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Disordered Adrenocorticotropin Secretion in Women with Major Depression

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Context: Major depression is accompanied by activation of the hypothalamic pituitary axis and evidence of abnormalities in circadian and ultradian hormone rhythms. In addition, diminished negative feedback of cortisol on ACTH has been found.

Objective: The objective of the study was to compare ACTH and cortisol hormonal patterns in women with major depression with normal control women.

Design: This was a case control study.

Setting: The study was conducted at a general clinical research center.

Patients and Other Participants: Healthy, drug-free, premenopausal women with major depression and age and menstrual cycle day-matched healthy control women were included in the study.

Main Outcome Measure: ACTH and cortisol data were measured every 10 min for 24 h analyzed with approximate entropy and cross-approximate entropy to determine orderliness of hormone secretion and relationship between ACTH and cortisol in terms of feedforward and feedback synchrony.

Results: Depressed women manifested increased approximate entropy, indicating more disorderly secretion, of ACTH and elevated forward cross-approximate entropy of ACTH on cortisol, denoting unopposed ACTH drive.

Conclusions: These data support other evidence of hormonal rhythm abnormalities in depression and are compatible with accentuated feedforward drive by ACTH. **(*J Clin Endocrinol Metab* 91: 1924–1928, 2006)**

ACTH AND CORTISOL are released in pulsatile fashion with circadian and ultradian rhythms governing secretion of these hormones (1–5). Both are released approximately hourly, with ACTH pulses preceding cortisol pulses by approximately 10 min (4, 5). In addition to these approximately hourly pulses, an ultradian rhythm of cortisol of 90–110 min has been found, which is linked to the basic rest-activity cycle, particularly the alternating arousal-sleep cycle, which continues throughout the day (6, 7). Work by Van Cauter *et al.* (8) has found a strong bidirectional link between cortisol secretory episodes and arousal.

A number of different analytic techniques have been used to characterize these circadian and ultradian rhythms in ACTH and cortisol. Pulse detection algorithms are commonly used to define pulses; spectral analyses examine multiple frequencies in the time series data. In addition, a relative new technique, approximate entropy (ApEn) has been used to determine the regularity and predictability in a time series (9). Applications of this analysis demonstrated the ability to distinguish neuroendocrine tumors from normal secretion and changes due to puberty and aging (10). Thus, ApEn has benefit in determining regularity of hormone rhythms, determining whether the rhythms are more disorderly and whether disorderliness is a sign of diminished feedback as seen during aging or target gland failure. A recent adaptation of ApEn (cross-ApEn, X-ApEn,) examines the relationship between two coupled hormone series, such as ACTH and cortisol (11, 12). Forward X-ApEn examines the synchrony in feedforward drive, whereas reverse X-ApEn examines the synchrony of feedback within the hypothalamic-pituitary-adrenal (HPA) axis. X-ApEn allows us to examine both forward drive and negative feedback under basal conditions rather than using a challenge such as dexamethasone.

Major depression is accompanied by activation of the HPA axis (5, 13–15). Most 24-h sampling studies have shown approximately 30% of patients with nonpsychotic depression have increased cortisol secretion (5, 13–15). Whereas studies have found increased adrenal response to $ACTH_{1-24}$ in depression (16, 17), it is generally believed that the increased cortisol is secondary to increased CRH and arginine vasopressin from the hypothalamus and consequent increased ACTH secretion from the pituitary. In addition to increased mean cortisol, some studies (18, 19) have suggested alteration in the circadian rhythm of cortisol. Other indications of a more general disturbance in circadian systems include early onset of rapid eye movement sleep and alterations in melatonin amplitude (19–23) and rhythms in LH secretion (24). Decreased circadian rhythm entrainment (25) has been found in depression along with dampened circadian activity with less stability in circadian rhythms (26) across days and decreased electroencephalographic temporal coherence during

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Abbreviations: ApEn, Approximate entropy; HPA, hypothalamic-pituitary-adrenal; SCID, structured clinical interview for axis I Diagnostic and Statistical Manual of Mental Disorders; X-ApEn, Cross-ApEn.

sleep (27). All of these circadian alterations appear to be more prominent in depressed women than men (27). These findings suggest a general disruption in circadian and ultradian rhythms across multiple systems in major depression, which could affect the regularity of hormonal secretion. Because of evidence of altered circadian rhythm entrainment and decreased temporal coherence during sleep, we hypothesized that depression would be accompanied by increased disorderliness in ACTH and cortisol hormone secretion. We used ApEn to characterize the orderliness of ACTH and cortisol secretion and X-ApEn to characterize the relationship between these hormone systems. We expected that major depression in women would be accompanied by evidence of increased central drive and diminished negative feedback.

