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Thyroid hormones and treatment of obesity

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Thyroid hormones have important thermogenic function. Nevertheless, thyroid dysfunctions are often associated with minor changes in body weight and fat mass. On the other hand, both overfeeding and fasting have important effects on iodothyronine metabolism and regulation of deiodinase activity. Although under debate, there are clinical and theoretical reasons to administer low-dose thyroid hormones (T3) in selected obese patients. This short review deals with both pathophysiological and clinical aspects of thyroid hormone used in the therapy of obesity. *International Journal of Obesity* (2000) **24,** Suppl 2, S116–S119

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Thyroid hormones are prototypes of thermogenetic agents

The first publication indicating thyroid hormones (TH) as agents involved in energy homeostasis appeared as early as 1895 by Magnus Levy.[1] Although more than 100 y have elapsed since this first publication, the mechanism of calorigenic effect of TH is not fully elucidated and debate is still in progress.

Food intake

It is well established that food intake is generally decreased in hypothyroidism and increased in hyperthyroid state. The reduction in basal metabolic rate (BMR) in hypothyroidism increases the ratio of energy intake to energy expenditure relative to euthyroid subjects consuming the same amount of food. The contrary is true for hyperthyroidism.

Body weight

Body weight is on average decreased in hyperthyroidism by 15% (in comparison with body weight before) and an increase in body weight is an important sign of a response to therapy. On average hypothyroid patients weigh 15–30% more than during euthyroid state and decrease their weight during replacement therapy, but 17% still maintain their higher body weight, in spite of otherwise adequate substitution.

Overweight

Overweight is also common (15–17%) among post hyperthyroid patients[2] after successful therapy (thyroidectomy, radio-iodine treatment) on substitution with thyroxine (T4). Obesity syndromes share also several similarities to signs and symptoms of subclinical hypothyroidism.

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TH in treatment of obesity

Not surprisingly, TH though not universally recommended, belongs to the oldest arsenal of anti-obesity preparations. Desiccated thyroid, thyroglobulin, USP and the colloid protein of the thyroid gland were very popular during the forties. They were used together with diuretics during the fifties and together with amphetamine and amphetamine derivates during the sixties. TH therapy continued later with synthetic T4 and more recently with T3 and T2.

Thyroid hormone is one of the most commonly prescribed medications in Western countries. In the USA in the national prescription audit, synthroid (L-thyroxin, Boots Pharmacy Inc) was ranked fifth among new and repeat prescriptions.

Is the use of TH in obesity treatment scientifically warranted?

Hyperphagia and overfeeding even in a limited form (as one big meal) leads to increased activity of sympathetic nervous system (SNS) and to a concomitant activation of 5-monodeiodinase 1, responsible for deiodination of T4 to T3 and T2. Increased activity of the SNS and increased availability of T3 and T2 act synergically to increase BMR. (Thermogenesis increases after administration of norepinephrin and T3 separately 2-fold, but 20-fold when given together). The contrary is true for hypophagia, low calorie intake and most spectacularly for fasting (VLCD). Apart from lowering of SNS activity and decreased concentration of T3, fasting is associated with decreased tissue sensitivity to T3, increased concentrations of reverse T3 (rT3), decreased

concentrations of thyroxine binding globulin (TBG) and pre-albumin (TBPA) and decreased production of pro-TRH messenger RNA as well as blunted response of TSH to TRH.[3]

What is a target tissue for TH thermogenic action?

Short-term and long-term effects of TH

Calorigenic effect of TH is divided into short-term effect occurring within 6 h and disappearing totally after 48 h, and the long-term effect which is observed after 30 h and lasts up to 60 days.[4] Short-term effect involves a direct interaction of T2 with mitochondrial enzymes and is not attenuated by actinomycin D. Long-term effects are attributable to modulation of cellularity of different tissues and involve interaction of T3 with nuclear receptors (TR alfa 1-2, TR beta 1-2) that bind to regulatory regions of genes (thyroid hormone response element-THRE). T3 receptor genes are located on chromosomes 17 and 3 and are expressed in almost all tissues.[5] The clinical findings in hypo- and hyperthyroidism are the net results of action of products of variety of genes whose expression is directly or indirectly regulated by T3. One of the important effects of T3 is influence on the family of uncoupling proteins ($UCP_{1,2,3}$). In humans the most important is UCP-3, expressed in deep white abdominal adipose tissue and in abdominal organs (colon, gall bladder) and muscles.[6] (Figure 1).

