Pituitary-Adrenal-System Regulation and Psychopathology During Amitriptyline Treatment in Elderly Depressed Patients and Normal Comparison Subjects

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Objective: This study was done to compare the effects of 6-week treatment with amitriptyline on hypothalamic-pituitary-adrenocortical (HPA) regulation in elderly depressed patients and age-matched comparison subjects. Method: A combined dexamethasone-suppression/CRH-stimulation (dexamethasone/CRH) test was administered before initiation of amitriptyline treatment and at the end of weeks 1, 3, and 6 of treatment. Thirty-nine depressed inpatients, mean age=69 years, completed the study. Fourteen normal volunteers, mean age=67 years, served as comparison subjects. Results: In relation to the comparison subjects, the depressed patients had a profoundly abnormal HPA response, in particular an exaggerated cortisol release in the dexamethasone/CRH test. This abnormality began to disappear after 1 week of treatment with amitriptyline. In contrast, amitriptyline did not affect neuroendocrine regulation in the comparison subjects at any time during the test period. Conclusions: The data suggest that amitriptyline affects HPA regulation in hypercortisolemic depression only, and they raise the possibility that normalization of its feedback control is related to the antidepressive effect of amitriptyline.

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Abnormal regulation of hypothalamic-pituitary-adrenocortical (HPA) system feedback is common during depressive illness, albeit not specific for this disorder (for a review, see reference 1). A current concept of neuroendocrine regulation in depression assumes that increased central production and/or release of corticotropic-releasing hormone (CRH) initiates and possibly maintains the endocrine abnormalities found in depressed patients (2). This concept is supported by studies showing high CRH levels in CSF and a lower than normal number of central CRH receptors among depressed patients (3, 4). Also compatible with this notion are results from the dexamethasone suppression test (DST) (5) and from CRH-stimulation tests that demonstrate a blunted adrenocorticotropic hormone (ACTH) response to CRH in patients with major depression (6–8).

Studies from our laboratory (9) have shown that in normal subjects pretreatment with dexamethasone suppresses in a dose-dependent manner pituitary-adrenocortical responsiveness to CRH (dexamethasone/CRH test), whereas in depressed patients this same pretreatment results in an increased hormonal response to CRH. The dexamethasone/CRH test consists of two parts. In the pre-CRH segment cortisol concentrations correspond to those in the conventional DST, and test results presumably reflect a mixture of glucocorticoid feedback and endogenous CRH drive and therefore represent global control of adrenal function. Application of a standardized amount of CRH (post-CRH part) ensures a similar input stimulus and then tests feedback. Thus, it is assumed that the dexamethasone/CRH test provides additional and more specific information on regulation of HPA system feedback in depression.

Previous studies of HPA function in depression have demonstrated that successful antidepressant treatment leads to normalization of baseline neuroendocrine abnormalities as assessed by the DST (for a review, see reference 10). It is still a matter of debate whether this neuroendocrine normalization is secondary to resolution of depressive symptoms or an effect of the antidepressant treatment per se. Preclinical studies have generated the hypothesis that antidepressant-induced restoration of negative feedback is required for the clinical efficacy of these drugs, and such investigations have renewed the interest in studying HPA function in depression in order to examine whether the assumptions about the mechanisms of action of antidepress-
TABLE 1. ACTH, Cortisol, and Depression Measures for Elderly Depressed Patients, Grouped by Response to Treatment, and Age-Matched Comparison Subjects Receiving Amitriptyline Treatment Who Were Given the Dexamethasone-Suppression/CRH-Stimulation Test

