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Review

Obesity and thyroid function

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ABSTRACT

A moderate elevation of thyrotropin (TSH) concentrations, which is associated with triiodothyronine (T3) values in or slightly above the upper normal range, is frequently found in obese humans. These alterations seem rather a consequence than a cause of obesity since weight loss leads to a normalization of elevated thyroid hormone levels. Elevated thyroid hormone concentrations increase the resting energy expenditure (REE). The underlying pathways are not fully understood. As a consequence of the increased REE, the availability of accumulated energy for conversion into fat is diminished. In conclusion, the alterations of thyroid hormones in obesity suggest an adaptation process. Since rapid weight loss is associated with a decrease of TSH and T3, the resulting decrease in REE may contribute towards the difficulties maintaining weight loss. Leptin seems to be a promising link between obesity and alterations of thyroid hormones since leptin concentrations influence TSH release.

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1. Introduction

Since the birth of civilization, humans have faced various periods of famine and scarcity. People who survived those conditions most probably had a greater capacity for storing energy whenever food was available and refilling the consumed stores as soon as supplies became available again. However, the same properties that once constituted an evolutionary advantage can nowadays make individuals more susceptible to become obese during times of abundance. Indeed, this thrifty genotype exposed to modern and industrialized societies, characterized by food security and reduced physical activity levels, recently culminated in an obesity epidemic of gigantic proportions (Ogden et al., 2007; Levin, 2006). Even more alarming than the figures regarding adult obesity (Ogden et al., 2006) is the increasing rate of obese children (Ogden et al., 2002). The ascending epidemiological curves of obesity, particularly in children, and the associated metabolic burden, brought about an estimation of decreased life expectancy at birth in the United States during the first half of this century (Olshansky et al., 2005).

While the prevalence of obesity increases worldwide, the understanding of its pathogenesis and metabolic consequences markedly advances. The white adipose tissue, previously considered to be the largest, although inert, energy store in the body, actively produces various hormones, cytokines, and chemokines, which together

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exert important roles in homeostasis and in thyroid hormone regulation (Rosen and Spiegelman, 2006; Ahima and Flier, 2000). In the recent years, there has been an increasing focus on the relationship between thyroid function and weight status. While it is well known that hyperthyroidism leads to weight loss and hypothyroidism is associated with weight gain, the changes of thyroid function are discussed controversially in obesity.

2. Impact of thyroid hormones on weight status

Weight status is a consequence of the relationship between energy intake and energy consumption. Energy consumption is determined by physical activity and mainly by resting energy expenditure (REE).

While it is clear that thyroid hormones can modulate numerous cellular processes that are relevant for REE (Danforth and Burger, 1984; Onur et al., 2005), the exact mechanisms that underlie this effect in humans remain unclear (Kim et al., 2000). Thyroid hormones have been demonstrated to modulate the behaviour of many metabolic pathways potentially relevant for the basal metabolic rate. In general terms, the major candidate mechanisms include uncoupling of cellular metabolism from adenosine triphosphate (ATP) synthesis, or changes in the efficiency of metabolic processes downstream from the mitochondria. The latter category includes "futile cycles" and "substrate cycles". "Futile cycles" occur when single reversible steps in metabolism proceed simultaneously. "Substrate cycles" are present when opposing energy-requiring pathways of metabolism proceed simultaneously, for example, glycolysis and gluconeogenesis (Bianco et al., 2005). Alternatively, changes in ion fluxes linked to ATP utilization or kinase activities may lead to increased metabolic inefficiency and heat generation. They could increase the protein turnover and perhaps bone turnover. Data exist to support the concept that thyroid hormones act in each of these ways, at least in pathologic states of thyroid hormone excess or deficiency (Roti et al., 2000). But it still remains to be determined which are physiologically the most relevant in euthyroid subjects.

