Cortisol Levels Predict Cognitive Impairment Induced by Electroconvulsive Therapy

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Background: *Elevated glucocorticoids may increase the vulnerability of the brain to the adverse effects of repeated seizures. This study tested the hypothesis that higher ambient cortisol levels would predict increased cognitive impairment in depressed patients subsequent to receiving electroconvulsive therapy (ECT) for major depression.*

Methods: *Sixteen subjects provided three samples of saliva the day before receiving unilateral nondominant ECT. Measures of mood, global cognitive functioning, attention, executive function, verbal and visuospatial memory, and visuospatial processing speed were obtained 1 day before the first ECT and 1 day after the sixth ECT treatment. The relationship between basal salivary cortisol obtained before the first ECT treatment and the change score of each cognitive measure after the sixth ECT treatment was examined and tested with Pearson correlation coefficients.*

Results: *Electroconvulsive therapy treatments delivered over 2 weeks resulted in a significant improvement in mood and a decline in most measures of cognitive performance. Elevated basal cortisol was associated with a greater decline in performance of executive function, visuospatial processing speed, and verbal memory.*

Conclusions: *Although this study is limited by the small number of subjects and the high number of comparisons, all significant correlations were consistent with the hypothesis that elevated cortisol predicts a greater degree of ECT-induced cognitive impairment.* Biol Psychiatry 2001;50: 331–336

Key Words: Cortisol, major depression, electroconvulsive therapy, cognitive impairment, memory

Introduction

The cognitive effects of electroconvulsive therapy (ECT) have been extensively studied (Squire 1986) and have engendered the most concern about the safety of ECT (Sachs and Gelenberg 1988). The American Psychiatric Association's Task Force Report on the Practice of Electroconvulsive Therapy (American Psychiatric Association 1990) affirmed the safety of ECT and concluded that to date there is no objective evidence that ECT, as administered by contemporary standards, results in any permanent loss in the ability to learn new information or to retrieve memories that were intact before treatment. Electroconvulsive therapy causes an acute confusional state and anterograde and retrograde amnesia for events proximal to the treatment administration (Daniel and Crovitz 1986; Sackheim et al 1986). The postictal memory loss is similar to that experienced by patients with epilepsy (Sachs and Gelenberg 1988). The memory loss for events immediately preceding, during, and after the treatment course can be permanent (Squire 1986). The ability to learn new information and to retrieve memories that were intact before treatment returns within weeks of completing treatments (Steif et al 1986; Weiner et al 1986).

Most studies that have examined predictors of the cognitive side effects of ECT have focused on methods of anesthesia, electrical stimulus parameters, electrode placement, or concurrent use of psychotropic medications (Miller et al 1985; Sackeim et al 2000; Sackheim et al 1986; Weiner et al 1986). Very little is known about patient-related factors that contribute to ECT-induced cognitive impairment. Theoretically, if risk factors for ECT-related cognitive side effects were better characterized, clinicians would be able to inform patients of this risk and potentially implement prophylactic interventions. Kiraly et al (1999) reported that a small group of subjects defined as having elevated cortisol either immediately before or after ECT had more postictal confusion rated 5–6 hours after ECT than subjects without elevated cortisol at either time point. However, it is unclear in this study if this relationship was driven by patients who had more potent electrical stimuli or had longer seizures in which greater confusion and higher cortisol levels would be ex-

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pected (Aperia et al 1985; Florkowski et al 1996). If higher diurnal cortisol levels before starting treatment predict worse cognitive impairment resulting from ECT, then pre-ECT administration of antiglucocorticoid agents may have the potential to limit the iatrogenic memory disturbance.

