

## Review Article

# Role of Type 2 Deiodinase in Hypothalamic Control of Feeding Behavior

Miriam Oliveira Ribeiro\*

*Developmental Disorders Program - CCBS, University Presbyterian Mackenzie, Rua da Consolação, 930 Bld 28, São Paulo - SP Brazil***Abstract**

The amount of energy in the body is highly regulated. The hypothalamus is a key neural structure involved in this process, keeping the intake of food in step with the energy expenditure. The main hypothalamic nuclei involved in energetic metabolism regulation are the arcuate, periventricular, dorsomedial and ventromedial that integrates several peripheral signals, such as leptin and adiponectin. Although it is well known that T3 regulates basal metabolism, it also has an important role in feeding behavior regulation since it stimulates neurons that express orexigenic neuropeptides, such as AgRP and NPY found in the arcuate hypothalamic nuclei. The amount of T3 available in the brain depends on the activity of the type 2 deiodinase (D2) that transforms T4 in T3. D2 is expressed in glial cells that are in close contact with the AgRP/NPY expressing neurons in the arcuate hypothalamic nuclei, suggesting that D2 has an important role in the regulation of the feeding behavior and in the body weight.

**INTRODUCTION**

The control of the amount of energy in the body is a highly regulated process [1]. The intake must be kept in step with overall consumption and every cell in the body should remain in nutritional balance. The mechanisms developed to regulate cell's energy must be integrated with the systems of the whole organism. Which structures responsible for sensing and integrating the energetic needs of the organism is an important question that remains to be fully answered.

Mammals evolved to be homeothermic with a high body temperature that implicates in an extraordinary energy demand [2]. It also brought them another challenge that is to fight hyperthermia and hypothermia under whatever environmental conditions. To meet this high energy demand, fat in large discrete depots emerged with birds and mammals [3], which gave them the ability to manage energy supply and demand. Giving that, fat is a very interesting tissue from the evolutionary point of view considering the environment where the man evolved, with considerable difficulties to obtain food. Men evolved in an environment struggling against starvation and with no food in abundance.

Fat is not just a highly energetic substrate, but also an endocrine gland, which releases leptin (proinflammatory) and adiponectin (antiinflammatory), 2 hormones that signal to hypothalamus about feeding. Fat also participates fighting pathogens since it secretes proinflammatory molecules, such as TNF (tumor necrosis factor) and IL-6 (interleukin-6) [4-6]. In

addition, macrophages recruited to the fat depots activate and release additional proinflammatory molecules. This process is important, but in excess, as observed in obesity, can lead to the development of several abnormalities related to metabolic syndrome [7].

Several homeostatic mechanisms regulate body weight. When energy intake exceeds even minimally the energy expenditure, weight gain is observed [8]. The increasing prevalence of obesity is likely to result from shift in life style and access to palatable foods and reduced physical activity.

**Hypothalamus and thyroid hormone in energy homeostasis**

The hypothalamus has long been recognized as a key structure in homeostatic mechanisms, integrating endocrine signals and modulating a myriad of physiological processes, including body energy homeostasis [9]. The mediobasal nuclei in hypothalamus seems to be the main site for sensing availability of nutrients and for generating an integrated adaptive response to maintain the amount of energetic substrate in the body [10]. From the energy homeostasis point of view, the most relevant hypothalamic nuclei are the Arcuate (ARC), Periventricular (PVH), Dorsomedial (DMH), and Ventromedial (VMH) [11-13]. These nuclei integrate several afferent signals such as glucose, amino acids, and lipids, as well as hormones such as leptin, ghrelin, Adiponectin (ADPN), Resistin (RSTN), Glucagon-like Peptide-1 (GLP1), insulin, estrogens, and Thyroid Hormone (TH) [11-14] that results in adjustments in energy balance.

## Special Issue on

**Role of Thyroid Hormone in Metabolic Homeostasis****\*Corresponding author**

Miriam Oliveira Ribeiro, Developmental Disorders Program, Center for Health and Biological Sciences, Mackenzie Presbyterian University Sao Paulo, Brazil, CEP 01302-907, Tel: +551121148254; Email: miriamribeiro@mackenzie.br

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Thyroid hormone has been known as a key molecule in basal metabolic rate regulation for more than a century [15-17]. The majority of these effects have been attributed to the direct actions of TH in liver, white and brown adipose tissue (WAT and BAT), heart, and skeletal muscle [16-19]. However, several studies have shown that TH not only increases the metabolic rate through peripheral effects but also affects food intake, energy expenditure, and metabolism by acting at the central level. In fact, it is well known that hyperthyroidism induces hyperphagia in 85% of hyperthyroid patients [20]. In line with this evidence, acute central infusion of T<sub>3</sub> in mice also induces hyperphagia [21]. The human thyroid gland produces ~90% of thyroxine (T<sub>4</sub>), considered as a prohormone that does not efficiently bind the Thyroid Hormone Receptor (TR), and produces ~10% of 3,5,3'-triiodothyronine (T<sub>3</sub>), that presents high affinity to the TRs. Given that, T<sub>4</sub> has to be converted into T<sub>3</sub> in order to bind the TR and initiate its effects.

