

ORIGINAL ARTICLE

PSYCHONEUROENDOCRINE EFFECTS OF COMBINED THYROXINE AND TRIIODOTHYRONINE VERSUS TYROSINE DURING PROLONGED ANTARCTIC RESIDENCE

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Received 7 September 2007; Accepted 6 November 2007

ABSTRACT

Objectives. We previously reported that cognitive function improves with thyroxine and that there is a circannual pattern to mood and human TSH during Antarctic residence. To extend these findings, we examined the effects of tyrosine and a combined levothyroxine/ liothyronine supplement in euthyroid men and women who spent the austral summer (n=43) and/or winter (n=42) in Antarctica.

Study Design. Randomized, placebo-controlled, clinical trial.

Methods. Subjects were randomized to receive the following each day for 91.6±3.2 days in summer and/or 138.0± 3.2 days in winter: (1) 12g tyrosine mixed in 113g applesauce; (2) 50ug of levothyroxine and 12.5ug of liothyronine (T4-T3 Supplement); or (3) placebo. Cognitive performance and mood were assessed using the Automatic Neuropsychological Assessment Metric – Isolated and Confined Environments.

Results. With placebo in summer, mood did not change while TSH decreased by 28%; in winter, there was a 136% degradation in mood ($p<0.01$) and TSH increased by 18%. With combined T4-T3 supplement, there was a 51% degradation in mood in summer compared with placebo ($p<0.05$) and TSH decreased by 57%; in winter there was a 135% degradation in mood while TSH was reduced by 26% ($p<0.05$). Tyrosine use in summer was associated with no change in mood and a 30% decline in TSH, while in winter there was a 47% improvement in mood and TSH decreased by 28% along with a 6% increase in fT3 ($p<0.05$).

Conclusions. Administration of tyrosine leads to a significant reduction in serum TSH and improvement in mood in winter compared with placebo, while the combined T4-T3 supplement leads to a worsening of mood in summer and no improvement in winter. There appears to be a seasonal influence on the psychological response to interventions and the relationship to changes in TSH reductions. (*Int J Circumpolar Health* 2007; 66(5):401-417)

Keywords: mood, cognition, cold, thyroid hormones, clinical trial, tyrosine

INTRODUCTION

Polar expeditioners and residents in the circumpolar regions of the Arctic and Antarctic experience a constellation of physiological and hormonal changes called the Polar T₃ Syndrome (1–3). This syndrome is characterized by an elevation in the thyrotropin-releasing hormone (TRH), stimulated thyrotropin (TSH) (3) and non-stimulated TSH (2,4) in the absence of pituitary resistance to thyroid hormones (5). TSH in Antarctic expeditioners exhibits a circ-annual pattern with peaks in November and July and a trough in March (6). Additionally, a small decline in serum-free triiodothyronine (fT₃) and free thyroxine (fT₄), a doubling in both T₃ distribution volume and plasma appearance and clearance rate, as well as a small decrease in T₄ distribution volume further help define this condition (4,7). Physiologically, and presumably as part of hypothermic cold adaptation (5), polar expeditioners in the Antarctic have been

found to experience a fall in body temperature (8) and an apparent 70% increase in daily energy requirements (3,9). A similar seasonal pattern of alteration in thyroid hormones has also been observed in residents living in the Arctic (10).

The circulating thyroid hormone values observed with Antarctic residence (AR) suggest, at least in part, a cerebral and pituitary hypothyroxinemia that appears to be associated with impairments in cognition and mood. Hypothyroidism is known to be associated with cognitive deficits, mood alterations (11) and changes in visually evoked potentials (12). Cognition and mood are also affected in subclinical hypothyroidism where serum TSH is minimally elevated and the peripheral products are normal (13). Memory may be affected in some individuals even when the serum TSH is in the upper half of the normal range (14). In a previous study of 2 groups of euthyroid Antarctic expeditioners, we found significant

positive associations between FT_3 and vigour ($p < 0.001$) and between TT_4 and complex cognitive task response time ($p < 0.05$), and significant inverse associations between FT_4 and fatigue ($p < 0.05$) and depression ($p < 0.01$) (15). Cold-related changes in thyroid hormones may therefore contribute to the increased levels of depressed mood, anger and irritability, sleep disorders and impairment in cognitive performance reported in polar expeditioners in the Antarctic (16), as well as increased rates of seasonal and other psychiatric disorders among residents of circumpolar regions (17,18).

Administration of thyroxine improves mood and cognitive performance in individuals with subclinical hypothyroidism (13,19). A study by Bunevicius and colleagues (20) found an improvement in memory and mood when T_4 was used in combination with T_3 supplementation. In a previous study, we found that normalizing these circulating thyroid hormone parameters with thyroxine supplementation resulted in a significant improvement in cognitive performance and mood state (6). An 11% decline in performance on a computerized matching-to-sample test cognition was reversed with a daily supplement of thyroxine (64 nmol/d (50 μ g)). The change in accuracy on the matching-to-sample cognitive performance task was correlated with the change in FT_4 ($p < 0.01$), and increases in serum TSH preceded worsening Profile of Mood State scores in depression, tension, anger, lack of vigour and total mood disturbance ($p < 0.001$) during the austral winter (Feb.–Aug.) (6,21). Thyroxine supplementation also resulted in significant improvements in self-reported measures of fatigue and confusion.

