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The thyroid axis, prolactin, and exercise in humans

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Abstract

The thyroid hormones thyroxine and triiodothyronine as well as the anterior pituitary hormone prolactin each serve vital roles in humans. When challenged by stressful situations, all of these hormones respond in an attempt to maintain homeostasis. One powerful stressor to invoke the release of these hormones is physical activity, that is, exercise. The thyroids and prolactin each have independent roles allowing the body to accommodate to exercise. But they also share an interrelation in their responses. Hypothalamic thyrotropin-releasing hormone release invoked by stress stimulates the release of thyroid-stimulating hormone and thus the thyroids as well as the release of prolactin. Likewise, estrogen serves as an interconnective regulatory link by stimulating the release of both the thyroids and prolactin. The roles of these hormones in exercise are multifaceted, but one overlapping and common function is their combined aid and support of the tissue inflammatory responses after exercise. This is highly critical for facilitating elements of the adaptive-recovery procedures to exercise and exercise training.

Keywords

Stress; Exercise training; Sport; Endocrine; Hormones

Introduction

From a classic physiological viewpoint, the endocrine system is defined as a series of glandular tissues located throughout the human body which secrete chemical messenger substances (i.e., hormones) to modify and regulate the biological function of a multitude of target cells, tissues, and organs away from the gland of production (i.e., the definition of endocrine action). Many hormones not only have such endocrine effects but also exhibit autocrine- and paracrine-like function on cells and tissues at or near the specific endocrine gland producing the hormone, but interestingly, during the last few decades science has

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Conflict of interest

Nothing declared.

Appendix A. Supplementary data

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identified that many non-glandular tissues in many species secrete hormones (e.g., adipocytes → leptin) or hormonal-like substances such as cytokines (e.g., skeletal muscle → interleukin-6). The discovery of such action by nonglandular tissue adds to the complexity of trying to understand the hormonal controls in humans and present a challenge for any endocrinologist trying to study the multitudes of potential interactions within the system. This pursuit of understanding is further complicated when stress, a major stimulant to the endocrine system, is added to the human organism. Although there is a multitude of stresses, the intent of this chapter is to provide an overview of contemporary literature which addresses how the ‘physical stress’ of exercise impacts on aspects of the thyroid and anterior pituitary glands, with a focus on the major thyroid hormones and the hormone prolactin. For this purpose, our operational definition of “exercise” is a physical activity requiring bodily effort, intentionally carried out to sustain or improve overall health and fitness levels. Exercise findings are organized around activities that tax the aerobic energy systems (e.g., running) versus anabolic energy systems (e.g., sprinting, weight lifting), addressing acute and chronic effects.

Thyroid hormones function and regulation

Most experts agree that the thyroid gland is an extremely important endocrine gland in humans because of its divergent effects. The gland secretes the following three hormones into the bloodstream: thyroxine (3,5,3',5'-tetraiodothyronine [T_4]), triiodothyronine (3,5,3'-triiodothyronine [T_3]), and calcitonin. One of the reasons for the criticality of both T_4 and T_3 being essential for the normal physiologic function is because of their broad spectrum of actions on a number of tissues and organs [1]. This action is due to their ability to modulate metabolism and act in a synergistic and permissive fashion with other hormones. Calcitonin, however, is a key regulator for maintaining the levels of calcium in the blood. This latter process occurs via the influence of this hormone on bone osteoblastic—osteoclastic cellular activity and renal excretion of calcium [1]. The focus of this chapter is delimited to discussions of T_4 and T_3 only. For brevity purposes, these hormones will be collectively referred to as the ‘thyroids’.

The glandular production and secretion of the thyroids is controlled by the thyroid-stimulating hormone (TSH, also called, thyrotropin), a glycoprotein-based hormone released from the anterior pituitary. The release of TSH is due to thyrotropin-releasing hormone (TRH) which is produced by the hypothalamus. The control and release of all of these hormones involve a negative feedback regulatory loop referred to as the hypothalamic–pituitary–thyroid axis [2]. Table 1 lists those factors associated with influencing the axis either in a stimulatory or inhibitory fashion.