<table>
<thead>
<tr>
<th>Time and Group</th>
<th>Basal Plasma ACTH</th>
<th>Basal Plasma Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level (pmol/liter)</td>
<td>Significant Difference</td>
</tr>
<tr>
<td>Placebo week</td>
<td>Mean SD t df PC</td>
<td>420 ± 20 70 ± 10</td>
</tr>
<tr>
<td>Responders (N=21)</td>
<td>3.2 ± 2.0 3.0b 33 ± 0.01</td>
<td>420 ± 20 70 ± 10</td>
</tr>
<tr>
<td>Nonresponders (N=18)</td>
<td>3.7 ± 1.7 4.5a 30 ± 0.01</td>
<td>280 ± 22 180 ± 10</td>
</tr>
<tr>
<td>Comparison subjects (N=14)</td>
<td>1.5 ± 0.9 3.7a 51 ± 0.01</td>
<td>410 ± 32 40 ± 10</td>
</tr>
<tr>
<td>After treatment week 1</td>
<td>Responders (N=21)</td>
<td>2.3 ± 1.2 2.5d 30 ± 0.02</td>
</tr>
<tr>
<td>Nonresponders (N=18)</td>
<td>2.8 ± 1.5 2.5d 30 ± 0.02</td>
<td>260 ± 21 120 ± 10</td>
</tr>
<tr>
<td>Comparison subjects (N=14)</td>
<td>1.6 ± 1.2 2.1e 51 ± 0.05</td>
<td>410 ± 32 40 ± 10</td>
</tr>
<tr>
<td>After treatment week 3</td>
<td>Responders (N=21)</td>
<td>2.2 ± 0.9 2.8c 31 ± 0.01</td>
</tr>
<tr>
<td>Nonresponders (N=18)</td>
<td>2.5 ± 1.3 2.7c 28 ± 0.02</td>
<td>240 ± 25 100 ± 10</td>
</tr>
<tr>
<td>Comparison subjects (N=12)</td>
<td>1.3 ± 0.8 2.9c 49 ± 0.01</td>
<td>280 ± 16 30 ± 10</td>
</tr>
<tr>
<td>After treatment week 6</td>
<td>Responders (N=21)</td>
<td>2.7 ± 1.9 2.4c 31 ± 0.05</td>
</tr>
<tr>
<td>Nonresponders (N=18)</td>
<td>2.5 ± 1.2 3.0a 28 ± 0.01</td>
<td>220 ± 17 100 ± 10</td>
</tr>
<tr>
<td>Comparison subjects (N=12)</td>
<td>1.3 ± 0.9 2.7c 49 ± 0.01</td>
<td>300 ± 16 40 ± 10</td>
</tr>
</tbody>
</table>

*N=21* dexamethasone, 1.5 mg, was administered at 11:00 p.m. the previous night. Human CRH, 100 µg, was administered at 3:00 p.m. Basal ACTH and cortisol were measured between 2:00 and 3:00 p.m. ACTH and cortisol areas under the curve, reflecting response to stimulation and measured between 3:00 and 6:00 p.m., were corrected for baseline values. Response to amitriptyline was defined as a drop in Hamilton score after 6 weeks of treatment of at least 30% from the baseline value or to below 10.

Subjects derived from the animal models can be extended to humans. A previous study from our laboratory (12) demonstrated that when depression and older age coincide, glucocorticoid dysregulation becomes more obvious. In addition, we have gathered experimental evidence that even in normal aging—without depression—an age-associated increase in HPA system activity (as determined by dexamethasone/CRH tests) occurs (13). Therefore, we chose to study only elderly individuals, assuming that older age would magnify drug effects on abnormal glucocorticoid regulation.

The objectives of the present study were therefore twofold. The first objective was to elucidate the time course of changes in dexamethasone/CRH test results and of psychopathological symptoms during treatment of depression. Therefore, we measured psychopathology and HPA status repeatedly before and three times during treatment. Second, to better understand the effects of antidepressant drugs on neuroendocrine status independent of underlying psychopathology we conducted an identical study protocol with age-matched physically and mentally healthy comparison subjects.

METHOD

Subjects

All patients admitted to the hospital were asked to participate in the study if they met the following inclusion criteria: age over 60 years, a present episode of major depression according to DSM-III-R, and a score of 18 or higher on the 21-item version of the Hamilton Depression Rating Scale (14). Patients with major medical disorders (e.g., stroke, heart failure, thyroid disorder, diabetes) were excluded, although subjects with mild and well-controlled hypertension were not. Also, patients with other major psychiatric disorders (e.g., dementia, substance dependence) were not enrolled in the study.