Subjects and Methods

Experimental subjects

All subjects were premenopausal women who ranged in age from 20 to 50 yr. Depressed women were recruited from patients presenting to the University of Michigan Mood Disorders program for treatment. All studies were approved by the University of Michigan Institutional Review Board. All subjects were medically healthy and untreated for the current episode at the time of the study. No subjects were regular smokers because smoking was not permitted during the study. All were free of psychotropics and any other medications except for nonprescription pain medications, for more than 3 months. No subject engaged in shift work or traveled across more than three time zones within the 3 months before study. Subjects were studied on the general medical Clinical Research Center, to which they were admitted for 26 h. All subjects signed an informed consent. A Structured clinical interview for axis I Diagnostic and Statistical Manual of Mental Disorders (SCID)-IV interview and structured Hamilton rating was conducted on all patients by our research nurse to confirm the diagnosis. Agreement between the treating clinician and SCID diagnosis for major depression was required for inclusion. All patients were interviewed by the same SCID interviewer, who showed interrater reliability of 98% with other trained interviewers in our system. Seven patients were studied in the first episode of major depression, 16 patients met criteria for recurrent unipolar depression, and one patient met criteria for bipolar II, depressed. In seven subjects, dysthymia preceded the onset of the current episode of depression. Nine of the subjects met criteria for at least one anxiety disorder: two with generalized anxiety, four with panic disorder, five with simple phobias, and two with social phobia. Normal controls had no previous psychiatric diagnosis as confirmed by SCID-nonpatient conducted by our research nurse. They had no first-degree relative with any axis I disorder and no second-degree relative with an anxiety or mood disorder as ascertained by questioning the subject on all relatives. All subjects underwent a screening physical exam, blood work, and urine drug screen. All controls were individually matched to each patient and matched on age, menstrual cycle day, and length. Racial/ethnic composition for the patient group was: two Hispanic, two Asian, two black, and 18 white. Racial/ethnic composition for the controls was three black and 21 whites.

Protocol

Subjects presented to the Clinical Research Center at 0800 h on d 1, when an iv catheter was inserted. After a 60-min recovery period, 10-min sampling was initiated for 24 h. Normal saline was infused throughout the study. Although subjects were able to get up to go to the bathroom, they remained at bed rest for the 24 h of the study. All meals were standardized in time and content. Eating between meals was not permitted, but decaffeinated beverages were provided at set times. Subjects were free to turn off the lights at their usual sleep times, but all lights were off by 2400 h. During overnight sampling, blood was drawn with the aid of a flashlight and nurses recorded whether the subjects were awake or asleep with each 10-min sample. All samples were drawn in a plastic syringe and mixed with EDTA in a polypropylene tube. Samples were immediately placed on ice and spun at least every 2 h. Previous studies in our laboratory have validated the stability of ACTH and cortisol when samples remained on ice for 4 h.

Hormone assays

ACTH was assayed with Allegro HS ACTH immunoradiometric assay (Nichols Diagnostics, San Juan Capistrano, CA), a two-site assay highly specific for intact ACTH. The sensitivity of the assay is 5 pg/ml. Intraassay variability averaged 9% and interassay variability of the internal control sample averaged 19%. Cortisol was assayed with Coat-a-Count assay (Diagnostic Products Corp., Los Angeles, CA), a solid-phase RIA. The detection limit of the assay is 0.2 μg/dl. Intraassay variability averaged 5% and interassay variability of the internal control sample averaged 8%. All samples collected were assayed for ACTH first and then cortisol to avoid loss of ACTH secondary to freezing and thawing. Each patient's samples were assayed with her matching control in both assays, which reduces the possibility of interassay variability contributing to the findings. Each assay measured only one patient and her matched control (290 samples total).

