



Thyroid hormones and the interrelationship of cortisol and prolactin: influence of prolonged, exhaustive exercise

Hormony tarczycy a wzajemne relacje między stężeniem kortyzolu i prolaktyny: wpływ długotrwałego, wyczerpującego wysiłku fizycznego

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Abstract

Background: This study examined how prolonged, exhaustive exercise affects: (1) thyroid hormones, and (2) the interrelationship of cortisol and prolactin responses to such exercise on thyroid hormones.

Material and methods: Male subjects performed a treadmill run at their individual ventilatory threshold until exhaustion. Blood samples were taken before exercise at rest, baseline (BL), at exhaustion (EXH), 30-60-90-minutes into recovery (30 mR, 60 mR, 90 mR), and 24-hours into recovery from exercise (24 hR). Blood was analyzed for free T₃ (fT₃), free T₄ (fT₄), thyroid-stimulating hormone (TSH), cortisol and prolactin.

Results: ANOVA analysis revealed that at EXH all hormones were increased ($p < 0.01$) from BL levels. At 30 mR and 60 mR the thyroid hormones had decreased and returned to BL levels; however, cortisol and prolactin remained significantly increased ($p < 0.05$). At 90 mR all hormones were not different from BL levels. By 24 hR, cortisol, fT₃ and TSH were decreased from BL ($p < 0.05$). Correlations revealed EXH cortisol responses were related to the 24 hR TSH responses ($r_s = -0.69$, $p < 0.01$). In addition, EXH cortisol and 24 hR fT₃ responses were related ($r_s = -0.51$, $p < 0.02$). Furthermore, the EXH prolactin and TSH responses were related ($r_s = +0.56$, $p < 0.01$), and the 30 mR prolactin responses were related to the EXH TSH responses ($r_s = +0.43$, $p < 0.05$).

Conclusions: Exhaustive exercise; (1) decreases select thyroid hormones by 24 hours into recovery, (2) cortisol responses are inversely related to these thyroid reductions, and (3) prolactin responses (increases) are directly related to TSH changes.

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Key words: thyroid hormones, prolactin, cortisol, exercise, stress, glucocorticoids, fatigue

Streszczenie

Wstęp: Celem niniejszego badania było określenie wpływu długotrwałego, wyczerpującego wysiłku fizycznego na: (1) stężenia wybranych hormonów tarczycy i (2) współzależności między wydzielaniem kortyzolu i prolaktyny w odpowiedzi na ćwiczenia a stężeniami hormonów tarczycy.

Materiał i metody: Zdrowe, wytrenowane osoby ($n = 22$) ćwiczyły na bieżni pochyłej ze zwykłą dla siebie intensywnością określona na podstawie progu wentylacyjnego do momentu, kiedy poczuły zmęczenie ($84,8 \pm 3,8$ min). Próbkę krwi pobrano przed rozpoczęciem ćwiczeń, kiedy badane osoby były wypoczęte (BL, *baseline*), a następnie w momencie, gdy nastąpiło wyczerpanie po wysiłku (EXH, *exhaustion*), po 30-, 60-, i 90-minutowym odpoczynku i 24 godziny po zakończeniu ćwiczeń (24 hR). Oznaczono stężenia wolnej T₃ (fT₃), wolnej T₄ (fT₄), hormonu tyreotropowego (TSH, *thyroid stimulating hormone*), prolaktyny i kortyzolu.