Human and animal studies have also found that tyrosine, a nutrient precursor of catechol-

amines, appears to enhance catecholaminergic function and prevent cold-induced decrements in mood and cognitive performance (22–24). Gibson and Wurtman (22) demonstrated that tyrosine can increase the rate at which norepinephrine (NE) is synthesized in the CNS of rats during acute ambient cold exposure (4°C) relative to rats not administered tyrosine and exposed to cold. Rauch and Lieberman (24) found that behavioural depression induced by hypothermia was reversed by pretreatment with 400 mg/kg L-tyrosine. Dosages of 100 and 200 mg/kg L-tyrosine were found to significantly improve overall matching accuracy relative to saline, but did not completely reverse the effect of cold exposure (25). Shurtleff and colleagues (26) demonstrated in humans that pretreatment with 150 mg/kg tyrosine reverses cold-related declines in performance on a delayed matching-to-sample task. However, these studies have involved acute treatment of short duration. The effect of long-term use of tyrosine to prevent cold-related decrements in cognitive performance or mood has yet to be determined.

In this paper we report the effects of tyrosine, a combined supplement of thyroxine (64 nmol·day⁻¹[0.05 mg·day⁻¹]) and triiodothyronine (16 nmol·day⁻¹[0.012 mg·day⁻¹]) and placebo during AR upon cognition, mood and serum thyroid hormones. The objective of this study was to determine if the combined thyroid supplement or tyrosine could effectively prevent decrements in mood and cognitive performance in euthyroid men and women during an extended residence in Antarctica under actual field conditions. Our hypothesis was that participants receiving either intervention would exhibit significantly smaller decrements in mood and cognitive performance than participants in a placebo or control condition.

MATERIALS AND METHODS

Subjects

Sixty-five (40 male and 25 female) healthy euthyroid subjects participated in this study. Forty-three (31 men and 12 women) subjects participated in the summer phase, and 42 (23 men and 19 women) participated in the winter phase, with 25 subjects participating in both summer and winter phases. Participants were recruited prior to their deployment to Antarctica (n=30), within their first month of deployment (n=14) or at the end of the summer season (n=21). The protocol was approved by the University of California, San Diego Institutional Review Board, and all subjects gave written informed consent. Our original study group included 67 subjects, one of whom had subclinical hypothyroidism and the other who was non-compliant with the protocol causing both to be excluded from further study. No subject had a history of depressive or thyroid disease, and all were screened by a standardized physical and psychological assessment. Available diet contained a minimum of 1,182 nmol/day (150 mcg) of iodine (2,7) and no chronic medications were taken.

During outdoor activity, each subject wore standard polar cold-weather clothing with which the face is commonly exposed. Average temperatures varied from a high of -2.9°C in January and a low of -26.1°C in August at McMurdo Station, and a high of -27.5°C in December and a low of -60°C in August at South Pole Station. During the summer season, the minimum outside exposure at both stations was approximately 0.5 hr·day⁻¹ (3,7), indoor fluorescent lighting of normal intensity was used, and all subjects maintained routine 8 hr·day⁻¹ sleep cycles. During the

winter season, the minimum outdoor exposure at McMurdo Station was 0.5 hr·day⁻¹ (1) while minimum outdoor exposure at South Pole Station was reduced, in most instances, to 0.25 hr·day⁻¹. The indoor living compartment temperature in both summer and winter at both stations was between 18 and 25°C, although there is a substantial vertical thermal gradient in Antarctica (27).

Study Protocol

Baseline measures of physiology, biochemistry and behaviour (mood and cognitive performance) were obtained over a 2-week period between 7 and 23 November for the summer season and a 7-week period between 14 March and 2 May for the winter season. End-of-season measures were obtained over a 5-week period between 29 January and 5 March for the summer season and over a 7-week period between 11 August and 9 October for the winter season. For most (88%) participants, data collection was conducted in the morning hours (between 8:00 and 12:00) and occurred in the following order: physiological measurement, blood draw and cognitive/mood assessments. For the remaining 12% of study participants, data were collected in the late afternoon (between 14:00 and 17:00) to accommodate shift-work schedules.

Following baseline measurements at both summer and winter, the subjects were randomly assigned to 1 of 3 groups: tyrosine, thyroid supplement (T₄-T₃) and placebo. The placebo group was further randomized into 2 groups: tyrosine placebo and T₄-T₃ placebo. Although not part of the original study design, an additional 8 participants volunteered to serve as a control group during the winter months because they were interested in the

study and because their work schedules were shorter than in the summer. The tyrosine group consumed 12 g of tyrosine, mixed with 113 g of applesauce daily. The tyrosine placebo group consumed 12 g of cellulose, mixed with applesauce daily. The T₄-T₃ group consumed daily a pharmaceutical-grade, opaque, blue-green capsule containing 64 nmol (0.05 mg) of levothyroxine (LT₄) (Levoxyl®, Daniels Pharmaceuticals, Inc., St. Petersburg, FL) and 16 nmol (0.0125 mg) of triiodothyronine (T₃). The T₄-T₃ placebo group consumed a capsule containing gelatin. Summer participants were given 90 pills or 1.1 kg of powder and winter participants were given 150 pills or 1.8 g of powder and 150 113 g containers of applesauce. Individuals who participated in both summer and winter phases of the study were given no medication or placebo during a 30-day “washout period” prior to the winter phase. At the time of follow-up testing, subjects were instructed to return any remaining pills or containers of powder.

During the summer, 43 participants were randomized into the 3 groups, and 32 (74.4%) completed the study. There were no significant differences in withdrawal rates by treatment group. During the winter, 34 participants were randomized into 3 groups, and 33 (97.1%) completed the study. An additional 8 participants served as controls during the winter.

