ORIGINAL ARTICLE

Serum Thyrotropin Concentrations and Bioactivity During Sleep Deprivation in Depression

David N. Orth, MD; Richard C. Shelton, MD; Wendell E. Nicholson, BS; Paolo Beck-Peccoz, MD; Andrew J. Tomarken, PhD; Luca Persani, MD; Peter T. Loosen, MD, PhD

Background: One night of sleep deprivation induces a brief remission in about half of depressed patients. Subclinical hypothyroidism may be associated with depression, and changes in hypothalamic-pituitary-thyroid function may affect the mood response to sleep deprivation. We wished to define precisely the status of the hypothalamic-pituitary-thyroid axis of depressed patients during sleep deprivation and the possible relationship of hypothalamic-pituitary-thyroid function to the mood response.

Methods: We studied 18 patients with major depressive disorder and 10 normal volunteers. We assessed mood before and after sleep. We measured serum thyrotropin every 15 minutes during the night of sleep deprivation, thyrotropin bioactivity, the thyrotropin response to protirelin the next afternoon, and other indexes of hypothalamic-pituitary-thyroid function. To determine if the changes were limited to the hypothalamic-pituitary-thyroid axis, we measured serum cortisol, which also has a circadian secretory pattern.

Results: Nocturnal serum thyrotropin concentrations were consistently higher in responders, entirely because of elevated levels in the women reponders. Responders had exaggerated responses to protirelin the next afternoon. The bioactivity of thyrotropin in nonresponders was significantly greater than in responders ($F_{1,8.99}=7.52$; $P=.02$). Other thyroid indexes and serum cortisol concentrations were similar among groups.

Conclusions: Depressed patients have mild compensated thyroid resistance to thyrotropin action, not subclinical autoimmune primary hypothyroidism. Sleep deprivation responders compensate by secreting more thyrotropin with normal bioactivity; nonresponders compensate by secreting thyrotropin with increased bioactivity.

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From the Departments of Medicine (Drs Orth and Loosen and Mr Nicholson) and Psychiatry (Drs Shelton and Loosen), Vanderbilt University Medical Center, Nashville, Tenn; Istituto di Scienze Endocrine, Ospedale Maggiore Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy (Dr Beck-Peccoz); Department of Psychology, Vanderbilt University, Nashville (Dr Tomarken); Universitá di Milano, Istituto Auxologico Italiano IRCCS, Milan (Dr Persani); and Psychiatry Service,Veterans Affairs Hospital, Nashville (Dr Loosen).

ONE NIGHT of sleep deprivation (SD) induces a rapid, albeit transient, remission in about 60% of patients with major depressive disorder (MDD),[1,2] but the mechanism by which SD exerts its antidepressant effect is unknown. Some findings suggest a relationship between diurnal rhythm and the effects of SD: SD has been shown to alter the sleep-wake cycle,[3,4] diurnal mood variability predicts the antidepressant effect of SD,[1,2,5] and phase advance and light therapy are sometimes effective in MDD.[6-9] Alterations in hypothalamic-pituitary-thyroid axis (HPT) function may be involved in MDD.[10-13] Major depressive disorder is common in hypothyroid patients,[10] and some[12-14] but not all[15,16] studies indicate that some patients with MDD have subclinical primary hypothyroidism. However, rather than having the exaggerated thyrotropin response to protirelin characteristic of hypothyroidism, about 30% of depressed euthyroid patients have blunted responses to protirelin.[10,11] Finally, protirelin has been shown to have antidepressant effects in some[10,17] but not all[18,19] patients. These observations support HPT involvement in MDD, with endocrinologically distinct MDD subgroups.[20]

The HPT also may be involved in the mood response to SD. Protirelin causes acute changes in sleep electroencephalograms in normal volunteers.[21,22] Thyrotropin secretion normally demonstrates a circadian rhythm, peaking during early sleep,[23] but nocturnal serum thyrotropin level continues to rise during SD,[24-27] associated with clinical improvement in some[25,26] but not all[24,27] studies. However, most investigators measured serum thyrotropin level infrequently or only compared hormone levels before and after SD. Therefore, little is known about detailed thyrotropin secretion during SD in depression. Thyroxine administration dur-

