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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-ProNH₂) 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 (T₄) and triiodothyronine (T₃) synthesis in the thyroid gland as well as their release into the peripheral circulation. Under normal conditions only a small fraction of T₃ is generated by the thyroid gland, the remainder of T₃, which is available for binding sites in the plasma and body cells, is produced by monodeiodination of T₄ (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 T₃, 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 ($TR\alpha$ and $TR\beta$) 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 hypophyseal portal blood (Rondeel et al., 1992), pituitary levels of TSH β 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 T₄ serum levels within 3 days, while T₃ 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 T₄ and T₃ 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 thyrotrophs induced by starvation (Bavli, 1980; St Germain & Galton, 1985; van Doorn 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 hypophyseal 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 T₃ 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 hypophysiotrophic 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 T₄ 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; Pellemounter 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 (Vermees & 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 tanocytes 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 thyrotrophs 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 from 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; T₃: 74 ± 2.7 ng/dl; T₄: 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.

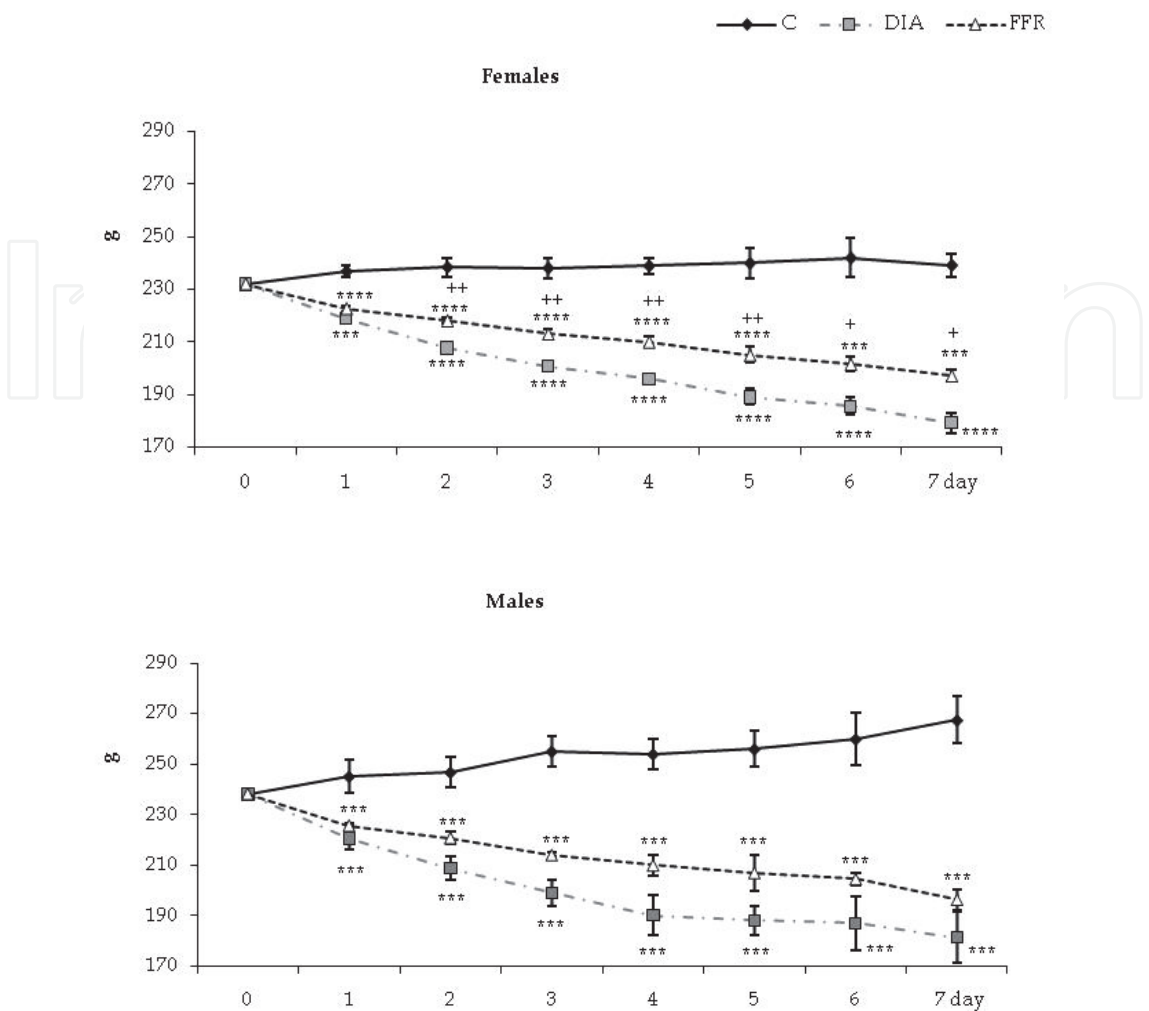


Fig. 1. Body weight of female and male adult rats subjected to dehydration-induced anorexia model or to forced-food restriction during 7 days. Controls: C, dehydrated-induced anorexic: DIA, forced-food restricted animals FFR. Values are expressed as the mean \pm SEM in grams (n= 6/group). Modified from 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 T₃ 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, T₄ and T₃ 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 T₃ 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 T₃ 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 T₄ in the active hormone T₃ 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 T₃ 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.

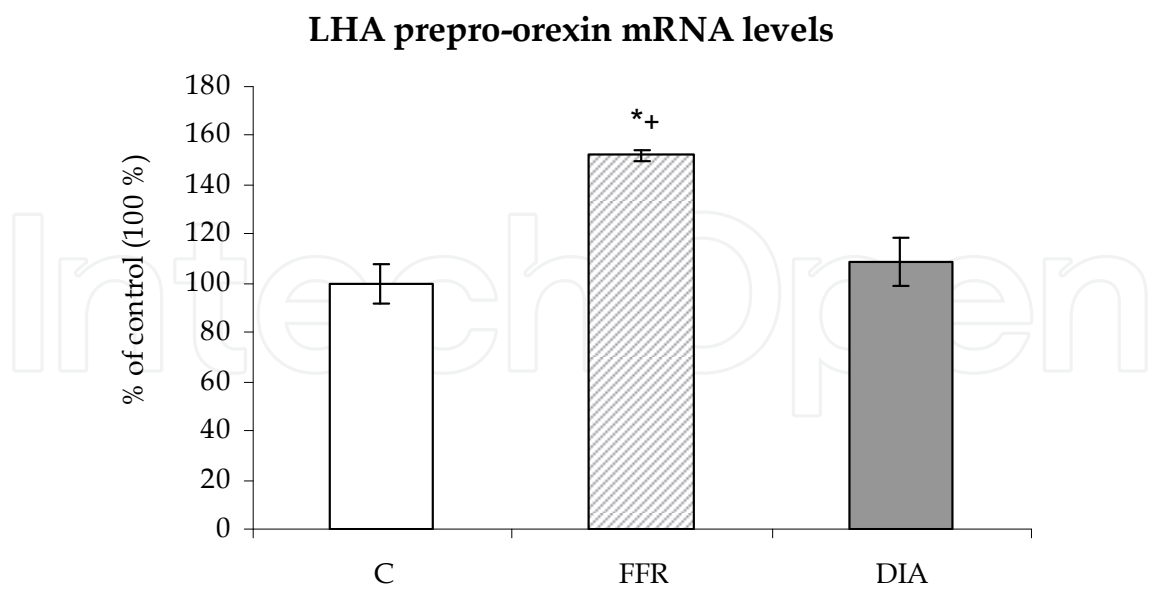


Fig. 2. Prepro-orexin mRNA levels in the lateral hypothalamic area (LHA), mRNA levels were semi-quantified by RT-PCR. Values (in percentage) are the ratio of prepro-orexin cDNA/cyclophilin cDNA expressed as the mean \pm SEM calculated as % of naïve values (C= 100 %), n=8. *p<0.01 vs naïve, +p<0.001 FFR 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 $288 \pm 25\%$

compared to the control group (saline injected and also subjected to DIA, $100 \pm 26\%$). 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.