Thirty-nine inpatients (32 women and seven men) completed the study. They had a mean age of 69 years (SD=6, range=60–82), and their mean age at onset of depressive illness (i.e., first major depressive episode ever to occur) was 56 years (SD=15, range=21–80). Overall duration of illness averaged 13 years (SD=15, range=0–49), and the mean number of episodes (including the index episode) was 5 (SD=5, range=1–20). The degree of severity of depression ranged from moderate to severe; the mean score on the 21-item Hamilton depression scale was 26 (SD=6, range=18–40). None of the patients had been treated chronically (more than 6 months) with slow-release antipsychotics, benzodiazepines, barbiturates, lithium, or carbamazepine.

The mean body mass index of the patients was 24.5 kg/m² (SD=3.8, range=17–34).

Adepressed comparison subjects were recruited through newspaper advertisements; the exclusion criteria were identical to those for the patients. After a detailed explanation of the purposes and risks of the study protocol, the subjects who were willing to participate received the same thorough medical and psychiatric workup as the patients. Thereafter the subjects who were considered suitable for the study underwent the same study procedures as the patients, except that the normal control subjects were not hospitalized.

Fourteen volunteers (nine men and five women), with a mean age of 67 years (SD=5, range=60–76), served as normal comparison subjects. All comparison subjects were in good medical condition, were free of any psychoactive drugs, and had no personal or family history of psychiatric or neurodegenerative disorder. The body mass index of the volunteers averaged 24.5 kg/m² (SD=2.6, range=21–29).

Study Design

Upon admission to the study all previous psychoactive medications of the patients were tapered and discontinued, and the patients were kept free of psychoactive medications thereafter for at least 5 days. Subsequently, a placebo was administered for 1 week (baseline interval), at the end of which a dexamethasone/CRH test (to be described) was done, depression severity (Hamilton score) was assessed, and EEG...
and ECG recordings were made. After this baseline period, all participants received an oral dose of 75 mg of a slow-release preparation of amitriptyline, which they received at 10:00 p.m. daily for 6 consecutive weeks. After weeks 1, 3, and 6 of active treatment, dexamethasone/CRH tests were repeated and, for the patients, Hamilton scores were determined. Plasma levels of amitriptyline and nortriptyline were determined weekly. The patients’ primary care psychiatrists were kept blind to the plasma drug concentrations. Response to treatment was defined as a drop in Hamilton score after 6 weeks of active treatment of at least 50% from the baseline value or to below 10.

The protocol was approved by an independent ethics committee, and all participants gave written informed consent.

Dexamethasone/CRH Test

Each subject received an oral dose of 1.5 mg of dexamethasone at 11:00 p.m. the preceding night. At 1:30 p.m. the subject rested supine on a bed in a room alone, where he or she was observed by means of a video system and an intercom; a monitor and a speaker were located in the adjacent laboratory unit. An intravenous forearm catheter was connected to a long tube and passed through a soundproof lock into the laboratory. Heart rate and blood pressure were monitored automatically by means of a DINAMAP (Critikon, Norderstedt, Germany) throughout the test. Blood samples were drawn through the tubing every 15 minutes from 2:00 to 6:00 p.m. Blood samples from the intravenous line were kept patent with normal saline. At 3:00 p.m., 100 μg of human CRH reconstituted in 1 ml of 0.02% HCl in 0.9% saline were given as a bolus within 30 seconds. Blood was collected into prechilled tubes and was immediately centrifuged at 4 °C, and the plasma was frozen and stored at −20 °C (cortisol) or −80 °C (ACTH).

ACTH was measured by dual antibody immunoradiometric assay by means of a commercial kit. The intra-assay variability was 4% at an average concentration of 11 pmol/liter, and the interassay variability was less than 4% with a lower limit of detection at 1 pmol/liter. Cortisol was measured by using a commercial radioimmunoassay. Intra-assay variation was 4%–7%, and interassay variation was 5%–8%. Plasma levels of amitriptyline and nortriptyline were determined by high-pressure liquid chromatography with ultraviolet detection; interassay variability was below 8%.

### Data Analysis

For the dexamethasone/CRH tests, the mean cortisol and ACTH concentrations in the samples obtained between 2:00 p.m. and 3:00 p.m. were calculated and are reported as basal concentrations. The integrated stimulation responses after CRH infusion were calculated for each hormone according to the trapezoidal rule and are expressed as area under the time course curve corrected for baseline (area under the curve). The DST status was determined by the highest plasma cortisol level between 2:00 p.m. and 3:00 p.m.; a cutoff at 110 nmol/liter was used to define nonsuppression.