### Involvement of type 2 deiodinase in hypothalamus control of energy expenditure

Once the thyroid hormones are transported into the cell through membrane transporters, the prohormone T<sub>4</sub> can be transformed into T<sub>3</sub> via the type 2 deiodinase (D2), or it can be inactivated to reverse T<sub>3</sub> via the type 3 deiodinase (D3). Thus, the thyroid hormone signaling in tissues is regulated through the action of the deiodinases that control the amount of T<sub>3</sub> available in the cells. D2 expression confers cells with the capacity to produce additional amounts of T<sub>3</sub> and thus enhances thyroid hormone signaling. In contrast, expression of D3 results in the opposite action. All this occurs in the cell and without changes in plasma thyroid hormone levels. Therefore, thyroid hormone signaling in the tissues is turned on or off via deiodination pathways that are taking place inside the target cells, independently from the thyroid hormone plasma levels [22].

Deiodinases are selenoproteins presented as a dimeric integral-membrane of about 60 kDa (dimer) [23-26]. Each dimer consists of a selenocysteine anchored to cellular membranes through a single amino-terminal transmembrane segment. D2 is an endoplasmic reticulum (ER)-resident protein that supplies T<sub>3</sub> to the nuclei [27]. On the other hand, most D3 is located in the plasma membrane [23]. Studies of D2 and D3 in knockout animal models have shown the relevance of these enzymes in thyroid hormone signaling in several tissues. D2 knockout mice (D2KO) presents obesity, glucose intolerance, and hepatic steatosis when kept at thermoneutrality (30°C) [28], are unable to sustain a normal body temperature following cold exposure despite a normal circulating T<sub>3</sub> concentration [29], are deaf [30,31] and have brittle bones [32].

In the human brain, the amount of T<sub>3</sub> locally generated results from the balance between D2 and D3 activity. D2 is the protein responsible for producing T<sub>3</sub> in the human brain [33], while D3 is able to inactivate T<sub>4</sub> to reverse T<sub>3</sub> [34]. D2 is expressed in glial cells, in the astrocytes and tanycytes, the specialized glial cells that line walls and floor of the third ventricle of the mediobasal hypothalamus [35-37] while D3 expression in the brain is restricted to neurons [38]. The relevance of D2 in generating local T<sub>3</sub> in the brain is shown by the fact that neonatal D2KO mice have a 25–50% reduction in the concentrations of T<sub>3</sub> in the tissue

throughout the brain, which is similar to that seen in hypothyroid wild-type littermate mice. The reduced concentration of T<sub>3</sub> in neonatal D2KO mice does not result from increased T<sub>3</sub> degradation, as activity of the inactivating DIO3 enzyme is not altered in any brain regions [21].

The mechanisms underlying the orexigenic effect of T<sub>3</sub> and the role of D2 in this effect have been addressed in several studies. Rats present a peak in D2 mRNA levels in hypothalamus during diurnal dark phase [39] consistent with an increase in T<sub>3</sub> levels in this same tissue [40]. At the same time many neuropeptides involved in the regulation of food intake show a similar diurnal expression pattern, *i.e.* AgRP [41], NPY and POMC [42]. In fact, D2-expressing glial cells are in direct contact with AgRP/ NPY neurons in ARC, important nuclei involved in feeding regulation, as discussed earlier [39].

Food deprivation also stimulates D2 activity in glial cells in hypothalamus. Previous study has shown that hypothalamic D2 mRNA expression increases after a prolonged, 72-h fasting [43], leading to a local rise in T<sub>3</sub> levels. The increase in T<sub>3</sub> results in UCP2 activation leading to mitochondrial proliferation in AgRP/ NPY neurons with consequent increased excitability of the orexigenic neurons and increased appetite [44]. The expression and activity of UCP2 are stimulated by central infusion of T<sub>3</sub> and inhibited by hypothyroidism, indicating direct action of T<sub>3</sub> on the UCP2–AgRP/ NPY axis [44].

The fact that T<sub>3</sub> increases food intake could be interpreted as a compensatory mechanism for the increase in metabolic rate induced by thyroid hormone. Nonetheless, there are evidences suggesting that T<sub>3</sub> exerts dissociated actions on hypothalamic metabolic sensors: T<sub>3</sub> regulates feeding through mTOR in the ARC, while modulating energy expenditure via AMPK in the VMH [45,46].

The data presented here reinforce the idea that deiodinases have an important role in the energy intake and energy balance through central nervous system. However, the important question to be addressed is the relevance of these central actions on human pathology, not only in syndromes related to alterations of the thyroid economy *per se*. It is important to pursue new strategies to treat energy balance disorders.

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