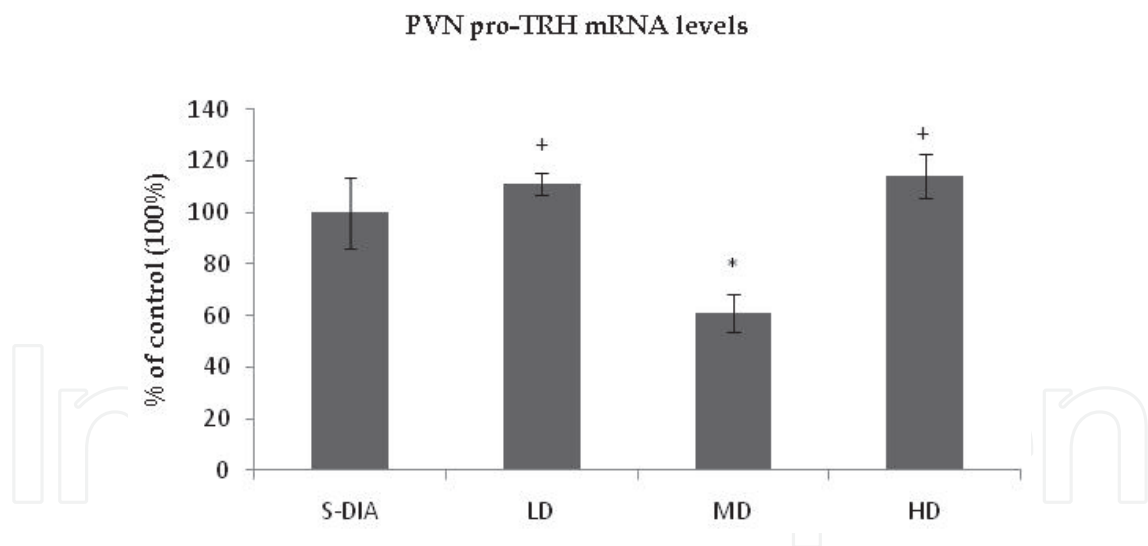


Fig. 3. Expression changes of pro-TRH mRNA levels in the PVN of dehydrated male animals injected with a specific antagonist of CRH-R2 (antisauvagina-30, ASG-30) directly in the PVN during seven days. S-DIA: saline injected dehydrated animals; LD, low-dose group of dehydrated animals and injected with 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 \pm 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 and 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 μ M when compared to one of 25 μ M 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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7. References

- Ahima, R.S.; Prabakaran, D.; Mantzoros, C.; Qu, D.; Lowell, B.; Maratos-Flier, E. & Flier, J.S. (1996). Role of leptin in the neuroendocrine response to fasting. *Nature*, Vol. 382, No. 6588, (July 1996), pp. (250-252).
- Ahima, R.S.; Saper, C.B.; Flier, J.S. & Elmquist, J.K. (2000). Leptin regulation of neuroendocrine systems. *Front Neuroendocrinol*, Vol. 21, No. 3, (July 2000), pp. (263-307).

- Arase, K.; York, D.A.; Shimizu, H.; Shargill, N. & Bray, G.A. (1988). Effects of corticotropin-releasing factor on food intake and brown adipose tissue thermogenesis in rats. *Am J Physiol*, Vol. 255, No. 3 Pt 1, (September 1988), pp. (E255-E259).
- Araujo, R.L.; de Andrade, B.M.; de Figueiredo, A.S.; da Silva, M.L.; Marassi, M.P.; Pereira, V.S.; Bouskela, E. & Carvalho, D.P. (2008). Low replacement doses of thyroxine during food restriction restores type 1 deiodinase activity in rats and promotes body protein loss. *J Endocrinol*, Vol. 198, No. 1, (July 2008), pp. (119-125).
- Backberg, M.; Hervieu, G.; Wilson, S. & Meister, B. (2002). Orexin receptor-1 (OX-R1) immunoreactivity in chemically identified neurons of the hypothalamus: focus on orexin targets involved in control of food and water intake. *Eur J Neurosci*, Vol. 15, No. 2, (January 2002), pp. (315-328).
- Ballinger, A.B.; Williams, G.; Corder, R.; El-Haj, T. & Farthing, M.J. (2001). Role of hypothalamic neuropeptide Y and orexigenic peptides in anorexia associated with experimental colitis in the rat. *Clin Sci (Lond)*, Vol. 100, No. 2, (February 2001), pp. (221-229).
- Baratti-Elbaz, C.; Ghinea, N.; Lahuna, O.; Loosfelt, H.; Pichon, C. & Milgrom, E. (1999). Internalization and recycling pathways of the thyrotropin receptor. *Mol Endocrinol*, Vol. 13, No. 10, (October 1999), pp. (1751-1765).
- Bauer, K. (1988). Degradation and biological inactivation of thyrotropin releasing hormone (TRH): regulation of the membrane-bound TRH-degrading enzyme from rat anterior pituitary by estrogens and thyroid hormones. *Biochimie*, Vol. 70, No. 1, (January 1988), pp. (69-74).
- Bavli, S.Z. (1980). Fasting, but not glucagon administration, decreases anterior pituitary nuclear thyroid hormone receptors in rats. *Metabolism*, Vol. 29, No. 7, (July 1980), pp. (636-642).
- Becskei, C.; Riediger, T.; Hernadfalvy, N.; Arsenijevic, D.; Lutz, T.A. & Langhans, W. (2008). Inhibitory effects of lipopolysaccharide on hypothalamic nuclei implicated in the control of food intake. *Brain Behav Immun*, Vol. 22, No. 1, (January 2008), pp. (56-64).
- Bowers, C.Y.; Lee, K.L. & Schally, A.V. (1968). A study on the interaction of the thyrotropin-releasing factor and L-triiodothyronine: effects of puromycin and cycloheximide. *Endocrinology*, Vol. 82, No. 1, (January 1968), pp. (75-82).
- Brady, L.S.; Smith, M.A.; Gold, P.W. & Herkenham, M. (1990). Altered expression of hypothalamic neuropeptide mRNAs in food-restricted and food-deprived rats. *Neuroendocrinology*, Vol. 52, No. 5, (November 1990), pp. (441-447).
- Broberger, C.; Johansen, J.; Johansson, C.; Schalling, M. & Hokfelt, T. (1998). The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc Natl Acad Sci U S A*, Vol. 95, No. 25, (December 1998), pp. (15043-15048).
- Broberger, C.; Visser, T.J.; Kuhar, M.J. & Hokfelt, T. (1999). Neuropeptide Y innervation and neuropeptide-Y-Y1-receptor-expressing neurons in the paraventricular hypothalamic nucleus of the mouse. *Neuroendocrinology*, Vol. 70, No. 5, (November 1999), pp. (295-305).
- Campfield, L.A.; Smith, F.J.; Guisez, Y.; Devos, R. & Burn, P. (July 1995). Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science*, Vol. 269, No. 5223, (July 1995), pp. (546-549).

