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ORIGINAL PAPER

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Serotonergic and dopaminergic neuroendocrine responses of male depressive patients before and after a therapeutic ECT course

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Abstract *Background* Electroconvulsive therapy (ECT) is an effective treatment for major depressive illness, even for patients who do not respond to antidepressant drugs. According to the prevailing neurophysiological hypotheses for depression, it can be expected that an ECT therapeutic course modulates the responsivity of central neurotransmitter systems, but the results up to now have been inconclusive. To test such hypotheses, we studied possible changes in the serotonergic and in dopaminergic systems' responsivity in 11 male patients with major depression by performing neuroendocrine challenge tests before and after a therapeutic ECT course. *Methods* Serotonergic responsivity was assessed by measuring the prolactin and cortisol responses to i. v. administration of the serotonin uptake inhibitor clomipramine (CMI test), and dopaminergic responsivity by measuring the prolactin responses to the dopamine receptor blocker haloperidol (HAL test), administered intramuscularly. The prolactin and cortisol responses during the first and the last ECT of the course (8 to 13 sessions) were also assessed. The CMI and HAL tests were also performed in 13 male healthy subjects. *Results* The prolactin responses to CMI were significantly blunted in the patient group compared to the control group, and remained unaltered at the end of the ECT course, although the depressive symptomatology was substantially reduced from 27.8 ± 7.1 to 4.8 ± 2.3 points in the Hamilton Depression Rating Scale. The cortisol responses to CMI were blunted before the ECT course compared to controls, but not after the course: there was a moderate increase of cortisol at + 30 min in the CMI test after the ECT course compared to that before ECT ($p = 0.05$). The prolactin and cortisol responses to the electrical stimulus during the first and the last ECT were identical. *Conclusions* The strong therapeutic effect of ECT in depression, observed already at the end of the course, is not a result of considerable modifications in central serotonergic or dopaminergic responsivity, as revealed by the neuroendocrine challenge tests and the hormone responses to the electrical stimulus. The enhancement of the cortisol responses to CMI after the course may indicate a moderate increase in 5-HT1A receptor responsivity.

Key words ECT · depression · clomipramine · haloperidol · prolactin · cortisol

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Introduction

The efficacy of electroconvulsive treatment (ECT), even in drug-resistant major depression, has motivated many investigators to look closer at its mechanism of action, with the hope of contributing to the understanding of the neuropathophysiology of depression. Most of the studies have focused on its effects on neurotransmitter systems, mainly serotonergic, dopaminergic, noradrenergic, and GABAergic (for review see [14, 16]).

There are some indications from animal studies that repeated electroconvulsive shock (ECS) increases the sensitivity of postsynaptic 5-HT1A receptors, but this has not been shown to be the case in humans: the blunted hypothermic and cortisol responses to the 5-HT1A receptor agonist ipsapirone remained unaltered after a therapeutic ECT course in depressive patients [24]. The lack of an acute effect of ECT on 5-HT1A receptors is supported by the findings that pindolol, a 5-HT1A partial agonist, given prior to ECT, does not influence the PRL release elicited by the electrical stimulus [19]. Treatment with ECT lowered plasma cortisol levels, but the cortisol responses to the 5-HT-releasing agent fenfluramine remained unchanged [17]. Shapira et al. [23], however, found enhanced responses of prolactin to

fenfluramine after an ECT course, and proposed that ECT treatment enhances central serotonergic receptor responsivity.

Although most animal studies found that repeated ECS enhances dopaminergic activity [24], studies in humans have given inconclusive results, with either no change [5] or increases [21] in the main dopamine metabolite homovanillic acid in CSF. The growth hormone response to the dopamine agonist apomorphine does not seem to be changed by a therapeutic ECT course [2], and the prolactin increases, induced by the electrical stimulus itself, remain unaltered in depressive patients after a substantial amelioration in their symptomatology by the ECT course [13].

In this study, we assessed both serotonergic and dopaminergic neuroendocrine responsivities in a group of male patients with major depression, before and after a therapeutic ECT course, and searched for possible influences of the course on the hormone response patterns. Plasma prolactin and cortisol levels were measured after i. v. clomipramine, and i. m. haloperidol administration. The changes in the two hormones during the administration of the first and the last ECT of the course were also assessed.

