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PROLACTIN RESPONSE TO TRH IN DEPRESSION

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Summary—We studied the prolactin response to TRH in 53 unmedicated psychiatric inpatients. The prolactin response of females was significantly greater than the response of male subjects. There was no significant difference in the prolactin response to TRH between depressed patients and those with other psychiatric diagnoses. There was no significant relationship between the prolactin response to TRH and the severity of depression, the TSH response to TRH or the resistance to suppression of cortisol secretion by dexamethasone.

INTRODUCTION

THE THYROTROPIN (TSH) response to the thyrotropin-releasing hormone (TRH) in depression has been the subject of numerous studies. It is well established that the TSH response to TRH is decreased in some depressed patients (LOOSEN and PRANGE, 1982). Studies of the prolactin (PRL) response to TRH in depression are fewer and the results are less consistent: the PRL response to TRH in these patients has been reported as increased, decreased or normal (LOOSEN and PRANGE, 1982). In this study we examined the PRL response to TRH in 53 unmedicated psychiatric inpatients. In addition, we investigated the relationship between the PRL and TSH response to TRH and the relationship between resistance to suppression of cortisol secretion by dexamethasone and the PRL response to TRH.

SUBJECTS AND METHODS

We studied 53 psychiatric inpatients (29 women, 24 men). Subjects gave written consent to participate in the study and were drug free for at least one week (usually 10–14 days) prior to the study. Patients were euthyroid as determined by measurement of T_4 RIA, T_3 resin uptake and basal TSH. Patients who had received lithium salts in the three months preceding the study were excluded. Diagnoses were made according to the Research Diagnostic Criteria (RDC) (SPITZER *et al.*, 1975) on the basis of all clinical information and a structured interview (SPITZER and ENDICOTT, 1975) and without access to laboratory results.

After an overnight fast, subjects were awakened between 6:30 and 7:00 a.m. An intravenous catheter was inserted between 8:00 and 8:30 a.m. and 500 μg of TRH (Relefact, Hoehst-Roussel) were injected intravenously at 9:30 a.m. Subjects remained supine in bed

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for the duration of the experiment. Blood was drawn 15 min and immediately before, and 15, 30, 60, 90 and 120 min after the injection. Samples were immediately centrifuged and stored at −20°C. PRL was measured by RIA using antibody and standard donated by the National Pituitary Agency, Baltimore, Maryland, U.S.A. The interassay and intraassay coefficients of variation were 6.5% and 5.5% respectively. the linear range of the assay was 0.5–200 ng/ml. TSH was measured by RIA using the Kallestad TSH Kit reagents, Austin, Texas, U.S.A. Interassay and intraassay coefficients of variation were 8.8% and 6.0% respectively at a TSH concentration of 5.9 μu/ml.

Within four days following the TRH infusion patients received dexamethasone (1 mg) at 11:30 p.m. Cortisol was measured by the transcortin method of Murphy (MURPHY, 1967). Interassay and intraassay coefficients of variation were 5.6% and 8.9% at a cortisol concentration of 10.15 μg/dl.

Data were analysed by repeated measures analysis of variance using all time points. Subjects were grouped by sex and diagnosis. Additional grouping factors were the Dexamethasone Suppression Test results (DST) and ΔTSH. A cortisol level higher than 5 μg/dl at either 4:00 p.m. or 11:00 p.m. was considered abnormal (escape). A ΔTSH value (defined as maximal TSH after TRH minus zero point baseline) equal to or below 7 μu/ml was considered blunted. The relationship between ΔPRL (defined as maximal PRL after TRH minus zero point baseline) and age, HRS score and ΔTSH was examined by the Pearson product moment correlation coefficient. The repeated measures analysis of variance and Pearson product moment correlation coefficient were performed after logarithmic transformation (log 10) of the hormonal values.

Thirty-two patients, 20 women and 12 men met RDC criteria for Major Depressive Disorder (MDD). The remaining 21 patients, 9 women and 12 men, served as Psychiatric Controls. Their diagnoses were as follows: Schizophrenia $n=8$ (2 women, 6 men), Mania $n=7$ (5 women, 2 men), Miscellaneous Diagnoses $n=6$ (2 women, 4 men). Mean age ± SD was 39.9 ± 14.7 for the MDD group and 32.5 ± 14.1 for the Psychiatric Control group. Of the 32 patients with MDD, 21 scored at least 15 on the Hamilton Rating Scale (HRS), 17-item vesion. HRS score was missing in one patient. Of the 53 patients, 18 (12 women, 6 men) had abnormal DST results. Twelve of these 18 received a diagnosis of MDD. DST results were missing in one patient. Of the 53 patients, 12 (5 women, 7 men) had a blunted TSH response to TRH. Of these 12, six received a diagnosis of MDD.