- Caulfield, L.E.; Zavaleta, N.; Shankar, A.H. & Merialdi, M. (1998). Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. *Am J Clin Nutr*, Vol. 68, No. 2 Suppl, (August 1998), pp. (499S-508S).
- Charli, J.L.; Vargas, M.A.; Cisneros, M.; de, G.P.; Baeza, M.A.; Jasso, P.; Bourdais, J.; Perez, L.; Uribe, R.M. & Joseph-Bravo, P. (1998). TRH inactivation in the extracellular compartment: role of pyroglutamyl peptidase II. *Neurobiology (Bp)*, Vol. 6, No. 1, (1998), pp. (45-57).
- Chesters, J.K. & Quartermann, J. (December 1970). Effects of zinc deficiency on food intake and feeding patterns of rats. *Br J Nutr*, Vol. 24, No. 4, (1970), pp. (1061-1069).
- Ching, M.C. & Utiger, R.D. (1983). Hypothalamic portal blood immunoreactive TRH in the rat: lack of effect of hypothyroidism and thyroid hormone treatment. *J Endocrinol Invest*, Vol. 6, No. 5, (October 1983), pp. (347-352).
- Choi, Y.H.; Hartzell, D.; Azain, M.J. & Baile, C.A. (2002). TRH decreases food intake and increases water intake and body temperature in rats. *Physiol Behav*, Vol. 77, No. 1, (September 2002), pp. (1-4).
- Coppola, A.; Hughes, J.; Esposito, E.; Schiavo, L.; Meli, R. & Diano, S. (2005). Suppression of hypothalamic deiodinase type II activity blunts TRH mRNA decline during fasting. *FEBS Lett*, Vol. 579, No. 21, (August 2005), pp. (4654-4658).
- Coppola, A.; Liu, Z.W.; Andrews, Z.B.; Paradis, E.; Roy, M.C.; Friedman, J.M.; Ricquier, D.; Richard, D.; Horvath, T.L.; Gao, X.B. and others (2007). A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. *Cell Metab*, Vol. 5, No. 1, (January 2007), pp. (21-33).
- Coppola, A.; Meli, R. & Diano, S. (2005). Inverse shift in circulating corticosterone and leptin levels elevates hypothalamic deiodinase type 2 in fasted rats. *Endocrinology*, Vol. 146, No. 6, (June 2005), pp. (2827-2833).
- Danforth E Jr (1983). The role of thyroid hormones and insulin in the regulation of energy metabolism. *Am J Clin Nutr*, Vol. 38, No. 6, (December 1983), pp. (1006-1017).
- Davies, N.T. & Williams, R.B. (1977). The effect of pregnancy and lactation on the absorption of zinc and lysine by the rat duodenum in situ. *Br J Nutr*, Vol. 38, No. 3, (November 1977), pp. (417-423).
- De Groot, L.J. (1999). Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *J Clin Endocrinol Metab*, Vol. 84, No. 1, (January 1999), pp. (151-164).
- de Gortari, P.; González-Alzati, M.E.; Cisneros, M.; Joseph-Bravo P. (2000). Effect of fasting on the content of thyrotropin-releasing hormone and its RNAm in the central nervous system and pyroglutamyl peptidase II activity in the anterior pituitary of post-weaned and adult rats. *Neuroscience*, Vol. 3, pp. (255-65).
- de, Gortari, P.; Mancera, K.; Cote-Velez, A.; Amaya, M.I.; Martinez, A.; Jaimes-Hoy, L. & Joseph-Bravo, P. (2009). Involvement of CRH-R2 receptor in eating behavior and in the response of the HPT axis in rats subjected to dehydration-induced anorexia. *Psychoneuroendocrinology*, Vol. 34, No. 2, (February 2009), pp. (259-272).
- Debaveye, Y.; Ellger, B.; Mebis, L.; Darras, V.M. & Van den Berghe, G. (2008). Regulation of tissue iodothyronine deiodinase activity in a model of prolonged critical illness. *Thyroid*, Vol. 18, No. 5, (May 2008), pp. (551-560).
- Denereaz, N. & Lemarchand-Beraud, T. (1995). Severe but not mild alterations of thyroid function modulate the density of thyroid-stimulating hormone receptors in the rat thyroid gland. *Endocrinology*, Vol. 136, No. 4, (April 1995), pp. (1694-1700).

- Diano, S.; Naftolin, F.; Goglia, F. & Horvath, T.L. (1998). Fasting-induced increase in type II iodothyronine deiodinase activity and messenger ribonucleic acid levels is not reversed by thyroxine in the rat hypothalamus. *Endocrinology*, Vol. 139, No. 6, (June 1998), pp. (2879-2884).
- Diaz-Gallardo, M.Y.; Cote-Velez, A.; Charli, J.L. & Joseph-Bravo, P. (2010). A rapid interference between glucocorticoids and cAMP-activated signalling in hypothalamic neurones prevents binding of phosphorylated cAMP response element binding protein and glucocorticoid receptor at the CRE-Like and composite GRE sites of thyrotrophin-releasing hormone gene promoter. *J Neuroendocrinol*, Vol. 22, No. 4, (April 2010), pp. (282-293).
- Eide, D.J. (2004). The SLC39 family of metal ion transporters. *Pflugers Arch*, Vol. 447, No. 5, (February 2004), pp. (796-800).
- Espinosa, V.P.; Ferrini, M.; Shen, X.; Lutfy, K.; Nillni, E.A. & Friedman, T.C. (2007). Cellular colocalization and coregulation between hypothalamic pro-TRH and prohormone convertases in hypothyroidism. *Am J Physiol Endocrinol Metab*, Vol. 292, No. 1, (January 2007), pp. (E175-E186).
- Essatara, M.B.; Levine, A.S.; Morley, J.E. & McClain, C.J. (1984). Zinc deficiency and anorexia in rats: normal feeding patterns and stress induced feeding. *Physiol Behav*, Vol. 32, No. 3, (March 1984), pp. (469-474).
- Evans, R.M. (1988). The steroid and thyroid hormone receptor superfamily. *Science*, Vol. 240, No. 4854, (May 1988), pp. (889-895).
- Evans, S.A.; Overton, J.M.; Alshingiti, A. & Levenson, C.W. (2004). Regulation of metabolic rate and substrate utilization by zinc deficiency. *Metabolism*, Vol. 53, No. 6, (June 2004), pp. (727-732).
- Fekete, C.; Gereben, B.; Doleschall, M.; Harney, J.W.; Dora, J.M.; Bianco, A.C.; Sarkar, S.; Liposits, Z.; Rand, W.; Emerson, C. and others (2004). Lipopolysaccharide induces type 2 iodothyronine deiodinase in the mediobasal hypothalamus: implications for the nonthyroidal illness syndrome. *Endocrinology*, Vol. 145, No. 4, (April 2004), pp. (1649-1655).
- Fekete, C.; Kelly, J.; Mihaly, E.; Sarkar, S.; Rand, W.M.; Legradi, G.; Emerson, C.H. & Lechan, R.M. (2001). Neuropeptide Y has a central inhibitory action on the hypothalamic-pituitary-thyroid axis. *Endocrinology*, Vol. 142, No. 6, (June 2001), pp. (2606-2613).
- Fekete, C.; Legradi, G.; Mihaly, E.; Tatro, J.B.; Rand, W.M. & Lechan, R.M. (2000a). alpha-Melanocyte stimulating hormone prevents fasting-induced suppression of corticotropin-releasing hormone gene expression in the rat hypothalamic paraventricular nucleus. *Neurosci Lett*, Vol. 289, No. 2, (August 2000), pp. (152-156).
- Fekete, C.; Mihaly, E.; Luo, L.G.; Kelly, J.; Clausen, J.T.; Mao, Q.; Rand, W.M.; Moss, L.G.; Kuhar, M.; Emerson, C.H. and others (2000b). Association of cocaine- and amphetamine-regulated transcript-immunoreactive elements with thyrotropin-releasing hormone-synthesizing neurons in the hypothalamic paraventricular nucleus and its role in the regulation of the hypothalamic-pituitary-thyroid axis during fasting. *J Neurosci*, Vol. 20, No. 24, (December 2000), pp. (9224-9234).
- Fekete, C.; Sarkar, S.; Rand, W.M.; Harney, J.W.; Emerson, C.H.; Bianco, A.C. & Lechan, R.M. (2002). Agouti-related protein (AGRP) has a central inhibitory action on the hypothalamic-pituitary-thyroid (HPT) axis; comparisons between the effect of AGRP and neuropeptide Y on energy homeostasis and the HPT axis. *Endocrinology*, Vol. 143, No. 10, (October 2002), pp. (3846-3853).

