The TRH Stimulation Test in Alzheimer's Disease and Major Depression:
Relationship to Clinical and CSF Measures

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A blunted thyroid-stimulating hormone (TSH) response to exogenous thyrotropin-releasing hormone (TRH) has been reported to occur consistently in patients with major depression and less consistently in patients with Alzheimer's disease (AD). In this study we compared the TSH response to TRH in a large group (n = 40) of AD patients, elderly patients with major depression (n = 17), and age-matched controls (n = 14) to further characterize how it may relate to clinical variables, baseline thyroid function tests, and cerebrospinal fluid measures. Comparisons of TRH stimulation test response across all three groups revealed that patients with major depression had lower stimulated TSH levels (ΔmaxTSH) ($p < 0.02$) and higher (though still within normal limits) mean thyroxine (T_4) levels ($p < 0.05$) than the AD patients or controls. AD patients with a blunted TSH response had a significantly higher mean free T_4 (FT_4) level ($p < 0.03$) and tended to be more severely demented ($p < 0.01$) than those with a nonblunted response.

Introduction

Neuroendocrine tests such as the dexamethasone stimulation test and the thyrotropin-releasing hormone (TRH) stimulation test have been examined in patients with various neuropsychiatric disorders as a possible window to the underlying neurotransmitter pathophysiology (Loosen 1987). This idea is complicated by the interacting regulatory and feedback mechanisms present in the body for each neurotransmitter and each associated hormonal signal (Loosen 1987). Still, it is felt that neuroendocrine tests may give us clues regarding the pathophysiology and course of certain disorders or symptoms, particularly in delineating different biological subgroups of neuropsychiatric disorders. The study of neuroendocrine abnormalities in Alzheimer's disease (AD) may be of particular

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interest, in that alterations in neurotransmitters and their metabolites have already been studied extensively in plasma, CSF, and postmortem brains, making AD one of the most well-characterized neuropsychiatric illnesses in terms of specific pathology and associated neurochemical changes (Perry 1987).

A blunted thyroid-stimulating hormone (TSH) response to intravenously administered TRH has been reported to occur in 25%–75% (depending on the cutoff value used to define a blunted TSH response) of patients with major depression (Loosen 1987). Patients with major depression and AD often have overlapping clinical symptoms (Reding et al 1985; Reifler et al 1986), and studies of the TRH stimulation test in AD have shown that up to 47% of patients have a blunted TSH response (Sunderland et al 1985; Thomas et al 1987). Other researchers have reported no blunting of the TSH response to TRH in AD patients (El Sobky et al 1986; Peabody et al 1986; Franceschi et al 1988; Lampe et al 1988; Warner et al 1990). To help clarify the ongoing scientific debate concerning the TRH stimulation test in AD, we studied the TSH response to TRH in a large group of AD patients, a group of elderly patients with major depression, and age-matched normal controls. Given the substantial number of AD subjects in this study, we also examined the TSH response with reference to clinical and biological characteristics including baseline thyroid function tests (TFTs), CSF monoamine metabolites, and CSF somatostatin-like immunoreactivity (SLI).

Subjects and Methods

Fifty patients with probable AD, 21 older patients diagnosed with major depression, and 18 age-matched controls participated in the study. Probable primary degenerative dementia of the Alzheimer type and major depression were diagnosed according to DSM-IIIR criteria (American Psychiatric Association 1987). In addition, patients diagnosed with major depression had a history of prior depressive episodes, had no significant cognitive impairment, and recovered after treatment with antidepressant medication or electroconvulsive therapy. Some of the AD patients had prior or concurrent depressive symptoms, but the dementia was established as the primary diagnosis. Significant medical problems were ruled out in all patients and controls by physical examination and laboratory tests. Normal controls were screened to exclude any personal or significant family history of medical, cognitive, or psychiatric disorder. Controls were recruited from the community and paid for their participation. All subjects gave written informed consent prior to participation in the study (for AD patients, a relative also signed the consent form). The AD and major depression patients were studied during hospitalization at the NIMH and the normals as outpatients; all tests and ratings were done within a 3-week period. Subjects were free of all psychotropic medications for at least 3 weeks prior to participation.

