludrocortisone were less likely to have a first episode and had more previous depressive episodes, we repeated the analyses adjusting for these variables but this did not change results.

3.3. Endocrinology

Repeated-measures ANCOVA adjusted for age, sex, smoking, and body mass index revealed no main effect of treatment on cortisol values but a time $\times$ treatment interaction ($F = 2.4$, $p = 0.04$). Plasma cortisol declined during fludrocortisone treatment and increased during spironolactone treatment (Fig. 4a). Within the fludrocortisone group, cortisol declined from 261 ± 126 ng/ml at

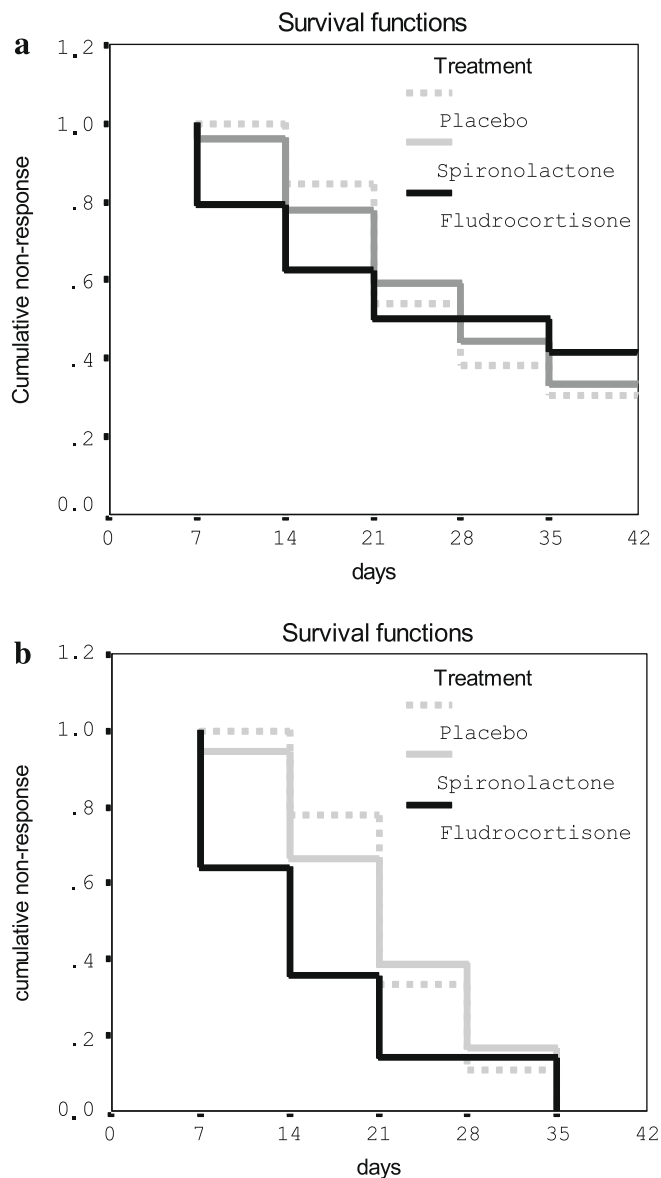


Fig. 2. (a) All patients, (b) Responders. Cumulative non-response rate, response = $>50\%$ improvement in HAMD baseline score; add-on treatment was given between day 1 and 21.

baseline to 213 ± 108 ng/ml at day 21 (paired *t*-test, $p = 0.01$). The decline in cortisol was not correlated with mean changes in HAMD scores. However, in the fludrocortisone group, responders had lower cortisol levels compared to non-responders throughout the study period (Fig. 4b, $F = 5.1$, $p = 0.04$). In contrast, initial severity of depression was not different between responders and non-responders (HAMD-17 baseline score: responder 26.1 ± 4.6 vs. non-responder 27.5 ± 4.7 , $p = \text{n.s.}$) (Fig. 5).

For plasma aldosterone, rm-ANCOVA demonstrated a main effect of treatment ($F = 15.1$, $p < 0.01$) and a significant treat-

Table 2
HAMD and BDI according to treatment.