- Fliers, E.; Alkemade, A. & Wiersinga, W.M. (2001). The hypothalamic-pituitary-thyroid axis in critical illness. *Best Pract Res Clin Endocrinol Metab*, Vol. 15, No. 4, (December 2001), pp. (453-464).
- Fliers, E.; Guldenaar, S.E.; Wiersinga, W.M. & Swaab, D.F. (1997). Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. *J Clin Endocrinol Metab*, Vol. 82, No. 12, (December 1997), pp. (4032-4036).
- Freeman, M.E.; Kanyicska, B.; Lerant, A. & Nagy, G. (2000). Prolactin: structure, function, and regulation of secretion. *Physiol Rev*, Vol. 80, No. 4, (October 2000), pp. (1523-1631).
- Friedman, T.C.; Yanovski, J.A.; Jayasvasti, V.; Yanovski, S.Z.; Koenig, R.J. & Wilk, S. (1995). Pyroglutamyl peptidase-II ("thyroliberinase") activity in human serum: influence of weight and thyroid status. *J Clin Endocrinol Metab*, Vol. 80, No. 4, (April 1995), pp. (1086-1089).
- Gaetke, L.M.; Frederich, R.C.; Oz, H.S. & McClain, C.J. (2002). Decreased food intake rather than zinc deficiency is associated with changes in plasma leptin, metabolic rate, and activity levels in zinc deficient rats(small star, filled). *J Nutr Biochem*, Vol. 13, No. 4, (April 2002), pp. (237-244).
- Garcia-Belenguer, S.; Oliver, C. & Mormede, P. (1993). Facilitation and feedback in the hypothalamo-pituitary-adrenal axis during food restriction in rats. *J Neuroendocrinol*, Vol. 5, No. 6, (December 1993), pp. (663-668).
- García-Luna, C.; Amaya, M.I.; Alvarez-Salas, E.; de Gortari, P. (2010). Prepro-orexin and feeding-related peptides receptors expression in dehydration-induced anorexia. *Regul Pept*, Vol.159, No. 1-3, (January 2010), pp. (54-60).
- Grosvenor, C.E. & Mena, F. (1980). Evidence that thyrotropin-releasing hormone and a hypothalamic prolactin-releasing factor may function in the release of prolactin in the lactating rat. *Endocrinology*, Vol. 107, No. 4, (October 1980), pp. (863-868).
- Grunfeld, C.; Zhao, C.; Fuller, J.; Pollack, A.; Moser, A.; Friedman, J. & Feingold, K.R. (1996). Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. *J Clin Invest*, Vol. 97, No. 9, (May 1996), pp. (2152-2157).
- Harris, A.R.; Christianson, D.; Smith, M.S.; Fang, S.L.; Braverman, L.E. & Vagenakis, A.G. (1978). The physiological role of thyrotropin-releasing hormone in the regulation of thyroid-stimulating hormone and prolactin secretion in the rat. *J Clin Invest*, Vol. 61, No. 2, (February 1978), pp. (441-448).
- Harris, M.; Aschkenasi, C.; Elias, C.F.; Chandrankunnel, A.; Nillni, E.A.; Bjorbaek, C.; Elmquist, J.K.; Flier, J.S. & Hollenberg, A.N. (2001). Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling. *J Clin Invest*, Vol. 107, No. 1, (January 2001), pp. (111-120).
- Heuer, H.; Schafer, M.K.; O'Donnell, D.; Walker, P. & Bauer, K. (2000). Expression of thyrotropin-releasing hormone receptor 2 (TRH-R2) in the central nervous system of rats. *J Comp Neurol*, Vol. 428, No. 2, (December 2000), pp. (319-336).
- Hoadley, J.E.; Leinart, A.S. & Cousins, R.J. (1987). Kinetic analysis of zinc uptake and serosal transfer by vascularly perfused rat intestine. *Am J Physiol*, Vol. 252, No. 6 Pt 1, (June 1987), pp. (G825-G831).
- Horita, A. (1998). An update on the CNS actions of TRH and its analogs. *Life Sci*, Vol. 62, No. 17-18, (1998), pp. (1443-1448).
- Imaki, T.; Naruse, M.; Harada, S.; Chikada, N.; Imaki, J.; Onodera, H.; Demura, H. & Vale, W. (1996). Corticotropin-releasing factor up-regulates its own receptor mRNA in

- the paraventricular nucleus of the hypothalamus. *Brain Res Mol Brain Res*, Vol. 38, No. 1, (May 1996), pp. (166-170).
- Ishikawa, K.; Taniguchi, Y.; Inoue, K.; Kurosumi, K. & Suzuki, M. (1988). Immunocytochemical delineation of thyrotrophic area: origin of thyrotropin-releasing hormone in the median eminence. *Neuroendocrinology*, Vol. 47, No. 5, (May 1988), pp. (384-388).
- Ishikawa, K.; Taniguchi, Y.; Kurosumi, K. & Suzuki, M. (1986). Origin of septal thyrotropin-releasing hormone in the rat. *Neuroendocrinology*, Vol. 44, No. 1, (1986), pp. (54-58).
- Isse, T.; Ueta, Y.; Serino, R.; Noguchi, J.; Yamamoto, Y.; Nomura, M.; Shibuya, I.; Lightman, S.L. & Yamashita, H. (1999). Effects of leptin on fasting-induced inhibition of neuronal nitric oxide synthase mRNA in the paraventricular and supraoptic nuclei of rats. *Brain Res*, Vol. 846, No. 2, (November 1999), pp. (229-235).
- Jaimes-Hoy, L.; Joseph-Bravo, P. & de, G.P. (2008). Differential response of TRHergic neurons of the hypothalamic paraventricular nucleus (PVN) in female animals submitted to food-restriction or dehydration-induced anorexia and cold exposure. *Horm Behav*, Vol. 53, No. 2, (February 2008), pp. (366-377).
- Jaszberenyi, M.; Bujdoso, E.; Kiss, E.; Pataki, I. & Telegdy, G. (2002). The role of NPY in the mediation of orexin-induced hypothermia. *Regul Pept*, Vol. 104, No. 1-3, (March 2002), pp. (55-59).
- Karydis, I. & Tolis, G. (1998). Orexin, anorexia, and thyrotropin-releasing hormone. *Thyroid*, Vol. 8, No. 10, (October 1998), pp. (947-950).
- Kasarskis EJ; Sparks DL & Slevin JT (1996). Changes in hypothalamic noradrenergic systems during the anorexia of zinc deficiency. *Biological Trace Element Research*, Vol. 9, No. 1, (1996), pp. (25-35).
- Kawano, H.; Tsuruo, Y.; Bando, H. & Daikoku, S. (1991). Hypophysiotrophic TRH-producing neurons identified by combining immunohistochemistry for pro-TRH and retrograde tracing. *J Comp Neurol*, Vol. 307, No. 4, (May 1991), pp. (531-538).
- Kelleher, S.L. & Lonnerdal, B. (2002). Zinc transporters in the rat mammary gland respond to marginal zinc and vitamin A intakes during lactation. *J Nutr*, Vol. 132, No. 11, (November 2002), pp. (3280-3285).
- Kelly, A.B. & Watts, A.G. (1996). Mediation of dehydration-induced peptidergic gene expression in the rat lateral hypothalamic area by forebrain afferent projections. *J Comp Neurol*, Vol. 370, No. 2, (June 1996), pp. (231-246).
- Krahn, D.D.; Gosnell, B.A. & Majchrzak, M.J. (1990). The anorectic effects of CRH and restraint stress decrease with repeated exposures. *Biol Psychiatry*, Vol. 27, No. 10, (May 1990), pp. (1094-1102).
- Kralik, A.; Eder, K. & Kirchgessner, M. (1996). Influence of zinc and selenium deficiency on parameters relating to thyroid hormone metabolism. *Horm Metab Res*, Vol. 28, No. 5, (May 1996), pp. (223-226).
- Krebs, N.F. (1998). Zinc supplementation during lactation. *Am J Clin Nutr*, Vol. 68, No. 2 Suppl, (August 1998), pp. (509S-512S).
- Lechan RM & Hollenberg A (2003). Thyrotropin-releasing hormone (TRH), In: *Encyclopedia of Hormones*, Henry H.L. & Norman A.W., (Ed.), pp. (510-524), Academic Press, ISBN 0-12-341103-3, San Diego, CA
- Lechan, R.M. & Fekete, C. (2004). Feedback regulation of thyrotropin-releasing hormone (TRH): mechanisms for the non-thyroidal illness syndrome. *J Endocrinol Invest*, Vol. 27, No. 6 Suppl, (2004), pp. (105-119).