To explore the data set for global differences between patients and comparison subjects with regard to the dexamethasone/CRH test variables, a two-factor multivariate analysis of variance (MANOVA) with repeated measures design was performed. Group (patients versus comparison subjects) was the between-subjects factor and time [placebo (baseline) and weeks 1, 3, and 6 after treatment] was the within-subjects factor. In the case of a significant global effect, indicated by a p value less than 0.05 for the Wilks’s lambda, each dexamethasone/CRH test variable (basal concentration, area under the curve) was examined for effects of group and time by using tests with contrasts.

Repeated measures analysis of variance (ANOVA) was also used for statistical evaluation of different patient subgroups (responders versus nonresponders, DST suppressors versus DST nonsuppressors). Forward linear stepwise regression was computed in order to estimate the proportion of variance explained by different independent variables. Correlations among variables, expressed by Pearson’s correlation coefficients, were tested for significance by means of the t distribution (test of noncorrelation).

### RESULTS

#### Clinical Data

In the overall patient group there was a continuous drop in the degree of severity of depression throughout the 6 weeks of treatment (F=41.4, df=3, 38, p<0.0001). The first statistically significant decrease occurred only after 3 weeks of drug treatment (table 1).

There were no significant correlations between Hamilton depression score at baseline (placebo week) and number of previous episodes, overall duration of illness, or age. The patients’ mean steady-state plasma concentration of the tricyclic drug (amitriptyline plus nortriptyline) was 180 ng/ml (SD=80, range=70–430). Regression analysis revealed that only age had a major impact on the drug’s plasma concentration (r=0.6, N=39, p<0.01) when Hamilton scores at placebo week and at week 6, basal cortisol and ACTH concentrations at these two time points, and age were entered into the regression model.

In the comparison group, two female subjects were unable to complete the study because they experienced drowsiness, hypotension, and severe finger tremor after receiving amitriptyline for only a few days. Hence, baseline data from 14 subjects and treatment data from 12 subjects are reported. None of the remaining individuals complained about unpleasant effects of the drug; some reported easier
sleep onset at night while taking amitriptyline. The mean steady-state plasma concentration of amitriptyline plus nortriptyline was 118 ng/ml (SD=40, range=32–199).

Dexamethasone/CRH Test Results

Patients versus comparison subjects (table 1). MANOVA revealed a global difference between patients and comparison subjects with regard to dexamethasone/CRH test outcome variables (Wilks's lambda=0.41; F=3.1, df=16, 34, p<0.01). Repeated measures ANOVA, including all four time points, showed that there were significant differences between the patients and comparison subjects for ACTH basal concentration (F=14.1, df=1, 49, p<0.001), cortisol basal concentration (F=3.9, df=1, 49, p<0.05), and cortisol area under the curve (F=11.2, df=1, 49, p<0.01).

Pairwise comparison clarified that in the placebo week and in weeks 1, 3, and 6 the ACTH basal concentration was higher in the patients than in the comparison subjects (table 1). Only in the placebo week was the basal cortisol concentration significantly higher in the patients than in the comparison subjects, whereas the area under the curve for cortisol was larger for the patients in the placebo week and at weeks 1 and 3 but not at week 6.

Individual subject groups. Within the group of the 12 normal comparison subjects, repeated measures ANOVA revealed no time effect for the hormonal variables, all of which remained remarkably stable individually throughout the study (table 1). The nonsignificant decrease at week 3 of mean cortisol area under

TABLE 2. ACTH, Cortisol, and Depression Measures for Elderly Depressed Patients, Grouped by Response to Dexamethasone Suppression Test and Age-Matched Comparison Subjects Receiving Amitriptyline Treatment Who Were Given the Dexamethasone-Suppression/CRH-Stimulation Testa

