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Differential Adaptations of the Hypothalamus-Pituitary-Thyroid Axis Between Food Restriction and Anorexia

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1. Introduction

The hypothalamic-pituitary thyroid (HPT) axis plays a critical role in mediating changes in metabolism and thermogenesis. Its regulation is mainly determined by thyrotropin-releasing hormone (TRH), which is a tripeptide (pGlu-His-ProNH_2) synthesized in the paraventricular nucleus (PVN) of the hypothalamus. TRH-containing-neurons of medial and periventricular parvocellular compartments of the PVN are essential for HPT axis regulation since they are the only ones with hypophysiotrophic properties (Lechan & Fekete, 2006). Axon terminals of TRHergic neurons are highly dense in the median eminence (ME), in close apposition to capillaries of the hypophysial-portal system (Toni & Lechan, 1993), where TRH is released and able to stimulate the synthesis and release of thyrotropin (TSH) and prolactin from anterior pituitary (Bowers et al., 1968; Harris et al., 1978). TSH then stimulates thyroxine (T_4) and triiodothyronine (T_3) synthesis in the thyroid gland as well as their release into the peripheral circulation. Under normal conditions only a small fraction of T_3 is generated by the thyroid gland, the remainder of T_3, which is available for binding sites in the plasma and body cells, is produced by monodeiodination of T_4 (Danforth, 1983). This action is catalyzed by both type 1 (D1) or type 2 (D2) iodothyronine deiodinases, the first is abundant in liver, kidney and pituitary (Araujo et al., 2008) whereas the latter is mainly present in brown adipose tissue (BAT), pituitary and Central Nervous System (CNS) (Diano et al., 1998). The enzyme activity of the liver and kidney is responsive to the nutritional status of an organism and is found to be more active during states of accelerated glucose metabolism (Danforth, 1983).

Thyroid hormones (TH) are highly active in the metabolism and necessary for most bodily functions such as growth, development and maintenance of homeostasis; they are able to increase metabolic rate by accelerating fuel oxidation in nearly all tissues: TH activate lipolysis, glucose metabolism and protein synthesis (Yen, 2001).

Hypothalamic TRH expression in the PVN and TSH release from the anterior pituitary are inhibited by T_3, performing a negative feedback loop that regulates HPT axis function

(Ching & Utiger, 1983; Lechan & Hollenberg, 2003; Reichlin et al., 1978). TRH synthesis is negatively controlled by T_3 that acts through its binding to thyroid hormone receptor (TR); TRs are derived from two genes (TRα and TRβ) encoding different T_3-binding TR active isoforms (Yen, 2001). TRs are DNA binding transcription factors able to recognize specific DNA sequences in the promoter regions of T_3 target genes; in fact, T_3 regulates DNA-dependent RNA polymerase enzyme activity increasing or decreasing content of several mRNAs. Pro-TRH gene promoter contains a consensus region for the thyroid-hormone response element (TRE) (Segerson et al., 1987). Hyperthyroidism facilitates that TR sites are occupied by its ligand, which in turn are translocated to the nucleus and by binding to the TRE region in the DNA, inhibit TRH transcription. In contrast, when a decreased T_3 tissue concentration is present, un-liganded TR is bound to a co-activator protein, increasing pro-TRH transcription (Lechan & Kakucska, 1992; Perello et al., 2006).

Besides its regulation at the transcription level, THs are also involved in the processing of the large inactive precursor (pre-pro-TRH): once proTRH is transported from the endoplasmic reticulum (ER) to the trans-Golgi network (TGN), a proteolytic processing occurs. Those processes are conducted by two prohormone convertases (PCs), PC1/3 and PC2, which cleave proTRH at basic residues flanking TRH sequence (Nillni et al., 1995, 1996; Schaner et al., 1997). PCs activity may also be regulated by TH (Espinosa et al., 2007; Perello et al., 2006). During hypothyroidism, end products of proTRH processing increase (Perello et al., 2006), while a decreased post-translational processing of proTRH is observed in T_4 treatment-induced hyperthyroidism (Segerson et al., 1987) rendering an accumulation of TRH unprocessed intermediate forms combined with a down-regulation of PCs (Perello et al., 2006). Several studies suggest that thyroid hormones negatively regulate the PC expression through the binding of its receptors to a consensus region localized in PC genes promoters (Li et al., 1999, 2000; Shen et al., 2005). Therefore, HPT axis regulation by thyroid status in the PVN may lead to an altered hormonal biosynthesis.

Besides TH control of proTRH transcription, corticosterone is also able to regulate it. Rat TRH gene promoter also contains a consensus region for glucocorticoids; it is a composite GRE element (cGRE) that is located at -218, -197 bp. It has been studied the effect of corticosterone or the synthetic corticosteroid dexamethasone under different conditions: it is observed *in vivo* that adrenalectomized animals present an increased TRH expression in the PVN, while administering rats with glucocorticoids on their drinking water, it is induced a decrease in peptide mRNA levels. Moreover, hypothalamic primary cultured cells added with dexamethasone present a reduced TRH synthesis. Furthermore, although nuclear extracts of hypothalamic cells incubated with 8Br-cAMP, present an increased transcription rate of TRH, the combined effect of glucocorticoids and cAMP pathway activators, is unable to elevate peptide synthesis (Diaz-Gallardo et al., 2010).

Degradation of the released peptide is achieved by the pyroglutamyl peptidase II (PPII, EC 3.4.19.6). It is a highly specific membrane-bound metallopeptidase that exclusively hydrolyzes the pyroglutamyl-histidyl peptide bond of TRH (Charli et al., 1998) in the extracellular space. PPII is widely distributed in the CNS and in some peripheral tissues (Heuer et al., 2000; Vargas et al., 1987). Its soluble form is named thyroliberinase present in serum, which is thought to be synthesized in the liver and derived from the same gene than PPII.

Anterior pituitary PPII enzyme is regulated by different factors and hormones: low serum TH levels decrease its activity and mRNA content, while hyperthyroidism increases both, suggesting that PPII regulation participates in the negative feedback of the TH that controls the HPT axis function (Bauer, 1988; Ponce et al., 1988; Schomburg & Bauer, 1995). Estrogens in contrast, affect PPII activity negatively, which may allow TRH to increase the duration of its effect in the anterior pituitary (Bauer, 1988). On the other hand, the addition of TRH to pituitary cultured cells induces a down-regulation of both PPII mRNA levels and activity (Vargas et al., 1994, 1998); furthermore, incubation with activators of cAMP pathway may mimic TRH effect on PPII (Vargas et al., 1998).

Body weight changes in obesity, fasting or food restriction are associated to alterations in circulating TH content. *In vivo* studies have shown that inhibition of pituitary PPII, increases the duration of TRH-induced release of TSH (Scalabrino et al., 2007), thus it is likely that PPII regulation might contribute to the reestablishment of the HPT axis homeostasis. The activity in serum of the soluble enzyme thyroliberinase, is known to be modified by body weight changes in obese humans independently of their thyroid hormone levels (Friedman et al., 1995). Thus, all those data support that TRH degradation plays a regulating role in the HPT axis function.

2. Adaptive hypothyroidism

Adaptive function of HPT axis allows animals to respond to changes in energy demands during growth, gestation, lactation or sickness periods. Nutrient availability that is modified with seasons or changing weather, triggers adaptive changes in the HPT function leading organisms to enlarge fat and glycogen deposits or to slow its degradation, depending on energy needs.

