# Endocrine responses after thyrotrophin-releasing hormone stimulation and dexamethasone suppression tests in the major depressive syndrome

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## Summary

The effects of dexamethasone 1 mg on plasma cortisol levels and of thyrotrophin-releasing hormone (TRH) 200 $\mu$g on thyrotrophin (TSH), growth hormone and prolactin levels in 107 patients with a major depressive disorder (MDD) were compared with those in 87 healthy subjects. Individual hormonal responses and combinations of hormonal responses after administration of dexamethasone and TRH were evaluated as diagnostic aids for MDD by calculating sensitivity, specificity and efficiency for single and multiple hormonal abnormalities. In patients suffering from MDD, 65% of men, 74% of reproductive women and 71% of menopausal or hysterectomized (H/M) women had abnormal responses (sensitivity) to a dexamethasone suppression test (DST). When the DST and TSH responses to TRH were combined, 85% of men, 87% of reproductive women and 84% of H/M women had abnormal results. If the efficiency of the different combinations of hormone responses is calculated, a totally different picture emerges.


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Diagnosis of a major depressive disorder (MDD) remains a difficult problem because of the diverse modes of presentation. In the absence of precise knowledge of the biochemical abnormalities involved, the search is still on for biological markers of the disease. Such markers can either be related to the disease in its active form or may reflect an underlying abnormality. Numerous variables[1,2] have been investigated over the past 20 years, ranging from measurement of hormone, amine, trace element and neurotransmitter levels, to sleep deprivation and EEG recordings. The two endocrine tests most often used as diagnostic aids in depression are the dexamethasone suppression test (DST) and the thyrotrophin-releasing hormone (TRH) stimulation test. Although it is most important to realize that these tests should be used to confirm a surmise[3] and not to make a diagnosis, the abnormal responses in depressed patients may give clues to the causes of depression.

The endocrine responses to the DST and the TRH stimulation test in a homogeneous group of patients suffering from MDD were compared with those of a group of healthy subjects. Specific cut-off values were used to determine abnormal responses, and single and combinations of abnormal responses in controls and patients were used to calculate the percentage of abnormal responses. This permitted the determination of the efficiency of responses, a far better indicator of the validity of the test than the sensitivity or specificity on its own. Although there are different versions of the DST and TRH stimulation test, it was decided to use dexamethasone 1 mg[4] with cortisol determinations at 08h00, 16h00 and 23h00 for the DST and TRH 200 $\mu$g for thyrotrophin (TSH), growth hormone (GH) and prolactin (PRL) determinations.

## Patients and methods

A group of 107 carefully selected patients with primary unipolar MDD with melancholia (DSM III)[5] was compared with 87 healthy subjects. All subjects were evaluated by a psychiatrist using the polydiagnostic approach. For this purpose the DSM III unipolar/bipolar and primary/secondary criteria as well as the criteria to identify genetic subgroups suffering from unipolar depressive disorder[6] were used. The Hamilton depression and anxiety rating scales, the Beck self-evaluation scale and the visual analogue scales for motivation, anxiety and depression were also used.

The subjects had to be physically healthy and exclusion criteria for this study were: ischaemic heart disease, pregnancy, asthma, drug or alcohol abuse, steroids or any other medication. All control subjects were psychiatrically healthy and without a history of psychiatric illness. They were, however, similar to the depressive subjects with respect to sex, age (Table I) and geographical area (Western Cape) from which they were drawn.

**TABLE I. AGE OF SUBJECTS IN DIFFERENT HORMONAL SUBGROUPS**

| | Men | Women (reprod) | Women (H/M) |
|---|---|---|---|
| **Controls** | | | |
| **No.** | **38** | **35** | **14** |
| **Age (yrs)** | **40 ± 13,5** | **33 ± 7,9** | **51 ± 10,2** |
| **Patients** | | | |
| **No.** | **20** | **38** | **49** |
| **Age (yrs)** | **45 ± 17,6** | **34 ± 10,0** | **52 ± 13,2** |

H/M = menopausal/hysterectomized.

