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Endocrine changes and clinical profiles in depression: II. The thyrotropin-releasing hormone test

S. P. CALLOWAY,[1] R. J. DOLAN, P. FONAGY, V. F. A. DE SOUZA AND A. WAKELING

From the Academic Department of Psychiatry, Royal Free Hospital, London

SYNOPSIS Thirty-one (43%) of 68 patients with primary depression were found to have a blunted thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH). Increased thyroid activity, as measured by the free thyroxine index (FTI), was present in 16 (24%) of the patients. Patients with blunted responses had a higher mean FTI level than those with normal responses. Patients with blunted responses were significantly more likely to exhibit the symptoms of depersonalization, derealization and agitation. There was no clear association between blunting and any particular diagnostic category of depression.

Patients with blunted responses and high FTI values were more likely to report significant long-term environmental difficulties than patients with blunted responses and normal FTI values. It is suggested that there may be more than one mechanism responsible for blunting of the TSH response in depressed patients. In some patients blunting may be due to negative feedback from increased output of thyroid hormones, possibly released as part of a stress response. In other patients blunting may be due to a different mechanism, possibly involving pituitary gland dysfunction. These mechanisms would not necessarily be mutually exclusive in any one patient.

INTRODUCTION

There has been recent interest in the hypothalamic–pituitary–thyroid axis in depression, following reports that a proportion of depressed patients have blunted thyroid-stimulating hormone (TSH) responses to thyrotropin-releasing hormone (TRH) (Kastin *et al.* 1972; Prange *et al.* 1972). Depressed patients have been shown to have blunted responses of TSH to TRH in comparison with patients with other psychiatric illnesses and normal controls (Kirkegaard *et al.* 1978; Extein *et al.* 1981). The proportion of depressed patients with a blunted TSH response to TRH has been found to vary from 25% to 70% across different studies (Loosen & Prange, 1982). There is, however, little detailed information about the clinical characteristics of patients with blunted responses. Gold *et al.* (1980) found that patients with unipolar illnesses had blunted responses, whereas those with bipolar illness had augmented responses; other studies have been unable to confirm this finding (Linkowski *et al.* 1981; Kirkegaard *et al.* 1978). More recently, the TRH-test has been suggested as a diagnostic aid in major depressive disorder (Extein *et al.* 1981; Targum *et al.* 1982).

The significance of the blunted response in depression is unclear. Hatotani *et al.* (1977) suggested that it may be due to reduced thyroid function. On the other hand, Loosen & Prange (1982) suggested that during depression there is hypersecretion of TRH with a transient increase in thyroid activity, producing blunting by negative feedback. Studies measuring levels of thyroid hormones in depressed patients have produced conflicting results (Ferrari, 1973; Yamaguchi *et al.* 1977; Rieneris *et al.* 1978). However, longitudinal studies, and those assessing thyroid function during depressive episodes and again after recovery, suggest that thyroid levels are high during depression and fall on recovery (Board *et al.* 1957; Kirkegaard & Faber, 1981). However, free thyroxine index (FTI) levels have not been shown to be related to the blunted TRH-test (Kirkegaard & Faber, 1981).

[1] Address for correspondence: Dr S. P. Calloway, Academic Department of Psychiatry, Royal Free Hospital, Pond Street, London NW3 2QG

Raised cortisol levels may cause blunting of the TSH response (Re *et al.* 1976; Otsuki *et al.* 1973). Loosen *et al.* (1978) found, in a small group of depressed patients, that blunting was associated with elevated cortisol levels. A study by Agren & Wide (1982) also reported an inverse relationship between TSH response and cortisol levels, but this association was not confirmed by Gold *et al.* (1980) and Davis *et al.* (1981). Moreover, there appears to be no association between a positive dexamethasone suppression test (DST) and blunting of the TRH-test (Extein *et al.* 1981; Targum *et al.* 1982).

The conflicting results in this area of research may be due in part to inadequate clinical definitions of the populations under study, as well as the relatively small number of patients in the early studies. The aim of the present study was to investigate a group of drug-free patients with primary depression in order to identify possible causes of blunting in depression. Furthermore, it was hoped to delineate more precisely the clinical features of patients with blunted TSH responses to TRH.

