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EFFECTS OF SINGLE AND REPEATED ELECTROCONVULSIVE THERAPY SESSIONS ON PLASMA ACTH, PROLACTIN, GROWTH HORMONE AND CORTISOL CONCENTRATIONS

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SUMMARY

To study the effects of electroconvulsive therapy (ECT) on hormone release, we measured circulating concentrations of adrenocorticotropic hormone (ACTH), prolactin (PRL), growth hormone (GH) and cortisol (CORT) immediately before and at 2 min, 5 min, 15 min, and 30 min following ECT. Compared to pre-ECT concentrations, there were significant increases in post-ECT plasma ACTH, PRL and CORT. GH did not change consistently. No significant difference between unilateral and bilateral ECT was observed. Compared to the first ECT, repeated treatments were associated with a significant decrease in the magnitude of hormone surge. These hormonal changes induced by ECT may reflect changes at the neurotransmitter level.

INTRODUCTION

ALTHOUGH more than 50 years old, ECT remains one of the most effective, though sometimes controversial, treatments in psychiatry. Research and clinical experience over the years have resulted in a clear delineation of clinical indications, potential risks, and possible side effects (Weiner, 1979). A number of technical refinements have improved the safety of the procedure and reduced the frequency and severity of side effects. However, there is still a large gap in our knowledge of the mechanism(s) of action of ECT. Postulated theories about the mechanism of action include increase in the permeability of the blood-brain barrier (Bolwig *et al.*, 1977), changes in the rate of metabolism of specific neurotransmitters (Modigh, 1976), alterations in specific neurotransmitter receptor functions (Lerer & Belmaker, 1982), and changes in the pattern of hormonal secretion (Fink, 1980). While none of these mechanisms has gained universal acceptance as the principal mechanism by which ECT works, there is reason to believe that some of these mechanisms are interrelated. An increase in the rate of secretion of a specific neurotransmitter, for instance, may lead to downregulation of a specific neurotransmitter receptor and may also alter the rate of secretion of a specific hormone.

Several studies have shown that ECT is associated with a selective release of specific hormones (Whalley *et al.*, 1982). Whereas most reports indicate an increase in ACTH, PRL, and/or CORT levels following ECT (Aperia *et al.*, 1985; Whalley *et al.*, 1987), there is still

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controversy regarding the release of other hormones such as GH (Skrbanek *et al.*, 1981; Whalley *et al.*, 1987). Furthermore, little information is available regarding the effects on hormone release of treatment variables such as unilateral vs. bilateral electrode placement, duration of the seizure, and repeated ECT sessions. The present study was undertaken in an attempt to clarify some of these issues.

SUBJECTS AND METHODS

Subjects

Subjects for the study (n = 23) were all hospitalized psychiatric patients who were referred for ECT by their respective attending physicians. The mean (±SD) age was 44.9±15.7 yr. Seven patients were male; sixteen were female. Psychiatric diagnoses were made independently in accordance with the Diagnostic and Statistical Manual (DSM-III) by at least two psychiatrists: Nineteen patients were suffering from major depressive disorder; two were schizo-affective; one was manic; and one had catatonic schizophrenia. Patients with organic brain syndromes, endocrine diseases or neurological disorders were excluded. Nineteen patients were receiving one or more of the following medications: antidepressants (n = 7), neuroleptics (n = 7), lithium carbonate (n = 4), sedative-hypnotics (n = 2). Four patients were not receiving any psychotropic medications. Repeat hormonal assessment was performed on 13 patients at their last treatment. By then, these patients had received a mean (±SD) of 8.15± 0.99 (range 7–11) ECT sessions. Over the course of ECT, medications remained unchanged in 10 patients; one patient had his neuroleptic medication discontinued; one patient was started on an antidepressant; and one patient had his neuroleptic changed to an antidepressant. The procedure was explained to the patients and an informed consent was obtained.

ECT Procedures

ECT was administered between 0800h and 1000h three times per week following an overnight fast. All patients were premedicated with atropine sulfate (1.0 mg) intramuscularly given approximately 30 min prior to ECT. Anesthesia was induced with methohexital (0.75 mg/kg b.w.) given intravenously. Muscle relaxation was obtained with succinylcholine (0.5 mg/kg b.w.), also given intravenously. This was followed by an electrical stimulus provided by the MECTA machine, calibrated to provide a pulse width of 1.5 msec, a stimulus duration of 2.0 sec, and a pulse frequency of 30–50 Hz. Unilateral or bilateral electrode placement was carried out in accordance with the recommendation of the referring physician. Seizure duration was measured both clinically using the inflatable "cuff" technique and by an electroencephalogram (EEG). Ventilatory assistance was provided throughout the procedure, with 100% O_2. Over the course of ECT, the treatment stimulus was unchanged in eight patients. Pulse frequency was increased in four patients and was decreased in one patient. Pulse width and stimulus duration were unchanged throughout.