- Lechan, R.M. & Fekete, C. (2005). Role of thyroid hormone deiodination in the hypothalamus. *Thyroid*, Vol. 15, No. 8, (August 2005), pp. (883-897).
- Lechan, R.M. & Fekete, C. (2006). The TRH neuron: a hypothalamic integrator of energy metabolism. *Prog Brain Res*, Vol. 153, No. 2006, pp. (209-235).
- Lechan, R.M. & Kakucska, I. (1992). Feedback regulation of thyrotropin-releasing hormone gene expression by thyroid hormone in the hypothalamic paraventricular nucleus. *Ciba Found Symp*, Vol. 168, No. 1992, pp. (144-158).
- LeFeuvre, R.A.; Rothwell, N.J. & Stock, M.J. (1987). Activation of brown fat thermogenesis in response to central injection of corticotropin releasing hormone in the rat. *Neuropharmacology*, Vol. 26, No. 8, (August 1987), pp. (1217-1221).
- Legradi, G.; Emerson, C.H.; Ahima, R.S.; Flier, J.S. & Lechan, R.M. (1997). Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. *Endocrinology*, Vol. 138, No. 6, (June 1997), pp. (2569-2576).
- Legradi, G. & Lechan, R.M. (1998). The arcuate nucleus is the major source for neuropeptide Y-innervation of thyrotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. *Endocrinology*, Vol. 139, No. 7, (July 1998), pp. (3262-3270).
- Levin, B.E. (2006). Central regulation of energy homeostasis intelligent design: how to build the perfect survivor. *Obesity (Silver Spring)*, Vol. 14 Suppl 5, No. August 2006, pp. (192S-196S).
- Li, Q.L.; Jansen, E.; Brent, G.A.; Naqvi, S.; Wilber, J.F. & Friedman, T.C. (2000). Interactions between the prohormone convertase 2 promoter and the thyroid hormone receptor. *Endocrinology*, Vol. 141, No. 9, (September 2000), pp. (3256-3266).
- Li, Q.L.; Jansen, E. & Friedman, T.C. (1999). Regulation of prohormone convertase 1 (PC1) by gp130-related cytokines. *Mol Cell Endocrinol*, Vol. 158, No. 1-2, (December 1999), pp. (143-152).
- Lin, L.; Faraco, J.; Li, R.; Kadotani, H.; Rogers, W.; Lin, X.; Qiu, X.; de Jong, P.J.; Nishino, S. & Mignot, E. (1999). The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell*, Vol. 98, No. 3, (August 1999), pp. (365-376).
- Liuzzi, J.P. & Cousins, R.J. (2004). Mammalian zinc transporters. *Annu Rev Nutr*, Vol. 24, No. 2004, pp. (151-172).
- Mahajan, S.D.; Aalinkeel, R.; Singh, S.; Shah, P.; Gupta, N. & Kochupillai, N. (2005). Thyroid hormone dysregulation in intrauterine growth retardation associated with maternal malnutrition and/or anemia. *Horm Metab Res*, Vol. 37, No. 10, (October 2005), pp. (633-640).
- Makino, S.; Nishiyama, M.; Asaba, K.; Gold, P.W. & Hashimoto, K. (1998). Altered expression of type 2 CRH receptor mRNA in the VMH by glucocorticoids and starvation. *Am J Physiol*, Vol. 275, No. 4 Pt 2, (October 1998), pp. (R1138-R1145).
- Mansi, J.A.; Rivest, S. & Drolet, G. (1996). Regulation of corticotropin-releasing factor type 1 (CRF1) receptor messenger ribonucleic acid in the paraventricular nucleus of rat hypothalamus by exogenous CRF. *Endocrinology*, Vol. 137, No. 11, (November 1996), pp. (4619-4629).
- Merchenthaler, I. & Liposits, Z. (1994). Mapping of thyrotropin-releasing hormone (TRH) neuronal systems of rat forebrain projecting to the median eminence and the OVLT. Immunocytochemistry combined with retrograde labeling at the light and electron microscopic levels. *Acta Biol Hung*, Vol. 45, No. 2-4, (1994), pp. (361-374).

- Mitev, Y.; Almeida, O.F. & Patchev, V. (1993). Pituitary-adrenal function and hypothalamic beta-endorphin release in vitro following food deprivation. *Brain Res Bull*, Vol. 30, No. 1-2, (1993), pp. (7-10).
- Mitsuma, T.; Hirooka, Y.; Mori, Y.; Kayama, M.; Adachi, K.; Rhue, N.; Ping, J. & Nogimori, T. (1999). Effects of orexin A on thyrotropin-releasing hormone and thyrotropin secretion in rats. *Horm Metab Res*, Vol. 31, No. 11, (November 1999), pp. (606-609).
- Miyamoto, T.; Sakurai, A. & DeGroot, L.J. (1991). Effects of zinc and other divalent metals on deoxyribonucleic acid binding and hormone-binding activity of human alpha 1 thyroid hormone receptor expressed in Escherichia coli. *Endocrinology*, Vol. 129, No. 6, (December 1991), pp. (3027-3033).
- Moore, M.E.; Moran, J.R. & Greene, H.L. (1984). Zinc supplementation in lactating women: evidence for mammary control of zinc secretion. *J Pediatr*, Vol. 105, No. 4, (October 1984), pp. (600-602).
- Morley, J.E.; Gordon, J. & Hershman, J.M. (1980). Zinc deficiency, chronic starvation, and hypothalamic-pituitary-thyroid function. *Am J Clin Nutr*, Vol. 33, No. 8, (August 1980), pp. (1767-1770).
- Morley, J.E. & Levine, A.S. (1980). Thyrotropin releasing hormone (TRH) suppresses stress induced eating. *Life Sci*, Vol. 27, No. 3, (July 1980), pp. (269-274).
- Morley, J.E. & Levine, A.S. (1982). Corticotrophin releasing factor, grooming and ingestive behavior. *Life Sci*, Vol. 31, No. 14, (October 1982), pp. (1459-1464).
- Morrison, S.F.; Nakamura, K. & Madden, C.J. (July 2008). Central control of thermogenesis in mammals. *Exp Physiol*, Vol. 93, No. 7, (July 2008), pp. (773-797).
- Morton, G.J.; Cummings, D.E.; Baskin, D.G.; Barsh, G.S. & Schwartz, M.W. (2006). Central nervous system control of food intake and body weight. *Nature*, Vol. 443, No. 7109, (September 2006), pp. (289-295).
- Moser-Veillon, P.B. (1995). Zinc needs and homeostasis during lactation. *Analyst*, Vol. 120, No. 3, (March 1995), pp. (895-897).
- Murgia, C.; Vespignani, I.; Cerase, J.; Nobili, F. & Perozzi, G. (1999). Cloning, expression, and vesicular localization of zinc transporter Dri 27/ZnT4 in intestinal tissue and cells. *Am J Physiol*, Vol. 277, No. 6 Pt 1, (December 1999), pp. (G1231-G1239).
- Muroya, S.; Funahashi, H.; Yamanaka, A.; Kohno, D.; Uramura, K.; Nambu, T.; Shibahara, M.; Kuramochi, M.; Takigawa, M.; Yanagisawa, M. and others (2004). Orexins (hypocretins) directly interact with neuropeptide Y, POMC and glucose-responsive neurons to regulate Ca²⁺ signaling in a reciprocal manner to leptin: orexigenic neuronal pathways in the mediobasal hypothalamus. *Eur J Neurosci*, Vol. 19, No. 6, (March 2004), pp. (1524-1534).
- Nillni, E.A. (2010). Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Front Neuroendocrinol*, Vol. 31, No. 2, (April 2010), pp. (134-156).
- Nillni, E.A.; Friedman, T.C.; Todd, R.B.; Birch, N.P.; Loh, Y.P. & Jackson, I.M. (1995). Pro-thyrotropin-releasing hormone processing by recombinant PC1. *J Neurochem*, Vol. 65, No. 6, (December 1995), pp. (2462-2472).
- Nillni, E.A.; Luo, L.G.; Jackson, I.M. & McMillan, P. (1996). Identification of the thyrotropin-releasing hormone precursor, its processing products, and its coexpression with convertase 1 in primary cultures of hypothalamic neurons: anatomic distribution of PC1 and PC2. *Endocrinology*, Vol. 137, No. 12, (December 1996), pp. (5651-5661).

