Loss of Glucocorticoid Fast Feedback in Depression

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• A rate-sensitive fast-feedback inhibition of stress-induced corticotropin secretion by glucocorticoids is well documented in rats. Studies in patients with Cushing's disease or adrenal insufficiency have also supported the existence of fast feedback in humans. However, few studies exist in normal healthy subjects or depressed patients. This study compared fast-feedback inhibition of β-endorphin/β-lipotropin secretion by hydrocortisone in 16 control subjects and 16 depressed patients. A fast-feedback effect of hydrocortisone on β-endorphin/β-lipotropin secretion during the hour of the hydrocortisone infusion was demonstrated in control subjects. Depressed patients demonstrated no increase in β-endorphin/β-lipotropin concentrations during the infusion. These data suggest a decreased sensitivity to glucocorticoid fast feedback in depressed patients and complement existing studies demonstrating decreased sensitivity to proportional feedback by dexamethasone in depressed patients. We believe the data presented herein are the first demonstration that abnormal feedback occurs at the level of the brain rather than pituitary in depressed patients.
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The precise nature of the hypothalamic-pituitary-adrenal (HPA) axis dysregulation in depression has yet to be fully defined despite the repeated demonstration of hypercortisolemia in depressed patients.[1-6] This increased cortisol secretion has been interpreted as a manifestation of limbic-hippocampal activation in depression.[2] Most studies of dysregulated glucocorticoid feedback on the HPA axis have utilized dexamethasone, which has a high affinity for pituitary glucocorticoid receptors. Dexamethasone does not bind to hippocampal glucocorticoid receptors in vivo,[7] and local implants of dexamethasone in the hippocampus are not able to reverse adrenalectomy-induced HPA activation.[8,9] Dexamethasone, therefore, may exert its principal feedback effects at the pituitary rather than brain.[7,10,11] Because dexamethasone is unlikely to be a suitable challenge for evaluating the role of limbic activation in depression, other experimental strategies are needed to evaluate the role of neuronal elements in feedback regulation of corticotropin secretion in normal and depressed patients. Glucocorticoid fast feedback is one form of feedback that appears to involve neuronal feedback elements.

The existence of a rapid, rate-sensitive feedback mechanism was demonstrated in rats in a series of experiments by Dallman, Jones, and collaborators.[10,12-16] Beginning within 5 minutes of infusion of corticosterone, an inhibitory action of corticosterone on stress-induced secretion of adrenal steroids occurs while the plasma corticosterone concentrations are rapidly rising. The "rate" dependency of this feedback is evidenced by the fact that the system seems to detect the rate of change in steroid concentrations rather than the absolute concentration of steroids; ie, a slower corticosterone infusion rate that produces a slower rate of rise of plasma corticosterone level does not evoke this inhibitory effect on the stress response even if the infusion is continued to achieve similar plasma corticosterone concentrations.

Possible mechanisms for this rapid feedback include a direct antagonistic action of glucocorticoids on corticotropin-releasing factor binding to its pituitary receptor,[17,18] or antagonism of corticotropin-releasing factor–dependent cyclic adenosine monophosphate generation in the corticotroph.[19] Although glucocorticoids have been shown to have rapid effects at the pituitary,[20] a number of other studies suggest that the brain is the predominant site of fast-feedback regulation, particularly the hypothalamus and hippocampus.[21-24] Increased glucocorticoid concentrations that either follow chronic exogenous administration or are secreted in response to chronic stress paradigms have been demonstrated to inhibit fast feedback in vivo[22,25] and to down-regulate hippocampal glucocorticoid receptors selectively.[25] Because fast feedback seems to depend on the neuronal elements of the HPA axis, studies examining fast feedback can provide a unique means of evaluating the involvement of the neuronal-hippocampal feedback elements in the HPA axis dysregulation of depression.

Previous studies using infusion of hydrocortisone in the morning have suggested the existence of fast feedback in humans. Reports by Carey[26] and Fehm et al[27] demonstrated the existence of fast feedback in patients with

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Cushing's disease. Both reports used infusions of 50 mg of hydrocortisone per hour for 2 hours. Fehm et al[27] found that hydrocortisone infusion in patients with adrenal insufficiency resulted in a prompt decline in plasma corticotropin level, with the onset of suppression varying between 15 and 30 minutes and continuing throughout the course of the infusion. Daly et al[28] were able to show the existence of negative feedback on spontaneous corticotropin secretion in normal humans by the use of a hydrocortisone infusion of 3 mg/h for 5 hours. In a further elaboration on these findings, Reader et al[29] found decreases in corticotropin level following the infusion of hydrocortisone at rates of 3 and 6 mg/h. These data were interpreted to indicate the existence of fast-feedback mechanisms in normal humans. It should be noted that these conclusions are based on the study of two normal subjects. Reus et al[30] used a dose of hydrocortisone of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and were able to demonstrate an effect on corticotropin concentrations in three of four normal control subjects. Taken as a whole, these existing studies suggest that fast feedback does exist in humans, but a total of only nine normal subjects have been studied among all these studies, with two of the nine demonstrating baseline corticotropin concentrations too low to measure suppression accurately. The present studies were undertaken to characterize the fast-feedback effects of hydrocortisone sodium succinate administration to normal subjects and compare these findings with fast feedback in depressed patients.