<table>
<thead>
<tr>
<th>Time and Group</th>
<th>Basal Plasma ACTH</th>
<th>ACTH Area Under the Curve</th>
<th>Basal Plasma Cortisol</th>
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<tr>
<td></td>
<td>Level (pmol/liter)</td>
<td>Significant Difference</td>
<td>Level (nmol/liter)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>t</td>
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<tr>
<td>Placebo week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppressors (N=26)</td>
<td>3.1</td>
<td>1.7</td>
<td>3.2b</td>
</tr>
<tr>
<td>Nonsuppressors (N=13)</td>
<td>4.3</td>
<td>2.0</td>
<td>4.8d</td>
</tr>
<tr>
<td>Comparison subjects (N=14)</td>
<td>1.5</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>After treatment week 1</td>
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<td></td>
</tr>
<tr>
<td>Suppressors (N=26)</td>
<td>2.4</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Nonsuppressors (N=13)</td>
<td>2.9</td>
<td>1.7</td>
<td>2.4d</td>
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<td>Comparison subjects (N=14)</td>
<td>1.6</td>
<td>1.2</td>
<td></td>
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<tr>
<td>After treatment week 3</td>
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<td>Nonsuppressors (N=13)</td>
<td>2.6</td>
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<td>2.7d</td>
</tr>
<tr>
<td>Comparison subjects (N=12)</td>
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<td>0.8</td>
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<tr>
<td>After treatment week 6</td>
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<td>Suppressors (N=26)</td>
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<td>Nonsuppressors (N=13)</td>
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<td>1.3</td>
<td>2.7d</td>
</tr>
<tr>
<td>Comparison subjects (N=12)</td>
<td>1.3</td>
<td>0.9</td>
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</tr>
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</table>

aDexamethasone, 1.5 mg, was administered at 11:00 p.m. the previous night. Human CRH, 100 µg, was administered at 3:00 p.m. Basal ACTH and cortisol were measured between 2:00 and 3:00 p.m. ACTH and cortisol areas under the curve, reflecting response to stimulation and measured between 3:00 and 6:00 p.m., were corrected for baseline values. Nonsuppression on the dexamethasone suppression test was defined as a cortisol level above 110 nmol/liter between 2:00 and 3:00 p.m.
the curve is mainly due to the two comparison subjects who dropped out of the study after 1 week of amitriptyline administration because of unpleasant side effects. None of the normal volunteers escaped cortisol suppression after dexamethasone administration at any of the four tests. No significant correlation between any hormone variable and age, body mass index, or steady-state plasma concentration of amitriptyline plus nortriptyline was detectable.

As shown in figure 1, for the depressed patients there were significant time effects for basal plasma concentrations of both ACTH (F=9.2, df=3, 38, p<0.0001) and cortisol (F=6.3, df=3, 38, p<0.001). These hormone variables were highest in the placebo week, markedly decreased after 1 week of amitriptyline administration, and showed no further significant decrease; the differences between the placebo week and week 1 were significant for both ACTH (t=5.4, df=38, p<0.01) and cortisol (t=2.8, df=38, p<0.05). The areas under the curve for ACTH were similar at the four test occasions, whereas the areas under the curves for cortisol differed significantly (F=5.8, df=3, 38, p<0.001): the placebo week's area under the curve was larger than that at either week 3 (t=2.9, df=38, p<0.01) or week 6 (t=3.9, df=38, p<0.03), and the area under the curve at week 1 was greater than at week 6 (t=2.5, df=38, p<0.05) but did not differ significantly from that at week 3.

Basal cortisol concentration in the placebo week correlated best with severity of depression, as represented by the Hamilton depression scale score (r=0.6, N=39, p<0.01), when stepwise regression analysis was used with age, body mass index, duration of illness, age at onset, Hamilton score, and ACTH basal concentration in the placebo week as independent variables. The other dexamethasone/CRH outcome variables were not significantly correlated with severity of depression.

**Responders versus nonresponders (table 1).** For the purpose of the following analysis, response status was defined after 6 weeks of treatment with 75 mg/day of amitriptyline. Twenty-one patients (54%) were considered responders, and 18 (46%) were considered nonresponders. The two response groups did not differ in age, duration of illness, number of episodes, steady-state plasma drug level, or severity of depression at baseline evaluation. Repeated measures ANOVA showed time effects similar to those described for the entire patient group; thus, only group differences are reported here. Overall, no significant group differences were found for any ACTH variable or for cortisol area under the curve; from placebo week to week 6, cortisol areas under the curve were reduced to similar degrees (−40%) in the responders and nonresponders.