Main function of the thyroid gland is to maintain the basal metabolic rate in all cells. Thyroid hormone levels are challenged during the transition from fed to a starvation state; during starvation a reduced metabolic rate helps to preserve energy stores. This response is considered as the major evolutionary mechanism designed to ensure survival when food is scarce, although nowadays it may represent a risk to become obese during times of great food availability (Levin, 2006; Ogden et al., 2007a, 2007b).

During food restriction and starvation the feedback mechanism exerted by TH on hypothalamus and pituitary, is altered. Low body weight accompanied by decreased leptin serum levels induce a decrease in TH serum concentration (Ahima et al., 1996). In spite of the induced hypothyroidism, food deprivation for 3 days reduces the hypothalamic proTRH mRNA content, the amount of proTRH-derived peptides in the PVN, TRH release into hypophysial portal blood (Rondeel et al., 1992), pituitary levels of TSHβ mRNA and TSH plasma levels; it also induces a marked increase in plasma corticosterone content (van Haasteren et al., 1995). Re-feeding of starved male rats normalizes T_4 serum levels within 3 days, while T_3 and TSH content increases above the values observed before starvation.

Both male and female rats respond to a 4 day food deprivation with a body weight loss however, females have a better adaptation to energy deficit than males: they present decreased T_4 and T_3 levels together with reduced TSH serum levels after starvation (Rondeel et al., 1992), also their basal hypothalamic TRH release is lower than in males (Rondeel et al.,

1992). HPT axis adaptation depends on the age of animals: fasted weaning rats do not decelerate the HPT axis function; in spite of its 30% loss of weight compared to non fasted animals, TRH release remains active, TSH serum levels do not decay and PPII enzymatic activity is reduced, presumably allowing the peptide to exert its effects on the pituitary for a longer time (de Gortari et al., 2000). In contrast, adult animals after 72 h of fasting show a decreased TRH content in the ME, reduced TSH serum levels and no change in PPII activity (de Gortari et al., 2000). The fact that TSH does not change or is reduced when T_3 and T_4 serum levels are low is probably due to a decreased expression of the thyroid receptors in thyrotrophes induced by starvation (Bavli, 1980; St Germain & Galton, 1985; van Doom et al., 1984). A more recent explanation involves a central deregulation of deiodinases activities causing the fasting-associated changes in thyroid function.

Food deprivation is a stressful situation that enhances adrenal release of corticosteroids (Garcia-Belenguer et al., 1993; Mitev et al., 1993; Woodward et al., 1991). Starvation-induced corticosterone secretion reduces TRH and TSH-β synthesis and release; dexamethasone treatment also reduces the hypothalamic TRH secretion into hypophysial portal blood (van Haasteren et al., 1995). Thus, corticosterone is a factor that may be participating in the HPT adaptive changes to nutrient deficit.

2.1 Underlying factors of negative energy balance-associated hypothyroidism

Some factors have been studied as contributors to decreased synthesis of TRH in the PVN during fasting or food restriction, such as the activity of deiodinases. Type 2 deiodinase (D2) enzyme activity and its mRNA content in the tanycytes of the medial basal hypothalamus, increases with fasting (Lechan & Fekete, 2005); D2 converts T_4 to T_3 and therefore is responsible for the maintenance of the medial basal hypothalamic (MBH) local T_3 concentration (Diano et al., 1998), thus the inhibition of TRH expression observed in the medial PVN of starved rats may be a consequence of a higher production of local T_3 (Coppola et al., 2005).

Besides corticosterone and deiodinase activity, leptin peripheral administration can prevent the fall of TH in starved rodents, and the reduced expression of proTRH in the PVN after fasting (Ahima et al., 1996; Legradi et al., 1997). In other words, fasting-induced decrease of serum leptin content is able to reduce proTRH expression in the PVN, also to facilitate the high secretion of corticosterone that contributes to elevate D2 activity (Coppola et al., 2005) around the third ventricle. Thus, starvation and food restriction create a state of tertiary hypothyroidism and of reduced metabolic rate in the whole body that might serve as an important energy-conserving mechanism until re-feeding occurs.

Leptin is not only modified in situations of negative energy balance; patients with primary hypothyroidism due to autoimmune thyroid disease, present an increase in body weight, decreased appetite and low leptin serum levels, so it is suggested that changes in leptin levels do not explain the alterations in appetite usually found in these patients; but as mentioned, lower leptin serum levels could contribute to the decrease in energy expenditure in hypothyroidism (Valcavi et al., 1997).

At the central level, the hypothalamus is the primary component in the nervous system that interprets adiposity or nutrient related inputs; it finally directs hormonal and behavioral responses to regulate energy intake. Neurons in the hypothalamic arcuate nucleus (ARC)

receive circulating adiposity levels and relay their responses to second-order neurons in the PVN and lateral hypothalamus to mediate effects on food intake and energy homeostasis; TRHergic neurons are among those second-order neurons stimulated by the melanocortin system (Nillni, 2010).

Hypophysiotrophic TRH neurons receive inputs from other regions of the brain as well as from the circulation. The most important afferent connections to PVN TRHergic cells include catecholamine neurons from the brainstem (Sawchenko & Swanson, 1982) and from the ARC, a nucleus with a prominent role in energy homeostasis.

Two are the main populations of neurons arising from ARC that send their axons to PVN TRHergic cells: those co-expressing neuropeptide Y and agouti-related protein (NPY/AgRP) (Broberger et al., 1998) and those co-expressing cocaine and amphetamine regulated transcript and α-melanocyte stimulating hormone (CART/α-MSH) (Vrang et al., 1999). Both NPY and AgRP stimulate food intake, whereas CART/ α-MSH reduce it. Hypothalamic T_3 production, catalyzed by D2, triggers the synthesis of mitochondrial uncoupling protein 2, which is critical for the activation of NPY/AgRP neurons during fasting (Coppola et al., 2007). NPY and AgRP inhibit TRH gene expression on hypophysiotrophic TRH neurons (Fekete et al., 2001, 2002), in contrast, CART/α-MSH stimulate TRH gene expression in the PVN, and this effect is enhanced by leptin (Fekete et al., 2000a, 2000b); both neuronal populations of ARC express leptin receptors and are inversely regulated by circulating leptin concentrations (Ahima et al., 2000).

Neuropeptides derived from the ARC play a significant role in the response of thyroid axis to both starvation and illness. Physiologically, the interaction of the ARC inputs on hypophysiotropic TRH neurons may be the primary mechanism for the development of central hypothyroidism associated with fasting, initiated by leptin (Ahima et al., 1996; Lechan & Fekete, 2004; Legradi et al., 1997). Serum leptin concentrations drop dramatically during fasting, and leptin replacement partly prevents starvation-induced decrease in serum T_4 levels and increases serum corticosterone in mice (Ahima et al., 1996). In general, leptin has a central physiologic role in providing information about energy stores and energy balance to brain centers that regulate appetite, energy expenditure and neuroendocrine functions (Campfield et al., 1995; Pelleymounter et al., 1995).The fall in circulating levels of leptin is sensed by the hypothalamus, which triggers increased appetite, decreased energy expenditure and a changed neuroendocrine function in a direction that favors survival.