SUBJECTS AND METHODS

SUBJECTS

The study protocol was approved by the Vanderbilt University Institutional Review Board—Human Subjects (Nashville, Tenn), and written informed consent was obtained from all subjects. We studied 8 male and 10 female outpatients aged 28 to 62 years (mean±1 SD, 43.6±9.31 years), diagnosed as having MDD according to the Structured Clinical Interview for *DSM-III-R*—Patient Version,[30] who scored at least 18 on the first 17 items of the Hamilton Rating Scale for Depression.[31] Patients had no history of substance abuse for 6 months and no lifetime history of psychosis or bipolar disorder. Before SD, none had taken lithium carbonate for 3 months; fluoxetine, benzodiazepines, or other psychotropics with long half-lives for 3 weeks; or other antidepressants for 2 weeks. We recruited some patients from those being seen for outpatient treatment, and other patients and all normal volunteers from advertisements posted in the community. We studied 10 normal volunteer controls of similar age and sex (5 men and 5 women aged 29 to 50 years [mean±SD, 41.0±7.44 years]). Controls were free of Axis I mental disorders according to the Structured Clinical Interview for *DSM-III-R*—Patient Version and scored less than 8 on the Hamilton Rating Scale for Depression.[31] All participants were physically healthy as determined by clinical history, physical examination, routine serum chemistry studies, and electrocardiogram and were able to give informed consent. None had a personal or family history of thyroid disease or evidence of thyroid dysfunction. We excluded any subject whose urine tested positive for illicit drugs and any woman who was pregnant, lactating, or of childbearing potential and not using reliable birth control. We advised patients that SD might transiently improve their depression. We paid all participants $50.

PROCEDURES

Participants were admitted to the Vanderbilt General Clinical Research Center during the morning of the first day. Mealtimes were 8 AM, noon, and 8 PM. Participants remained awake and ambulated and signed a record sheet every 30 minutes for 36 hours under constant observation by the research center staff in daytime lighting conditions.[1,4] They had no snacks, caffeinated beverages, or cigarettes. At 8 PM on the first day, we inserted an intravenous heparin lock. At 10 PM, we began withdrawing blood every 15 minutes for 12 hours. At 4 PM the following day, we performed the standard protirelin stimulation test.[11]

We assessed severity of depression at recruitment, the day before SD, and 1 week after SD by means of the 17-item Hamilton Rating Scale for Depression.[31] We excluded subjects if they showed greater than 20% improvement before SD. We also rated depression between 8 AM and 10 AM for 7 days before and the day after SD by means of the Sleep Deprivation Depression Rating Scale (SDDRS), a modified Hamilton Rating Scale for Depression.[32] This scale excludes insomnia, weight loss, diurnal variation, depersonalization, paranoia, and obsessive-compulsive items and adds elements that rate fatigue, social withdrawal, increased appetite, increased eating, carbohydrate craving, weight gain, and hypersomnia. We defined response to SD as 30% or more reduction in the SDDRS score the morning after SD.[24,32]

Two years later, we recalled the 14 available patients with MDD and all 10 controls for interval history, Structured Clinical Interview for *DSM-III-R*—Patient Version (patients with MDD), physical examination, and thyroid function studies.

