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*Corresponding author: Anna Lembke, M.D., Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford, CA, 94305; alembke@stanford.edu; phone 650 725-9570, fax 650 724-9900.

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Authors contributions:

Anna Lembke: Study design, data collection, manuscript preparation

Rowena Gomez: Study design, data collection, data analysis, manuscript preparation

Lakshika Tenakoon: Data collection, data analysis

Jennifer Keller: Study design, data collection, data analysis

Gregory Cohen: Data collection, data analysis

Gordon H. Williams: Data collection, manuscript preparation

Fredric B. Kraemer: Data collection, data analysis

Alan F. Schatzberg: Study design, data analysis, manuscript preparation

Intellectual Property

Named inventor on pharmacogenetic use patents on prediction of antidepressant response and glucocorticoid antagonists in psychiatry.

<u>Consultant</u>	<u>Equity</u>
BrainCells	Amnestix
CeNeRx	BrainCells
CNS Response	CeNeRx
Eli Lilly	Corcept (co-founder)
Forest Labs	Delpor
GSK	Forest Labs
Jazz	Merck
Lundbeck	Neurocrine
Merck	Novadel
Neuronetics	Pfizer
Novadel	PharmaNeuroBoost
Novartis	Somaxon
Pathway Diagnostics	Synosia
Pfizer	
PharmaNeuroBoost	
Quintiles	
Sanofi-Aventis	
Sunovion	
Synosia	
Takeda	
Xytis	
Wyeth	

The mineralocorticoid receptor agonist, fludrocortisone, differentially inhibits pituitary-adrenal activity in humans with psychotic major depression

Anna Lembke^{1,*}, Rowena Gomez¹, Lakshika Tenakoon¹, Jennifer Keller¹, Gregory Cohen², Gordon H. Williams³, Fredric B. Kraemer⁴, and Alan F. Schatzberg¹

¹Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

²Mailman School of Public Health, Columbia University

³Harvard Medical School and Brigham and Women's Hospital

⁴Division of Endocrinology, Gerontology and Metabolism, VA Palo Alto Health Care System and Stanford University School of Medicine

Abstract

Introduction—Hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been linked with major depression, particularly psychotic major depression (PMD), with mineralocorticoid receptors (MRs) playing a role in HPA-axis regulation and the pathophysiology of depression. Herein we hypothesize that the MR agonist fludrocortisone differentially inhibits the HPA axis of psychotic major depression subjects (PMDs), non-psychotic major depression subjects (NPMDs), and healthy control subjects (HCs).

Methods—Fourteen PMDs, 16 NPMDs, and 19 HCs were admitted to the Stanford University Hospital General Clinical Research Center. Serum cortisol levels were sampled at baseline and every hour from 18:00 to 23:00 h, when greatest MR activity is expected, on two consecutive nights. On the second afternoon at 16:00 h all subjects were given 0.5 mg fludrocortisone. Mean cortisol levels pre- and post-fludrocortisone and percent change in cortisol levels were computed.

Results—There were no significant group differences for cortisol at baseline: $F(2,47) = .19$, $p = .83$. There were significant group differences for post-fludrocortisone cortisol: $F(2,47) = 5.13$, $p = .01$, which were significantly higher in PMDs compared to HCs ($p = .007$), but not compared to NPMDs ($p = .18$). There were no differences between NPMD's and HC's ($p = .61$). Also, PMDs had a lower percent change from baseline in cortisol levels at 2200 hrs than NPMDs ($p = .01$) or HCs ($p = .009$).

Conclusions—Individuals with psychotic major depression compared to healthy control subjects have diminished feedback inhibition of the hypothalamic-pituitary-adrenal (HPA) axis in response to the mineralocorticoid receptor agonist fludrocortisone. To our knowledge, this is the first study to examine HPA axis response to MR stimulation in major depression (with and without psychosis), and only the third study to demonstrate that exogenously administered fludrocortisone can down-regulate the HPA axis in humans.