Although the hypothalamic effects of leptin are mediated via the melanocortin system, which plays a role in feeding behavior, evidence exists about a direct role of leptin on PVN TRHergic cells (Harris et al., 2001; Nillni et al., 2000); nevertheless, ARC-derived neuropeptides still play the most significant role in the regulation of proTRH neurons, via synaptic input from leptin-responsive POMC and NPY/AgRP neurons located in the ARC (Fekete et al., 2000; Legradi & Lechan, 1998; Schwartz et al., 1996).

As a consequence of negative energy balance, the normal feedback mechanism for the regulation of hypophysiotrophic TRH neurons is overridden and a state of central hypothyroidism is induced, commonly referred to as "nonthyroidal illness" or the "sick euthyroid syndrome" (Wiersinga & Boelen, 1996).

2.2 Non-thyroidal illness syndrome

Alterations in neuroendocrine axis develop secondary to illness. An activation of the hypothalamic-pituitary-adrenal (HPA) axis is well documented (Vermes & Beishuizen, 2001). Although acute or chronic sickness can cause alterations on TSH and/or T_4 concentrations in plasma (Fliers et al., 2001), low circulating T_3 levels are the most common consequence of HPT axis adaptations. The main accepted term to make reference to these changes on HPT axis is the non-thyroidal illness syndrome (NTIS) (Warner & Beckett, 2010), given that not primary alterations in the thyroid gland are involved and that patients are considered clinically euthyroid. Probably this reduction on HPT axis function is a beneficial adaptive response in order to reduce energy expenditure in a sick organism.

There are many factors involved in the hormonal changes that result in the NTIS; these include modifications to the hypothalamic-pituitary axis, altered binding of thyroid hormone to circulating binding proteins, a modified entry of thyroid hormones into tissues, changes in thyroid hormone metabolism or alterations that are due to a modified expression of deiodinase enzymes (Warner & Beckett, 2010).

It seems that the low TSH levels associated with critical illness (or failure of TSH to increase in the presence of low T_3 and T_4) arise from a central hypothyroidism caused by alterations in the set point of the HPT axis regulation. This idea is supported by the fact that the administration of TRH to patients with prolonged critical illness at least partially restores serum T_3, TSH and T_4 content (Van den Berghe et al., 1998, 1999). The underlying mechanisms for the decreased TRH in hypothalamic neurons in patients who died with serum biochemistry of the NTIS may include the secretion of pro-inflammatory cytokines (Fliers et al., 1997); a different cause may be the chronic low food intake.

As mentioned previously, activation and inactivation of TH are carried out by a group of three iodotiroinine deiodinases. Changes on peripheral deiodinase enzymes' activity during illness are known to be an effect rather than the cause of alterations on circulating T_3 and T_4 in the NTIS (Debaveye et al., 2008; O'Mara et al., 1993). The rapid fall in T_3 seen in acute illness is more likely due to either impaired thyroidal production of T_3 (induced by a central hypothyroidism) and/or the result of the acute phase response leading to a decrease in serum thyroid hormone-binding protein (Warner & Beckett, 2010).

Administration of bacterial lipopolysaccharide (LPS) is a manner to study acute infection and immune activation. It has been shown that after 12 h of LPS administration, type 2 deiodinase mRNA synthesis increases in tanycytes lining the third ventricle. The ensuing local thyrotoxicosis may suppress the HPT axis by local feedback inhibition of hypophysiotrophic TRH synthesis and contribute to the mechanism of central hypothyroidism associated to infection (Fekete et al., 2004), which as previously mentioned, is probably an homeostatic response to preserve energy deposits during illness (De Groot, 1999). Contrary to the mechanism of central hypothyroidism associated to fasting (Legradi et al., 1997; Rondeel et al., 1992; van Haasteren et al., 1995), infection increases the gene expression of pro-opiomelanocortin (POMC) (the precursor molecule of α-MSH) and CART in the ARC, it does not increase NPY expression (Sergeyev et al., 2001) and elevates circulating levels of leptin (Grunfeld et al., 1996). These changes should elevate TRH expression; nevertheless during infection, stimulation of D2 synthesis by the increased LPS-induced pro-inflammatory cytokines concentration, is a more powerful stimulus that

maintains low PVN TRH expression (Fekete et al., 2004). As happens during starvation, the increase in hypothalamic T_3 content may suppress the synthesis of TRH in hypophysiotrophic neurons either by local feedback inhibition through the release of T_3 from tanycytes' apical processes into the cerebrospinal fluid (CSF), or by its uptake from hypophysiotrophic TRH axonal processes in the median eminence and by its retrograde transport to the hypothalamic PVN. T_3 may also be released into the portal capillary system for conveyance to the anterior pituitary and exerts a direct effect on the thyrotrophes of the anterior pituitary where, it inhibits TSH secretion (Lechan & Fekete, 2005).

3. Dehydration-induced anorexia

There is a balance between food intake and energy utilization: an increased feeding behavior in animals compensates high energy waste. However, this equilibrium may be altered by different psychological and physiological stimuli that may induce the display of an aberrant behavior such as anorexia. Anorexia is defined as a loss of appetite despite of a low body weight and of an energy deficit. It may result during illness, after stress exposure, or as a response to homeostatic challenges such as cellular dehydration (Siegfried et al., 2003). In contrast to food restricted or dieting individuals, anorexic patients present normal or subnormal serum levels of T_4 and TSH (Stoving et al., 2001); also, a blunted TSH release form the pituitary after TRH administration (Tamai et al., 1986). Alterations of the HPT axis in anorexia nervosa have most likely a central origin, due to the reduced hypothalamic TRH secretion, and resemble those of the NTIS.

Besides its hypophysiotrophic role, TRH is implicated with neuromodulating effects in the CNS. As an icv injection of TRH in different animal species, reduces their food and liquid intake (Choi et al., 2002; Karydis & Tolis, 1998; Vijayan & McCann, 1977; Vogel et al., 1979), it has been proposed as an anorexigenic factor, which has been tested in *ad libitum* feeding animals, in those subjected to stress-induced eating models, and also in fasted and hungry animals during the re-feeding period (Horita, 1998; Morley & Levine, 1980; Steward et al., 2003; Suzuki et al., 1982; Vijayan & McCann, 1977). As mentioned, PVN TRHergic neurons express receptors for different feeding-regulating peptides synthesized in the ARC, such as NPY, AgRP, CART and α-MSH; also for leptin (Ob-Rb) which suggests that the hormone has an indirect effect on TRH expression by acting on feeding-related synthesizing neurons of the ARC, but also has a direct action on PVN TRHergic cells (Wittmann et al., 2009). As TRHergic neurons of the anterior part of the PVN are known to have projections to the ARC, to dorsomedial and to ventromedial hypothalamic nuclei, it is likely that besides its role in energy homeostasis, motivational aspects related to food intake might also be under TRH control.

To investigate TRH participation in feeding motivation we have used the dehydration-induced anorexia (DIA) model. Male and female adult animals subjected to this paradigm ingest a hyperosmolar solution of NaCl (2.5%) during 7 days, which reduces its food intake and body weight since day 1. Analysis of the expression of feeding-regulating peptides in the ARC of males after 5 days has shown a decreased synthesis of POMC and increased NPY mRNA levels (Watts et al., 1999), which have anorexigenic and orexigenic effects, respectively. All those changes are signals that should be increasing appetite and food ingestion in animals, however feeding is suppressed in dehydrated rats, which suggests that inhibitory control networks, other than those of the ARC, are activated (Watts, 2001, 2007).