SUBJECTS AND METHODS

A total of 16 normal and 16 depressed subjects were studied, with eight male and eight female subjects in each group. The ages of the male and female controls were matched within 3 years. Informed consent was obtained from all subjects before the initiation of the studies. All normal subjects received a physical examination and screening blood work as well as a drug screen. The Schedule for Affective Disorders and Schizophrenia was administered to each subject to exclude psychiatric disorders in the control subjects. All subjects were admitted to the Clinical Research Center, University of Michigan Medical Center, Ann Arbor, for the nights preceding each of the 2 infusion days. On each day, an intravenous catheter was inserted between 6:30 and 7 AM in each arm. One catheter was used for infusion of hydrocortisone or saline and the other for withdrawal of blood samples. The first sample was drawn at 7:45, and a second sample (baseline) was drawn at 8 AM immediately before beginning the infusion, which lasted for 1 hour. On the first day, subjects received saline and on the second day hydrocortisone sodium succinate, $5 \mu g \cdot kg^{-1} \cdot min^{-1}$, although the subjects were "blind" to the order of the infusion. The order of the infusion was not randomized, since the first study day was considered an adaptation day, and the infusion of a large dose of hydrocortisone on day 1 would be expected to influence the "basal" secretion pattern on day 2. During the first 15 minutes of the infusion, blood samples were drawn every 5 minutes to characterize the rise in hydrocortisone concentrations and the interval between the onset of the rapidly rising plasma hydrocortisone concentrations and the inhibition of β-endorphin/β-lipotropin (β-END/β-LPH) secretion. Samples were then drawn every 15 minutes until 10 AM. Subjects fasted for the duration of the study.

All depressed patients had presented for evaluation at the outpatient clinic of the University of Michigan Depression Program. Patients and controls were age and sex matched. Patients received a standard clinical interview and a Schedule for Affective Disorder and Schizophrenia interview, followed by a consensus Research Diagnostic Criteria diagnosis. All patients met Research Diagnostic Criteria for major depressive disorder. Twelve of the 16 met criteria for probable or definite endogenous subtype. The 17-item Hamilton Depression Rating Scale (HDRS) was completed on all patients within 3 days of the study. At the time of initial evaluation, all depressed patients had HDRS scores of 15 or greater. On the actual day of the study, two patients, one male and one female, had HDRS scores below 15. All patients were a minimum of 2 weeks free of any medication and were taking no hormonal replacements. There was no evidence of any medical or endocrine abnormalities in the initial evaluation phase. Female patients were studied during random phases of the menstrual cycle, although estradiol and progesterone concentrations were determined on the saline infusion day. Patients were admitted to the Clinical Research Center and completed a protocol identical to that of the control subjects.

Plasma samples were drawn through a heparin lock into sodium–edetic acid tubes. After withdrawal, the samples were centrifuged immediately and the plasma separated and frozen on dry ice. The samples were stored at −70°C until extraction. Corticotropin is synthesized as part of a larger precursor protein, proopiomelanocortin, which is processed to yield corticotropin and β-END/β-LPH. For each molecule of corticotropin secreted, a molecule of β-END/β-LPH is secreted. Thus, either corticotropin or β-END/β-LPH provides an accurate measure of corticotroph secretion.[31] We prefer to measure β-END/β-LPH since we have a very sensitive radioimmunoassay available for measurement of β-END/β-LPH as well as a large data set (>200 subjects) evaluating β-END/β-LPH secretion before and after dexamethasone administration in normal controls and depressed patients. This β-END/β-LPH radioimmunoassay is more sensitive than corticotropin radioimmunoassays available at the time these studies were conducted (1987 to 1989) and better able to detect steroid-induced inhibition of corticotroph secretion in normal controls. In addition, the half-life of corticotropin is short (5 to 10 minutes), and it is often difficult to detect the secretory pulses of corticotropin that stimulate adrenal cortisol secretion.[32,33] Because the half-life of β-END/β-LPH is longer, the secretory pulses of β-END/β-LPH are slower to disappear and could provide a more constant baseline to determine inhibition of corticotroph secretion. Unfortunately, limits on the total volume of blood permitted to be drawn from patients and controls precluded assaying both corticotropin and β-END/β-LPH in these studies.

The samples were extracted with octododecyl sulfate cartridges and assayed for plasma β-END/β-LPH as described in Cahill et al.[34] All samples were assayed in triplicate. The equivalent of 2 mL of plasma is used per assay tube. The antibody (Brenda) is used at a final dilution of 1:40 000. The antibody demonstrates equal affinity for β-END and β-LPH and consequently measures β-END and β-LPH, the C-terminal fragments of pro opiomelanocortin processing. The radiolabeled tracer is iodine 125–labeled $\beta\text{-END}_h$ and the standards are $\beta\text{-END}_h$. The sample and standards are dissolved in 0.1% human serum albumin, acidified to a pH of 3.0 with 1N hydrochloric acid. The assay buffer is 150 mmol/L of phosphate buffer, pH 8.2, with 0.3% bovine serum albumin. Disequilibrium kinetics are used to increase sensitivity. The sensitivity (20% inhibition) of the β-END/β-LPH assay for these studies is 0.5 fmol/mL of plasma β-END/β-LPH, and the median inhibitory concentration is 6 to 8 fmol/mL of plasma β-END/β-LPH. Cortisol samples are drawn into heparin sodium tubes and assayed by competitive protein binding assay. The samples are extracted with ethanol saline and are assayed in triplicate.

