
Thyroid Hypofunction in Patients with Rapid-Cycling Bipolar Disorder after Lithium Challenge

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Background: *There is debate whether patients with rapid-cycling bipolar disorder (BD) are predisposed to thyroid axis abnormalities and whether this may contribute to development of rapid mood shifts. Using lithium carbonate as a challenge to the hypothalamic-pituitary-thyroid (HPT) system, we determined whether patients with rapid-cycling BD are sensitive to the “antithyroid” properties of lithium.*

Methods: *We studied the response to thyrotropin-releasing hormone (TRH) of HPT system hormones in 20 medication-free patients with rapid-cycling BD and compared these measurements with those of 20 healthy age- and gender-matched control subjects. The same measurements were repeated after both groups had received lithium carbonate for 4 weeks in sufficient doses to maintain blood levels between .7–1.2 mEq/L.*

Results: *At baseline, the results of thyroid function tests, including the TRH challenge test, did not differ between patients and control subjects. After treatment with lithium, serum concentrations of thyroxine significantly decreased, whereas basal thyrotropin (TSH) and ΔTSH_{max} significantly increased in both patients and control subjects; however, patients had significantly higher ΔTSH_{max} after TRH stimulation. More patients than control subjects developed laboratory evidence consistent with grade III hypothyroidism after lithium treatment.*

Conclusions: *Rapid-cycling BD is associated with a latent hypofunction of the HPT system. This dysfunction becomes manifest with short-term lithium challenge.* Biol Psychiatry 2003;53:899–905 © 2003 Society of Biological Psychiatry

Key Words: Bipolar disorder, rapid cycling, thyroid, lithium, TRH test, healthy control subjects

Introduction

The rapid-cycling variant of bipolar disorder (BD) affects 10%–15% of all bipolar patients who have, by definition, suffered four or more episodes of illness during the previous 12 months (Bauer et al 1994; Dunner and Fieve 1974). There is debate whether rapid-cycling bipolar patients are predisposed to thyroid axis abnormalities and whether such dysfunction may contribute to the development of rapid mood shifts. At least seven studies have found an association among indices of low thyroid function or clinical hypothyroidism (or both) and rapid-cycling BD (Bartalena et al 1990; Bauer et al 1990; Cho et al 1979; Cowdry et al 1983; Kusalic 1992; McKeon et al 1992; Oomen et al 1996). Other studies refute this association (Coryell et al 1992; Joffe et al 1988; Kupka et al 2002; Maj et al 1994; Post et al 1997; Wehr et al 1988); however, the conclusions to be drawn from these studies are often limited by their retrospective design (Coryell et al 1992; Wehr et al 1988) and by the lack of a healthy control comparison group (Bauer et al 1990; Cho et al 1979; Coryell et al 1992; Cowdry et al 1983; Joffe et al 1988; Kusalic 1992; McKeon et al 1992; Oomen et al 1996; Wehr et al 1988). Most important, many of these studies included patients with rapid-cycling BD who were receiving prophylactic long-term lithium treatment (Bartalena et al 1990; Bauer et al 1990; Cho et al 1979; Coryell et al 1992; Cowdry et al 1983; Joffe et al 1988; Kusalic 1992; Oomen et al 1996; Wehr et al 1988), an agent which has been demonstrated to have “antithyroid” properties (Lazarus 1998). Cross-sectional studies of unmedicated rapid-cycling bipolar patients, on the other hand, found no abnormalities in basal thyrotropin (TSH) and thyroxine levels in this patient population (Bauer et al 1990; Post et al 1997; Sack et al 1988).

Bauer et al (1990) postulated that BD patients with rapid cycling may manifest no thyroid abnormalities until physiologically challenged by “antithyroid” stressors.