Wyniki: W analizie ANOVA dla powtarzalnych pomiarów wykazano, że stężenia wszystkich hormonów były podwyższone w fazie EXH ($p < 0,01$) w stosunku do wartości wyjściowych (BL, *baseline*). Po 30- i 60-minutowym odpoczynku stężenia hormonów tarczycy zmniejszyły się do wartości wyjściowych ($p > 0,05$); jednak stężenia kortyzolu i prolaktyny nadal były wyższe niż przed wysiłkiem (BL) ($p < 0,05$). Po upływie 90 minut stężenia żadnego z hormonów nie różniły się istotnie ($p > 0,05$) od poziomu BL. Po 24 godzinach odpoczynku (24 hR) stężenia kortyzolu, fT₃ i TSH były niższe niż wartości BL ($p < 0,05$). Ocena korelacji wykazała zależność między stężeniem kortyzolu w fazie zmęczenia po wysiłku a stężeniem TSH 24 po wysiłku ($r_s = -0,69$, $p < 0,01$). Stężenie kortyzolu w fazie EXH i stężenie fT₃ po 24 godzinach były związane w sposób statystycznie istotny ($r_s = -0,51$, $p < 0,02$). Ponadto stwierdzono wzajemną zależność między stężeniem prolaktyny i TSH w fazie EXH ($r_s = 0,56$, $p < 0,01$), a stężenie prolaktyny po 30 minutach odpoczynku było związane ze stężeniem TSH w fazie EXH ($r_s = 0,43$, $p < 0,05$).

Wnioski: Wyniki uzyskane w niniejszym badaniu sugerują, że po wyczerpujących ćwiczeniach (1) następuje zmniejszenie wydzielania wybranych hormonów tarczycy po 24 godzinach wypoczynku, a zmiany te są zależne od stężenia kortyzolu, (2) zwiększenie stężenia prolaktyny spowodowane wysiłkiem jest proporcjonalne do wzrostu wydzielania TSH. (Endokrynol Pol 2009; 60 (4): 252-257)

Słowa kluczowe: hormony tarczycy, prolaktyna, kortyzol, wysiłek fizyczny, stres, glikokortykoidy, zmęczenie



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Introduction

The principle hormones released by the thyroid gland are thyroxine (T_4) and 3,5,3'-triiodothyronine (T_3) which circulate in free (f) and bound forms — collectively these are referred to as the total hormone amount. The glandular production of T_4 and T_3 is controlled by thyroid stimulating hormone (TSH) released from the anterior pituitary; although, conversion of T_4 into T_3 can also occur at some peripheral tissues [1]. The release of TSH is dictated by the discharge of thyrotropin-releasing hormone (TRH) from the hypothalamus which is stimulated by hypoglycaemia, cold exposure, hypoxemia and pregnancy as well as low circulating T_4 or T_3 levels [1].

Even though thyroid hormones are critical to many physiologic systems, the research findings concerning the effect of physical exercise upon these hormones is however still an issue of some uncertainty. Several research studies report that exercise induces significant reductions in T_3 , T_4 , and TSH concentrations [3], while other studies report that exercise has no influence whatsoever on any of these hormone [1, 3]. However, other studies report increased thyroid hormone levels in response to exercise [3]. The lack of uniformity within research findings may be attributed to differences in methodology, experimental procedures, and/or differing subject population parameters within the studies. This ambiguity within the research findings suggests that further investigations are warranted on this topic in an attempt to provide clarity.

As noted above, some previously published data supports the theory exercise causes reductions in certain circulating thyroid hormones [3]. It is currently unclear how such reductions in the thyroid gland hormones occur (*e.g.* hemodilution of blood concentrations, increases in metabolic clearance rate, regulatory feedback-loop adjustments). One potential mechanism influencing such changes is the relationship between exercise-related glucocorticoid response and circulating thyroid hormones. The principle glucocorticoid in humans, cortisol, is known as a potent inhibitor of thyroid function within the hypothalamic-pituitary-thyroid regulatory axis [1, 3]. However, it does not appear that exercise-related glucocorticoid effects have been examined thoroughly in relation to thyroid function, or to how such hormonal responses might interrelate [3]. Cortisol is considered a stress-marker hormone by many endocrinologists. Another such stress hormone is prolactin, which has also been linked to water balance, reproduction and immune function physiologically [4, 5]. With respect to this last role, recent evidence promotes prolactin as playing a key role in activation of the immune system following exercise, since the prolactin receptor is widely expressed by immune cells and some types of

lymphocytes synthesize-secrete prolactin (*i.e.*, these cells are active following exercise) [3–6]. Thus, prolactin can potentially act as an autocrine, paracrine and an endocrine modulator of immune activity as part of the recovery process from physical exercise [6–8]. Copious research also indicates that exercise (*e.g.* sports training and competitions) results in a significant and substantial increases in the circulating level of prolactin [3]. Interestingly, a powerful stimulant to the release of prolactin is the key thyroidal hormone TRH [1]; however, it appears researchers have not attempted to examine the inter-relationship between thyroid hormones and prolactin responses to exercise.