RESULTS

There were no differences in baseline PRL levels between men and women ($F=0.2$, df 1,51, ns), or between patients with MDD and psychiatric controls ($F=0.1$, df 1,51, ns).

The administration of 500 μg TRH stimulated PRL release ($F=248.5$, df 6,294, $p<0.0001$) (Fig. 1). There was a significant main effect for sex ($F=8.1$, df 1,49, $p<0.01$). Neither the main effect for diagnosis ($F=0.0$, df 1,49, ns) nor the sex by diagnosis interaction ($F=0.4$, df 1,49, ns) were significant. There were no signifcant differences in the PRL response to TRH between patients with normal and abnormal DST results ($F=1.7$, df 1.48, ns) nor between patients with a normal and a blunted TSH response ($F=0.6$, df 1,49, ns). There were also no significant differences in the PRL response to TRH of MDD patients with a HRS score above or below 15 ($F=3.7$, df 1,29, ns), nor between MDD patients

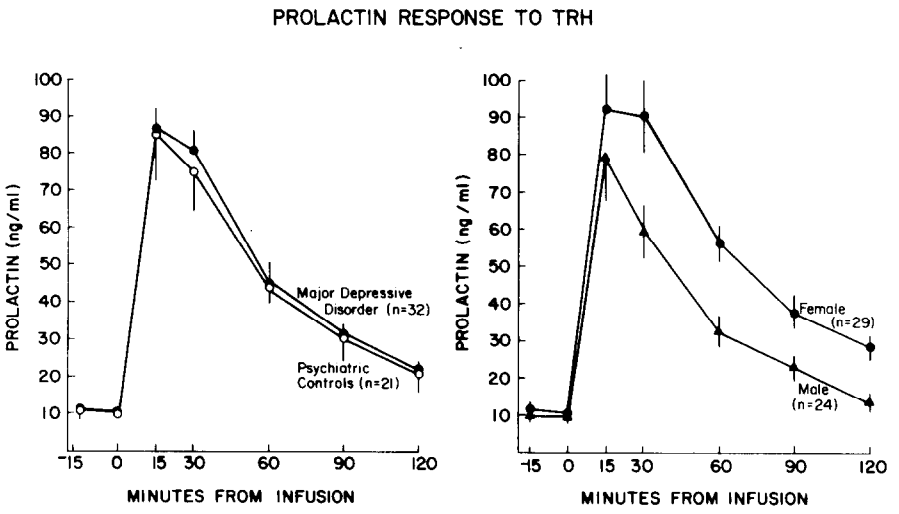

FIG 1. Prolactin response to 500 μg of TRH in psychiatric inpatients ($n = 53$).

with a HRS score ≥ 15 and manic and schizophrenic patients ($F = 1.5$, df 1,34, ns). There was a weak positive correlation between ΔPRL and age ($r = 0.279$, df 51, $p < 0.05$). Neither the correlation between ΔPRL and ΔTSH ($r = 0.249$, df 51, ns), nor the correlation between ΔPRL and HRS score in patients with MDD ($r = -0.057$, df 29, ns) were significant.

DISCUSSION

The data presented here indicate that there is no difference in the PRL response to TRH between patients with MDD and those with other psychiatric diagnoses. There was also no evidence that the severity of depression was associated with the PRL response to TRH. The response was significantly greater in women which is consistent with earlier reports in normal subjects (JACOBS *et al.*, 1971). The relationship between age and PRL response although significant, accounted for only 7.8% of the variance and was not significant when data from male and female subjects were analyzed separately. Our data were insufficient to examine the relationship between ovarian status and the response of our female subjects.

