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Bioenergetic impact of tissue-specific regulation of iodothyronine deiodinases during nutritional imbalance

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Abstract The regulation of energy homeostasis by thyroid hormones is unquestionable, and iodothyronine deiodinases are enzymes involved in the metabolic activation or inactivation of these hormones at the cellular level. T3 is produced through the outer ring deiodination of the prohormone T4, which is catalyzed by types 1 and 2 iodothyronine deiodinases, D1 and D2. Conversely, type 3 iodothyronine deiodinase (D3) catalyzes the inner ring deiodination, leading to the inactivation of T4 into reverse triiodothyronine (rT3). Leptin acts as an important modulator of central and peripheral iodothyronine deiodinases, thus regulating cellular availability of T3. Decreased serum leptin during negative energy balance is involved in the down regulation of liver and kidney D1 and BAT D2 activities. Moreover, in high fat diet induced obesity, instead of increased serum T_3 and T_4 secondary to higher circulating leptin and thyrotropin levels, elevated serum rT3 is found, a mechanism that might impair the further increase in oxygen consumption.

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In adult mammals, energy homeostasis depends on a highly integrated and redundant neurohumoral system that prevents the occurrence of relevant fluctuations in energy balance, so that body mass and fat content remain relatively stable for long periods of time (Mercer 1998). Body mass stability depends largely on energy balance that is achieved when energy intake (ingestion and absorption of macronutrients) equals energy output (energy expenditure). A progressive loss of energy balance can result in diseases such as obesity (positive energy balance) and anorexia (negative energy balance).

The involvement of thyroid hormones (TH) in the regulation of energy homeostasis has been well-recognized for over a century from observations made by Magnus-Levy, a physiologist-physician, who reported a positive correlation between oxygen consumption and serum concentrations of TH in patients with thyroid dysfunction (hypothyroidism or hyperthyroidism) (Magnus-Levy 1895). On the other hand, the description of the involvement of leptin in the regulation of energy homeostasis is more recent, after the discovery of this hormone in 1994 (Zhang et al. 1994). Leptin is mainly synthesized and secreted by adipocytes and decreases food intake while increasing energy expenditure when administered to animals.

The relationship between the thyroid axis and leptin has been extensively studied over the past decades and substantial progress has been achieved (Ahima et al. 1996; Rosenbaum et al. 2002; Araujo et al. 2008 and 2009).

As typical for other hormone systems, the actions of the thyroid hormones (TH) differ from tissue to tissue, depending upon a number of variables. In addition to variable expression levels of TH receptors and transporters, different

patterns of TH metabolism provide a critical mechanism through which TH action can be regulated in target cells depending on the needs of the organism (Hulbert 2000).

Nowadays, a well-accepted paradigm has emerged based on the fact that iodothyronine deiodinases are important enzymes involved in the control of thyroid hormone action at the cellular level (Bianco et al. 2002). Thyroxine or 3, 5, 3′, 5′ –tetraiodothyronine (T4) is the main product of thyroid secretion. However, T4 is mainly a prohormone that must be activated through deiodination into T3, the active metabolite of T4. This outer ring or 5′-deiodination reaction is catalyzed by the types 1 and 2 iodothyronine deiodinases, D1 and D2. On the other hand, type 3 iodothyronine deiodinases (D3) catalyzes the inner ring or 5-deiodination reaction leading to the inactivation of T4 into 3, 3′, 5′-triiodothyronine or reverse triiodothyronine (rT3), an inactive metabolite of T4 (Bianco et al. 2002) (Fig. 1). In this context, leptin acts as an important regulator of central and peripheral iodothyronine deiodinases activities (Araujo et al. 2009; Coppola et al. 2007).

This minireview focuses on the most recent reports on the tissue-specific regulation of TH metabolism by iodothyronine deiodinases during nutritional imbalance, such as food restriction and diet-induced obesity.

Relationship between energy balance and thyroid hormone homeostasis

In conditions of normal energy balance, serum TH concentrations are maintained relatively stable, as a result of a finely tuned control between: i) pool of stored TH in the thyroid gland; ii) negative feedback system dependent on the hypothalamus-pituitary-thyroid (HPT) axis; iii) peripheral metabolism of TH (ex: reactions of deiodination).