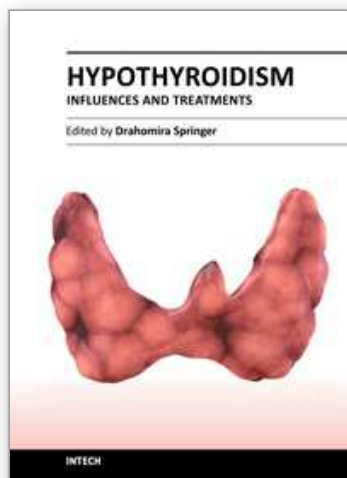
- Nillni, E.A.; Vaslet, C.; Harris, M.; Hollenberg, A.; Bjorbak, C. & Flier, J.S. (2000). Leptin regulates prothyrotropin-releasing hormone biosynthesis. Evidence for direct and indirect pathways. *J Biol Chem*, Vol. 275, No. 46, (November 2000), pp. (36124-36133).
- Nishiyama, T.; Kawano, H.; Tsuruo, Y.; Maegawa, M.; Hisano, S.; Adachi, T.; Daikoku, S. & Suzuki, M. (1985). Hypothalamic thyrotropin-releasing hormone (TRH)-containing neurons involved in the hypothalamic-hypophyseal-thyroid axis. Light microscopic immunohistochemistry. *Brain Res*, Vol. 345, No. 2, (October 1985), pp. (205-218).
- O'Mara, B.A.; Dittrich, W.; Lauterio, T.J. & St Germain, D.L. (1993). Pretranslational regulation of type I 5'-deiodinase by thyroid hormones and in fasted and diabetic rats. *Endocrinology*, Vol. 133, No. 4, (October 1993), pp. (1715-1723).
- Ogden, C.L.; Carroll, M.D.; McDowell, M.A. & Flegal, K.M. (2007a). Obesity among adults in the United States--no statistically significant change since 2003-2004. *NCHS Data Brief*, Vol. 1, (November 2007), pp. (1-8).
- Ogden, C.L.; Yanovski, S.Z.; Carroll, M.D. & Flegal, K.M. (2007b). The epidemiology of obesity. *Gastroenterology*, Vol. 132, No. 6, (May 2007), pp. (2087-2102).
- Pekary, A.E.; Lukaski, H.C.; Mena, I. & Hershman, J.M. (September 1991). Processing of TRH precursor peptides in rat brain and pituitary is zinc dependent. *Peptides*, Vol. 12, No. 5, (September 1991), pp. (1025-1032).
- Pelleymounter, M.A.; Cullen, M.J.; Baker, M.B.; Hecht, R.; Winters, D.; Boone, T. & Collins, F. (1995). Effects of the obese gene product on body weight regulation in ob/ob mice. *Science*, Vol. 269, No. 5223, (July 1995), pp. (540-543).
- Perello, M.; Friedman, T.; Paez-Espinosa, V.; Shen, X.; Stuart, R.C. & Nillni, E.A. (2006). Thyroid hormones selectively regulate the posttranslational processing of prothyrotropin-releasing hormone in the paraventricular nucleus of the hypothalamus. *Endocrinology*, Vol. 147, No. 6, (June 2006), pp. (2705-2716).
- Peyron, C.; Tighe, D.K.; van den Pol, A.N.; de, L.L.; Heller, H.C.; Sutcliffe, J.G. & Kilduff, T.S. (1998). Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci*, Vol. 18, No. 23, (December 1998), pp. (9996-10015).
- Ponce, G.; Charli, J.L.; Pasten, J.A.; Aceves, C. & Joseph-Bravo, P. (1988). Tissue-specific regulation of pyroglutamate aminopeptidase II activity by thyroid hormones. *Neuroendocrinology*, Vol. 48, No. 2, (August 1988), pp. (211-213).
- Prasad, A.S. (1984). Discovery and importance of zinc in human nutrition. *Fed Proc*, Vol. 43, No. 13, (October 1984), pp. (2829-2834).
- Prokai, L. (2002). Central nervous system effects of thyrotropin-releasing hormone and its analogues: opportunities and perspectives for drug discovery and development. *Prog Drug Res*, Vol. 59, No. 2002, pp. (133-169).
- Rabadan-Diehl, C.; Kiss, A.; Camacho, C. & Aguilera, G. (1996). Regulation of messenger ribonucleic acid for corticotropin releasing hormone receptor in the pituitary during stress. *Endocrinology*, Vol. 137, No. 9, (September 1996), pp. (3808-3814).
- Rains, T.M.; Hedrick, S.; Randall, A.C.; Lee, R.G.; Kennedy, K.J. & Shay, N.F. (1998). Food intake patterns are altered during long-term zinc deficiency in rats. *Physiol Behav*, Vol. 65, No. 3, (December 1998), pp. (473-478).
- Reeves, P.G.; Briske-Anderson, M. & Johnson, L. (December 2001). Pre-treatment of Caco-2 cells with zinc during the differentiation phase alters the kinetics of zinc uptake and transport(2). *J Nutr Biochem*, Vol. 12, No. 12, (December 2001), pp. (674-684).