The involvement of some hypothalamic peptides in feeding motivation may be identified using this paradigm, since changes in their synthesis due to dehydration in DIA animals are compared to those of a forced food-restricted group (pair-fed, FFR) that eat the exact amount of food ingested by DIA

Studies from other laboratories and ours have shown that when sacrificed either after 5 or 7 days (Jaimes-Hoy et al., 2008; Watts et al., 1999), both experimental animals from DIA and FFR groups present reduced leptin serum levels and high corticosterone concentrations (Table 1). Thus, both groups have a negative energy balance that only in FFR animals, activates feeding.

	TSH	T_3	T_4	Leptin	Corticosterone	Prolactin
Control	100 ± 13	100 ± 4	100 ± 2.5	100 ± 8	100 ± 7	100 ± 9
DIA	151 ± 21*+	64 ± 3*	99 ± 16	37 ± 5*	218 ± 17*	101 ± 9+
FFR	73 ± 12*	74 ± 9*	75 ± 9	33 ± 4*	263 ± 23*	20 ± 4*

Table 1. Serum hormones content in female rats after 7 days of dehydration or food restriction. Values are expressed as the mean ± SEM in percentage of difference vs C= 100%, n= 8 animals/group). Control values of TSH: 2.1 ± 0.22 ng/ml; T_3: 74 ± 2.7 ng/dl; T_4: 1.58 ± 0.09 µg/dl; leptin: 425 ± 33 pg/ml; corticosterone: 151 ± 15 ng/ml; prolactin: 0.97 ± 0.09 ng/ml) *p<0.05 vs C, +p<0.05 vs FFR. Modified from Jaimes-Hoy et al., 2008.

In order to identify changes in HPT axis function during those metabolic alterations, and with the notion that an icv injection of TRH has an anorectic role, female and male Wistar rats have been subjected to DIA paradigm for 7 days; their body weight and food intake is registered daily and is compared to that of FFR animals and to those of a control (C) group that is offered food *ad libitum* and tap water along the experiment. When compared food ingestion of animals from the same group by gender, results show that males eat more than females: dehydration induces a drastic decrease in food intake of males during the first four days, and a steady intake thereafter (Table 2); in contrast, females continuously decrease their food consumption up to day 6. DIA group of males have a dramatic weight loss since the first day, achieving a reduction of 32% of body weight by the 7th day when compared to controls (C=100%, FFR =73%, DIA = 68%). Females do not have such a drastic decrease, by the end of the experiment they lose 25% of controls' weight (C=100%, FFR =82.4%, DIA = 75%). Despite FFR group is pair-fed to dehydrated animals their body weight loss is less pronounced than in DIA rats (Figure 1).

	Day 0	1	2	3	4	5	6	7
				Females				
Control	100 ± 1	100 ± 3	100 ± 7	100 ± 6	100 ± 5	100± 11	100± 10	100 ± 4
DIA	100 ± 1	48 ± 3**	25 ± 5**	15 ± 4**	12 ± 3**	6 ± 2**	3 ± 2**	5 ± 3**
				Males				
Control	100 ± 1	100 ± 6	100 ± 8	100 ± 5	100 ± 5	100± 10	100± 10	100 ± 7
DIA	100 ± 1	55 ± 2*	22 ± 2*	12 ± 2*	11 ± 3*	9 ± 3**	9.4 ± 4**	10 ± 4*

Table 2. Food intake of female and male adult rats subjected to dehydration-induced anorexia model during 7 days. Values are expressed as the mean ± SEM as percentage of controls (C=100%) (n= 6 animals/group). *p<0.001, **p<0.0001 vs. control values.

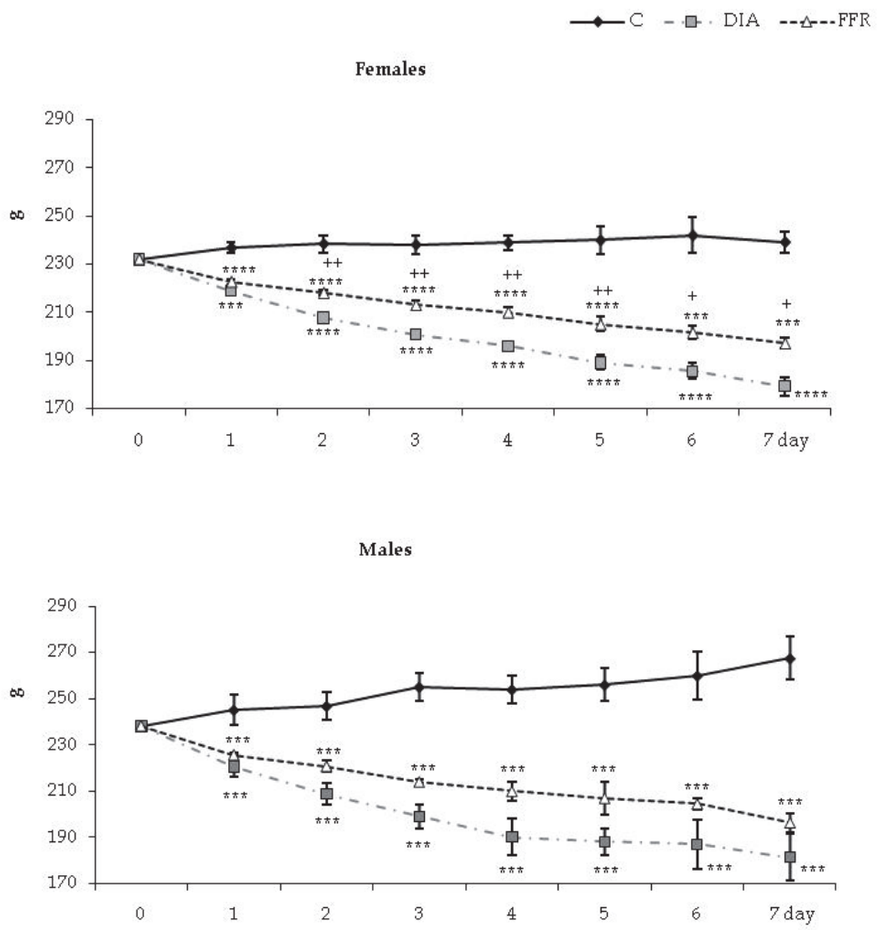


Fig. 1. Body weight of female and male adult rats subjected to dehydration-induced anorexia model or to forced-food restriction during 7 days. Controls: C, dehydrated-induced anorexic: DIA, forced-food restricted animals FFR. Values are expressed as the mean ± SEM in grams (n= 6/group). Modified from de Gortari et al., 2009. ***p<0.001, ****p<0.0001 vs. control group; +p<0.05, ++p<0.01 vs FFR.

We have also analyzed weight changes in white and brown adipose tissue of females affected by dehydration or food restriction, but there is no change. Thus, dehydration seems to contribute to the greater body weight loss of DIA animals. Different analysis of muscle hormonal content, such as T_3 local levels produced by deiodinases activity, would be necessary to identify a specific high catabolic rate of dehydrated animals in that tissue.

Measuring the content of TRH (by radioimmunoassay) in the ME of dehydrated and FFR animals, it is observed that DIA group of both sexes has reduced peptide content. Analysis of some other parameters of the HPT axis function, such as TSH, T_4 and T_3 serum levels have been described; also, TRH mRNA levels in the PVN and expression of TRH-R1 and of PPII in the anterior pituitary. As TSH levels increase after 7 days of dehydration, and TRH content in the ME is low (and is high in FFR), we have inferred an active peptide release from the hypothalamus in dehydrated animals that maintains elevated TSH serum content (Table 1). Knowing that at least in cultured cells, TRH addition down-regulates synthesis of

its receptor (Yang & Tashjian, Jr., 1993), the reduced expression of anterior pituitary TRH-R1 of male and female DIA animals (Table 3) have supported that TRH is being released only after dehydration.