Treatment group	HAMD D 0	HAMD D 21	HAMD D 35	BDI D 0	BDI D 21	BDI D 35
Fludrocortisone	26.0 $\pm$ 4.4	15.3 $\pm$ 8.8	13.1 $\pm$ 9.6	31.1 $\pm$ 9.9	18.0 $\pm$ 10.7	18.5 $\pm$ 13.5
Spironolactone	27.1 $\pm$ 5.2	15.8 $\pm$ 6.9	12.6 $\pm$ 7.6	31.2 $\pm$ 9.7	19.8 $\pm$ 14.2	17.3 $\pm$ 14.1
Placebo	27.3 $\pm$ 4.2	13.3 $\pm$ 7.7	14.4 $\pm$ 7.7	30.1 $\pm$ 9.8	18.3 $\pm$ 9.1	15.9 $\pm$ 6.4

All values given as mean $\pm$ SD. HAMD = Hamilton Depression Rating Scale, BDI = Beck Depression Inventory.

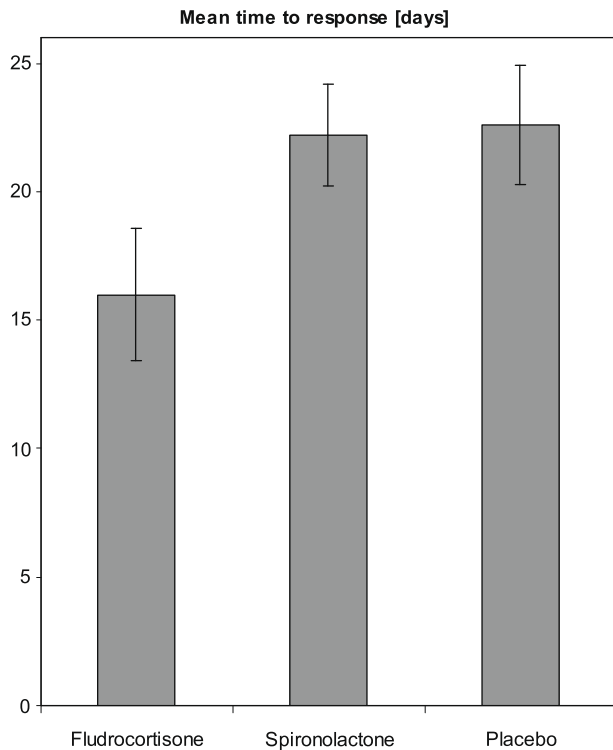


Fig. 3. Difference between treatment groups in ANOVA: $F = 3.8$, $p = 0.03$ among the responders.

ment $\times$ time interaction ($F = 4.8$, $p < 0.01$) indicating that aldosterone was largely increased during spironolactone treatment.

3.4. Tolerability

The study medication was well tolerated, and no serious adverse effects occurred. No differences emerged between treatment groups on any adverse event including nausea, abdominal discomfort, headaches, drowsiness, somnolence, insomnia, agitation, sweating, and dry mouth (all p -values $> .15$). We did not observe any alterations in general clinical chemistry parameters. We monitored sodium and potassium levels weekly throughout the study period, no significant effects of treatment or time $\times$ treatment interactions emerged between treatment groups.

3.5. Compliance and comedication

In all patients, escitalopram levels were detected in plasma collected on day 14 indicating that each patient took the medication as prescribed. Mean escitalopram levels were $18.3 \text{ ng/ml} \pm 13.3$ without differences between the three treatment groups (ANOVA, $p > 0.1$). Furthermore, there was no difference in mean escitalopram dosage at any time point during the 5 weeks (all p -values > 0.3). Mean escitalopram dosage after 5 weeks is shown in Table 1. Finally, no between-group differences emerged for lorazepam or zolpidem/zopiclone use (Table 1).

4. Discussion

We found that in depressed patients treated with escitalopram, adding fludrocortisone accelerated the treatment response by 6 days in the group of responders. However, no effects emerged on mean HAMD change scores and time to response in the group as a whole. Plasma cortisol concentrations increased during spiro-

