Central and peripheral mechanisms that modulate energy intake, partition and expenditure determine energy homeostasis. Thyroid hormones (TH) regulate energy expenditure through the control of basal metabolic rate and thermogenesis; they also modulate food intake. TH concentrations are regulated by the hypothalamus-pituitary-thyroid (HPT) axis, and by transport and metabolism in blood and target tissues. In mammals, hypophysiotropic thyrotropin-releasing hormone (TRH) neurons of the paraventricular nucleus of the hypothalamus integrate energy-related information. They project to the external zone of the median eminence (ME), a brain circumventricular organ rich in neuron terminal varicosities and buttons, tanycytes, other glial cells and capillaries. These capillary vessels form a portal system that links the base of the hypothalamus with the anterior pituitary. Tanycytes of the medio-basal hypothalamus express a repertoire of proteins involved in transport, sensing, and metabolism of TH; among them is type 2 deiodinase, a source of 3,3′,5-triiodo-L-thyronine necessary for negative feedback on TRH neurons. Tanycyte subtypes are distinguished by position and phenotype. The end-feet of β2-tanycytes intermingle with TRH varicosities and terminals in the external layer of the ME and terminate close to the ME capillaries. Besides type 2 deiodinase, β2-tanycytes express the TRH-degrading ectoenzyme (TRH-DE); this enzyme likely controls the amount of TRH entering portal vessels. TRH-DE is rapidly upregulated by TH, contributing to TH negative feedback on HPT axis. Alterations in energy balance also regulate the expression and activity of TRH-DE in the ME, making β2-tanycytes a hub for energy-related regulation of HPT axis activity. β2-tanycytes also express TRH-R1, which mediates positive effects of TRH on TRH-DE activity and the size of β2-tanycyte end-feet contacts with the basal lamina adjacent to ME capillaries. These end-feet associations with ME capillaries, and TRH-DE activity, appear to coordinately control HPT axis activity. Thus, down-stream of neuronal control of TRH release by action potentials arrival in the
external layer of the median eminence, imbricated intercellular processes may coordinate the flux of TRH into the portal capillaries. In conclusion, β2-tanycytes appear as a critical cellular element for the somatic and post-secretory control of TRH flux into portal vessels, and HPT axis regulation in mammals.

Keywords: thyrotropin releasing hormone (TRH), thyroid hormone, tanyocyte, median eminence, thyrotropin (TSH–thyroid-stimulating hormone), TRH degrading ectoenzyme, paraventricular (PVN), third ventricle

INTRODUCTION

Thyroid Hormones (TH) are pleiotropic hormones that regulate body physiology throughout vertebrate life. TH are critical in the perinatal period; anomalies in maternal thyroid status have a severe impact on central nervous system development (1, 2). Growth and adult life are dependent on energy homeostasis, maintained by central and peripheral mechanisms modulating energy intake, partition, and expenditure. When organisms are challenged by novel environments, whether changing availability of nutrients, climate, reproductive, or internal energy demands, they use mechanisms of adaptation involving, among others, adjustments of TH levels (3). In coordination with sympathetic activation, TH play an important role in maintaining basal metabolic rate and thermogenesis in homeothermic organisms (4), they also control carbohydrate and lipid metabolism (3) and have a direct influence on hypothalamic nuclei that control energy intake and expenditure (5–8). Alterations in TH homeostasis are accompanied by several pathologies related to energy imbalances (9, 10).

The hypothalamus-pituitary-thyroid (HPT) axis of mammals integrates TH negative feedback, nutritional-, metabolic-, stress-related information, and other environmental, and social stimuli, to set circulating and local concentrations of TH, generally within narrow limits. This integration occurs in part at neurons that synthesize Thyrotropin-Releasing Hormone (TRH, pGlu-His-Pro-NH₂) localized in the paraventricular nuclei (PVN) of the hypothalamus (11), nuclei bilaterally situated in the dorsal vicinity of the third ventricle (12). TRH neurons are localized in almost all parvocellular subdivisions of the PVN but only neurons present in the median and caudal regions of the PVN in rat (only median in mouse) are hypophysiotropic; their axons project to the external zone of the median eminence (ME) (13–15), the ventral part of the hypothalamus that connects it to the infundibulum. The median eminence forms a highly irrigated interface which serves both as a sensory and a secretory organ between the hypothalamus and the circulation (16).