In the circulatory system, these thyroid hormones exist either in a bound or free (unbound) form. In the bound forms, the carrier proteins for the thyroids are thyroidbinding globulin (70% of binding), thyroxine-binding pre-albumin (10–15%), and albumin (15–20%). The free forms of T_4 (free T_4 ~ 0.03%) and T_3 (free T_3 ~ 0.3%) are a small portion for each hormone’s respective total amounts. The free forms are the most biologically active versions of each hormone [1,2]. Circulating T_4 levels exceeds those of T_3 , but T_3 is considered the more biologically powerful of the hormones [2].

The turnover rate of the thyroids is very low relative to the existing large extracellular hormonal pool. This fact can make it complex and challenging for researchers to detect hormonal changes (even relatively large ones) in thyroid gland activity after an affecting event, such as physical exercise [3]. As noted, the thyroids greatly influence a multitude of tissue and organ functions as well as growth and development across the human lifespan, although, this effect is mitigated as an individual age [4]. Examples of these physiologic actions, especially relevant to a person's ability to exercise, are as follows [1-3]:

- Increased oxidative phosphorylation metabolism at the mitochondria and thus can elevate basal metabolic rate,
- Increased tissue responsiveness to the catecholamines (permissive action), which can have a cardiogenic effect, increasing heart rate, and contractility of the myocardium,
- Synergistic effects on growth hormone and thereby magnify the actions of this hormone,
- Facilitation of the neuronal maturation process thus affecting the development and responsiveness of the central and peripheral nervous system, and
- Augmentation of lipid metabolism within the skeletal muscle as well as enhancement of hepatic glycogenolysis, both of which affect the blood glucose turnover rate.

Exercise effects on the thyroid hormones

Short-duration, graded exercise (20 min) results in elevated blood TSH levels, as long as an intensity threshold of approximately 60% of maximal oxygen uptake (VO_{2max}) or above the lactate threshold is achieved [5,6]. Interestingly, with this TSH elevation the expected increase in total and free T_4 is seen, but total and free T_3 become reduced [5]. The hormonal increases observed appear primarily brought about by exercise-induced hemoconcentration (i.e., many carrier proteins such as thyroid-binding globulin are trapped in the vascular space). It is unclear if the reductions observed are due to decreases in production or enhanced target tissue uptake [6]. It is important to note when examining thyroid hormonal changes, there exists an inherent delay in the stimulus-secretion response of the gland [1]. To that end, if a blood sampling protocol is not extended long enough after exercise, thyroid changes may not be detected, which is why some studies find no changes. Similarly, if influential factors such as environment, dietary practices, and diurnal hormonal secretion patterns are not controlled effectively, findings are confounded and the influence of exercise alone not detected [7].

More prolonged, steady-state submaximal exercise (60 min) effects on the thyroids are debatable. Some investigations report no effect on TSH levels [8], whereas others indicate TSH and/or free T_3 [9] to increase progressively or reach a steady-state plateau by approximately 40 min of exercise [5]. During very prolonged sub-maximal exercise (~3 h), Berchtold et al [8] found total T_4 becomes elevated but then declines after the exercise (i.e., in recovery). Conversely, in the same study, total T_3 was found to decline continuously

during the exercise. Others investigators reported total T_3 was unchanged but total T_4 to be increased by 60 min into a prolonged steady-state submaximal exercise session [10]. On the other hand, strenuous, prolonged endurance exercise to exhaustion increased only circulating free T_4 levels [6]. Similarly, strenuous exercise of a maximal exhaustive level but shorter duration (graded exercise test) was associated with decreases in TSH and fT_4 but rises in total T_3 [11]. Finally, Opstad as well as others report repeated days of low-intensity but demanding physical activity (i.e., military field operations involving sleep deprivation and caloric restrictions) substantially reduces resting T_4 , T_3 , and TSH levels [12].

It is important to note that differences in ambient temperature can alter the response of the thyroid to exercise. For example, Deligiannis et al. looked at thyroid responses in swimmers exercising in different water temperatures. They found TSH and fT_4 were profoundly elevated in colder water, were unchanged at 26 °C, and became reduced in warmer temperature water (T_3 levels were unaffected) [13]. This is in line with the work of others as stimulation of cold receptors regulates changes in TRH and TSH levels [14].