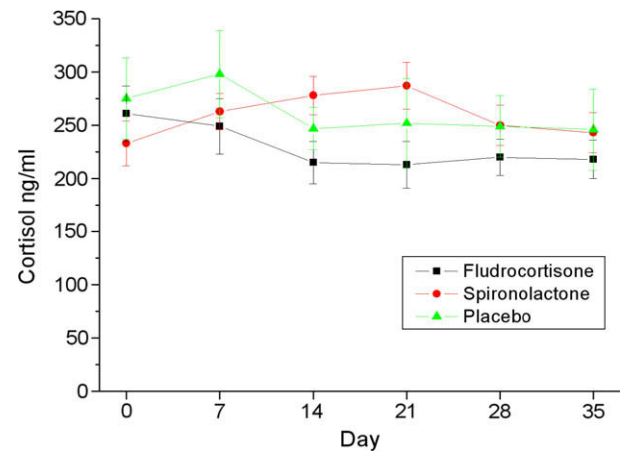


Fig. 4a. Mean values of plasma cortisol during the treatment period of 5 weeks; add-on treatment was given between day 1 and 21. Repeated-measures ANCOVA adjusted for age, sex, smoking, and body mass index: time $\times$ treatment interaction, $F = 2.4$, $p = 0.04$.

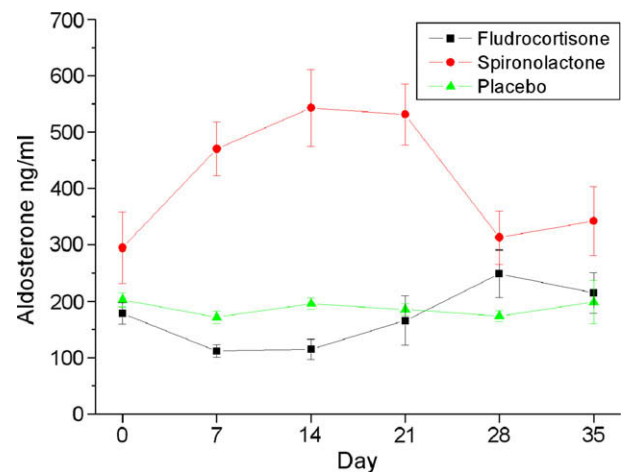


Fig. 4b. Mean values of plasma aldosterone during the treatment period of 5 weeks; add-on treatment was given between day 1 and 21. Repeated-measures ANCOVA adjusted for age, sex, smoking, and body mass index: time $\times$ treatment interaction, $F = 2.4$, $p = 0.04$.

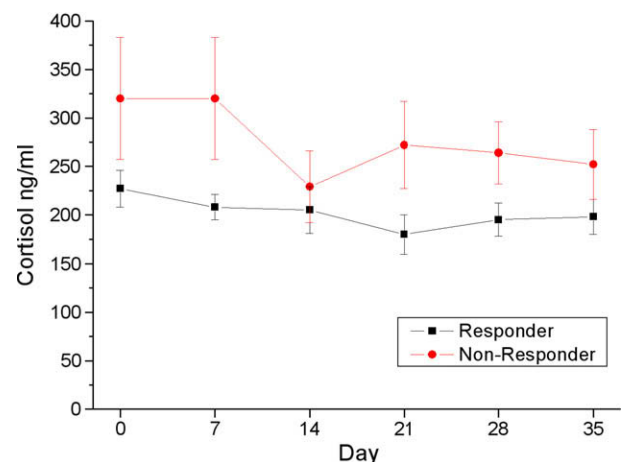


Fig. 5. Plasma cortisol in responders and non-responders within the fludrocortisone treatment group. Repeated-measures ANOVA: group effect $F = 5.1$, $p = 0.04$.

nolactone and decreased during fludrocortisone treatment. All treatments were well tolerated without serious adverse effects.

Our findings suggest that stimulation of MR accelerates the antidepressive effects of SSRI, at least in those patients who respond to antidepressant treatment. This, in turn, might have important consequences for public health. An earlier response to antidepressants is crucial in order to reduce mortality due to suicide, personal suffering, social sequelae as well as mental health care costs. In Germany, an ever-increasing number of patients are treated in psychiatric hospitals for depressive episodes or recurrent depression (year 2000: $n = 110,000$; year 2006, $n = 178,000$), while there is only a moderate decline in length of duration of hospital treatment (year 2000–2006: 38–34 days) (Bundesgesundheitsberichterstattung, 2008). A reduction of only 1 day stayed in hospital corresponds with more than 35 million € savings per year just in Germany. In our study, adding fludrocortisone to standard antidepressant treatment reduced the number of days until response from 22 to 16 among those patients who did respond.