Physiological measurements

Prior to cognitive testing, each subject was evaluated for physiological status. Height was measured at baseline only using a tape measure. Weight and percent body fat were measured in bare feet using a Healthometer (Model BFM950: Sunbeam Products, Inc., Purvis MS) Digital Battery Body Fat Monitor

and Weight Scale. Weight was measured in kilograms. Blood pressure, heart rate and ear temperature were each measured three times at 10-minute intervals while the subject was sitting. The average of the 3 measures was then taken. Tympanic temperature was measured using a Braun Thermoscan (Model 6012: Braun, Kronberg, Germany). Blood pressure was measured using a standard sphygmomanometer, and pulse rate was assessed by counting the number of beats detected in the wrist over a 15-second period and multiplying by 4 to obtain beats per minute.

Biochemical measurements

Sampling at baseline and at follow-up during both seasons was completed following a 12-hour fast. To control for diurnal variation in hormonal profiles, blood samples obtained at post-season were obtained +/- one hour of the same time as the baseline assessment. Blood samples (13 ml) were obtained by antecubital venipuncture into glass tubes containing EDTA (Terumo Venoject, Terumo Corp., Leuven, Belgium). Within 10 minutes, the samples were centrifuged (1500 x g, 10 min.) to harvest the plasma. The plasma was immediately transferred to polypropylene tubes (Nalge Nunc International, Rochester, NY, USA) for storage at -70°C. From Antarctica, all summer baseline samples were transported in December 2002 at -70° C to San Diego, CA, where they remained at this temperature until co-assayed in duplicate using a batch method for subject and assay. End-of-summer and winter samples were stored at -70°C and transported from Antarctica to San Diego in November 2003.

All assays were performed at Quest Diagnostics Laboratories in San Diego and San

Juan Capistrano, CA. Cholesterol and serum lipids were commercially analysed by spectrophotometry (Olympus Corp. and Roche Diagnostics, Mannheim, Germany) with intraassay coefficient of variance (CV) of 1.5% for cholesterol, 2.5% for triglycerides and 3.5% for HDL and LDL. Cortisol, fT₃, tT₃ and TSH were commercially analysed by immunoassay (Bayer Corp, Leverkusen, Germany) with intraassay coefficient of variance (CV) of less than 5.3 % for cortisol, 2.7% for fT₃, 6% for tT₃ and 5% for TSH and assay detection limits of 5.52 nmol/L, 5.15 pmol/L, 1.69 pmol/L and 0.03 mU/L, respectively. Free T₄ and tT₄ were commercially assayed by direct equilibrium dialysis, radioimmunoassay and chemiluminescence (Bayer Corp.) with an intraassay CV of 4.2% and 3.7% and assay detection limit of 10.3 - 34.7 pmol/L and 72.1–176.3 nmol/L, respectively. Thyroxine Binding Globulin (TBG) was assessed by immunoassay (Quest Diagnostics, San Diego, CA) with an intraassay CV of 3.0%. Epinephrine and norepinephrine were analysed by HPLC, Electrochemical Detection using standards and controls from Biorad (Hercules, CA) with an intraassay CV of 12% for both catecholamines and assay detection limits of <518.7 pmol/L for epinephrine and 1.28-6.55 nmol/L for norepinephrine.

Assessment of cognitive performance and mood

The Automated Neuropsychological Assessment Metric (28) for Isolated and Confined Environments (ANAM-ICE) version was used to assess cognitive performance and mood. Subtests of the ANAM system have been designed to assess attention and concentration,

mental flexibility, spatial processing, cognitive processing efficiency, mood, arousal/fatigue level and memory. The subjects were introduced to the test battery prior to the experiments. For each of the cognitive tests, the percentage of accurate responses, response times (RT) for the correct responses and efficiency were determined. The efficiency, or throughput, is a measure that includes both speed and accuracy in one score. It is computed as the number of correct responses times 100 divided by response time.

The ANAM-ICE included 6 complex tasks and 1 simple task. The complex tasks were as follows: (1) Code Substitution (CDS), derived from the WAIS-R, Digit Symbol, and Symbol Digit Modalities Test (29) and designed to measure ability for sustained attention and concentration, verbal learning and numeric and symbolic facility; (2) Code Substitution – Delayed (CDD), presented at the end of the battery of cognitive tasks and which is a procedure essentially the same as the CDS, but the subject has to indicate whether or not the displayed pair is correct or incorrect based on recollection of the paired associates presented during the learning trial; (3) Continuous Performance (CPT), a continuous recall task requiring encoding and storage and use of the working memory (30); (4) Logical Reasoning (LRS), a task of abstract reasoning and verbal syntax (31) requiring a subject to compare a single sequence (e.g., & precedes #) and a pictorial relation (e.g., & #) to determine if the former is an accurate description of the latter; (5) Matching-To-Sample test (MTS), a test of attention, spatial and short-term or working memory, which requires the subject to correctly identify which 4x4 comparison matrix matches the sample matrix (32); and

(6) the Sternberg Memory Search (Sternberg-6: ST6), which is based on Sternberg's (33) paradigm of reaction time and measures encoding, categorization, response selection, execution and visual and short-term memory. For the simple task, cognitive performance was assessed using the Simple Reaction Time (SRT) task that measures simple visuomotor mental flexibility. The accuracy on this task was 100% for all participants; hence, only measures of efficiency and response time are calculated.

Mood was assessed from an adjective checklist constructed and validated by Ryman, Biersner and LaRocco (34). It consists of 6 adjective subscales that include 6 adjectives each. The subscales are vigour, happiness, fatigue, depression, anger and anxiety. Participants used a visual analog scale to indicate how much they experienced a particular feeling.