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## Biochemical evaluation

The TRH stimulation test and the DST were performed on all subjects. Medication was withheld for at least 3-4 days before the tests. After an overnight fast an intravenous drip was installed at 07h00. During the entire test patients remained recumbent. At 08h00 blood samples were taken for liver and kidney function tests, fasting blood sugar values, free tri-iodothyronine ($T_3$) and free thyroxine ($T_4$) levels as well as basal levels of TSH, GH and PRL. This was followed by the intravenous injection of TRH 200 $\mu$g. All controls and 61 patients received TRH 200 $\mu$g, while 46 patients received TRH 500 $\mu$g.

Two concentrations were used to ascertain differences in TSH, GH and PRL responses;[7] the only statistically significant difference was in the GH response to TRH, all other responses showing no statistical differences. Any statistical analysis involving GH was done on the results from the 61 patients given TRH 200 $\mu$g.

After 20 minutes, 60 minutes and 90 minutes further blood samples were taken for TSH, GH and PRL levels. The delta maximum ($\Delta_{max}$) value for each hormone was obtained by subtracting the basal value from the highest level measured for each hormone after administration of TRH. Subjects with a basal level of TSH $>$ 5 mU/l (2 controls, 4 patients) or a $\Delta_{max}$ TSH $>$ 20 mU/l (12 controls, 11 patients) were excluded from the study on the assumption that they might be (pre-)hypothyroid.[8] At 23h00 on the day of the TRH stimulation test, dexamethasone 1 mg (Decadron; MSD) was given orally. The next day cortisol levels were determined at 08h00, 16h00 and 23h00. The following values were considered to indicate an abnormal response to the TRH stimulation test and insufficient suppression by dexamethasone respectively: $\Delta_{max}$ TSH $<$ 7 mU/l; $\Delta_{max}$ GH $>$ 0,0 mU/l; $\Delta_{max}$ PRL $>$ 21,5 $\mu$g/l; and cortisol $>$ 140 nmol/l.

Hormone levels were determined by radio-immunoassay. The TSH level was measured by the iodine-125 NHS-TSH kit (Diagnostic Products Corp., Los Angeles, California), cortisol and PRL levels by a GammaDab $^{125}$I prolactin radio-immunoassay kit (Clinical Assays, Cambridge, Massachusetts), while the GH was estimated by the Pharmacia Diagnostics test (National Institute for Biological Standard and Control, Hamstead). The intra- and inter-assay coefficients of variation were respectively (reference values in brackets):

| | | | |
|---|---|---|---|
| TSH | 4,5% | 5,5% | (0,5-5 mU/l) |
| PRL | 5,0% | 5,4% | (0-12 $\mu$g/l, males) |
| | | | (0-20 $\mu$g/l, females) |
| GH | 5,2% | 8,3% | (1-5 $\mu$g/l) |
| Cortisol | 5,0% | 7,0% | (08h00 193-690 nmol/l) |
| | | | (24h00 55-248 nmol/l) |

## Analysis

To determine the diagnostic importance of the hormonal response, singly or in different combinations, the sensitivity

$$\text{(percentage true positive} = \frac{\text{true positive}}{\text{true positive} + \text{false negative}} \times 100\text{)},$$

the specificity

$$\text{(percentage true negative} = \frac{\text{true negative}}{\text{true negative} + \text{false positive}} \times 100\text{)}$$

and the efficiency

$$\text{(percentage correct} = \frac{\text{true positive} + \text{true negative}}{\text{total tested}} \times 100\text{)}$$

was calculated for each hormone and hormone combinations. The efficiency indicates whether a test is worth performing (a value of at least 80% is required) and is a better parameter than sensitivity or specificity alone because both the latter parameters are taken into account when efficiency is calculated.