To understand the overall spectrum of thyroid hormones-related effects on energy homeostasis, the definition of the major components of energy expenditure is of value. Metabolic rate is an essential feature of all living organisms and is the total sum of energy consumption (expenditure) that occurs in a biological system (vegetal or animal) at any given time (Galgani and Ravussin 2008). The minimum energy expenditure that allows normal cell function is called the basal metabolic rate (BMR). In animals, the BMR is the amount of energy necessary to sustain minimal homeostatic functions measured at rest, in a 12-hour-fasted state, in a fully relaxed subject kept at thermoneutrality (Schutz 1995). It includes various forms of biological work, of which the major categories are: (i) ionic cycles, particularly in the excitable tissues; (ii) metabolic cycles, particularly in the liver, muscle, and adipose tissue; (iii) muscle function, e.g., heart rate, respiratory movements, and vasomotor tonus, and (iv) basal secretion of exocrine glands and glands annex to the intestinal tract (Hulbert 2000; Rolfe and Brown 1997; Schutz 1995). Adenosine triphosphate (ATP) hydrolysis that is fundamental for the above mentioned reactions results in substantial heat production (Nelson and Cox 2005).

T3 activates several energy consuming intracellular processes leading to increased oxygen consumption, such as ions transport across membranes, and diverse metabolic pathways related to glucose homeostasis, lipid metabolism, and mitochondria function (Hulbert 2000; Danforth and Burger 1984). As a result, T3 is known as a thermogenic

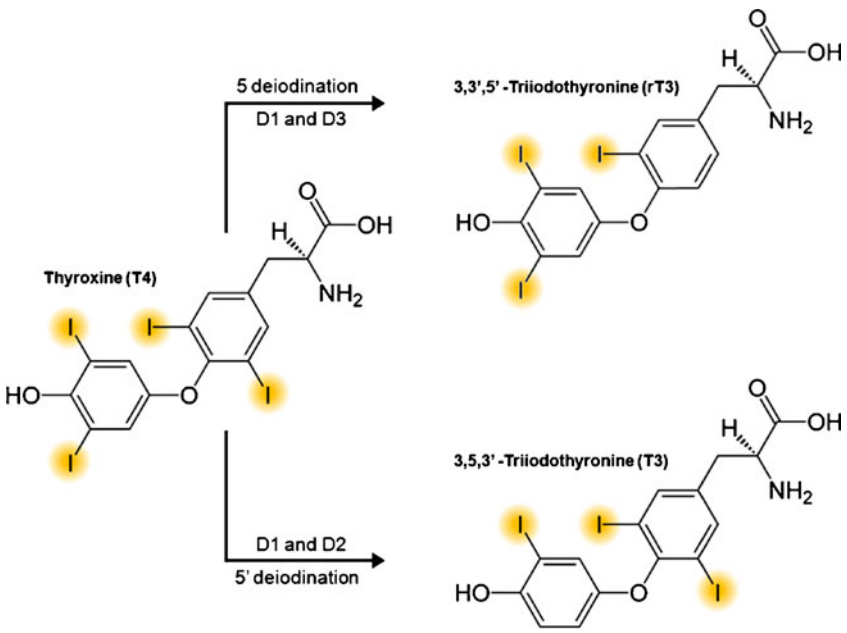

Fig. 1 Metabolic pathways of thyroid hormone activation and inactivation that are catalyzed by iodothyronine deiodinases. The iodothyronine deiodinases are abbreviated D1, D2 and D3 for types 1, 2 and 3 deiodinases, respectively

hormone in such a way that hypothyroid animals are cold intolerant, and hyperthyroidism leads to increased heat production (López et al. 2010;Golozoubova et al. 2004; de Jesus et al. 2001). In conclusion, T3 increases energy expenditure in the organism as a whole and in all tissues tested so far. Also, T3 activates cerebral pathways leading to increased food intake, being considered an orexigenic hormone. The local production of T3 in the hypothalamus seems to be an important mechanism related to increased hunger that accompanies negative energy balance caused by starvation (López et al. 2010).