ApEn and X-ApEn

ApEn is a scale- and model-independent univariate regularity statistic used to quantitate the orderliness (subpattern consistency) of serial measurements (28, 29). Mathematical models and feedback experiments establish that pattern orderliness monitors feedback and/or feedforward interactions within an interlinked axis with high sensitivity and specificity (both $>$ 90%) (30–32). To normalize comparisons among subjects, ApEn is first computed on the measured time series (observed ApEn) and then recalculated each of 1000 times that the series is shuffled randomly [rearranged by order without replacement or loss (random ApEn)] (29). The shuffling procedure allows calculation of the mean and SD of random ApEn at a given series length, hormone assay, and experimental condition. Normalized measures are taken as the mean of 1000 ratios of observed to empirically random ApEn and the number of SDs separating observed from mean random ApEn (z score). A ratio of unity or z score of zero reflects expected process randomness, whereas lower ApEn ratios and higher absolute z scores denote more orderly (regular) patterns.

X-ApEn is a scale- and model-independent two-variable regularity statistic used to quantitate the relative pattern synchrony of coupled time series (9, 10). Clinical experiments establish that changes in two-hormone synchrony monitor feedback and/or feedforward adaptations within an interlinked axis with high sensitivity and specificity (11, 12, 33). To normalize comparisons among subjects, X-ApEn is computed on the paired original time series (observed X-ApEn) and then recalculated 1000 times after each series in a pair is shuffled randomly [rearranged in order or sequence without replacement or loss (random X-ApEn)]. Repetition of the permutation procedure allows calculation of the maximum, mean, and SD of random X-ApEn for a given series length and assay pair. A normalized distributional measure is then the number of SDs (z scores) separating observed from the maximum or mean random X-ApEn. Higher absolute z scores denote more synchronous patterns. Lower X-ApEn ratios and higher absolute z scores denote greater pattern synchrony between (coordinate control of) the interlinked signals. Reduced regularity of hormone secretion typifies puberty, aging, diminished negative feedback due to target-gland failure, fixed exogenous stimulation, and autonomous neuroendocrine tumors (29, 31, 34). In neuroendocrine systems, the statistic may be applied to as few as 13 data points. The only mathematical requirement is that the series under comparison have the same length.

Statistical analyses

Results for ApEn and X-ApEn analyses were compared by paired *t* test. Analysis for menstrual cycle phase used two-way ANOVA with group and menstrual phase as the two factors. Analysis of mean ACTH and cortisol was conducted using 1-h means by repeated-measure ANOVA. Significance was defined as $P \leq 0.05$.

Results

The pulsatile and circadian analyses of ACTH and cortisol in these subjects are described elsewhere (5). The demographic data for these 24 pairs of subjects is given in Table 1. The mean 24-h data for ACTH and cortisol are shown in Table 2. Mean ACTH and cortisol did not differ by repeated-measure ANOVA ($F = 0.09$, $df = 1$, $P = 0.36$ for group for ACTH; $F = 1.02$, $df = 1$, $P = 0.31$ for cortisol). The ApEn data are also shown in Table 2. As can be seen, the ApEn mean value is significantly greater for ACTH from depressed patients (Fig. 1). However, the cortisol ApEn mean values are identical between patients and controls (Table 2). The forward X-ApEn of ACTH-cortisol, which looks at the synchrony of the feedforward drive, was also elevated, *i.e.* more disorderly (Fig. 2), whereas the reverse X-ApEn, which looks at the synchrony between cortisol and ACTH in terms of feedback signal, was similar in depressed patients and normal controls (Table 2). No menstrual cycle phase differences in ApEn were found ($F = 0.7$, $df = 1$, $P = NS$).

