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Strenuous, Fatiguing Exercise: Relationship of Cortisol to Circulating Thyroid Hormones

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The purposes of this study were to determine how strenuous, fatiguing running exercise affects: 1) selective thyroid hormones, and 2) the relationship of glucocorticoid responses to such exercise with thyroid hormones.

Materials and Methods: Well-trained subjects (n=12) performed a treadmill run at individual ventilatory threshold (74±8% of maximal aerobic capacity) until volitional fatigue (68.3±12.3 min). Blood samples were taken before exercise as a resting baseline (B0), at fatigue (FG), 90-minutes into recovery (90mR), and 24-hours into recovery (24hR). Blood was analyzed for free T_3 (fT_3), free T4 (fT_4), thyroid-stimulating hormone (TSH), and cortisol.

Results: Significant increases in fT_3 and TSH concentrations between B0 and FG (fT_3= 1.70 pg/mL vs. 2.08 pg/mL; TSH=1.69 µIU/mL vs. 2.43 µIU/mL, $p<0.01$) were observed, but by 24hR, significant decreases from B0 were present (fT_3 and TSH=1.48 pg/mL and 1.20 µIU/ml, respectively; $p<0.05$). FG fT_4 demonstrated a non-significant increase from B0 (FG fT_4=1.84 ng/dL) but by 24hR fT_4 was significantly lower than FG (24hR fT_4=1.67 ng/dL, $p<0.01$). FG cortisol levels increased significantly from B0 (476.1 to 843.9 nmol/L, $p<0.01$) and remained elevated at 90mR (892.2 nmol/L) but returned to baseline by 24hR. Spearman correlation analysis yielded a significant negative correlation between FG cortisol and 24hR TSH ($r= -0.65$, $p<0.05$). A strong trend was also noted between FG cortisol and 24hR ft_3 ($r = -0.55$, $p<0.07$).

Conclusion: These findings suggest that exhaustive exercise decreases the level of selective thyroid hormones by 24 hours into recovery, and that cortisol levels after fatiguing exercise are negatively related to circulating TSH at this point into recovery.

Key Words: Stress, Glucocorticoids, Fatigue, Thyroid function, Exercise

Introduction

The thyroid gland is an integral part of the human endocrine system, essential to maintenance of physiological homeostasis. The principle hormones released by the thyroid gland are thyroxine (T_4), and 3,5,3'-triiodothyronine (T_3) which circulate in free (f) or bound forms [which collectively are referred to as the total (t) hormonal amount]. The production of T_4 and T_3 are directly controlled by thyroid stimulating hormone (TSH) released from the anterior pituitary; while,

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conversion of T_4 into T_3 occurs at some peripheral tissues.[1]

Research findings concerning the effect of an acute exercise bout upon the circulating levels of thyroid hormones appear somewhat ambiguous. Several research groups have reported that exercise results in significant reductions in T_3, T_4, and TSH concentrations.[2,3] Other investigators have reported exercise to exhibit no influence whatsoever on thyroid hormone concentrations,[4,5] and still others have reported increased hormonal levels in response to exercise.[6] The lack of continuity within these findings may perhaps be attributed to differences in methodology, procedures, and exercise protocols, and/or subject population parameters amongst the research studies. This ambiguity within the research findings, nevertheless, suggests that further investigations are necessary on this topic in an attempt to reach consensus.

When the magnitude of the exercise dosage (relative exercise intensity times exercise duration) is great enough, it does appear that certain circulating thyroid hormones are reduced. Previous published data from our,[7] and other laboratories supports this contention.[2,3,8,9] It is presently unclear how such reductions in the thyroid gland function occur (e.g. hemodilution of the blood, increases in metabolic clearance rate, regulatory feedback-loop alterations). One potential mechanism influencing this change is the relationship exercise glucocorticoid response has upon circulating thyroid hormones. That is, glucocorticoids such as cortisol, are known potent inhibitors of thyroid function at several points within the hypothalamic-pituitary-thyroid regulatory axis.[1,10] It does not appear however that such exercise glucocorticoid effects have been examined thoroughly in relation to thyroid function or how such responses might interrelate.[11] Therefore the present study was conducted with a twofold purpose: 1) to examine the effect of intensive, strenuous exercise on circulating thyroid hormones, and 2) to examine the relationship exercise glucocorticoid (i.e., cortisol) response has upon circulating thyroid hormones.

