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# Hormone Response to Repeated Electroconvulsive Therapy: Effects of Naloxone

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*Plasma prolactin (PRL), cortisol, and growth hormone (GH) were measured before, and at 15-min intervals for 1 hr after, electroconvulsive therapy (ECT). This was repeated over a series of 6 consecutive treatments for each of 12 depressed drug-free inpatients. Patients received naloxone, 2 mg or 20 mg, by intravenous infusion before the third and fifth treatment. ECT was consistently followed by a release of PRL and cortisol, although two patterns of PRL response could be distinguished. In eight patients, the PRL response did not change significantly with repeated ECT, whereas in four patients, the plasma PRL increased tenfold after the first treatment and decreased after each successive treatment. The GH level varied widely, with no evidence of a reliable response to ECT. Opiate receptor blockade with low- or high-dose naloxone did not alter the release of PRL or cortisol after ECT. These findings demonstrate a reliable PRL and cortisol response to ECT, but do not support a role for endogenous opiates in these hormonal changes.*

## Introduction

Plasma levels of prolactin (PRL) increase after the administration of electroconvulsive therapy (ECT) (Ohman et al. 1976; O'Dea et al. 1978; Skrabanek et al. 1981; Arato and Bagdy 1982; Balldin 1982; Whalley et al. 1982). Several observations suggest that this PRL release is the result of the generalized seizure. Unmodified ECT (no anesthesia or muscle relaxant) produced a definite increase in PRL levels (Klimes et al. 1978), whereas simulated ECT (anesthesia without electrical stimulus) produced either a nonsignificant PRL increase (Arato et al. 1980) or a significantly smaller PRL increase than "real" ECT (Deakin et al. 1983). Elevated PRL levels have also been reported after spontaneous generalized seizures in patients suffering from epilepsy (Trimble 1978; Abbott et al. 1980), whereas PRL release was not observed after partial, hysterical, or pseudo seizures (Collins et al. 1983).

Identifying the mechanisms that mediate this hypothalamopituitary response to ECT might increase our understanding of the central neurotransmitter changes associated with

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this treatment. Reports from several studies suggest that endogenous opiates are involved in certain PRL responses. PRL is released after the administration of morphine (Tolis et al. 1975; Extein et al. 1980; Zis et al. in press) and  $\beta$ -endorphin (Catlin et al. 1980), and the PRL response to an enkephalin analog is attenuated by prior infusion of the opiate antagonist, naloxone (Stubbs et al. 1978). Naloxone blocks the PRL response to physical exercise (Moretti et al. 1983) and gynecological surgery (Corenblum and Taylor 1981), but does not appear to significantly influence PRL release in the tonic/basal state (Volavka et al. 1980; Cohen et al. 1983) or following hypoglycemia (Grossman et al. 1981), sleep (Martin et al. 1979), and gastroscopy (Morley et al. 1980). Circulating levels of  $\beta$ -endorphin are reported to increase after ECT (Emrich et al. 1979; Alexopoulos et al. 1983; Misiaszek et al. 1984), although no relationship has been demonstrated between these endogenous opiates and neuroendocrine response to ECT. There has, however, been some speculation that the release of peptides in the hypothalamus-pituitary system may be related to the therapeutic effects of ECT (Fink 1982).

We report the effect of ECT on PRL, cortisol, and growth hormone (GH), with repeated measurements over a series of six consecutive treatments. The present study also examines the hypothesis that the ECT-induced PRL response was a manifestation of endogenous opiate release by observing the effects of pretreatment with the opiate antagonist, naloxone.

## Methods

Twelve patients, nine women and three men, who met the Research Diagnostic Criteria (Spitzer et al. 1978) for either major depressive disorder-endogenous subtype or schizoaffective disorder-depressed type were included in this study. Their mean age was 42.7 years (range 30-71) and the mean pretreatment score on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) was 24.3 (range 13-36). All patients were free of psychotropic medication for at least 5 days prior to ECT and for the duration of the study. Each patient, at a separate interview, had consented to his or her treating psychiatrist's recommendation for ECT before informed consent to this study was obtained.

The first six ECT treatments, administered three times per week, were included in the experimental protocol. The treating psychiatrist determined the total number of treatments for each patient according to clinical response (mean 10.3, range 6-16). All patients had fasted since midnight, and the intravenous catheter used for administration of the anesthetic agents was inserted into the patient's forearm approximately 1 hr before treatment and was kept patent with heparinized saline. Patients were taken to the treatment room approximately 30 min before ECT and remained there for 1 hr after completion of the treatment. All treatments were given between 8:00 and 9:30 AM.