Accordingly, the present study was conducted with a twofold purpose: (1) to examine the effect of prolonged exhaustive exercise on circulating thyroid hormones, and (2) to examine the inter-relationship between thyroid hormones and the cortisol and prolactin responses to prolonged exercise.

Material and methods

Male endurance-trained athletes ($n = 22$) were recruited as research subjects. All subjects were in excellent physical health with no medical abnormalities or illnesses related to the endocrine, musculoskeletal, or cardio-respiratory systems. Each subject had been participating in endurance activity training for a minimum of 5 days a week for the last 2 years. The subjects volunteered to participate and signed a "Consent to Act as a Human Subject" form, as approved for use by the Institutional Review Board of the University of North Carolina. The physical characteristics of the subjects appear in Table I.

The subjects reported to our laboratory for three separate experimental testing sessions. At the first session the subjects completed a medical history form, an exercise training log, and underwent a medical-physical examination to insure their ability to participate safely in the study. After body mass (kg) and height (cm) were measured, the subjects underwent a modified Åstrand treadmill maximal exercise test to determine maximal oxygen uptake (VO_{2max}) [2, 9]. Respiratory gases were collected continuously throughout the maximal exercise test using a TrueMax 2400 open-circuit spirometry system (Parvo Medics Inc., UT, USA). The following criteria were used to determine each subject's attainment of VO_{2max} response: individual oxygen uptake (VO_2) did not increase by more than 0.15 L/min despite an increase in workload, heart rate failed to increase despite an increase in workload, and the subjects' rating of perceived exertion (RPE; Borg scale) was ≥ 18 [9]. The respiratory gas data collected during the maximal exercise test was used to determine each subject's ventilatory threshold (VT; see Table I) based upon earlier published criteria [2, 9].

Table I. Descriptive characteristics of the endurance-trained male research subjects ($n = 22$)**Tabela I.** Opisowa charakterystyka badanej grupy złożonej z wytrenowanych mężczyzn ($n = 22$)

Measure	Mean	SD
Age (yr)	24.6	3.8
Mass [kg]	74.1	8.0
Height [cm]	177.8	7.0
Percentage Body Fat (%)	8.8	3.3
Years in Training (yr)	8.3	5.6
VO _{2max} [ml/kg/min]	62.1	5.2
Ventilatory Threshold [% VO _{2max}]	73.4	7.5

SD — standard deviation

Approximately one week after VO_{2max} testing, the subjects reported for their second experimental session which involved a prolonged treadmill run to exhaustion. For this exercise session the subjects arrived at the laboratory between 13:00 and 15:00 in a 3-hour fasted state and having completely abstained from physical activity, alcohol, caffeine, and sexual activity for the 24 hours prior to the session. For the 72 hours prior to the prolonged exhaustive treadmill run the subjects were directed to eat a diet high in carbohydrate (~ 60% of daily caloric intake), with moderate protein (~ 15%) and fat (~ 25%) content. At this second experimental session prior to exercising, each subjects' body height, mass and total body water (by bioelectrical impedance [Valhalla Inc., CA, USA]) were assessed [9]. Next, an indwelling 20-gauge catheter was placed into an antecubital vein of each subject's dominant arm. This was followed by a 30-minute supine rest. At the end of the 30-minute rest, a baseline blood sample was taken (BL). A heart rate monitor (Polar Electro Oy, Finland) was then fitted around their chest to assess heart rate. The subjects next then performed 5 minutes of active warm-up exercise (cycling) and stretching calisthenics. At the end of the 5 minutes, the subjects began their prolonged run on the treadmill until they reached exhaustion. The treadmill running speed was set to correspond to approximately 100% of their individual VT ($\pm 3\%$) and remained fixed throughout the exercise session [2]. These exercise parameters were utilized in an attempt to mimic what the subjects might experience in a strenuous, prolonged sporting competition.