Materials and Methods

Endurance trained male athletes (n=12) were recruited to participate in this study. All subjects were in excellent physical condition with no medical abnormalities or illnesses related to the endocrine, musculoskeletal, or cardiopulmonary systems. They had been participating in endurance-type training for a minimum of 5 days a week for the last 2 years. The subjects were volunteers who signed a "Consent to Act as a Human Subject" form, as approved for use by the Academic Affairs Institutional Review Board of the University of North Carolina, prior to participation. Their physical characteristics were as follows: age 22±2 years, body height 186±5 cm, body mass 73.5±7.8 kg (mean±SD).

The subjects reported to our laboratory for three separate sessions. At the first session they completed a medical history form, an exercise training log, and underwent a medical-physical examination to insure their ability to participate in this study. After body height (cm) and mass (kg) measurements were taken, subjects underwent a modified Åstrand treadmill maximal exercise test to determine their maximal oxygen uptake (VO_2 max).[12] Respiratory gases were collected continuously throughout the exercise test using a TrueMax 2400 open-circuit spirometry system (Parvo Medics Inc., UT). The following criteria were used to determine subjects' attainment of VO_2 max:oxygen uptake did not increase by more than 0.15 L/min despite an increase in workload, heart rate failed to in-

crease despite an increase in workload, and subjects' rating of perceived exertion (RPE) was >17.[13,14] The mean (±SD) VO_2 max obtained by the subjects was 63.4±6.1 mL/kg/min. From the respiratory gas data collected during the maximal exercise test, each subject's ventilatory threshold (VT) was calculated using the criteria of Wasserman.[15]

Approximately one week after the VO_2 maxtesting the subjects reported for their second session involving an exhaustive exercise run. For this session the subjects arrived at our laboratory between 1300 and 1500 hours in a 3-hour fasting state having abstained from strenuous activity, alcohol, and sexual activity for the 24-hours and caffeine for the 12 hours prior to this visit. For the 72 hours prior to the exhaustive exercise the subjects were directed to eat a diet high in carbohydrate (~60% daily caloric intake), with moderate protein (~15%) and fat (~25%) content. Once at the laboratory, subjects' height, body mass and total body water by bioelectrical impedance were assessed.[16,17] Next an indwelling 20-gauge catheter was placed into the antecubitalvein of their dominant arm, and then they began a 30-minute rest in the supine position. At the end of the 30-minute rest, a baseline blood sample was taken (B0). A Polar® heart rate monitor (Polar Electro Oy, Finland) was then fitted around their chest. The subjects were then allowed five minutes to actively warm-up (cycle exercise) and stretch. At the end of the five minutes, subjects began a prolonged exercise run on the treadmill until they reached volitional fatigue. The treadmill running speed was set to correspond to approximately 100% of their VT (±3%). These exercise parameters were utilized to mimic what an athlete might experience in a prolonged running sports competition or a strenuous training session.

During the run to volitional fatigue, physiological data were collected (VO_2 heart rate [HR], rating of perceived exertion [RPE], percentage of VT achieved [%VT]) at 5, 30, 60, and 75 minutes into the run and at volitional fatigue. When subjects indicated volitional fatigue, investigators provided strong verbal encouragement. This was done to motivate the subjects and ensure that they did not stop exercise until truly fatigued. At the point of fatigue the running was stopped, and a second blood sample was immediately taken (FG). Subjects were then allowed a five minute active cool-down before resting in a supine position through a 90-minute recovery period, after which another recovery blood sample (90mR) was taken. This sampling protocol was chosen based upon hormonal half-life values.[1,11]

The third and final session at the laboratory occurred 24 hours later. At this session, subjects' body mass and total body water were assessed as previously noted. They then rested in a supine position for 30 minutes, after which a final blood sample was taken (24hR) using veni-puncture procedures (corresponding to the previous B0 sampling time). During this latter 24-hour period the subjects were to maintain their diet (noted above), not perform any additional exercise training, avoid sexual activity, and consume appropriate amounts of water.

