Eur Arch Psychiatry Clin Neurosci (2002) 252 : 166 – 171 DOI 10.1007/s00406-002-0377-2

ORIGINAL PAPER

Manolis Markianos · John Hatzimanolis · Lefteris Lykouras

Relationship between prolactin responses to ECT and dopaminergic and serotonergic responsivity in depressed patients

Received: 5 March 2002 / Accepted: 15 July 2002

Abstract The prolactin (PRL) increases in plasma, induced by the electrical stimulus during electroconvulsive therapy (ECT), is a consistent finding that can be studied in order to obtain information about its actions on the brain neurotransmitter systems, the most probable candidates being the serotonergic and the dopaminergic system. Central serotonergic and dopaminergic responsivity may also be assessed using neuroendocrine challenge tests. In this study, we measured the PRL responses during the first ECT of a therapeutic course in 15 male depressive patients, of mean age 49.2 ± 14.5 (range 22 to 68 years), and score in the HDRS of 29 ± 8 (range 18 to 43 points). Before the ECT course, we assessed the central serotonergic and dopaminergic responsivities, by measuring the PRL responses to the administration of the serotonin uptake inhibitor clomipramine (CMI) intravenously, and, two days later, the PRL responses dopamine receptor blocker haloperidol (HAL), administered intramuscularly. The CMI and HAL tests were also performed in 15 healthy male subjects. The PRL responses to CMI of the patients were blunted compared to healthy controls, while the PRL responses to HAL were not significantly different from controls. Searching for correlations among the maximal PRL responses to the three stimuli in the patient's group, we found that the PRL responses to ECT were significantly correlated to the PRL responses to i. m. HAL ($r = 0.8205$, $N = 15$, $p < 0.001$) and not to the PRL responses to i. v. CMI ($r = 0.1713$, n. s.). It is suggested that the rises in PRL during ECT reflect the responsivity of the hypothalamus-pituitary dopaminergic system, and seem to be the result of a transient decrease in the inhibitory dopaminergic input of the hypothalamus to the pituitary lactotrophs, caused by the electrical stimulus and the subsequent seizure.

Key words depression · electroconvulsive therapy · clomipramine · haloperidol · prolactin

Dr. Manolis Markianos, PhD (✉) · J. Hatzimanolis, M. D. · L. Lykouras, M. D.
Athens University Medical School
Psychiatric Clinic, Eginition Hospital
Vas. Sophias 74
Athens 11528, Greece
Tel.: +30-1/72-8 92 66
Fax: +30-1/72-4 20 32
E-Mail: markian@otenet.gr

EAPCN 377

Introduction

The increases in plasma prolactin (PRL) during electroconvulsive therapy (ECT), as a reflection of cerebral stimulation, have been much studied with the prospective to obtain information about its neurobiological mode of action, especially on neurotransmitter systems that may be involved, the most probable candidates being serotonin and dopamine. In this respect, pretreatment with various drugs has been used in a series of studies, in attempts to influence the prolactin increases induced by ECT. Pharmacological probes that have been found not to affect the prolactin release by ECT, include the non-specific 5-HT2 serotonin receptor antagonists ketanserin [27], the more specific 5-HT2 receptor antagonist ritanserin [22], the 5-HT3 receptor antagonist ondansetron [26], the selective 5-HT1D receptor agonist sumatriptan [17], while the effects of pindolol, a 5-HT1A receptor antagonist, are inconclusive [28, 23]. ECT course did not change the hypothermic, growth hormone, and cortisol responses to the 5-HT1A receptor agonist ipsapirone [25], indicating that ECT may not act by inducing an increased sensitivity of these receptors, as it had been suggested by previous studies. Serotonin mediated neuroendocrine function seems not to change after a therapeutic ECT course in depressed patients, as measured by the prolactin responses to the serotonergic agent fenfluramine [14, 15], although enhanced responsivity has been reported in one study [24].

An attenuation of the prolactin response to ECT was found after pretreatment with the nonselective serotonin antagonist methysergide [21], a drug that also possesses dopamine receptor agonistic activity as well. A to-

tal blockade of the prolactin increases by ECT has been reported by Zis et al. [29] when the dopamine receptor antagonist metoclopramide, which is also a 5-HT3 receptor antagonist, was given intravenously 30 min before ECT in five patients. The drug causes a substantial elevation of plasma PRL to a mean of 196 ng/ml, and the application of the electrical stimulus did not cause any further increases. The authors conclude that seizure-induced PRL increases occur only when some degree of dopaminergic inhibitory tone on the pituitary lactotroph is operative.