Of the 21 responders, there were four nonsuppressors at baseline, two after week 1, none after week 3, and one after week 6. Of the 18 nonresponders, there were nine nonsuppressors at baseline, seven after week 1, four after week 3, and five after week 6. Repeated measures ANOVA revealed the baseline cortisol concentration to be significantly higher in the nonresponders (F=11.0, df=1, 37, p<0.01), but it decreased in both groups to similar degrees (responders, −43%; nonresponders, −44%) during treatment (table 1).

**DST suppressors versus DST nonsuppressors (table 2).** For the purpose of this analysis, DST status in the placebo week was used to define nonsuppression. Again, the time effects were similar to those of the entire patient group. Thus, they are not reported here. Of the 39 patients, 13 (33%) escaped dexamethasone suppression. None of the variables age, number of previous episodes, body mass index, or age at onset differentiated the nonsuppressors from the suppressors. The nonsuppressors were more severely depressed than the suppressors (F=7.9, df=1, 37, p<0.01). In pairwise testing this difference was significant in the placebo week, in week 1, and in week 6. ACTH basal plasma levels and cortisol areas under the curve were similar at all time points. Basal cortisol plasma concentrations were higher in the nonsuppressors (F=35.5, df=1, 37, p<0.0001); this difference was significant (t tests) for all time points in the study. Five of the 13 nonsuppressors in the placebo week did not change DST status at any of the later test occasions.

**DISCUSSION**

This study confirms and extends several earlier findings about the relationship between HPA system dysfunction and the clinical course of treatment in major dep-
expression (15). First, the initially high cortisol concentrations after dexamethasone pretreatment decreased during amitriptyline treatment in advance of clinical improvement. As a group, the treatment responders had basal cortisol concentrations similar to those of the comparison subjects at baseline. After 1 week of treatment and a clinically minimal reduction of the Hamilton depression score, from 25 to 21 (−16%), the small number of nonsuppressors in this group (N=21) was already reduced from four to two. With complete clinical recovery after 6 weeks and a reduction of more than 70% in Hamilton scores, only one responder escaped cortisol suppression. Even the nonresponders (reduction in Hamilton score of only 14% after 6 weeks of amitriptyline) had a reduction in basal cortisol concentration of 44% from initial concentrations, and the number of nonsuppressors in this group (N=18) was reduced from nine to five. The basal cortisol concentration was the only dexamethasone/CRH test outcome variable significantly associated with clinical severity of depression.

Second, the cortisol response after dexamethasone pretreatment and CRH stimulation (cortisol area under the curve) was similarly abnormal in the responders and nonresponders whether they had been suppressors or nonsuppressors at baseline. The normalization of cortisol area under the curve continued over the time of the study in all patient groups. It was incomplete but reached, in all subgroups, a degree similar (−40%) to the degree of normalization of basal cortisol concentration. Changes in the cortisol area under the curve were independent of the clinical treatment response.

Third, the higher ACTH concentrations after dexamethasone pretreatment (ACTH basal concentration) in the patients than in the comparison subjects was not reversed by amitriptyline treatment within the observation period and was not explained by responder or suppressor status.

Fourth, HPA regulation in the normal comparison subjects remained unaffected by amitriptyline.

The data from this study and from preclinical research offer intriguing new material for discussion of how HPA system abnormalities, psychopathology, and drug effects might be intertwined. Throughout this study, normalization of psychopathology and of HPA axis function were interrelated, as reflected by the association between hormonal secretion and response to therapy. Yet the time course of this relationship is hardly compatible with the assumption that normalization of the HPA axis is secondary to normalization of depressive symptoms; in that case, a delayed response of HPA axis function to treatment would have been expected.