Many patients with major depression have hypercortisolemia or hypercortisoluria, suggesting a dysregulation of the limbic–hypothalamic–pituitary–adrenal axis (American Psychiatric Association 1987; Carroll et al 1981; Reus 1985; Rubinow et al 1984). Several studies have shown that depressed patients with hypercortisolemia have more cognitive impairment (Reus 1982; Rubinow et al 1984; Winokur et al 1987; Wolkowitz et al 1990), but few studies have examined whether hypercortisolemia predicts greater deficits after cognition-disrupting interventions. Horne et al (1984) found that patients administered dexamethasone while receiving ECT had more memory impairment and less of an antidepressant response than patients receiving placebos. If similar effects were seen with endogenous hypercortisolism, this would suggest that patients with elevated pre-ECT cortisol levels might suffer greater post-ECT memory impairment and less of an antidepressant response.

Elevated cortisol increases the vulnerability of the brain to the adverse effects of repeated seizures (Elliott et al 1993; Smith-Swintosky et al 1996; Stein-Behrens et al 1994). Thus, it is possible that depressed patients with hypercortisolism may have greater cognitive impairment induced by ECT. This study was designed to test this hypothesis by examining the relationship between ambient cortisol levels immediately before a course of ECT therapy and the decrement in cognitive performance induced by convulsive therapy. Secondarily, we sought to determine if ambient cortisol levels predicted the antidepressant efficacy of ECT.

Methods and Materials

This study examines the relationship between basal salivary cortisol and seizure-related cognitive impairment in patients before and after receiving six unilateral, nondominant ECT treatments titrated to 2.5 times the seizure threshold. The study involved a convenience sample of 16 patients who for clinical reasons had consented to ECT for treatment of major depression. After complete description of the study to the subjects, written informed consent was obtained. The research protocol and consent procedures were approved by the institutional review board of the California Pacific Medical Center. Subjects were included if they met the DSM-III-R diagnosis of major depression or bipolar disorder, depressed; were at least 21 years old; and were able to understand the procedures to give informed consent and to participate voluntarily. Subjects were excluded if they met DSM-III-R criteria for alcohol or drug dependence within the past 6 months; had a history of multi-infarct dementia, Parkinson's disease, or other neurologic disorder; or were taking benzodiazepine, anticholinergic, or anticonvulsive medication. Subjects over the age of 55 had a brain computed tomogram or magnetic resonance image and were excluded if there was evidence of brain disease. Our sample included 11 women and five men with a mean age of 49.9 (SD = 11.6). Our subjects had an average of 14.9 years of education (SD = 1.7), most were right-handed ($n = 15$), and all were on concurrent antidepressant medication.

Patients received six unilateral nondominant hemisphere ECT treatments on mornings over a period of approximately 2 weeks. The 2-week interval between the two cognitive assessments was chosen because most patients require at least six treatments and most have some degree of ECT-induced cognitive impairment at that time (Squire and Slater 1983). The ECT stimulus was administered to the nondominant hemisphere at the d'Elia frontoparietal electrode placement (d'Elia 1970) using 2.5 times the seizure threshold determined at the first treatment (Sackeim et al 1987). The ECT device used was a Mecta (Lake Oswego, Oregon) SR-2 model that delivers an electric stimulus in volleys of brief pulses of bidirectional square waves. As is the standard of ECT practice, the patients were monitored by electrocardiogram, oximetry, electroencephalogram, and blood pressure measurement. All patients were hyperoxygenated during the procedure, as this has been found to reduce ECT-induced cognitive impairment (Sachs and Gelenberg 1988). To limit the variability to which patients are exposed to drugs that affect memory, the anesthesia was standardized to include the following agents: sodium pentothal for barbiturate anesthesia, succinyl choline for neuromuscular blockade, and esmolol if attenuation of tachycardia and hypertension was judged by the anesthesiologist to be necessary.

Subjects gave samples of saliva at 8:00 AM, 4:00 PM, and 10 PM the day before their first ECT treatment. Saliva was sampled in 2-mL aliquots and stored frozen at −70°C. Salivary cortisol was assayed by radioimmunoassay at Aeron Laboratories in San Leandro, California, which report a coefficient of variability (CV) of 10% for a target of 4.0 ng/mL.