Increases in the concentrations of the dopamine main metabolite homovanillic acid (HVA) but not of the serotonin or noradrenaline metabolites, 5-hydroxyindoleacetic acid (5-HIAA) and methoxyhydroxyphenylglycol (MHPG), respectively, have been found in CSF samples taken one day after the first ECT, compared to samples taken one day before ECT [5]. The increases were not present in samples taken one day after the final ECT of the course.

Most animal studies suggest that repeated electroconvulsive shock enhances dopaminergic activity, while the results in humans are inconclusive. Costain et al. [6] reported significant increases in the growth hormone response to dopamine agonist apomorphine after an ECT course in 15 depressed patients, while Christie et al. [4] found the responses unaltered. Similarly, the prolactin responses to ECT were not modified after an ECT course in fifteen female depressed patients, and their magnitude was not related to the therapeutic effect [13]. The prolactin release by ECT can be caused just by a transient increase in serotonergic activity, and/or a transient inhibition of dopaminergic input in the hypothalamus-pituitary axis.

Neuroendocrine challenge tests have been widely used to assess the responsivity of central dopaminergic and serotonergic receptors. Dopaminergic receptor responsivity can be assessed by measuring the increases in plasma prolactin caused by administration of dopamine receptor blockers, like haloperidol [10, 16]. Administration of clomipramine, a drug that enhances serotonergic activity by inhibiting 5-HT reuptake, causes increases in plasma prolactin and cortisol, and has been used as a probe to study the responsivity of central serotonin receptors [11, 9, 1]. When administered intravenously, it acts mainly on the 5-HT system, since the production of its demethylated metabolite, which has noradrenaline uptake inhibiting properties, is avoided [8].

Clomipramine infusion can cause gastrointestinal discomfort for a short period of time at the end of the infusion, mainly nausea and possibly emesis. These unpleasant effects have been considered as non-specific stress that may influence hormonal responses, especially growth hormone response [8]. In a previous study [2], we have evaluated the influence of these side effects, and found no association of nausea or emesis to the growth hormone responses to the infusion of 25 mg clomipramine. Similar results for the same clomipramine dose had been reported by Laakmann et al. [11]. It seems that nausea is related to an enhanced serotonin action on 5-HT3 receptors which are not involved in the hormone responses, since pretreatment with the selective 5-HT3 receptor antagonist ondansetron reduces nausea without affecting the prolactin responses to clomipramine infusion [12].

In this study, we assessed the prolactin responses to the serotonergic agent clomipramine, and to the dopaminergic agent haloperidol, in a group of patients with depression referred for ECT before the beginning of the ECT course, and searched for correlations to the prolactin responses measured during the first ECT.

Subjects and methods

Fifteen male patients were studied. They were hospitalized during a major depressive episode in the Athens University Medical School Psychiatric Clinic, Eginition Hospital, and referred for ECT as the clinically indicated treatment. 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 with melancholic features. Nine patients fulfilled criteria for major depressive disorder, and six for bipolar I disorder, while seven patients had psychotic features. After hospitalization, all patients were kept drug-free for one week before entering the study, with the exception of 2 mg lorazepam, given at bed time. The severity of depression was evaluated using the Hamilton Depression Rating Scale (HDRS).

The majority of the patients had been treated during the present episode with two different regiments of antidepressants (heterocyclic, SSRI, SNRI) in monotherapy, with poor or no response. Three patients showed psychomotor retardation and/or suicide attempt at the current episode, and one patient had responded only to ECT in two previous depressive episodes.

Fifteen healthy male control subjects, not taking any drugs, were recruited from hospital staff for the clomipramine and haloperidol tests. Two of them refused the haloperidol test. All subjects gave informed consent, and the protocol of the study was approved by the Ethics Committee of the Hospital.

Before the first ECT, neuroendocrine challenge tests were performed by administration of the serotonin reuptake inhibitor clomipramine, and of the dopamine receptor blocker haloperidol. All tests were performed after an overnight fast, beginning between 08:00 and 09:00 hours. The clomipramine test was performed by administering intravenously 25 mg of the drug in 100 ml saline within 10–15 minutes, with blood samples withdrawn at times 0, 15, 30, 45, and 60 minutes. Four healthy subjects and two patients experienced moderate or severe nausea at the end of the clomipramine infusion, which lasted for a few minutes. Two days later, the haloperidol test was performed by administration of 5 mg of the drug intramuscularly, and blood samples withdrawn at times 0, 30, 60, 90, and 120 minutes. Two healthy subjects refused the haloperidol test. No significant side effects that needed any intervention were observed during the haloperidol test.