Thus, the cellular availability of T3 will drive the activation or inactivation of several metabolic processes that culminate with the control of energy balance at the cellular level, reflecting in the rate of oxygen consumption in the organism as a whole. T3 effects are mainly mediated through the nuclear thyroid hormone receptors that correspond to ligand-regulated transcription factors (Yen 2001).

Iodothyronine deiodinases

As mentioned above, three types of deiodinases catalyze the reactions of iodothryronines deiodination: type 1 (D1), type 2 (D2) and type 3 (D3).

The iodothyronine deiodinases constitute a family of dimeric thioredoxin fold-containing selenoproteins that selectively remove iodine from thyroxine and its derivatives, thus activating or inactivating these molecules. The molecular weights of deiodinases vary between 29 and 33 kDa, and their sequence identity is lower than approximately 50%; nevertheless, they all share an approximately 15 amino acid-long conserved selenocysteine-containing active center, and all have one transmembrane domain. The sub-cellular localization of the enzymes varies according to the enzyme type, and might be related to their systemic (plasmatic) versus cellular contributions to TH homeostasis and action (Fig. 2). The deiodinases appear to serve varying functions that are important in regulating metabolic processes, TH action during development, and feedback control of the thyroid axis (Gereben et al. 2008).

D1 is an enzyme with both outer and inner ring deiodination activities that can give rise to either active (T3) or inactive (rT3) metabolites of T4. Using flag tagged enzymes, Baqui et al. (2000), located D1 at the plasma membrane in transiently transfected HEK293 cells. This sub-cellular localization of D1 in peripheral tissues suggests a major function in the maintenance of plasma T3 levels (Baqui et al. 2000).

D2 exclusively catalyses outer ring deiodination (Gereben et al. 2008) and is located in the endoplasmic reticulum (Baqui et al. 2000) a favorable location for providing T3 to the nuclear compartment of the cell, leading to thyroid hormone nuclear receptor activation. As a result, tissue-specific regulation of D2 is related to a cell-specific control of gene expression by T3.

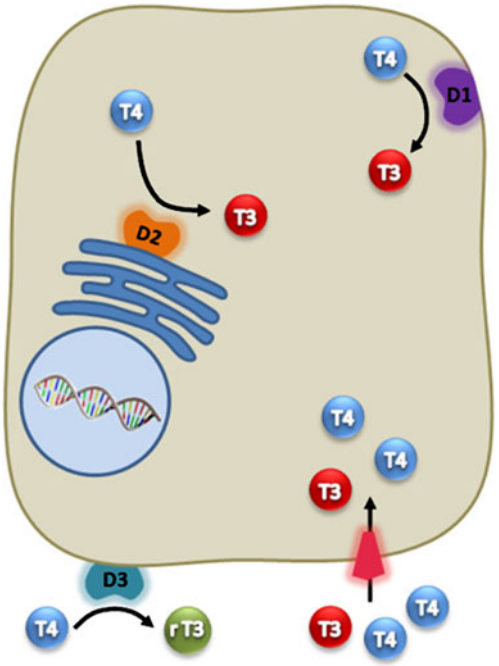

Fig. 2 Schematic diagram of thyroid hormone activation and inactivation in a prototype cell expressing D1, D2 and D3. The circulating thyroxine (T4) or triiodothyronine (T3) can enter the cell and be deiodinated

D3 only catalyses the inner ring deiodination, resulting in the inactivation of T4 into rT3 or the conversion of T3 into 3, 3′ –T2. D3 is located at the plasma membrane, and could impair the activation of thyroid hormone receptors by T3 due to its decreased intracellular content that results from either T4 or T3 inactivation (Baqui et al. 2003).

Negative energy balance—food restriction

Reduction in caloric intake promotes suppression of hypothalamic-pituitary-thyroid axis, a well-known adaptive response to reduce energy expenditure in both humans and rodents. Such homeostatic mechanisms impair further weight loss after longer periods of food restriction, indicating that the regulation of thyroid function plays an important role in the mechanisms that adjust metabolic rate according to energy availability (Boelen et al. 2006; Bianco et al. 2002, 1987; Berry et al. 1991).