Statistical analysis

Prior to the study, we calculated that a sample size of 10 in each group would be sufficient to detect an effect size of .35 or greater with 80% power (with a Type I error rate of $\alpha=.05$) between each treatment group and the respective placebo group. This number was based on a previous study evaluating levothyroxine treatment ($64 \text{ nmol}\cdot\text{day}^{-1}$ [$0.05 \text{ mg}\cdot\text{day}^{-1}$]) in a similar group of Antarctic expeditioners (6). Two sets of comparisons were performed: (1) thyroid medication versus placebo (plus control during the winter), and (2) tyrosine versus placebo (control). The placebo groups for the 2 interventions and the winter control group were combined to increase sample size after it was determined that there were no significant differences in any of the outcome

measures between those taking placebo pills, cellulose (the placebo for tyrosine) and the winter controls (those who did not take anything).

Three measures of cognitive performance were derived for each task: percent accurate responses, efficiency of responses and response time (RT) for each correct response. Comparisons were conducted for each task and for summary measures of accuracy, efficiency and response time for all complex cognitive tasks combined (code substitution, code substitution delayed, continuous performance, matching-to-sample, logical reasoning and Sternberg-6) and for efficiency and response time on the Simple Reaction Time task. A Global Mood Score was calculated by subtracting the sum of the scores of the individual negative mood subscales (fatigue, depression, anger and anxiety) from the sum of the scores of the individual positive mood subscales (vigour and happiness). Parametric (analysis of variance, paired-sample t-test) or nonparametric (Wilcoxon signed rank test, Mann-Whitney U test) analysis was used, depending on the results of tests (Shapiro-Wilk test) examining assumptions of the statistical model. A 2-tailed .05 significance level was used for all parameters. Analyses were performed with SPSS, version 15.0. Comparisons of percent changes in performance, physiological and biochemical measures between the 2 treatment groups and the placebo/control group were performed using one-way analysis of variance or Wilcoxon's test as appropriate. Comparisons of baseline and post-season measures for the placebo/control group were performed using paired-sample t-tests or Mann-Whitney U test as appropriate.

RESULTS

A comparison of demographic characteristics and number of days spent in the study is provided in Table I. There were no significant differences between treatment groups with respect to age, gender, station and number of days in the study. Subjects were also similar to one another with regard to age, body mass index (BMI), percent body fat, tympanic temperature, systolic and diastolic blood pressure, and heart rate at the beginning of each season and time of day data were collected (data not shown). Three of the study participants had high TSH values (≥ 5.0 mU/L) in the summer and 2 participants had similar values at the beginning of winter; these individuals were not included in subsequent analyses.

Seasonal changes in physiological and psychological status

Comparisons of physiological and psychological measures of the placebo group at the beginning and end of both the summer and winter seasons are provided in Table II. During the summer, there were significant declines in

plasma epinephrine ($p < 0.05$) and norepinephrine ($p < 0.01$), as well as serum fT_4 ($p < 0.05$) and TSH ($p < 0.05$). There were no significant changes in mood scores or measures of cognitive performance in this period. During the winter, there were significant declines in systolic blood pressure ($p < 0.001$), total ($p < 0.05$) and LDL cholesterol ($p < 0.05$). There were also small but significant increases in accuracy (3.6%) ($p < 0.01$) and efficiency (7.0%) ($p < 0.05$) in performance of complex cognitive tasks. However, in contrast, there was a 136% degradation of mood ($p = 0.031$) in this group during the winter.

Effect of the interventions by both treatment and by time for the hormonal and physiological measures compared with placebo

During the summer, the T_4 - T_3 group experienced a significantly greater decrease (57.4%) in TSH compared with placebo (28.0%) ($p < 0.05$) (Fig. 1a). They also experienced a significantly smaller decrease (8.0%) in fT_4 compared with placebo (21.3%) ($p = 0.036$), and a smaller decrease in tympanic temperature (0.8% vs. 8.9%, $p < 0.05$, data not shown).

Table I. Subject demographics by treatment group.

	Tyrosine	Thyroid supplement	Placebo	Total
Summer	n=12	n=12	n=8	n=32
% Female	8.3	50.0	25.0	28.1
Mean (\pm SE) Age (Yr)	38.7 \pm 2.8	33.3 \pm 2.0	38.2 \pm 3.5	36.6 \pm 1.6
% South Pole	50.0	66.7	37.5	53.1
Mean (\pm SE) No. of days in study	89.2 \pm 5.0	88.4 \pm 5.5	98.0 \pm 6.7	91.0 \pm 3.2
Winter	n=10	n=11	n=20	n=41
% Female	40.0	54.5	45.0	46.3
Mean (\pm SE) Age (Yr)	35.2 \pm 2.4	37.1 \pm 2.4	37.7 \pm 2.0	36.9 \pm 1.3
% South Pole	50.0	36.4	20.0	31.7
Mean (\pm SE) No. of days in study	146.4 \pm 7.5	136.2 \pm 5.2	134.7 \pm 4.5	138.0 \pm 3.2

During the winter season, the T_4 - T_3 group experienced a 26.0% decrease in TSH versus an increase of 18.4% in the placebo group ($p<0.05$), and a significantly greater percent increase in serum fT_4 compared with placebo (28.0% versus 13.3%, $p=0.022$) (Fig. 1b). The tyrosine group experienced a 28.4% decrease

in TSH compared with an 18.4% increase in the placebo group ($p=0.008$), and a 5.5% increase in fT_3 versus a 1.4% decrease in the placebo group ($p=0.039$). They also experienced a 12.4% increase in heart rate compared with a 4.1% decrease in the placebo group ($p<0.01$, data not shown).

Table II. Seasonal changes in physiological and psychological status, placebo group.