Hormone Measurements

Two sets of blood samples were drawn from a previously inserted forearm catheter at 2 min before and at 2 min, 5 min, 15 min, and 30 min following the start of the electrically-induced seizure. One blood sample was collected in a chilled tube containing edetic acid (EDTA) and used for measuring ACTH; the other sample was collected in a heparinized tube and used for measurements of PRL, GH and CORT. Plasma samples were separated by centrifugation as soon as possible after drawing and stored at -20° C.

All hormone measures were performed at the Clinical Research Center of the University of Iowa Medical Center, by radioimmunoassay as previously described (Pfohl *et al.*, 1985). For each hormone, all samples from a given patient were run in the same assay. The intra-assay coefficients of variation for all the hormones were <12%. The interassay coefficients of variation were <15%.

Statistical Analysis

Repeated measures analysis of variance (ANOVA) was conducted on the five consecutive measurements for each hormone. Where overall differences were significant, comparisons between baseline (pre-ECT hormone level) and each of the four post-ECT hormone concentrations were made for each hormone using paired *t*-tests. Similarly, comparisons of ECT-induced changes in hormone concentrations between the first and the last ECT were made with repeated measures ANOVA and subsequent paired *t*-test analysis. ANOVA also was used to

test for differences between unilateral and bilateral electrode placement during the first treatment. Correlations between seizure duration (both observed and EEG-measured) and post-ECT maximum hormone surge (Δ_{max}) defined as the difference between the highest post-ECT hormone value and the pre-ECT baseline value, were assessed with Pearson's r, which also were used to examine correlations between changes in seizure duration (both observed and EEG-measured) between the first and last ECT and significant changes in hormone release over the course of treatment. All tests were considered statistically significant at $p<0.05$, two-tailed. Results are expressed as means ± SD.

RESULTS

The effects of ECT on plasma ACTH concentrations are shown in Fig. 1. We found a significant effect of ECT on plasma ACTH [$F(4,52)=13.96$; $p<0.0001$]. Compared to pre-ECT baseline values, all four post-ECT ACTH concentrations were significantly elevated.

The effects of ECT on plasma PRL concentrations are shown in Fig. 2. Here also, we found a significant effect of ECT on plasma PRL [$F(4,60)=21.22$, $p<0.0001$]. Again, all four post-ECT PRL values were significantly higher than pre-ECT baseline values.

Figure 3 summarizes the changes in plasma GH concentrations as a result of ECT. There was a weak but nevertheless significant overall effect of ECT on plasma GH [$F(4,56)=2.67$, $p<0.05$]. However, there were no significant differences between baseline values and any of the four post-ECT plasma GH concentrations individually.

The changes in plasma CORT concentrations are shown in Fig. 4. There was a significant overall effect of ECT on plasma CORT [$F(4,56)=11.94$, $p<0.0001$]. This effect was due mostly to significant elevations in plasma CORT concentrations at 15 and 30 min following ECT. Plasma concentrations measured at 2 and 5 min following ECT were not significantly different from baseline.

Nine patients received unilateral ECT to the right (nondominant) cerebral hemisphere. Their mean (± SD) age was 48.2 ± 18.5 yr. Fourteen patients received bilateral ECT; their mean (± SD) age was 42.7 ± 14.0 yr. To examine the effects of unilateral and bilateral electrode placement on hormone release, we compared Δ_{max} between the two groups. There were no significant differences between unilateral and bilateral electrode placement in the maximum surge of any of the hormones studied (Table I).

We also examined the effect of seizure duration on the post-ECT maximum hormone surge. As expected, there was a strong correlation between the duration of the observed clinical seizure as determined by the "cuff" method and duration of the seizure activity as reflected in the EEG ($r=.71$; $p<0.001$). Table II shows the Pearson correlation coefficients between the observed seizure duration and Δ_{max} for ACTH, PRL, GH and CORT. There was a trend ($p<0.10$) for a positive correlation between seizure duration and maximum ACTH surge. However, there were significant associations between observed seizure duration and the maximum surge of PRL, GH or CORT. Similarly, there were no significant associations between the EEG seizure duration and Δ_{max} for any of the four hormones (data not shown).