Studies in rodents demonstrated that the reduction in serum leptin levels that occurs during weight loss, signals to the central nervous system, leading to decreased energy expenditure (Ahima 2000, 1996; Hamann and Matthaei 1996). It is well documented that thyrotropin-releasing hormone (TRH) gene expression is positively regulated by leptin. TRH is an important hypothalamic integrator of

energy metabolism, through stimulatory effects on TSH secretion by the anterior pituitary and also through central effects on feeding behavior, thermogenesis, locomotor activation and autonomic regulation (Hollenberg 2008). Recently, it was shown that leptin stimulates TRH gene expression both directly in the paraventricular nucleus of the hypothalamus and indirectly via the arcuate nucleus (Ghamari-Langroudi et al. 2010). Hence, a negative energy balance results in decreased TRH and so on thyroid-stimulating hormone (TSH) secretion leading to low plasma levels of T4 and T3 (Ahima 2000; Krotkiewski 2000; Orban et al. 1998).

Low dose administration of leptin reverses weight-loss-induced reductions in T_4 and T_3 and raises energy expenditure to pre-weight-loss values in humans and rodents (Kozlowska and Rosolowska-Huszcz 2004; Rosenbaum et al. 2002). These findings confirm that reduced circulating leptin accounts for some of the major endocrine and metabolic adaptive responses induced by weight loss (Rosenbaum et al. 2002). As previously suggested, apart from the central effects of leptin on the hypothalamic-pituitary axis, decreased serum thyroid hormone during caloric deprivation could also be related to the reduced liver type 1 deiodinase (D1) activity (Bianco et al. 2002; Cettour-Rose et al. 2002). We have recently shown that low replacement doses of T4 during food restriction restore liver D1 activity and serum T3, suggesting that decreased liver D1 is a consequence rather than the cause of reduced serum T3 during food restriction (Araujo et al. 2008).

Indeed, a possible direct effect of leptin on the thyroid gland and/or modulation of other deiodinases should also occur. Recently, elegant studies in humans submitted to 8 weeks of food restriction showed that low-dose leptin replacement during maintenance of reduced body weight reversed the effects of sustained weight reduction on the circulating concentrations of thyroid hormones, without normalizing TSH (Rosenbaum et al. 2005). These observations suggested a direct stimulatory effect of leptin on the thyroid gland or on the peripheral metabolism of T4 and T3. In fact, 10 days of low-dose leptin replacement in food-restricted rats did not normalize serum T4 concentrations; however, serum T3 concentrations were significantly increased by exogenous leptin administration (Araujo et al. 2009). We thus hypothesize that the mechanism underlying the normalization of serum T3 by leptin administration during food restriction could be related to changes in the peripheral metabolism of T4 besides the known effects of leptin in the hypothalamic-pituitary axis. These results differ from studies in humans (Rosenbaum et al. 2005), which described significant increments in both serum T3 and T4 after leptin administration, without significant changes in circulating TSH. These differences can be due to species-specific effects of leptin, but also to the duration of treatment and the dose administered, or the different nutritional status of the subjects.