The TRH stimulation test was done between 8:30 and 10:30 AM after an overnight fast. An 18-gauge catheter was inserted into an antecubital vein and baseline blood samples were collected through the catheter at least 20 min after IV insertion. After collection of the −15 and 0 time point samples, 0.5 mg of TRH (Protirelin) was administered as an IV bolus. Subsequent blood samples were collected 15, 20, 30, and 45 min following the TRH injection. TSH levels were determined by double-antibody radioimmunoassay (RIA) by the NIH Clinical Center laboratory (normal range 0.4–4.6 μIU/ml). The coefficients of variation for this assay for low, midrange, and high concentrations are 6.2%, 5.1%, and 5.0%, respectively. Baseline TFTs and TSH levels were measured in serum, on the day in which they were collected. Triiodothyronine (T_3) (normal range 88–162

Table 1. Clinical Data on Alzheimer's Disease Patients (n = 40)

Clinical measure	Mean ± SD
Illness duration (yr)	3.8 ± 2.1
Dementia severity	
Clinical Dementia Rating	1.7 ± 0.7
Global Deterioration Scale	4.5 ± 0.9
Wechsler Memory Scale	68.0 ± 13.0
DMAS (17 item)[a]	19.5 ± 10.5
Bunney–Hamburg Global Scales	
Depression	3.4 ± 1.7
Anxiety	4.2 ± 1.9
Sadness	4.6 ± 2.2
Anger	2.7 ± 1.8
Psychosis	1.7 ± 1.3

[a]Dementia Mood Assessment Scale.

ng/dl) and free T_4 (FT_4) (normal range 1.0–2.1 ng/dl) were measured by RIA, and thyroxine (T_4) (normal range 5.0–10.0 μg/dl) by fluorescence polarization immunoassay.

Dementia severity was rated using the Clinical Dementia Rating (CDR) (Hughes et al 1982) and the Global Deterioration Scale (GDS) (Reisberg et al 1982). The degree of depression in the AD patients was evaluated using the Dementia Mood Assessment Scale (DMAS) (Sunderland et al 1988a, 1988b), a 24-item scale, the first 17 of which were designed to measure depression in dementia patients; the last 7 items measure cognitive and functional impairment. The Bunney–Hamburg Global Behavioral Rating Scales were used to evaluate aspects of behavior, mood, and impairment (Bunney and Hamburg 1963; Sunderland et al 1988a) in both patient groups. The depressed patients were also evaluated with the Hamilton Depression Scale (Hamilton 1960).

Lumbar punctures (LPs) were done between 8:00 and 9:00 AM, in the lateral decubitus position, after an overnight fast. Subjects were on bed rest prior to the LP, except for voiding. CSF from early aliquots was frozen at −70°C and later used for measurement of the neurotransmitter metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA), as described elsewhere (Scheinen et al 1983). The 26th ml of collected CSF was immediately frozen without preservatives on dry ice and stored at −70°C for later measurement of SLI by RIA, as described elsewhere (Rubinow 1986).

Data Analysis

For comparisons among subject groups, data were analyzed using subjects with completely normal baseline TFTs (Table 1), unless otherwise specified. Subjects with TFTs outside of the normal range were excluded in order to standardize conditions for the analysis of TRH stimulation test results as much as possible, so that results would better reflect changes related to the illnesses being studied, rather than primary thyroid conditions, in view of the high prevalence of thyroid abnormalities in the elderly (Targum et al 1989). Between-group differences in age, baseline TFTs, and the mean maximum increase of TSH (ΔmaxTSH) from the mean baseline value (the sum of the values at the −15 and 0 time points, divided by 2) were evaluated using one-way analysis of variance (ANOVA) and post hoc t-tests.

The time course of the TSH response to TRH was compared among groups using repeated-measures ANOVA, followed by one-way ANOVAs accompanied by post hoc *t*-tests at each time point. Also, the area under the curves (AUC) of the TSH response to TRH among subject groups was compared using one-way ANOVA and post hoc *t*-tests. Missing data points (2%) for the time course and AUC analyses were estimated by linear interpolation.

"Blunted" when used in the text refers to ΔmaxTSH levels of ≤7 μIU/ml, unless otherwise specified. Fisher's exact test was used to compare the rate of blunted responses (using cutoff values of both ≤7 μIU/ml and ≤5 μIU/ml) among diagnostic groups (Loosen 1987). One-tailed statistics were used based on prior studies showing either a blunted response, or no difference from normals in AD and depressed patients. One-way ANOVA and post hoc *t*-tests were used to compare mean ΔmaxTSH between genders, within and among diagnostic groups. Differences in baseline TFTs, TSH response, and clinical variables were examined between genders and between blunters and nonblunters within each diagnostic group by *t*-tests (two-tailed). A correlation (Pearson's) matrix was generated to explore possible relationships between the clinical and biological variables.