HORMONE ASSAYS

We measured serum thyrotropin with an immunoradiometric assay (Allégro; Quest, San Juan Capistrano, Calif), and thyrotropin-α and thyrotropin-β subunits with in-house radioimmunoassays with sensitivities of 5 and 2.8 pmol/L of plasma, respectively. Thyrotropin cross-reacted 27% and 3.1% in the thyrotropin-α and thyrotropin-β radioimmunoassays, respectively; thyrotropin-α cross-reacted 0.6% and 1.2% in the thyrotropin immunoradiometric assay and thyrotropin-β radioimmunoassay, respectively; and thyrotropin-β cross-reacted less than 0.0004% and less than 0.01% in the thyrotropin immunoradiometric assay and thyrotropin-α radioimmunoassay, respectively. We measured thyrotropin bioactivity in pooled aliquots of all nocturnal samples after immunoaffinity purification (recovery, 48% to 68%) and ultrafiltration.[33-35] Results (mean±1 SD of 3 experiments) are expressed as the bioactivity to immunoreactivity ratio (B/I). We measured serum free thyroxine, total triiodothyronine, anti–thyroid peroxidase and anti–thyroglobulin antibody titers, and serum cortisol by means of commercial kits.

ing SD can facilitate complete and sustained remission after SD,[28] suggesting that altered HPT function also mediates behavioral effects of SD.

We postulated that the nocturnal pattern of serum thyrotropin concentration in patients with MDD differs from that of normal subjects and that the clinical response to SD correlates with this altered pattern. We analyzed HPT activity, including serum thyrotropin bioactivity, during SD in patients with MDD and normal subjects and measured serum concentrations of cortisol to determine whether changes were specific to the HPT. We reexamined subjects 2 years later to determine whether they developed overt hypothyroidism.[29]

RESULTS

MOOD EFFECTS OF SLEEP DEPRIVATION

The mean SDDRS score of all 18 patients with MDD declined by 34% (range, –7% to 78%), from 20.7±5.2 (mean±1 SD) to 13.1±5.5; that of the 10 responders, by 56% (range, 38% to 78%), from 22.2±5.5 to 9.8±4.0; and that of the 8 nonresponders, by 6% (range, –7% to 27%), from 18.8±4.5 to 17.3±4.2. The ANOVAs disclosed no differences in baseline scores between responders and nonresponders ($F_{1,16}$=2.07; P=.17), but a decline for the whole MDD group ($F_{1,16}$=69.96;

STATISTICAL ANALYSES

The primary analyses compared the nocturnal serum thyrotropin levels and thyrotropin B/I during SD and serum thyrotropin responses to protirelin (peak level minus the mean of 2 prechallenge baseline levels) of responders, nonresponders, and normal control subjects. We computed nocturnal serum thyrotropin means in 4-hour sampling blocks (10 PM to 2 AM, 2:15 AM to 6 AM, and 6:15 AM to 10 AM).

Levene tests[36] indicated significant between-group heterogeneity of variance in thyrotropin B/I and protirelin response ($F_{2,24}=8.05$; $P<.005$; and $F_{2,23}=4.27$; $P<.05$, respectively). A likelihood ratio test[37] indicated significant between-group heterogeneity of across-time covariance matrices in nocturnal serum thyrotropin ($\chi^2_{12}=35.87$; $P<.001$). One- and 2-way analyses of variance (ANOVAs) often demonstrate excessive type I error rates and/or insufficient power with heterogeneous variances and unequal sample sizes.[38,39] Consequently, we conducted generalized Welch approximate degrees of freedom (WADF) tests[40-42] to assess effects in our 3 primary measures. The WADF tests do not assume equality of population variances across groups, and their type I error performance and power are typically superior to those of ANOVA under variance heterogeneity.[39,43,44]

We conducted a group (responder, nonresponder, control) × time (blocks 1-3) WADF test on nocturnal serum thyrotropin levels. Our original intent was to assess only group effects, but inspection of cell means indicated potential main effects or interactions involving sex. Therefore, we also conducted group × sex × time WADF tests. We present both results because the small numbers of subjects (ie, 3 to 7) of some group × sex × time cells merit cautious interpretation. The main effect for group yielded by the group × sex × time WADF test used a type III sum of squares approach to assess differences among unweighted group means averaged across sex.[43,45] For the repeated-measures effects, the pattern of significant results yielded by the WADF test was identical to that yielded by the improved general approximation test, a more conservative alternative.[46] In a parallel fashion, we conducted group and group × sex WADF tests on responses to protirelin and thyrotropin B/I. We set the critical α level for all effects at .05, the denominator as the number of variables analyzed. All tests were 2 tailed.