	Summer (n=8)		Winter (n=20)	
	Beginning	End	Beginning	End
Physiology	Mean \pm SE	Mean \pm SE	Mean \pm SE	Mean \pm SE
BMI (kg.m ⁻²)	27.1 \pm 1.7	27.0 \pm 1.7	25.7 \pm 0.9	25.7 \pm 0.8
T _y Body temp (C)	36.9 \pm 0.3	33.6 \pm 1.2	35.8 \pm 0.6	36.5 \pm 0.5
Systolic BP (mmHg)	117.9 \pm 4.1	118.8 \pm 4.2	112.9 \pm 2.8	98.2 \pm 2.8***
Diastolic BP (mmHg)	74.3 \pm 3.1	78.5 \pm 3.3	73.2 \pm 3.1	72.9 \pm 2.9
Heart rate	71.6 \pm 3.2	65.3 \pm 4.8	68.1 \pm 2.6	65.3 \pm 1.9
Plasma lipids				
Total cholesterol (mmol/L)	5.17 \pm 0.33	5.05 \pm 0.39	4.99 \pm 0.21	4.66 \pm 0.19*
Triglycerides (mmol/L)	1.38 \pm 0.30	1.21 \pm 0.17	1.12 \pm 0.10	1.09 \pm 0.11
HDL (mmol/L)	1.39 \pm 0.15	1.46 \pm 0.13	1.47 \pm 0.10	1.43 \pm 0.09
LDL (mmol/L)	3.15 \pm 0.28	3.04 \pm 0.39	3.01 \pm 0.21	2.73 \pm 0.18*
Hormones				
Epinephrine (pmol/L)	553.6 \pm 28.4	297.0 \pm 29.5*	241.3 \pm 9.8	242.4 \pm 13.1
Norepinephrine (nmol/L)	6.02 \pm 1.53	2.86 \pm 0.51**	2.65 \pm 0.30	2.57 \pm 0.19
Cortisol (nmol/L)	604.2 \pm 44.1	438.7 \pm 44.1	458.0 \pm 35.9	502.1 \pm 38.6
fT_3 (pmol/L)	5.22 \pm 0.16	5.11 \pm 0.41	4.78 \pm 0.18	4.71 \pm 0.14
tT_3 (nmol/L)	2.12 \pm 0.13	2.06 \pm 0.22	1.81 \pm 0.10	1.84 \pm 0.10
fT_4 (pmol/L)	21.8 \pm 1.3	17.1 \pm 1.0*	17.4 \pm 1.0	19.7 \pm 1.3
tT_4 (nmol/L)	88.2 \pm 5.0	97.8 \pm 4.9	91.4 \pm 4.1	94.7 \pm 4.2
TSH (mU/L)	2.46 \pm 0.47	1.77 \pm 0.33*	2.12 \pm 0.22	2.51 \pm 0.37
TBG (mg/L)	18.6 \pm 0.7	22.4 \pm 1.6	20.2 \pm 1.2	20.4 \pm 1.5
Cognitive performance				
Accuracy (% correct)				
Complex tasks	86.8 \pm 3.8	93.1 \pm 2.1	91.4 \pm 1.5	94.7 \pm 0.9**
Efficiency				
Simple reaction time	203.0 \pm 10.5	204.2 \pm 10.1	200.2 \pm 8.8	211.9 \pm 7.1
Complex tasks	46.5 \pm 4.8	51.4 \pm 5.1	51.1 \pm 2.9	54.7 \pm 2.1*
Response time (msec)				
Simple reaction time	278.8 \pm 16.2	287.6 \pm 16.3	278.5 \pm 9.9	277.6 \pm 10.1
Complex tasks	1165.4 \pm 63.7	1262.7 \pm 96.9	1224.4 \pm 57.9	1175.4 \pm 47.0
Mood				
Global Mood Score	9.53 \pm 1.31	7.89 \pm 1.95	8.17 \pm 1.61	4.50 \pm 1.67*

* $p<0.05$, * $p<0.01$, *** $p<0.001$

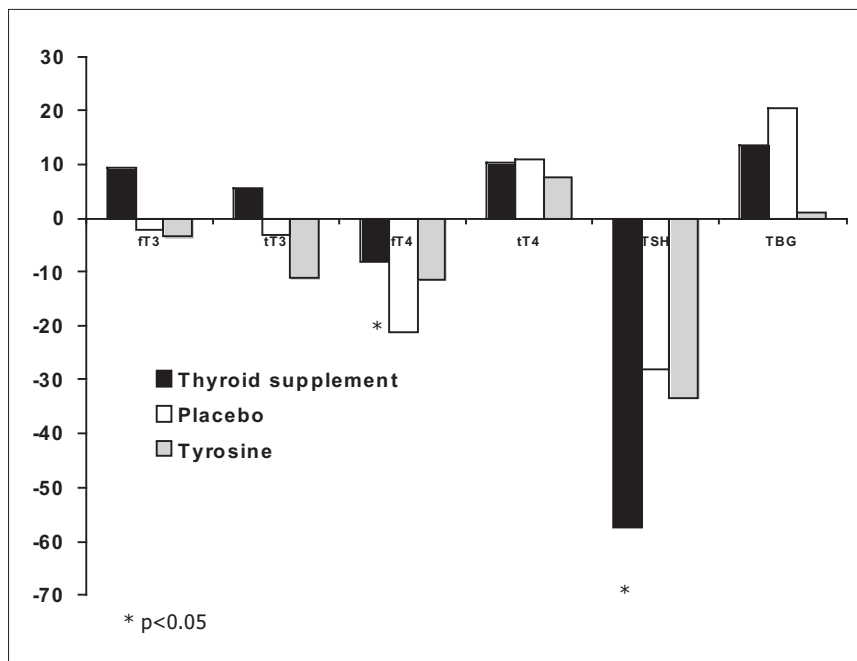


Figure 1a. Percent changes in serum thyroid hormones by treatment group, summer.

