Mineralocorticoid Receptor Function in Major Depression

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Background: Negative feedback regulation of the hypothalamic-pituitary-adrenal axis occurs through a dual-receptor system of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). Their affinity for cortisol and their distribution in the brain differ. Studies using an MR antagonist have demonstrated that MR is active throughout the circadian rhythm. Because major depression is accompanied by increased glucocorticoid secretion and insensitivity to glucocorticoid feedback, and because glucocorticoids are capable of down-regulating MR and GR, we expected that major depression would be accompanied by decreased MR activity.

Methods: To test this hypothesis, we administered spironolactone, an MR antagonist, to individuals with major depression and matched control subjects and assessed levels of corticotropin and cortisol secretion in response to this acute challenge. Studies were conducted in the morning, the time of peak activation of the hypothalamic-pituitary-adrenal axis. All patients were currently depressed and free of all medications. All controls were free of all psychiatric diagnoses and of all medications.

Results: Spironolactone treatment resulted in a significant increase in cortisol secretion levels in both groups. Depressed patients demonstrated higher cortisol secretion levels than control subjects. In addition, depressed patients demonstrated a different pattern of increase in cortisol secretion levels after spironolactone administration. Furthermore, a significant effect of spironolactone treatment on corticotropin secretion levels can be observed in depressed patients, whereas controls show no such effect.

Conclusions: Despite high baseline cortisol levels, patients with major depression show high functional activity of the MR system. Paired with the body of evidence regarding decreased sensitivity to GR agonists, these data suggest an imbalance in the MR/GR ratio. The balance of MR and GR is known to affect brain serotonin systems and may play an etiologic role in serotonin receptor changes observed in patients with major depression.

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NEGATIVE FEEDBACK regulation of the hypothalamic-pituitary-adrenal (HPA) axis occurs through a dual-receptor system of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR).[1-3] These receptors differ in their affinity for glucocorticoids, with MR demonstrating the highest affinity for cortisol and GR demonstrating lower affinity for cortisol.[1-3] In addition, their distribution in rodent brain differs, with MR predominantly in limbic areas, particularly the hippocampus, and GR more widely distributed across all brain regions[4,5]; in primates, MR is also found in cortex and subcortical structures.[6] Thus, MR is a high-affinity, low-capacity receptor, whereas GR is a low-affinity, high-capacity receptor. A variety of studies[7-9] in animals have documented the importance of MR in stress regulation. Because of the low levels of circulating cortisol in the nadir, MR is believed to be more important in the regulation of HPA axis drive in the evening, the time when depressed patients are most likely to demonstrate increased central drive.[2,3,10-13] However, studies using an MR antagonist in rodents[14] and in humans[15] have demonstrated that MR is active throughout the circadian rhythm and that antagonism results in increased cortisol secretion in both the morning and evening.

Because major depression is accompanied by increased glucocorticoid secretion and insensitivity to dexamethasone, and glucocorticoids are capable of down-regulating MR and GR,[16-21] we expected that major depression would be accompanied by decreased MR activity. Furthermore, postmortem studies[22] on depressed suicide victims have also observed decreased MR messenger RNA in the hip-

pocampus compared with healthy individuals. To test this hypothesis, we administered spironolactone, an MR antagonist, to patients with major depression and matched control subjects and assessed corticotropin and cortisol secretion in response to this acute challenge.

METHODS

PARTICIPANTS

Twelve depressed patients and 12 age- and sex-matched controls were studied. Depressed patients were recruited from patients at the University of Michigan Mood Disorders Program who were seeking treatment for new episodes of depression or in response to advertisements for untreated depressed individuals. Controls were recruited through newspaper advertising. All subjects were medically healthy and had not been treated for the current episode of depression. None were taking psychotropic medications, oral contraceptives, or any other medications, except aspirin or acetaminophen, for more than 3 months before the study. No participants engaged in shift work for more than 3 months before the study. No subject was breastfeeding, pregnant, or within 1 year of childbirth. Findings from screening blood work were within the reference range. Smokers were excluded from the protocol. Results of the urine drug screens were negative for all participants at the time of the study.