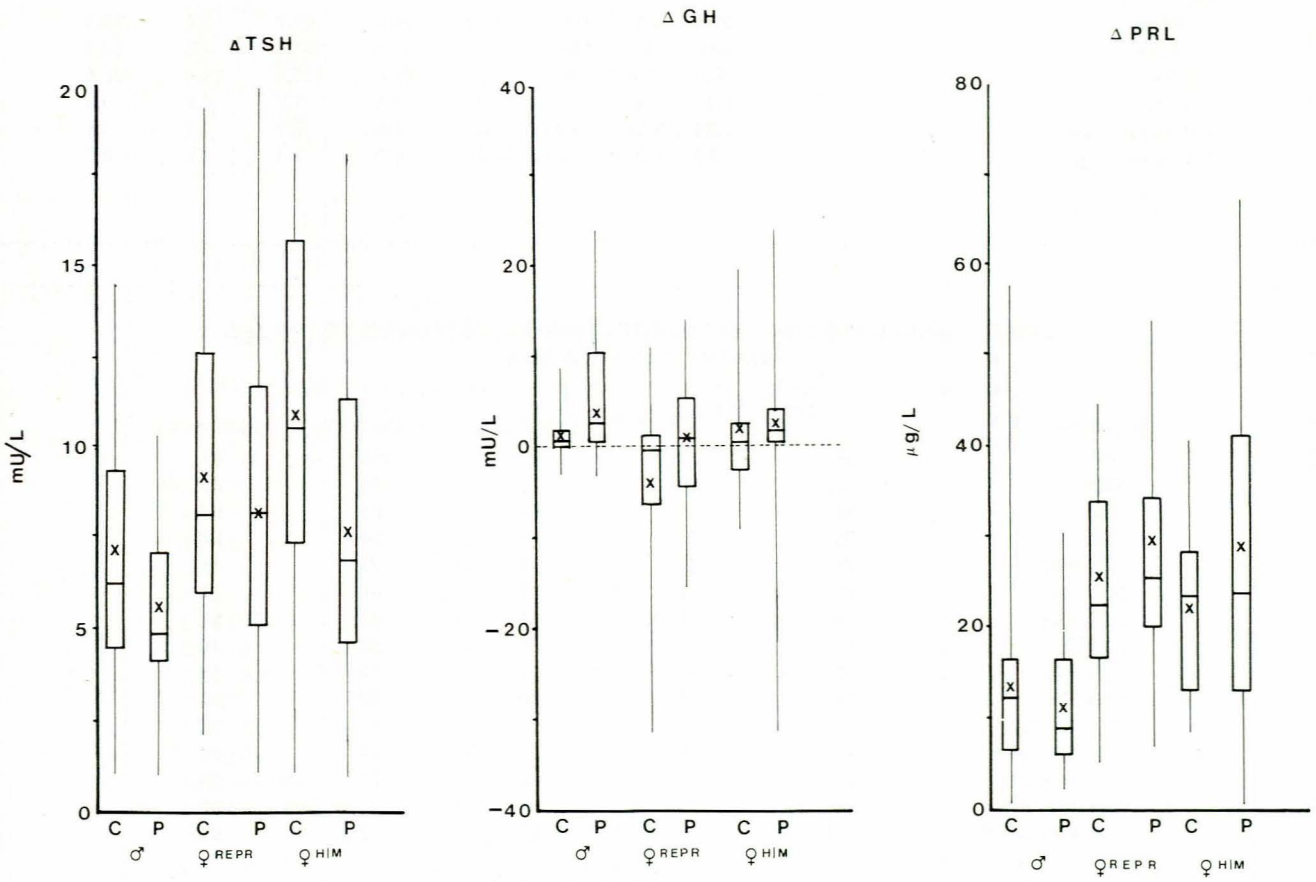


**Fig. 1. Box plots display basic information on the Δ TSH, Δ GH and Δ PRL of the controls (C) and patients (P). Upper and lower bars represent the 75th and 25th percentile respectively, with the median as the middle bar. Means are represented by X (repr = reproductive; H/M = hysterectomy/menopause).**