- Reichlin S; Martin JB & Jackson IMD (1978). Regulation of thyroid-stimulating hormone (TSH) secretion., In: *The endocrine hypothalamus*, Jeffcoste AL & Hutchinson JSM, (Ed.), pp. (229-269), Academic Press Inc., ISBN 0-12-382150-9, London, UK.
- Rondeel, J.M.; Heide, R.; de Greef, W.J.; van, T.H.; van Haasteren, G.A.; Klootwijk, W. & Visser, T.J. (1992). Effect of starvation and subsequent refeeding on thyroid function and release of hypothalamic thyrotropin-releasing hormone. *Neuroendocrinology*, Vol. 56, No. 3, (September 1992), pp. (348-353).
- Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R.M.; Tanaka, H.; Williams, S.C.; Richardson, J.A.; Kozlowski, G.P.; Wilson, S. and others (1998). Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*, Vol. 92, No. 5, (March 1998), pp. (1-13).
- Sanchez, E.; Uribe, R.M.; Corkidi, G.; Zoeller, R.T.; Cisneros, M.; Zacarias, M.; Morales-Chapa, C.; Charli, J.L. & Joseph-Bravo, P. (2001). Differential responses of thyrotropin-releasing hormone (TRH) neurons to cold exposure or suckling indicate functional heterogeneity of the TRH system in the paraventricular nucleus of the rat hypothalamus. *Neuroendocrinology*, Vol. 74, No. 6, (December 2001), pp. (407-422).
- Sawchenko, P.E. & Swanson, L.W. (1982). The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. *Brain Res*, Vol. 257, No. 3, (November 1982), pp. (275-325).
- Scalabrino, G.A.; Hogan, N.; O'Boyle, K.M.; Slator, G.R.; Gregg, D.J.; Fitchett, C.M.; Draper, S.M.; Bennett, G.W.; Hinkle, P.M.; Bauer, K. and others (2007). Discovery of a dual action first-in-class peptide that mimics and enhances CNS-mediated actions of thyrotropin-releasing hormone. *Neuropharmacology*, Vol. 52, No. 7, (June 2007), pp. (1472-1481).
- Schaner, P.; Todd, R.B.; Seidah, N.G. & Nillni, E.A. (1997). Processing of prothyrotropin-releasing hormone by the family of prohormone convertases. *J Biol Chem*, Vol. 272, No. 32, (August 1997), pp. (19958-19968).
- Schomburg, L. & Bauer, K. (1995). Thyroid hormones rapidly and stringently regulate the messenger RNA levels of the thyrotropin-releasing hormone (TRH) receptor and the TRH-degrading ectoenzyme. *Endocrinology*, Vol. 136, No. 8, (August 1995), pp. (3480-3485).
- Schuhler, S.; Warner, A.; Finney, N.; Bennett, G.W.; Ebling, F.J. & Brameld, J.M. (2007). Thyrotrophin-releasing hormone decreases feeding and increases body temperature, activity and oxygen consumption in Siberian hamsters. *J Neuroendocrinol*, Vol. 19, No. 4, (April 2007), pp. (239-249).
- Schwartz, M.W.; Seeley, R.J.; Campfield, L.A.; Burn, P. & Baskin, D.G. (1996). Identification of targets of leptin action in rat hypothalamus. *J Clin Invest*, Vol. 98, No. 5, (September 1996), pp. (1101-1106).
- Seal, C.J. & Mathers, J.C. (1989). Intestinal zinc transfer by everted gut sacs from rats given diets containing different amounts and types of dietary fibre. *Br J Nutr*, Vol. 62, No. 1, (July 1989), pp. (151-163).
- Segerson, T.P.; Kauer, J.; Wolfe, H.C.; Mobtaker, H.; Wu, P.; Jackson, I.M. & Lechan, R.M. (1987). Thyroid hormone regulates TRH biosynthesis in the paraventricular nucleus of the rat hypothalamus. *Science*, Vol. 238, No. 4823, (October 1987), pp. (78-80).
- Selvais, P.L.; Labuche, C.; Nguyen, X.N.; Ketelslegers, J.M.; Deneuf, J.F. & Maiter, D.M. (1997). Cyclic feeding behaviour and changes in hypothalamic galanin and neuropeptide Y

- gene expression induced by zinc deficiency in the rat. *J Neuroendocrinol*, Vol. 9, No. 1, (January 1997), pp. (55-62).
- Sergeyev, V.; Broberger, C. & Hokfelt, T. (2001). Effect of LPS administration on the expression of POMC, NPY, galanin, CART and MCH mRNAs in the rat hypothalamus. *Brain Res Mol Brain Res*, Vol. 90, No. 2, (June 2001), pp. (93-100).
- Shah, D. & Sachdev, H.P. (2001). Effect of gestational zinc deficiency on pregnancy outcomes: summary of observation studies and zinc supplementation trials. *Br J Nutr*, Vol. 85 Suppl 2, No. May 2001, pp. (S101-S108).
- Shen, X.; Li, Q.L.; Brent, G.A. & Friedman, T.C. (2005). Regulation of regional expression in rat brain PC2 by thyroid hormone/characterization of novel negative thyroid hormone response elements in the PC2 promoter. *Am J Physiol Endocrinol Metab*, Vol. 288, No. 1, (January 2005), pp. (E236-E245).
- Siegel, J.M. (1999). Narcolepsy: a key role for hypocretins (orexins). *Cell*, Vol. 98, No. 4, (August 1999), pp. (409-412).
- Siegfried, Z.; Berry, E.M.; Hao, S. & Avraham, Y. (2003). Animal models in the investigation of anorexia. *Physiol Behav*, Vol. 79, No. 1, (June 2003), pp. (39-45).
- Smagin, G.N.; Howell, L.A.; Ryan, D.H.; De Souza, E.B. & Harris, R.B. (1998). The role of CRF2 receptors in corticotropin-releasing factor- and urocortin-induced anorexia. *Neuroreport*, Vol. 9, No. 7, (May 1998), pp. (1601-1606).
- St Germain, D.L. & Galton, V.A. (1985). Comparative study of pituitary-thyroid hormone economy in fasting and hypothyroid rats. *J Clin Invest*, Vol. 75, No. 2, (February 1985), pp. (679-688).
- Steward, C.A.; Horan, T.L.; Schuhler, S.; Bennett, G.W. & Ebling, F.J. (2003). Central administration of thyrotropin releasing hormone (TRH) and related peptides inhibits feeding behavior in the Siberian hamster. *Neuroreport*, Vol. 14, No. 5, (April 2003), pp. (687-691).
- Stoving, R.K.; Hangaard, J. & Hagen, C. (2001). Update on endocrine disturbances in anorexia nervosa. *J Pediatr Endocrinol Metab*, Vol. 14, No. 5, (May 2001), pp. (459-480).
- Suzuki, T.; Kohno, H.; Sakurada, T.; Tadano, T. & Kisara, K. (1982). Intracranial injection of thyrotropin releasing hormone (TRH) suppresses starvation-induced feeding and drinking in rats. *Pharmacol Biochem Behav*, Vol. 17, No. 2, (August 1982), pp. (249-253).
- Tacnet, F.; Watkins, D.W. & Ripoche, P. (1990). Studies of zinc transport into brush-border membrane vesicles isolated from pig small intestine. *Biochim Biophys Acta*, Vol. 1024, No. 2, (May 1990), pp. (323-330).
- Tamai, H.; Mori, K.; Matsubayashi, S.; Kiyohara, K.; Nakagawa, T.; Okimura, M.C.; Walter, R.M., Jr.; Kumagai, L.F. & Nagataki, S. (1986). Hypothalamic-pituitary-thyroidal dysfunctions in anorexia nervosa. *Psychother Psychosom*, Vol. 46, No. 3, (1986), pp. (127-131).
- Toni, R. & Lechan, R.M. (1993). Neuroendocrine regulation of thyrotropin-releasing hormone (TRH) in the tuberoinfundibular system. *J Endocrinol Invest*, Vol. 16, No. 9, (October 1993), pp. (715-753).
- Turnbull, A.V. & Rivier, C. (1997). Corticotropin-releasing factor (CRF) and endocrine responses to stress: CRF receptors, binding protein, and related peptides. *Proc Soc Exp Biol Med*, Vol. 215, No. 1, (May 1997), pp. (1-10).
- Valcavi, R.; Zini, M.; Peino, R.; Casanueva, F.F. & Dieguez, C. (1997). Influence of thyroid status on serum immunoreactive leptin levels. *J Clin Endocrinol Metab*, Vol. 82, No. 5, (May 1997), pp. (1632-1634).