Data analysis utilized two-way repeated-measures analysis of variance (RM-ANOVA, Stat View 512+) comparing β-END/β-LPH profiles in depressed patients and normal controls over the 1-hour infusion on the hydrocortisone infusion day. For the purpose of these analyses, only the data points between 8 and 9 AM were included, since the infusion began at 8 AM and earlier data points might have been affected by intravenous line insertion. To preserve the regularity of the sampling times (every 15 minutes), the data points from 8:05 and 8:10 AM were not included in the statistical analyses. However, these points were used to determine the changes in plasma cortisol level resulting from hydrocortisone infusion.

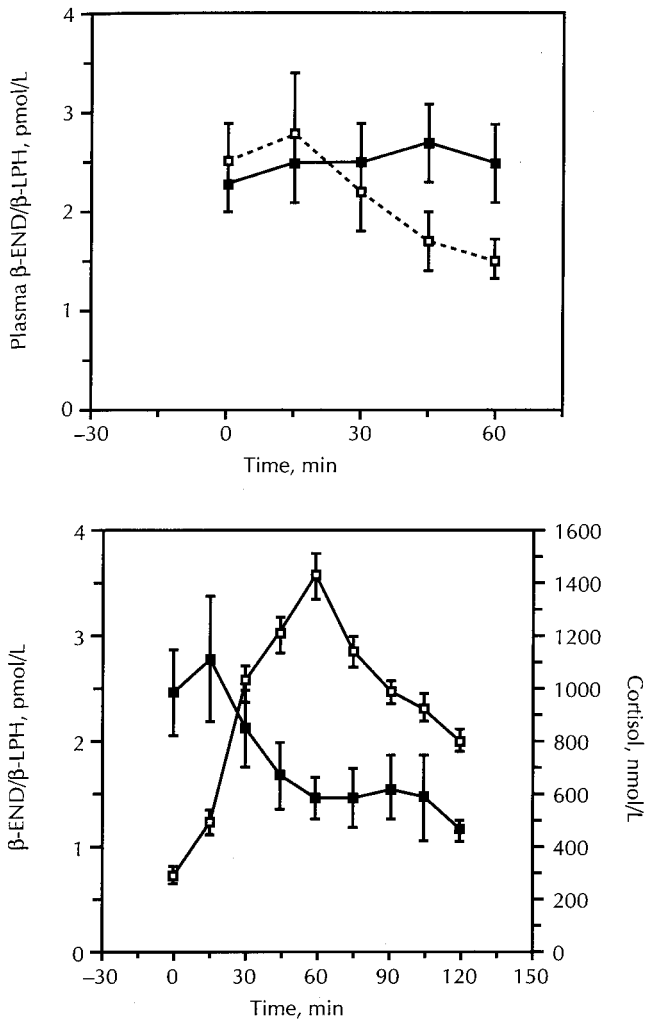

Fig 1.—*Top, The effect of hydrocortisone infusion, 5 μg·kg^{-1}·min^{-1} (broken line), vs saline infusion (solid line), on β-endorphin/β-lipotropin (β-END/β-LPH) secretion in 16 normal control subjects (eight male, eight female). The infusion lasted for 1 hour and began at 8 AM. The baseline β-END/β-LPH concentrations at 8 AM were similar between the two test conditions. Hydrocortisone infusion results in a rapid decline in β-END/β-LPH concentrations following the 8:15 AM sample. Bottom, Plasma β-END/β-LPH (solid line) vs cortisol rise (broken line) on the hydrocortisone infusion day. Note the prompt decline in β-END/β-LPH secretion during the time of rapidly rising cortisol levels (open squares). The plasma concentrations of β-END/β-LPH remain suppressed for the hour following the hydrocortisone infusion.*

RESULTS

Normal Control Subjects

As a group, the normal controls demonstrated a significant effect of hydrocortisone on β-END/β-LPH secretion (Fig 1) during the hour of the infusion. While there was no significant effect of saline infusion on β-END/β-LPH secretion on the baseline day (RM-ANOVA F=0.5, $P=.7$) there was a significant effect of hydrocortisone infusion on β-END/β-LPH secretion on the hydrocortisone infusion day (RM-ANOVA F=4.6, $P=.0028$). This indicates that hydrocortisone is "turning off" secretion of β-END/β-LPH. To examine further the time of onset of the fast-feedback effect, we compared the time of the suppression of β-END/β-LPH with the time of hydrocortisone rise (Fig 1, bottom). Because the hydrocortisone level was measured every 5 minutes for the first 15 minutes of the study, it became clear that the hydrocortisone concentrations were slow to change. Five minutes following the start of the infusion, there was no change in hydrocortisone concentrations. By 15 minutes into the infusion, most subjects had shown a clear increase in hydrocortisone level. Consequently, the time of rapidly rising plasma hydrocortisone concentration began between the 10- and 15-minute periods (rate of hydrocortisone rise, 30.25 nmol·L^{-1}·min^{-1}). The hydrocortisone concentrations continued to rise rapidly between 15 and 30 minutes (rate, 33 nmol·L^{-1}·min^{-1}), then rose more slowly until the end of the infusion (rate, 13.75 nmol·L^{-1}·min^{-1}). In normal controls, the suppressive effects of hydrocortisone on β-END/β-LPH began at 15 minutes and continued throughout the infusion. Concentrations of β-END/β-LPH also remained suppressed during the hour following the infusion (Fig 1, bottom). Thus, the onset of this inhibitory action of hydrocortisone was relatively fast, occurring 5 to 10 minutes after the hydrocortisone concentration actually rose.