Bilateral ECT was given to the patients two to four days after the haloperidol test, with the electrodes placed in the bitemporal position, using a pulse current device (Siemens Konvulsator 622), at dial settings appropriate for the patient's age. The procedure included administration of atropine, sodium thiopental, succinylcholine, and oxygenation. In all patients included in the study the seizure was elicited with the first electrical stimulation. Seizure duration was monitored with the cuff technique, and blood samples were taken at times –10, 0, 15, 30, 45, and 60 minutes.

Plasma was separated by centrifugation and stored at –30 °C until estimation of the prolactin levels, for which commercially available radioimmunoassay kits were used (BioChem ImmunoSystems, Italy). The inter- and intra-assay coefficients of variation were below 5 %.

Statistical evaluation of the data included analysis of variance for

repeated measures for the comparison of the hormone release patterns between patients and controls for the clomipramine and haloperidol challenge tests. Age of the subjects was used as a covariate. Correlation coefficient tests (Pearson and Spearman) were used in searching for associations between maximal responses of prolactin to ECT, to clomipramine, and to haloperidol in the patients' group, as well as to age and severity of illness. Multiple regression analysis was also performed in search of associations of the prolactin response to ECT to the clinical and to the neuroendocrine measures of the patient's group.

Results

The ages of the patients ranged from 22 to 68 years (mean 49.2, SD = 14.5), and their scores in the Hamilton Depression Rating Scale from 18 to 43 points (mean 29, SD = 8). The ages in the group of control subjects ranged from 21 to 50 years (mean 31.4, SD = 10.2), significantly lower than that of the patients' group ($F = 15.16$, $p < 0.001$). All subjects had normal body weight, with mean values 77.7 (SD = 8.0) kg for the patients' group, and 79.4 (SD = 12.4) for controls.

Duration of illness of the patients ranged from 0.4 to 7 years (mean 3.1 years, SD = 2.3), and seizure times measured during ECT ranged from 24 to 64 s (mean 39.9, SD = 10.8).

The two groups had similar baseline plasma prolactin levels (Table 1). In the patients' group, there were no significant correlations between baseline hormone levels and age, duration of illness, HDRS score, or seizure time during the first ECT.

The PRL responses of the patients to CMI administration were blunted compared to controls (ANOVAR, $F_{4,112} = 6.25$, $p = 0.001$), while the PRL responses to HAL were lower, but not significantly different from those of the group of healthy subjects (Fig. 1).

The main objective of this study was to relate the prolactin responses to ECT of the patients to their serotonergic and to dopaminergic systems responsivities, as measured by the prolactin increases after clomipramine and after haloperidol administration. Thus, the maximal PRL responses to these agents were calculated by taking the highest post-drug prolactin level minus the baseline level of each patient. Linear regression analysis showed that the PRL increases induced by ECT were not related to the serotonergic responsivity (PRL responses to CMI, $r = 0.1713$, $p = 0.57$), but were positively correlated to the increases caused by haloperidol (Fig. 2). The correlation coefficient between the maximal PRL responses to HAL and to ECT had a value of 0.8205 ($N = 15$, $p < 0.001$), which means that 67 % of the variation in PRL responses to ECT can be explained by an effect on the dopaminergic neuronal activity. The correlation remains significant when the outlier with the highest responses (Fig. 2) is omitted ($N = 14$, $r = 0.5555$, $p = 0.039$), while using the non-parametric Spearman correlation coefficient test