Cognitive function was assessed the afternoon of the day before the first ECT treatment and the afternoon of the day after the sixth ECT treatment. The measures are listed according to the domain they quantify: 1) mood, Hamilton Depression Scale (Hamilton 1967); 2) global cognitive functioning, Mattis Dementia Rating Scale (Mattis 1976); 3) attention/concentration, Trail-making Test (Army Individual Test Battery 1944; Reitan 1958); 4) executive function, Stroop Color and Word Test (Golden 1976, 1978; Stroop 1935) and the Symbol Digit Modalities Test (Smith 1968, 1973); 5) visuospatial memory, Wechsler Memory Test subtest of Visual Recall (Wechsler 1945); 6) visuospatial processing speed, Employee Aptitude Survey (Ford et al 1958); and 7) verbal memory, California Verbal Learning Test (CVLT) (Delis et al 1988). This battery of tests took on average 90 min to administer.

The effect of ECT on mood and the cognitive measures was examined and tested with paired *t* tests (two tailed). The relationship between basal salivary cortisol obtained at 8:00 AM, 4:00 PM, and 10 PM and the change score of each of 12 cognitive measures was examined and tested with Pearson correlation coefficients.

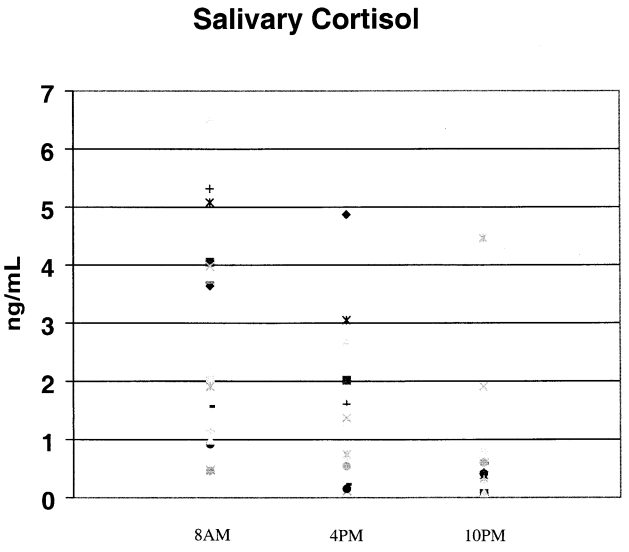

Figure 1. Salivary cortisol levels for the 16 subjects.

Results

The salivary cortisol levels for the 16 subjects are presented in Figure 1. The highest and lowest levels were found in the morning and evening samples, respectively, showing the expected diurnal pattern of cortisol release. There were no significant correlations between salivary cortisol levels, at any of the three sample times, and baseline mood, number of previous depressive episodes, duration of the current depressive episode, or baseline performance on the cognitive measures.

The effect of ECT on mood and cognition is presented in Table 1. Electroconvulsive therapy resulted in a statistically robust improvement in ratings of depression. Electroconvulsive therapy also was associated with a decline in cognitive functioning for most but not all measures of cognitive performance. Although all subjects received nondominant unilateral ECT, the largest decrements in performance were in the measures of delayed verbal recall. Visual processing speed, but not visual memory, significantly worsened with ECT treatment. Global cognitive functioning and executive function also deteriorated with moderate to large effect sizes. Attention was only modestly affected by ECT treatment. There was no significant correlation between the change in Hamilton depression rating in response to ECT and the change in any of the 12 cognitive measures.