During the prolonged treadmill run, select physiological variables were assessed (oxygen uptake [VO₂], heart rate [HR], and RPE) at 5, 30, 60, and 75-minutes into the run and at the point of volitional fatigue, *i.e.* exhaustion. When the subjects indicated they were at the point of fatigue and wished to stop running, inve-

stigators provided strong verbal encouragement to motivate and encourage them not to stop exercising until truly exhausted. At the point when the treadmill run finally did end (*i.e.*, exhaustion), a second blood sample was immediately taken (EXH). The subjects were then allowed a five-minute active cool-down before beginning a one-and-a-half-hour supine rest — recovery period, during which blood samples were obtained at 30 minutes (30 mR), 60 minutes (60 mR) and 90 minutes (90 mR) of recovery from the treadmill run.

A third and final experimental session at the laboratory occurred ~24 hours later; *i.e.*, after the treadmill run. At this session, the subjects' body mass and total body water was assessed again as previously noted. The subjects then had a 30-minute supine rest, after which a final blood sample was taken (exactly 24 hours after the BL sampling [24 hR]) using veni-puncture procedures. During this 24-hour period the subjects were instructed to maintain their normal diet regime, not perform any physical activity other than normal ambulation, avoid sexual activity, and consume appropriate amounts of water.

All blood samples were collected into EDTA-treated Vacutainer® tubes (Becton-Dickinson Co., NJ, USA) and placed immediately on ice. Whole blood specimens were analyzed for haematocrit (Hct; micro-capillary technique) and haemoglobin (Hb; cyanmethoglobin reaction-colorimetric). The remaining blood was centrifuged at 4°C for 15 minutes at 3000 *g* (Centra-8R IEC, MA, USA). Separated plasma was stored frozen at -80°C until later hormonal analysis. Triplicate measurements of Hct and Hb were used to estimate plasma volume shifts [2]. Hormone levels of cortisol, prolactin, fT₄, fT₃, and TSH were determined in the plasma (duplicate analysis) using standard single-antibody solid-phase radioimmunoassay (RIA) kits specific for each hormone (DSLabs Inc., TX, USA; DPC Inc., CA, USA). For all RIA assays the between and within assay coefficients of variation were less than 10%.

Repeated measures analysis of variance (ANOVA) were used to statistically detect significant changes within hormonal measures over time. Where appropriate following ANOVA analysis, Fisher LSD post-hoc procedures were used to locate specific mean differences. Finally, Spearman (r_s) correlation analysis was used to determine the relationship between hormonal measurements. The significance for all statistical analysis was set at $p \leq 0.05$.

Results

The treadmill running time to exhaustion was 84.8 ± 3.8 minutes (Mean \pm SEM) at an intensity that represented between 71.5% and 78.5% of each subject's

Table II. Exercise variable responses during the prolonged treadmill run (mean \pm SEM)Tabela II. Parametry dotyczące reakcji na wysiłek fizyczny podczas długotrwałego biegu na bieżni pochylej (średnia \pm błąd standardowy średniej)

Measure	5 min	30 min	60 min	75 min	Exhaustion
VO ₂ [l/min]	3.29 \pm 0.08	3.44 \pm 0.08	3.43 \pm 0.08	3.51 \pm 0.08	3.61 \pm 0.07
HR [bpm]	158 \pm 3	171 \pm 2	178 \pm 2	180 \pm 2	183 \pm 2
RPE	11 \pm 1	13 \pm 1	15 \pm 1	16 \pm 1	19 \pm 1
VT (%)	99 \pm 2	103 \pm 1	103 \pm 2	105 \pm 2	109 \pm 2

Table III. Hormonal responses to prolonged exercise treadmill run. The values are means (\pm SEM). The *denotes that a values is significantly different from the representative baseline measurement. Normal resting, basal ranges for these hormones are reported below the table (10)Tabela III. Zmiany stężeń hormonów spowodowane długotrwałym biegiem na bieżni pochylej. Dane przedstawiono jako średnie (\pm błąd standardowy średniej). Symbol * oznacza, że dana wartość różni się istotnie od odpowiedniej wartości wyjściowej. Prawidłowe stężenia hormonów w stanie spoczynku zamieszczono pod tabelą [10]