Table 1 summarizes the results of previous studies of the PRL response to TRH in depression that we are able to locate and which included at least eight depressed subjects. Four studies did not include a comparison group as part of the study (EHRENSING *et al.*, 1974; GREGOIRE *et al.*, 1977; BRAMBILLA *et al.*, 1978; LINNOILA *et al.*, 1979). Instead, the results were compared to normative data obtained in the same laboratory in a different study or to data obtained at a different research setting. Of the studies which did include a comparison group, one reports increased response compared to healthy volunteers (MAEDA *et al.*, 1975), one reports a decreased response in postmenopausal but normal response in premenopausal females (LINKOWSKI *et al.*, 1980), one reports a normal response in 75%, increased in 7% and blunted response in 18% of the depressed subjects (WINOKUR *et al.*, 1983) and one reports a decrease response in endogenously depressed women (WITSCHY

TABLE 1. PRL RESPONSE TO TRH: SUMMARY OF 14 STUDIES

Study	Number of depressed subjects	Number of control subjects	Response
EHRENSING *et al.* (1974)	8	0	Blunted response in 3 patients
MAEDA *et al.* (1975)	13	16 healthy volunteers	Increased
GREGOIRE *et al.* (1977)	19	0	Low normal
BRAMBILLA *et al.* (1978)	16	0	Normal
NAEIJE *et al.* (1978)	8	8 healthy volunteers 8 barbiturate coma	No difference
LINNOILA *et al.* (1979)	8	0	Blunted response in 7 patients
LANGER *et al.* (1980)	28	13 healthy volunteers	No difference
COPPEN *et al.* (1980)	16	16 healthy volunteers	No difference
LINKOWSKI *et al.* (1980)	51	38 healthy volunteers	Decreased in post-menopausal women No difference in premenopausal women
KIRKEGAARD *et al.* (1981)	18	9 healthy volunteers 8 psychiatric controls	No difference
TARGUM *et al.* (1982)	35	13 psychiatric controls	No difference
WINOKUR *et al.* (1983)	45	32 healthy volunteers	Normal $n = 34$ Blunted $n = 8$ Increased $n = 3$
WITSCHY *et al.* (1984)	25	20 healthy volunteers	Decreased in endogenously depressed women
ZIS *et al.* (present study)	32	21 psychiatric controls	No difference

et al., 1984). The remaining five controlled studies report no difference between depressed patients and healthy volunteers or psychiatric controls (NAEIJE *et al.*, 1978; LANGER *et al.*, 1980; COPPEN *et al.*, 1980; KIRKEGAARD *et al.*, 1981; TARGUM *et al.*, 1982). We were also unable to demonstrate a difference between our depressed subjects and psychiatric controls. This, however, does not exclude the possibility that the response of some of our depressed subjects and psychiatric controls would have been found either increased or decreased if compared to age- and sex-matched healthy volunteers studied under identical conditions. It must also be noted that some evidence for the presence of an impairment in the PRL response to TRH in depression is derived from reports of increased responsiveness on repeat testing after recovery (GREGOIRE *et al.*, 1977; LANGER *et al.*, 1980; KIRKEGAARD *et al.*, 1981; D'AGATA *et al.*, 1979; ASNIS *et al.*, 1981). Repeat testing, however, was conducted in most of these studies while many of the patients were still on tricyclic antidepressants and this finding has not been always confirmed (LINKOWSKI *et al.*, 1980).

The administration of exogenous steroids can affect the PRL response to various stimuli including TRH (COPINSCHI *et al.*, 1975; SOWERS *et al.*, 1977; ROSSIER *et al.*, 1980). Thus, it is possible that decreased PRL response to TRH when present in certain patients, is associated with the presence of disinhibited hypothalamic–pituitary–adrenal cortex function. Unlike the results of WITSCHY *et al.* (1984), we did not find a relationship between the presence of abnormal DST results and the PRL response to TRH. The reasons for this discrepancy are not readily apparent. Finally, in this study we examined the relationship

between the TSH and PRL response to TRH. This question is of some, at least theoretical, importance; it has been postulated that the simultaneous presence of a decreased TSH and a decreased PRL response to TRH could be the result of increased dopaminergic tone (LOOSEN and PRANGE, 1982). Few studies have addressed this question systematically. Recently TARGUM *et al.* (1982) and WITSCHY *et al.* (1984) reported an association between blunted TSH and decreased PRL response to TRH in depressed patients. LOOSEN *et al.* (1983), however, found normal prolactin levels following TRH in depressed patients showing TSH blunting. Similarly, we were unable to demonstrate a statistically significant relationship between the TSH and PRL response to TRH. Although methodological differences (i.e. differences in sex distribution) could be responsible, the exact reasons for this discrepancy are not really apparent. Whatever the case it must be emphasized that the simultaneous presence of an attenuated TSH and PRL response does not necessarily reflect alterations in monoaminergic tone but could be the result of changes in the bioavailability of TRH.

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