Discussion

We applied ApEn and X-ApEn to ACTH and cortisol secretion data from 24 pairs of depressed women and age- and menstrual cycle day-matched controls to determine whether the regularity of ACTH and cortisol secretion and ACTH feedback signals were similar in depressed patients and controls. The data from this study found increased ApEn of ACTH secretion in women with major depression, thus indicating more disorderly outflow of ACTH. From these data, it is not possible to know whether increased ApEn of ACTH secretion originates centrally or at the level of the pituitary. However, the findings of abnormalities in circadian rhythm stability, decreased electroencephalographic temporal coherence, and altered frequencies in LH secretion in depressed women (24–27) may point to a more general brain driven rhythm disorder in women with major depression. In fact, the depressed subjects characterized in this report demonstrated altered LH rhythms (24), again suggesting a more general disturbance of hormone rhythms in women with major depression. Furthermore, the links between ACTH and cortisol secretory episodes and arousal are believed to reflect the role of central corticotropin releasing hormone system in arousal (35, 36). Whereas we expected that ApEn for cortisol would also be increased, *i.e.* more disorderly, this was not seen. The absence of a change in ApEn of cortisol secretion is consistent with the lesser degree of coupling observed between ACTH and cortisol in the forward X-ApEn analysis.

Despite the documented resistance to glucocorticoid in patients with major depression (37, 38), no differences were observed between patients and matched control subjects in reverse X-ApEn, which measures pattern synchrony of cortisol feedback on ACTH. This may be because the resistance to glucocorticoids seen in depression is one of degree rather than of timing disruption, thus preserving cortisol and ACTH synchrony. Furthermore, the increased ACTH ApEn is consistent with findings of reduced feedback secondary to target-gland failure (34). However, because cortisol was not decreased in women with major depression, the increased ACTH drive in the face of normal to increased cortisol supports resistance to negative feedback in these depressed women. It should be noted that ApEn was more sensitive in detecting the increased ACTH drive than ordinary statistics such as ANOVA, in which no significant differences in ACTH secretion were observed (Table 2). However, our pulse analysis did observe significantly increased area under the curve ACTH in the basal (nonpulsatile) secretion of ACTH in depressed women (5). Thus, ApEn may be more

TABLE 1. Descriptive data on depressed and control subjects

	Controls	Depressed patients
Age (yr)	29.25 ± 7.8	29.25 ± 7.9
Body mass index (kg/m^2)	24 ± 4.5	25 ± 4.8
Menstrual phase	12 F: 12 L	12 F: 12 L
Hamilton Depression Rating Scale	1.05 ± 1.5	17.3 ± 4.56

Data are expressed as mean ± SD. F, Follicular; L, luteal.

TABLE 2. ApEn data from depressed and control subjects

Measure	Controls (n = 24)	Depressed patients (n = 24)	*P*
Mean 24-h ACTH	3.67 ± 1.3	3.96 ± 1.5	ns
Mean 24-h cortisol	7.6 ± 2.5	8.4 ± 2.9	ns
ACTH ApEn	1.02 ± 0.04	1.13 ± 0.03	0.03
Cortisol ApEn	1.07 ± 0.03	1.08 ± 0.02	ns
ACTH-cortisol X-ApEn	1.29 ± 0.04	1.36 ± 0.03	0.05
Cortisol-ACTH X-ApEn	1.25 ± 0.03	1.30 ± 0.02	ns

Data are expressed as mean ± SD. ns, Not significant.

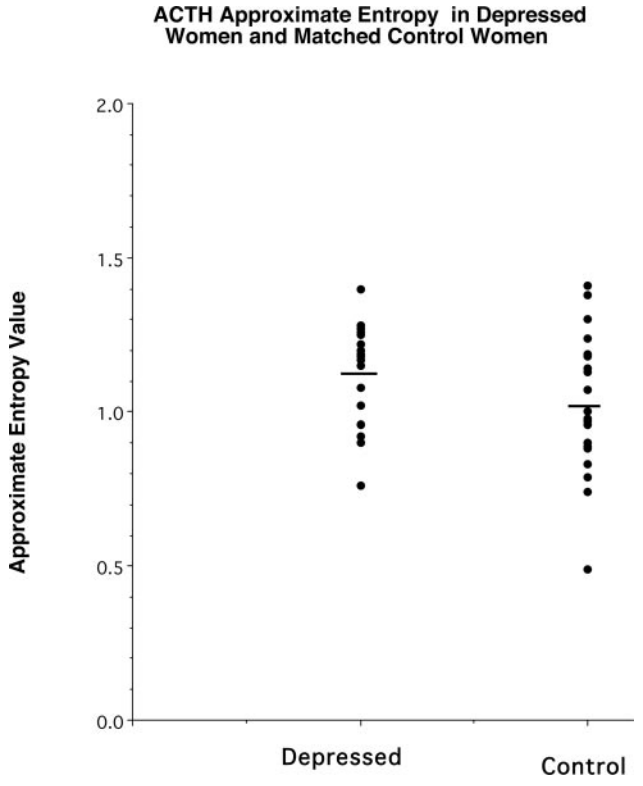

FIG. 1. Plot of ACTH ApEn values for 24 matched pairs of subjects. As can be seen, depressed women demonstrate a shift to higher numbers of ApEn, indicating more disorderly secretion. *Bars* indicate mean values.