Our results are consistent with other preclinical and clinical studies that explored the role of MR in depression. In preclinical studies, many animal studies have shown that one of the earliest effects of antidepressants is upregulation of MR, especially in the hippocampus (Brady et al., 1991; Seckl and Fink, 1992; Reul et al., 1993; Barden et al., 1995; Yau et al., 1995, 2002). Furthermore, predominant MR activation in adrenalectomized mice led to decreased anxiety and arousal (Brinks et al., 2007) while two studies demonstrated that transgenic mice overexpressing MR in the forebrain displayed decreased anxiety (Lai et al., 2007; Rozeboom et al., 2007). These findings are compatible with the idea that increased MR signalling, either through direct stimulation as in our study or due to up-regulated MR (Seckl and Fink, 1992; Yau et al., 1995) might accelerate antidepressant effects. It is possible that stimulation of MR restores a MR/GR dysbalance that has been hypothesized to be involved in the pathogenesis of depression (deKloet et al., 2007).

In clinical populations, the importance of MR in depression is supported by recent findings that polymorphisms of the MR gene are associated with depression (Kuningas et al., 2006). Furthermore, MR density is reduced in depressed suicide victims (Lopez et al., 1998), consistent with the idea that stimulating MR might be beneficial in depression. It has also been shown that non-response to multi-modal treatment including cognitive behavioural therapy and antidepressant pharmacotherapy is predicted by impaired MR function, which appeared to be intact in patients responding to treatment (Jurueña et al., 2006, 2009). Earlier studies examining antidepressive effects of HPA axis interventions are also compatible with beneficial effects of MR. Jahn et al. (2004) demonstrated that treatment with metyrapone, a cortisol synthesis inhibitor, in adjunction to standard antidepressant treatment lead to enhanced antidepressive effects. They hypothesized that the antidepressive effects of metyrapone are at least in part mediated by upregulation of MR in the hippocampus. GR antagonists such as mifepristone have demonstrated beneficial effects in psychotic depression (DeBattista et al., 2006) and have also been shown to up-regulate MR in animal studies (Bachmann et al., 2003). Therefore, it is possible that a shift in MR/GR balance towards predominant MR effects after GR antagonism is responsible for the beneficial effects of GR antagonists. Finally, studies have shown antidepressive properties of CRH antagonists (Zobel et al., 2000) although findings are equivocal (Binneman et al., 2008). MR have been shown to restrain CRH activity (Gesing et al., 2001). Therefore, stimulation of MR might dampen CRH activity in depressed patients supporting an accelerated antidepressive response. In summary, all earlier strategies are compatible with an MR-mediated antidepressive effect.

To our knowledge, no study has yet assessed the effects of fludrocortisone in major depression. However, two previous studies failed to show beneficial effects of fludrocortisone as monotherapy on depressive symptoms in patients with chronic fatigue syndrome (Rowe et al., 2001; Blockmans et al., 2003). In our study, we also failed to demonstrate significant effects of fludrocortisone regarding mean changes of HAMD scores from baseline, but demonstrated a significantly shortened time until response in the responders. It is possible, that fludrocortisone acts as an accelerator in a subgroup of patients with major depression but does not improve overall psychopathology over the course of several weeks. We found that within the fludrocortisone group, plasma cortisol was elevated among the non-responders compared to responders. This was not explained by greater initial severity of depression in the non-responders. Fludrocortisone inhibits cortisol secretion in healthy subjects (Otte et al., 2003a,b; Buckley et al., 2007) and we also found cortisol inhibition in the fludrocortisone group. However, in our study, cortisol changes during fludrocortisone treatment were not correlated with changes in psychopathology.

Nevertheless, apart from direct effects on HPA activity, there are additional plausible mechanisms by which stimulation of MR might exert antidepressive effects. MR overexpression in transgenic mice resulted in increased 5-HT_{1A} receptor expression (Rozeboom et al., 2007) which is known to be reduced in depression (Drevets et al., 1999). Therefore, a possible mechanism might be an upregulation of 5-HT_{1A} receptors through stimulated MR. This is plausible because 5-HT_{1A}-receptors and MR are co-expressed in the hippocampus (Joels, 2008). However, to our knowledge there is no study so far, that has directly demonstrated 5-HT_{1A} upregulation through MR activation.