Keywords

Mineralocorticoid receptor; HPA axis; Fludrocortisone; Psychotic Major Depression; Cortisol; Hippocampus

1. Introduction

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been linked with major depression, most notably enhanced stimulation by corticotrophin releasing hormone (CRH) and reduced feedback inhibition by endogenous glucocorticoids (GCs). Under normal circumstances, endogenous GCs bind to the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) in the brain, and act as negative regulators of HPA axis activity. Numerous studies have shown that the synthetic glucocorticoid dexamethasone provides potent feedback inhibition of the HPA axis in healthy controls (HCs) by binding to GRs, markedly lowering plasma cortisol levels for up to 24 hours; whereas in individuals with severe forms of major depression, the HPA axis is often only moderately to minimally suppressed by pharmacological stimulation of the GR (Pariante and Lightman 2008).

Psychotic major depression (PMD) is a sub-type of depression characterized by symptoms of depression accompanied by symptoms of psychosis (delusions, hallucinations, formal thought disorders). Evidence suggests that the HPA axis dysregulation in this sub-type is more pronounced. Nelson and Davis found that 64% of study participants with psychotic major depression did not suppress cortisol in response to exogenous dexamethasone, compared to 41% of participants with non-psychotic major depression (NPMD) (Nelson and Davis 1997). When the authors explored other potential factors of non-suppression, including illness severity, melancholia, and hospital status, only the presence or absence of psychosis reliably predicted suppression. Posener et al reported lower cortisol amplitude in non-psychotic major depression, and higher 24-hour mean adrenocorticotrophic hormone (ACTH) levels in PMDs compared to HCs (Posener, DeBattista et al. 2000), suggesting distinct mechanisms of dysregulation for different depression sub-types.

Most of the data linking major depression, and in particular PMD to reduced feedback inhibition by endogenous glucocorticoids, are derived from research on GRs. However, MRs play a vital role in HPA-axis regulation. In the brain, MRs have ten times the affinity of GRs to GCs and are in a key position to mediate basal HPA activity through tonic inhibition, vital to controlling the HPA response to stress (de Kloet, Joels et al. 2005).

MRs, in addition to mediating HPA-axis regulation, have been shown to be involved in other aspects of the pathophysiology of depression and treatment for depression (de Kloet, Joels et al. 2005). Animal studies have reported that antidepressants increase central mineralocorticoid receptors (Brady, Whitfield Jr et al. 1991; Seckl and Fink 1992; Reul, Stec et al. 1993; Barden, Reul et al. 1995; Yau, Hibberd et al. 2002). Young et al showed that individuals with major depression have higher cortisol secretion in response to the MR antagonist spironolactone compared to healthy individuals (Young, Lopez et al. 2003); and Holsboer et al reported that spironolactone decreases the antidepressant efficacy of amitriptyline, a potent antidepressant in persons with major depression (Holsboer 1999). A study of depressed individuals who suicided revealed decreased mineralocorticoid receptor expression in the hippocampus and prefrontal cortex (López, Chalmers et al. 1998). Combining the mineralocorticoid receptor agonist fludrocortisone with the antidepressant escitalopram has been shown to decrease plasma cortisol levels and speed up time to response (Otte, Hinkelmann et al. 2010).

Despite the importance of the MRs to HPA axis regulation, and evidence showing a link between MRs and major depression, we know of no prior studies comparing HPA axis feedback inhibition in response to a mineralocorticoid receptor agonist in patients with major depression, vs healthy controls. Two prior studies, one using metyrapone pre-treatment (Otte, Jahn et al. 2003), and one using fludrocortisone only (Buckley, Mullen et al. 2007), have shown that fludrocortisone is a potent inhibitor of pituitary-adrenal activity in

healthy humans. In a treatment study of participants with major depression using the mineralocorticoid receptor agonist (fludrocortisone) vs the antagonist (spironolactone) as an adjunct to antidepressant treatment (escitalopram), Otte et al showed that fludrocortisone (0.2 mg/d) administered daily for three weeks lowered cortisol levels from baseline compared to placebo and spironolactone (Otte, Hinkelmann et al. 2010). However, this study did not assess HPA axis feedback inhibition, did not compare those with major depression to healthy controls, and did not study sub-types of depression such as PMD.