Table 1.—Subject Characteristics*

	Controls (n=16)	Patients (n=16)
Psychiatric history	Never mentally ill	MDD by RDC
Drug free, d	14	14
Sex, F/M	8/8	8/8
Age, y, mean ± SD		
F	32 ± 9.4	33 ± 8.6
M	32.8 ± 9	32.5 ± 9.9
HDRS score, mean ± SD	. . .	17.5 ± 4

*MDD indicates major depressive disorder; RDC, Research Diagnostic Criteria; and HDRS, Hamilton Depression Rating Scale.

Table 2.—Summary of Statistical Comparisons of Patients and Controls*

Group	No.	Hormone	Drug Day†	F	P
Depressed vs control	16	β-END/β-LPH	Saline	1.3	NS
		Cortisol	Saline	1.98	NS
		β-END/β-LPH	Hydrocortisone	3.01	.02
		Cortisol	Hydrocortisone	0.72	NS
Depressed vs control, M	8	β-END/β-LPH	Saline	6.1	.03
		Cortisol	Saline	0.03	NS
Depressed vs control, F	8	β-END/β-LPH	Saline	0.22	NS
		Cortisol	Saline	2.0	NS
Controls, M vs F	8	β-END/β-LPH	Saline	0.83	NS
		β-END/β-LPH	Hydrocortisone	0.37	NS
Patients, M vs F	8	β-END/β-LPH	Saline	1.4	NS
		β-END/β-LPH	Hydrocortisone	3.8	.07

*β-END indicates β-endorphin; β-LPH, β-lipotropin; and NS, not significant. F and P values are for interaction; ie, profiles of secretion are nonparallel.

†Indicates the drug that was administered the day value was obtained. See "Subjects and Methods" section.

Comparison With Depressed Patients

All patients met Research Diagnostic Criteria for major depressive disorder. Six met criteria for definite and another six for probable endogenous depression. One patient met criteria for bipolar depression and nine for recurrent unipolar depression. Further comparisons of the patients and controls are given in Table 1. As noted in the design, patients and controls were age and sex

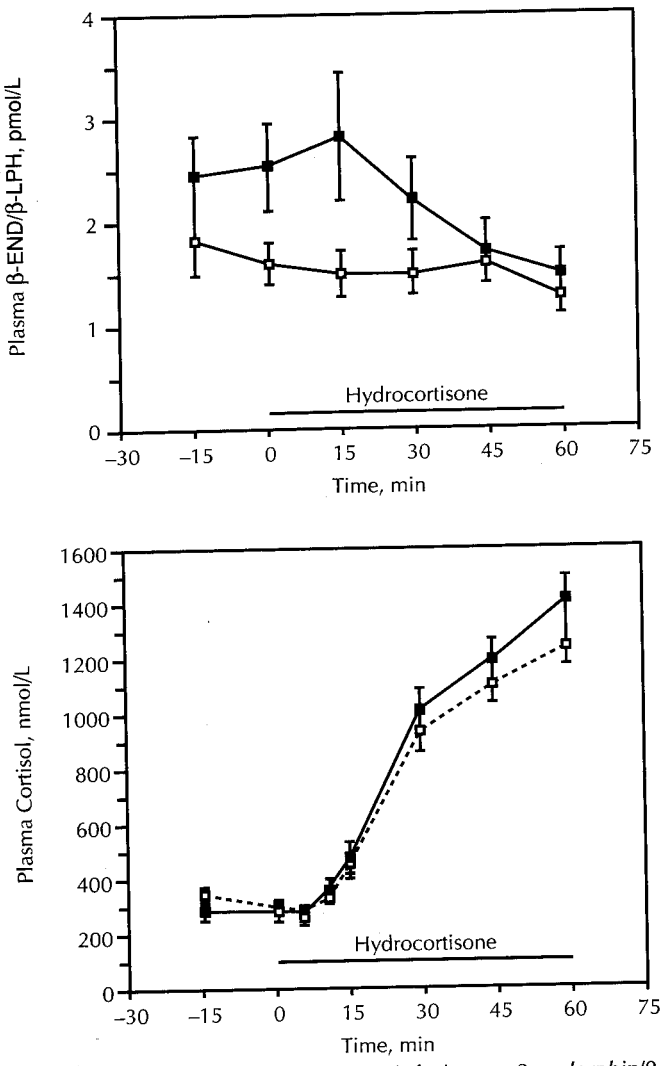

Fig 2.—*Top, Effect of hydrocortisone infusion on β-endorphin/β-lipotropin (β-END/β-LPH) concentrations in 16 normal controls (solid squares) and 16 depressed patients (open squares). The data for −15 minutes are included to show the stability of plasma β-END/β-LPH concentrations. An effect of hydrocortisone is clearly visible in the normal controls but not in the depressed patients. Repeated-measures analysis of variance demonstrated a significant interaction between time and group during the hydrocortisone infusion (F=3.0, P=.02). However, there was no difference in the cortisol concentrations between patients and controls (bottom) during the infusion.*