Our findings of beneficial effects of fludrocortisone are compatible with preliminary studies that have demonstrated detrimental effects of spironolactone in antidepressant treatment with amitriptyline (Holsboer, 1999) and impairing effects on cognition in healthy men (Otte et al., 2007). However, there also exist studies that have shown beneficial effects of spironolactone on mood in premenstrual syndrome (O'Brien et al., 1979; Wang et al., 1995), in bulimia nervosa (Wernze, 2000), and on residual symptoms in euthymic patients with bipolar disorder (Jurueña et al., 2008). We did not find any effects of spironolactone compared to placebo on psychopathology but a large increase of aldosterone after spironolactone. Therefore, our study does not support a role of aldosterone in the pathophysiology and treatment of major depression as has been suggested earlier (Murck et al., 2003).

While most of the existing studies in depression are consistent with our findings, some are more difficult to reconcile with our results. Young et al. (2003) found increased MR function in depressed patients compared to healthy controls. However, MR function was measured by plasma ACTH and cortisol responses to spironolactone in both groups. Peripheral endocrine responses might not necessarily reflect central MR function in relevant brain areas such as the hippocampus or prefrontal cortex, those brain areas that show highest MR density. Another level of complexity regarding MR function is added by the recently discovered low-affinity membrane version of the MR in addition to the high-affinity MR in the nucleus (Joels et al., 2008).

Fludrocortisone has some affinity for GR although much lower compared to its affinity to MR (Grossmann et al., 2004). Thus, we cannot exclude that some of the effects exerted by fludrocortisone are in fact mediated by GR. This idea would be compatible with earlier findings that demonstrated acute antidepressant effects of dexamethasone (Arana et al., 1995), a potent GR agonist and of intravenous hydrocortisone that stimulates both GR and MR (DeBattista et al., 2000). It is also possible that a higher dosage of fludrocortisone for a shorter period of time leading to greater GR

effects would have been more successful in accelerating the response.

It appears that HPA alterations in depressed patients depend on the severity and subtype of depression. Several studies demonstrated that increased HPA activity is predominantly found in melancholic and especially psychotic depression (Nelson and Davis, 1997; Posener et al., 2000). In our study, psychotic depression was an exclusion criterion. Further studies should examine if fludrocortisone treatment exerts different effects in the treatment of psychotic depression.

Strengths of our study include the sample of “real-world”, treatment-seeking patients with moderate to severe depression as reflected in HAMD scores and the fact that about two thirds of patients were admitted as inpatients. Also, all ratings were performed by the same two experienced and trained psychiatrists. However, several limitations must also be considered. We had limited power to detect effects above and beyond those of escitalopram, a standard antidepressant that has demonstrated superiority compared to other antidepressants in the treatment of severe depression (Montgomery et al., 2007). This could be one reason why we did not find significant effects on our a priori defined outcome criteria but only in post hoc analyses (survival analysis in the group of responders). Therefore, our results should be considered exploratory or hypothesis generating until they are confirmed in a larger randomized controlled trial. However, given the unmet need for faster and better medications, a recent consensus meeting released a call to action for these smaller and early-stage but well-designed proof-of-concept studies that might inform the design of larger randomized controlled trials (Gelenberg et al., 2008). Given the relatively short duration of the trial, we were not able to examine remission rates, the gold standard in antidepressant research (Keller, 2003). Cortisol and aldosterone were measured at single time points and not continuously over a longer period of time. Still, we were able to demonstrate clear endocrine effects of fludrocortisone and spironolactone. We only determined escitalopram blood levels. Therefore, we cannot be sure that patients were compliant with regard to fludrocortisone and spironolactone. However, the pronounced endocrine changes in cortisol and aldosterone make it less likely that patients did not take the study medication.

In summary, we found that in depressed patients treated with escitalopram, adding fludrocortisone significantly accelerated the treatment response by 6 days in the responders. A larger randomized controlled trial examining the effects of fludrocortisone over a longer period of time in a larger sample of depressed patients is warranted.

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Contributors

CO, KW, and MK designed the study and wrote the protocol. CO and KH treated the study patients. CO, KH, SM, AY, HJ, KW, and MK managed the literature searches and analyses and critically revised the paper. Authors CO, SM and AY LP undertook the statistical analysis, and CO wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Disclosure/Conflict of interest

