Thyroid Function and Response to 48-Hour Sleep Deprivation in Treatment-Resistant Depressed Patients

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Background: Clinical depression is associated with abnormalities of the hypothalamic–pituitary–thyroid axis. Changes in thyroid function during sleep deprivation may be related to its antidepressant effects.

Methods: Levels of thyroid-stimulating hormone, tri-iodothyronine, tri-iodothyronine uptake, thyroxine, and free thyroxine were measured before, during, and after a 48-hour sleep deprivation in nine treatment-resistant depressed patients. Clinical state was assessed every 4 hours. A retrospective study of 26 similar patients was added for cross-validation.

Results: Significant increases in thyroid-stimulating hormone and tri-iodothyronine during sleep deprivation were not correlated with clinical improvement. Sleep deprivation responders had lower tri-iodothyronine uptake levels than nonresponders in both the prospective (p < .02) and the retrospective (p < .03) samples.

Conclusions: The lower tri-iodothyronine uptake values in responders may identify a subgroup of depressed patients who respond to sleep deprivation by virtue of some abnormality of the hypothalamic–pituitary–thyroid axis that is temporarily corrected by sleep deprivation.

Key Words: Sleep deprivation, thyroid, thyroid-stimulating hormone, tri-iodothyronine uptake, treatment-resistant depression, affective disorders

Introduction

A disruption of the normal homeostasis of the hypothalamic–pituitary–thyroid axis may be of etiologic significance in depressive illness (Stein and Avni 1988). Total sleep deprivation (SD), which temporarily ameliorates depressive symptoms in over 60% of patients (Wu and Bunney 1990), is a heuristic method by which this hypothesis may be tested.

Although differences in thyroid function between SD responders and nonresponders have not been demonstrated consistently, some studies have found thyroid function to be predictive of SD response. An increase in thyroid-stimulating hormone (TSH) during SD has been reliably demonstrated (Baumgartner et al 1990a, 1990b; Kaschka et al 1989; Kasper et al 1988; Parekh et al 1998), although a causal link between TSH and clinical response has not been firmly established. The finding by Southmayd et al (1992) that thyroxine (T4) can reliably prolong the clinical improvement induced by SD strongly suggests that changes in thyroid function are etiologically relevant to this antidepressant effect.

Our study examined thyroid function before, during, and after SD. It differs from previous studies by incorporating an extended (48-hour) SD period, 4-hour assessments of clinical state, and measurements of tri-iodothyronine uptake (T3U). A retrospective study of thyroid function before SD in an independent patient sample is also described, for cross-validation.

Methods and Materials

Prospective Study

Nine treatment-resistant inpatients (seven female, two male; mean age 41 years) with unipolar major depression (DSM-IV; American Psychiatric Association 1994) underwent a 48-hour SD. At baseline, the 17-item Hamilton Rating Scale for Depression (Hamilton 1967) mean score was 24.8. Two patients had been medication free for 3 weeks or more; seven were on stable psychotropic medication regimes for at least 2 weeks, with no new antidepressants having been introduced for 6 weeks. The women were between days 2 and 7 of their menstrual cycles; none were taking hormones.

During the 3-day baseline subjects were awake between 6:00 AM and 10:00 PM. They then remained awake for 48 hours. Subjects slept between 6:00 AM and 12:00 PM on day 5, returning to the baseline schedule for 2 “recovery” days. Brief structured videotaped interviews were conducted at 4-hour intervals during wakefulness to assess clinical state. These were rated on a visual analogue scale (Aitken 1969), independently and in random
order, by two clinicians blinded to time and date. Sleep deprivation response was defined as an improvement of least 2 standard deviations from the baseline mean, or clinical state reaching the normal range during SD (Southmayd et al 1990). Subjects whose moods reached the normal range at any point during baseline were excluded.

Blood samples were drawn at 9:00 AM and 9:00 PM from day 2 through day 6 (except 9:00 AM on day 5, when subjects slept). Tests for TSH, T3, T4, free T4 (fT4), and T3U were performed by a commercial medical laboratory on batched samples using automated instruments.

Changes in thyroid function were assessed using a multivariate analysis of variance, with group (responders and nonresponders) as the between-subjects variable and time (9:00AM and 9:00 PM) and phase (baseline, SD, and recovery) as within-subjects variables. The linear component of the phase effect contrasted recovery with baseline; the quadratic component contrasted SD with the average of baseline and recovery.

A correlational analysis compared the quadratic component of the phase effect for the thyroid measures with the corresponding effect for clinical state.

**Retrospective Study**

Twenty-six subjects were selected who 1) had completed a 40-hour SD with clinical ratings, 2) had major depression or bipolar mood disorder and were depressed at baseline, 3) had records of thyroid function before SD, and 4) had normal TSH and were not taking thyroid supplements.