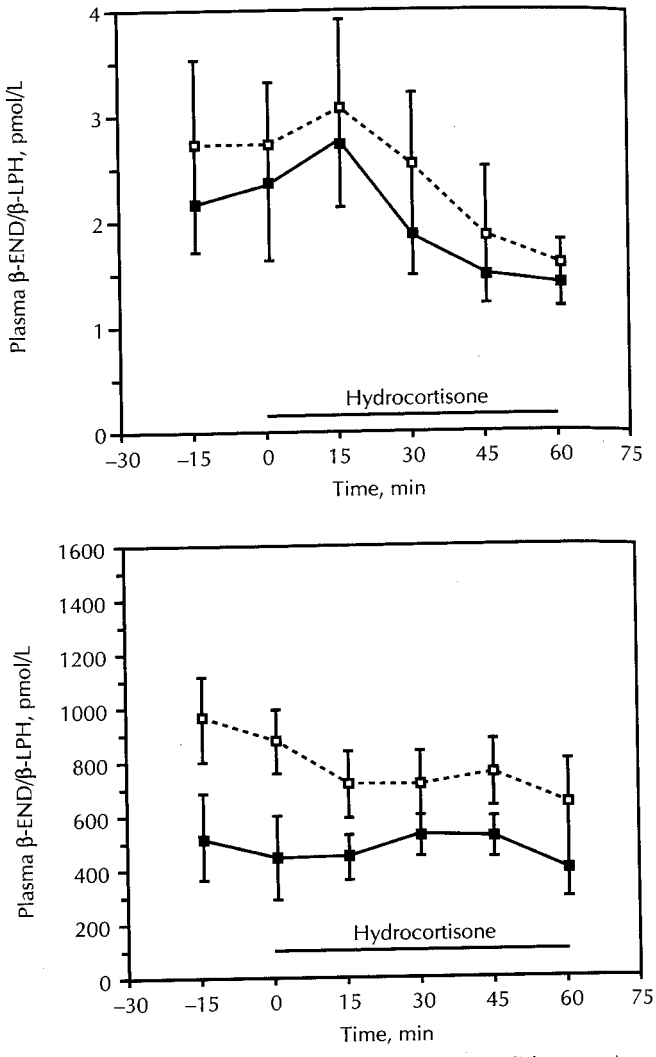

Fig 3.—*Effect of hydrocortisone infusion on male (solid squares) and female (open squares) controls (top) and male (solid squares) and female (open squares) depressed patients (bottom). Again, the data for −15 minutes are included to show the stability of baseline β-endorphin/β-lipotropin (β-END/β-LPH) concentrations. The β-END/β-LPH profiles are similar between male and female subjects in each group, but the controls demonstrate a decrease in secretion and the patients demonstrate a flat profile.*

matched. The male and female patients were also age matched. On the baseline day, the patients demonstrated β-END/β-LPH plasma concentrations similar to the controls (F=0.7, not significant, Table 2). The baseline cortisol concentrations of the patients were also similar to those of the control subjects (F=1.98, not significant, Table 2). The effects of hydrocortisone infusion differed between the patients and controls. A comparison of the β-END/β-LPH profiles of patients with the controls during the hydrocortisone infusion is shown in Fig 2, top. While the controls demonstrated an inhibition of β-END/β-LPH secretion, the patients demonstrated a flat profile of β-END/β-LPH secretion. This difference is verified by a significant interaction effect between group (patient vs control) and time (F=3.0, P=.02) in the RM-ANOVA; ie, the slopes of the two lines are not parallel. When examining this absence of suppression in patients vs normal controls, the hydrocortisone concentrations achieved did not differ between the patients and controls during the infusion (Fig 2, bottom; RM-ANOVA F=0.7, not significant). The rate of rise of hydrocortisone level during the infusion was also similar between patients and control subjects.

These data were also analyzed by sex. On the baseline day, female patients did not differ from female controls in β-END/β-LPH or cortisol concentrations (Table 2). The male patients demonstrated significantly lower β-END/β-LPH but not cortisol concentrations than their male controls (Table 2). Consequently, the ratio of mean cortisol (nanomoles per liter) to mean β-END/β-LPH (picomoles per liter) on the saline infusion day was significantly higher in the male patients than the male controls (controls, 121±22; patients, 211±22; P=.01, two-tailed *t* test). On the hydrocortisone infusion day, male and female controls did not differ in their response to the hydrocortisone infusion (Fig 3, top; F=0.6, not significant). Neither was there a difference in male and female patients in their response to hydrocortisone infusion (Fig 3, bottom), but there was a trend toward lower β-END/β-LPH concentrations in the male patients (F=3.77, P=.07).

COMMENT

These studies demonstrate a fast-feedback effect of hydrocortisone on corticotroph secretion in normal controls that seems to occur concomitantly with the rapidly rising

concentrations of plasma hydrocortisone. These β-END/β-LPH concentrations remained suppressed in the hour following the infusion. The rate of rise of hydrocortisone (30.25 to 33 nmol·L^{-1}·min^{-1}) was similar to the rate of rise of corticosterone needed to invoke fast feedback in rats.[15,16] However, this fast-feedback effect of hydrocortisone was absent in depressed patients.