In addition to the data obtained at the first ECT session, 13 patients had a repeat hormonal assessments at their last ECT. Figure 5 shows the effect of repeated ECT on plasma ACTH concentrations. The pattern of ACTH release was somewhat different between the first and last ECT sessions [$F(4,32)=2.648$, $p=0.051$]. This, however, was not because of significant differences in peak ACTH values, i.e., Δ_{max} ACTH [$F(1,12)=0.455$, $p=$ n.s.], but because of significant decreases in ACTH release at 15 min ($p<0.01$) and 30 min ($p<0.05$) following ECT during the last ECT session.

There also were significant differences in the pattern of PRL release between the first and

last ECT [$F(4,32)=3.832$, $p=0.012$]. As Fig. 6 indicates, these were at 15 and 30 min following ECT. Furthermore, unlike ACTH, peak PRL concentrations (Δ_{max} PRL) were significantly lower during the last ECT compared to the first [$F(1,12)=4.887$, $p=0.047$].

There were no significant differences between the first and last ECT in either the baseline or the four different post-ECT values for either plasma GH or CORT concentrations (data not shown).

There was a significant decrease in seizure duration between the first and last ECT, evident both when seizure duration was observed clinically ($t=4.253$; df=12; $p=0.001$) and as recorded on the EEG ($t=3.083$; df=12; $p=0.009$). We therefore investigated possible relationships between change in seizure duration over the course of treatment and changes in pattern or peak of hormone release. The only significant correlation was between the decrease in seizure duration between the first and last ECT as recorded by the EEG and the decrease in peak PRL release ($r=0.62$; n=13; $p<0.05$).

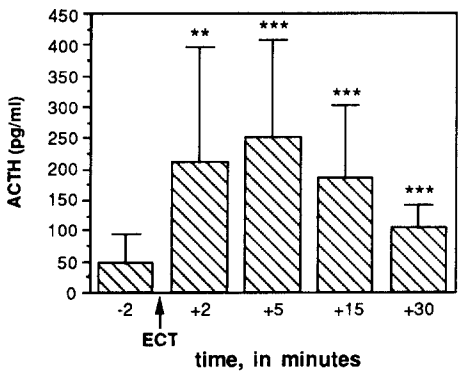


FIG. 1

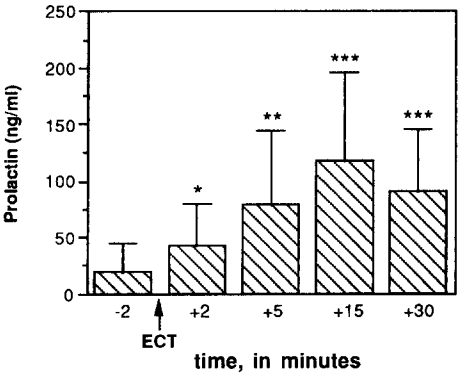


FIG. 2

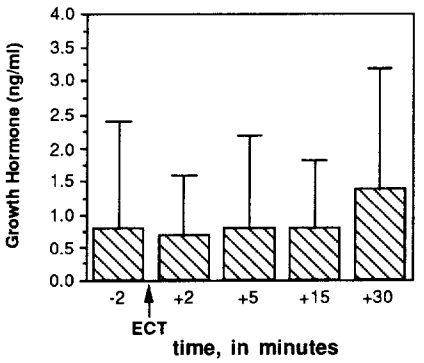


FIG. 3

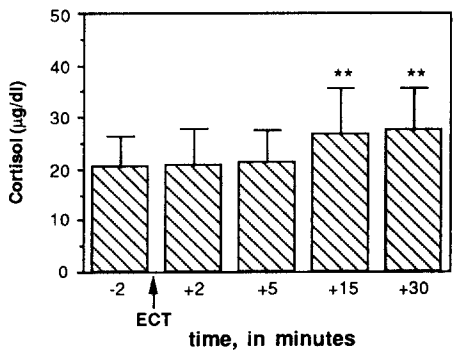


FIG. 4

FIGS. 1–4: Effects (mean + SD) of one ECT on plasma ACTH (Fig. 1), PRL (Fig. 2), GH (Fig. 3), and CORT (Fig. 4). For all figures, comparisons are between baseline and the different post-ECT values. $^{*}p<0.01$; $^{**}p<0.001$; $^{***}p<0.0001$.

