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Hypothalamic effects of thyroid hormones on metabolism

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Over the past few decades, obesity and its related metabolic disorders have increased at an epidemic rate in the developed and developing world. New signals and factors involved in the modulation of energy balance and metabolism are continuously being discovered, providing potential novel drug targets for the treatment of metabolic disease. A parallel strategy is to better understand how hormonal signals, with an already established role in energy metabolism, work, and how manipulation of the pathways involved may lead to amelioration of metabolic dysfunction. The thyroid hormones belong to the latter category, with dysregulation of the thyroid axis leading to marked alterations in energy balance. The potential of thyroid hormones in the treatment of obesity has been known for decades, but their therapeutic use has been hampered because of side-effects. Data gleaned over the past few years, however, have uncovered new features at the mechanisms of action involved in thyroid hormones. Sophisticated neurobiological approaches have allowed the identification of specific energy sensors, such as AMP-activated protein kinase and

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mechanistic target of rapamycin, acting in specific groups of hypothalamic neurons, mediating many of the effects of thyroid hormones on food intake, energy expenditure, glucose, lipid metabolism, and cardiovascular function. More extensive knowledge about these molecular mechanisms will be of great relevance for the treatment of obesity and metabolic syndrome.

Introduction: thyroid hormones and their 'orthodox' role on metabolism

Thyroid hormones (THs) control a vastness of physiological processes, such as growth, development and metabolic rate [1–6]. The thyroid gland mainly produces thyroxine (3,3′,5,5′ tetraiodothyroxyne or T4), with low biological activity. Removal of an outer-ring iodine to produce 3,3′,5-triiodothyronine (T3) increases TH activity, with T3 having about a 100-fold greater affinity for the TH receptor (TR) compared with T4. This critical step in TH action is catalysed by type 1 and type 2 iodothyronine deiodinases (D1 and D2) [1–6]. TH signalling is inactivated by the type 3 deiodinase (D3), converting T3 into 3,5-diiodo-L-thyronine (T2) and T4 into 3,3′,5′-triiodothyronine (reverse T3 or rT3) [1–6]. THs exert their major effects through nuclear hormone receptors, TRα and TRβ, encoded by two separate genes. The transcripts from the TRβ gene produce three (TRβ1-3) ligand-binding proteins with a conserved C-terminal region, including DNA and ligand-binding domains but with different N-terminal portions. The situation is more complex with the TRα gene. Just one of the two major products of the TRα gene, TRα1, gives rise to a ligand-receptor, whereas the other three main isoforms, namely TRα2, TRα3 and TRα4, do not bind to the ligand but sustain DNA-binding capabilities, although their function *in vivo* is unclear [1–6]. Many of the well known effects of THs are mediated at the transcriptional level, with regulation of targets genes by nuclear TRs [3,4]. Alternative mechanisms, not linked to transcriptional regulation, have been suggested for some of the metabolic effects of THs [3,4,7].

It has been known for more than a century that THs increase basal metabolic rate [8]. In fact, the role of THs in the regulation of energy homeostasis is exemplified in patients with thyroid dysfunction. Hyperthyroidism is a clinical syndrome in which overactive tissue within the thyroid gland overproduces T3 and T4, leading to excess circulating THs. Remarkably, up to 85% of patients with thyrotoxicosis show weight loss, despite the fact that many of them have elevated food consumption [6,9]. Hypothyroidism, on the other hand, is associated with decreased metabolic rate, and patients gain weight despite reduced food intake [6,9]. Epidemiological studies have shown an incidence of up to 20% of hypothyroidism in obese people, suggesting a role for thyroid hormones in the development of obesity [10–15]. Typically, most of these effects have been connected to direct actions of THs on metabolically active tissues, such as liver, white adipose tissue (WAT), brown adipose tissue (BAT), skeletal muscle and heart [5,6,9,16–20]. However, data gleaned in the last 5 years (see below) account for the central nervous system as highly relevant in the action of how thyroid hormones regulate metabolism.

Peripheral versus central effects of thyroid hormones on thermogenesis and energy expenditure

In homeotherm ('warm-blooded') species THs increase metabolic rate and thermogenesis [6,9,21–23]. This key effect is supported by the well-described intolerance to cold or heat of animals and humans with hypothyroidism or hyperthyroidism, respectively [6,9]. Thus, homeotherm species generate more heat than poikilotherm ('cold-blooded') species due to a more active metabolism and a lower thermodynamic efficiency, effects that are both largely dependent on THs [6,9]. Certainly, in the absence of THs, a homeotherm animal develops cold intolerance and becomes almost poikilotherm. Thus, THs are critical for 'obligatory thermogenesis': the heat production automatically caused by the metabolic rate [6,9,24].