Hormone	Baseline	Exhaustion	30 mR	60 Mr	90 mR	24 hR
Cortisol [nmol/L]	316 \pm 24	666 \pm 30*	725 \pm 25*	646 \pm 32*	410 \pm 19	201 \pm 10*
Prolactin [μ g/L]	6.0 \pm 1.0	28.3 \pm 5.3*	22.5 \pm 4.3*	13.9 \pm 2.3*	9.4 \pm 2.1	5.1 \pm 0.8
TSH [μ IU/MI]	1.88 \pm 0.15	2.69 \pm 0.20*	2.22 \pm 0.16	1.91 \pm 0.15	1.98 \pm 0.17	1.36 \pm 0.12*
fT ₄ [ng/dL]	1.8 \pm 0.06	1.90 \pm 0.08*	1.87 \pm 0.08	1.85 \pm 0.07	1.84 \pm 0.06	1.72 \pm 0.07
fT ₃ [pg/mL]	1.78 \pm 0.05	2.16 \pm 0.06*	2.10 \pm 0.05	1.90 \pm 0.03	1.80 \pm 0.06	1.52 \pm 0.03*

Cortisol = 83–441 nmol/L; Prolactin = 0–20 μ g/L; TSH = 0.7–4.5 μ IU/mL; fT₄ = 0.8–2.3 ng/dL; fT₃ = 1.4–4.4 pg/mL

individual VO_{2max}. Table II presents the physiological responses to the treadmill exercise. These responses collectively suggest that the subjects were exercising at a high level of intensity and reached a point of maximal fatigue (exhaustion) by the end of their exercise runs [9].

Table III presents the hormonal results of the experiment. The resting baseline (BL) hormonal values were all within clinical normative ranges (see Table III; [10]), and were representative for these subjects based upon their participation in previous research studies involving endocrine profiling. By the end of the treadmill run (EXH time point), all hormones were significantly ($p < 0.01$) increased and greater than BL levels. At 30 mR and 60 mR of recovery the thyroid hormones had decreased and returned to BL levels however, cortisol and prolactin remained significantly greater than BL ($p < 0.05$). At 90 mR of recovery all hormones were not different from BL levels. By 24 hours of recovery (24 hR), cortisol, fT₃ and TSH were significantly decreased from BL levels ($p < 0.05$). In addition, fT₄ was decreased at 24 hR from BL and this change approached significance ($p = 0.07$).

The magnitude of all significant hormonal changes (increases and decreases) noted above was greater than the degree of calculated corresponding haemodynamic

plasma volume shifts observed [2]. This latter point suggests that hormonal changes were not just a function of fluid movements in and out of the vascular bed.

The results of the correlation analysis revealed several substantial significant relationships. First, the EXH cortisol responses were negatively related to the 24 hR TSH responses ($r_s = -0.69$, $p < 0.01$). Additionally, EXH cortisol and 24 hR fT₃ responses had a negative relation that were also significant ($r_s = -0.51$, $p < 0.02$). Secondly, prolactin and TSH conversely displayed significant positive relationships. At EXH the prolactin and TSH responses were significantly correlated with one another ($r_s = +0.56$, $p < 0.01$). Also, the prolactin responses at 30 mR were significantly related to the EXH TSH responses ($r_s = +0.43$, $p < 0.05$).

Correlations were also examined between the treadmill running time and hormonal responses to determine whether exercise duration was a factor in the correlation results noted above. These analyses revealed no significant relationships.

At the 24 hours of recovery session neither the subject's body mass nor their total body water content was significantly different from the second experimental session BL measurements. These body mass and total body water data are not reported.