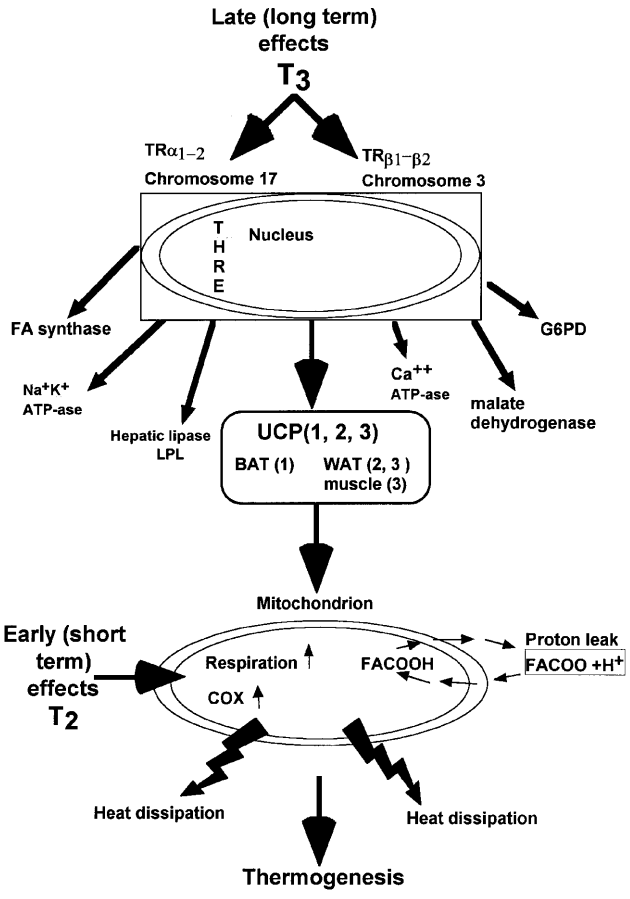

Figure 1 Short-term effects of TH take some hours to occur (6 h, disappear totally after 48 h) and involve interaction of T_2 (3,5 and 3.3 diiodothyronines) with mitochondrial enzymes (Va subunit of cytochrome C oxidase) with consequent abolition of ATP-induced inhibition of enzyme activity and enhanced respiration/heat dissipation. Long-terms effects of TH take several days to occur (30 h, last up to 60 days) and involve interaction of T_3 with $TR_{\alpha 1}$ and $TR_{\beta 1\text{-}2}$ nuclear receptors. Complex interactions (through thyroid hormone response elements, THRE) with different genes include increased expression of UCP_3 with consequent uncoupling of oxidative phosphorylation and dissipation of heat.

UCP-3 levels are decreased three-fold in hypothyroidism and increased six-fold in hyperthyroidism. UCP-3 RNA levels are regulated by hormonal and dietary manipulations, decreased during starvation, increased during overfeeding after administration of T3, leptin and beta-3-adrenergic agonists.[7]

The uncoupling of oxidative phosphorylation by fatty acids is facilitated by SNS and T3, directly through SNS-T3 effect on lipolysis (UCP is steeply modified by the concentration of fatty acids) and indirectly by an effect of T3 on blood flow in adipose tissue. Blood flow influences binding of fatty acids to FABP (fatty acids binding protein) and their consecutive outflow and oxidation in muscles.

Responses to both norephinephrine and T3 occurs at transcriptional level and the protein synthesis is not necessary for obtaining the thermogenic effect.