Subjects and methods

Eleven male patients with major depressive disorder were studied. They were hospitalized in the Psychiatric Clinic of the Athens University Medical School, Eginition Hospital, and referred for ECT, as the clinically indicated treatment. Their ages ranged from 22 to 65 years (mean = 45.5, SD = 14.8), and the severity of the illness, as measured with the Hamilton Depression rating Scale (HDRS), ranged from 18 to 39 points (mean = 27.8, SD = 7.1). The duration of illness ranged from 0.5 to 7 years (mean = 3.0, SD = 2.4). All patients were drug-free for at least one week before entering the study, with the exception of 2 mg lorazepam, given at bed time. After complete description of the study, written informed consent was obtained from all subjects.

Diagnoses were established on the basis of Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV). All patients met DSM-IV criteria for major depressive episode, seven in the context of major depressive disorder and four of bipolar I disorder, while four patients had psychotic features. Eight patients had been treated during the present episode with antidepressants with adequate doses and for an adequate time, with poor or no response, so that they can be characterized as drug resistant. Three patients showed psychomotor retardation and/or had attempted suicide at the current episode.

For the assessment of central serotonergic responsivity, we administered 25 mg of the serotonin uptake inhibitor clomipramine intravenously within 10 to 15 minutes, and measured the prolactin and cortisol responses in blood samples taken at times 0, 15, 30, 45, and 60 minutes. Two to four days later, we assessed the responsivity of the dopaminergic system that participates in the prolactin release, by administering 5 mg of the D2 dopamine receptor blocker haloperidol intramuscularly, and measuring the plasma prolactin levels in blood samples taken at times 0, 30, 60, 90, and 120 minutes.

The increases in prolactin and cortisol during the first ECT session were also measured in blood samples taken at times –10, 0, 15, 30, 45, and 60 minutes, which was given two to four days after the haloperidol test. Bilateral ECT was given, with the electrodes placed in the bitemporal position. The procedure included administration of atropine, sodium thiopental, succinylcholine, and oxygenation, and the dial settings were appropriate for the patient's age. Seizure duration was monitored with the cuff technique, and ranged in the 11 patients from 24 to 49 seconds (mean = 39, SD = 7).

Bilateral ECT was given, because in our experience, it is more effective than unilateral, fewer sessions are needed for recovery, and we have seldom observed side effects. The course included 8 to 13 sessions, administered 2–3 sessions per week, and was completed within 28 ± 5 days (range 22 to 35 days). During that time, patients remained drug-free. During the last ECT, with seizure times ranging from 25 to 58 seconds, blood samples were again collected as in the first ECT. The neuroendocrine challenge tests with CMI and haloperidol were repeated two and four days after the last ECT. These two tests were also performed in 13 healthy male subjects aged 21 to 50 years (mean = 31.8, SD = 10.9), in the same manner, to establish the prolactin and cortisol responses in normal subjects.

Plasma was separated by centrifugation and stored at –30 °C until the estimation of the hormone levels. Commercially available radioimmunoassay kits were used (BioChem ImmunoSystems, Italy, for prolactin, and DiaSorin, U. S. A., for cortisol), with coefficients of variation below 5 %.

For the statistical evaluation of the hormone response patterns of patients and controls, and of patients before and after the ECT course, we used analysis of variance with repeated measures (ANOVAR), followed by planned comparisons if the group–time interaction was significant. Age was used as covariate for comparisons between patients and controls. Correlation coefficients (linear regression and Spearman) between clinical and neuroendocrine data were also calculated.

Results

The neuroendocrine data of the patients and controls are shown in Table 1. The ECT course resulted in signif-

Table 1 Clinical and neuroendocrine data of the 11 patients and 13 healthy control subjects. The prolactin (PRL-R, ng/ml) and cortisol (CORT-R, ng/ml) responses to clomipramine (CMI), the prolactin responses to haloperidol (HAL, ng/ml), and the responses to first and last ECT of the course are the differences of the maximal post-stimulus value minus baseline. The data of the patients before and after the ECT course are compared to controls (*C* controls, *PB* patients before, *PA* patients after the ECT course), and between them. Mean values ± SD, and p values are given.