## Results

The cortisol DST in the controls was homogeneous, i.e. no significant differences could be related to sex or age. The TRH stimulation test, however, showed that the controls could be divided into three subgroups with significantly different hormonal responses: men, reproductive women and menopausal/hysterectomized (H/M) women. The basal TSH and GH levels were significantly higher ($P = 0{,}0025$ and $P = 0{,}0402$ respectively) in the H/M group than in the reproductive group. The basal GH level was also significantly higher ($P < 0{,}001$) in men than in women. After TRH stimulation the women, as a group, had a significantly higher $\Delta_{max}$ TSH ($P = 0{,}0104$) and $\Delta_{max}$ PRL ($P < 0{,}001$) response than men. The men, however, had a significantly higher $\Delta_{max}$ GH ($P = 0{,}0156$) than the women.

The Mann-Whitney *U*-test was used for statistical analyses. All the results obtained from the patients were subsequently compared with these three subgroups. Table II and Fig. 1 summarize all the

**TABLE II. SUMMARY OF CORTISOL, BASAL TSH, BASAL GH AND BASAL PRL LEVELS**

| | No. | | Mean ± SD | | Median | | $\frac{Q_3 - Q_2}{2}$ | |
|---|---|---|---|---|---|---|---|---|
| | C | P | P | C | P | C | P | C |
| **Men** | **38** | **20** | | | | | | |
| **DST (nmol/l)** | | | | | | | | |
| **08h00** | | | **58,0 ± 10,5** | **216,0 ± 227,6*** | **55,0** | **74,0** | **—** | **186,0** |
| **16h00** | | | **58,0 ± 9,8** | **191,0 ± 150,5*** | **55,0** | **181,0** | **—** | **112,0** |
| **23h00** | | | **64,0 ± 20,9** | **212,0 ± 173,8*** | **55,0** | **165,0** | **1,5** | **133,0** |
| **TSH basal (mU/l)** | | | **1,6 ± 0,7** | **1,39 ± 0,42** | **1,35** | **1,35** | **0,49** | **0,3** |
| **GH basal (mU/l)** | | | **1,2 ± 1,76** | **3,3 ± 7,89** | **0,5** | **0,6** | **0,3** | **0,8** |
| **PRL basal (μg/l)** | | | **6,3 ± 2,15** | **5,3 ± 0,58×** | **5,5** | **5,0** | **0,8** | **0,1** |
| **Women (reprod)** | **35** | **38** | | | | | | |
| **DST (nmol/l)** | | | | | | | | |
| **08h00** | | | **60,0 ± 11,5** | **147,0 ± 163,9*** | **55,0** | **58,0** | **1,5** | **64,0** |
| **16h00** | | | **66,0 ± 31,9** | **228,0 ± 170,2*** | **55,0** | **179,0** | **—** | **142,0** |
| **23h00** | | | **65,0 ± 20,9** | **165,0 ± 120,3*** | **57,0** | **105,0** | **3,5** | **91,0** |
| **TSH basal (mU/l)** | | | **1,49 ± 0,61** | **1,58 ± 0,7** | **1,30** | **1,35** | **0,4** | **0,5** |
| **GH basal (mU/l)** | | | **7,2 ± 9,1** | **6,1 ± 7,8** | **3,4** | **4,1** | **4,5** | **4,3** |
| **PRL basal (μg/l)** | | | **8,8 ± 9,5** | **8,3 ± 5,7** | **6,4** | **6,6** | **2,1** | **2,0** |
| **Women (H/M)** | **14** | **49** | | | | | | |
| **DST (nmol/l)** | | | | | | | | |
| **08h00** | | | **59,0 ± 9,0** | **156,0 ± 146,6*** | **55,0** | **82,0** | **2,0** | **89,0** |
| **16h00** | | | **60,0 ± 11,6** | **190,0 ± 144,4*** | **55,0** | **181,0** | **2,0** | **87,0** |
| **23h00** | | | **76,0 ± 30,9** | **196,0 ± 172,7*** | **57,0** | **135,0** | **29,0** | **96,0** |
| **TSH basal (mU/l)** | | | **2,36 ± 0,98** | **1,76 ± 0,75+** | **2,3** | **1,7** | **0,9** | **0,6** |
| **GH basal (mU/l)** | | | **2,35 ± 3,16** | **3,44 ± 6,56** | **0,9** | **0,7** | **1,2** | **1,1** |
| **PRL basal (μg/l)** | | | **7,02 ± 2,3** | **6,5 ± 2,86** | **6,3** | **5,1** | **2,0** | **0,7** |