Results

Ten AD patients had abnormal baseline TFTs; most of these had a slightly elevated baseline TSH. Two depressed patients and two normal controls had an elevated baseline TSH, and two in each of these groups had an elevated FT_4. Therefore, 10 of 50 (20.0%) AD, 4 of 21 (19.0%) depressed, and 4 of 18 (22.2%) control subjects had baseline TFT abnormalities, and were therefore excluded from further analyses. These numbers are consistent with prior studies showing that the prevalence of thyroid abnormalities is not significantly different between AD patients and controls (Lawlor et al 1988).

When all subjects (including those with abnormal baseline TFTs) are included, the rates of blunting are as follows: 11 of 50 (22.0%) of the AD patients ($p < 0.26$ different from normals), 9 of 21 (42.9%) of the depressed patients ($p < 0.03$ different from normals, $p < 0.07$ different from AD patients), and 2 of 18 (11.1%) of the normals. When those subjects with normal TFTs were compared (Table 1), the group of patients with major depression had a higher rate of TSH blunting than the normals (7 of 17 [41%] versus 1 of 14 [7%], $p < 0.04$). The rate of blunting in the AD group (11 of 40, or 27.5%) differed from normals at a trend level of significance ($p < 0.10$) and did not differ from that of the depressed group ($p < 0.24$) (Table 3). When a cutoff of ≤5 μIU/ml was used for ΔmaxTSH, 6 of 40 (15%) (4 men, 2 women) of AD patients ($p < 0.10$ different from normals), 5 of 17 (29.4%) (4 men, 1 woman) of depressed patients ($p < 0.04$ different from normals, $p < 0.18$ different from AD patients), and no normals had a blunted response.

The major depression patients had a significantly lower mean ΔmaxTSH ($F[2, 70] = 4.96$, $p < 0.01$) than both the AD patients ($p < 0.003$) and the elderly controls ($p < 0.02$) (Table 2). Repeated-measures ANOVA revealed an overall significant difference between subject groups (group × time interaction $F[2.6, 88.5] = 4.38$, $p < 0.01$) for the time course of the TSH response to TRH shown in Figure 1. This overall difference resulted because stimulated TSH levels in the depressed group were significantly lower at all time points than those of both the AD and normal subjects, who did not differ from each other. The trend towards a significant difference in AUC ($F[2, 68] = 2.94$, $p <$

Table 2. Demographic and Biological Data on Patients and Normal Controls

Variable	Alzheimer's Disease (n = 40)	Major Depression (n = 17)	Normal Controls (n = 14)
Age (yr)	64.2 ± 7.8	65.8 ± 8.1	62.3 ± 8.1
Gender	25M, 15F	8M, 10F	9M, 6F
Δmax TSH (μIU/ml)	12.8 ± 6.1	7.0 ± 6.7[a]	12.5 ± 6.7
Baseline TSH (μIU/ml)	2.6 ± 1.2	2.3 ± 1.2	2.7 ± 1.2
Total T_4 (μg/dl)	7.8 ± 1.0	8.9 ± 1.3[a]	7.5 ± 1.4
Free T_4 (ng/dl)	1.4 ± 0.4	1.7 ± 0.4[a]	1.4 ± 0.4
T_3 (ng/dl)	125.8 ± 25.5	122.4 ± 25.5	119.5 ± 26.4

[a] $p < 0.05$ different from Alzheimer's patients and controls.

0.06) also resulted because the depressed patients had a smaller area than both the AD and normal subjects.

Table 2 summarizes mean baseline TFT data for all subjects. Baseline TFT data on patients with a blunted as compared with a nonblunted response is summarized in Table 3. Table 4 summarizes TSH response and baseline TFTs by gender. Comparison of mean ΔmaxTSH of female subjects among diagnostic groups revealed statistically significant differences ($F[2, 26] = 3.43$, $p < 0.05$); paired comparisons were significant only between the depressed and control groups ($p < 0.05$) (Table 4). Significant differences of ΔmaxTSH were also found among diagnostic groups of male subjects ($F[2, 39] = 5.56$, $p < 0.008$), with paired comparisons significant only between the AD and depressed groups ($p < 0.05$) (Table 4).