Given the strong link between psychotic major depression and HPA axis dysregulation, the relative paucity of data on mineralocorticoid receptor-mediated feedback inhibition in major depression, and the recent evidence that fludrocortisone, a mineralocorticoid receptor agonist, suppresses HPA axis activity in healthy humans, we measured hourly cortisol levels during a 5- hour nocturnal window before and after fludrocortisone-treatment, comparing individuals with PMD, with NPMD, and HCs. Based on prior findings in the literature, we hypothesized that participants with PMD would show reduced HPA axis feedback inhibition (i.e. higher post-fludrocortisone plasma cortisol levels) compared to participants with NPMD and HCs.

2. Methods

2.1 Participants

Participants were recruited from outpatient psychiatric clinics at Stanford University and through advertisements in the surrounding communities as part of a larger study about the hypothalamus-pituitary-adrenal (HPA) activity in depression from 2000 to 2011, described elsewhere (Gomez, Fleming et al. 2006). Psychiatrically healthy adult participants had to score less than 6 on the HAM-D and have no current or past Axis I diagnoses as assessed using the SCID. Participants with major depression and psychotic depression had to have diagnosis confirmed by the Structured Clinical Interview for DSM-IV (First and Spitzer 1997), and had to meet minimum standard requirements on mood and/or psychosis rating scales. Minimal depression scores for inclusion were 21 on the 21-item Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960), and 6 on the Thase Endogenomorphic Subscale (Thase, Hersen et al. 1983). Endogenous symptoms of depression refer to those closely linked to a physiological disturbance, such as insomnia, psychomotor retardation/agitation, weight loss, diurnal variation in mood, etc. For the psychotic major depression (PMD) group, the minimal psychosis score for inclusion was 5 on the positive symptom subscale of the Brief Psychiatric Rating Scale (Overall and D 1962). Participants with non-psychotic major depression (NPMD) and participants who were healthy control (HC) subjects had to score no greater than a 4 on the positive symptom subscale (indicating no psychotic symptoms).

Exclusion criteria for all participants were active suicidal behavior, obsessive-compulsive disorder, bipolar disorder, dementia, schizophrenia or schizoaffective disorder, substance abuse or dependence in the past six months, electroconvulsive shock therapy (ECT) in the past six months, major medical illness, history of seizures or head injury, steroid use or use of any substance with well-known impact on HPA activity, pregnancy, lactation, use of estrogen supplements or birth control pills, and younger than 18 years of age. Participants were allowed to continue their psychiatric medications if any, and were required to maintain a stable medication regimen for at least one week before entering the study. The study included 14 participants with psychotic major depression, 17 participants with non-psychotic major depression, and 19 healthy comparison participants.

All participants gave written informed consent and received \$250 for their participation. The protocol for this study was approved by the Stanford University School of Medicine Institutional Review Board.

2.2 Procedures

Eligible participants were admitted to the Stanford University Hospital General Clinical Research Center (GCRC) on Baseline Day 1. At 1600 hours on Baseline Day 1, an open-IV line was inserted and 5 cc's of blood were taken for cortisol levels. The catheter remained in place over the 2-day period. Blood was drawn every hour after that starting from 1800 hours to 2300 hours. At 1500 hours on Day 2, patients were administered 0.5mg (5 matched 0.1mg tablets) of fludrocortisone. Blood samples (five cc's at each time point) were again taken every hour from 1800 hours to 2300 hours. The rationale for studying the 1800 hours to 2300hrs 5-hour time-frame was based on the following: 1.) MR activity relative to GR activity is greatest around the nadir of the HPA axis circadian rhythm (around midnight and just before cortisol levels naturally begin to rise again); 2.) previously published data indicate that fludrocortisone's effect is most pronounced three to six hours after administration (Otte, Jahn et al. 2003); and 3.) in healthy humans, fludrocortisone significantly reduces cortisol levels between 1800 hours to 2300hrs (Otte, Jahn et al. 2003). Also, fludrocortisone in healthy humans significantly reduces cortisol levels between 1800 hours to 2300hrs (Buckley, Mullen et al. 2007). At 2400 hours (midnight), vital signs were assessed and a comprehensive metabolic panel (3 cc's) was completed as a safety measure following fludrocortisone administration. The IV line was removed after the last blood draw.