Intensive anaerobic exercise (sometimes referred to as high-intensity interval training) increases fT_4 , fT_3 , and total T_4 levels initially after the exercise, but by 12 h of recovery, fT_3 was reduced and reverse T_3 was increased, suggesting a reduced peripheral conversion of T_4 to T_3 [14,15]. These changes are due in part, but not entirely to hemoconcentration effects. However, it is uncertain to what degree the hormonal changes are from the increased secretion or a suppressed metabolic clearance rate [7]. This remains to be elucidated. Research on the effects of resistance and strength exercises, usually more anaerobic in form, on the thyroids is sparse. McMurray and associates did perform one criterial study looking at thyroids immediately afterward and 12 h into recovery (during the night) from intensive resistance exercise [16]. Hemoconcentration-induced transient but significant elevations in total T_4 and T_3 occurred immediately after exercise. During the night total T_3 , there was significant nocturnal elevation. These investigators proposed these changes were due to a thyroid-mediated increase in metabolism needed for tissue repairs and an increase in protein synthesis [1,15].

Research findings on the effects of exercise training programs (chronic exposure) on basal, resting thyroids are not drastically altered from the sedentary normal population. A few studies support that the rate of T_4 secretion is higher in exercise-trained individuals than in untrained individuals, although this is not a universal finding [17]. Likewise, Rone et al. [18] reported increases in T_3 production and turnover rates in exercise-trained male athletes in comparison to sedentary men. On the other hand, Galbo [6] reported a short-term, intensive exercise training periods results in significant reductions in levels of select thyroids, a finding collaborated by others [19]. The discrepancy in these findings may be related to the fact these studies failed to completely account for nutrient balance influences on the thyroid turnover rate. This last point is critical as a negative energy balance substantially reduces the thyroids [11,12].

As noted, the turnover rate of thyroid hormones appears increased in training athletes, and perhaps tissue sensitivity too [17,18], which could account for the changes in the levels of the thyroids as just discussed. It is important to note that the exercise-induced change in free

levels of the thyroids does not seem due to changes in the capacity of the binding protein, either in response to acute or chronic exercise exposure [20]. This suggests that either production/secretion or metabolic clearance rate alterations are bringing about these changes with training.

While some patterns of consistent response appear within research data, the lack of consistent outcomes on some thyroid parameters clearly indicates that more research is needed on the exercise influence on thyroid gland function.

Prolactin function and regulation

The hormone prolactin is principally secreted by the lactotroph cells of the anterior pituitary gland; however, it is also secreted from the breast, the decidua, adipose tissue, and parts of the central nervous system as well as some components of the immune system. It serves as a multifunctional hormone and numerous tissues within humans express prolactin receptors. To that end, the release of the hormone and its physiological functions are connected to emotional and physical stress response, water balance regulation, fetal surfactant development, immune system activation, and reproductive function. A vast majority of the historical prolactin research addresses this last topic because of the fact that prolactin has long been associated with lactogenesis in mothers and increased levels are associated with gonadal suppression in both women and men. In addition to circulating levels changing due to stimulatory or inhibitory stimuli, prolactin displays a diurnal secretion pattern with peak levels during rapid eye movement (REM) sleep [21].

The secretion of pituitary prolactin is under a constant inhibition via dopamine from the hypothalamus. Estrogen is another key regulator of prolactin and increases the production and secretion of prolactin from the pituitary gland. In addition to dopamine and estrogen, a whole range of other hormones can both increase and decrease the amount of prolactin released in the body, with some examples being TRH, oxytocin, and antidiuretic hormone. Figure 1 presents a schematic illustration of the major factors associated with stimulation and inhibition of prolactin release [21,22].

Exercise effects on prolactin

Circulating prolactin levels increase in the blood during exercise, with the magnitude of the increase approximately proportional to the intensity of the physical activity. Whether there is a specific intensity threshold required to induce a hormonal response is unclear, but most exercise above the anaerobic threshold initiates substantial and rapid prolactin elevations [3]. However, if exercise is intense enough, but of a short-term duration, the peak prolactin response may actually occur after the exercise ends. Interestingly, excessive emotional stress can cause an anticipatory increase in prolactin even before an exercise session begins [3,6].

During prolonged sustained exercise, the prolactin response is proportional to the intensity at which the exercise is performed, and there is a plateau in the level observed. However, extending the duration of the exercise session can result in a graduate increase in the magnitude of the prolactin response [23,24]. This change in prolactin with prolonged exercise seems strongly driven by the elevation in core temperature occurring with the

exercise, as cooling an individual mitigates in part the response [25,26]. Remarkably, during the night after a day-time exercise session, there are reports of a two- to three-fold increase in the nocturnal levels of prolactin [27].