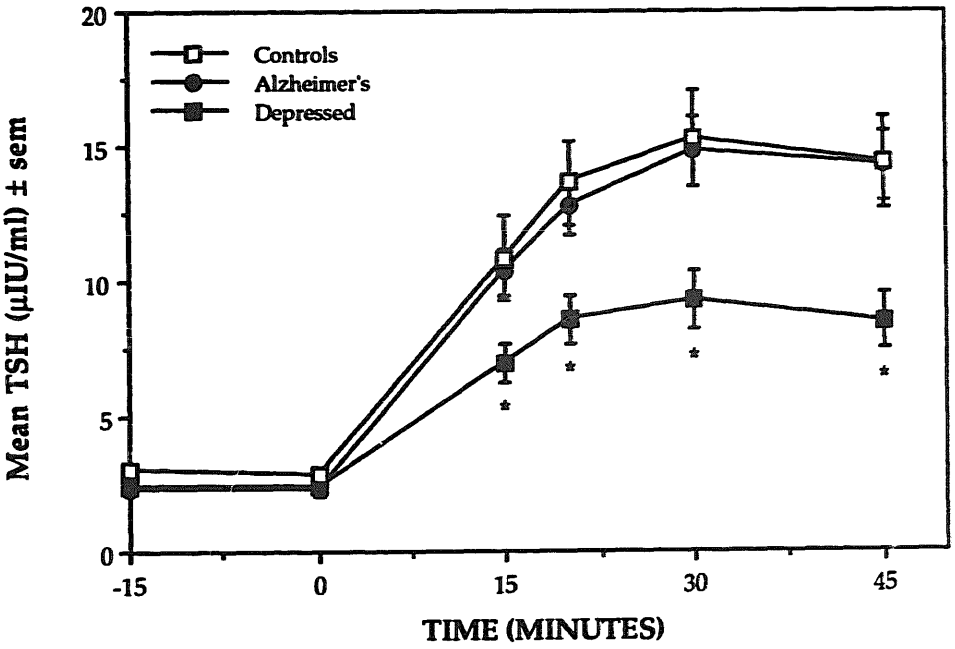

Figure 1. TSH responses to TRH across time in AD patients, depressed patients, and elderly controls. *$p < 0.05$, different from AD patients and controls.

Table 3. Baseline Thyroid Function Tests and Ratings on Patients with Blunted TSH Response (ΔmaxTSH ≤ 7 μIU/ml) versus Nonblunted TSH Response (ΔmaxTSH > 7 μIU/ml)[a]

	ΔmaxTSH[b] (μIU/ml)	TSH (μIU/ml)	T_4 (μg/dl)	FT_4 (ng/dl)	T_3 (ng/dl)	Global Deterioration Scale
Alzheimer's						
Blunted (n = 11)	5.0 ± 1.8	2.1 ± 1.5	8.2 ± 0.8	1.5 ± 0.3[c]	123.1 ± 38.2	4.8 ± 1.0[d]
Nonblunted (n = 29)	15.4 ± 6.8	2.8 ± 1.5	7.7 ± 1.3	1.3 ± 0.3	126.9 ± 26.6	4.3 ± 0.9
						Hamilton (17 item)
Depressed						
Blunted (n = 7)	4.0 ± 1.9	1.7 ± 0.8[c]	8.9 ± 1.3	1.9 ± 0.2[d]	123.9 ± 23.9	25.3 ± 9.8
Nonblunted (n = 10)	9.6 ± 2.7	2.9 ± 0.9	8.6 ± 1.8	1.6 ± 0.2	117.3 ± 25.5	21.5 ± 7.2

[a]Data are expressed as mean ± SD.
[b]The maximal elevation of TSH after TRH administration minus baseline TSH.
[c]$p < 0.05$.
[d]$p < 0.1$.

In the group of AD patients, ΔmaxTSH correlated significantly with baseline TSH (r = 0.51, $p < 0.001$, n = 37), T_4 (r = −0.39, $p < 0.02$, n = 37), and FT_4 (r = −0.52, $p < 0.001$, n = 40). AD patients with a blunted as compared with a nonblunted TSH response tended to be more severely demented as measured by the GDS (Table 3) and the Global Functional Impairment Scale (blunters = 8.9 ± 2.0, nonblunters = 6.9 ± 1.8; t = −2.5, $p < 0.01$, df = 29). ΔmaxTSH did not correlate with measures of depression. T_3 correlated with the Global ratings of depression (r = 0.49, $p < 0.01$, n = 26), anxiety (r = 0.42, $p < 0.03$, n = 26), and sadness (r = 0.47, $p < 0.02$, n = 26). FT_4 and CSF MHPG correlated at a trend level of significance (r = 0.33, $p <$ 0.1, n = 25). Of the severity and behavioral measures, CSF MHPG correlated at a trend level of significance with two measures of dementia severity, the CDR (r = 0.34, $p <$ 0.07, n = 29) and the GDS (r = 0.36, $p < 0.06$, n = 28). There were no correlations between ΔmaxTSH and CSF monoamine metabolites or CSF SLI.