2.3 Laboratory parameters

The serum samples were kept frozen. The cortisol assays were conducted by the Brigham Women's Hospital, General Clinical Research Laboratory in Boston. Only the cortisol collected hourly from 1800 hours to 2300hrs was used in this study. (See above). The analytic sensitivity for cortisol was 0.4 micograms/dl with a coefficient of variation less than 7.9%.

2.4 Data Analyses

Areas under the curve (AUC) were calculated for each participant's cortisol from 1800hrs to 2300hrs at baseline (Day 1) and post-fludrocortisone (Day 2). Between-subject ANOVAs were conducted to detect any significant group differences in AUC cortisol levels separately for baseline (pre- fludrocortisone) and post fludrocortisone. If a significant effect of clinical group was found, post-hoc Bonferroni corrected pair-wise comparisons were conducted. To control for baseline cortisol, a hierarchical regression was conducted with post fludrocortisone (Day 2) - cortisol as the dependent variable, Baseline (Day 1) cortisol as the covariate entered at Step 1, and the clinical group as the predictor entered at Step 2. Clinical group was 'dummy' coded for the regression. Last as additional analyses, ROC analyses were conducted between clinical groups to determine how well pre and post fludrocortisone cortisol can distinguish between clinical groups.

3. Results

3.1 Study sample

Table 1 provides demographic and psychiatric ratings measures for the sample. While there was no significant difference in age, there was a significant effect of clinical groups in years of education. When post-hoc comparisons were conducted with Bonferroni corrections, no group was significantly different from another ($p > .05$) in years of education. Depression severity as measured by the HDRS was significantly different between groups, with PMD's

having the highest severity, then NPMD's, then HC's. The post-hoc comparisons with Bonferroni corrections indicated that all groups were significantly different from each other ($p < .001$). On the Thase Endogenomorphic Subscale, there was a significant effect of clinical group with PMD's and NPMD's having significantly higher scores than HCs ($p < .001$), but not significantly different from each other ($p = .54$). Lastly, on the BPRS, there was a significant effect of clinical group with PMD's having the highest scores, indicating the worst disease severity, then NPMD's, then HC's. The post-hoc comparisons with Bonferroni corrections indicated that all groups were significantly different from each other on the BPRS ($p < .001$). The results of nine of eighteen healthy participants included in this analysis were previously published in Buckley et al 2007 (Buckley, Mullen et al. 2007).

3.2 Main Analyses

ANOVA analyses indicated that there were no significant group differences on AUC for cortisol at baseline: $F(2,47) = .19$, $p = .83$. There were, however, significant differences for cortisol post fludrocortisone: $F(2,47) = 5.13$, $p = .01$. Pairwise comparisons using Bonferroni correction indicated that in the PMD group, cortisol levels were significantly higher than controls ($p = .007$), but not higher than those in the NPMD group ($p = .18$). There were no differences in cortisol levels between NPMDs and HCs ($p = .61$).

In a hierarchical regression, baseline cortisol accounted for 51% of the variance for post fludrocortisone cortisol at Step 1, $F = 48.96$, $p < .001$. In Step 2, the regression indicated that clinical group significantly explained an additional 14% of the variance, $F = 9.04$, $p = .001$. Thus, there was still an effect of clinical group on post fludrocortisone cortisol, regardless of baseline cortisol levels.

As seen in Figure 2, following fludrocortisone administration, PMDs not only appear to demonstrate less suppression at most time points than the other groups, but also begin to escape from suppression at 2200hrs. ANOVA analyses at the 2200hr time point alone indicated that there were significant differences between the three clinical groups for the 2200hrs ($p = .004$). Pairwise comparisons using Bonferroni corrections for the 2200 hrs cortisol value indicate that in the PMD group, change in cortisol level was significantly lower than for HCs ($p = .009$), or NPMDs ($p = .01$). No significant difference was observed between the NPMDs and controls ($p = 1.0$).