Studies evaluating the effects of exogenous leptin on thyroid economy during short term-fasting in animal models (24 to 72 h) are conflicting. In 1996, it was shown that serum thyroxine decreased within 48 h of fasting and that a single intraperitoneal dose of leptin could attenuate the fall in thyroxine but did not restore it to control levels. Chronic leptin treatment could also prevent the fall in T4 determined by 70 h of fasting (Ahima et al. 1999). On the other hand, other studies have shown that leptin (20 ug/0.5 ml twice a day) did not restore the decreased serum T3 and T4 in 24-h-fasted mice, despite serum leptin normalization (Boelen et al. 2006). Lujan et al. (2006), using rhesus monkeys submitted to a prolonged dietary regimen, also observed that leptin infusion for 16 weeks did not restore serum T3. These conflicting data show that different approaches lead to controversial results. Therefore, further studies are needed in order to understand the influence of leptin on the thyroid axis during fasting and food restriction, which correspond to quite different physiological conditions. Boelen et al. (2006) showed that refeeding after 24 h of fasting in mice resulted in marked increase in serum leptin levels; however, it did not result in a complete recovery of serum T4 and T3 levels. These results indicate that normalization of leptin levels does not always parallel restoration of serum thyroid hormone levels, suggesting that other peripheral signals may play a role in the regulation of thyroid gland economy during caloric deprivation. In addition to decreased leptin, serum corticosterone is significantly increased during food restriction (Bianco et al. 1987, Jennings and Ferguson 1984). Some authors found that leptin administration is able to reverse the increased serum corticosterone, however we have recently demonstrated that serum corticosterone remains elevated after 10 days of leptin administration to food-restricted rats (Araujo et al. 2009; Coppola et al. 2005b; Ahima et al. 1996). The fall in serum T3 concentrations determined by food restriction was diminished in the leptin-treated group, and leptin was able to restore liver and kidney D1 activity, as well as D2 activity in brown adipose tissue (BAT), contributing to the increase in serum T3 (Araujo et al. 2009). These data are in accordance with reports that show an important stimulatory effect of leptin on peripheral D1 and D2 activities (Lisboa et al. 2003; Cettour-Rose et al. 2002). On the other hand, decreased D1 in the thyroid was not restored by leptin replacement, regardless of normal serum thyrotropin (TSH). Since serum corticosterone remained high in the food-restricted animals treated with leptin, we suggest that corticosterone might directly influence thyroid D1 activity. Thus during food restriction the decreased thyroid D1 activity might be related to the diminished serum TSH, or to increased serum corticoste-

rone. Thus, thyroid D1 was not normalized by leptin replacement, probably due to a direct effect of corticosterone that was not counterbalanced by the normalization of serum TSH.

Hence, the ability of leptin to restore serum thyroid hormones during a situation of negative energy balance might depend on the concerted normalization of serum corticosterone levels. Also, the sustained decrease of serum T4 and T3 might be a result of increased peripheral inactivating metabolism of T4 and T3 during food restriction, just as recently reported in another situation, such as myocardial injury (Olivares et al. 2007). A previous study (Coppola et al. 2005a; Coppola et al. 2005b) showed that the combination of low serum leptin and high serum corticosterone during food deprivation leads to increased hypothalamic D2 activity, and as a consequence decreased TRH expression and TSH secretion. We have also shown that prolonged food restriction also increases hypothalamic D2 activity, which is normalized by leptin administration, notwithstanding the fact that serum corticosterone remained elevated. Thus, leptin replacement per se is able to restore serum TSH during food restriction, possibly through the decrease in hypothalamic D2 activity. These results are consistent with the notion that increased hypothalamic D2 activity during food deprivation results in elevated local T3 production, which in turn decreases thyrotropin releasing hormone (TRH) expression and as a consequence serum TSH (Coppola et al. 2005a, b). It has recently been demonstrated that D2 is present in glial cells that are in direct contact with neurons coexpressing neuropeptide Y (NPY), agouti-related protein (AgRP), and uncoupling protein 2 (UCP2) (Coppola et al. 2007). The increased D2 during fasting induces T3-mediated UCP2 activation, which results in increased excitability of NPY/AgRP neurons. These neurons from the arcuate nucleus might be important for the regulation of TRH secretion by the paraventricular hypothalamus (Coppola et al. 2007).

In summary, during negative energy balance, independent of serum TSH the thyroid gland seems to be directly affected by changes in leptin and corticosterone. Decreased serum leptin levels contribute to the suppression of the hypothalamic-pituitary axis; however, the direct effect of leptin on the thyroid seems to be mainly inhibitory. On the other hand, leptin positively regulates liver and kidney D1 and BAT D2, which might be related to the increase in serum T3 in food-restricted animals treated with leptin. In conclusion, apart from its central action regulating the hypothalamic-pituitary-thyroid axis, leptin exerts direct peripheral effects on both thyroid gland and deiodinase activities.

These findings demonstrate that reduced circulating leptin accounts for some of the major endocrine and metabolic adaptive responses induced by weight loss (Boelen et al. 2006; Bianco et al. 2002). Conversely, in obese subjects increased circulating leptin levels would be expected to elevate serum T_3 and T_4 concentrations, which could serve as a mechanism to increase metabolic rate and confer a relative protection against the development of obesity. Importantly, there is no consistent evidence that circulating TH is increased in obesity.