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Such stressors may include spontaneously occurring thyroid disease or goiterogenic drugs such as lithium. Lithium interferes with the synthesis and release of thyroid hormones at various sites, including the reduction of iodine uptake into the thyroid gland *in vivo* and *in vitro*, inhibition of the conversion from tetraiodothyronine (T4) to triiodothyronine (T3), and retardation of the release of thyroid hormones from the thyroid gland (Kushner and Wartofsky 1988; Lazarus 1998). Furthermore, lithium has been reported to inhibit TSH-induced stimulation of adenylate cyclase activity (Mori et al 1989).

Consistent with these physiologic actions, some prospective studies indicate that short-term treatment with lithium leads to diminished thyroid function both in healthy control subjects (Child et al 1977; Grof et al 1984; Lauridsen et al 1974; Perrild et al 1984) and in unselected bipolar patients (Grof et al 1984; Lazarus and Bennie 1972; Lombardi et al 1993; McLarty et al 1975; Myers et al 1985; Smigan et al 1984; Takahashi et al 1975; Villeneuve et al 1974); however, there is only one small study comparing the effect of lithium on thyroid function in patients with BD and healthy control subjects (Grof et al 1984) and no difference between those with BD and the control subjects was found (Grof et al 1984). There are no studies that have compared thyroid axis indices in the rapid-cycling bipolar phenotype with age- and gender-matched healthy control subjects using a lithium challenge paradigm.

Thus, we undertook a prospective study to compare thyroid axis function in unmedicated rapid-cycling bipolar patients and healthy euthyroid control subjects before and after a 4-week challenge of lithium carbonate at doses sufficient to achieve therapeutic serum levels. Our primary hypothesis was that thyroid function in unmedicated rapid-cycling bipolar patients will be more sensitive to disruption by lithium challenge, as measured by higher basal TSH and $\Delta\text{TSH}_{\text{max}}$ after thyrotropin-releasing hormone (TRH) stimulation than in healthy euthyroid control subjects.

Methods and Materials

Subjects

This was a single-site study at the Department of Psychiatry of the University of Pennsylvania Medical Center (UPMC), Philadelphia. Bipolar patients with a rapid-cycling course were recruited from the Bipolar Disorders Program and the clinical programs of UPMC. Healthy volunteers were recruited from the UPMC and through advertisements in local newspapers. All subjects gave written informed consent to participate in the study. The study protocol was approved by the local Human Subjects Committee.

All consecutively admitted patients and control subjects were screened for and, if appropriate, offered participation in the study. Screening procedures included a complete medical and

physical examination, a routine laboratory evaluation (blood count, blood chemistry, urine analysis, and urine drug toxicology) and an electrocardiogram (ECG). All subjects underwent a Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al 1989) supplemented by a structured interview for diagnosis of the rapidly cycling course (unpublished instrument) and a Personality Disorders Examination (PDE; Loranger 1988). Consensus diagnoses were made using information from the SCID, PDE, and all available medical records by a panel of two research psychiatrists and one psychologist. Affective symptomatology was assessed with the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) and the Young Mania Rating Scale (YMRS; Young et al 1978) on the same day as HPT system evaluation was performed.

Patients and control subjects, between the ages of 18–65, were age- (within 5 years) and gender-matched. Patients met standard DSM-III-R criteria for BD and the Dunner–Fieve criterion, which serves as the basis for DSM-IV rapid-cycling course modifier, of four or more affective episodes during the 12-month period before study entry (Dunner and Fieve 1974). Five patients had “truncated” episode rapid cycling, which does not differ from DSM-IV–defined rapid cycling by any identifiable demographic, clinical, or course of illness characteristics (Bauer et al 1994). Patients with current or past (within 2 years) substance dependence or substance abuse were excluded. Rapid-cycling patients were also excluded from study participation if they had an abnormality on laboratory evaluations (except on thyroid function tests) or electrocardiogram, had been treated with lithium salts or thyroid hormones during a 3-month period before study entry, or if they had received any psychotropic medication in the 2 weeks before study entry. Patients admitted to the study could enroll in any mood condition. The time from the last episode prior to study entry ranged from a few days to 9 months, although in many individuals the exact time interval could not be definitively assessed largely because of the patients’ inability to provide accurate data.