Indirect yet complementary techniques have shown that TRH release from the median eminence is dynamic in multiple contexts. As studies on electrophysiological traces of TRH neuronal activity are scarce (17), many hypotheses on TRH neuron activity have been based on measurements of Trh mRNA levels (18, 19), and cFOS or phosphorylated cyclic-AMP response element binding protein (pCREB) induction in TRH neurons (10, 20, 21). Inferences about TRH release from ME have been made by measuring rapid changes in TRH content in ME (22). Information about the extracellular concentration of TRH came from the use of in vivo push-pull perfusion of the ME (23, 24) and surgical approaches to sample micro volumes of portal blood (25). Detailed descriptions of the inputs to TRH neurons, together with receptor localization and pharmacological tools (10) have led to a functional cartography of inputs onto TRH neurons, albeit their time resolution is poor (at best various min), and many unknowns remain.

Once released from hypophysiotropic nerve terminals into ME extracellular space, TRH enter fenestrated primary portal capillaries, which deliver it to the anterior pituitary pars distalis. Upon reaching the thyrotrope in the distal part of the anterior pituitary, TRH binds to TRH receptor 1 (TRH-R1), a G-protein-coupled receptor (GPCR) expressed in pituitary thyrotropes (26). This interaction activates Ga11, increases intracellular calcium concentration and protein kinase C activity (27), and stimulates synthesis and release of Thyroid-Stimulating Hormone (TSH). TSH synthesis is regulated at levels of transcription and translation of α- and β-TSH subunits, their glycosylation and dimerization; bioactivity of released TSH depends on proper glycosylation (28, 29). The circulating concentration of TSH has been taken as a proxy for TRH secretion from ME, but the existence of multiple regulators of TSH secretion make firm conclusions difficult. Thus, Somatostatin (SRIF) neurons that originate in the periventricular nucleus of the hypothalamus (30) are other hypophysiotropic neurons involved in the central control of the HPT axis. The interaction of SRIF with its receptors, some of which are on thyrotropes (31), inhibits TSH secretion (32, 33). Although SRIF output can be modulated in ways consistent with a role in TSH control (34, 35), its function will not be further reviewed.

TSH reaches follicular cells of the thyroid gland and binds to the TSH receptor, a GPCR that stimulates the uptake of iodine and the activity of enzymes involved in the biosynthesis of 3,3’,5-triiodo-L-thyronine (T3) and thyroxine (T4); both are secreted (36). A major fraction of circulating TH is reversibly bound to carrier proteins in blood (37, 38), the small fraction of free TH can bind to membrane bound receptors (39) or enters cells through transporters (40). Multiple membrane transporters have the capacity to carry TH from the extracellular space into the cytosol, and vice versa. The most important is the Monocarboxylate Transporter 8 (MCT8, gene abbreviation: Slc16a2), which takes T4 and T3 from the extracellular space and the Organic Anion Transporter Polypeptide 1c1 (OATP1c1, gene abbreviation: Slc2a1), which has preference for T4 and reverse T3 (rT3) uptake (41).
T3 is the biologically active Iodo-Thyronine acting through nuclear TH receptors (TR); binding to α1-, β1-, or β2-TR controls transcription of multiple genes in almost all cell types (42). Local T3 concentrations depend mostly on its conversion from T4 by the tissue specific Deiodinases (D) type 1 and 2. D1 produces T3 by removing an iodine atom from the outer ring of T4 but can also remove it from the inner ring forming rT3, and deiodinates rT3 to T2. D2 catalyzes the transformation of T4 to T3. Finally, biologically inactive metabolites are produced by Deiodinase 3 (D3), which removes iodine from the T4 inner ring to produce rT3 or from T3 to produce 3, 3'-diodothyronine, products with no binding affinity for TR (43). Extra- and intracellular carrier proteins, plasma membrane transporters and biotransformations not only shape the local concentrations of TH, but also contribute to modulate their systemic effects (44).