We conducted several computer simulations to test the properties of the 2-way WADF test for sample sizes, degrees of variance heterogeneity, and distributional shapes similar to those observed in our study. These yielded empirical type I error rates that were consistently acceptable.[43] As an additional test of the small-sample properties of our group × sex analyses, we compared our WADF test results with those yielded by bootstrap versions of the WADF test that yielded empirically generated sampling distributions based on a heteroscedastic resampling model.[47,48] For all omnibus tests and planned and post hoc comparisons, the bootstrap results and conclusions were identical to those of the theoretically based WADF test. For brevity, we report only the latter results.

We also computed 2-tailed WADF planned comparisons ($\alpha=.05$) that compared responders and nonresponders on the 3 primary thyrotropin measures.[49] We conducted post hoc WADF tests of the pairwise differences between the control group and the other 2 groups only when omnibus WADF analyses yielded significant main effects for group. Post hoc comparisons followed the Fisher least significant difference strategy, which is optimal when the group number equals 3 and only pairwise post hoc comparisons are contemplated.[50,51] Significant group × sex interactions were followed by WADF omnibus ANOVAs that compared the 3 groups within each category of sex. We set the critical α level of these analyses at .05/2=.025, where 2 is the number of sexes, to control familywise type I error rates.[45] Follow-up contrasts used the same critical α level.

In addition to between-group analyses, we computed Spearman correlations to assess the relationship between pre- and post-SD SDDRS scores of the depressed patients and each of our 3 primary thyrotropin measures.

We conducted ANOVAs (or WADF tests, when variance heterogeneity was observed) comparing responders, nonresponders, and controls on 3 additional thyrotropin measures during SD (thyrotropin-α, thyrotropin-β, and the ratio of thyrotropin-β to thyrotropin-α [thyrotropin-β/thyrotropin-α]). For brevity, we report only the group × sex analyses. We set the critical α level for each effect to .05/3=.0167, where 3 is the number of thyrotropin measures. We also tested for between-group differences in thyrotropin measures at follow-up. One-way between-group tests were performed because data from only 4 nonresponders were available. We conducted a group × sex × time ANOVA on nocturnal serum cortisol during SD. As was true of the primary dependent measures, resampling analyses (bootstrapping and/or permutation tests) of each of these supplementary measures produced results and conclusions that were identical to those of the normal-theory WADF tests and ANOVAs. For brevity, we present only the latter results.

$P<.001$) that was greater for responders than nonresponders ($F_{1,16}=43.02$; $P<.001$).

Seven of the 10 responders and 3 of the 8 nonresponders were female (Fisher exact test, $P=.34$). There were no significant age differences among the responders (43.8±10.0 years), nonresponders (43.2±9.02 years), and controls (41.0±7.44 years) ($F_{2,25}=0.29$; $P=.75$).

NOCTURNAL SERUM THYROTROPIN CONCENTRATIONS

Responders had higher serum thyrotropin levels than the other groups at every sampling time (**Figure 1**). Eight of the 10 responders had 1 or more nocturnal thyrotropin values greater than normal (>4.2 mU/L), as did 1 of 8 nonresponders and 2 of 10 controls. No participant had a concentration less than normal (<0.9 mU/L). The planned contrast indicated higher thyrotropin levels in responders than nonresponders ($F_{1,15.73}=7.20$; $P=.02$). Omnibus group × time WADF analysis of the 4-hour pools indicated a main effect for group ($F_{2,15.07}=6.64$; $P=.009$). Post hoc contrasts indicated that responders had higher levels than controls ($F_{1,13.52}=13.53$; $P<.001$). A time effect ($F_{2,13.63}=13.23$; $P>.001$), but no group × time interaction ($F_{4,15.51}=0.82$; $P=.53$), was observed. Thyrotropin level peaked during