	PVN pro-TRH mRNA	ME TRH content	Pituitary TRH-R1 mRNA
Control	100 ± 4.8	100 ± 11	100 ± 16
DIA	130 ± 9*+	76 ± 4*+	77 ± 10*+
FFR	62 ± 5*	148 ± 10*	138 ± 22*

Table 3. PVN proTRH expression, peptide content in the ME, and TRH-R1 mRNA levels in the pituitary of female rats exposed to dehydration for 7 days. Expression changes are measured by RT-PCR. Values are expressed as the mean ± SEM as percentage of controls (C=100%) (n= 6 animals/group). *p<0.05 vs. control; +p<0.05 vs. FFR. (Jaimes-Hoy et al., 2008)

The low expression of TRH-R1 in the pituitary of anorexic animals resembles the delayed response of TSH to a TRH injection in anorexic patients (Tamai et al., 1986). The down-regulation of TRH-R1 receptors is most likely a result of the high release of TRH from the ME of DIA animals that in a long term may alter the function of the pituitary.

In spite of the high TSH serum levels observed in DIA, a low T_3 serum content is present when compared to C and FFR groups. It is possible that in the thyroid gland of dehydrated animals, the TSH receptor is internalized as is observed in hypothyroid conditions using both *in vivo* and *in vitro* studies (Baratti-Elbaz et al., 1999; Denereaz & Lemarchand-Beraud, 1995) when TSH content is elevated; results suggest a low binding of TSH to its receptor that is observed (up to 70%) in the hypothyroid condition when compared to euthyroid subjects but only when T_3 levels decrease (Denereaz & Lemarchand-Beraud, 1995).

An elevation of pro-TRH expression, analyzed by RT-PCR is observed in both males and in female dehydrated animals when compared to C and to FFR (Table 3). As expected, FFR of both gender present reduced TRH mRNA levels in the PVN (Table 3). Among the factors that are known to affect PVN TRH expression, we can mention the decreased leptin and increased corticosterone serum levels. However, since the concentration of those hormones is similarly changed in both experimental animals, the differential mRNA levels of TRH between DIA and FFR cannot be attributed to their hypothalamic effects. It would be possible, that D2 activity in the medial basal hypothalamus is decreased in DIA animals. As previously stated, D2 converts T_4 in the active hormone T_3 controlling its hypothalamic levels that may differ from those in the peripheral content. If dehydration causes a decrease on D2 activity, this would lead to a low T_3 local content that may stimulate TRH synthesis. The opposite has been shown in fasted animals: an increased D2 expression and activity seems responsible for the low TRH mRNA levels in the PVN during a negative energy balance.

All changes in the HPT axis of DIA group are representative of a primary hypothyroidism that is paradoxical since animals are under a negative energy balance and is contrasting to the tertiary hypothyroidism developed in fasting or food restriction.

However, it is still un-known which TRHergic neurons of the PVN are activated during dehydration.

TRHergic cells of the anterior part of the PVN (aPVN) do not project to the median eminence (Ishikawa et al., 1988; Kawano et al., 1991; Merchenthaler & Liposits, 1994) thus, they are neither hypophysiotropic nor under negative feedback by TH (Nishiyama et al., 1985; Segerson et al., 1987). Two of the major projection fields of aPVN TRH neurons are the ARC and the dorsomedial hypothalamus (DMH) (Morton et al., 2006; Wittmann et al., 2009) thus, it is possible that the observed anorectic effect of the icv administered TRH is mediated by neurons of that subdivision (Wittmann et al., 2009), but it awaits to be elucidated. Feeding-regulating role of TRH from the anterior part of the PVN TRH is also supported by studies showing an unaltered expression of the peptide in suckling rats (Sanchez et al., 2001) that are known to develop hyperphagia during lactation periods (Xu et al., 2009). It is likely that the lack of increase in TRH synthesis only in the aPVN of suckling rats would allow them to increase their food intake. Moreover, NPY from DMH is responsible for the hyperphagic drive during lactation, a major projection field of TRHergic neurons from the aPVN (Wittmann et al., 2009).

TRH from the aPVN may also have different roles to those related to food intake. Through its connections with the preoptic area, TRH from that subdivision of the PVN may regulate thermogenesis by activating the sympathetic nervous system (Morrison et al., 2008). This idea is supported by the fact that DIA female animals exposed to cold do not have a further increase on TRH expression than those maintained at room temperature (Jaimes-Hoy et al., 2008).

Activation of TRHergic neurons of the aPVN during dehydration, would be explaining the lack of decrease prolactin serum levels present in female rats subjected to DIA (Jaimes-Hoy et al., 2008) when compared to FFR rats (Table 1); besides its direct effect on prolactin secretion from pituitary lactotrophs (Grosvenor & Mena, 1980), TRH from the aPVN is able to inhibit the tuberoinfundibular dopaminergic system (Goldstein et al., 2007) increasing hormone release from the anterior pituitary to the blood. The main projection of aPVN TRH neurons is the dorsomedial part of the ARC (Wittmann et al., 2009), a region involved in the regulation of prolactin secretion (Freeman et al., 2000), suggests that aPVN subdivision may be involved in changes induced by dehydration, however, speculations may be confirmed by in situ hybridization analysis that would allow the identification of PVN TRHergic neurons activated in DIA.

Different signals that regulate food intake may be responsible for the paradoxical HPT function and the increased TRH mRNA levels of the PVN in dehydrated rats. One of them is the orexinergic system. During fasting, pre-pro-orexin-synthesizing cells in the lateral hypothalamic area (LHA) are activated; its derived peptides, orexin A and B, are factors that stimulate feeding (Sakurai et al., 1998). Orexins-containing neurons from LHA project to the PVN (Peyron et al., 1998) where its receptors have been identified (Backberg et al., 2002). Those are findings that support orexins participation in energy homeostasis (Yamamoto et al., 1999) and thermoregulation (Jaszberenyi et al., 2002). Orexin A is the peptide involved in activation of food intake, its injection increases feeding and decreases body temperature (Jaszberenyi et al., 2002). Those effects of orexin A are mediated through its interaction with

the NPY system (Muroya et al., 2004). In contrast, orexin B is implicated in arousal and with wakefulness effects (Lin et al., 1999; Siegel, 1999).

Besides information arriving from LHA orexinergic neurons, PVN also receives connections from the ARC including NPY-synthesizing neurons. In the PVN, some of the target cells of NPY are those that synthesize TRH that contain NPY-Y1 receptors (Broberger et al., 1999); NPY-Y1 receptors are activated during fasting or food restriction by the increased release of NPY, which in turn inhibits TRH synthesis (Fekete et al., 2001, 2002).

Thus, changes in the LHA pre-pro-orexin (Ox) mRNA levels and PVN orexin (Ox-1R) and NPY (Y1, Y5) receptors of male rats subjected to DIA paradigm for seven days, have been analyzed and compared to those of animals that are food-restricted. As PVN receives direct information from circulating leptin levels concerning size and volume of adiposities and TRHergic neurons of that hypothalamic region contain Ob-Rb receptors, thus studies have been made to analyze alterations in the expression of PVN leptin receptor that would account for the differential expression of TRH between DIA and FFR male animals.