Discussion

The purpose of this study was to examine the effect of prolonged, exhaustive exercise on circulating thyroid hormones, and to determine the relationship between exercise cortisol and prolactin responses to those of the thyroid hormones. There are several major findings from the study. First, the results suggest that exercise cortisol responses have a negative relationship with thyroid function, although temporally there is a delayed development in this association (*i.e.* during the extended recovery from exercise, being specifically between post-exercise cortisol and TSH, fT_3). Similar findings and relationships have been reported previously, but primarily in non-exercise related research [1, 3, 11]. For example, clinical studies looking at Cushing's Syndrome or other medical conditions involving hypercortisolaemic states typically report primary hypothyroidism involving suppressed TSH levels [1, 11]. The mechanism of how cortisol acts to suppress thyroid function has not been completely elucidated but it is well established that the hypothalamic-pituitary-thyroidal regulatory axis is susceptible to disruption at several points by cortisol [1, 11]. The physiologic usefulness of thyroid suppression after exercise is uncertain. It is perhaps an energy conservation mechanism in response to the high-energy output with prolonged exercise. Our speculation on this last point warrants further investigation.

The second major finding of this study is that prolactin responses to exercise are positively related to the thyroidal responses, specifically TSH. This finding is logical physiologically since TRH (which promotes TSH release) is known to serve as a stimulator of prolactin release [4, 5, 12]. This well-established positive relationship has, to our knowledge has not been shown in the context of an exercise research setting until now. The role prolactin plays in response to exercise is an issue of much debate and continued investigation. Current perspectives promote the possibility that prolactin plays a key role in activation of the immune system following exercise. The prolactin receptor is widely expressed by immune cells, and some types of lymphocytes even synthesize and secrete prolactin [4–6]. These observations suggest that prolactin may act as an autocrine, paracrine and endocrine modulator of immune activity [6–8]. Thus, the hormone may serve as a mediator to the post-exercise inflammatory process and as a means to initiate aspects of the recovery-regeneration and adaptation process to exercise.

The finding of significant reductions in fT_3 and fT_4 at 24 hours following the exercise is in agreement with previously published research [1, 3]. However, not all investigators have reported such findings following prolonged exercise [3]. This lack of agreement among

studies may be due to blood sampling protocol differences, as most exercise studies have not sampled as long into the recovery period as we currently did. There was no significant correlation between the observed changes within TSH, fT_3 or fT_4 . This finding was expected as circulating T_3 and T_4 levels are influenced not only by anterior pituitary (*i.e.* TSH) control but also by peripheral factors (*i.e.* T_4 peripheral conversion to T_3). Interestingly enough, this peripheral process is also influenced by cortisol as it inhibits 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 (rT_3) hormone [1]. We did not systematically assess the peripheral process in the current study. However, we did choose to examine rT_3 in one representative subject and found levels of this less biologically active thyroid hormone to be substantially elevated at the 24 hR time point. This suggests that perhaps such peripheral events were taking place and thus possibly account in some part for the lack of significant correlations between TSH and fT_3 or fT_4 . Furthermore, it is unlikely that these changes at 24 hours of recovery were a function of body fluid shifts (dehydration or hyper-hydration) or energy status (*i.e.* caloric deficiency) [1, 9]. This judgement is based upon the subjects reporting that they were compliant with their directions to consume adequate amounts of food and water during the recovery period, and the finding that their body mass and total body water values did not differ between 24 hR and BL.

Conclusions

To conclude, the findings suggest that the prolonged, exhausting exercise results: (1) in significant reductions in key thyroid hormones by 24 hours after the exercise, (2) the reductions in select thyroid hormones are negatively related to the elevations in cortisol precipitated by the exercise; however, this relationship is temporally delayed, and (3) the prolactin responses to exercise are directly related to select thyroid hormonal responses, perhaps mediated by TRH. Regrettably, we were unable to measure TRH in this study, which is a design limitation, and thus confirm our speculation about the role of this hormone. Future work is planned in our laboratory to allow us to address this issue.

Collectively, these findings would suggest that the thyroid function of men participating in endurance-related sports might need longer than 24 hours to completely recover from the stress of their physically demanding exercise activities. For clinicians who examine and evaluate such sportsmen it is important to recognize

that blood specimens collected 24 hours after prolonged exercise may not be representative of normal basal thyroid hormone concentrations in these men.

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