Standard anesthetic procedure included a premedication with glycopyrrolate (0-0.5 mg), which was administered approximately 1 hr before the treatment. Anesthesia was induced with methohexital sodium (40-100 mg), muscle relaxation was obtained with succinylcholine chloride (50-80 mg), and oxygenation was provided by assisted ventilation throughout the procedure. ECT was administered using a Medcraft machine with bitemporal electrode placement. Electrical stimulus ranged from 120 to 160 V for 0.4-1.0 sec. Seizure duration was monitored in one limb that was not exposed to the muscle relaxant due to the prior inflation of a sphygmomanometer to suprasystolic pressures.

Blood samples were obtained through a three-way tap in the intravenous line after the

first 1–2 ml of blood were discarded. Blood was collected in heparinized tubes, packed in ice, centrifuged within 30 min, and stored at  $-20^{\circ}\text{C}$ . Samples were drawn before anesthesia, after anesthesia but before the electrical stimulus, and 15, 30, 45, and 60 min after the generalized seizure. All plasma samples from a single subject were analyzed in the same assay. Before treatments 3 and 5, naloxone was administered through the intravenous line after the first blood sample and immediately preceding the anesthesia. Subjects 1 through 8 received 2 mg naloxone over 1 min, and subjects 9 through 12 received 20 mg naloxone over 5–10 min.

Plasma PRL was measured by an established double-antibody radioimmunoassay technique (Sinha et al. 1973). The antibody and primary standard were kindly donated by the NIH National Pituitary Agency and prepared by Dr. A. F. Parlow of Harbor General Hospital, Torrance, CA. The linear range of the assay was 0.5–200.0 ng/ml. Samples above 200 ng/ml were serially diluted until they fell within the assay range. Total plasma corticoids (“cortisol”) were measured by the transcortin method of Murphy (1967). GH measurement utilized a radioimmunoassay supplied by Serono.

## Results

### *Hormone Release after Successive ECT Treatment*

A definite increase in plasma PRL and cortisol occurred after each ECT treatment (Figures 1 and 2). The peak levels of PRL and cortisol occurred 15 and 30 min, respectively, after the induced seizure. GH responses were extremely variable, and the mean plasma levels did not change significantly after ECT (Figure 3). The mean baseline levels of PRL and cortisol did not vary significantly between treatment days ( $F = 0.45$ ,  $df = 5,55$ ,  $p = 0.81$  and  $F = 0.17$ ,  $df = 5,55$ ,  $p = 0.97$ , respectively).

The mean PRL response (peak minus baseline,  $\Delta\text{PRL}$ ) after each of the six treatments decreased from 94.0 ng/ml after treatment 1 to 53.6  $\mu\text{g}/\text{ml}$  after treatment 6 (Table 1). Inspection of the data, however, suggests that this change in  $\Delta\text{PRL}$  occurred predominantly in four subjects (1, 5, 6, and 7), with an unusually large  $\Delta\text{PRL}$  after treatment 1 (range 116.6–292.0 ng/ml). Figure 4 shows the  $\Delta\text{PRL}$  after each treatment for two subgroups of patients selected according to whether the  $\Delta\text{PRL}$  after treatment 1 was greater ( $N = 4$ ) or less ( $N = 8$ ) than the mean  $\Delta\text{PRL}$  for all patients after that treatment. We performed a two-way analysis of variance with treatment number as a repeated measures factor and  $\Delta\text{PRL}$  as a grouping factor. The PRL response showed a significant effect for Group ( $F = 24.22$ ,  $df = 1,10$ ,  $p = 0.0006$ ) and Treatment Number ( $F = 14.92$ ,  $df = 5,50$ ,  $p = 0.0000$ ). Trend analysis of the Treatment Number main effect revealed a significant linear component ( $F = 34.56$ ,  $df = 1,10$ ,  $p = 0.0002$ ), which reflected the overall change (decrease) in mean  $\Delta\text{PRL}$  with successive treatments. The presence of a significant quadratic component ( $F = 8.32$ ,  $df = 1,10$ ,  $p = 0.0163$ ) reflected the much larger decreases in mean  $\Delta\text{PRL}$  between treatments 1, 2, and 3 than between treatment 3, 4, 5, and 6. The Group by Treatment Number interaction effect was significant ( $F = 13.38$ ,  $df = 5,50$ ;  $p = 0.0000$ ), and trend analysis revealed a significant linear component ( $F = 34.85$ ,  $df = 1,10$ ;  $p = 0.0002$ ). This reflected the different between-treatment change in mean  $\Delta\text{PRL}$  for the four patients with large initial  $\Delta\text{PRL}$  values compared with the other eight patients with lower  $\Delta\text{PRL}$  values. Baseline PRL levels were not significantly different between the two subgroups of patients. The mean cortisol response (peak minus baseline,  $\Delta\text{cortisol}$ ) after each treatment did not change significantly between treatments ( $F = 1.67$ ,  $df = 5,55$ ;  $p = 0.18$ ).