The most clear-cut example of thyroid hormone-dependent energy expenditure is not related to the basal metabolic rate, but rather adaptive thermogenesis. Adaptive thermogenesis is characterized by an uncoupling of oxidative phosphorylation in cold-exposed brown adipose tissue (BAT) which is dependent on locally generated thyroid hormone. In small mammals, sympathetic adrenergic stimulation of BAT induces uncoupling protein-1 (UCP-1). UCP-1 is a protein that uncouples the mitochondrial proton gradient from ATP production promoting the generation of heat. A critical element in this pathway is the type 2 deiodinase (D2), which increases local, intracellular triiodothyronine (T3) production from thyroxine (T4) to such an extent that thyroid hormone receptor saturation increases from 70% to nearly 100% upon cold exposure (Bianco and Silva, 1987). Serum T3 levels do not appear to be affected in this condition (Bianco and Silva, 1987). The increased cyclic adenosine monophosphate (cAMP) synergistically combines with the increased, locally produced T3 such that UCP-1 is upregulated. Studies of the D2-knockout mouse have confirmed the centrality of D2-generated T3 in cold-induced BAT thermogenesis: these mice have an impairment in nonshivering thermogenesis response to cold exposure that can be rescued by administration of T3 (de Jesus et al., 2001). This mechanism also illustrates the molecular links between the adrenergic signaling cascade (sympathetic innervation) and thyroid hormone action. This relationship has been shown to be important for both thermogenic and nonthermogenic roles of thyroid hormone (Silva, 1995, 2006; Ojamaa et al., 2000).

The thermogenic role played by brown adipose tissue in small mammals is assumed by skeletal muscle in humans, a tissue with sufficient mass, innervation, and metabolic activity. A significant portion of the variation in basal metabolic rate among normal humans could be attributable to this tissue alone (Lowell, 2002; Sims and Danforth, 1987). Considerable data exist in support of a role for T3 in skeletal muscle-based obligatory thermogenesis. The breath of possibilities is highlighted by a recent microarray-based study that examined the effect of 75 μg of T4 daily on the vastus lateralis transcriptosome in healthy male volunteers. This study reported that 8 genes related to glucose and lipid metabolism were upregulated, while 22 genes related to mitochondrial energy metabolism were upregulated, as were uncoupling-related genes including UCP-3 and adenine nucleotide translocases 1 and 2 (Clement et al., 2002). In the same study, major changes were also seen for genes related to protein synthesis and catabolism, another of the candidates for T3-related metabolic pathways. Several studies have produced constant evidence that T3 promotes the uncoupling of ATP hydrolysis from sarcoplasmic calcium cycling, increasing the energy turnover associated with calcium cycling during contraction and rest via transcriptional regulation of the sarcoplasmic reticulum calcium ATPase isoform 1 in muscles (Bianco et al., 2005; Simonides et al., 2001). This mechanism has been best studied in the cardiac muscle, but could also potentially explain at least some of thyroid hormone's effects on skeletal muscle energy expenditure.

In addition, skeletal muscle is also a primary site for many other T3-responsive pathways with potential relevance for energy expenditure, though weighing their relative importance remains difficult. For example, a regulatory effect of T3 on the expression of the Na–K–ATPase is well established (Everts, 1996). Thyroid hormones also might regulate glucose metabolism, with the glucose transporter (GLUT-4) being one notable T3-sensitive control point (Zorzano et al., 2005). It has been demonstrated that short-term T3 administration to healthy human subjects leads to a T3-driven uncoupling mechanism in the skeletal muscle with an increase in tricarboxylic acid cycle flux without changing the rate of ATP synthesis (Lebon et al., 2001). The molecules connecting T3 with the metabolic uncoupling seen in the muscle of these subjects have not been precisely determined. Furthermore, it must also be noted that other approaches towards establishing a link between T3 and uncoupling in nonBAT tissues have met with limited success (Silva, 2006). It was once thought that the third member of the uncoupling protein family, UCP-3, could be the missing link given its highly T3-responsive expression in skeletal muscle. However, this molecule has not been proven to have a role in uncoupling and its overall role in metabolism remains controversial (Clapham et al., 2000; Hesselink and Schrauwen, 2005).

Of course, T3-driven mechanisms in tissues other than skeletal muscle may ultimately prove to be important as well, for example, the work done by the heart, which may be responsible for up to 15% of overall energy expenditure at rest (Danforth and Burger, 1984), or perhaps cycling of fatty acids (Oppenheimer et al., 1991). Indeed, if one performs a similar analysis as done here for skeletal muscle, it becomes apparent that numerous studies have identified potential mechanisms for T3-mediated energy expenditure in liver, kidney, and other tissues (Roti et al., 2000). In summary, thyroid hormones are one major determinant of human REE (and therefore weight status) while not all underlying pathways are fully understood.

3. The relationship between thyroid hormones and obesity

Since thyroid hormones upregulate many metabolic pathways relevant for REE, it is not surprising that patients with thyroid diseases usually exhibit changes in body weight, thermogenesis, and lipolysis in adipose tissue. Hypothyroidism is usually associated with a modest weight gain, decreased thermogenesis and metabolic