METHOD

Details of the selection of patients and the procedure of the study are described in the preceding paper (Calloway *et al.* 1984). The TRH-test was performed two days after the DST. After an overnight fast, an intravenous butterfly needle was inserted at 8.15 a.m. (time varying between 8 a.m. and 8.45 a.m.) and the line was kept open with heparin. Initial blood samples were taken 15 minutes after insertion. Half an hour later the baseline sample was taken, and 400 μg of TRH (Roche) was administered over a 1 minute period. Further blood samples were taken at 20 minutes and 60 minutes after TRH administration. TRH-tests were performed on 68 of the 72 patients. In the remaining 4 cases the test failed because of problems with the intravenous line.

Serum thyroxine (T4) and T3 uptake were measured in the baseline sample by radioimmunoassay, using the RIA-UK kit. The intra-assay coefficients of variation were 6% and 7% respectively. FTI was calculated by multiplying the two values and dividing by 100. The normal range for FTI using this method is 18–45 nmol/l. TSH was measured in duplicate by double antibody RIA techniques, using an Amerlex TSH RIA kit. The inter-assay coefficient of variation was 3·2%.

Using the criteria of Kirstein *et al.* (1981), blunting was defined as no response greater than 7 μU/ml. These authors found that using a cut-off point of 7 μU/ml rather than 5 μU/ml increased sensitivity from 38% to 78% and reduced specificity from 89% to 80% in distinguishing depressed patients from psychiatric and normal controls. The degree of blunting depends partly on the dose of TRH used. In the majority of recent studies, 400 or 500 μg of TRH has been used (Kirstein *et al.* 1981; Extein *et al.* 1981; Targum *et al.* 1982), although a number of studies have used lower doses (Kirkegaard *et al.* 1975). With lower doses of TRH there may be a dose-related response, so that body weight could influence TSH response; with doses of 400 μg and above this does not appear to be the case (Snyder & Utiger, 1972). An augmented TSH response was taken as one greater than 19·5 μU/ml, as defined by Yamaguchi *et al.* (1977).

RESULTS

(a) Relationship between endocrine variables

Baseline T4, T3 uptake, FTI and results from the TRH-test were obtained from 68 of the 72 patients. The 24-hour urinary free cortisol (UFC) was measured in 64 of these patients. The mean T4 level of the patients was 11·9 nmol/l (S.D. = 3·7, range 5·3–25·5) and the mean FTI was 38·9 nmol/l (S.D. = 10·9, range 16·0–76·6). Sixteen (23·5%) patients had FTI levels above the upper limit of 45 nmol/l. The mean maximum response of TSH to TRH (Δ_{max} TSH) was 10·0 μU/ml (S.D. = 10·5, range 0·5–71·0). Using a cut-off point of 7 μU/ml, 31 patients (43·1%) had blunted responses. When the cut-off point was taken as 19·5 μU/ml, 6 patients had an augmented response, and 3 of these had responses greater than 28 μU/ml.

Patients were divided into three groups: those with blunted, normal or augmented resposes on the TRH test. Table 1 shows the mean UFC, FTI and Δ_{max} TSH levels for these groups. A one-way analysis of variance revealed that patients with blunted responses tended to have higher FTI levels than those with normal responses, who in turn had higher levels than patients with augmented responses ($F = 4·32$, df = 1,58; $P < 0·05$: $F = 4·41$; df = 1,35; $P < 0·05$). In

Table 1. *Values (mean ± S.D.) of basal TSH, Δ_{max} TSH, FTI and UFC for patients with normal, blunted and augmented TSH responses to TRH*

	Blunted ($N = 31$)	Normal ($N = 31$)	Augmented ($N = 6$)
Basal TSH (μU/ml)	2·03 ± 2·04	2·20 ± 2·30	4·14 ± 6·70
Δ_{max} TSH (μU/ml)	4·56 ± 1·74	9·69 ± 1·28	34·2 ± 19·5
FTI (nmol/l)	42·6 ± 11·0	37·1 ± 9·0	28·3 ± 10·8
UFC (μg/24 h)	176·5 ± 65·2	127·9 ± 82·8	168·2 ± 45·5

Table 2. *Correlation matrix of endocrine and other variables in depressed patients ($N = 68$)*

	FTI	Δ_{max} TSH	UFC	Age	Hamilton score
Δ_{max} TSH	−0·334**	—	—	—	—
UFC	0·133	−0·044	—	—	—
Age	−0·053	−0·112	−0·106	—	—
Hamilton score	0·061	−0·168	0·293*	0·237	—
PSE score	0·153	−0·229	0·376**	0·019	0·754**

* $P < 0·01$; ** $P < 0·005$.

addition, patients with blunted responses and patients with augmented responses tended to have higher UFC values than those with normal responses ($F = 5·91$; df = 1,54; $P < 0·05$: $F = 0·28$; df = 1,66; NS). The higher mean basal TSH found among patients with augmented responses was largely due to one patient having a level of 19 μU/mL.