LHA of dehydrated animals, present unchanged expression of the pre-pro-orexin mRNA content, in contrast to that of FFR rats that have increased synthesis of the orexigenic peptide (Figure 2), supporting that this area is responsive to the negative energy balance. It has been previously described that *c-fos* expression is not activated in LHA orexinergic cells in DIA paradigm (Watts et al., 2007). Furthermore, non-responding orexinergic neurons have been observed in animals where an anorexic behavior is induced by a LPS injection (Becskei et al., 2008). Results support that the anorexic behavior presented by DIA animals may be due to an inactivation of the orexinergic system in the LHA that should be stimulating energy intake through its connections to the PVN (Peyron et al., 1998). It is known that orexins act directly on NPYergic projections coming from the ARC and afferent to the PVN through its orexin receptors expressed in NPY-synthesizing neurons. Thus, it would be possible that TRH expression in the PVN is increased in DIA animals by the impaired inhibiting effect of the orexinergic system during dehydration.

In the PVN of FFR animals, the expression of the orexin-receptor is lower than in DIA and C groups; this may be due to the inferred increased orexins release in the PVN that as for other receptors induces a desensitization mechanism that leads to a protein down-regulation. DIA animals present a higher synthesis of Ox-R1 than that of FFR, which may be interpreted as a compensatory increase due to poor peptide release in those animals, and also as an impaired receptor signaling; it has been observed in other models of anorexia (Ballinger et al., 2001). It is likely that orexins released in the PVN or food-restricted rats inhibit TRH release, and in consequence, TSH serum levels also are low, as has been observed by an icv injection of orexins (Mitsuma et al., 1999). Using the DIA paradigm it is evident that anorexic animals do not have that pathway activated thus, the differential change in Ox-R1 mRNA levels between FFR and DIA groups could be an additional responsible factor for the enhanced expression of proTRH in the PVN of dehydrated rats. Since LHA orexin-containing neurons send projections to magnocellular and also to parvocellular neurons of the PVN (Backberg et al., 2002), it is possible that orexins may be affecting energy homeostasis, but also that they may be participating in regulation of water balance or blood pressure, processes in which TRH has also been implicated.

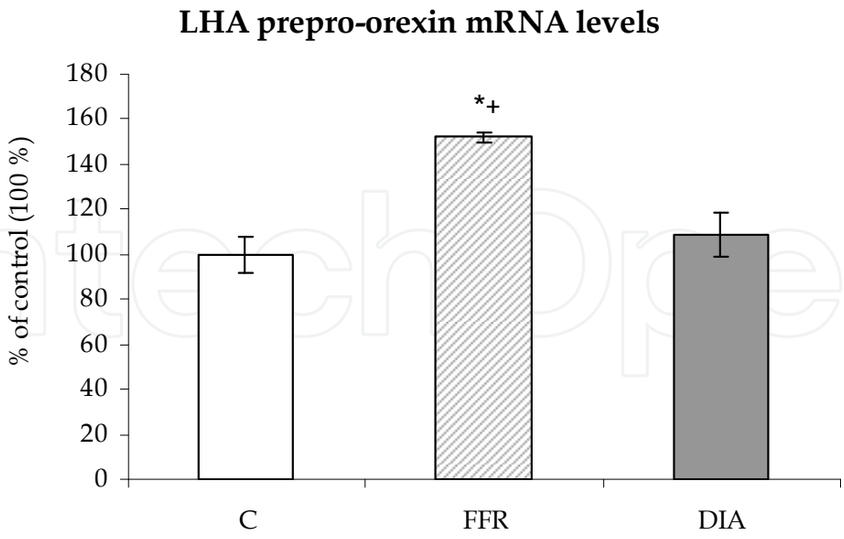


Fig. 2. Prepro-orexin mRNA levels in the lateral hypothalamic area (LHA), mRNA levels were semi-quantified by RT-PCR. Values (in percentage) are the ratio of prepro-orexin cDNA/cyclophilin cDNA expressed as the mean ± SEM calculated as % of naïve values (C= 100 %), n=8. *p<0.01 vs naïve, +p<0.001 FFR vs.DIA. Modified from García-Luna et al., 2010.

Besides orexins in the LHA, TRH expression is also differentially altered in this nucleus between anorexic and food restricted animals. Synthesis of TRH is reduced only in the FFR rats, while it increases after 7 days of DIA. LHA TRHergic cells send projections to the septum, an area involved in arousal (Ishikawa et al., 1986; Prokai, 2002), thus, it is not unlikely that the peptide synthesized in LHA has functions related to maintain an alertness state in food restricted animals.

As both DIA and FFR groups have increased synthesis of NPY in the ARC (Watts et al., 1999), and leptin serum levels are similarly low, it is not possible to think that behavioral differences in feeding motivation of those groups are due to an impaired response of ARC NPYergic neurons to the decreased leptin serum content. However, an alteration in the downstream pathway of leptin signaling in the PVN of DIA animals, may contribute to the development of anorexia after dehydration. We have found an increased expression of the Ob-Rb in the PVN of FFR group only when compared to DIA. This suggests that leptin receptors in dehydrated animals are at least, slightly activated vs FFR; this difference could be compensating the low leptin levels and may increase PVN TRH synthesis. In FFR, Ob-Rb seems not to be functional, thus TRH expression remains low. Reduced serum leptin content may not be correlating with hormonal levels in the cerebrospinal fluid of dehydrated animals due to alterations in the peptide transport to the brain that has been proposed in anorexic and in obese patients (Schwartz et al., 1996). It is not unlikely either, that dehydration is increasing sensitivity and affinity of Ob-Rb receptors for their ligand, which is overcoming the low leptin serum levels and is contributing to the development of anorexia in DIA animals.

By the analysis of the expression of NPY receptors in the PVN, we have observed that only FFR animals present decreased Y1 mRNA levels, when compared to DIA animals that have

similar values to the control group. This suggests that NPY in FFR is able to activate Y1 and to favor food-seeking behavior; the unchanged synthesis in anorexic animals may be related to a failed inhibition of their PVN TRH synthesis. A similar NPY release than a control group and a differential expression of NPY-Y1 occurs in another model of anorexia (Ballinger et al., 2001); furthermore, an Y1 agonist injection facilitates a positive energy balance. Thus, an impaired function of the Y1 receptor in the PVN may also be participating in the anorexic behavior of dehydrated animals.

3.1 CRH actions on the regulation of HPT axis in anorexic animals

CRH and its receptors regulate in concert, the autonomic, behavioral, immunologic and endocrine responses of the organism allowing it to face a changing environment. Starvation, body weight loss and negative energy balance are some of the stressful conditions that induce differential changes in the hypothalamus-pituitary adrenal axis (HPA) axis, as well as in central CRH metabolism, enabling the organism to adapt to situations of nutrient deficit. CRH also participates in the regulation of energy intake and utilization through its actions on the sympathetic nervous system, activating thermogenesis in the BAT (Arase et al., 1988; LeFeuvre et al., 1987).