3.3 Additional Analyses

As mentioned earlier, ROC analyses were also conducted on baseline (pre-fludrocortisone) cortisol. Results indicated that the ROC differentiated poorly and close to chance (50% accuracy) for all group comparisons: PMDs and HCs (55.3% accuracy), PMDs and NPMDs (51.3% accuracy), and NPMDs and HCs (53.2% accuracy). ROC analyses were also conducted to determine if post-fludrocortisone cortisol could better discriminate between the clinical groups. Results indicated that the ROC differentiated best between PMDs and HCs (77.1% accuracy), and somewhat less well between PMDs and NPMDs (64.3% accuracy); or between NPMDs and HCs (63.5% accuracy).

4. Discussion

These data demonstrate that individuals with psychotic major depression compared to healthy control subjects have diminished feedback inhibition of the hypothalamic-pituitary adrenal (HPA) axis in response to the MR agonist fludrocortisone. To our knowledge, this is the first study to compare HPA axis response to MR stimulation in major depression (with and without psychosis) with HCs, and only the third study to show that exogenously administered fludrocortisone can down-regulate the HPA axis in humans. Our data further

point to fludrocortisone as exerting an effect without pretreatment with metyrapone (to suppress synthesis), and suggest that MRs in humans are not fully occupied under basal conditions.

Our findings are consistent with prior studies showing impaired feedback inhibition of the HPA axis with exogenously administered dexamethasone (glucocorticoid receptor agonist) in individuals with psychotic major depression compared to healthy controls, as well as the broader literature showing impaired HPA axis dysregulation in individuals with major depression (Pariante and Lightman 2008). The lack of cortisol differences at baseline in contrast to differences in response to fludrocortisone is also consistent with other studies of HPA activity in depression, in which subjects demonstrate more dramatic differences in response to a psychological or pharmacological challenge (Carroll 1982; Heim, Newport et al. 2000). The response of the HPA axis to external challenges may provide better differentiation among groups than baseline ambient or resting measures.. The data reported add to the growing body of evidence which suggests that psychotic major depression exhibits a greater degree of HPA axis malfunction than depression without psychosis, and represents a distinct sub-type of depression with its own characteristics and pathophysiology (Nelson and Davis 1997).

Although fludrocortisone has glucocorticoid receptor activity, its affinity at the mineralocorticoid receptors in rats is approximately 15 times higher, with even greater affinity than the natural hormone aldosterone (Agarwal, Coupry et al. 1977). This finding of increased affinity of fludrocortisone at the MR has not to our knowledge been replicated in humans. Nonetheless, the relative specificity of fludrocortisone for MR binding potentially allows for deeper exploration of the role of MRs in the pathophysiology of depression. To wit, our data suggest that mineralocorticoid receptors in individuals with major depression are fewer and/or less responsive than in healthy controls. This finding supports the idea of an MR/GR imbalance, hypothesized to be physiologically at the root of the depression syndrome (DeRijk and de Kloet 2008). Prior studies in animals and humans have shown that major depression is associated with an overall decrease in MRs in the brain (López, Chalmers et al. 1998), and that treatment with antidepressants leads to an increase in brain MR expression (Brady, Whitfield Jr et al. 1991; Seckl and Fink 1992; Reul, Stec et al. 1993; Barden, Reul et al. 1995; Yau, Hibberd et al. 2002). Alternatively, reduced feedback suppression of the HPA axis with an MR agonist may reflect an inability to overcome increased drive by CRH; however, we did not observe significant differences in baseline values in this sample. This dynamic mirrors earlier debates regarding the relative contributions of drive vs. feedback to increased HPA axis activity in depression. We are currently combining assessment of allelic variations for HPA axis genes and their relationship to activity, to better understand the dysfunction in major depression, particularly in those patients with psychotic features.