Values of FTI and Δ_{max} TSH showed a log-normal distribution, and log transforms were therefore performed on all these values. Product-moment correlations were computed between all the endocrine variables. These results are shown in Table 2. A significant negative correlation, independent of cortisol levels, emerged between FTI levels and Δ_{max} TSH ($r = -0·334$, $P < 0·001$). The partial correlation coefficient (which statistically removed the effect of cortisol) was only slightly smaller than the original correlation ($r = -0·311$). There was no association between UFC levels and FTI or Δ_{max} TSH.

(b) Relationship between blunted responses and diagnostic categories

The patient group was classified using a number of commonly used classificatory systems for depression. The proportion of patients with blunted responses in each category is shown in Table 3. When the patients were classified into major and minor depressive disorder by means of the Research Diagnostic Criteria (RDC) there was no difference in the incidence of blunted and non-blunted responses. However, patients with blunted responses appeared with greater than chance frequency among those classified as definite 'endogenous' depressive disorder as opposed to those with 'non-endogenous' depressive disorder on the RDC ($S_c = 348·8$, $P < 0·01$). The proportion of patients with blunted responses was similar in patients classified as endogenous and those classified as neurotic by the Newcastle Diagnostic Index. There was, however, an association betwen the endogenous category of Feinberg & Carroll's (1982) Discriminant Index and blunted responses. The bipolar/unipolar classification and the Iowa Classification did not discriminate between the blunted and non-blunted patients. The PSE CATEGO classes did not distinguish between patients with blunted and non-blunted responses, although in the small group of patients classed as depressive psychosis 5 out of 6 patients had blunted responses.

(c) Relationship between blunting and clinical and demographic features

The clinical features associated with patients with blunted and non-blunted responses were examined. Sex, height, weight and the height/weight ratio did not differ between the two groups. There were no differences between the groups in terms of age, age of onset, number of

Table 3. *Number and percentage of patients with blunted responses in various diagnostic sub-divisions of depression*

	Total no. of patients	Patients with blunted response No.	(%)	Statistics
Research Diagnosis Criteria				
A. Major depressive disorder				
(i) Definitive	50	26	(52)	
(ii) Probable	9	2	(22·2)	$S_c = 189{\cdot}8$*
B. Minor depressive disorder	9	3	(33·3)	NS
A. Endogenous depressive disorder				
(i) Definite	32	20	(62·5)	
(ii) Probable	13	4	(30·8)	$S_c = 348{\cdot}8$*
B. Non-endogenous depressive disorder	23	7	(30·4)	$P < 0{\cdot}01$
Newcastle Diagnostic Index				
A. Endogenous	34	16	(44·1)	$\chi^2 = 0{\cdot}054$†
B. Neurotic	34	15	(47·1)	NS
Discriminant Index (Feinberg & Carroll, 1982)				
A. Endogenous	33	20	(60·6)	
B. Uncertain	17	6	(33·3)	$S_c = 338{\cdot}7$*
C. Non-endogenous	18	5	(27·8)	$P < 0{\cdot}05$
PSE classes				
A. Depressive psychosis	6	5	(83·3)	
B. Retarded depression	33	15	(45·5)	$\chi^2 = 4{\cdot}92$†
C. Neurotic depression	25	8	(32·0)	NS
Iowa Classification				
A. Bipolar (I+II)	7	3	(42·8)	$\chi^2 = 0{\cdot}063$†
B. Unipolar	61	28	(45·9)	NS
(i) Pure familial depressive disease	17	5	(29·4)	
(ii) Sporadic depressive disease	24	13	(54·2)	$\chi^2 = 2{\cdot}58$†
(iii) Depressive spectrum disease	20	8	(40·0)	NS

* Results of Jonckheere's test.
† Results of chi-squared test.