All significant and trend level correlations between baseline cortisol measures and the change (time 2 − time 1) in cognitive performance are presented in Table 2. Significant inverse correlations between basal cortisol and change in cognition were found for the Symbol Digits Modalities Test, Perseverations and Percent recall consistency in the CVLT, the Stroop Color and Word Test, and visuospatial processing speed as indexed by the Employee Aptitude Survey. All of these correlations were consistent with the hypothesis that higher baseline cortisol levels predicted more ECT-induced cognitive impairment. Trend-level inverse correlations were found for the Mattis Dementia Rating Scale and the Stroop Color Test, which is also consistent with our main hypothesis. The only trend-level correlation between baseline cortisol and change in cognitive performance that was not consistent with our hypothesis was the number of recognition hits on the CVLT. Of note, as seen in Table 1, the change in recognition hits was not significantly affected by ECT treatments. Unlike the study reported by Horne et al (1984), elevated cortisol at baseline was not associated with diminished antidepressant response. Cortisol levels were not related to seizure duration or mean electrical charge per ECT treatment.

Discussion

This study provides preliminary support for the hypothesis that elevated cortisol levels predict more cognitive impairment induced by a course of ECT. The study is limited by the small sample size, the use of point measures of cortisol, and the large number of comparisons that increase the experimentwise error rate. Thus, the correlation of basal cortisol with the decline in performance on any one of the cognitive measures has to be interpreted cautiously because of the high likelihood of false positive results. However, the strength of the findings lies in the near consistency of the group of significant correlations that show the positive relationship between baseline cortisol and the magnitude of ECT-related impairment. The only finding not consistent with this relationship was the trend-level correlation between baseline cortisol and change in recognition hits on the CVLT. Of note, this association was the only significant or trend-level correlation found with the 8:00 AM saliva samples, where the variability in cortisol levels is the highest. Several studies have shown that abnormalities in the diurnal cortisol rhythm in depressed subjects are best detectable in evening cortisol levels (Young et al 1994).

These data indirectly support the hypothesis posed by Sapolsky and others that elevated glucocorticoids predispose the brain to greater malfunction and injury from seizures (Sapolsky 1985, 1986a, 1986b). Elevated levels of glucocorticoids may endanger the brain or compromise its function by a number of mechanisms including altering brain glucose metabolism, potentiating the toxic effect of excitatory amino acids such as glutamate, and impairing neurotrophic factors that may be crucial for neuronal recovery from injury (Sapolsky 1996). Electroconvulsive therapy is known to result in the release of glutamate, which theoretically can

Table 1. Effect of Six Electroconvulsive Therapy (ECT) Treatments on Mood and Cognitive Measures

Measure	Baseline mean (SD)	Post-ECT mean (SD)	Effect size[a]	*p* two tailed
Mood				
Total Hamilton	46.0 (8.5)	25.0 (15.2)	1.2	.000
Global cognitive functioning				
Mattis Dementia total	137.0 (11.3)	128.7 (15.9)	0.8	.009
Attention				
Trails A total	41.1 (17.9)	48.1 (22.4)	0.5	.065
Executive function				
Stroop Word	91.7 (20.1)	80.6 (16.9)	0.7	.016
Stroop Color and Word	37.3 (8.8)	34.7 (11.7)	0.4	.142
Symbol Digits total	41.1 (15.6)	32.2 (14.6)	0.7	.010
Visuospatial memory				
Wechsler delayed recall	5.4 (2.7)	4.0 (3.2)	0.5	.066
Visuospatial processing speed				
Employee Aptitude Survey	68.6 (23.3)	51.7 (29.4)	0.9	.002
Verbal memory (California Verbal Learning Test)				
Recall measures				
Trials 1–5 total	45.4 (13.3)	30.6 (13.4)	1.1	.000
Learning characteristics				
% recall consistency	79.3 (12.3)	65.9 (20.0)	0.7	.016
Response discrimination				
Perseverations	4.4 (4.3)	1.9 (2.0)	0.7	.011
Recognition hits	12.5 (2.9)	11.4 (4.0)	0.5	.084
Discriminability	88.7 (9.4)	78.5 (13.2)	1.1	.000

[a]Effect size equals the difference in means divided by the SD of subjects' change scores.

participate in a cascade of neuronal dysfunction (Charberlin and Tsai 1998). Glucocorticoids increase the extracellular concentrations of excitatory amino acids (EAAs), increase the postsynaptic sensitivity to EAAs, and mobilize calcium, which in turn may lead to cellular malfunction or injury (Sapolsky 1996).