Numerous studies with dexamethasone have demonstrated abnormal suppression of cortisol in depressed patients, but recent findings have confounded this interpretation.[35-37] One confound is the accelerated metabolism of dexamethasone in dexamethasone nonsuppressor subjects.[38,39] The lower plasma dexamethasone concentrations in dexamethasone nonsuppressors as well as the demonstration of apparent adrenal hypertrophy with increased sensitivity of the adrenal to corticotropin in depressed subjects[40,41] suggests that measurement of cortisol values only following dexamethasone challenge is not easily interpretable. The current findings of altered fast-feedback sensitivity in depression suggest an insensitivity to steroid feedback, similar to that reported with dexamethasone using longer-term feedback paradigms. Unlike the dexamethasone studies, in the current studies equivalent rates of rise of hydrocortisone and equivalent plasma concentrations of hydrocortisone were achieved. Consequently, these data give strong support for the existence of a defect in steroid feedback in depression. Previous studies examining fast feedback in depression have been inconclusive because of the small number of control and depressed subjects.[30,42] However, the studies of Reus et al[30] did suggest abnormal feedback regulation in the depressed subjects. Data from Daly et al[28] suggested that subjects with Cushing's disease require higher rates of rise of cortisol than normal subjects to demonstrate a fast-feedback effect of cortisol. This may also be the case with depressed patients.

A disruption of the hippocampal glucocorticoid receptors as well as possible loss of hippocampal neurons has been suggested as the site of HPA axis dysregulation in depression.[22] Previous studies in rats have suggested that treatments that result in decreased hippocampal glucocorticoid receptors can affect the fast-feedback inhibition by glucocorticoids of stress-induced corticotropin and corticosterone secretion.[22,25] Such data suggest that the hippocampus is an important site that mediates fast-feedback inhibition of corticotropin secretion. This speculation is consistent with a large body of data suggesting the importance of the hippocampus in learning and memory, both of which are disrupted in depression. Recent studies by Issa and coworkers[43] have found that only those aged rats with demonstrable memory defects show impaired negative feedback to stress, and that these same rats show lower hippocampal glucocorticoid receptors than cognitively unimpaired aged rats. These data of altered fast-feedback regulation in depression lend further support to the hypothesis that alterations of glucocorticoid receptors at the level of the hippocampus may be involved in the HPA axis dysregulation in depression. However, this demonstration of absent fast feedback in depressed patients does not exclude the possibility of increased corticotropin-releasing factor secretory drive contributing to the HPA axis abnormalities seen in depression. Indeed, a defect in negative feedback would be expected to lead to increased corticotropin-releasing factor drive.

In previous HPA axis studies of depressed patients, elevated plasma cortisol level was interpreted as evidence in favor of increased corticotropin-releasing factor drive secondary to brain neurotransmitter alteration.[2,44] Since secretion represents a balance between the feed-forward drive (corticotropin-releasing factor) and the feedback elements (glucocorticoid negative feedback), it is difficult in a closed-loop system to ascertain whether the HPA axis defect in depression represents increased drive or decreased sensitivity to negative feedback or both. Recent studies have utilized corticotropin-releasing factor challenge, and numerous investigators have agreed that there is a decreased corticotroph response but a normal adrenal cortisol response to corticotropin-releasing factor in depressed subjects.[44-47] However, in a number of studies, the depressed subjects exhibited elevated cortisol concentrations, so it was impossible to determine whether the data supported decreased corticotropin-releasing factor receptor number on the corticotroph vs excessive negative feedback appropriately restraining corticotroph secretion. More recent studies of depressed patients with no evidence of hypercortisolemia have continued to observe a decreased corticotroph response to corticotropin-releasing factor, suggesting that a defect in negative feedback alone cannot explain the HPA axis abnormalities seen with corticotropin-releasing factor administration.[46,47] In further support of the hypothesis of increased drive are the data of Nemeroff et al,[48] demonstrating increased corticotropin-releasing factor concentrations in the cerebrospinal fluid.

Apart from fast-feedback alterations, these data demonstrate a difference in β-END/β-LPH concentrations between the control and depressed male subjects on the baseline (saline infusion) day. Since these depressed male subjects had low plasma β-END/β-LPH concentrations but normal cortisol concentrations, these subjects presumably demonstrate increased cortisol production in response to low corticotropin secretion. In these individuals, the low baseline β-END/β-LPH concentrations in plasma may represent an HPA axis adaptation to prevent hypercortisolemia. Again, these data underscore the closed-loop nature of the system and the physiological importance of maintaining cortisol concentrations within a critical window to prevent the dangerous sequelae of hypercortisolemia.

In conclusion, this study demonstrates a fast-feedback effect of cortisol on corticotroph secretion in normal subjects. This fast-feedback mechanism is absent in depressed patients. Because fast feedback is believed to involve higher brain centers (eg, hypothalamus and hippocampus) rather than the pituitary, these findings suggest that depression is accompanied by a decreased sensitivity of brain sites to steroid feedback. In addition, these data lend support to the previous findings of altered glucocorticoid feedback in depressed patients in response to dexamethasone challenge. A similar loss of fast-feedback inhibition has been demonstrated in chronically stressed rats, aged rats, and rats that received high-dose corticosterone treatment, which is known to down-regulate hippocampal glucocorticoid receptors.[22,25] The possible involvement of hippocampal glucocorticoid receptors in the feedback abnormalities of depression merits further research.