Of the patient sample, 10 patients had used lithium in the past, 2 had never been on psychiatric medications, and 10 had never taken lithium. All patients had been off lithium for 3 months as per protocol but six of them were off for between 1–10 years. Only one patient had received levothyroxine in the past (for treatment of her mood disorder) and had stopped taking it 12 weeks before study entry (she had normal thyroid function tests at study entry). All medications were tapered before the first TRH stimulation test, as follows: monoamine oxidase inhibitors (two patients), selective serotonin reuptake inhibitors (one patient), benzodiazepines (four patients), bupropion (one patient), divalproex (one patient), carbamazepine (one patient), and neuroleptics (two patients).

To be included, control subjects had to be medically healthy, without current DSM-III-R Axis I disorder, and without any medication for at least 2 weeks before the study. We included one control subject who gave history of mild bulimia nervosa 7 years before study entry. She had not experienced any symptoms over the 7 intervening years. Another control subject had suffered mild panic disorder 3 years before study entry without symptoms over the last 3 years. These exceptions were considered acceptable by the investigators because the illnesses were

short, mild, occurred once, and were without sequelae after full symptom resolution. Control subjects with any significant abnormalities in the laboratory or physical examinations were excluded. It is important to note that we excluded those with abnormal thyroid indices at baseline because it was our intent to compare the lithium challenge in the rapid-cycling bipolar patients with the response to lithium in those with a healthy normal thyroid axis function. Female patients and control subjects of reproductive age who used oral contraceptives were also excluded.

Study Design

LITHIUM CHALLENGE. The initial dose for all subjects was 300 mg of lithium carbonate (not sustained release) three times daily, immediately following the baseline neuroendocrine procedures. The lithium dosage was adjusted to achieve therapeutic serum levels of .5–1.2 mEq/L within the first 2 weeks of treatment. All subjects then received lithium carbonate for 4 weeks at therapeutic serum levels. Subjects were investigated on two occasions before and after lithium treatment with an identical set of procedures including a clinical interview, physical examination, psychiatric rating scales, routine laboratory tests, and thyroid function tests plus a TRH stimulation test. (A 4-week period of lithium challenge was chosen because repeated testing within less than 2 weeks has been shown to diminish TSH response to TRH in normal subjects; Winkour et al 1984).

NEUROENDOCRINE PROCEDURES. The neuroendocrine procedures were performed at the Clinical Research Center (CRC) of the UPMC. Subjects were admitted to the CRC at 7:00 AM having fasted, except for water, from midnight. Subjects sat in a comfortable position for the neuroendocrine tests and an intravenous cannula was inserted for the TRH stimulation test. Thirty minutes after the intravenous line was placed, and 15 min before the intravenous injection of 400 μ g of protirelin (TRH), baseline blood sampling began. Blood samples for measurement of total thyroxine (T4), free thyroxine (fT4), triiodothyronine (T3), reverse triiodothyronine (rT3), thyroglobulin (TBG), anti-thyroglobulin, and antimicrosomal thyroid autoantibodies were collected before TRH injection. TRH was injected as a bolus. Blood samples for measurement of thyrotropin (TSH) were drawn immediately before and at 15, 30, 45, 60, and 90 min postinjection, spun down and immediately frozen at -80°C until assay. The $\Delta\text{TSH}_{\text{max}}$ was calculated as the maximal rise in TSH level during 90 min after infusion of TRH minus basal TSH level.