Dr. Otte is on the speaker's board of GlaxoSmithKline and Servier, received travel grants from Wyeth, and received a honorarium for contributing a review article to a scientific journal from Servier. He also received a peer-reviewed research award “Depression and Anxiety” endowed by Wyeth and a peer-reviewed research award for “Biological Psychiatry” endowed by Essex pharma. Dr. Hinkelmann received a travel grant from Lundbeck. Dr. Moritz received support for conducting a workshop on “metacognitive training for schizophrenia” by Janssen-Cilag who also supported the promotion of this intervention. Dr. Jahn received honoraria and reimbursements for the performance of clinical trials, lectures and travel expenses from Janssen-Cilag, Myriad Pharmaceuticals, Neurochem Inc, Novartis, Merck, Sanofi-Aventis, Servier and Wyeth. In 2005 he received a peer-reviewed research award “Depression and Anxiety” endowed by Wyeth. Dr. Wiedemann served as a consultant to, or has been on the speakers boards of AstraZeneca, Bristol-MyersSquibb, Janssen, Pfizer, Servier and Wyeth. Dr. Kellner received funding for investigator initiated trials by Lundbeck and Pfizer. He is a member of an advisory board for Wyeth. He received support for congress attendance by Pfizer, AstraZeneca, and Servier.

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References

- Arana GW, Santos AB, Laraia MT, McLeod-Bryant S, Beale MD, Rames LJ, et al. Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. *American Journal of Psychiatry* 1995;152:265–7.
- Bachmann CG, Linthorst ACE, Holsboer F, Reul JMHM. Effect of chronic administration of selective glucocorticoid receptor antagonists on the rat hypothalamic–pituitary–adrenocortical axis. *Neuropsychopharmacology* 2003;28:1056.
- Barden N, Reul JM, Holsboer F. Do antidepressants stabilize mood through actions on the hypothalamic–pituitary–adrenocortical system? *Trends in Neurosciences* 1995;18:6–11.
- Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C, et al. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biological Psychiatry* 2002;52:386–92.
- Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. *American Journal of Psychiatry* 2008;165:617–20.
- Bitran D, Shiekh M, Dowd JA, Dugan MM, Renda P. Corticosterone is permissive to the anxiolytic effect that results from the blockade of hippocampal mineralocorticoid receptors. *Pharmacology Biochemistry and Behaviour* 1998;60:879–87.
- Blockmans D, Persoons P, Van Houdenhove B, Lejeune M, Bobbaers H. Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. *The American Journal of Medicine* 2003;114:736.
- Brady LS, Whitfield Jr HJ, Fox RJ, Gold PW, Herkenham M. Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. Therapeutic implications. *Journal of Clinical Investigation* 1991;87:831–7.
- Brinks V, vanderMark M, deKloet E, Oitzl MS. Differential MR/GR activation in mice results in emotional states beneficial or impairing for cognition. *Neural Plasticity*, 2007 [Article ID 90163].
- Buckley TM, Mullen BC, Schatzberg AF. The acute effects of a mineralocorticoid receptor (MR) agonist on nocturnal hypothalamic–adrenal–pituitary (HPA) axis activity in healthy controls. *Psychoneuroendocrinology* 2007;32:859–64.
- Bundesgesundheitsberichterstattung, 2008. <<http://www.gbe-bund.de/>>.
- de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience* 2005;6:463–75.