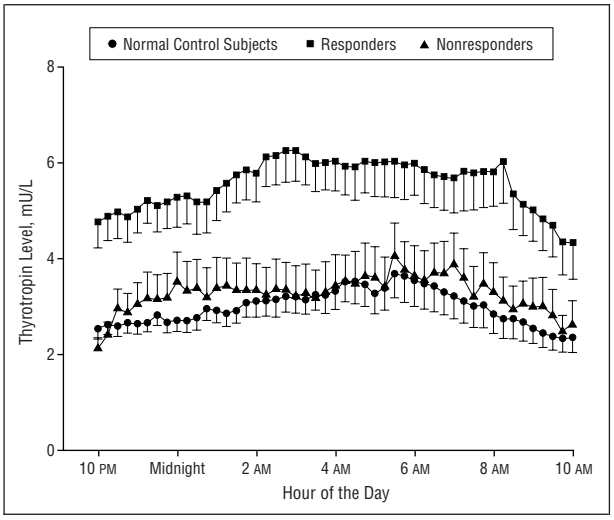

Figure 1. *Nocturnal secretion of serum thyrotropin in 10 depressed sleep deprivation responders, 8 depressed nonresponders, and 10 normal volunteers. Points indicate the mean of 7 to 10 values; brackets indicate the SEM.*

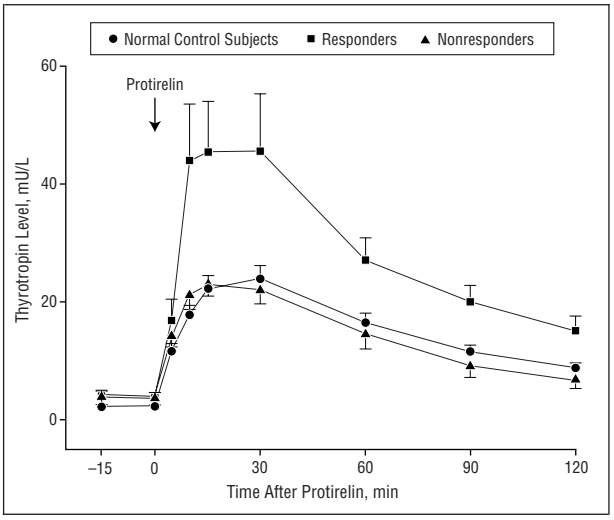

Figure 2. *Responses of serum thyrotropin to administration of protirelin in 10 depressed sleep deprivation responders, 8 depressed nonresponders, and 10 normal volunteers. Points indicate the mean of 7 to 10 values; brackets indicate the SEM.*

the period from 2:15 to 6 AM (post hoc contrast $F_{1,19.70}=25.90$; $P<.001$).

The group × sex × time unweighted means WADF analysis also indicated a main effect for group ($F_{2,10.76}=6.72$, $P=.01$) and an identical pattern of between-group differences on planned and post hoc contrasts (responders vs nonresponders, $F_{1,9.23}=6.50$; $P=.03$; responders vs controls, $F_{1,10.97}=12.75$; $P=.004$). However, the effects of group were moderated by sex (group × sex interaction, $F_{2,22}=6.16$; $P=.008$). Follow-up WADF analyses indicated between-group differences for women ($F_{2,6.34}=18.68$; $P=.002$), but not for men ($F_{2,6.00}=0.05$; $P=.95$). Female responders had higher thyrotropin levels (6.45±1.09 mU/L) than female nonresponders (3.06±0.80 mU/L) ($F_{1,5.29}=30.02$; $P=.002$) and female controls (2.80±1.19 mU/L) ($F_{1,8.22}=27.95$; $P<.001$).

NOCTURNAL SERUM THYROTROPIN B/I RATIOS

Planned WADF contrasts indicated that nonresponders had higher ratios (2.92±1.36) than responders (1.50±0.58) (1-way design contrast, $F_{1,8.99}=7.52$; $P=.02$; 2-way design contrast, $F_{1,8.18}=6.59$; $P=.03$). Omnibus tests suggested a trend toward overall between-group differences (1-way design group, $F_{2,13.76}=3.63$; $P=.054$; 2-way design group, $F_{2,7.57}=3.15$; $P=.10$) (control mean, 1.74±0.45). No main effects or interactions involving sex were found in the 2-way analyses (sex main effect, $F_{1,9.16}=0.006$; $P=.94$; group × sex interaction, $F_{2,7.57}=2.18$; $P=.18$).