TABLE I. COMPARISON OF UNILATERAL AND BILATERAL ELECTRODE PLACEMENT ON MEAN (±SD) POST-ECT MAXIMUM HORMONE SURGE (Δ_{MAX})

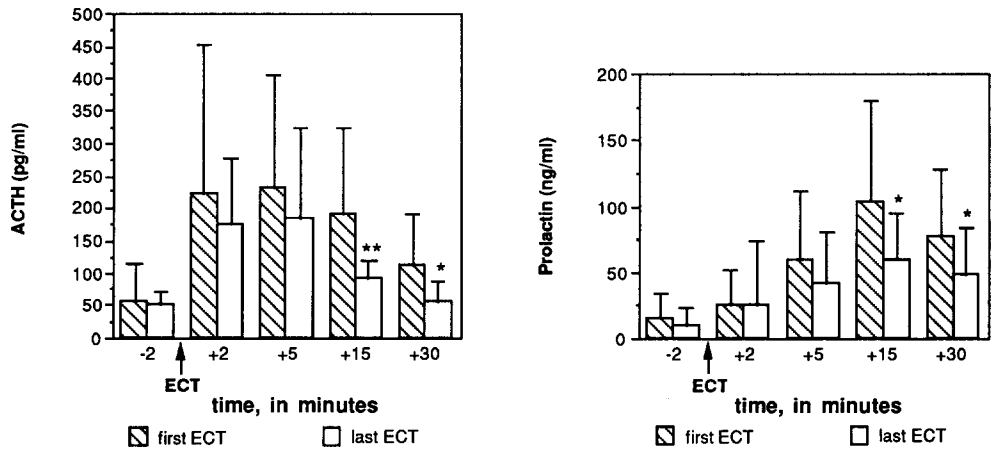
ECT Modality (n)	Δ_{max} ACTH (pg/ml)	Δ_{max} Prolactin (ng/ml)	Δ_{max} GH (ng/ml)	Δ_{max} Cortisol (μg/dl)
Unilateral (9)	257 ± 155	82 ± 76	0.86 ± 0.98	8.5 ± 6.6
Bilateral (14)	182 ± 126	103 ± 73	1.73 ± 2.15	9.8 ± 6.1
p	NS	NS	NS	NS

NS = not significant

TABLE II. CORRELATIONS BETWEEN OBSERVED SEIZURE DURATION AND POST-ECT MAXIMUM HORMONE SURGE (Δ_{MAX})

	Δ_{max} ACTH	Δ_{max} Prolactin	Δ_{max} GH	Δ_{max} Cortisol
Pearson's *r*	0.38	-0.19	-0.04	0.07
n	21	22	22	22
p	0.09	NS	NS	NS

NS = not significant



FIGS. 5–6: Effects (mean + SD) of repeated ECT on plasma ACTH (Fig. 5, left) and PRL (Fig. 6, right). For both figures, comparisons are between the first ECT and the last ECT.
*$p < 0.05$; **$p < 0.01$.

DISCUSSION

The purpose of this study was (1) to compare the circulating concentrations of ACTH, PRL, GH and CORT in relation to the administration of one session of ECT, (2) to examine the effect of unilateral vs. bilateral treatment on hormone release, (3) to examine the effect of seizure duration on hormone release, and (4) to compare the hormonal profiles of first and last ECT sessions.

Our findings show that one session of ECT produces a marked and significant increase in ACTH. This increase is already apparent 2 min following ECT, reaches its peak by 5 min following ECT, and starts to decline by 15 min following ECT. By 30 min, ACTH levels still are significantly elevated above baseline. These findings are consistent with the work of other investigators (Aperia *et al.*, 1984; Mathe *et al.*, 1987; Whalley *et al.*, 1987).

Similarly, one session of ECT produces a marked and significant increase in PRL, which reaches a peak at 15 min following ECT and starts to decline by 30 min. Again, these findings confirm previous reports (Whalley *et al.*, 1982; Deakin *et al.*, 1983; Aperia *et al.*, 1985; Whalley *et al.*, 1987).

The literature regarding the effects of ECT on GH release is rather confusing. Most researchers noted a wide variability in GH release following ECT, with no significant changes in either direction (Deakin *et al.*, 1983; Linnoila *et al.*, 1984; Haskett *et al.*, 1985). Some investigators noted a significant decline in GH release after ECT (Whalley *et al.*, 1987; Weizman *et al.*, 1987), while others noted a significant increase (Skrbanek *et al.*, 1981). Our results confirm the wide range of the GH response but do indicate a weak, albeit significant, effect of ECT on GH release. In addition to interindividual variability, part of the confusion in the literature is probably related to sampling time. Obviously, the more frequent the sampling time, the more the likelihood of detecting significant differences if such differences exist. It is therefore possible that, with more frequent sampling, our finding of an increase in GH release following ECT would have been more robust.