- DeBattista C, Belanoff J, Glass S, Khan A, Horne RL, Blasey C, et al. Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. *Biological Psychiatry* 2006;60:1343–9.
- DeBattista C, Posener JA, Kalebzan BM, Schatzberg AF. Acute antidepressant effects of intravenous hydrocortisone and CRH in depressed patients: a double-blind, placebo-controlled study. *American Journal of Psychiatry* 2000;157:1334–7.
- deKloet E, deRijk R, Meijer O. Therapy Insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nature Clinical Practice Endocrinology and Metabolism* 2007;3:168–79.
- Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al. PET imaging of serotonin 1A receptor binding in depression. *Biological Psychiatry* 1999;46:1375–87.
- Gallagher P, Malik N, Newham J, Young AH, Ferrier IN, Mackin P. Antiglucocorticoid treatments for mood disorders. *Cochrane Database of Systematic Reviews*, 2008, CD005168.
- Gelenberg A, Thase M, Meyer R, Goodwin F, Katz M, Kraemer H, et al. The history and current state of antidepressant clinical trial design: a call to action for proof-of-concept studies. *Journal of Clinical Psychiatry* 2008;69:1513–28.
- Gesing A, Bilang-Bleuel A, Droste SK, Linthorst AC, Holsboer F, Reul JM. Psychological stress increases hippocampal mineralocorticoid receptor levels: involvement of corticotropin-releasing hormone. *Journal of Neurosciences* 2001;21:4822–9.
- Grossmann C, Scholz T, Rochel M, Bumke-Vogt C, Oelkers W, Pfeiffer AF, et al. Transactivation via the human glucocorticoid and mineralocorticoid receptor by therapeutically used steroids in CV-1 cells: a comparison of their glucocorticoid and mineralocorticoid properties. *European Journal of Endocrinology* 2004;151:397–406.
- Hlavacova N, Jezova D. Chronic treatment with the mineralocorticoid hormone aldosterone results in increased anxiety-like behavior. *Hormones and Behaviour* 2008;54:90–7.
- Holsboer F. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. *Journal of Psychiatric Research* 1999;33:181–214.
- Holsboer F, Ising M. Central CRH system in depression and anxiety – evidence from clinical studies with CRH1 receptor antagonists. *European Journal of Pharmacology* 2008;583:350–7.
- Insel TR, Charney DS. Research on major depression: strategies and priorities. *JAMA* 2003;289:3167–8.
- Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Archives of General Psychiatry* 2004;61:1235–44.
- Joels M. Functional actions of corticosteroids in the hippocampus. *European Journal of Pharmacology* 2008;583:312–21.
- Joels M, Karst H, DeRijk R, de Kloet ER. The coming out of the brain mineralocorticoid receptor. *Trends in Neurosciences* 2008;31:1–7.
- Juruena M, Cleare A, Papadopoulos A, Poon L, Lightman S, Pariante C. Different responses to dexamethasone and prednisolone in the same depressed patients. *Psychopharmacology* 2006;189:225.
- Juruena MF, Gama CS, Berk M, Belmonte-de-Abreu PS. Improved stress response in bipolar affective disorder with adjunctive spironolactone (mineralocorticoid receptor antagonist): case series. *Journal of Psychopharmacology* 2008.
- Juruena MF, Pariante CM, Papadopoulos AS, Poon L, Lightman S, Cleare AJ. Prednisolone suppression test in depression: prospective study of the role of HPA axis dysfunction in treatment resistance. *The British Journal of Psychiatry* 2009;194:342–9.
- Keller M. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA* 2003;289:3152–60.
- Kellner M, Wiedemann K. Mineralocorticoid receptors in brain, in health and disease: possibilities for new pharmacotherapy. *European Journal of Pharmacology* 2008;583:372–8.
- Korte SM, de Boer SF, de Kloet ER, Bohus B. Anxiolytic-like effects of selective mineralocorticoid and glucocorticoid antagonists on fear-enhanced behavior in the elevated plus-maze. *Psychoneuroendocrinology* 1995;20:385–94.
- Kuningas M, de Rijk RH, Westendorp RGJ, Jolles J, Eline Slagboom P, van Heemst D. Mental performance in old age dependent on cortisol and genetic variance in the mineralocorticoid and glucocorticoid receptors. *Neuropsychopharmacology* 2006;32:1295.
- Lai M, Horsburgh K, Bae S-E, Carter RN, Stenvers DJ, Fowler JH, et al. Forebrain mineralocorticoid receptor overexpression enhances memory, reduces anxiety and attenuates neuronal loss in cerebral ischaemia. *European Journal of Neuroscience* 2007;25:1832–42.
- Lopez J, Little K, Lopez-Figueroa A, Lopez-Figueroa M, Watson S. Glucocorticoid and mineralocorticoid receptor mRNA levels in the hippocampus and prefrontal cortex of subjects with mood disorders and schizophrenia. *Biological Psychiatry* 2003;53:173S.
- Lopez JF, Chalmers DT, Little KY, Watson SJA.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biological Psychiatry* 1998;43:547–73.