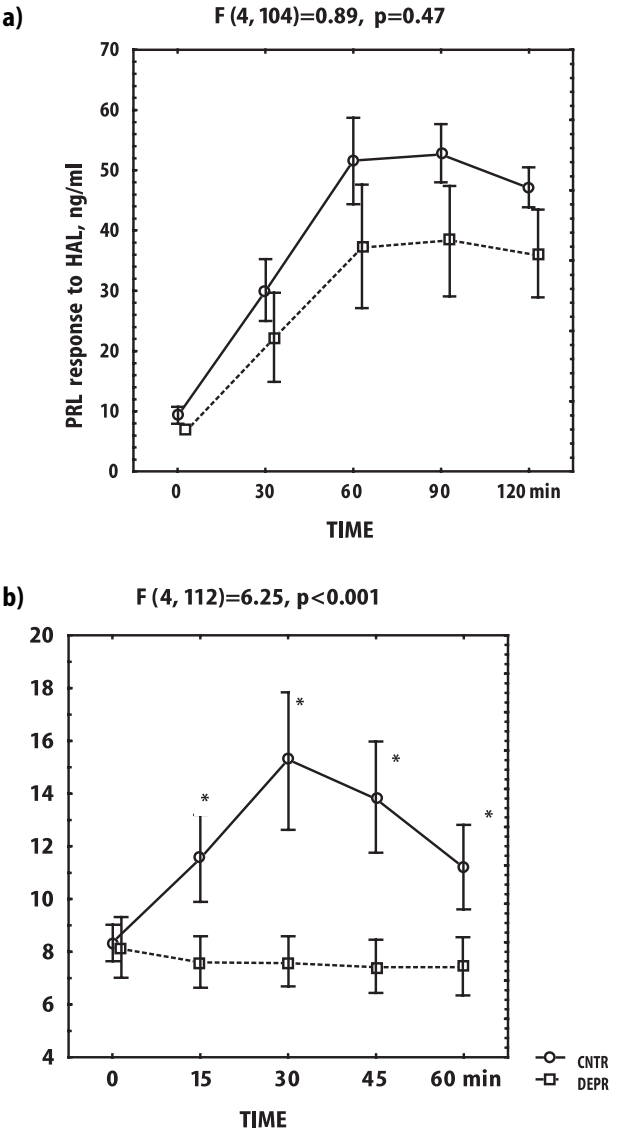

Fig. 1 Prolactin responses to i. m. haloperidol (**a**) and to i. v. clomipramine (**b**) of 15 male depressive patients and 15 (13 for haloperidol) healthy male subjects. Group interactions (ANOVA for repeated measures) are given. Asterisks indicate significant planned comparisons.

Table 1 Clinical and neuroendocrine data (mean ± SD) of patients and healthy controls. The maximal prolactin responses (maximal post-stimulus value minus baseline value) to clomipramine, to haloperidol, and to ECT are given in ng/ml plasma. Statistical evaluation of the endocrine data by ANOVA with age as covariate

Variable	Controls	Patients	F (1, 28)	p
N	15	15		
Age	31.4±10.1	49.2±14.5	15.16	0.001
Duration of illness		3.1±2.3		
HDRS score		29.0±7.8		
Seizure time, s		39.9±10.8		
			F (1, 27)	p
PRL, baseline	8.3±2.8	8.1±4.7	0.45	0.51
CMI-PRLmax	8.9±9.8	0.2±2.7	5.16	0.03
HAL-PRLmax	48.6±20.0 (N = 13)	37.1±37.9	0.03	0.81
ECT-PRLmax		26.8±21.2		