Preclinical research has provided descriptions of some mechanisms through which tricyclic antidepressants may affect regulation of the HPA axis. Studies with rats have demonstrated that glucocorticoid secretion is under the regulatory control of two different receptors: the mineralocorticoid receptor and the glucocorticoid receptor, both of which bind glucocorticoids (for a review, see reference 16). Glucocorticoid receptors are widely distributed throughout the brain, whereas mineralocorticoid receptors predominate in the hippocampus. Under baseline conditions, hippocampal mineralocorticoid receptors attenuate HPA axis activity while glucocorticoid receptors oppose this action. Under conditions of high glucocorticoid secretion, the inhibitory effects of hypothalamic and pituitary glucocorticoid receptors dominate. Long-term exposure to high glucocorticoid concentrations, as in depression, may alter the relative capacity of glucocorticoid and mineralocorticoid receptors, resulting in altered feedback control of CRH, ACTH, and cortisol secretion. It is postulated that the abnormalities observed during the stimulation part of the dexamethasone/CRH test in depressed patients are correlates of these receptor alterations. In preclinical studies amitriptyline and other antidepressants have been shown to increase concentrations of both mineralocorticoid receptor mRNA (17) and glucocorticoid receptor mRNA (18) and to reduce levels of CRH mRNA (17). Further, Reul et al. (19) observed a rise in hippocampal mineralocorticoid receptors, a decrease of corticosterone, and an up-regulation of hypothalamic glucocorticoid receptors during amitriptyline treatment of rats. Finally, a recent study of depressed patients treated with the 11-β-hydroxylase inhibitor ketoconazole (20) suggests that strategies aimed at glucocorticoid regulation might be promising treatments for depression (21).

Unlike Reul et al. (19), we failed to observe an effect of amitriptyline on HPA function in normal elderly comparison subjects. The doses administered to rats in the cited preclinical studies were approximately three times as high (per weight) as those given to our human subjects but were compensated for by a higher rate of metabolism and resulted in similar plasma concentrations. Still, it might well be that the plasma drug levels in the comparison subjects were below a hypothetical threshold necessary to affect HPA system function in healthy human comparison subjects to a degree sufficient to be reflected in dexamethasone/CRH testing. In addition, since we had only a small number of female comparison subjects, the lack of effect of amitriptyline on HPA system function should be regarded as preliminary. It could be that postmenopausal women, who tend to have more pronounced HPA system dysregulation (13) with aging than do men, respond to amitriptyline. On the other hand, it is well known that physiological systems in healthy humans do not respond to pharmacological interventions the way dysregulated systems do; for instance, aspirin does not lower temperature in nonfebrile humans, and diuretics do not lower blood pressure at doses effective in hypertensive patients.

Further findings worth commenting on are the discrepancies between basal ACTH and cortisol concentrations and responses. Although this is a phenomenon well known from studies of the HPA and other hormonal systems (22, 23), its underlying mechanism has not
been elucidated. A potential explanation may be that since cortisol is the regulated variable in the HPA axis and ACTH is one of the regulators, cortisol may represent the activity of the system, whereas ACTH concentrations may be partially determined by the rate of change in the activity of the HPA system. Also, there is evidence that mild adrenal hyperplasia, secondary to increased pituitary ACTH release, occurs in depressed patients, possibly resulting in a dissociation between amounts of ACTH and cortisol secreted during neuroendocrine test procedures (24, 25). Finally, a recent study with aged rats suggests a loss of sensitivity of the adrenal gland to plasma ACTH levels (26).

Finally, this study demonstrates some new characteristics of the dexamethasone/CRH test. First, the data from the normal comparison subjects indicate a high stability of dexamethasone/CRH test outcome. Second, the data from the depressed patients show that the basal concentration (the “DST part” of the dexamethasone/CRH test) and the stimulation values (cortisol area under the curve) reflect two independent aspects of HPA function; while the DST status before initiation of treatment shows a good correlation with the severity of depression, cortisol area under the curve reflects an abnormality of HPA system feedback regulation that is common to responders and nonresponders and to suppressors and nonsuppressors and that gradually normalizes during amitriptyline treatment.

In summary, our data support the notion of a major role of the normalization of HPA function in the response to tricyclic medication in depressed patients. The characteristics of the response are in accordance with the assumption of a specific effect of tricyclic medication on HPA function and its control mechanisms as a determinant of antidepressive efficacy.

REFERENCES

8. Amsterdam JD, Maislin G, Winokur A, Klinger M, Gold P: Pituitary and adrenocortical responses to the ovine corticotropin-releasing hormone in depressed patients and healthy volunteers. Arch Gen Psychiatry 1987; 44:775–781
25. Amsterdam JD, Maislin G, Winokur A, Klinger M, Gold P: Pituitary and adrenocortical responses to the ovine corticotropin-releasing hormone in depressed patients and healthy volunteers. Arch Gen Psychiatry 1987; 44:775–781