THYROID FUNCTION ASSAYS. Levels of T4, fT4, T3, rT3, TBG, and TSH from frozen serum were estimated by standard ultrasensitive radioimmunoassays kits (RIA) using double antibody methods. Assay characteristics (sensitivity, intra- and interassay coefficients of variation) have been reported earlier (Bauer et al 1990; Gary et al 1996). Antithyroid antibody assays were performed with a hemagglutination kit with lowest detectable titers of 1:10 for antithyroglobulin and 1:100 for antimicrosomal antibodies (Bauer et al 1990). All measurements were performed in duplicate. Normal values for thyroid hormones, TBG, and TSH were as follows: T4 4.4–12.5 $\mu\text{g}/\text{dL}$, fT4 1.3–3.8

ng/dL, T3 .9–2.0 ng/mL, rT3 100–500 pg/mL, and TSH .4–3.8 $\mu\text{U}/\text{mL}$. For classification of TRH stimulation test results, we used an upper limit for $\Delta\text{TSH}_{\text{max}}$ of 32 $\mu\text{U}/\text{mL}$ for female subjects and 19 $\mu\text{U}/\text{mL}$ for male subjects, as according to Wenzel et al (1974). Thyroid function abnormalities were classified as grade I to III, adapted from Wenzel et al, grade I was defined as decreased serum T4 level, grade II as an increased serum basal TSH with normal serum T4 level, and grade III as the presence of an isolated exaggeration of the TSH response to TRH stimulation, with normal basal TSH levels (Wenzel et al 1974).

STATISTICAL ANALYSES. Clinical and demographic differences between groups were tested with chi-square to compare categorical variables, such as gender and BD type, and the two-sample *t* test was employed for continuous variables such as age and duration of lithium treatment. Skewed variables such as YMRS and HRSD-17 were compared using a Mann–Whitney *U* (Wilcoxon) test.

A generalized estimating equations (GEE) approach was used to fit models to explain thyroid function parameters as a function of both diagnosis and lithium treatment. The GEE approach is an extension of traditional linear models that allows the mean of a population to depend on a linear predictor through a nonlinear link function and allows the response probability distribution to be any member of an exponential family of distributions (Albert 1999; Zeger et al 1988). It provides a practical method with reasonable statistical efficiency to analyze correlated data and uses a procedure called quasi-likelihood estimation, which is a generalization of maximum likelihood estimation of correlated data. Inferences are made by treating the Wald test (the estimated regression coefficient divided by its robust SE) as a normal standardized deviate (*Z*). We used a computer program (SAS Institute, Cary, NC) to estimate the parameters and calculate the predicted values based on the models fit using GEE. The dependent variables were the various thyroid function indices. We fit TSH and $\Delta\text{TSH}_{\text{max}}$ using the natural logarithm scale because they were skewed, whereas other thyroid functions were fit using the original scale. The explanatory variables were subject diagnosis (patient vs. control subject), treatment (none vs. lithium), and an interaction term between the diagnosis and treatment effect. Because the measurements corresponded to no treatment as a pretreatment and lithium to a posttreatment measurement, we included the treatment as a repeated-measures time effect, allowing for a correlation between these two repeats on the same subject. Finally, the baseline value for the Hamilton Rating Scale for Depression was used as a covariate. We used the coefficients from the fitted models to estimate predicted values based on values of covariates (group, treatment, HRSD). Although there is theoretically a complete confounding between the time effect and the treatment effect because the measurements were separated by a short interval, the effect is totally attributable to lithium treatment not the time sequence of the measurements. For comparison of proportion of subjects having a diagnosis of abnormal thyroid function, we performed chi-squares tests. Finally, zero-order Pearson correlations were used to detect associations between continuous variables. All tests were two-tailed. Significance was set at $p \leq .05$.