All blood samples were drawn into EDTA-treated vacutainer tubes and placed on ice until processing. Whole blood aliquot samples were analyzed for hematocrit (Hct) and hemoglobin (Hb). The remaining sample aliquots were centrifuged at 4°C for 15 minutes at 3000 × g (Centra-8R IEC, MA). Separated plasma was stored frozen at –80°C until hormonal analysis. Triplicate measurements of Hct and Hb were used to estimate plasma volume shifts (ΔPV).[18] Hormone levels of

cortisol, fT_4, fT_3, and TSH were determined using standard single antibody solid phase radioimmunoassay (RIA) kits specific for each hormone (DSLabs Inc., TX; DPC Inc., CA). All RIA assay between and within assay coefficients of variation were less than 10%.

Repeated measures analysis of variance (ANOVA) was used to detect significant changes within hormonal measures over time. When necessary, Fisher LSD was used to locate the significance among means. Finally, Spearman correlation analysis was used to determine relationship among hormonal measurements. Significance for all statistical analysis was set at $p<0.05$.

Results

The mean treadmill running time to volitional fatigue was 68.3±12.3 minutes at an intensity that represented 74±8% of the subjects' individual VO_2 max. This corresponded to a mean running velocity of 14.3±1.8 km/hr. By the end of the run, the subjects' mean HR was 190±10 b/min (96±5% of maximal HR) and the mean RPE was 19±1 (20 point Borg scale). These findings collectively suggest that the subjects reached a point of near maximal fatigue by the end of their exercise run.

Table 1 presents the hormonal results from the exhaustive exercise run (Fig. 1 depicts these data graphically). The resting baseline (B0) hormonal values were all within clinical norms,[19] and were representative for these subjects (i.e., the subjects had participated in previous research involving endocrine profiling). All hormones, with the exception of fT_4, were significantly elevated from B0 by the end of the exercise run (FG time point). At 90mR of recovery, only cortisol was still significantly elevated from B0, while the other hormones had returned to resting levels. Finally, at 24hR of recovery, fT_3 and TSH were reduced significantly below B0 baseline levels and the fT_4 change approached significant reductions ($p>0.05<0.10$). The magnitude of all significant hormonal changes noted was greater than the degree of calculated ΔPV reduction observed.

The results of the correlation analysis revealed that the FG cortisol response had a significant negative correlation with the 24hR TSH response ($r=-0.65$, $p=0.022$). A similar negative correlation was seen between FG cortisol and FG TSH ($r=-0.55$, $p=0.064$) as well as FG cortisol and 90mR TSH ($r=-0.56$, $p=0.058$). Each of these latter relationships nearly reached statistical significance. Additionally, FG cortisol and 24hR fT_3 had a negative correlation that also approached significance ($r=-0.55$, $p=0.064$).

Correlations were also examined between the running time to fatigue and the TSH responses to determine whether changes were truly related to cortisol responses, and not just the duration of the exercise. This analysis revealed that TSH responses at FG, 90mR, and 24hR were not related to the duration of the exercise ($r< -0.13$, $p>0.664$).

At the third laboratory session (24 hours of recovery) neither the subject's body mass or total body water content was significantly different from the second session B0 measurements. This suggests the subjects had consumed adequate amounts of food and water during the recovery to allow themselves not to be in an energy deficient or dehydrated condition at the 24hR blood sampling.

Table 1. The hormonal responses to the strenuous, fatiguing exercise run. The values are means (SEM)

Hormones	Blood Sampling Times			
	B0	FG	90mR	24hR
fT_4 (ng/dL)	1.73 (0.08)	1.84 (0.06)	1.78 (0.06)	1.67 (0.07)
fT_3 (pg/mL)	1.70 (0.08)	2.08 (0.08)*	1.69 (0.11)	1.48 (0.07)*
TSH (μIU/mL)	1.69 (0.17)	2.43 (0.26)*	1.80 (0.18)	1.20 (0.16)*
Cortisol (nmol/L)	476.1 (47.8)	844.0 (31.0)*	892.2 (30.7)*	409.3 (21.9)