* $P < 0{,}0001$; × $P < 0{,}01$; + $P < 0{,}05$ Mann-Whitney *U*-test.
C = controls; P = depressed patients.

**TABLE III. SINGLE AND COMBINATIONS OF ABNORMAL RESPONSES TO TRH AND DEXAMETHASONE IN MEN**

| | No. | | | | |
|---|---|---|---|---|---|
| Hormone | C | P | % sensitivity | % specificity | % efficiency |
| **DST** | **35** | **20** | **65** | **100** | **87** |
| **TSH** | **38** | **20** | **75** | **45** | **55** |
| **GH** | **38** | **9** | **67** | **61** | **62** |
| **PRL** | **38** | **20** | **5** | **84** | **57** |
| **DST PRL** | **35** | **20** | **65** | **83** | **76** |
| **DST GH** | **35** | **9** | **89** | **66** | **71** |
| **DST TSH** | **35** | **20** | **85** | **43** | **58** |
| **GH PRL** | **38** | **9** | **33** | **59** | **45** |
| **TSH PRL** | **38** | **20** | **75** | **34** | **48** |
| **TSH GH** | **38** | **9** | **89** | **29** | **40** |
| **TSH GH PRL** | **35** | **9** | **56** | **71** | **68** |
| **DST GH PRL** | **35** | **9** | **45** | **94** | **84** |
| **DST TSH GH** | **35** | **9** | **89** | **77** | **80** |
| **DST TSH PRL** | **35** | **20** | **55** | **94** | **80** |
| **DST TSH GH PRL** | **35** | **9** | **33** | **97** | **84** |

Sensitivity = $\frac{TP}{TP + FN} \times 100$; specificity = $\frac{TN}{TN + FP} \times 100$; efficiency = $\frac{TP + TN}{\text{Total tested}} \times 100$.
T = true; N = negative; P = positive; F = false.
C = controls; P = patients.

data. Because the data were often skewly distributed the mean, median and interquartile range are included. Tables III - V show the sensitivity, specificity and efficiency of hormonal responses: (*i*) when only one hormone was used for the diagnosis of depression; (*ii*) when a combination of two hormones was used and one or two results were abnormal; (*iii*) when a combination of three hormones was used and two or more results were abnormal; and (*iv*) when a combination of four hormones was used and two or more results were abnormal.

From the Tables it is clear that the same combinations of hormonal responses to confirm the diagnosis of MDD for all the subgroups cannot be used. Should a single test be chosen to confirm a diagnosis of depression, the DST is the one of choice. Should a combination of different hormonal responses be applied, different diagnostic subgroups should be considered (Tables III-V).

In men the DST and the DST, TSH and GH combination are useful aids. In the H/M group the same combinations, as well as the DST and TSH combination, can be used.

In the group of reproductive women the DST, or the DST and TSH, or even the DST, TSH and PRL combinations give high efficiencies.

Table II is a summary of the basal hormone levels and the cortisol levels obtained in each subgroup. It is worth noting that all the controls had normal DST results. Fig. 1 summarizes the different hormonal responses to TRH stimulation in the respective subgroups.