Table 1. Clinical Variables in Rapid-Cycling Bipolar Patients and Healthy Control Subjects during the Study Protocol

	Patients (n = 20)	Control Subjects (n = 20)	p Value
Lithium Management during the Study			
Duration of Lithium Treatment (days)	36.1 ± 17.1	39.7 ± 8.3	ns
Lithium Dose (mg/day)	1094.6 ± 241.6	1137.4 ± 225.3	ns
Lithium Dose (mg/kg/day)	15.6 ± 4.6	16.4 ± 4.2	ns
Final Lithium Level (mEq/L)	.77 ± .26	.84 ± .26	ns
Mood Ratings during the Study			
Initial HRSD-17	6 (0–24)	0 (0–2)	.001
Final HRSD-17	5 (0–25)	0 (0–8)	.01
Initial YMRS	1.5 (0–13)	0 (0–2)	.01
Final YMRS	1 (0–11)	0 (0–3)	.03

HRSD-17, Hamilton Rating Scale for Depression, 17-item version; YMRS, Young Mania Rating Scale. Values are expressed as mean ± SD for treatment related variables and median and range for mood rating scales.

Results

Demographic and Clinical Data

Patients and control subjects did not differ in age (34.5 ± 9.6, 36.7 ± 10.5, respectively). There were 10 female and 10 male subjects in each group. Sixteen patients satisfied criteria for BD with hypomanic episodes only (bipolar type II) and four patients met criteria for BD type I. One patient had personality disorder not otherwise specified (NOS), one had borderline personality disorder, and one had histrionic and narcissistic personality disorder. Nine patients had not been diagnosed with BD prior to entering our bipolar program. At study entry, seven patients had scores greater than 15 on the HDRS or 12 on the YMRS, indicating that they were in a mood episode; all other patients were in remission (mean ratings of mood during the study period are reported in Table 1). Neither HRSD nor YMRS changed significantly by the end of the study (Table 1). Control subjects were euthymic throughout the study. The duration of the lithium treatment, the average daily lithium dose, and the final lithium serum level were not different in the two groups (Table 1).

Baseline Thyroid Function Indices

There were no differences between patients and control subjects in the levels of TSH basal and Δ TSH_{max}, or T4,

fT4, T3, rT3, and TBG while medication-free, before lithium treatment (Table 2). The averages of T4, basal TSH, and Δ TSH_{max}, as well as the other thyroid indices, were within normal limits for both patients and control subjects before lithium treatment (Tables 2 and 3). All patients and control subjects had normal basal TSH values. In these baseline studies, two patients and one control subject had an exaggerated TSH response to TRH stimulation (patient no. 1 had 21.1 μ U/mL, patient no. 20 had 41.17 μ U/mL, and control no. 15 had 36.65 μ U/mL). Chi-square test indicates no statistical difference between patients and control subjects in the proportion of abnormalities in Δ TSH_{max} prior lithium treatment ($p = .99$).

Thyroid Function Indices after Lithium Challenge

Lithium treatment increased basal TSH and Δ TSH_{max} values both in rapid-cycling bipolar patients and in control subjects (Table 3). Δ TSH_{max} increased more in patients than in control subjects ($Z = 2.27$; $p < .023$). The GEE-predicted values of Δ TSH_{max} increased by 17.8 μ U/mL in rapid-cycling bipolar patients and by 11.5 μ U/mL in healthy control subjects after treatment with lithium. This model assumed HDRS to be 0 in both groups both pre- and posttreatment with lithium. In a second analysis, we excluded all outliers of Δ TSH_{max} from both

Table 2. Serum Thyroid Function Indices in Rapid-Cycling Bipolar Patients and Healthy Control Subjects

	Patients (n = 20)		Control Subjects (n = 20)		Diagnosis Effect p	Treatment Effect p	Treatment × Diagnosis Interaction p
	Pretreatment	Posttreatment	Pretreatment	Posttreatment			
T4 (μ g/dL)	6.88 ± 2.17	5.98 ± 1.13	6.39 ± 1.52	5.49 ± 1.45	ns	.015	ns
fT4 (ng/dL)	2.10 ± .51	1.97 ± .42	1.99 ± .78	1.72 ± .81	ns	ns	ns
T3 (ng/mL)	1.45 ± .36	1.39 ± .39	1.37 ± .40	1.46 ± .52	ns	ns	ns
rT3 (pg/mL)	236.96 ± 185.43	217.22 ± 103.26	226.31 ± 125.91	224.40 ± 143.26	ns	ns	ns
TBG (μ g/mL)	29.90 ± 8.26	29.02 ± 6.22	28.33 ± 10.38	29.32 ± 9.25	ns	ns	ns