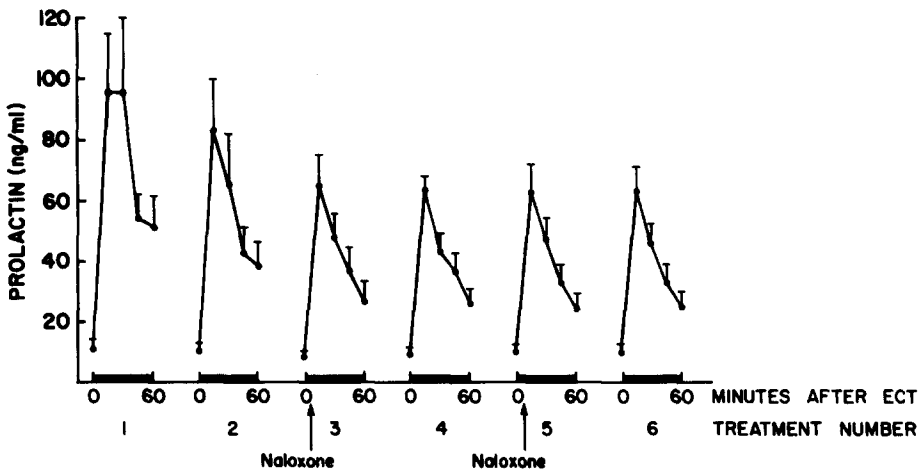


Figure 1. Plasma prolactin concentrations (mean and SEM) before and 15, 30, 45, and 60 min after first six treatments with ECT ( $N = 12$ ).

#### *Effect of Naloxone Pretreatment*

Figures 5 and 6 show the results of naloxone pretreatment on the PRL and cortisol response after ECT. We performed a three-way analysis of variance with pretreatment drug (naloxone versus control) and order (treatments 3 and 4 versus 5 and 6) as repeated measures factors and naloxone dosage (2 mg versus 20 mg) as a between-groups factor. This analysis excluded treatments 1 and 2 because of the variable change in  $\Delta$ PRL described above and compared treatments 3 and 5 (naloxone pretreatment) with treatments 4 and 6 (control). There were no significant effects for naloxone pretreatment, treatment order, or naloxone dosage on either PRL or cortisol response.

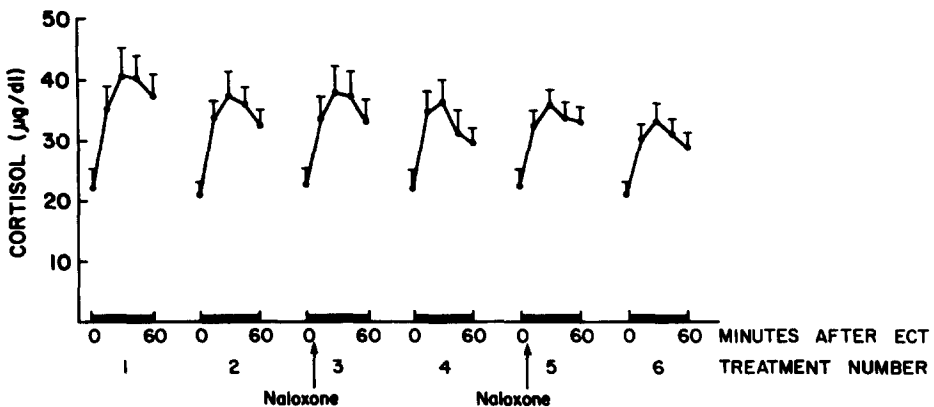


Figure 2. Plasma cortisol concentrations (mean and SEM) before and 15, 30, 45, and 60 min after first six treatments with ECT ( $N = 12$ ).