All depressed patients underwent a Structured Clinical Interview for *DSM-IV* to confirm the presence of major depressive disorder. Controls underwent the Structured Clinical Interview for *DSM-IV*, nonpatient version. A structured 17-item Hamilton Depression Rating Scale interview was administered by a trained clinician (clinical nurse specialist V.M.-W.) to rate severity of depression.

PROTOCOL

The study consisted of a 2-day protocol with administration of placebo on day 1 and spironolactone (200 mg) on day 2. Participants arrived at the research area between 6:30 and 7 AM, and an intravenous catheter was inserted at that time. Participants were given an hour to adapt before administration of either placebo or spironolactone. Blood samples for corticotropin and cortisol measurement were drawn every 30 minutes between 8 AM and 2 PM. Participants ate a standardized breakfast at 7 AM and then fasted until completion of blood drawing at 2 PM. Blood samples were collected on ice and centrifuged immediately. Corticotropin was assayed using Allegro HS-IRMA (Nichols Lab, San Juan Capistrano, Calif). Cortisol was assayed using DPC Coat-a-Count Assay Kits (Diagnostic Products Corp, Los Angeles, Calif).

DATA ANALYSIS

All hormone data were log transformed before analyses. Data were analyzed using repeated-measures analysis of variance, with treatment (spironolactone vs placebo), group (depressed patients vs control subjects), and time (repeated measures) as factors.

RESULTS

We studied 12 patients with major depression (5 men and 7 women; mean±SD age, 31.6±9.11 years). The 12 age- and sex-matched control subjects had a mean±SD age of 31.5±8.6 years. All patients met the Research Diagnostic Criteria for primary major depressive disorder.

Of patients with major depression, 4 were experiencing their first episode of major depression, 7 were recurrent unipolar, and 1 was bipolar. In 4 patients, dysthymia preceded the onset of major depression. Three patients demonstrated currently active comorbid anxiety disorders, and 3 additional patients had a history of anxiety disorders. Patients with any other Axis I disorders were excluded. The mean±SD Hamilton Depression Rating Scale score for depressed patients was 18.0±4.5.

Cortisol data for depressed patients and matched controls are shown in **Figure 1**. As in a previous study,[15] spironolactone treatment resulted in a significant increase in cortisol secretion ($F_1=7.4$; $P=.009$). As would be expected, there was also a significant effect of time on cortisol secretion, reflecting the normal circadian fall ($F_{12}=13.9$; $P<.001$). Depressed patients demonstrated higher cortisol secretion than control subjects on both days ($F_1=4.0$; $P=.05$ for group). In addition, depressed patients demonstrated a different pattern in response to spironolactone administration, which is an actual increase in cortisol secretion rather than a delay in the circadian fall, as seen in control subjects (significant interaction between group and time, $F_{12}=5.0$; $P<.001$). This is further illustrated by comparing controls and depressed patients on the spironolactone treatment day only, starting at 9 AM, after the circadian fall in both groups, where there is a significant interaction between group and repeated measures ($F_9=1.98$; $P=.04$).

As in a previous study,[15] the effect of spironolactone treatment on corticotropin secretion levels in patients and controls was transient (**Figure 2**). Although in previous studies an effect on corticotropin secretion levels was not observed, an effect was found in this study (interaction between treatment and time, $F_{12}=1.8$; $P=.04$). This effect is predominantly caused by depressed patients because a significant effect of spironolactone treatment on corticotropin secretion levels was observed in depressed patients alone (interaction between time and treatment, $F_{12}=2.0$; $P=.02$), whereas controls showed no such interaction ($F_{12}=0.7$; $P=.7$). We also observed differences in depressed patients and control subjects over time in corticotropin levels, such that overall, depressed patients demonstrated higher corticotropin levels on both days (Figure 2A vs B, $F_{12}=1.97$; $P=.02$ for group).