T4, total thyroxine; fT4, free thyroxine; T3, triiodothyronine; rT3, reverse triiodothyronine; TSH, thyrotropin; TBG, thyroglobulin. Values are expressed as mean ± SD.

Table 3. Serum TSH Basal and Δ TSH in Rapid-Cycling Bipolar Patients and Healthy Control Subjects

	Patients (<i>n</i> = 20)		Control Subjects (<i>n</i> = 20)		Diagnosis Effect <i>p</i>	Treatment Effect <i>p</i>	Treatment × Diagnosis Interaction <i>p</i>
	Pretreatment	Posttreatment	Pretreatment	Posttreatment			
TSH basal (μ U/mL)	1.58 (.60–3.30)	3.60 (2.21–14.50)	1.50 (.40–2.96)	2.91 (.70–7.40)	<i>ns</i>	.0001	.262
Δ TSH (μ U/mL)	12.55 (4.13–41.17)	29.54 (11.16–87.06)	13.24 (6.05–36.65)	21.79 (11.97–69.50)	<i>ns</i>	.0001	.023

TSH, thyrotropin. Values are expressed as median (range); *p* values are based on fit on log scale.

the patient (*n* = 2) and control (*n* = 3) groups (because the departure from normality may have been too large) and used the same GEE model that we used for the whole sample. This reanalysis also showed that Δ TSH_{max} increased more in patients than in control subjects (Z = 3.00; p < .0027). The average serum concentrations of T4 significantly decreased both in patients and control subjects after lithium treatment (Z = 2.43; p < .02), whereas values of fT4, T3, rT3, and TBG did not change (Table 3).

More patients (*n* = 15) than control subjects (*n* = 8) showed an increase in Δ TSH_{max} above normal limits after lithium challenge (serum evidence of grade III hypothyroidism) (χ^2 = 5.01; *df* 1; p = .025). None of the patients and control subjects developed serum evidence of grade I hypothyroidism after lithium challenge. There was no statistical difference in the number of subjects with grade II hypothyroidism (eight patients, four control subjects; p = .30, chi-square test).

Additional Findings

Neither antimicrosomal nor antithyroglobulin antibodies were detectable before or after lithium challenge in either subject group. For both groups combined, there was no correlation between any of the thyroid function indices and the scores of the HRS and YMRS at any time during the study. None of the thyroid function indices at the end of the study correlated with either the average lithium dose or the final lithium level, nor did the duration of lithium treatment correlate with any of the thyroid function indices at the end of the study.

Discussion

To our knowledge, this is the first prospective evaluation of the hypothalamic-pituitary-thyroid (HPT) axis in unmedicated rapid-cycling bipolar patients, compared with age- and gender-matched normal control subjects, while under lithium challenge. The findings of this study lend support to our earlier hypothesis, which proposed that individuals with rapid-cycling BD are sensitive to goiterogenic stresses (Bauer et al 1990).

This study demonstrated no baseline, medication-free differences between patients and control subjects on any