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References

1. Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukush DK, Gallagher TF. Disrupted 24-hour patterns of cortisol secretion in psychotic depressives. *Arch Gen Psychiatry.* 1973;28:19-24.
2. Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression, I: limbic system–adrenocortical dysfunction. *Arch Gen Psychiatry.* 1976;33:1039-1044.
3. Pfohl B, Sherman B, Schlecter J, Stone R. Pituitary/adrenal axis rhythm disturbances in psychiatric patients. *Arch Gen Psychiatry.* 1985;42:897-903.
4. Halbreich U, Asnis GM, Schindledecker R, Zurnoff B, Nathan RS. Cortisol secretion in endogenous depression, I: basal plasma levels. *Arch Gen Psychiatry.* 1985;42:909-914.
5. Rubin RT, Poland RE, Lesser IM, Winston RA, Blodgett N. Neuroendocrine aspects of primary endogenous depression, I: cortisol secretory dynamics in patients and matched controls. *Arch Gen Psychiatry.* 1987;44:328-336.
6. Linkowski P, Mendelwicz J, Kerkhofs M, LeClercq R, Goldstein J, Brasseur M, Copinschi G, van Cauter E. 24 Hour profiles of ACTH, cortisol and growth hormone in major depressive illness: effect of antidepressant treatment. *J Clin Endocrinol Metab.* 1987;65:141-152.
7. deKloet R, Wallach G, McEwen BS. Differences in corticosterone and dexamethasone binding to rat brain and pituitary. *Endocrinology.* 1975;76:598-609.
8. Sawchenko PE. Adrenalectomy-induced enhancement of CRF and vasopressin immunoreactivity in parvocellular neurosecretory neurons: anatomy, peptide and steroid specificity. *Neuroscience.* 1987;7:1093-1106.
9. Kovacs K, Makara GB. Corticosterone and dexamethasone act at different sites to inhibit adrenalectomy induced adrenocorticotropin hypersecretion. *Brain Res.* 1988;474:205-210.
10. Keller-Wood ME, Dallman MF. Corticosteroid inhibition of ACTH secretion. *Endocr Rev.* 1985;5:1-24.
11. Dallman MF, Akana SF, Cascio ES, Darlington DN, Jacobson L, Levin N. Regulation of ACTH secretion: variations on a theme of B. *Recent Prog Horm Res.* 1987;43:113-173.
12. Jones MT, Hillhouse EW. Structure activity relationship and mode of action of corticosteroid feedback on the secretion of corticotrophin releasing factor (corticoliberin). *J Steroid Biochem.* 1976;7:1189-1200.
13. Dallman MF, Yates FE. Dynamic asymmetries in the corticosteroid feedback path and distribution-metabolism-binding elements of adrenocortical system. *Ann N Y Acad Sci.* 1969;156:696-721.
14. Jones MT, Brush FR, Neame RLB. Characteristics of fast feedback control of corticotrophin release by corticosteroids. *J Endocrinol.* 1972;55:489-497.
15. Hillhouse EW, Jones MT. Effect of bilateral adrenalectomy and corticosteroid therapy on secretion of corticotropin-releasing factor activity from the hypothalamus of the rat in vitro. *J Endocrinol.* 1976;71:21-30.
16. Jones MT, Tiptaft EM, Brush FR, Fergusson DAN, Neame RLB. Evidence for dual corticosterone receptor mechanism in the control of adrenocorticotropin secretion. *J Endocrinol.* 1974;60:223-233.
17. Childs GV, Morell JL, Niendorf A, Aguilera G. Cytochemical studies of corticotropin releasing factor receptors in anterior lobe corticotrophs: binding, glucocorticoid regulation and endocytosis of [Biotinyl-Ser^1] CRF. *Endocrinology.* 1986;119:2129-2142.
18. Schwartz J, Billestrup N, Perrin M, Rivier J, Vale W. Identification of corticotropin releasing factor target cells and effects of dexamethasone on binding in anterior pituitary using a fluorescent analog of CRF. *Endocrinology.* 1986;119:2376-2382.
19. Bilezikjian LM, Vale WW. Glucocorticoids inhibit corticotropin-releasing factor-induced production of adenosine 3',5'-monophosphate in cultured anterior pituitary cells. *Endocrinology.* 1983;113:657-662.
20. Widmaier EP, Dallman MF. The effects of corticotropin-releasing factor on adrenocorticotropin secretion from perfused pituitaries in vitro: rapid inhibition by glucocorticoids. *Endocrinology.* 1984;115:2368-2374.
21. Herman JP, Schafer MKH, Young EA, Thompson RC, Douglass JO, Akil H, Watson SJ. Hippocampal regulation of the hypothalamo-pituitary-adrenocortical axis: *in situ* hybridization analysis of CRF and vasopressin messenger RNA expression in the hypothalamic paraventricular nucleus following hippocampectomy. *J Neurosci.* 1989;9:3072-3082.
22. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev.* 1986;7:284-301.
23. Kaneko M, Kiroshige T. Site of fast, rate-sensitive inhibition of adrenocorticotropin secretion during stress. *Am J Physiol.* 1978;234:R46-R51.
24. Mahmoud SN, Scaccianoce S, Scraggs PR, Nicholson SA, Gillham B, Jones MT. Characteristics of corticosteroid inhibition of adrenocorticotropin release from the anterior pituitary gland of the rat. *J Endocrinol.* 1984;102:33-42.
25. Young EA, Akana S, Dallman MF. Decreased sensitivity to glucocorticoid fast feedback in chronically stressed rats. *Neuroendocrinology.* 1990;51:536-542.
26. Carey RM. Suppression of ACTH by cortisol in dexamethasone-nonsuppressible Cushing's disease. *N Engl J Med.* 1980;302:275-279.
27. Fehm FL, Voight KH, Kummer K, Lang R, Pfeiffer OF. Positive rate sensitive corticosteroid feedback mechanism of ACTH secretion in Cushing's disease. *J Clin Invest.* 1979;64:102-108.
28. Daly JR, Reader SCJ, Alaghband J, Haisman P. Observations on feedback regulation of corticotropin (ACTH) secretion in man. In: Jones MT, Dallman MF, Gillham B, Chattopadhay S, eds. *Interaction Within the Brain-Pituitary-Adrenocortical System.* Orlando, Fla: Academic Press Inc; 1979:181-188.
29. Reader SCJ, Alaghband-Zadeh J, Daly JR, Robertson WR. Negative, rate sensitive feedback effects on adrenocorticotropin secretion by cortisol in normal subjects. *J Endocrinol.* 1982;92:433-448.
30. Reus VI, Joseph M, Dallman MF. Regulation of ACTH and cortisol in depression. *Peptides.* 1983;4:785-788.
31. Eipper BA, Mains RE. Structure and function of pro-adrenocorticotropin/endorphin and related peptides. *Endocr Rev.* 1980;1:247-262.
32. Krishnan KRR, Ritchie JC, Saunders W, Nemeroff CB, Carroll B. Nocturnal and early morning secretion of ACTH and cortisol in humans. *Biol Psychiatry.* 1990;28:47-57.
33. Krishnan KRR, Ritchie JC, Manepalli AN, Nemeroff CB, Carroll BJ. Adrenocortical sensitivity to ACTH in humans. *Biol Psychiatry.* 1988;24:105-108.
34. Cahill CA, Matthews JD, Akil H. Human plasma β-endorphin–like peptides: a rapid, high recovery extraction technique and validation of radioimmunoassay. *J Clin Endocrinol Metab.* 1983;56:992-997.
35. Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression, II: discrimination of depressed from non-depressed subjects. *Arch Gen Psychiatry.* 1976;33:1051-1058.
36. Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol Z, Lohr N, Steiner M, de Vigne JP, Young EA. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. *Arch Gen Psychiatry.* 1981;38:15-22.
37. Poland RE, Rubin RT, Lesser IM, Lane LA, Hart PJ. Neuroendocrine aspects of primary endogenous depression, II: serum dexamethasone concentrations and hypothalamic pituitary adrenal activity as determinants of the dexamethasone suppression test response. *Arch Gen Psychiatry.* 1987;44:790-795.
38. Arana GW, Workman RJ, Baldessarini RJ. Association between low plasma levels of dexamethasone and elevated levels of cortisol in psychiatric patients given dexamethasone. *Am J*