RESPONSE TO PROTIRELIN STIMULATION

All groups responded to protirelin ($F_{1,11.23}=74.45$; $P<.001$) (**Figure 2**). Eight of the 10 responders had higher than normal thyrotropin responses (>28.3 mU/L for women, >23.8 mU/L for men), as did 2 of the 6 nonresponders and 4 of the 10 controls; no participant had a less than normal response (<10.1 mU/L for women, <3.8 mU/L for men). Although 1-way omnibus WADF analysis indicated only a trend for group ($F_{2,13.85}=3.41$; $P=.06$), the planned contrast indicated that responders had greater thyrotropin increments than nonresponders ($F_{1,10.20}=7.08$; $P=.02$). The planned contrast linked to the group × sex WADF analysis also indicated that responders had greater thyrotropin increments than nonresponders ($F_{1,8.80}=8.49$; $P=.02$). In addition, the omnibus group × sex WADF analysis indicated between-group differences in thyrotropin increments (group main effect, $F_{2,12.29}=4.04$; $P=.04$). Follow-up contrasts of the omnibus effect indicated that responders had greater increments than controls ($F_{1,9.93}=7.42$; $P=.02$). Nonresponders and controls did not differ ($F_{1,10.77}=0.06$; $P=.82$). Women responded more robustly than men ($F_{1,10.89}=9.49$; $P=.01$). The group × sex interaction was not significant ($F_{2,12.29}=2.60$; $P=.11$).

EFFECT SIZES

We computed Cohen's effect size index d[52] to estimate the magnitude of differences between the responders and nonresponders for the 3 thyrotropin measures. The d values for nocturnal thyrotropin, thyrotropin B/I ratios, and thyrotropin increments in response to challenge were 1.26, 1.45, and 1.07, respectively. In light of Cohen's stated criteria of 0.5 for a medium effect size and 0.8 for a large effect size,[52] these d values underscore the magnitude of the thyrotropin differences between responders and nonresponders.

CORRELATIONS BETWEEN PRIMARY THYROTROPIN MEASURES AND SDDRS SCORES

We computed Spearman correlations among pre- and post-SD SDDRS scores and the 3 primary thyrotropin measures (**Table 1**). Post-SD SDDRS scores were significantly correlated with all 3 thyrotropin measures despite the relatively small sample sizes: lower post-SD SDDRS scores were associated with higher nocturnal se-

Table 1. Correlations Between SDDRS Scores and Thyrotropin Measures*

	SDDRS Measures			Thyrotropin Measures	
	SDDRS Before SD	SDDRS After SD	ΔSDDRS	Nocturnal Serum Thyrotropin	Nocturnal Thyrotropin B/I
SDDRS before SD					
SDDRS after SD	0.37†				
ΔSDDRS	−0.46‡	0.61§			
Nocturnal thyrotropin	0.07	−0.49‖	−0.46‡		
Nocturnal thyrotropin B/I	0.03	0.58‖	0.56‖	−0.65§	
Thyrotropin increment after protirelin	−0.05	−0.59‖	−0.32	0.55‖	−0.52‖

*SDDRS indicates Sleep Deprivation Depression Rating Scale[32]; SD, sleep deprivation; Δ, change; and B/I, bioactivity to immunoreactivity ratio.
†n = 18 for all correlations except those involving thyrotropin increment, for which n = 16.
‡P<.10.
§P<.01.
‖P<.05.

rum thyrotropin level, greater thyrotropin response to protirelin, and lower thyrotropin B/I. The magnitudes of the associations indicate that thyrotropin measures accounted for between 25% and 35% of the variance in SDDRS scores. In addition, nocturnal serum thyrotropin level and thyrotropin B/I predicted declines in SDDRS scores after SD. Serum thyrotropin level and thyrotropin response to protirelin were positively correlated, while both measures were negatively correlated with thyrotropin B/I.