Circulating TH generate negative feedback loops maintaining their serum concentration between set limits, although these limits can be changed according to metabolic challenges. A negative correlation exists between serum TH levels and Trh expression in the PVN (45–47). This negative correlation extends to TRH concentration in the PVN neurons (48, 49) and in portal vessels (25, 50, 51). The feedback depends on TH entering the brain through the MCT8 and OATP1c1 transporters (52–55), and on the interaction of β1-TR and β2-TR with T3 (28, 42), which are expressed in THR neurons (56).

The basic HPT axis hierarchy is embedded in multiple regulatory circuits that adjust the local and global impact of TH according to physiological influences, or physio-pathological alterations (10, 11, 57, 58). A recently discovered level of HPT axis control relies on tanyocytes, specialized ependymal cells present in sensory and secretory circumventricular organs (CVO) of the brain (16, 59), including the floor and the ventrolateral walls of the third ventricle (60–62). While astrocytes supply T3 to brain cells, tanyocytes that border the dorso-, ventromedial, and arcuate nuclei, as well as the median eminence, referred here as medio-basal hypothalamus (MBH) tanyocytes, contribute to TH feedback on HPT axis, TH control of MBH circuits involved in energy homeostasis (10), as well as regulation of the amount of TRH entering the portal vessels (63, 64). We focus this review on the bidirectional pathways linking MBH tanyocytes with TRH neurons activity and TRH entrance into portal vessels in mammals. We summarize knowledge about tanyocytes and their phenotypic variation, demonstrate their critical involvement in TH feedback and adjustment of HPT axis activity according to energy related clues, introduce issues related to tanyocyte programing of HPT axis and finally state some of the existing challenges in non-mammalian vertebrates.

MULTIPLE TYPES OF TANCYCYES LINE THE VENTRAL AND LATERAL WALLS OF THE THIRD VENTRICLE

As ependymocytes, tanyocytes have a small body lining some ventricle walls. In the MBH a long, basal process is directed to the hypothalamic parenchyma or blood vessels; MBH tanyocytes have plenty of small and large protrusions full of endosomes directed to the third ventricle, which may have a secretory or transport function (60, 65). They express markers of caveolae- and/or clathrin- dependent endocytosis in their apical and basal domains, suggesting they can internalize molecules from the cerebrospinal fluid (CSF) and/or median eminence extracellular fluid (ECF) and transport some by transcytosis (66).

MBH tanyocytes have been cataloged in 4 subtypes: α1-, α2-, β1-, and β2-tanyocytes, according to location, expression of lineage and differentiation markers (67), as well as based on mitochondrial structures and secretory granules abundance (62). However, single-cell transcriptome and ultrastructural analyses suggest that each tanyocyte subtype may be further subdivided (62, 68–70). α1-Tanyocytes extend their process to dorsomedial and ventromedial nuclei (DMN and VMN) of the hypothalamus, while α2-tanyocytes are restricted to the dorsomedial extent of the arcuate nucleus (ARC). At their basal pole, α-tanyocytes contact and ensheathe laterally located blood brain barrier (BBB) vessels; cell bodies and initial segment of α-tanyocytes additionally contact dendrites from ARC neurons (60, 62, 71). β1- and β2-tanyocytes reside in the ventral limits of the third ventricle and their end-feet are proximal to fenestrated vessels of the ME; they form a barrier at their apical pole between the CSF and the periphery (62, 72) (Figure 1). In addition, β1-tanyocytes delimit the borders of the adjacent ventromedial ARC and the ME. Along their processes they show interchained proteins, zona occludens, and macula adherens, which join β1-tanyocytes in bundles. This arrangement may contribute to a barrier that impedes the diffusion of molecules from the ME into the ARC in basal conditions (60, 71, 72), but a definitive functional evidence is lacking. Alternative mechanisms such as forces emanating from vessels cannot be discarded.