The potential involvement of MR in the physiology of major depression, especially psychotic major depression, suggests potential novel pharmacologic strategies in the treatment of depression. Numerous prior studies have targeted the HPA axis in the treatment of depression by means other than MR, for example use of the GR antagonist mifepristone (Belanoff, Rothschild et al. 2002; Debattista, Belanoff et al. 2006), CRH1 antagonists (Zobel, Nickel et al. 2000; Binneman, Feltner et al. 2008; Holsboer and Ising 2008), steroid synthesis inhibitors metyrapone (Jahn, Schick et al. 2004) or ketoconazole (Wolkowitz, Reus et al. 1999), but only one prior study by Otte et al has considered mineralocorticoid receptor modulation as a pathway to depression treatment (Otte, Hinkelmann et al. 2010). They used fludrocortisone as an adjunctive therapy in the treatment of depression, and found that among responders, the addition of fludrocortisone to escitalopram (an antidepressant) sped recovery by almost a week, which is a significant difference when one considers

lifetime morbidity and health cost dollars. Otte et al excluded for psychotic depression, but given our data, one might speculate that individuals with psychotic major depression might have an even more robust response to fludrocortisone adjuvants than those without psychosis. On the other hand, although reasonably well-tolerated in the Otte et al study, fludrocortisone at higher doses may not be a practical long-term treatment due to intolerable side effects such as hypertension. In addition, our results suggest MR agonists produce a less sustained effect in PMD, indicating the need for developing alternative strategies that might combine effects on GRs or in reducing HPA axis drive.

Our findings did not show a difference between psychotic and non-psychotic major depression for the area under the curve, but looking at the percent change in cortisol due to fludrocortisone at specific time points, a significant separation between psychotic and non-psychotic depression is apparent at 2200 hours, when cortisol levels in the psychotic major depression group rise steeply compared to the non-psychotic major depression group. In a clinical setting it can sometimes be difficult differentiating psychotic from non-psychotic major depression, and the difference has important treatment implications, for example to add an antipsychotic to the antidepressant or not. If a chemical probe, such as administration of a onetime dose of fludrocortisone, followed the next day by measurement of cortisol levels, might help in making the distinction between psychotic and non-psychotic major depression, this relatively safe and quick test might help clarify treatment decisions and speed recovery. Further research will be required not only to replicate any differences observed among the clinical groups, but also to determine whether the test could provide sufficient sensitivity and specificity to be useful clinically.

Limitations of our study include the small sample size, and the lack of a placebo control group to assess for possible acclimatization to the research environment on the second day of the experiment. We assume that the observed HPA axis suppression is predominantly due to fludrocortisone binding at MR, but fludrocortisone can bind to GR and that may contribute as well to the HPA axis down-regulation. Indeed it is possible that fludrocortisone effect in this study might be due in part to effects on GR. Our results should be considered exploratory and hypothesis generating until confirmed by a larger trial.

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Figure 1. Mean Serum Cortisol Levels at Baseline and after Fludrocortisone Administration in PMDs, NPMDs, and HCs

Figure 2. Percent Change in Mean Serum Cortisol Levels before and after Fludrocortisone Administration in PMDs, NPMDs, and HCs

Table 1

Demographic Variables & Clinical Characteristics for PMDs, NPMDS, and HCs.

	PMD			NPMDS			HC			F	P
	N	M	(SD)	N	M	(SD)	N	M	(SD)		
Age		37.86	(13.24)		43.88	(13.02)		36.89	(11.53)	1.57	.22
Education		14.71	(2.30)		14.71	(2.30)		16.26	(1.79)	3.20	.05
Gender											
Male	8			9			8				
Female	6			7			11				
HamD total		31.15	(5.34)		23.12	(3.43)		.68	(1.57)	344.38	<.001
BPRS total		46.85	(8.53)		32.18	(4.35)		1.40	(.32)	116.20	<.001

Table 2

ANOVAs Examining Differences in Cortisol by Clinical Groups

	PMD		NPMD		HC		F	p	Partial Eta ²
	M	(SD)	M	(SD)	M	(SD)			
Cortisol Area Under the Curve									
Pre FLU *	26.87	(15.50)	25.03	(12.81)	24.09	(10.81)	.19	.83	.01
Post FLU	16.95	(8.41)	12.74	(5.41)	10.15	(4.22)	5.13	.01	.18
Percent Change in Cortisol									
2200hr	.17	(.28)	.45	(.23)	.45	(.23)	6.22	.004	.21
2300hr	.13	(.25)	.37	(.57)	.30	(.86)	.53	.59	.02

* FLU=fludrocortisone