COMMENT

Because MR and GR participate in HPA axis regulation in depression, we evaluated functional MR tone in patients with major depression and matched control subjects using an MR antagonist (spironolactone). The results of this study indicate that MR is still quite active in patients with major depression, suggesting that MR is still playing an important role in restraining the HPA axis. This high level of MR activity occurs in depressed patients despite the higher cortisol level observed on the placebo day, which would be expected to downregulate MR. In fact, depressed patients demonstrate an increase in cortisol secretion in response to spironolactone treatment, suggesting that MR is functionally more active in depressed patients than in controls. This ob-
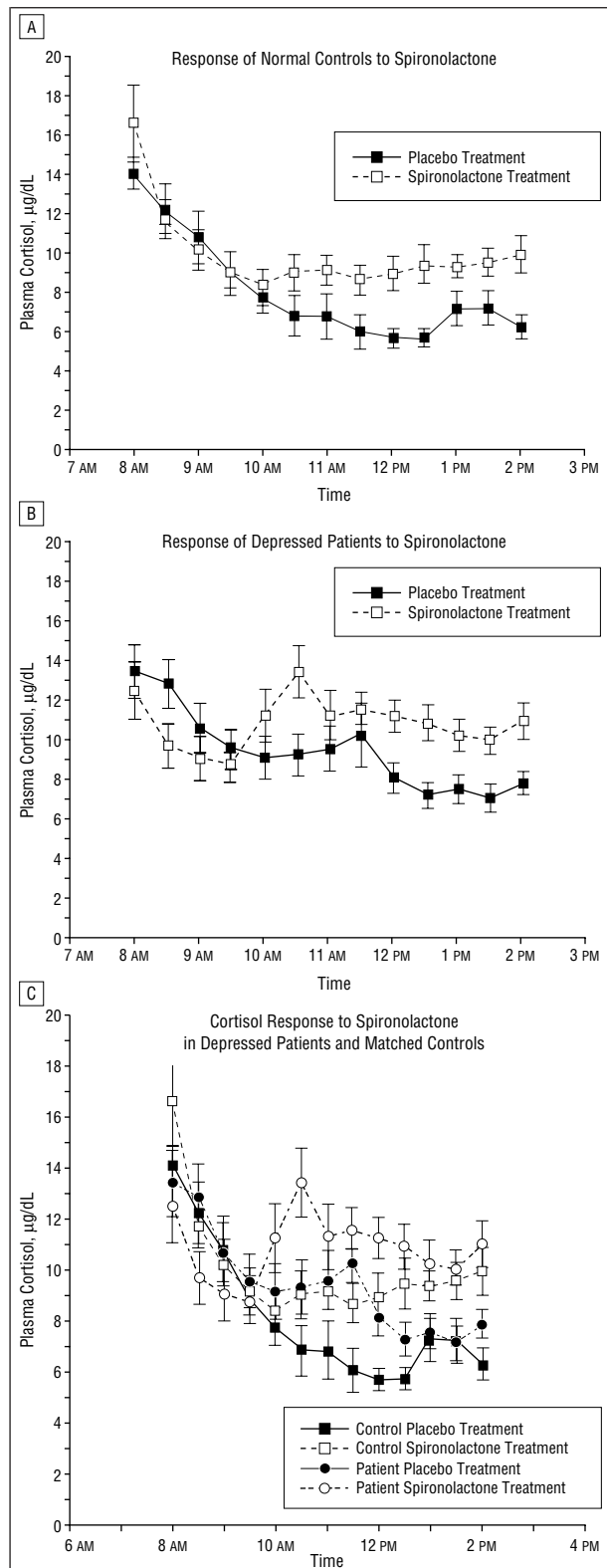
Figure 1. Mean cortisol response to spironolactone treatment in control subjects (A), depressed patients (B), and both (C). Patients demonstrated higher levels of cortisol secretion than controls on the baseline (placebo) and spironolactone days. Despite the already increased cortisol levels, patients responded to spironolactone administration with an increased level in cortisol secretion. In addition, the control response to cortisol secretion is predominantly a delay in the normal circadian decrease in cortisol secretion levels, whereas patients show an actual increase. Error bars represent SD. To convert cortisol from micrograms per deciliter to nanomoles per liter, multiply by 27.59.