Of the responders (11 female, four male; mean age 58.3 years), 14 were unipolar and one bipolar, four were medication free, and 11 were taking psychotropic medications. Of the nonresponders (six female, five male; mean age 50.3 years), eight were unipolar and three bipolar, two patients were medication free, and nine were taking psychotropic medications. Independent sample t tests evaluated group differences for TSH, T4, and T3U.

**Results**

**Prospective Study**

Sleep deprivation induced changes in TSH, as indicated by the phase effect \( F(2,14) = 8.239, \ p < 0.004 \). The quadratic component of the phase effect \( F(1,7) = 7.890, \ p < 0.03 \) reflects a rise during SD (Figure 1). The significant quadratic component of the phase by time interaction \( F(1,7) = 5.620, \ p < 0.05 \) reflects the fact that the rise in TSH during SD was only evident at 9:00 AM, counteracting an overall time of day effect whereby TSH was generally higher at 9:00 PM than at 9:00 AM \( F(1,7) = 13.136, \ p < 0.008 \). The linear component of the phase effect \( F(1,7) = 8.575, \ p < 0.03 \) indicates that recovery levels of TSH dropped below baseline.

Tri-iodothyronine was lower at 9:00 PM than at 9:00 AM \( F(1,7) = 5.590, \ p = 0.05 \) and rose significantly with SD, as indicated by the quadratic component of the phase effect \( F(1,7) = 6.590, \ p < 0.04 \).

Baseline T3U levels were significantly lower for the responders \( [n = 5; F(1,7) = 9.9662, \ p < 0.02] \) and remained stable. The frequency distribution of T3U was bimodal.

Given the small sample size, we evaluated the possibility of type II errors using power analyses. We placed an upper bound with 80% confidence on any critical effect where we were unable to reject the null hypothesis with 95% confidence. The results suggest it is unlikely that we have missed effects of clinically or theoretically important size.

The correlations between clinical state and various measures of thyroid function were not significant.

**Retrospective Study**

Results replicated those of the prospective study, with a significant group difference for T3U \( (t = 2.15, \ p = 0.03) \)
but not for T4 or TSH. Responders had lower T3U levels than nonresponders, with a bimodal frequency distribution similar to that of the prospective study (Figure 2).

Discussion

The rise in T3 during SD is consistent with other studies (Baumgartner et al 1990a, 1990b; Kaschka et al 1989; Parekh et al 1998); however, we did not observe previously documented increases in T4 and fT4 (Baumgartner et al 1990b; Kaschka et al 1989; Parekh et al 1998).

As reported by others (e.g., Baumgartner et al 1990a), TSH was generally higher at 9:00 PM than at 9:00 AM. Our study also replicates the reliable finding of an increase in TSH during SD. The rise in TSH at 9:00 AM during SD counteracted its diurnal rhythm, which supports the observation by Parker et al (1987) that the normal inhibition of TSH release occurring near sleep onset is temporarily bypassed by SD.

Whereas some studies found that the SD-related rise in TSH correlated with clinical improvement (Baumgartner et al 1990a; Parekh et al 1998), others, including ours, did not (Baumgartner et al 1990b; Kaschka et al 1989; Kasper et al 1988). This inconsistency may be related to methodological or sample differences. Furthermore, the potential connection between TSH and antidepressant response may not be a direct one. Elevated TSH may be a response to changes in those systems that may mediate the antidepressant response at a higher level. Despite the consistent effect of SD on TSH, the relevance and proximity of this rise in TSH to the antidepressant action remain unclear.

Differences in thyroid function between SD responders and nonresponders have not been demonstrated reliably. For example, Baumgartner et al (1990a, 1990b) reported higher T4 levels in responders, whereas others (e.g., Kaschka et al 1989), including ourselves, did not. This inconsistency between studies makes interpretation difficult.

To our knowledge, our study is the first to examine changes in T3U during SD. The robust group difference in T3U observed in the prospective study, and substantiated by the retrospective analysis of a larger independent sample, is noteworthy. It strongly suggests that T3U is a predictor of SD response.

Lower T3U, seen in the responders, reflects an increase in the number of unoccupied plasma T4-binding protein sites. This can be caused by an increased concentration of thyroid hormone–binding protein, although no causal factors (e.g., pregnancy, exogenous estrogens) applied in the present study. A more likely explanation is hypothyroidism, which some researchers (e.g., Hickie et al 1996), but not all (Joffe 1999), have found to occur more commonly in treatment-resistant depressed patients than in their non–treatment-resistant counterparts. If the lower T3U values in responders reflect subclinical hypothyroidism, the condition may be temporarily alleviated by SD, which increases T3 availability. This fits with the observation that exogenous T4 can extend the beneficial effects of SD (Southmayd et al 1992). Shelton et al (1992) found that, in comparison to nonresponders, SD responders had a more robust response to thyrotropin-releasing hormone stimulation, which can be a manifestation of subclinical hypothyroidism. Further study is needed to test this hypothyroidism hypothesis and to determine whether the lower T3U values in SD responders are state or trait specific.

References


American Psychiatric Association (1994): Diagnostic and Sta-