Psychiatry. 1984;141:1619-1621.
39. Lowy MT, Meltzer HY. Dexamethasone bioavailability: implications for DST research. *Biol Psychiatry*. 1987;22:373-385.
40. Amsterdam JC, Winokur A, Abelman E, Lucki I, Richels K. Co-syntropin (ACTH α^{1-24}) stimulation test in depressed patients and healthy subjects. *Am J Psychiatry*. 1983;140:907-909.
41. Jaeckle RS, Kathol RG, Lopez JF, Meller WH, Krummel SJ. Enhanced adrenal sensitivity to exogenous $ACTH_{1-24}$ stimulation in major depression: relationship to dexamethasone suppression test results. *Arch Gen Psychiatry*. 1987;44:233-240.
42. Carr DB, Wool C, Lydiard RB, Fisher J, Gelenberg A,Klerman G. Rate-sensitive inhibition of ACTH release in depression. *Am J Psychiatry*. 1984;141:590-592.
43. Issa AM, Rowe W, Gauthier S, Meaney MJ. Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *J Neurosci*. 1990;10:3247-3254.
44. Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH, Nielman LK, Post RM, Pickar D, Gallucci W, Avgerinos P, Paul S, Oldfield EH, Cutler GB, Chrousos GP. Response to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. *N Engl J Med*. 1986;314:1329-1335.
45. Holsboer F, Bardeleden U, Gerken A, Stalla G, Muller O. Blunted corticotropin and normal cortisol response to human corticotropin-releasing factor in depression. *N Engl J Med*. 1984;311:1127.
46. Amsterdam JD, Maislin G, Winokur A, Kling M, Gold P. Pituitary and adrenocortical responses to ovine corticotropin releasing hormone in depressed patients and healthy volunteers. *Arch Gen Psychiatry*. 1987;44:775-781.
47. Young EA, Watson SJ, Kotun J, Haskett RF, Grunhaus L, Murphy-Weinberg V, Vale W, Rivier J, Akil H. β-Lipotropin–β-endorphin response to low dose ovine corticotropin releasing factor in endogenous depression. *Arch Gen Psychiatry*. 1990;47:449-457.
48. Nemeroff CB, Widerlov E, Bisette G, Walleus H, Karlsson I, Eklund K, Kilts C, Loosen PT, Vale W. Elevated concentrations of CSF corticotropin-releasing-factor–like immunoreactivity in depressed patients. *Science*. 1984;226:1342-1344.