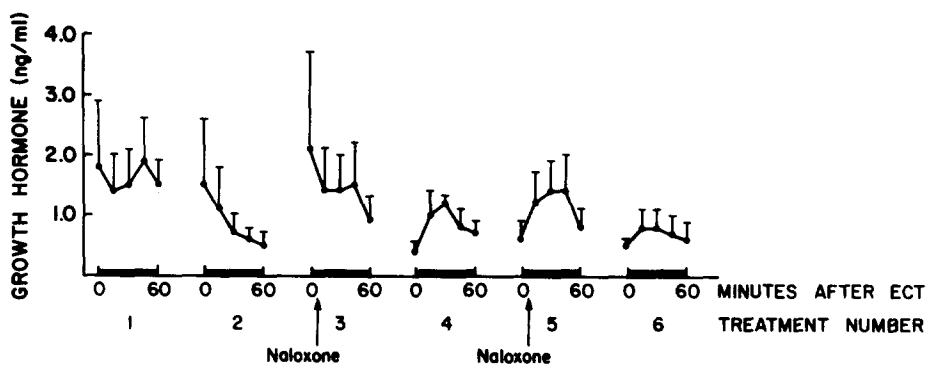


Figure 3. Plasma growth hormone concentrations (mean and SEM) before and 15, 30, 45, and 60 min after first six treatments with ECT ( $N = 12$ ).

#### *Relationship between Hormone Release and Treatment Response*

Three patients had an adequate clinical response to 6 treatments with ECT, and their HDRS scores decreased to 1, 2, and 4. The remaining 9 patients required an additional 1–10 treatments before the course of ECT was completed. When patients were grouped according to whether their  $\Delta$ PRL after treatment 1 was greater ( $N = 4$ ) or less ( $N = 8$ ) than the mean, there was no significant difference between the mean pretreatment HDRS scores (25.3 and 23.9, respectively) or mean numbers of ECT treatments received (8.5 and 9.75, respectively).

Table 1. Prolactin Response after ECT (Peak Minus Baseline, ng/ml)

	Treatment number						Mean
	1	2	3	4	5	6	
<i>Patient</i>							
1	292.0 <sup>a</sup>	207.1	69.4	114.7	92.9	81.0	142.8
2	52.4	43.3	40.5	51.1	46.9	31.7	44.3
3	53.0	33.5	33.0	18.4	32.4	63.9	39.0
4	41.3	35.8	26.1	24.3	19.4	57.6	34.1
5	116.6 <sup>a</sup>	117.1	76.4	80.5	65.9	51.5	84.7
6	191.4 <sup>a</sup>	124.9	102.6	99.0	86.0	75.3	113.2
7	147.1 <sup>a</sup>	105.1	124.2	63.5	60.3	48.5	91.4
8	71.6	88.0	72.5	67.7	99.8	97.1	82.8
9	54.4	42.7	50.0	42.6	57.7	46.6	49.0
10	31.4	45.5	46.5	45.6	41.0	51.1	43.5
11	48.8	35.2	36.3	29.8	32.1	31.2	35.6
12	27.6	14.4	12.7	6.4	12.4	8.3	13.6
<b>Mean</b>	<b>94.0</b>	<b>74.4</b>	<b>57.5</b>	<b>53.6</b>	<b>53.9</b>	<b>53.6</b>	<b>64.5</b>

<sup>a</sup>Subjects with  $\Delta$ PRL after treatment 1 greater than mean.

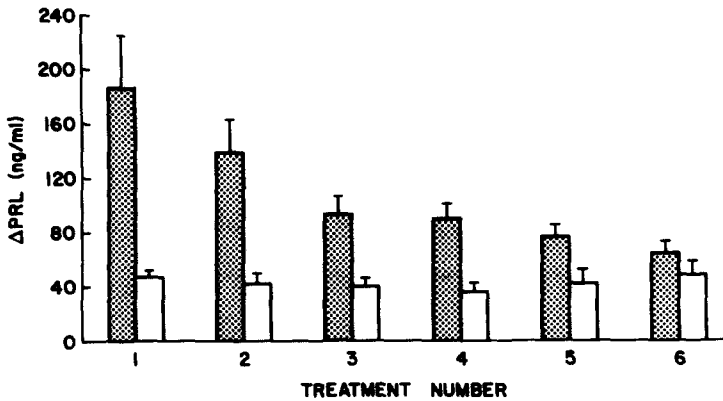


Figure 4. Prolactin response (mean and SEM) after first six treatments with ECT. There were four patients with  $\Delta$ PRL after treatment 1 that was greater than the group mean (shaded bars) and eight patients with  $\Delta$ PRL after treatment 1 less than the group mean (unshaded bars).