B0: baseline; FG: fatigue; 90mR: 90 minutes into recovery; 24hR: 24 hours into recovery
* $p<0.05$ compared with B0

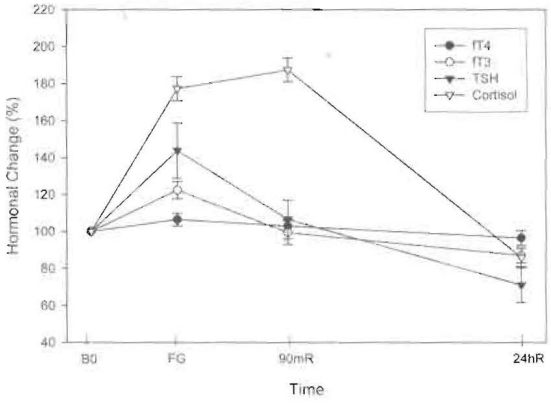

Fig. 1. The hormonal responses to the strenuous, fatiguing exercise run expressed as a percentage of the resting, baseline (B0) values. The values are ± the SEM expressed as a percentage.

Discussion

The purpose of the present study was to examine the effect of intensive, strenuous exercise on circulating thyroid hormones, and determine the effect of exercise induced glucocorticoid (i.e. cortisol) response has upon circulating thyroid hormones. The data suggest that cortisol has a negative relationship with thyroid function, although temporally there is delay in the association. The key specific finding within the data was the negative correlations between cortisol and TSH during the recovery from exercise. To our knowledge, the demonstration of this relationship in the context of an exercise research study is a novel finding. Similar findings and relationships, however, have been reported in previous non-exercise studies.[20] In particular, clinical studies, looking at Cushing's syndrome or other medical conditions involving hypercortisolemic states typically report primary hypothyroidism involving suppressed TSH levels.[1,20] The mechanism of how cortisol acts to suppress thyroid function has not been completely elucidated, but, the hypothalamic-pituitary-thyroidal regulatory axis is susceptible to disruption at several points by cortisol.[1,20]

The present findings suggest that the cortisol association with TSH may manifest many hours after exercise has ended. This delay phenomenon is not entirely unique, as persistent reductions in TSH following intensive exercise have been previously reported,[2,3] although, as noted, such reductions in TSH during the recovery from exercise have not been statistically linked to exercise cortisol responses as we have shown here.

The finding of significant reductions in fT_3 at 24 hours following the exercise also is in agreement with previously published research,[2,3] although, not all investigators have reported such findings following prolonged strenuous exercise.[4-6] This lack of agreement among studies may be due to blood sampling protocols, as most exercise studies have not sampled as long into the recovery period as we did. There was no significant correlation between the changes in TSH and fT_3 (or fT_4). This was expected as circulating T_3 and T_4 levels are influenced not only by anterior pituitary (i.e. TSH) control but also peripheral factors (i.e. T_4 peripheral conversion to T_3). Interestingly, this peripheral process is also influenced by glucocorticoids as they inhibit the 5'-deiodinase enzyme, which facilitates the peripheral conversion of T_4 to T_3. The inhibition of this enzyme allows for another enzyme (5-deiodinase) to be more active peripherally. The 5-deiodinase enzyme converts T_4 to the less biologically active reverse-T_3 thyroid hormone.[1] We did not systematically assess the peripheral process in the present study, although, we did examine reverse-T_3 in one representative subject and found levels of this less biologically active thyroid hormone to be substantially elevated at 24 hours of recovery.[1] This suggests that perhaps such peripheral events were taking place and thus possibly accounting in some part for the lack of significant correlations between TSH and fT_3 or fT_4.

To conclude, the findings suggest that the exhausting exercise results: (a) in significant reductions in key thyroid hormones by 24 hours after the exhaustive exercise, and (b) the reductions in selective thyroid hormones are negatively related to the elevations in cortisol precipitated by the exhausting exercise, however, this relation is temporally delayed. These findings would suggest that the thyroid function of athletic individuals may need longer than 24 hours to completely recover from the stress of demanding, strenuous exercise events. For clinicians who examine athletes, it is important to recognize that blood specimens collected 24 hours after strenuous fatiguing exercise may not have representative thyroid hormone concentrations.

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