SERUM THYROTROPIN SUBUNIT CONCENTRATIONS AND OTHER INDEXES OF HPT FUNCTION

Levene tests indicated variance heterogeneity in thyrotropin-α ($F_{5,22}$=12.04; P<.001). The WADF and resampling analyses of thyrotropin-α indicated no significant effects involving group (group main effect, $F_{2,11.25}$=0.98; P=.40; group × sex interaction, $F_{2,11.24}$=0.37; P=.70) (**Table 2**). The ANOVAs and resampling analyses of thyrotropin-β and thyrotropin-β/thyrotropin-α indicated no significant effects involving group (thyrotropin-β group main effect, $F_{2,22}$=0.28, P=.76; thyrotropin-β group × sex interaction, $F_{2,22}$=0.48, P=.62; thyrotropin-β/thyrotropin-α group main effect, $F_{2,22}$=0.71, P=.50; thyrotropin-β/thyrotropin-α group × sex interaction, $F_{2,22}$=1.18; P=.33).

TWO-YEAR FOLLOW-UP EVALUATION

Five subjects were taking antidepressants and 3 (1 female and 1 male responder and 1 female nonresponder) fulfilled MDD criteria. None had clinical hypothyroidism, goiter, or detectable antithyroid antibodies. One male responder had a low triiodothyronine level but a midnormal thyrotropin level. Three patients (2 responders and 1 nonresponder) had minimally elevated serum thyrotropin level (4.29 to 4.73 mU/L); their other thyroid indexes were normal. The serum thyrotropin levels of responders (2.48±1.15 mU/L), 4 available nonresponders (2.92±1.23 mU/L), and controls (1.53±0.66 mU/L) did not differ significantly ($F_{2,21}$=2.74; P=.09; responders vs nonresponders, t_{21}=0.64; P=.53).

Table 2. Immunoreactive Thyrotropin Subunit Measures During Sleep Deprivation*

	Responders (n = 10)	Nonresponders (n = 8)	Normal Control Subjects (n = 10)
Thyrotropin-α, pmol/L	101.0 ± 43.5	85.3 ± 63.9	140.0 ± 127.0
Thyrotropin-β, pmol/L	9.37 ± 1.19	8.55 ± 2.26	8.62 ± 1.39
Thyrotropin-β/thyrotropin-α	0.11 ± 0.04	0.13 ± 0.06	0.10 ± 0.06

*Values are mean ± SD.

SERUM CORTISOL

Mean nocturnal serum cortisol concentrations demonstrated a normal circadian increase in all groups (time, $F_{2,42}$=39.72; P<.001). Cortisol levels were similar and normal in all groups (responders, 256±68 nmol/L; nonresponders, 281±70 nmol/L; controls, 238±39 nmol/L [group main effect, $F_{2,21}$=1.65; P=.22]).

COMMENT

Consistent with previous reports,[1,2,53] 56% of our patients with MDD responded to 1 night of SD. Serum thyrotropin level increased during SD in all 3 groups, reaching a peak between 2:15 AM and 6 AM, confirming previous reports.[54] The elevated basal serum thyrotropin level in our SD responders increased in parallel with that of nonresponders and controls during SD but was higher throughout the sampling period; mean nocturnal serum thyrotropin level was above the upper normal limit in responders, but in none of the nonresponders or controls. The correlation of increased serum thyrotropin level with clinical response was robust in our patients, consistent with some[25,26] but not all[24,27] studies. The changes were limited to the HPT in our patients, since the circulating concentrations of cortisol, which also has a circadian secretory pattern, were normal and similar among the 3 groups. The results suggest that altered HPT function either plays a role in MDD and the mood response to SD or is an epiphenomenon reflecting altered HPT function in both.