## Discussion

Our data indicate that ECT is consistently followed by a release of PRL, which is in agreement with previous reports. We also examined this phenomenon over repeated treatments. Although the mean  $\Delta$ PRL for the total group decreased across the course of treatment, two patterns of response could be distinguished. In eight patients (67%), the magnitude of the  $\Delta$ PRL was six times the baseline value and did not change significantly with repeated ECT treatment. However, in four patients (33%), the plasma PRL increased tenfold after the first treatment, and  $\Delta$ PRL decreased after each successive treatment. By the sixth treatment, the  $\Delta$ PRL approached the mean value noted after each treatment in the other eight patients. The absence of any significant clinical differences between

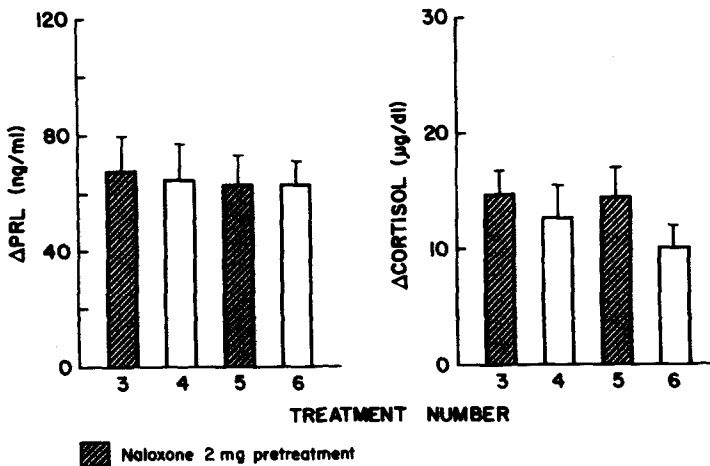


Figure 5. Prolactin and cortisol responses (mean and SEM) after ECT treatments 3-6. Patients received naloxone, 2 mg, before ECT treatments 3 and 5 ( $N = 8$ ).

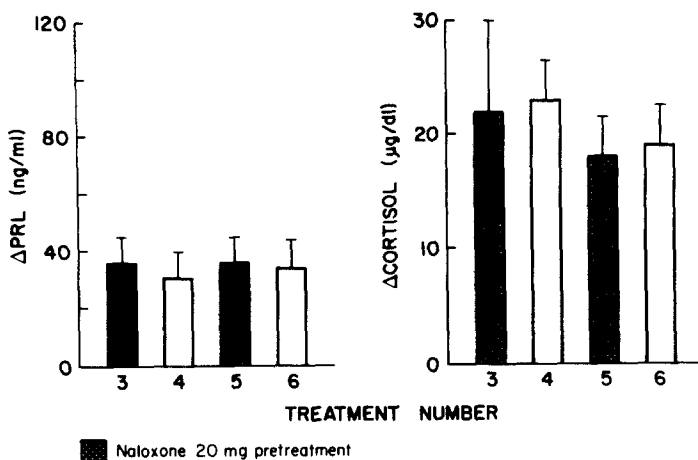


Figure 6. Prolactin and cortisol responses (mean and SEM) after ECT treatments 3-6. Patients received naloxone, 20 mg, before ECT treatments 3 and 5 ( $N = 4$ ).

these two subgroups of patients (mean pretreatment HDRS score and total number of treatments given in the course) suggests that the change in  $\Delta$ PRL is not related to the severity of illness or the speed of the clinical response to ECT.