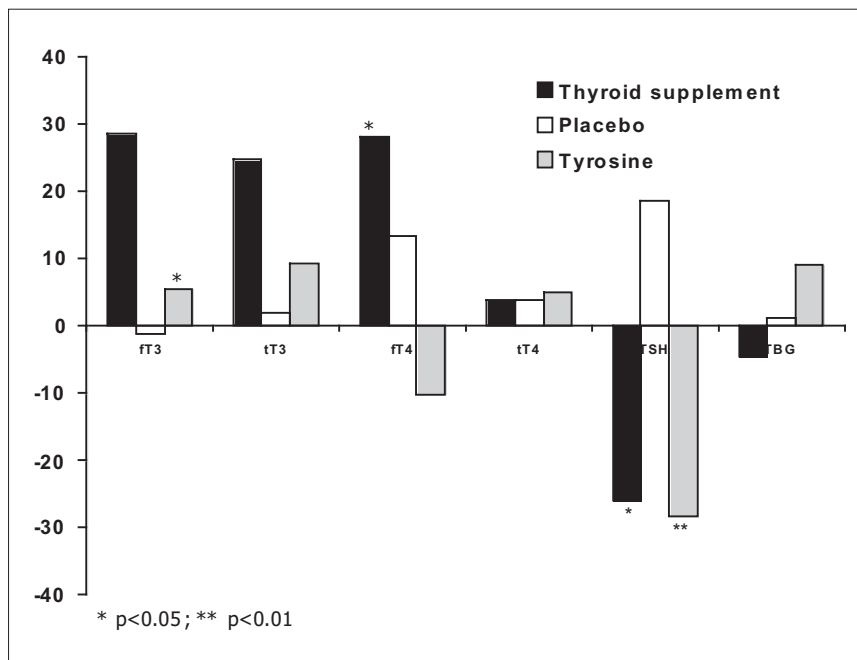


Figure 1b. Percent changes in serum thyroid hormones by treatment group, winter.

During the summer, the 18.3% decline in NE in the tyrosine group was significantly smaller than the 52.5% decline in the placebo group ($p=0.012$) (Fig. 2). During the winter, there were no significant differences in percent changes in catecholamines or cortisol between either the T_4 - T_3 group or the tyrosine group and the placebo group.

Effect of the interventions by both treatment and by time for cognitive performance and mood compared with placebo

Comparisons of changes in cognitive performance and mood by both treatment and time are presented in Figures 3a, 3b and 4. In both seasons,

efficiency in performance of complex cognitive tasks in the thyroid supplement group was significantly less than in the placebo group (summer: 0.4% increase versus 10.5% increase, $p=0.047$; winter: -0.8% decline versus 7.0% increase, $p=0.049$), respectively (Fig. 3a and Fig. 3b).

During summer, the 121.6% decline in Global Mood Score experienced by the T_4 - T_3 group was significantly larger than the 18.9% decline in the placebo group ($p<0.05$) (Fig. 4). During the winter, the 47% increase in Global Mood Score in the tyrosine group was significantly different from the 136% decrease in the placebo group ($p<0.05$).

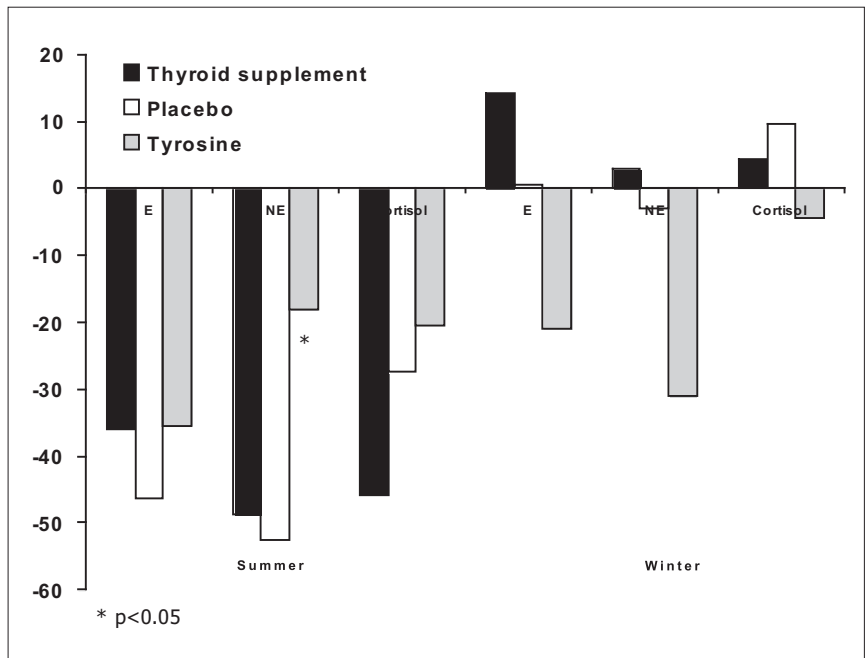


Figure 2. Percent changes in catecholamines and cortisol by treatment group, summer and winter.