Table 4. *Scores (mean ± S.D.) on psychiatric rating scales of patients with blunted responses and non-blunted responses*

	Blunted ($N = 31$)	Non-blunted ($N = 37$)	Statistics
Hamilton score	22·6 ± 7·8	18·2 ± 5·9	$F = 7{\cdot}17$; df = 1,66; $P < 0{\cdot}01$
Newcastle score	5·8 ± 2·4	5·2 ± 2·6	NS
Discriminant Index Score (Feinberg & Carroll, 1982)	35·5 ± 18·6	24·1 ± 13·9	$F = 8{\cdot}38$; df = 1,66; $P < 0{\cdot}005$
PSE score (total)	29·7 ± 10·1	23·1 ± 8·1	$F = 8{\cdot}17$; df = 1,66; $P < 0{\cdot}01$
PSE syndrome scores			
General Anxiety	1·94 ± 1·5	1·22 ± 1·1	$F = 4{\cdot}75$; df = 1,66; $P < 0{\cdot}05$
Depersonalization	0·58 ± 0·9	0·16 ± 0·4	$F = 5{\cdot}72$; df = 1,66; $P < 0{\cdot}05$
Slowness	1·61 ± 2·1	0·59 ± 1·1	$F = 5{\cdot}73$; df = 1,66; $P < 0{\cdot}05$
Agitation	1·03 ± 0·9	0·62 ± 0·8	$F = 9{\cdot}56$; df = 1,66; $P < 0{\cdot}005$

previous admissions, overall duration of the condition, or duration of the current episode. Previous treatment histories were identical in the two groups, as was the likelihood of being an in-patient and the presence of precipitating life events. Patients with normal TSH responses were more likely to have a family history of depression (54%) than those with blunted responses (29%) ($\chi^2 = 4{\cdot}32$, $P < 0{\cdot}05$). Patients with a blunted response were more likely (41·9%) to have marked difficulties (as measured by the Bedford College LEDS) in areas such as housing, work or relationships than patients with normal responses (16%) ($\chi^2 = 4{\cdot}34$, $P < 0{\cdot}05$).

It was found that patients with blunted responses and marked difficulties tended to have higher FTI levels than patients with blunted responses and no difficulties ($47{\cdot}5 \pm 10{\cdot}9$ cf. $39{\cdot}5 \pm 10{\cdot}5$ nmol/l: $F = 4{\cdot}62$; df = 1,29; $P < 0{\cdot}05$). Moreover, when the patients with blunted responses were divided into two groups – those with abnormally high FTI levels (above 45 nmol/l) and those with normal FTI levels – it was found that patients with blunted responses and high FTI levels were significantly more likely to have marked difficulties (73%) than those with blunted responses and normal FTI levels (25%) ($\chi^2 = 6{\cdot}64$, $P < 0{\cdot}01$). The same calculation was made using an arbitrary cut-off point for FTI of 40 nmol/l, which is at the upper end of normal. Of the 16 patients with high FTI values, 68·7% reported difficulties; only 2 (13%) of the patients with FTI values below 40 nmol/l reported difficulties ($\chi^2 = 8{\cdot}88$, $P < 0{\cdot}005$).

The mean scores on a number of psychiatric rating scales for blunted and normally responding patients are shown in Table 4. Patients with blunted responses had higher scores on the Hamilton Rating Scale and Feinberg & Carroll's Discriminant Index, and a higher total PSE score. The score on the PSE syndrome of Agitation differentiated between patients with blunted and non-blunted responses. Patients with blunted responses also tended to have higher scores for the following syndromes: GA (General Anxiety), made up of free-floating anxiety, panic attacks and observed anxiety; DE (Depersonalization), which consists of presence of depersonalization and/or derealization; and SL (Slowness), a measure of retardation of speech and movement.

In order to determine which of the PSE clinical syndromes were most important in identifying a patient as either blunted or non-blunted, a stepwise discriminant function analysis was performed. Only two variables, Agitation and Depersonalization, were entered into the function. Using a jack-knifed classification procedure, the discriminant function was able to identify 86·5% of those with normal responses on the TRH-test, but only 48·4% of those with blunted responses, indicating that patients with these PSE syndromes accounted for only half the patients with blunting, 69·1% of patients were correctly identified overall. The forcing of further variables into the function did not improve the discrimination. A number of individual PSE symptoms were significantly associated with blunting: these were depersonalization, derealization and agitation.

All 6 patients with augmented responses (over 19·5 μU) were women. Otherwise, their clinical characteristics in terms of demographic features and symptomatology did not appear to differ from the non-blunted group.