The effects of ECT on circulating levels of CORT have been more widely replicated. Most investigators have shown a modest, albeit statistically significant, increase in plasma CORT appearing 15–20 min following ECT (Deakin *et al.*, 1983; Aperia *et al.*, 1984; Whalley *et al.*, 1987; Weizman *et al.*, 1987). Our small but significant increases in plasma CORT concentrations at 15 and 30 min following ECT provide a further confirmation of these results. Occasional reports have failed to note an increase in CORT following ECT (Whalley *et al.*, 1982), but this may have been due to too short a sampling time.

Unilateral ECT has been presented as an alternative mode of treatment to bilateral ECT with possibly fewer side effects (Consensus Conference, 1985), but concerns about its efficacy have been raised (Abrams *et al.*, 1972). With regard to ECT-induced hormone release, it has been suggested that bilateral ECT was associated with a larger increment in hormone release than unilateral ECT, noted mostly in conjunction with PRL release (Swartz & Abrams, 1984). Little information is available regarding mode of treatment and release of other hormones. Our results show no significant difference in the magnitude of hormone release between unilateral and bilateral ECT for any of the hormones studied. However, contrary to most other studies comparing the effects of electrode placement on hormone release, our study made comparisons not within individual patients but between groups of patients treated with unilateral or bilateral ECT. The variation between subjects in hormone release following ECT is large and may have contributed to our negative results.

Another ECT variable which has attracted attention in regard to efficacy of the treatment and hormone release is duration of the seizure. Dykes *et al.* (1987) reported a strong correlation between the increase in TSH concentrations and duration of seizure activity. They hypothesized that there should exist a threshold of seizure activity to be overcome before there is an increase in the release of TSH. Again, little information is available regarding the effect of seizure duration on the release of other hormones. Our data show a non-significant trend ($p = 0.09$) for an association between seizure duration and ACTH release. There were no significant associations between seizure duration and the release of PRL, GH or CORT. These

negative results, however, do not exclude the possibility of a threshold effect as reported by Dykes *et al.* (1987), in that a threshold of seizure activity should be overcome to produce hormone release, but that once this threshold has been overcome, the magnitude of the hormone surge is independent of the duration of the seizure.

The effects of repeated ECT on hormone release have not been widely investigated. Our data indicate a significant blunting of the ACTH response to ECT with repeated sessions. These results are in agreement with those of Aperia *et al.* (1984; 1985) and Mathe *et al.* (1987), but not with those of Whalley *et al.* (1987). Similarly, our results show a blunting of the PRL response with repeated ECT, a finding which confirms the work of most (Deakin *et al.*, 1983; Aperia *et al.*, 1985; Whalley *et al.*, 1987) though not all (Weizman *et al.*, 1987) investigators. Our results indicating lack of consistent changes in GH with repeated ECT are in agreement with published reports (Deakin *et al.*, 1983; Weizman *et al.*, 1987; Whalley *et al.*, 1987). As to the effect of repeated ECT on CORT concentrations, our data showed no significant differences between first and last ECT. These results are similar to those obtained by Deakin *et al.* (1983), but are in conflict with those of Aperia *et al.* (1984; 1985), Weizman *et al.* (1987) and Mathe *et al.* (1987), who all reported a decrease in the magnitude of the CORT surge with repeated ECT.

We realize that our patients suffer from a variety of psychiatric disorders, although the majority had major depression. We also realize that many of our patients were receiving psychotropic medications at the time of ECT. However, the pattern of hormone release with ECT did not seem to change with psychiatric diagnosis or the use of psychotropic medications (data not shown). Similarly, over the course of ECT treatment, some patients had a change in medications while others did not, and some patients had changes in the ECT procedure while others did not. All these modifications were dictated by clinical considerations. Again, the difference in the pattern of hormonal release between the first and last ECT sessions did not seem to be affected by these changes in medications or ECT parameters.

How are our results to be interpreted? First, we believe that ECT produces an increase in the release of specific hormones, for example ACTH and PRL, but not a generalized, nonspecific stress response. Second, hormone release occurs, along with the seizure, in accordance with a "threshold" phenomenon. Once this threshold has been reached, the magnitude of hormone surge is independent of the duration of the seizure or the mode of treatment. Third, repeated ECT can produce physiological adaptation or blunting of hormone release, particularly with respect to ACTH and PRL. Fourth, although our study was not designed to test specific neurotransmitter function in ECT, the data are consistent with a major role for serotonin in ECT-induced hormone release. Serotonin is known to exert a stimulatory effect on the secretion of both ACTH (Bruni *et al.*, 1982) and PRL (Horn & Fink, 1985), and the serotonin receptor antagonist methysergide has been shown to significantly reduce the PRL surge following ECT (Zis *et al.*, 1989). Other neurotransmitters are also probably involved, but their role cannot be predicted from our data. The role of specific neurotransmitters in producing such changes needs to be addressed in future studies.

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