Positive energy balance—diet-induced obesity

The physiological adaptations that occur in the thyroid axis during energy deficient states in order to avoid weight loss are well established. On the other hand, changes in thyroid metabolism in obesity have been poorly defined, since the majority of studies have been conducted in humans, and correspond to heterogeneous models. In recent years, some efforts have been done towards understanding the endocrine mechanisms that regulate energy balance and metabolic partitioning under conditions of energy surplus, since the rising prevalence of obesity is one of the most prominent public health concerns with great impact on health costs worldwide (Galgani and Ravussin 2008; Lage et al. 2008; Pi-Sunyer 2002; Elmquist 1998; Hamann and Matthaei 1996).

In obese subjects, increased circulating leptin levels would be expected to elevate serum T_3 and T_4 concentrations, which could serve as a mechanism to promote energy dissipation and restrict weight gain. However, this does not seem to be the case, since there is no clear evidence that circulating TH are increased in obese subjects, despite significantly increased serum leptin concentrations (Reinehr 2009; Tagliaferri et al. 2001).

Data from our group are consistent with the concept that negative energy balance determines down regulation of the axis and positive energy balance determines up regulation of the axis. However, the axis regulation per se is not enough to explain the metabolic changes observed in obesity, since serum levels of T_4 and T_3 are not elevated, although serum TSH is higher.

It has been proposed by some authors that obese subjects develop subclinical hypothyroidism, showing increased serum concentrations of thyroid-stimulating hormone (TSH) with normal serum concentrations of TH (Tagliaferri et al. 2001). On the other hand, there are studies showing that in obese individuals increased TSH is accompanied by moderately elevated total and free T_3, without any significant alterations in circulating T_4 (De Pergola et al. 2007), while others have reported that obesity is correlated with normal T3 and decreased T4 (Knudsen et al. 2005).

In fact, there is no consensus regarding the serum profile of thyroid hormones in obesity. We cannot rule out the

interference of the different nutritional diet composition on thyroid function during positive energy balance. However, the disruption of the normal HPT axis function is a consensus, which could be caused by: a) dysfunction of the hypothalamic-pituitary axis; b) modifications in thyroid gland function per se and/or; c) alterations in iodothyronine deiodinase activities in central and peripheral tissues.

Recently, we investigated the effects of a high-fat-diet-induced obesity on several parameters related to the HPT axis function in a rodent model, and found that total and free circulating levels of T_4 and T_3 are not altered after 8 weeks of high-fat-diet, despite elevated mRNA expression of TRH in the hypothalamus and circulating TSH (Araujo et al. 2010). The thyroid responsiveness to its trophic hormone (TSH) was normal, as ascertained by increased iodide uptake and D1 activity in the gland. It has been previously reported that body mass index (BMI) can be positively correlated with serum TSH, probably due to increased serum leptin (De Pergola et al. 2007). A possible mechanistic hypothesis to explain the increase in serum TSH should be the down regulation of pituitary D2 activity. In 1979, Larsen et al. demonstrated the important role of D2 in the control of TSH in adult rats, and more recently the strongest evidence for a pivotal role of D2 in the feedback mechanism came from D2 knockout mice (Schneider et al. 2001). These animals have normal serum T_3 but increased serum levels of TSH. So far, decreased pituitary D2 activity leads to diminished local T_3 production, causing a local hypothyroidism that leads to increased TSH secretion. The reduction in the intra-pituitary content of T3 occurs in both high-fat-diet induced obesity and the knockout mice, but these two models differ in the cause of decreased pituitary D2. In diet-induced obese rats serum rT3 is increased, which could behave as a physiological inhibitor of D2 activity (Cettour-Rose et al. 2002).