Obesity is frequently associated with blunted food induced thermogenesis. Furthermore variations in concentrations of T3 contribute to observed inter-individual variances in energy expenditure (*ca* 600 kJ/day)[8] and may therefore contribute to development of obesity. Plasma concentration of T3 is not necessarily a good indicator of T3 concentration in different tissues and organs.[10] Furthermore, activity of deioidinase varies depending on lipolytic activity of different adipose tissue regions;[9] lower deiodinase activity may contribute to development of regional obesity[9] as well as to decrease of BMR and tendency to weight regain (yo-yo effect) during/after VLCD and LCD.

Results of the treatment—can administration of TH accelerate weight loss and prevent lowering of metabolic rate and energy expenditure?

There is no agreement on the effectiveness of thyroid hormones in inducing weight loss. Although administration of HT results in increased weight loss and BMR,[10–12] most of the studies used supraphysiological doses of T3 varying from 150 to 2000 μg T3/day.[10] High doses of T3 caused[11] several side effects such as serious cardiac problems, muscle weakness and excessive erosion of lean body mass.[10–13]

Moore *et al*[11] and Koppeschaar *et al*[12] reported a negative correlation between the body weight loss and the concentration of TH. Some studies have reported an increase in nitrogen excretion,[11–13] urinary excretion of methylhistidine[13] and zinc,[14] all

being indicators of increased of catabolism of muscles. The fall of T3 during fasting has been explained as physiologically aimed for preservation of lean tissues.

However, more recent studies using high[15] or physiological[16] doses of T3 did not find any increase of urinary nitrogen, or changes in leucine or lysine kinetics[16] nor increase of 3-methylhistidine excretion during VLCD. In all recent reports it is stressed that the start day of HT treatment in relation to the commencement of VLCD is of importance[15,16] and should be given after adaptation to fasting, ie once the body has shifted from glycolysis to lipolysis to spare protein. It is further concluded that the fall in serum T3 during VLCD mediates rather a decrease in hepatic glucose appearance than the protein sparing[16] and 'physiological' (small) doses of TH can be thus safely used as adjunct in dietary treatment of obesity.

Doses of T3 varying between 5 and 20 μg/day have been reported to ameliorate hyperlipidemia, prevent hypoglycemia during VLCD, influence concentration of SHBG and improve hormonal profile without major influence on either body weight or BMR[18] (although 5% increase of RER,[16] as well as a small but significant decrease of BMI[17] is reported by some studies).

Thus, it seems reasonable to recommend small doses of T3 as an adjunct to dietary treatment of obesity in the following groups of patients:

- In patients receiving beta-adrenergic receptor blockers, showing verified resistance to dietary therapy.
- In overweight patients on T4 replacement therapy after successful treatment of hyperthyroidism.
- In overweight patients on habitual food intake receiving T4 replacement therapy (previously hypothyroid).
- In patients showing 'dietary treatment-resistant' weight increase while stopping cigarette smoking.
- In patients on VLCD and/or LCD showing low T3, parallel to slowed rate of body weight loss in spite of continued calorie restriction.
- In patients with abdominal obesity and metabolic syndrome, resistant to dietary treatment or showing inadequate improvement in associated metabolic aberrations.
- In patients showing, before or during dietary treatment, signs and symptoms of sub-clinical hypothyroidism.

Value of supplementation with zinc, selenium, potassium and calcium, role of carbohydrates

Supplementation with zinc and selenium can to some extent prevent a decline in deiodinase activity (by 67% and 47% respectively) occurring with a long-term dietary regimen[20] with a similar effect to sufficient intake of carbohydrates.[21] Supplementation with potassium can prevent TH induced depletion of potassium in muscles, and supplementation with calcium can prevent TH induced osteopenia.[22]

While the available medical literature is hardly encouraging, for the use of TH for weight loss no other thermogenetic preparations are available.

Further investigation on the application and testing of clinical effects of diiodothyronine (T2) and the possible combination with ephedrine and/or beta-3 agonists with T3 or T2, would be worthwhile.[23]

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