The increased serum thyrotropin levels, normal thyroid hormone concentrations, and exaggerated thyrotropin responses to protirelin stimulation in the SD responders are consistent with subclinical primary hypothyroidism. This autoimmune disorder occurs in about 5% of mostly postmenopausal women.[55] Our patients had no evidence of autoimmune thyroiditis. Although the nocturnal serum thyrotropin level of SD nonresponders was normal and they did not have an exaggerated response to protirelin, their circulating thyrotropin had increased bioactivity. Furthermore, 2 years after SD, no patient with MDD was hypothyroid. If they had transient hypothyroidism caused by thyroiditis, it was of a kind not previously described. Transient thyroiditis with hypothyroidism is rare except post partum and is usually preceded by thyrotoxicosis.[56,57] However, the combination of increased serum thyrotropin level and normal serum thyroid hormone levels may explain the proposed association between MDD and subclinical primary hypothyroidism.[12-14]

Our results do not indicate central (ie, hypothalamic) hypothyroidism, which is typified by high serum thyrotropin concentrations, low serum thyroid hormone levels, an exaggerated response to protirelin, low thyrotropin B/I, and high serum concentrations of free thyrotropin-β subunit.[58-61] Our responders' thyrotropin-α and thyrotropin-β subunit concentrations and thyrotropin-β/thyrotropin-α ratios were not different from those of nonresponders or controls. Moreover, our results are not consistent with resistance to thyroid hormone action involving the pituitary gland, peripheral tissues, or both.[62,63]

We were surprised to find that responders had normal and nonresponders had increased thyrotropin B/I ratios; we anticipated decreased and normal ratios, respectively. Increased thyrotropin bioactivity, caused by decreased terminal sialic acid residues on thyrotropin carbohydrate side chains, occurs in healthy third-trimester human fetuses and patients with thyroid hormone resistance.[64,65] Decreased bioactivity caused by increased sialylation is found at night in healthy subjects and during daytime in hypothyroid patients; the latter is reversed with long-term thyroxine administration.[65,66] Our finding of increased thyrotropin bioactivity without evidence of thyroid hormone resistance in an adult is unprecedented.

Sleep deprivation responders had exaggerated serum thyrotropin responses to protirelin, and nonresponders had normal responses but greater thyrotropin bioactivity; none had a blunted response. Previous studies, in which protirelin usually was administered at 9 AM, report that about 30% of depressed patients have blunted thyrotropin responses.[10,11] Some studies report higher afternoon than morning responses to protirelin in patients with MDD.[67-69] Thus, our results may reflect either the timing of the protirelin injection or an effect of SD.

Our results suggest 2 different HPT phenomena, one associated with MDD and the other with the mood response to SD. The thyroid gland of patients with MDD appears to be resistant to thyrotropin action. This represents a novel form of transient compensated primary hypothyroidism with an unknown, but presumably central, mechanism. Although the HPT of patients with MDD appears to respond appropriately by increasing the level of biologically active thyrotropin, SD responders and nonresponders accomplish this by different means. Sleep deprivation responders appear to increase their serum thyrotropin concentration by increasing secretion of thyrotropin with normal bioactivity. In contrast, SD nonresponders appear to increase the bioactivity of their thyrotropin without increasing their thyrotropin secretion or serum thyrotropin concentration. The mechanism producing this phenomenon is also unknown. Perhaps a difference in the secretion or action of a protirelin antagonist mediates the different pituitary thyrotropin responses in the 2 groups.

The fact that increased nocturnal serum thyrotropin concentrations were limited to female patients with MDD is provocative. However, the small sizes of the groups of men and women mandate that any conclusions about sex differences be considered tentative.

The nature of the thyroid gland resistance to thyrotropin, the mechanisms that determine why and how individual patients with MDD increase either their thyrotropin secretion rate or their thyrotropin bioactivity to compensate for this resistance, and the relationship of these 2 mechanisms to MDD and SD response or nonresponse remain to be determined.

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Corresponding author: Peter T. Loosen, MD, PhD, Psychiatry Service (116A), Department of Veterans Affairs Medical Center, 1310 24th Ave S, Nashville, TN 37212-2637 (e-mail: ptloosen@aol.com).

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