The demonstration of these two disparate patterns of PRL response may provide an explanation for the apparent disagreement between reports that found a decrease in  $\Delta$ PRL over a course of treatments (Meco et al. 1978; Deakin et al. 1983) and those that found no significant variation (Skrabanek et al. 1981; Whalley et al. 1982; Linnoila et al. 1984). The etiology of this variability in PRL response between individuals, however, is not readily apparent. PRL secretion can be influenced by a wide variety of factors, for example, circulating estrogens have a stimulatory effect on PRL secretion and increase the responsivity of PRL to various stimuli (Frantz 1978). It is notable that all four patients with large  $\Delta$ PRL after ECT were women, mean age 41.3 years, whereas three of eight patients with lower and constant  $\Delta$ PRL after ECT were men and the mean age of the remaining five women was 54.4 years. All patients in this study were drug-free, and none had been recently withdrawn from neuroleptics or other drugs known to alter PRL secretion. Further examination of this variability in the pattern of PRL response is needed to determine whether it is an epiphenomenon, e.g., related to sex and estrogen levels, or a marker that distinguishes a valid subcategory of affective disorder.

The release of cortisol after ECT in these patients was also a stable and relatively uniform response that did not change significantly with repeated treatment. This agrees with most studies that have reported changes in cortisol or corticotropin (ACTH) after ECT (Elithorn et al. 1969; Allen et al. 1974; Delitala et al. 1977; Deakin et al. 1983). Whalley et al. (1982) were unable to demonstrate a cortisol response after ECT, but this discrepancy may have resulted from their failure to sample for longer than 6 min after the seizure. Although we did not measure levels of ACTH, it is likely that the observed cortisol response was preceded by an acute release of ACTH (Ylikorkala et al. 1976). As there is evidence that  $\beta$ -endorphin and ACTH are secreted concomitantly (Guillemin et al. 1977), we believe that our findings are consistent with the previous reports of an ECT-induced release of these pituitary hormones. The GH level in these patients varied

widely. Most studies have been unable to demonstrate a reliable GH response after ECT (Ryan et al. 1970; Allen et al. 1974; Delitala et al. 1977; Arato et al. 1980; Whalley et al. 1982; Deakin et al. 1983). Vigas et al. (1975) and Skrabanek et al. (1981) did report a GH response, although the patients in the first study received unmodified ECT.

The present data suggest that opiate receptor blockade does not alter the release of PRL and cortisol after ECT. Naloxone is a potent and specific opiate antagonist that rapidly crosses the blood-brain barrier. Maximum concentration of naloxone in the central nervous system (CNS) occurs within minutes of infusion and the plasma half-life is approximately 60 min (Fishman et al. 1973; Berkowitz et al. 1975). We administered intravenously naloxone infusions in low (2 mg, 0.02-0.05 mg/kg) and high (20 mg, 0.20-0.42 mg/kg) doses because there is evidence for the existence of several opiate receptor subtypes that have differing profiles of response to opiate agonists and antagonists (Lord et al. 1977; Chang and Cuatrecasas 1979). We expected the low dose of naloxone to abolish effects that were mediated by the  $\mu$ -receptors, as these have a high affinity for naloxone, whereas higher doses are needed to also block the relatively naloxone-insensitive  $\delta$ -receptors. It remains possible that even higher doses of naloxone could affect the ECT-induced PRL response, although it has been suggested that 16 mg naloxone produces maximal blockade of endogenous opiate tone in the hypothalamic-pituitary-adrenal axis (Grossman et al. 1982). In addition, Cohen et al. (1983) failed to show a naloxone dose-dependent effect on PRL secretion with naloxone doses up to 4 mg/kg. Although the administration of naloxone stimulates basal ACTH and cortisol secretion in normals (Volavka et al. 1980; Judd et al. 1981) and naloxone (10 mg) has been reported to enhance the cortisol response to gastroscopy (Morley et al. 1980), we found no difference in the cortisol response to ECT after naloxone.

This study established the reliability and consistency of the PRL and hypothalamic-pituitary-adrenocortical (HPA) axis responses to ECT, especially after treatment 3. PRL secretion and HPA axis function are influenced by multiple neurotransmitter systems, and these aspects of the neuroendocrine response to ECT deserve further study with other pharmacological probes. Recent evidence that exogenous opiates stimulate PRL release but inhibit cortisol secretion (Zis et al. in press) makes it less likely that endogenous opiates are responsible for these ECT-associated hormonal changes. The serotonergic system, however, may be of particular interest, as it has been demonstrated that serotonergic agonists can have a stimulatory effect on both PRL and cortisol release (see reviews by Checkley, 1980, and Reichlin, 1981). Systematic examination of these phenomena may eventually lead to clarification of the neurochemical events accompanying ECT.

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