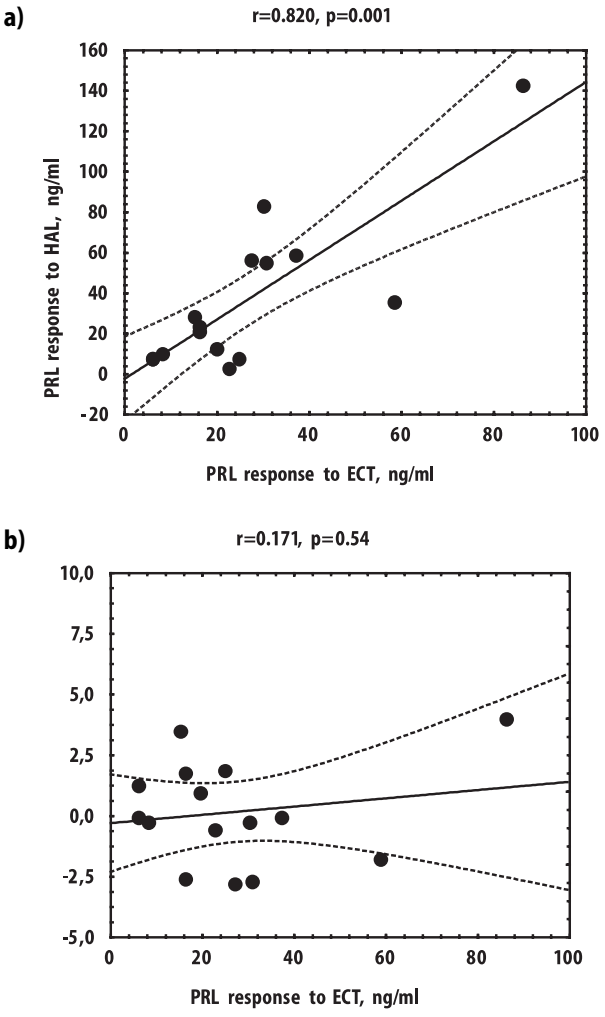

Fig. 2 Correlations between the prolactin responses to ECT of 15 male depressive patients, and their responses to i. m. haloperidol (**a**, significant), and to i. v. clomipramine (**b**, non-significant).

we obtained Rs = 0.6483, with p = 0.012 for N = 14 (the outlier excluded), while for N = 15 the coefficient is Rs = 0.7143, and p < 0.003.

In order to illustrate the dependence of the magnitude of PRL responses to ECT from the responsivity of the dopaminergic receptors, as measured by the PRL responses to i. m. haloperidol, and to provide a further statistical support of the finding, we formed two subgroups of patients using a median split, one with low PRL responses to haloperidol (7 patients, responses from 2.9 to 21.5 ng/ml, mean = 10.1), and the other with "high" responses (8 patients, responses from 23.7 to 142.9 ng/ml, mean = 60.7) and compared their PRL responses to ECT. The results are shown in Fig. 3, with the low PRL responders to HAL having significantly lower PRL responses to ECT.

In order to evaluate the contribution of other clinical and neuroendocrine variables in the magnitude of the PRL responses to HAL, we performed multiple regression analysis. Because of the relatively small number of patients, we evaluated separately the clinical variables

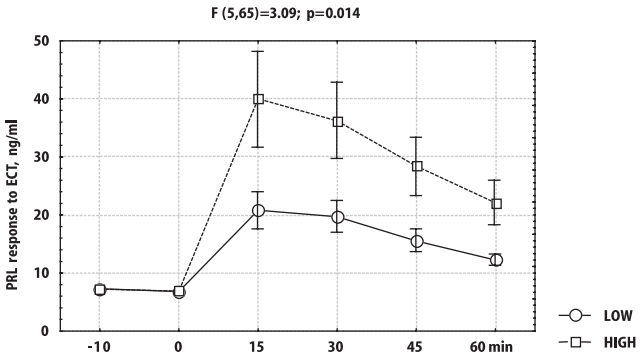

Fig. 3 Prolactin responses to ECT in subgroups of depressive patients with low (n = 6) and with high (n = 9) prolactin responses to i. m. haloperidol. Means and SEM.

and the neuroendocrine variables, with the maximal PRL response to ECT as dependent variable. With independent variables age, duration of illness, HDRS score, and form of illness (bipolar, with psychotic features), we calculated a multiple R = 0.437, df = 4,10, F = 0.59, p = 0.68, indicating that none of these variables can predict the PRL response. With independent variables baseline prolactin and the PRL responses to CMI and to ECT (3 variables), we obtained an R = 0.821, df = 3,11, F = 7.58, and p = 0.005, with a significant beta only for the PRL response to ECT (beta = 0.816, p = 0.001).

Discussion

The blunted prolactin responses to the serotonin uptake inhibitor clomipramine in depressive patients reported previously [1, 9], were also found in this study. The nature of this deficit could be attributed to a reduced responsivity of post-synaptic 5-HT receptors, mainly of 5-HT1C and 5-HT1A subtypes, since such receptors have been connected with the release of PRL by serotonin [1, 7].

One point in the study that has to be considered is the possible influence of the administration of 5 mg haloperidol on the PRL responses to ECT, two to four days later. One way to examine this possibility using the data of the present study is to compare the baseline PRL levels measured before the administration of haloperidol with the levels measured before ECT administration. Before the administration of haloperidol, PRL levels of the 15 patients ranged from 3.5 to 12.4 ng/ml (mean ± SD = 6.8 ± 3.1), and before ECT from 3.7 to 10.5 ng/ml (mean ± SD = 7.3 ± 1.8), the difference being non-significant (t-test for paired data, p = 0.33). There is thus no indication of any sustained blockade of D2 dopaminergic receptors by haloperidol, which, if present, should be expressed in elevated plasma PRL levels. In addition, we have previously shown that the PRL response to i. m. haloperidol is attenuated only when a considerable D2 dopamine blockade is present [16]. Nevertheless, prolactin released by the administration of the D2 receptor

antagonist chlorprothixene returns to baseline within 24 hours, despite the presence of the drug in plasma [3].