## Discussion

In this study 107 patients with primary unipolar MDD with melancholia were compared with 87 controls. Both the DST and TRH stimulation test were performed and levels of TSH, GH and PRL were measured. Any differences in basal levels of the hormones tested would be eliminated to a certain extent by the use of a $\Delta_{max}$ value. Although De Villiers *et al.* (in preparation) have shown that the basal cortisol values in

**TABLE IV. SINGLE AND COMBINATIONS OF ABNORMAL HORMONE RESPONSES TO TRH AND DEXAMETHASONE IN REPRODUCTIVE WOMEN**

| Hormone | No. C | No. P | % sensitivity | % specificity | % efficiency |
|---|---|---|---|---|---|
| **DST** | **34** | **38** | **74** | **94** | **85** |
| **TSH** | **35** | **38** | **45** | **71** | **58** |
| **GH** | **35** | **24** | **54** | **63** | **59** |
| **PRL** | **35** | **37** | **70** | **43** | **57** |
| **DST PRL** | **34** | **37** | **97** | **38** | **69** |
| **DST GH** | **34** | **24** | **83** | **65** | **76** |
| **DST TSH** | **34** | **38** | **87** | **68** | **78** |
| **GH PRL** | **35** | **24** | **84** | **29** | **51** |
| **TSH PRL** | **35** | **37** | **87** | **26** | **57** |
| **TSH GH** | **35** | **24** | **71** | **43** | **52** |
| **TSH GH PRL** | **35** | **24** | **63** | **69** | **66** |
| **DST GH PRL** | **34** | **24** | **71** | **74** | **72** |
| **DST TSH GH** | **34** | **24** | **59** | **88** | **76** |
| **DST TSH PRL** | **34** | **38** | **70** | **89** | **79** |
| **DST TSH** | **34** | **24** | **54** | **94** | **78** |

Sensitivity = $\frac{TP}{TP + FN}$ x 100; specificity = $\frac{TN}{TN + FP}$ x 100; efficiency = $\frac{TP + TN}{\text{Total tested}}$ x 100.

T = true; N = negative; P = positive; F = false.
C = controls; P = patients.

**TABLE V. SINGLE AND COMBINATIONS OF ABNORMAL HORMONE RESPONSES IN H/M WOMEN TO TRH AND DEXAMETHASONE**

| Hormone | No. C | No. P | % sensitivity | % specificity | % efficiency |
|---|---|---|---|---|---|
| **DST** | **14** | **49** | **71** | **100** | **78** |
| **TSH** | **14** | **49** | **53** | **79** | **59** |
| **GH** | **14** | **27** | **74** | **50** | **66** |
| **PRL** | **14** | **49** | **57** | **43** | **54** |
| **DST PRL** | **14** | **49** | **88** | **43** | **78** |
| **DST GH** | **14** | **27** | **96** | **50** | **81** |
| **DST TSH** | **14** | **49** | **84** | **79** | **83** |
| **GH PRL** | **14** | **27** | **93** | **21** | **68** |
| **TSH PRL** | **14** | **49** | **84** | **21** | **70** |
| **TSH GH** | **14** | **27** | **89** | **43** | **73** |
| **TSH GH PRL** | **14** | **27** | **70** | **57** | **68** |
| **DST GH PRL** | **14** | **27** | **74** | **71** | **73** |
| **DST TSH GH** | **14** | **27** | **85** | **86** | **85** |
| **DST TSH PRL** | **14** | **49** | **67** | **86** | **71** |
| **DST TSH GH PRL** | **14** | **27** | **59** | **100** | **73** |

Sensitivity = $\frac{TP}{TP + FN}$ x 100; specificity = $\frac{TN}{TN + FP}$ x 100; efficiency = $\frac{TP + TN}{\text{Total tested}}$ x 100.