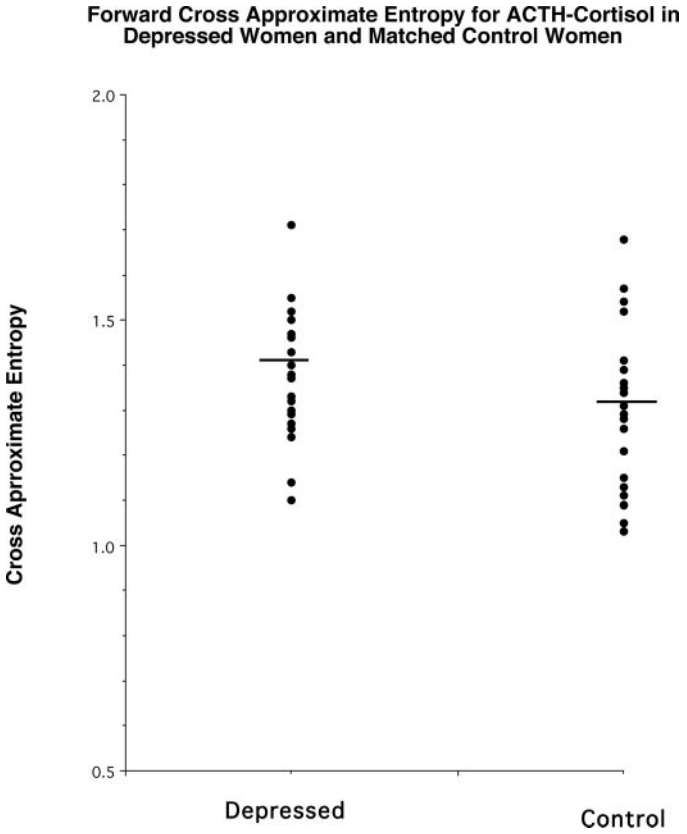

FIG. 2. Plots of forward X-ApEn (ACTH on cortisol) for 24 matched pairs of subjects. Again, depressed women demonstrate greater X-ApEn than their matched control women. *Bars* indicate mean values.

useful to evaluate the subtle changes in HPA axis regulation seen in major depression than the usual time series approaches.

In previous studies of normal subjects (11, 12), synchrony between ACTH and cortisol measured by forward X-ApEn was greater than for cortisol and ACTH assessed by reverse X-ApEn. However, in this study they appear to be the same. It is unclear whether this is related to subject differences, sex differences (our subjects were only women), or assay differences. Finally, there is one report of increased ApEn of cortisol in men with major depression (39) who were sampled only once per hour. Because this schedule does not examine pulsatile ACTH and cortisol secretion, the greater randomness reported for cortisol in that report more likely reflects alterations in the circadian pattern of cortisol secretion than alterations in ultradian rhythms as found in the current report. Because we do not have data on men, we do not know whether similar changes in ACTH ApEn would be found in men. However, we have reported a number of differences in HPA axis activity between men and women with major depression including increased basal morning cortisol in women but not men; increased β-endorphin drive under evening metyrapone blockade in depressed women, compared with depressed men; and greater nonsuppression to dexamethasone in depressed women, compared with depressed men (40).

In conclusion, our data demonstrate greater randomness of ACTH release patterns in women with major depression, compared with age- and menstrual cycle day-matched control women. In addition, there was greater randomness in forward X-ApEn of ACTH-cortisol series. These outcomes together demonstrate central (ACTH) and peripheral (ACTH-cortisol) dysregulation with evidence supportive of increased ACTH drive and diminished negative feedback of cortisol on the increased ACTH drive.

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