Based on our data, we hypothesize that iodothyronine deiodinases changes that are detected in different tissues might play an important role in the altered TH homeostasis seen in obese subjects. T4 secreted by the thyroid gland has been converted into rT3 in spite of T3. The mechanisms underlying the elevated serum rT3 are under investigation, however the absence of increased T3 surely protects the organism from increasing oxygen consumption. We first hypothesized that D3 induction should be the main contributor of increased serum rT3. However, no D3 mRNA expression in hepatic steatosis was observed in this model. Decreased BAT D2 might be a result of increased rT3 levels (Cettour-Rose et al. 2002), but further studies are needed in order to better evaluate D2 regulation in obesity. The role of D2, whose catalytic activity is limited to the conversion of T_4 into T_3, appears well defined. D2 activity is undoubtedly important for T_3 generation in tissues like brain, pituitary gland and BAT, and it also contributes to some extent to serum T_3 under both euthyroid and hypothyroid conditions (Coppola et al. 2007; Maia et al. 2005; Bianco et al. 2002).

D1 shows a broad substrate specificity and ability to either inactivate or activate TH, a feature that is less well understood (Bianco et al. 2002). We observed up regulation of liver and kidney D1 activity, but our data indicate that D1 in obesity may serve as a scanvenger enzyme to deiodinate T4 into inactive iodothyronines, since serum rT_3 concentrations were increased while serum T_3 concentrations were not altered. Our finding that D1 and D2 may compensate for the increased drive of the HPT axis is supported by Katzeff and Selgrad (1993), who showed alterations in thyroid hormone metabolism in obese Zucker rats resulting in impaired T_3 synthesis in tissues containing type 1 deiodinase, despite adequate T_4 availability.

In summary, despite stimulated hypothalamic-pituitary-thyroid axis, high fat diet-induced obese rats show tissue-specific modulation of peripheral thyroid hormones metabolism, which lead to normal serum T3 and oxygen consumption. These metabolic adaptations result in the maintenance of positive energy balance that might play an important role in the etiopathogenesis of obesity.

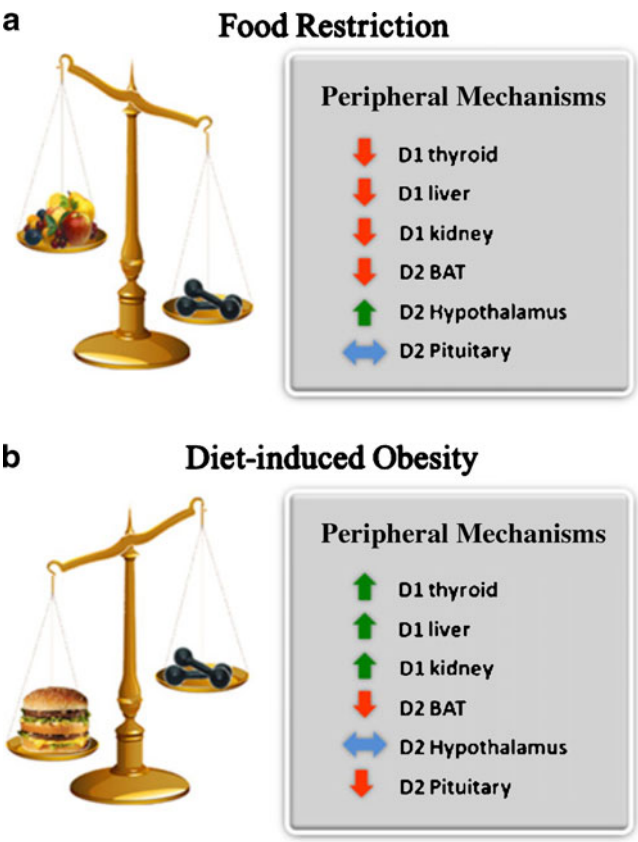

Fig. 3 Schematic representation of tissue-specific regulation of deiodinases enzymes during energy imbalance. Adapted from Araujo et al. 2009 and 2010

Final considerations

Energy homeostasis is critical for the survival of species. Throughout evolution, humans and animals have evolved redundant mechanisms promoting the accumulation of fat during periods of feast to survive during periods of famine. Therefore, multiple and complex mechanisms take place to regulate energy intake and expenditure in order to maintain body mass. Here we discuss that the regulation of iodothyronine deiodinases plays a crucial role in the adjustment of energy balance, as summarized in Fig. 3.

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Conflict of interest The authors declare no financial interests.

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