In DIA paradigm (Jaimes-Hoy et al., 2008; Watts et al., 1999), CRH expression in the PVN decreases in a greater extent than in food restricted rats (Brady et al., 1990; Isse et al., 1999) after 7 days. Although expression of CRH-R1 receptor in the PVN is up-regulated in several stressful conditions supposedly by CRH release into the PVN which in turn, up-regulates CRH expression (Imaki et al., 1996; Mansi et al., 1996; Turnbull & Rivier, 1997), CRH-R1 mRNA levels are unchanged in DIA animals. In contrast, the expression of CRH-R2 decreases only in the PVN of DIA group. The lack of response of FFR animals is coincident with that reported after starvation (Makino et al., 1998). CRH-R2 is the receptor involved in the anorexigenic effects of administered CRH (Arase et al., 1988; Krahn et al., 1990; Morley & Levine, 1982) since, the knockdown of CRH-R2, but not of CRH-R1, attenuates CRH-induced appetite and food intake reduction (Smagin et al., 1998).

CRH synthesis in the LHA of DIA animals is increased when compared to those of food-restricted and control groups (Watts et al., 1999). LHA CRHergic neurons have projections directly to the PVN, and are proposed as important targets for osmosensitive afferents from the forebrain, the middle preoptic nucleus and subfornical organ and from the fusiform nucleus of the bed nucleus of the *stria terminallis,* which are projections that mediate part of the response of peptidergic mRNAs in the LHA during dehydration (Kelly & Watts, 1996). It is possible that an increased release of CRH from the LHA impinges on CRH-R2 receptors of the PVN, causing a receptor down-regulation, as shown in the pituitary for CRH-R1 (Rabadan-Diehl et al., 1996).

Using *in vitro* studies with cultured hypothalamic cells, it is observed that the addition of CRH (10 nM) increases TRH mRNA levels after 1 h, analyzed by RT-PCR (de Gortari et al., 2009). Thus, it has been performed an injection in the PVN of a specific antagonist of CRH-R2 receptors to dehydration-subjected animals. Three different doses of antisauvagine-30 (ASG-30) have been administered since the first day of DIA paradigm. Anorexic animals injected with the middle dose (30 nM= MD) increase their food intake on day 4 to 288 ± 25%

compared to the control group (saline injected and also subjected to DIA, 100 ± 26%). Weight loss of those animals does not change in saline-injected DIA animals (S-DIA), in contrast, changes of the HPT axis induced by dehydration are antagonized by the intra-PVN injections of ASG-30: pro-TRH mRNA levels decrease when compared to saline-injected DIA group (Figure 3); TRH-R1 expression in anterior pituitary increases and serum levels of TSH and T_4 decrease with the administration of the medial and high doses of the CRH-R2 antagonist. Antagonizing CRH-R2 in the PVN of animals subjected to DIA paradigm, the anorexigenic effects of dehydration are attenuated and the ability of the HPT axis to adjust to the negative energy balance condition is restored. These results together with the *in vitro* stimulation of CRH on pro-TRH expression of hypothalamic cultured cells, suggest that the DIA-induced activation of HPT axis is affected at the PVN level by CRH through CRH-R2 activation. It however remains to be shown that the DIA-activated CRHergic neurons of the lateral hypothalamus, which project to the PVN, target TRH synthesizing cells and that those cells express CRH-R2. The negative correlation found between PVN-pro-TRH mRNA levels and food intake gives further support for TRH anorectic effects (Choi et al., 2002; Schuhler et al., 2007).

The failure of HPT adaptation during anorexia becomes deleterious to the subject as greater body weight loss is observed; it is possible that the use of CRH-R2 antagonists in anorexic patients ameliorates its reduced appetite.

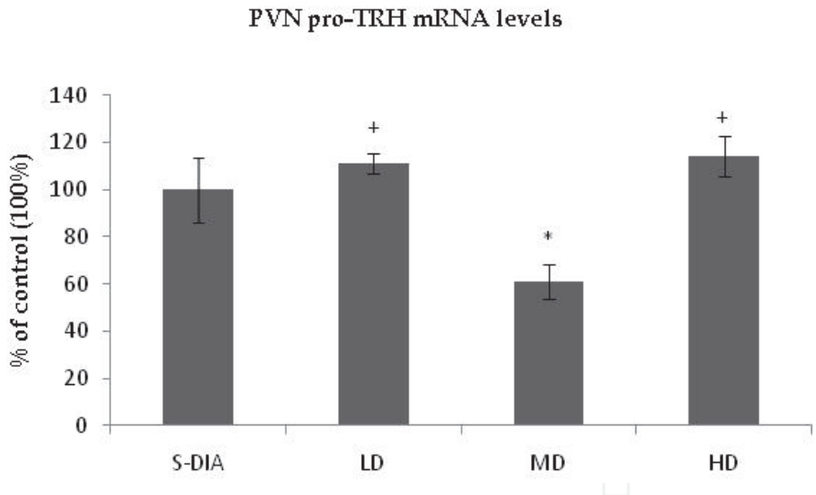


Fig. 3. Expression changes of pro-TRH mRNA levels in the PVN of dehydrated male animals injected with a specific antagonist of CRH-R2 (antisauvagina-30, ASG-30) directly in the PVN during seven days. S-DIA: saline injected dehydrated animals; LD, low-dose group of dehydrated animals and injected with 15 nM of ASG-30; MD, medium-dose group of dehydrated animals injected with 30 nM of ASG-30; HD, high dose group of dehydrated animals injected with 60 nM of ASG-30. Values are the means ± SEM of the ratio of proTRH cDNA/cyclophilin signal cDNA (arbitrary units); data is expressed as % of S-DIA values, considered as 100% (n=3 for LD, HD, n=6 for S-DIA and MD). +$p<0.05$ vs. MD group, *$p<0.05$ vs. S-DIA. Modified from de Gortari et al., 2009.

4. Developed hypothyroidism during zinc deficiency

Zinc is a mineral with a relevant role in growing, cell differentiation and regulation of metabolism. It participates in different biological functions such as DNA synthesis and genes expression (Vallee, 1977). It is also crucial to several enzymatic processes (Vallee & Falchuk, 1993), that in turn influence hormonal and neural transmissions (Xie & Smart, 1991).

There are both saturated a non-saturated mechanisms of Zn absorption (Seal & Mathers, 1989; Tacnet et al., 1990). Two main protein families are in charge of Zn transport: 1) at least 15 members of the ZIP (i.e., Zn-regulated metal transporter, Iron-regulated metal transporter-like protein) family (Eide, 2004) and 2) ten members of the ZnT (Zn Transporter) family (Liuzzi & Cousins, 2004). Absorption rate is able to adjust to Zn availability, i.e., there is an increase on the maximum Zn absorption rate in rat enterocytes cell cultures, following a reduction on dietary Zn (Hoadley et al., 1987), just as there is an increase on trans-epithelial Zn flux on CACO-2 cells after treatment with 5 μM when compared to one of 25 μM Zn (Reeves et al., 2001).

Zinc widespread functions impinge on several aspects of organism physiology, best demonstrated by the variety of symptoms associated with zinc-deficiency (Prasad, 1984). Clinic manifestations comprehend anorexia, growth retardation, dermatitis, diarrhea, weight loss and impaired immune responses. Among mineral deficiency causes we can mention malnutrition, alcoholism, absorption alterations, chronic renal insufficiency, etc.