servation is confirmed in the corticotropin data. In a previous study[15] on healthy individuals, an effect of spironolactone treatment on corticotropin secretion was not demonstrated, but in the present study, we observed this effect in depressed patients, whereas the effect was still too transient in control subjects to detect statistically. This suggests that depressed patients are more sensitive to MR antagonism, as manifested by the corticotropin and cortisol data, with increased MR activity at baseline. Both groups had increases in levels of cortisol secretion in response to spironolactone therapy, with the highest levels demonstrated in depressed patients after spironolactone administration.

Mineralocorticoid receptors and GR can form heterodimers and thus cooperate in the regulation of genes, and these heterodimers have been demonstrated to be more active than either MR-MR or GR-GR homodimers in some systems.[23] In agreement with these data, we found that antagonism of MR by administration of spironolactone resulted in elevated levels of cortisol secretion in both the morning and evening, despite the presence of cortisol levels in the morning in the middle of the GR range of feedback inhibition. These data suggested that MR and GR are active throughout the day in controls and depressed patients.

The response to spironolactone treatment combined with decreased sensitivity to dexamethasone, a GR agonist, suggests that major depression is accompanied by a shift in MR/GR balance. Because we did not measure GR function, we cannot be sure that decreased GR function is found in these individuals. However, even if GR function was normal, the MR/GR balance would be altered. Although MR and GR are synergistic in their effects on HPA axis inhibition, this was not the case in all systems.[24-28] In fact, the effects of MR and GR can be antagonistic, as has been demonstrated for neuronal excitability in the hippocampus.[26] Furthermore, other studies[26] have demonstrated that acute activation of MR lowers serotonin (5-HT) release and turnover and reduces 5-HT–mediated responses in the hippocampus. After MR downregulation, $5-HT_{1A}$ receptor–mediated hyperpolarization is decreased.[27] In contrast, high levels of glucocorticoids trigger GR-stimulated serotonin transmission and lead to increased 5-HT responses.[26]

In addition to the differential effect in 5-HT turnover and transmission, MR and GR have differential effects in 5-HT receptor expression. The MR seems to be the primary mediator of 5-HT1A down-regulation observed after chronic stress or elevated glucocorticoid levels,[27,28] whereas GR is the primary receptor involved in the $5-HT_{2A}$ increases after stress and exogenous glucocorticoid administration.[29-32] Major depression is accompanied by down-regulation of 5-HT1A receptors and messenger RNA in the brain and lymphocytes, as seen in postmortem studies[24,33] or in vivo imaging,[34,35] and increased 5-HT2A binding.[36-38] Thus, the increased MR activity demonstrated in this study would be expected to lead to 5-HT1A down-regulation.