Table 4. Gender Differences in TSH Response and Baseline Thyroid Function Tests[a]

Blunted TSH[b] (μIU/ml)		ΔmaxTSH (μIU/ml)	TSH (μIU/ml)	T_4 (μg/dl)	FT_4 (ng/dl)	T_3 (ng/dl)
Alzheimer's						
Male	5/25 (20.0%)	13.6 ± 7.6[c]	2.6 ± 1.3	7.6 ± 1.3	1.4 ± 0.3	123.4 ± 23.5
Female	6/15 (40.0%)	11.4 ± 7.3	2.6 ± 1.8	8.1 ± 1.0	1.3 ± 0.2	122.5 ± 29.4
Depressed						
Male	5/8 (62.5%)	5.3 ± 3.1	2.3 ± 1.1	7.5 ± 1.4	1.8 ± 0.4	113.2 ± 17.5
Female	3/9 (33.3%)	8.7 ± 3.3[d]	2.5 ± 1.1	9.6 ± 1.0	1.8 ± 0.2	125.6 ± 28.3
Normals						
Male	1/9 (11.1%)	9.6 ± 3.6[e]	2.9 ± 1.0	7.5 ± 1.2	1.4 ± 0.3	127.4 ± 21.9
Female	0/5	17.8 ± 6.7	3.1 ± 1.0	7.7 ± 1.4	1.4 ± 0.5	101.8 ± 6.4

[a]Data are expressed as mean ± SD.
[b]ΔmaxTSH ≤ 7 μIU/ml.
[c]$p < 0.05$ different from depressed men.
[d]$p < 0.05$ different from female controls.
[e]$p < 0.05$, different from female controls.

In the AD patients with a presenile as compared with senile onset of symptoms, there was no difference in ΔmaxTSH or baseline TFTs. Age correlated with ΔmaxTSH ($r = -0.37, p < 0.02$) within the group of AD patients, and not within the major depression or control groups. Within the AD group, age and ΔmaxTSH correlated significantly for men ($r = -0.46, p < 0.02$); for women the relationship was not significant ($r = -0.22, p < 0.44$).

Within the group of depressed patients, there were no correlations among measures of depression, CSF monoamine metabolites, or CSF SLI and ΔmaxTSH or other thyroid measures. Within the group of depressed patients with a blunted TSH response, ΔmaxTSH correlated significantly only with baseline TSH ($r = 0.73, p < 0.05, n = 8$). In the group of normal controls (excluding the one with a blunted response), there were no correlations between ΔmaxTSH and baseline TFTs.

Discussion

Our finding of an increased rate of blunting on the TRH stimulation test and a lower mean ΔmaxTSH in patients with major depression as compared with normals is consistent with the findings of most previous studies (Loosen 1987). A trend towards an increase in the rate of blunted responses in patients with AD is consistent with some (Sunderland et al 1985; Thomas et al 1987) but not all prior studies (El Sobky et al 1986; Peabody et al 1986; Lampe et al 1988; Franceschi et al 1988; Dysken et al 1990). Reasons for such discrepant results may include the heterogeneity of patients with AD, the study of patients at different stages of the illness, the small number of patients used in some of the studies, and the inclusion of subjects with slight baseline TFT abnormalities. Also, some studies included only male subjects (Lampe et al 1988; Peabody et al 1986), and men have generally been shown to have a lower ΔmaxTSH than women with age (Snyder and Utiger 1972; Sunderland et al 1985; Targum et al 1989; Dysken et al 1990), therefore making any differences between AD and control subjects more difficult to discern.

In our study, the AD patients with a blunted TSH response were more severely demented as measured by the GDS (at a trend level of significance) and the Global Functional Impairment Scale ($p < 0.01$) than those with a nonblunted response. We had previously reported a trend towards a correlation between increased dementia severity and TSH blunting in a different patient group (Sunderland et al 1985), though other studies have not found such a relationship (Franchesi et al 1988; Dysken et al 1990).