		Patients		p value		
	Controls	Before	After	C/PB	C/PA	PB/PA
Hamilton DRS		27.8±7.1	4.8±2.3			0.0001
PRL baseline	8.3±3.1	7.7±4.5	7.8±3.0	0.73	0.70	0.98
PRL-R, CMI	7.2±7.8	–0.4±2.0	0.8±2.2	0.005	0.015	0.19
PRL-R, HAL	50.5±23.0	34.8±25.8	32.4±25.0	0.13	0.08	0.83
CORT, baseline	113±55	145±56	154±45	0.16	0.06	0.68
CORT-R, CMI	42±48	5.4±27.7	36±55	0.036	0.76	0.12
		First ECT	Last ECT			
Seizure time, s		39.0±7.1	36.5±9.8			0.49
Maximal PRL-R		24.1±15.1	26.5±12.8			0.69
Maximal CORT-R		91±65	89±47			0.96

icant amelioration of the patients' symptomatology, with the HDRS score to fall from a mean ± SD of 27.8 ± 7.1 before, to 4.8 ± 2.3 at the end of the course.

The number of ECT sessions ranged from 8 to 13, and the total seizure time from 230 to 537 s (mean 352 ± 91). There were no differences in seizure times during the first and the last ECT ($F = 0.48$, $df = 1,20$, $p = 0.49$).

Baseline prolactin values of the patients were similar to controls, and remained unaltered after the ECT course. The mean baseline cortisol levels of the patients were 30 % higher than for the controls, but the difference was not significant. No significant changes in baseline plasma cortisol were found after the course.

The prolactin responses to CMI were significantly blunted in the patients' group compared to the responses of the control group, and remained blunted after the end of the ECT course (Fig. 1). The cortisol responses to CMI were also blunted compared to controls (Fig. 2). Comparison of the patients' responses before and after the course, however, revealed a significant state versus time interaction (Table 2, $p = 0.04$), with a significant increase in cortisol at + 30 min (planned comparisons, $p = 0.05$) in the test performed after the end of the ECT course. The maximal cortisol responses to CMI, calculated as the difference of the highest post-drug value minus baseline, were 5.4 ± 27.7 ng/ml before, and 36±55 after the course, significantly different from controls before ($p = 0.036$), but not after the course ($p = 0.76$).

The prolactin responses to haloperidol showed large variation both in the control and patients' groups. Thus, although the mean maximal responses of the patients were in the mean 31 % lower than controls, the difference did not reach statistical significance ($p = 0.13$ for the HAL test performed before the ECT course, and $p = 0.08$ for the test after the course). In any case, the responses of the patients before and after the course were similar (Table 2, Fig. 3, interaction $F = 0.11$, $p = 0.98$).

During the first ECT, the maximal increases in prolactin were 24.1 ± 15.1 (mean) ng/ml, and during the last ECT 26.5 ± 12.8 ng/ml (Table 2, $p = 0.69$). The maximal responses of cortisol were 91 ± 65, and 89±47 ng/ml, respectively ($p = 0.96$). Both response patterns were simi-

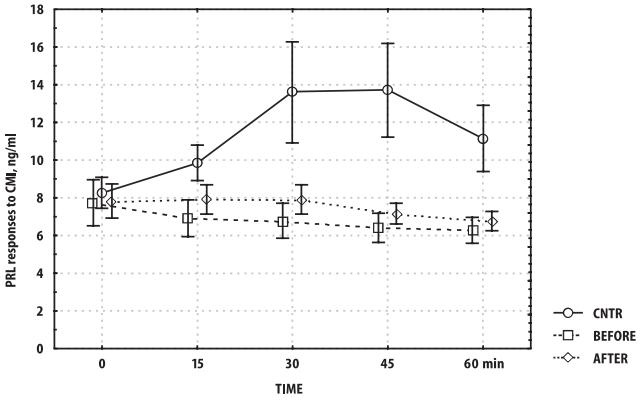

Fig. 1 Patterns of plasma prolactin responses (means ± SEM) to administration of clomipramine i. v. in 11 male patients with major depression, before and after a therapeutic ECT course (8 to 13 sessions). In both cases, the responses are significantly blunted compared with the responses of 13 healthy male subjects (CNTR).

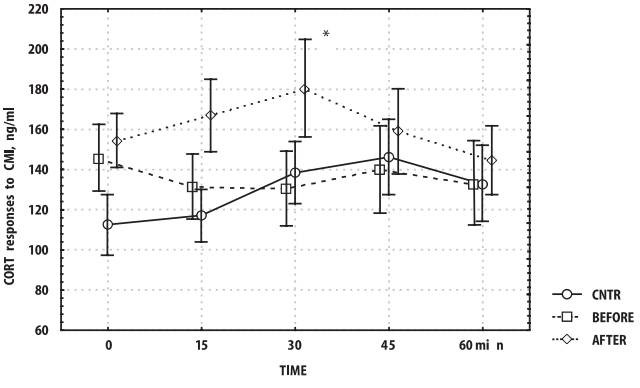

Fig. 2 Plasma cortisol responses (means ± SEM) to i. v. clomipramine of 13 healthy male subjects (CNTR) and 11 male depressive patients before and after an ECT course. The blunted responses before ECT are not normalized after the course, but there is a moderate increased response at + 30 minutes (asterisk, planned comparisons before/after ECT, $p = 0.05$).