(d) Results of DST and TRH-test

Seventeen patients had both an abnormal DST response and blunting of the TSH response; 14 had a blunted TSH response with a normal DST; 12 had an abnormal DST with normal TSH response; and 25 patients (37%) had normal responses on both tests. Thus, 63% of patients had one or both abnormalities. There was no association between the two abnormalities, and the presence of either abnormality was not associated with any particular diagnostic group. However, 5 of 6 patients with psychotic depression had both abnormalities.

DISCUSSION

Of this population of 68 patients with primary depression, 43% had blunted TSH responses to TRH. This is a similar proportion to that found by previous authors (Extein *et al.* 1981; Loosen & Prange, 1982). Blunting was found in patients of all diagnostic categories of depression, although there was a stronger association with the RDC endogenous sub-group. We found that blunting was associated with the global severity of depression and with greater depressed mood. Several authors have not found the severity of depression to be related to blunting (Loosen & Prange, 1982), but in a large study Agren & Wide (1982) found that severity differentiated patients with blunted responses from patients with normal responses. In the present study certain symptoms were found to be associated with blunting: namely, agitation, depersonalizaton, and derealization.

There was no relationship between patients with abnormal suppression on the DST and those with blunting of the TSH response, a finding reported by studies using similar test procedures (Extein *et al.* 1981; Targum *et al.* 1982). The combined results of the two tests did not increase the likelihood of being able to

identify any particular diagnostic group, although 5 out of 6 patients with psychotic depression had abnormal responses to both tests. Patients with blunted responses had higher predexamethasone urinary free cortisol levels than patients with normal responses. However, it is unlikely that high cortisol levels could explain the blunting, as there was no correlation between the degree of blunting and the cortisol levels. Moreover, many patients with blunted responses had normal cortisol levels. One possibility is that the increased levels found in patients with blunted responses is a spurious association: i.e. that some other feature in these patients accounted for both abnormalities. Other studies which have examined this relationship have produced conflicting results (Loosen *et al.* 1978; Gold *et al.* 1980; Agren & Wide, 1982; Targum *et al.* 1982). Although high cortisol output cannot fully explain the phenomenon of blunting in depression, it is possible that it may have an affect on the TSH response in some patients.

We found that about a quarter of the total group of patients had elevated levels of circulating thyroid hormone; a number of these patients, although not clinically hyperthyroid, had levels which were clearly in the hyperthyroid range. Kirkegaard and co-workers (Kirkegaard *et al.* 1978; Kirkegaard & Faber, 1981) also found elevations of thyroid hormones in depressed patients which decreased on clinical recovery. Our finding of an inverse relationship between FTI and TSH response to TRH, and the fact that patients with blunted responses tended to have higher FTI values than those with normal responses, suggests that blunting may be due to increased output of thyroid hormones with negative feedback operating at the level of the thyroid gland.

Some studies have suggested that stress, especially if prolonged, leads to increased output of thyroid hormones (Mason, 1968). It is possible that, in some depressed patients, blunting may be part of a stress response, producing a subclinical hyperthyroid state. The present finding that patients with blunted responses and high FTI levels had more long-term environmental difficulties would support this. There is evidence that prolonged, continued or repeated stress can precipitate thyrotoxicosis in predisposed subjects (Weiner, 1977).

However, not all patients with blunted responses had high FTI scores. An alternative mechanism such as pituitary gland dysfunction, with failure of normal TSH stimulation by TRH, may be responsible for blunting in these patients. The two processes would not necessarily be mutually exclusive. Six of the patients, all women, had augmented responses. These patients had low levels of circulating thyroid hormones, with lower FTI values, than patients with normal responses. They did not, however, have elevated basal TSH values. Targum *et al.* (1982) also found a sub-group of 6 women with augmented responses, and Yamaguchi *et al.* (1977) found that 6 out of 7 patients with augmented responses were women. It may be that there is a sub-group of depressed patients, usually women, who are mildly hypothyroid. It is of interest that, whereas most studies find relatively high levels of thyroid hormones during depression, one of the few studies to show that depressed patients had lower mean levels of thyroid hormone was that of Rieneris *et al.* (1978), in which all the patients were women. It has been shown that in some female patients T3 potentiates the antidepressant effects of tricyclics (Prange *et al.* 1972). It is possible that there may be a sub-clinically hypothyroid group of female patients with low thyroid levels, normal basal TSH levels but augmented TSH responses to TRH who represent the patients who respond to the addition of thyroid hormones to antidepressant medication.

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