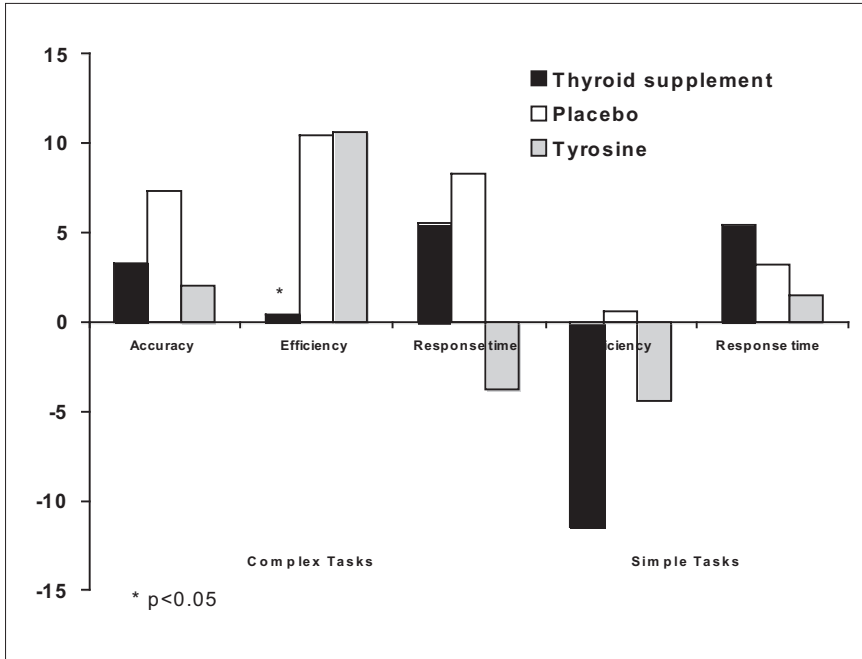


Figure 3a. Percent changes in cognitive performance and mood by treatment group, summer.

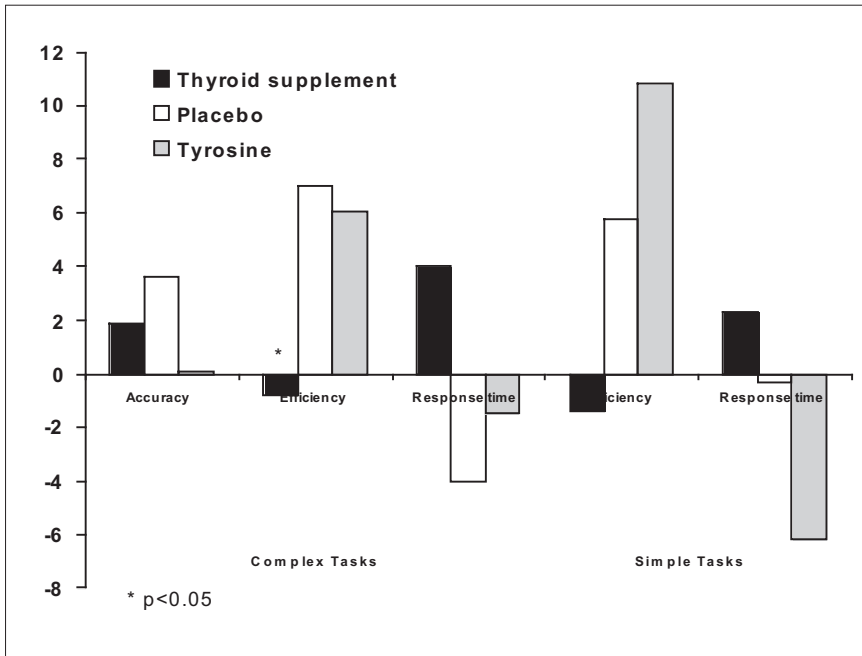


Figure 3b. Percent changes in cognitive performance and mood by treatment group, winter .

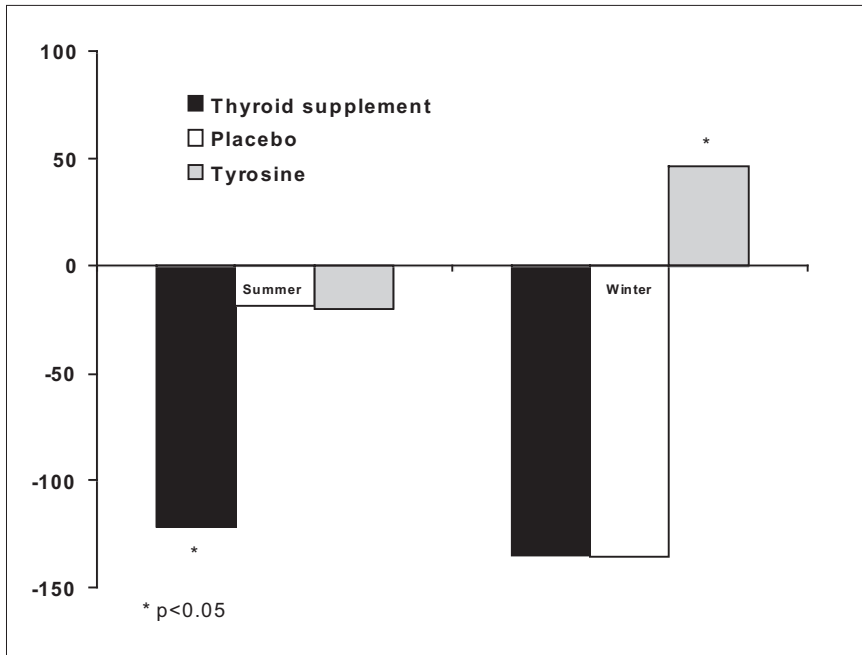


Figure 4. Percent changes in global mood score by treatment group, summer and winter.