- Vallee, B.L. (1977). Zinc biochemistry in normal and neoplastic growth processes. *Experientia*, Vol. 33, No. 5, (May 1977), pp. (600-601).
- Vallee, B.L. & Falchuk, K.H. (1993). The biochemical basis of zinc physiology. *Physiol Rev*, Vol. 73, No. 1, (January 1993), pp. (79-118).
- Van den Berghe, G.; de, Z.F.; Baxter, R.C.; Veldhuis, J.D.; Wouters, P.; Schetz, M.; Verwaest, C.; Van, d., V; Lauwers, P.; Bouillon, R. and others (1998). Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. *J Clin Endocrinol Metab*, Vol. 83, No. 2, (February 1998), pp. (309-319).
- Van den Berghe, G.; Wouters, P.; Weekers, F.; Mohan, S.; Baxter, R.C.; Veldhuis, J.D.; Bowers, C.Y. & Bouillon, R. (1999). Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab*, Vol. 84, No. 4, (April 1999), pp. (1311-1323).
- van Haasteren, G.A.; Linkels, E.; Klootwijk, W.; van, T.H.; Rondeel, J.M.; Themmen, A.P.; de Jong, F.H.; Valentijn, K.; Vaudry, H.; Bauer, K. and others (1995). Starvation-induced changes in the hypothalamic content of prothyrotrophin-releasing hormone (proTRH) mRNA and the hypothalamic release of proTRH-derived peptides: role of the adrenal gland. *J Endocrinol*, Vol. 145, No. 1, (April 1995), pp. (143-153).
- van Doorn, J.; van der Heide, D. & Roelfsema, F. (1984). The influence of partial food deprivation on the quantity and source of triiodothyronine in several tissues of athyreotic thyroxine-maintained rats. *Endocrinology*, Vol. 115, No. 2, (August 1984), pp. (705-711).
- Vargas, M.; Mendez, M.; Cisneros, M.; Joseph-Bravo, P. & Charli, J.L. (1987). Regional distribution of the membrane-bound pyroglutamate amino peptidase-degrading thyrotropin-releasing hormone in rat brain. *Neurosci Lett*, Vol. 79, No. 3, (August 1987), pp. (311-314).
- Vargas, M.A.; Bourdais, J.; Sanchez, S.; Uriostegui, B.; Moreno, E.; Joseph-Bravo, P. & Charli, J.L. (1998). Multiple hypothalamic factors regulate pyroglutamyl peptidase II in cultures of adenohypophyseal cells: role of the cAMP pathway. *J Neuroendocrinol*, Vol. 10, No. 3, (March 1998), pp. (199-206).
- Vargas, M.A.; Joseph-Bravo, P. & Charli, J.L. (1994). Thyrotropin-releasing hormone downregulates pyroglutamyl peptidase II activity in adenohypophyseal cells. *Neuroendocrinology*, Vol. 60, No. 3, (September 1994), pp. (323-330).
- Vermes, I. & Beishuizen, A. (2001). The hypothalamic-pituitary-adrenal response to critical illness. *Best Pract Res Clin Endocrinol Metab*, Vol. 15, No. 4, (December 2001), pp. (495-511).
- Vijayan, E. & McCann, S.M. (1977). Suppression of feeding and drinking activity in rats following intraventricular injection of thyrotropin releasing hormone (TRH). *Endocrinology*, Vol. 100, No. 6, (June 1977), pp. (1727-1730).
- Vogel, R.A.; Cooper, B.R.; Barlow, T.S.; Prange, A.J., Jr.; Mueller, R.A. & Breese, G.R. (1979). Effects of thyrotropin-releasing hormone on locomotor activity, operant performance and ingestive behavior. *J Pharmacol Exp Ther*, Vol. 208, No. 2, (February 1979), pp. (161-168).

- Vrang, N.; Larsen, P.J.; Clausen, J.T. & Kristensen, P. (1999). Neurochemical characterization of hypothalamic cocaine- amphetamine-regulated transcript neurons. *J Neurosci*, Vol. 19, No. 10, (May 1999), pp. (RC5-).
- Warner, M.H. & Beckett, G.J. (2010). Mechanisms behind the non-thyroidal illness syndrome: an update. *J Endocrinol*, Vol. 205, No. 1, (April 2010), pp. (1-13).
- Watts, A.G. (2001). Neuropeptides and the integration of motor responses to dehydration. *Annu Rev Neurosci*, Vol. 24, No. 2001, pp. (357-384).
- Watts, A.G.; Salter, D.S. & Neuner, C.M. (2007). Neural network interactions and ingestive behavior control during anorexia. *Physiol Behav*, Vol. 91, No. 4, (July 2007), pp. (389-396).
- Watts, A.G.; Sanchez-Watts, G. & Kelly, A.B. (1999). Distinct patterns of neuropeptide gene expression in the lateral hypothalamic area and arcuate nucleus are associated with dehydration-induced anorexia. *J Neurosci*, Vol. 19, No. 14, (July 1999), pp. (6111-6121).
- Wiersinga WM & Boelen A (1996). Thyroid hormone metabolism in nonthyroidal illness. *Current Opinion in Endocrinology, Diabetes and Obesity*, Vol. 3, No. 5, (1996), pp. (422-427).
- Williams, R.B. & Mills, C.F. (1970). The experimental production of zinc deficiency in the rat. *Br J Nutr*, Vol. 24, No. 4, (December 1970), pp. (989-1003).
- Wittmann, G.; Fuzesi, T.; Singru, P.S.; Liposits, Z.; Lechan, R.M. & Fekete, C. (2009). Efferent projections of thyrotropin-releasing hormone-synthesizing neurons residing in the anterior parvocellular subdivision of the hypothalamic paraventricular nucleus. *J Comp Neurol*, Vol. 515, No. 3, (July 2009), pp. (313-330).
- Woodward, C.J.; Hervey, G.R.; Oakey, R.E. & Whitaker, E.M. (1991). The effects of fasting on plasma corticosterone kinetics in rats. *Br J Nutr*, Vol. 66, No. 1, (July 1991), pp. (117-127).
- Xie, X.M. & Smart, T.G. (1991). A physiological role for endogenous zinc in rat hippocampal synaptic neurotransmission. *Nature*, Vol. 349, No. 6309, (February 1991), pp. (521-524).
- Xu, J.; Kirigiti, M.A.; Cowley, M.A.; Grove, K.L. & Smith, M.S. (2009). Suppression of basal spontaneous gonadotropin-releasing hormone neuronal activity during lactation: role of inhibitory effects of neuropeptide Y. *Endocrinology*, Vol. 150, No. 1, (January 2009), pp. (333-340).
- Yamamoto, Y.; Ueta, Y.; Date, Y.; Nakazato, M.; Hara, Y.; Serino, R.; Nomura, M.; Shibuya, I.; Matsukura, S. & Yamashita, H. (1999). Down regulation of the prepro-orexin gene expression in genetically obese mice. *Brain Res Mol Brain Res*, Vol. 65, No. 1, (February 1999), pp. (14-22).
- Yang, J. & Tashjian, A.H., Jr. (1993). Regulation of endogenous thyrotropin-releasing hormone (TRH) receptor messenger RNA by TRH in GH4C1 cells. *Mol Endocrinol*, Vol. 7, No. 6, (June 1993), pp. (753-758).
- Yen, P.M. (2001). Physiological and molecular basis of thyroid hormone action. *Physiol Rev*, Vol. 81, No. 3, (July 2001), pp. (1097-1142).



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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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