- Montgomery S, Baldwin D, Blier P, Fineberg N, Kasper S, Lader M, et al. Which antidepressants have demonstrated superior efficacy? A review of the evidence. *International Clinical Psychopharmacology* 2007;22:323–9.
- Murck H, Held K, Ziegenbein M, Kunzel H, Koch K, Steiger A. The Renin-Angiotensin-Aldosterone system in patients with depression compared to controls – a sleep-endocrine study. *BMC Psychiatry* 2003;3:15.
- Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis. *American Journal of Psychiatry* 1997;154:1497–503.
- Nemeroff CB, Owens MJ. Treatment of mood disorders. *Nature Neuroscience* 2002;5(Suppl.):1068–70.
- NIMH. Breaking ground, breaking through: the strategic plan for mood disorders research of the National Institute of Mental Health. 2003. <<http://www.nimh.nih.gov/strategic/mooddisorders.pdf>>.
- O'Brien PM, Craven D, Selby C, Symonds EM. Treatment of premenstrual syndrome by spironolactone. *British Journal of Obstetrics and Gynaecology* 1979;86:142–7.
- Otte C, Jahn H, Yassouridis A, Arlt J, Stober N, Maass P, et al. The mineralocorticoid receptor agonist, fludrocortisone, inhibits pituitary-adrenal activity in humans after pre-treatment with metyrapone. *Life Sciences* 2003a;73:1835–45.
- Otte C, Moritz S, Yassouridis A, Koop M, Madrischewski AM, Wiedemann K, et al. Blockade of the mineralocorticoid receptor in healthy men: effects on experimentally induced panic symptoms, stress hormones, and cognition. *Neuropsychopharmacology* 2007;32:232.
- Otte C, Yassouridis A, Jahn H, Maass P, Stober N, Wiedemann K, et al. Mineralocorticoid receptor-mediated inhibition of the hypothalamic-pituitary-adrenal axis in aged humans. *Journal of Gerontology A: Biological Sciences and Medical Sciences* 2003b;58:B900–5.
- Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences* 2008;31:464.
- Posener JA, DeBattista C, Williams GH, Chmura Kraemer H, Kalebzan BM, Schatzberg AF. 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Archives of General Psychiatry* 2000;57:755–60.
- Reul JM, Stec I, Soder M, Holsboer F. Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic-pituitary-adrenocortical system. *Endocrinology* 1993;133:312–20.
- Rowe PC, Calkins H, DeBusk K, McKenzie R, Anand R, Sharma G, et al. Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome: a randomized controlled trial. *JAMA* 2001;285:52–9.
- Rozeboom AM, Akil H, Seasholtz AF. Mineralocorticoid receptor overexpression in forebrain decreases anxiety-like behavior and alters the stress response in mice. *Proceedings of the National Academy of Sciences* 2007;104:4688–93.
- Schatzberg AF, Lindley S. Glucocorticoid antagonists in neuropsychiatric disorders. *European Journal of Pharmacology* 2008;583:358–64.
- Seckl JR, Fink G. Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus in vivo. *Neuroendocrinology* 1992;55:621–6.
- Smythe JW, Murphy D, Timothy C, Costall B. Hippocampal mineralocorticoid, but not glucocorticoid, receptors modulate anxiety-like behavior in rats. *Pharmacology Biochemistry and Behaviour* 1997;56:507–13.
- Wang M, Hammarback S, Lindhe BA, Backstrom T. Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. *Acta Obstetrica et Gynecologica Scandinavica* 1995;74:803–8.
- Wang SS, Kamphuis W, Huitinga I, Zhou JN, Swaab DF. Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: the presence of multiple receptor imbalances. *Molecular Psychiatry* 2008;13:786.
- Wernze H. Überraschende Wirkungen von Spironolacton auf Essverhalten und Befindensparameter bei Bulimie. *Psychopharmakotherapie* 2000;7:33–9.
- WHO. 2007. <http://www.who.int/whosis/whostat2007_10highlights.pdf>.
- Wolkowitz OM, Reus VI, Chan T, Manfredi F, Raum W, Johnson R, et al. Antiglucocorticoid treatment of depression: double-blind ketoconazole. *Biological Psychiatry* 1999;45:1070–4.
- Yau JL, Hibberd C, Noble J, Seckl JR. The effect of chronic fluoxetine treatment on brain corticosteroid receptor mRNA expression and spatial memory in young and aged rats. *Brain Research and Molecular Brain Research* 2002;106:117–23.
- Yau JL, Noble J, Hibberd C, Seckl JR. Short-term administration of fluoxetine and venlafaxine decreases corticosteroid receptor mRNA expression in the rat hippocampus. *Neuroscience Letters* 2001;306:161–4.
- Yau JL, Olsson T, Morris RG, Meaney MJ, Seckl JR. Glucocorticoids, hippocampal corticosteroid receptor gene expression and antidepressant treatment: relationship with spatial learning in young and aged rats. *Neuroscience* 1995;66:571–81.
- Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H. Mineralocorticoid receptor function in major depression. *Archives of General Psychiatry* 2003;60:24–8.
- Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *Journal of Psychiatric Research* 2000;34:171–81.