Table 2 Statistical evaluation of the prolactin and cortisol response patterns shown in the Figures. The patterns of the prolactin and cortisol responses to clomipramine, and the prolactin responses to haloperidol of patients before and after the ECT course are compared to the responses of the control group. The PRL and CORT responses before and after the ECT course of the patients to CMI, HAL, and to ECT are also compared. The F and p values of the analysis of variance with repeated measures are given.

		Control Before		Control After		Before/After	
		F	p	F	p	F	p
CMI-PRL	Group	5.01	0.036	4.03	0.057	0.34	0.56
	Time	2.80	0.03	3.62	0.009	3.28	0.015
	G x T	5.57	0.001	4.51	0.002	0.62	0.65
CMI-CORT	Group	0.08	0.78	1.83	0.19	0.95	0.34
	Time	2.28	0.07	3.42	0.012	1.29	0.28
	G x T	3.37	0.013	2.46	0.05	2.58	0.04
HAL-PRL	Group	4.08	0.056	2.39	0.14	0.14	0.71
	Time	43.15	0.000	45.27	0.000	26.02	0.000
	G x T	1.76	0.14	1.99	0.103	0.11	0.98
ECT-PRL	State					0.27	0.61
	Time					50.27	0.000
	S x T					0.18	0.97
ECT-CORT	State					0.22	0.64
	Time					28.33	0.000
	S x T					0.16	0.98

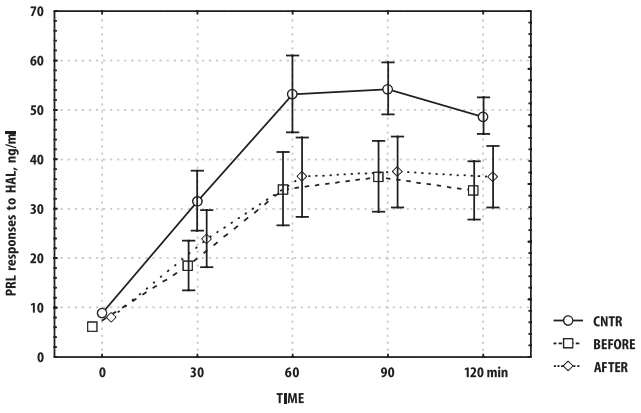

Fig. 3 Patterns of plasma prolactin increases (mean ± SEM) after D2 receptor blockade by i. m. administration of haloperidol in the 11 patients before and after an ECT course and the 13 healthy subjects (CNTR). The patients' responses are similar in both states, and lower than controls, but the differences do not reach significance.

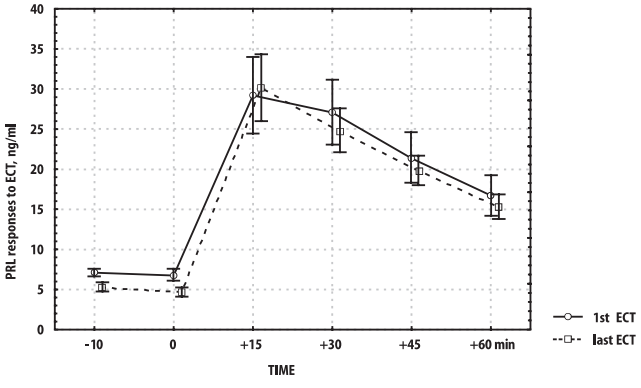

Fig. 4 Lack of influence of an ECT therapeutic course (8 to 13 sessions) on the plasma prolactin increases elicited by the electrical stimulus at the first and last ECT session in the 11 patients. The depressive symptomatology (Hamilton Depression Rating Scale) was reduced from 27.8 ± 7.1 points before, to 4.8 ± 2.3 after the ECT course.