At present, there is no evidence that ECT, as currently administered, causes brain damage (Devanand et al 1994). However, repeated high-dose electroconvulsive shock has been found to cause neuronal death in the hippocampus in studies of animals (Cavazos et al 1994). The electrical stimuli used in the animal studies are much higher than is clinically administered during ECT. Nevertheless, ECT-induced cognitive impairment may be related to a reversible neuronal injury that is potentiated by glucocorticoids. Interestingly, metyrapone, an inhibitor of cortisol synthesis, has been found to significantly reduce seizure-induced hippocampal damage caused by kainic acid in animals (Smith-Swintosky et al 1996; Stein and Sapolsky 1988). However, it is not known if antiglucocorticoid treatment would affect the reversible neuronal malfunction that is presumed to be induced by ECT in humans.

The pattern of ECT-related cognitive impairment is consistent with previous reports by Squire and others

Table 2. Significant and Trend-Level Correlations of Baseline Cortisol to Electroconvulsive Therapy–Related Decline in Cognitive Performance

Measure (time 2 − time 1)	8:00 AM *r* value (*p*[a])	4:00 PM *r* value (*p*[a])	10:00 PM *r* value (*p*[a])	Consistent with hypothesis?
Global cognitive functioning				
Mattis Dementia total		−.46 (.08)		Yes
Executive function				
Stroop Color and Word		−.50 (.046)		Yes
Symbol Digits total			−.54 (.03)	Yes
Visuospatial processing speed				
Employee Aptitude Survey		−.50 (.046)		Yes
Verbal memory				
% recall consistency		−.53 (.03)		Yes
Perseverations			.51 (.046)	Yes
Recognition hits	.48 (.06)			No

[a]Two tailed.

(Rubin et al 1993; Squire 1986). Our data suggest that multiple domains of cognition (e.g., memory, executive function, visuospatial processing speed) are affected by ECT. However, the results suggest that the most consistent set of correlations between basal cortisol and ECT-related cognitive impairment was predominantly in the domain of executive functioning. This suggests that the cortisol–ECT relationship preferentially involves the frontal lobes. The higher degree of perseverations with elevated cortisol on the CVLT adds further support to this hypothesis. Although much of the literature examining the effects of glucocorticoids on cognition and the brain has focused on the hippocampus, there is evidence that exogenous glucocorticoids affect frontal lobe functions such as working memory, executive control, selective attention, and response inhibition (Lupien et al 1999; Young et al 1999), though not all studies have found this (Newcomer et al 1999). Further, it is also known that, like the hippocampus, the frontal lobe has a high density of glucocorticoid receptors (Diorio et al 1993; McEwen et al 1968). Elevations in cortisol impair prefrontal dopamine metabolism and performance on tasks associated with the prefrontal cortex in rodents (Lindley et al 1999). It is possible that the most consistent set of correlations between cortisol and ECT-related cognitive impairment is found with frontal lobe function, since this area of the brain is directly stimulated by the ECT electrodes. The electrical stimulus may affect glucocorticoid-sensitive neurons and lead to more impairment to frontal lobe function in those subjects with higher cortisol levels.

Future studies will be needed to replicate the findings in this report and to examine if the relationship between cortisol levels and ECT-induced cognitive impairment is restricted to cognitive tasks that rely on brain structures, such as the hippocampus and the frontal lobes, that have a high density of glucocorticoid receptors. Future studies might employ region-specific neuropsychologic tests that index areas that are both sensitive and insensitive to the effects of glucocorticoids. If the results of this study are replicated, depressed subjects consenting to ECT should be screened for cortisol output and informed that elevated cortisol levels may increase the risk for treatment-induced cognitive impairment. It is theoretically possible that antiglucocorticoid treatment in depressed subjects with hypercortisolism will reduce the adverse cognitive effects of ECT.

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