measure of thyroid function including the TRH stimulation test. These findings are consistent with previous studies in unmedicated patients with rapid-cycling BD (Post et al 1997; Sack et al 1988). After treatment with lithium, levels of T4 significantly decreased and TSH basal and Δ TSH_{max} significantly increased in both patients and control subjects. This indicates that in both experimental groups the negative feedback control of the HPT system was intact; however, we found that the thyroid economy of rapid-cycling patients is more susceptible to the antithyroid effects of lithium than that of healthy control subjects as evidenced by a higher Δ TSH_{max} after TRH stimulation in rapid-cycling patients. In addition, rapid-cycling bipolar patients had a higher incidence of the serum profile of grade III hypothyroidism (presence of isolated exaggeration of the TSH response to TRH stimulation) than did healthy control subjects after challenge with lithium. This increased incidence of grade III hypothyroidism was not due to any insidious autoimmune process affecting the thyroid gland because neither antimicrosomal nor antithyroglobulin antibodies were detectable at any time during lithium treatment in either experimental group. The changes observed in thyroid functioning were not affected by either mood state, lithium dose, lithium serum levels, or the duration of lithium treatment.

This finding of thyroid hypofunction unmasked by lithium treatment provides a pathophysiologic model that may explain the potential role of the HPT axis in precipitating the rapid-cycling phenotype of BD. Under this model, a dysfunction in the HPT system is latent until the axis is challenged by the thyroprivic effect of lithium. Thus, whereas healthy control subjects had the same pattern of response to lithium challenge, underscoring that in both experimental groups the negative feedback control of the HPT system was intact, the patients had a higher Δ TSH_{max}. This higher incidence of grade III hypothyroidism after challenge with lithium suggests that a latent thyroid hypofunction is more often associated in patients with rapid-cycling BD compared with healthy control subjects; however, the specificity of thyroid hypofunction in the rapid-cycling variant of BD after lithium challenge needs to be established by further lithium-challenge stud-

ies in patients who suffer the nonrapid-cycling phenotype of BD.

The specific neurobiologic mechanisms that underlie the exaggerated TSH response to TRH in rapid-cycling patients after lithium challenge are unknown. Animal studies have demonstrated that lithium alters thyroid hormone metabolism at the cellular level (Lazarus 1998), specifically inhibiting the activity of type II 5'-deiodinase, the enzyme responsible for converting T4 to T3 in brain and the pituitary gland (Crantz et al 1982), in vitro (St. Germain 1987), and in vivo (Baumgartner 1997). Lithium also modulates the gene expression of thyroid hormone receptors in rat brain in vivo (Hahn et al 1999a) and in rat pituitary GH3 and neuroblastoma B103 cell lines (Hahn et al 1999b). Hence, lithium, when used in bipolar patients, may burden through these varied mechanisms the thyroid economy of the brain, specifically that of the pituitary gland, to create a relative neuronal thyroid hormone deficiency in predisposed individuals. This in turn may stimulate an increase in pituitary TSH and possibly an upregulation of pituitary TRH receptors.

Reciprocally, the results of this study may help to explain why treatment with levothyroxine (T₄), has been found to improve the course of rapid cycling in lithium-resistant bipolar patients (Bauer et al 2002; Bauer and Whybrow 1990; Whybrow 1994). If a "central" thyroid hypofunction is uncovered by lithium treatment then increasing the availability of thyroid hormone to brain in those receiving lithium therapy may be therapeutic, with consequent improved clinical outcome.

Our study also adds to the limited literature on the effects of lithium on the thyroid functioning of healthy subjects. We found only four studies in the literature prospectively investigating the effects of short-term lithium treatment in a total of 43 healthy control subjects (Child et al 1977; Grof et al 1984; Lauridsen et al 1974; Perrild et al 1984). All studies indicated a decrease in various thyroid function indices secondary to lithium burden. For example, two studies reported an increased TSH response to TRH after lithium (Grof et al 1984; Lauridsen et al 1974), but only one study found results similar to ours—a decreased serum T4 level, an increased basal TSH, and an exaggerated TRH test consistent with intact feedback regulation of the HPT system (Perrild et al 1984).

In summary, our study supports the hypotheses that the HPT axis has a potential role in the pathophysiology of rapid-cycling BD. Lithium challenge may offer a research paradigm valuable in uncovering latent HPT system abnormalities in affective disorder, including nonrapid-cycling BD, and other psychiatric syndromes.

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