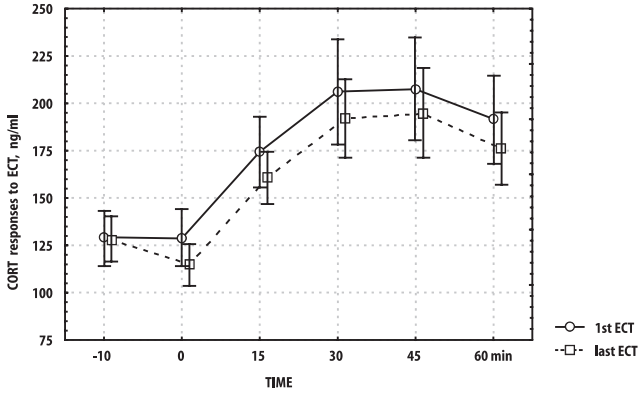

Fig. 5 Patterns of plasma cortisol responses during the first and the last ECT of the 11 male depressive patients. State x time interaction F = 0.16, p = 0.98 (repeated measures ANOVA).

lar, as shown in Fig. 4 for prolactin and Fig. 5 for cortisol.

Finally, the seizure time was not correlated to the prolactin or cortisol responses during the first or the last ECT, or to the hormone responses to CMI and HAL tests.

Discussion

Blunted prolactin responses to i. v. CMI in depressive patients have been previously reported [9], after administration of 10 mg of the drug intravenously. In this study, we obtained the same result with a larger dose of CMI. Blunted prolactin responses of depressive patients to other serotonergic drugs, mainly fenfluramine, have also been reported by many authors. Here we showed that the responses remain blunted after a therapeutic course of ECT, although there was a significant amelioration of the depressive symptomatology. The persistence of blunted prolactin responses to the serotonergic agent fenfluramine after recovery of depressed patients has been reported by Flory et al. [7], who studied subjects with a history of depression, not depressed for one year. Shapira et al. [23] reported enhanced PRL responses to fenfluramine after an ECT course in a group of 18 patients, 12 women and 6 men, with no correlation of the enhanced serotonergic responsivity with clinical outcome. The discrepancy may be due to the presence of a large number of female patients in the patients' sample who show stronger effects of fenfluramine on PRL release than men [7], but also to the different mode of action of the probes used. While clomipramine is a serotonin reuptake inhibitor, fenfluramine additionally enhances the release of serotonin and probably has receptor agonist actions. The difference in PRL release between the two drugs is also shown by the fact that in the study of Shapira et al. depressed patients gave significant increases in plasma PRL after fenfluramine administration at baseline, while in the present study no increases in plasma PRL were observed in the patients' group after clomipramine administration (Fig. 1).

The moderate increase in maximal cortisol response to CMI after the ECT course deserves consideration for two reasons. First, because of the controversial data regarding the effects of ECT on 5-HT1A receptor sensitivity, and the responses of patients with depression to 5-HT1A receptor agonists, and second, because there are some indications that an activation of postsynaptic 5-HT1A receptors can result in a rapid antidepressant effect [1]. Stimulation of hypothalamic 5-HT1A receptors in rats causes ACTH and corticosterone release [10, 8], and ipsapirone, a specific 5-HT1A receptor agonist, induces increases in ACTH and cortisol in man [12, 4]. This response has been found to be blunted in depressive patients by some investigators [11, 15] but not by others [20, 25]. Treatment with antidepressant drugs did not change the blunted cortisol response [11]. On the other hand, brain 5-HT1A receptor binding, measured by positron emission tomography, has been found to be reduced compared with healthy controls in both unmedicated and medicated depressive patients (22, for review see [6]).

Shapira et al. [24] reported blunted cortisol responses to the 5-HT1A receptor agonist ipsapirone in a group of seven depressive patients, five female and two male, and the response remained blunted after an ECT course of eight treatments. Our finding of a moderate increase in cortisol response after the ECT course disagrees with that report. The differences of the two studies are that we studied only male patients, who all were responders to ECT with reductions in the HDRS greater than 50% (range 67 to 94%), and the final HDRS scores ranged from 2 to 10, with only one patient having a score higher than 7, while in the previously mentioned study, only four of the seven patients were responders. It is possible that the moderate increases in cortisol response can be seen only if certain confounding factors like gender, menopausal status, and therapeutic response are eliminated. The increases in cortisol responses in the present study, however, were not significantly correlated to the patients' improvement.

The prolactin and cortisol responses to the electrical stimulus were the same during the first and the last ECT of the course, and this is in agreement with most previous reports [3]. The lack of changes implicate that the release of the hormones during ECT are caused by actions on mechanisms that are not connected to psychopathology. This conclusion also derives from studies which have shown no relation of the magnitude of the prolactin or cortisol responses to the therapeutic effect, or even type of psychopathology [18].

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