In our study, as in most prior studies, no correlation was found between clinical measures of depression and ΔmaxTSH (Loosen 1987). Consistent with our findings, depressed patients with a blunted TSH response have been shown in prior studies to have a lower basal TSH compared with patients whose response is normal or increased (Loosen 1987). Also consistent with some prior studies, the depressed patients had a higher mean T_4 level (and FT_4 level, significant at the trend level) than the AD and the control patients (Kirkegaard and Faber 1986). In the AD group, those with a blunted response had an increased FT_4, as shown previously in a smaller sample (Sunderland et al 1985), indicating normal feedback inhibition. Hypothalamic neuropathology has been documented in AD (Ishii 1966; McDuff and Sumi 1983), but most studies have not found a significant change in TRH concentration in AD brain (Yates et al 1983; Nemeroff et al 1989) or CSF (Nemeroff, personal communication), though one study did report a decrease in CSF TRH (Oram et al 1981). Interestingly, in one small study, TRH concentration in the amygdala of AD patients tended to correlate with senile plaque count ($r = -0.67, p <$

0.1, $n = 7$) (Biggins et al 1983), which has been shown to be related to dementia severity (Blessed et al 1968).

In our study, within the group of AD patients, women had a rate of blunting twice that of men though this was not statistically significant; there were no gender differences in baseline TFTs or other variables. Our findings are most consistent with those of one other report, in which no difference between genders was found (El Sobky et al 1986). This is of interest in that a significant age-related decrease in ΔmaxTSH in men relative to age-matched women (Snyder and Utiger 1972; Sunderland et al 1985; Targum et al 1989) was not seen in these studies in AD subjects, nor in depressed patients in the present study, though age correlated significantly with ΔmaxTSH within the group of male AD patients. Reasons for these findings are unknown. One study of AD patients found that men had a decreased ΔmaxTSH response as compared with women (Dysken et al 1990).

We found no correlations between ΔmaxTSH or baseline TSH and CSF monoamine metabolite levels in any of the subject groups. Prior studies of associations between TSH response and measures of monoamine metabolism in depressed patients have produced conflicting results (Loosen 1987). In general, evidence from human and animal studies indicate that norepinephrine has a stimulatory role and serotonin an inhibitory role in hypothalamic–pituitary–thyroid axis regulation (Loosen 1987).

In the present study, FT_4 correlated at a trend level of significance with CSF MHPG within the group of AD patients, which is consistent with a stimulatory effect of norepinephrine on the thyroid axis and the adjunctive role of thyroid hormones on noradrenergic function (Nemeroff and Evans 1989). Interestingly, in our group of AD patients, T_3 and T_4 correlated withmeasures of depression and anxiety. T_3 is sometimes added to augment antidepressant medication response, presumably through interactions with catecholamines (Nemeroff and Evans 1989).

We found no correlations between ΔmaxTSH or baseline TSH and CSF SLI. Somatostatin has been shown to have an inhibitory effect on TRH-stimulated TSH release, though no study to date has shown a relationship between CSF SLI and blunted TSH response (Loosen 1987).

In summary, the blunted TSH response in some AD patients is consistent with increased inhibition of TSH by relatively high levels of FT_4 (Loosen and Prange 1982). The feedback regulation of thyroid hormones appears then to be intact. Why these patients have increased FT_4 levels is unknown; the mechanism may involve decreased feedback or increased stimulation of thyroid hormones by some other substance, such as norepinephrine. This would be consistent with our finding of a positive correlation between FT_4 and CSF MHPG, which indicates that increased norepinephrine could be contributing to increased FT_4 levels. Also, patients with a blunted TSH response had significantly higher ratings of dementia severity, and dementia severity correlated positively with CSF MHPG, consistent with the findings of Raskind et al (1984).

In the patients with major depression, our findings are consistent with chronic hypersecretion of TRH as an etiology for blunted TSH responses, in that those with a blunted response had a low basal TSH that could be secondary to TSH receptor desensitization (Kirkegaard et al 1979; Banki et al 1988). Also, TRH itself stimulates thyroid hormone release (Griffiths 1985), so TRH hypersection could have contributed to increased T_4 and FT_4 levels. Increased thyroid hormone levels would further lower TSH levels by feedback inhibition.

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appears to be related to different clinical factors in these groups (to dementia severity and possibly age and gender in the AD patients) and to involve some different etiologic factors. Further studies utilizing the TRH stimulation test and other neuroendocrine tests may help to distinguish diagnostic subgroups and to clarify relationships among different neuropsychiatric illnesses.

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