T = true; N = negative; P = positive; F = false.
C = controls; P = patients.

depressed patients (444 ± 98 nmol/l) are significantly higher ($P < 0,01$) than in controls (339 ± 98 nmol/l) it is unlikely that non-suppression could solely be attributed to this factor because Sherman *et al.*[9] have shown that in suppressors circadian rhythm is lost while in non-suppressors this rhythm is maintained.

The reason for evaluating different hormonal *responses* was that hormonal functions can be affected in MDD due to the influence of the limbic system on the hypothalamic-pituitary axis. Abnormal hormonal responses may not only constitute specific diagnostic clues for MDD but may also present clues to abnormal biochemical processes in the brains of MDD patients, e.g. a decreased TSH response to TRH stimulation. With respect to the TRH stimulation test this study indicates quite clearly that the hormonal responses of healthy subjects exhibit sex differences related to the reproductive function in females. The H/M patients were grouped together by their history alone and no follicle-stimulating hormone levels were determined to confirm that this grouping was biochemically warranted. If the TRH stimulation test is therefore to be used for diagnostic purposes, the patient's hormonal response should be compared with that of controls in the appropriate subgroup. This proviso, although perhaps obvious, needs more emphasis than is accorded it by much of the literature.

Tables III-V demonstrate an important point: if only results reflecting sensitivity are observed, misleading assumptions can be made. Should specificity also be taken into account, a somewhat different picture emerges because if specificity is very low the hormonal response combination is not worth using. This is demonstrated in Table III where hormonal responses are combined. High sensitivities were observed but very low specificities, resulting in low efficiencies. Similar examples can be seen with other hormonal combinations.

Only a few previous investigators who used the TRH stimulation test have published data on hormonal responses, involving all the hormones measured in the present study.[10,11] Some authors have investigated TSH and PRL responses[12,13] to TRH, while others have reported on TSH and GH responses.[14,15] The majority of authors have reported on only the TSH response to TRH.[16–19] Some have combined the DST and TRH stimulation test.[20–22]

A comparison with the literature shows that the TSH response in our controls was considerably lower than that found by some authors.[19,23] This can probably be explained by the fact that those authors used TRH 500 μg instead of 200 μg. Our TSH responses were, however, similar to values obtained by authors who used TRH 200 μg.[24] The elevated PRL response in patients in this study contrasts with findings of Witschy *et al.*[13] and Grégoire *et al.*,[12] but is similar to the findings of Brambilla *et al.*[15] Since all three groups of authors used TRH 500 μg the differences in PRL response are difficult to explain. As regards GH, our results are atypical because any GH response to TRH would be regarded as abnormal. Some authors[10] found no GH response to TRH, while others observed a stimulation of GH.[11] In this study the GH response gave negative values in the reproductive women subgroup of controls (Fig. 1). The 'suppression' of GH may be due to a natural decrease in GH levels after a spontaneous peak, which is more often seen in MDD patients during daytime than in healthy subjects. Had basal values of GH been determined at several points before the TRH was injected, these GH responses could have been explained. This would be in accordance with observations by Mendlewicz *et al.*[25] on the diurnal hypersecretion of GH in depression.

When our findings are compared with those of other authors the results indicate that sensitivity for TSH response is as low as 45% in the group of reproductive women (Table IV) and as high as 75% in the men (Table III), which is comparable with the results observed by Extein *et al.*[26] The specificity for the TSH response was in no case as high as the 96% observed by the same authors. A combination of the DST and the TSH response had a sensitivity of more than 80%, which is comparable with the results of Aggernaes *et al.*[20] The sensitivity observed for the DST was in accordance with that reported by Carroll.[4]

Our results indicate that abnormal combined hormonal responses in MDD to dexamethasone or TRH challenge tend to differ between men and women; the reason is unknown. It is to be hoped, however, that further study of these differences may lead to an understanding of biochemical abnormalities in the brain manifested during MDD.

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