Data from the literature support the view that the prolactin release by ECT is not influenced by the administration of one single dose of haloperidol two to four days previously. Movin-Osswald and Hammarlund-Udenaes [19] showed, using the D2 dopamine receptor blocker remoxipride in two consecutive doses at several time intervals, that the prolactin pool is fully restored after 24 to 48 hours, and that the refractory period for a second prolactin release after remoxipride, similar to the first prolactin release, was 24 hours for most of the subjects [20].

The main finding of the study is that the PRL responses to ECT correlate to the PRL responses obtained after injection of haloperidol, which reflect the responsivity of the pituitary dopamine system, and were not related to the PRL responses to the serotonergic agent CMI. The lack of association to the PRL responses to CMI is obviously due to the low variation of the blunted responses, still the fact remains that the diminished serotonergic responsivity does not correspond to the PRL increases elicited by ECT. It can be suggested that the seizure induced by the electrical stimulus causes a transient reduction of the dopaminergic activity, which attenuates the tonic inhibition of PRL release. The reduction is short lasting, since plasma PRL concentrations are already reduced in the blood sample taken after the maximal value, in contrast to the samples during haloperidol, where the blockade of D2 dopamine receptors lasts longer. These results increase the evidence that the PRL release by ECT is a dopaminergic rather than a serotonergic effect. This is also indicated by previous studies, mentioned in the introduction: pretreatment with serotonergic receptor antagonists does not influence the PRL release during ECT, as has been shown for ketanserin [27] or ritanserin [22]. Pretreatment with drugs which possess dopamine receptor antagonistic activity, like methysergide [21] or metoclopramide [29], reduce or block the PRL release by ECT, indicating the involvement of mainly dopaminergic, and not serotonergic mechanisms in this effect of the electrical stimulus.