Furthermore, these 2 serotonin receptors are targets for antidepressant action, particularly tricyclic antidepressants. Rodent studies[39] have shown that long-term antidepressant drug administration results in
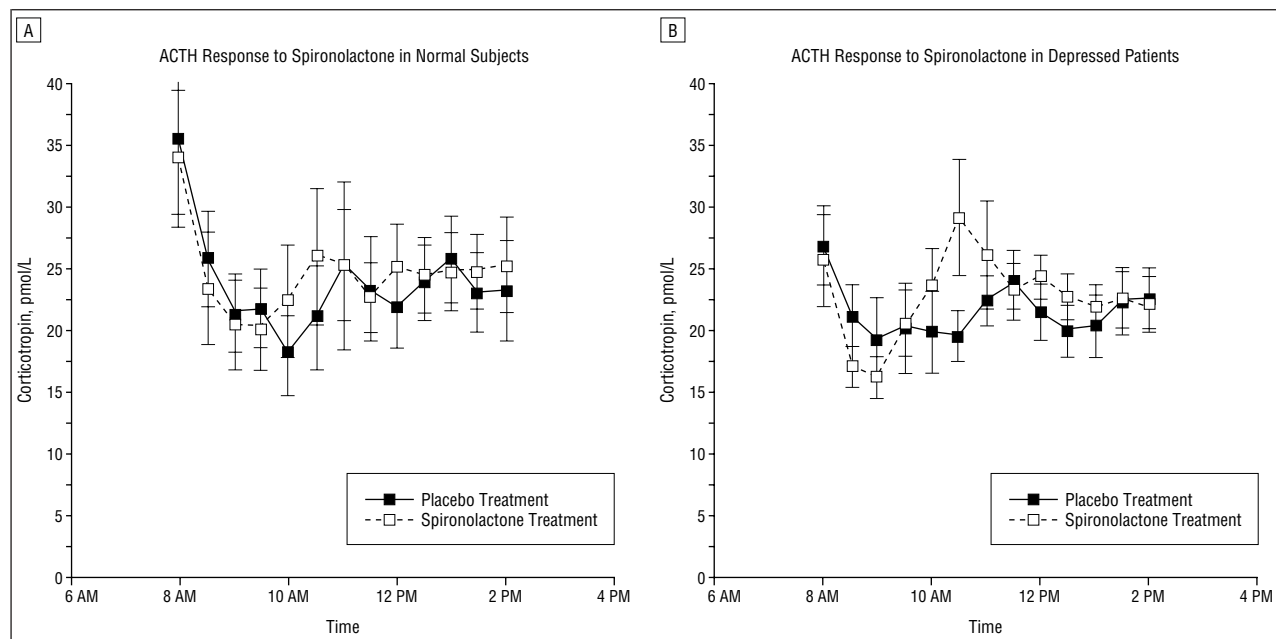
Figure 2. Corticotropin response to spironolactone treatment in control subjects (A) and depressed patients (B). As in previous studies, no effect of spironolactone use on corticotropin secretion levels was observed in control subjects. However, patients demonstrated a significant increase in corticotropin secretion levels in response to spironolactone treatment, indicating normal to increased mineralocorticoid receptor tone in depressed patients despite the elevated baseline value. Error bars represent SD. To convert corticotropin from picograms per milliliter to picomoles per liter, multiply by 0.22.

functional "up-regulation" of the postsynaptic 5-HT1A receptor in the hippocampus. Some studies have also reported a modest increase in 5-HT1A receptor numbers in the hippocampus after antidepressant drug administration to rodents.[40,41] Studies[42] have reported decreases in 5-HT2A binding in the prefrontal cortex after long-term antidepressant administration. These findings have led some investigators to propose that postsynaptic 5-HT1A and 5-HT2A receptors have functionally opposing effects,[43] that a disturbed balance of these receptors may be contributing to the pathophysiology of depression,[44] and that restoring this balance is necessary for antidepressant action.[45] Consequently, the increased functional activity of MR found in major depression suggests that even high levels of glucocorticoids are not engaging compensatory changes to buffer the MR effects on brain serotonin systems.

In conclusion, the results of this study demonstrate that despite high baseline cortisol levels, patients with major depression increased functional activity of the MR system. Paired with the body of evidence regarding decreased sensitivity to GR agonists, these data suggest an imbalance in the MR/GR ratio. The balance of MR and GR is known to affect brain serotonin systems and may play an etiologic role in serotonin receptor changes, particularly 5-HT1A down-regulation, observed in major depression.

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