DISCUSSION

Consistent with previous studies (1,3,6–8), the placebo group experienced small but significant declines in fT_4 and the seasonal nadir of TSH by January of the summer months, suggestive of the initial phases of the Polar T_3 Syndrome (6). The placebo group also experienced significant declines in the level of plasma catecholamines (E and NE) in the summer. This is also in agreement with previous studies in the Antarctic (35), and may indicate a pattern of cold acclimation where the initial increase in catecholamines in response to cold exposure eventually returns to baseline (36,37). Patterns of mood and cognitive performance in this study were consistent with some (38,39), documenting an

absence of significant decrements of cognitive performance and a seasonal pattern of decrements in mood (21,40,41).

The comparison to placebo with effect of treatment and season shows for the first time in our review that tyrosine intervention results in higher fT_3 and lower serum TSH in winter compared with placebo but not different that the combined T_4 - T_3 supplement. The combined T_4 - T_3 supplement also increased fT_4 in the winter compared with placebo but this was not seen with tyrosine, suggesting an alternative mechanism for the TSH reductions. Finally, plasma norepinephrine declined less with tyrosine than placebo in the summer but declined by 30% more than placebo in winter. Tyrosine compared with placebo also was associated with a significant improvement in

mood ($p < 0.05$). In summer, tyrosine was no different than placebo with respect to its effect on mood, but it was better than the T_4 - T_3 supplement which had a significantly negative effect on mood compared with placebo ($p < 0.05$).

The constellation of hormonal changes described above suggests that tyrosine may mediate some of its effects through plasma catecholamines and subsequently through T_3 production either in the thyroid or peripheral tissues. The association between catecholamines and mood has been well established (42,43). Catecholamine-mediated deiodination has been well reported and especially during cold exposure (44). Therefore, it may theoretically play a role either centrally or peripherally mediated by Type II deiodinase in this setting.

In contrast, use of thyroid supplements failed to provide any marked benefits with respect to cognitive performance or mood. During the summer season, thyroid supplement use adversely affected mood as evidenced by a significantly greater increase in negative mood (fatigue, depression, anger and anxiety) and a significantly smaller increase in complex task efficiency compared with placebo. In winter, the slight decline in complex task efficiency was significantly different from the increase in efficiency in the placebo group.

These results were in contrast with our previous research that demonstrated a significant improvement in mood and cognitive performance following daily administration of thyroxine alone given only in the winter months ($64 \text{ nmol} \cdot \text{day}^{-1}$ [$0.05 \text{ mg} \cdot \text{day}^{-1}$]) (6). The T_4 - T_3 group experienced in summer a significantly greater decrease in TSH but a signifi-

cantly smaller decrease in fT_4 compared with placebo, suggesting an intensification of the seasonal decline by the end of summer for TSH. During the winter, the T_4 - T_3 group had a significantly greater decrease in TSH and a significantly greater increase in fT_4 compared with placebo. There appears to be a seasonally dependent effect of reductions in TSH upon improved mood. This seasonal dependence may represent the differences in luminosity which may affect serum TSH in both its circadian and circannual patterns (4). An alternative explanation, suggested by the findings of Sou tre and colleagues (45), is that the desynchronization of the TSH circadian rhythm is a consequence rather than a cause of depressed mood. However, in contrast to the participants in that study, none of the participants in this study met clinical criteria for a depressive disorder. In summary, it appears that worsening the decline of TSH by whatever mechanism in summer worsens mood while decreasing TSH in winter with tyrosine may improve mood.

Differences in the results between this study and our previous study may be attributed to differences in population (military personnel versus civilians), medication (thyroxine only versus thyroxine and triiodothyronine) and differences in protocol (use of thyroid supplements in winter only with monthly assessments versus use of thyroid supplements in both summer and winter with assessments only at the beginning and end of each season). Several studies have recently reported that compared with levothyroxine alone, use of a combination of levothyroxine plus liothyronine produces no beneficial changes in cognitive performance in hypo-

thyroid subjects (46–48). Other studies have reported moderate or no effects with T_4 supplementation (49,50).

Given the significantly greater decline in TSH in the T_4 - T_3 supplement group and the significantly greater increase in fT_4 compared with placebo combined with the substantial associations between increased TSH and mood in the summer, it is possible that administration of the T_4 - T_3 supplement induced a state of very mild central thyroxine excess in summer and winter. Possibly, the addition of T_3 combined with the accelerated conversion of T_4 to T_3 reported in this group (7) resulted in excess T_3 in the central nervous system which in turn resulted in worsened mood than with simple reductions in TSH and elevations in T_3 by tyrosine alone. This would be consistent with previous studies documenting increased negative mood and impaired cognitive performance in individuals with subclinical hyperthyroidism (51) and an association between levels of serum total T_4 and mental status (52). Although the tyrosine users also experienced a significant decline in TSH compared with placebo during the winter, the percent decline was not as great (28% versus 53%).

Despite the evidence supporting these possibilities, caution should be exercised in interpretation and explanation of these results for a number of reasons, including the long 3 months in summer and 5 months in winter: interval between pre- and post-intervention measures of dependent and independent variables in the longitudinal analyses, the multiple comparisons conducted in the concurrent and longitudinal analyses and the small number of subjects in the individual placebo groups. Thus, further research is

required to substantiate the potential benefits of tyrosine administration and the potential risks associated with combination levothyroxine/liothyronine administration.

Based on these findings, tyrosine appears to be associated with improved cognitive performance and mood. However, the extent of improvement is not significantly greater than that observed in the placebo/control groups except in winter where the elevation in negative mood indicators is much less with tyrosine. We also cannot recommend the use of a combination levothyroxine/liothyronine supplement to prevent such decrements. Use of a small amount of levothyroxine alone as previously reported (6) remains the best solution to prevention of decrements of mood and cognitive performance in the extreme environments during the winter.

Acknowledgements

This study was supported by the U.S. National Science Foundation, grant number OPP-0090343.

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