Vigorous, high-intensive anaerobic exercise (i.e., high-intensity interval training) results in greater prolactin responses than typically seen in submaximal, steady-state aerobic exercise [28]. The effect of resistance or strength-based exercise on prolactin levels is poorly studied, but some evidence supports that this type of exercise elevates prolactin but the increase may occur actually after the exercise session, that is, during recovery [23].

Findings are highly contradictory with regards to the effect of chronic exercise training on basal, resting prolactin levels. Some studies report increases in resting levels, whereas others note decreased levels [29,30]. These ambiguities are likely related to differences in exercise training protocol components (e.g., intensity, frequency, and duration of training sessions). Interestingly, some investigators found the prolactin response to submaximal exercise in men is diminished after training but the maximal exercise response is amplified [31]. Also, evidence supports that in both men and women who have undergone a training program, the drug-stimulated prolactin response is greater (i.e., pituitary challenge tests) [32,33].

Interaction of thyroid hormones and prolactin

The thyroids and prolactin share certain common aspects of the regulation (see Table 1 and Figure 1) and as thus display inter-related responses. For instance, increases in hypothalamic TRH release stimulate the release of TSH and thus the thyroids as well as the release of prolactin. Moreover, estrogen serves as an inter-connective regulatory link as it stimulates the release of both the thyroids and prolactin. Therefore, the homeostatic disruptions that induce changes in TRH or estrogens (i.e., physical stress, menstrual cycle phase) result in thyroid and prolactin release [21]. Consequently, there is an inter-relationship between the thyroids and prolactin in response to an acute exercise session [34]. Specifically, Hackney and Dobridge found increases in TSH, free T_4 , and free T_3 as well as prolactin immediately after an intensive prolonged, endurance exercise session. This study also demonstrated that prolactin and thyroid responses were substantially related (i.e., correlation) to one another with changes TRH proposed as the common denominator stimulant [34].

A reasonable question is why would such hormonal changes occur with exercise? First and foremost, prolactin is an immunopermissive hormone, and the magnitude of exercise prolactin level responses can stimulate chemotaxis, phagocytosis, and microbicidal capacity of phagocytes [21,35]. Second, prolactin can cause a dose-dependent inhibition of the release of the cytokine, interleukin-6 which does have some proinflammatory properties as well as T-cell activation/proliferation [21,35,36]. Third, the thyroids are associated with modulation of macrophage function during exercise, specifically chemotaxis and phagocytosis [35]. Hence, prolactin and thyroids, in part, potentially aid and support the tissue inflammatory responses after exercise and, therefore, are elements in the adaptive-recovery procedures to exercise and exercise training [37].

Notably, in addition, the thyroids have a substantial function in energy metabolism during and after exercise due to both direct and indirect effects on substrate mobilization and biochemical pathway activation to enhance ATP turnover [37]. Conversely, the potential metabolic role of prolactin is via action on adipocytes and hepatocytes and lipolysis suppression, but whether these actions occur during the course of exercise is unknown [38]. Hence, further research is needed to address this latter point.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Papers of particular interest, published within the period of review, have been highlighted as:

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Figure 1.

Factors the influence the release of prolactin from the anterior pituitary. VIP, vasoactive intestinal polypeptide; TRH, thyrotrophin-releasing hormone; GnRH, gonadotrophin-releasing hormone; IL, interleukin; GABA, gamma-Aminobutyric acid; CREB, cAMP response element binding protein; C/EBP, CCAAT/enhancer binding protein.

Table 1

Select factors associated with the regulation and control of the hypothalamic-pituitary-thyroid axis in humans.

Hormone	Physiologic regulatory factors
TRH	+ Norepinephrine + Sleep + Emotion-Physical Stress + Low Ambient Temperatures – Somatostatin (GHRH); growth hormone releasing hormone – Dopamine
TSH	+ TRH + Estrogens – Growth Hormone – Glucocorticoids
T ₄ T ₃	+ TSH – T ₄ – T ₃

The [+] indicates a stimulatory effect while the [–] denotes an inhibitory effect.

TRH, thyrotropin-releasing hormone (hypothalamus); TSH, thyroid stimulating hormone (anterior pituitary); T₄, thyroxine; T₃, triiodothyronine.