In most studies, Zn deficiency results in an overall 40% to 50% decrease in food intake (Gaetke et al., 2002; Rains et al., 1998). However, in severe Zn deficiency, food intake can be reduced by as much as 70% (Essatara et al., 1984; Kasarskis et al., 1996). Although severe Zn deficiency is considered to be rare, mild or moderate deficiency is believed to be widespread throughout the world (Caulfield et al., 1998). In rodents, the most striking feature of experimental Zn deficiency is the cyclic feeding behavior that develops during Zn deprivation. Early studies report that this behavior is characterized by both a reduction of mean food intake, and periodic cyclic changes in daily food intake that disappear as soon as Zn is reintroduced in the diet (Chesters & Quarterman, 1970; Williams & Mills, 1970); an underlying alteration in hypothalamic galanin and NPY gene expression may be responsible for the altered feeding patterns in Zn deficient rats (Selvais et al., 1997).

Zinc deficient rats weight less than rats that consume the same amount of Zn-adequate food (Gaetke et al., 2002). This observation suggests that Zn deficiency has an impact on metabolic rate that is independent on food intake; however, it seems that the most profound effect of Zn status on metabolic rate and substrate utilization is the result of Zn deficiency-induced anorexia (Evans et al., 2004).

Both caloric restriction and Zn deficiency are known to reduce T_3 serum levels when compared to *ad libitum* fed animals, in addition, T_3 concentration is lower in Zn deficient vs. caloric restricted rats. In adult Zn deficient rats, a reduced hypothalamic TRH content and inhibited release from ME are observed, also T_4 and TSH levels are diminished. Because Zn deficiency causes a major decrease in serum free (fT_3) and fT_4 levels than caloric restriction, it seems that lack of Zn impairs the extra-thyroidal T_3 synthesis (Morley et al., 1980). In fact, there is a decrease in D1 liver activity secondary to Zn deficiency. Also Pekary et al., (Pekary et al., 1991) have shown that processing of the pro-TRH is altered, since the convertases are

Zn-dependent enzymes, moreover, T_3 receptors, in common with other members of the nuclear receptor family, are thought to be included among the nuclear zinc-binding proteins. They all contain nine invariant cysteine residues in the DNA-binding region (Evans, 1988). If Zn is removed through chelating processes, T_3 receptors produced from a bacterial expression system lose their ability to bind to DNA (Miyamoto et al., 1991), thus it is clear that Zn deficiency affects TH metabolism (Kralik et al., 1996).

Since during gestation and lactation periods metal demand increases, Zn requirements are also greater. In fact, it is recognized that around 80% of pregnant women world-wide are likely to have inadequate zinc intakes (Shah & Sachdev, 2001). The increased requirements need to be fulfilled by an enhanced ingestion or by adjusting metal homeostasis. One of these adjustments involves an increase on intestinal Zn absorption during both pregnancy and lactation (Davies & Williams, 1977; Moser-Veillon, 1995). Moreover, during lactation in humans and rodents, milk Zn concentration is maintained over a wide range of dietary Zn intake, and decreases only after plasma Zn concentration is reduced (Krebs, 1998; Moore et al., 1984). Zn transporters in the rat mammary gland respond to marginal Zn intake during lactation, when there is a reduced Zn-T1 protein level, thus allowing the mammary gland to reduce serosal Zn export through this ubiquitous transporter during Zn deficiency, also a higher ZnT-4 mRNA expression and protein levels is observed in order to maintain milk Zn concentration (Kelleher & Lonnerdal, 2002); this is due to the fact that vesicular ZnT-4 participates in the import of Zn into endocytotic or secretory vesicles, which ultimately releases Zn into milk (Murgia et al., 1999). Gestational Zn deficiency affects different processes where TRH has an active role: thyroid axis function, energetic homeostasis, body weight regulation, stress responses and growth. Offspring may present increases in T_4 content in the umbilical cord, decreased T_3 concentration, impaired TR function and a reduced body weight (Mahajan et al., 2005) as a result of intrauterine under nutrition. As pituitary PPII is a metalloenzyme and its activity depends on Zn, it might be affected during intrauterine Zn deficiency, leading to HPT alterations, although this remains to be studied.

It is possible that HPT axis adapts during Zn deficiency differently than in response to fast and malnutrition. This would be important, since animals with a Zn deficient diet have a reduction in the amount of food intake, thus it would be possible that some changes in the HPT axis function are due to an associated malnutrition however, there might be alterations that are only due to Zn deficiency.

5. Conclusions

Trying to identify if the degradation of TRH in the portal blood by the ectoenzyme pyroglutamyl aminopeptidase II (PPII) is an event involved in the adaptive regulation of the HPT axis during fasting, we evaluated PPII activity changes in the anterior pituitary of adults and young fasted animals and found a differential enzyme regulation that depends on the age of animals. While adults show the expected deceleration of the HPT axis function, the reduced TRH release and TSH serum content, weaning rats have a decreased PPII activity that may facilitate TRH effects on the thyrotrophes, which maintain elevated their TSH blood concentration, impairing adaptation of young animals to the negative energy balance. It supports that PPII-induced TRH degradation in the anterior pituitary may be a regulatory site of the HPT axis function that depends on the age of animals and on the etiology of hypothyroidism.

Using the model of DIA, we have been able to analyze the expression changes of peptides involved in feeding motivation, and to discriminate from those that decelerate energy utilization. DIA animals lose weight since day one of dehydration and develop an anorexic behavior.

We have found that a primary hypothyroidism is induced in anorexic rats, in contrast to the tertiary hypothyroidism of the pair-fed animals, despite of the negative energy balance developed in both groups. Dehydration impairs the adaptation of the HPT axis to the nutrient deficit: TRH expression is increased in the PVN, its release from the median eminence is active and TSH serum content is higher than in pair-fed and control animals. We also have found a reduced expression of the TRH receptors in the pituitary of anorexic animals that may be the result of the increased release of the peptide, as a desensitization mechanism. This resembles the blocked response of the pituitary to TRH administration in anorexic patients. Thus, we have been able to induce with this paradigm, changes of the HPT axis similar to those that are developed in anorexia nervosa.

The increased mRNA levels of TRH found in the PVN of anorexic animals and not in the pair-fed group support that the peptide of that hypothalamic region participates not only in energy homeostasis but in feeding motivation and anorexic behavior.

Given that TRHergic PVN neurons receive orexinergic input from LHA and NPYergic afferents from ARC, we analyzed changes in the LHA pre-pro-orexin (Ox) mRNA levels and PVN orexin (Ox-1R) and NPY (Y1, Y5) receptors of male rats. LHA prepro-orexinergic cells are activated in forced food restricted animals; Ox1-R and Y1 expression is reduced in food restricted vs. controls and anorexic group. Thus, compensatory changes in PVN receptor expression of some feeding-related peptides in anorexic rats may alter TRHergic neural response to energy demands.

CRH is another likely responsible factor for the increased TRH mRNA levels of the PVN of anorexic animals. Injection of a specific CRH-R2 antagonist in the PVN of dehydrated animals reduces TRH expression, the TSH blood concentration, and is able to attenuate anorexic behavior of DIA animals. Thus, specific antagonists of the CRHergic pathway may be potential therapeutic agents for anorexic patients.

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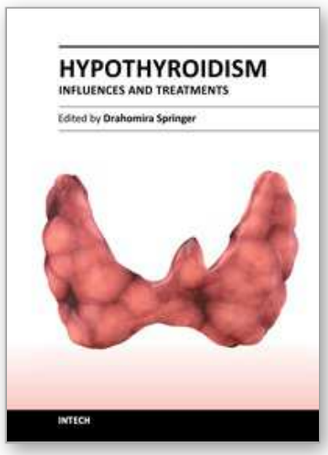
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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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