References

1. Anderson IM, Ware CJ, Da Rosa Davis JM, Cowen PJ (1992) Decreased 5-HT-mediated prolactin release in major depression. Brit J Psychiatry 160:372–378
2. Angelopoulos E, Markianos M, Daskalopoulou E, Tzemos J, Stefanis C (1997) Neuroendocrine responsivity to clomipramine challenge test in neuroleptic naïve psychotic patients before and after treatment with haloperidol. Eur Psychiatry 12:362–366
3. Bagli M, Suverkrup R, Quadflieg R, Hoflich G, Kasper S, Moller H-J, Langer M, Barlage U, Rao M-L (1999) Pharmacokinetic-pharmacodynamic modeling of tolerance to the prolactin-secreting effect of chlorprothixene after different modes of drug administration. J Pharmacol Exp Ther 291:547–554
4. Christie JE, Whalley LJ, Brown NS, Dick H (1982) Effect of ECT on the neuroendocrine responses to apomorphine in severely depressed patients. Br J Psychiatry 140:268–273
5. Cooper SJ, Leahey W, Green DF, King DJ (1988) The effect of electroconvulsive therapy on CSF amine metabolites in schizophrenic patients. Brit J Psychiatry 152:59–63
6. Costain DW, Cowen PJ, Gelder MG, Grahame-Smith DG (1982) Electroconvulsive therapy and the brain: evidence for increased dopamine-mediated responses. Lancet 2:400–404
7. Cowen PJ, Anderson IM, Gartside SE (1990) Endocrinological responses to 5-HT. Ann N Y Acad Sci 600:250–257
8. Golden RN, Hsiao J, Lane E, Ekstrom D, Rogers S, Potter WZ (1989) The effects of intravenous clomipramine on neurohormones in normal subjects. J Clin Endocrinol Metab 68:632–637
9. Golden RN, Hsiao J, Lane E, Ekstrom D, Rogers S, Hicks R, Potter WZ (1990) Abnormal neuroendocrine responsivity to acute i. v. clomipramine challenge in depressed patients. Psychiatry Res 31:39–47
10. Kolakowska R, Braddock L, Wiles D, Franklin M, Gelder M (1981) Neuroendocrine tests during treatment with neuroleptic drugs. I. Plasma prolactin response to haloperidol challenge. Brit J Psychiatry 139:400–404
11. Laakmann G, Gugath M, Kuss HJ, Zygan K (1984) Comparison of growth hormone and prolactin stimulation induced by clomipramine and desipramine in man in connection with clomipramine metabolism. Psychopharmacology 82:62–67
12. Leatherman ME, Bebchuk JM, Ekstrom RD, Heine AD, Carson SW, Golden RN (1999) The effects of serotonin3 receptor blockade on the psychobiological response to intravenous clomipramine in healthy human subjects. Biol Psychiatry 45:238–240
13. Lykouras L, Markianos M, Hatzimanolis J, Stefanis C (1991) Effects of ECT course on TSH and prolactin responses to TRH in depressed patients. J Affect Dis 23:191–197
14. Malone KM, Thase ME, Mieczkowski T, Myers JE, Stull SD, Cooper TB, Mann JJ (1993) Fenfluramine challenge test as a predictor of outcome in major depression. Psychopharmacol Bull 29:155–161
15. Mann JJ (1998) Neurobiological correlates of the antidepressant action of electroconvulsive therapy. J ECT 14:172–180
16. Markianos M, Sakellariou G, Bistolaki E (1991) Prolactin responses to haloperidol in drug-free and treated schizophrenic patients. J Neural Transm 83:37–42
17. Markianos M, Lykouras L, Hatzimanolis J, Stefanis C (1995) Prolactin and cortisol release during ECT are not influenced by pretreatment with the serotonin receptor agonist sumatriptan. Neuroendocrinol Lett 17:37–40
18. Markianos M, Hatzimanolis J, Lykouras L (2001) Neuroendocrine responsivities of the pituitary dopamine system in male schizophrenic patients during treatment with clozapine, olanzapine, risperidone, sulpiride, or haloperidol. Eur Arch Psychiatry Clin Neurosci 251:141–146
19. Movin-Osswald G, Hammarlund-Udenaes M (1995) Prolactin release after remoxipride by an integrated pharmacokinetic-pharmacodynamic model with intra- and interindividual aspects. J Pharmacol Exp Ther 274:921–927
20. Movin-Osswald G, Hammarlund-Udenaes M, Von Bahr C, Eneroth P, Walton-Bowen K (1995) Influence of the dosing interval on prolactin release after remoxipride. Brit J Clin Pharmacol 39:503–510
21. Papakostas Y, Markianos M, Stefanis C (1988) Methysergide reduces the prolactin response to ECT. Biol Psychiatry 24:465–468
22. Papakostas Y, Markianos M, Papadimitriou G, Stefanis C (1990) Ritanserin, a 5-HT2 receptor antagonist, does not modify ECT-induced prolactin release. Psychopharmacology 100:206–208
23. Papakostas Y, Markianos M, Papadimitriou G, Stefanis N, Lykouras L, Stefanis C (1993) Prolactin and thyrotropin responses to ECT after pindolol administration: a placebo-controlled study. Eur Neuropsychopharmacol 3:75–79
24. Shapira B, Lerer B, Kindler S, Lichtenberg P, Gropp C, Cooper T, Calev A (1992) Enhanced serotonergic responsivity following electroconvulsive therapy in patients with major depression. Brit J Psychiatry 160:223–229

25. Shapira B, Newman ME, Gelfin Y, Lerer B (2000) Blunted temperature and cortisol responses to ipsapirone in major depression: lack of enhancement by electroconvulsive therapy. Psychoneuroendocrinology 25:421–438
26. Yatham LN, Zis AP, Lam RW, Srisurapanont M, McGarvey K, Agbayewa O (1996) Role of serotonin3 receptors in prolactin release by electroconvulsive therapy: a study with ondansetron. Psychiatry Res 60:33–39
27. Zis AP, Manji HK, Remick RA, Grant BEK, Clark CM (1989) Effect of the 5-HT2 antagonist ketanserin on the ECT-induced prolactin release. Biol Psychiatry 26:102–106
28. Zis AP, Goumeniouk AD, Clark CM, Remick RA, Adams SA (1992) ECT induced PRL release: a 5-HT1A mediated event? Biol Psychiatry 31:415–418
29. Zis AP, McGarvey KA, Clark CM, Lam RW, Adams SA (1992) The role of dopamine in seizure-induced prolactin release in humans. Convulsive Ther 8:126–130