Despite stunning morphological and molecular similarities between radial glia and tanyocytes, the latter are not radial glia but their descendants (60). MBH tanyocytes are generated from hypothalamic progenitor cells in the last days of gestation and the first 2 weeks of life of the rat (60, 73). They express the intermediate filament proteins Nestin, Vimentin, and Glial Fibrillary Acidic Protein (74), the Dopamine- and cAMP-Regulated Phosphoprotein of 32 kDa (DARPP-32), a dopaminergic phosphoprotein (75), and proliferation and nuclear factors such as Antigen KI-67 and Sex Determining Region Y-Box 2 (74).

TANCYCYES AND THE MEDIAN EMINENCE

The ME is enriched with varicosities and terminal buttons from various hypophysiotropic neuron types, which release hypothalamic releasing factors into fenestrated capillaries directed to the pituitary. Furthermore, the ME harbors tanyocytes, astrocytes, microglia, oligodendrocyte precursors and blood vessels (62, 76, 77) (Figure 2). Many interactions may occur between neuron varicosities and terminals and other cellular elements, either through juxtacrine or paracrine communication. Although frequency and pattern of action potentials generated in the hypophysiotropic neuron soma likely contribute to define the amount and pattern of peptides/transmitters released into
Peroxidase injected into the third ventricle diffuses freely into the hypothalamic parenchyma and has no access to the ME (60). β2-tanycytes are barriers between the ME and the third ventricle, as they express tight junction proteins like Zonula Occludens 1 and Occludin in their apical side, which form a honeycomb pattern (60, 72), impeding the free exchange of substances coming from the ME and the cerebrospinal fluid. Among tanycyte transcripts highly expressed in the β2-clusters, Scn7a, and Col25a1 may be useful as specific markers of this subtype, since they are much less abundant in other tanycyte subtypes and glial cells (Figure 3).

About 80% of terminal buttons arriving into the mediolecular part of the external layer of the ME contain TRH (82), with an ample rostro-caudal distribution terminating in the infundibular stalk (83). The antero-posterior and medio-lateral distributions of rat β2-tanycyte processes and TRH varicosities and terminals in the ME indicate a substantial spatial coincidence; in addition, synaptoid contacts between both cell types are observed (14, 63, 83, 84), suggesting that functional interactions occur. We will review the evidences that β2-tanycyte properties make them a critical cellular element of the HPT axis.

A putative fifth subtype of tanycytes, γ-tanycytes (85), previously identified as astrocytic or subependymal tanycytes (65, 86, 87) is localized in the ME. These cells resemble β2-tanycytes, including an abundant smooth and rough endoplasmic reticulum, yet their apical side does not contact the third ventricle, their processes are poor in microtubules and organelles (62), they express distinctive markers, including Propiomelanocortin (85), and contain lipid droplets in the perikaryon, which may be a source of the median eminence prostaglandins. It has been proposed that these tanycytes should be reclassified as pituicytes; their position, ultrastructure and contacts suggest they are relevant for neuroendocrine control (62).

TANYCYTES AND NEUROGENESIS

Hypothalamic neurogenic niches have been observed in distinct populations of cells surrounding the third ventricle of the MBH, from ependymal cells to tanycytes. They act as progenitor cells that can differentiate into neurons or glia. New ARC, ventromedial and dorsomedial nuclei, and ME neurons may derive from tanycytes in postnatal animals. Thus, tanycytes may contribute to the programing/plasticity of adult hypothalamic circuits according to energy and/or nutritional signals [reviewed in Prevot et al. (81)]. Although unexplored, these events may impact on HPT axis regulation, as these MBH nuclei control hypophysiotropic TRH neurons.

TANYCYTES, THE HYPOTHALAMIC AVAILABILITY OF THYROID HORMONES, AND THE CONTROL OF TRH NEURONS ACTIVITY

More than 80% of adult brain T3 comes from deiodination of T4 (88–90). D2 is broadly distributed along multiple brain areas, expressed mostly in astrocytes, which capture T4 from blood...
vessels or CSF and deliver T3 to the neighboring neurons in the parenchyma. However, the MBH of euthyroid rats has a higher D2 activity than other brain areas (91). Cells expressing this deiodinase correspond to tanyocytes, and to a lower extent to astrocytes (92, 93). In the ME, the transporters MCT8 and OATP1c1 are present in tanyocyte processes (94, 95). Experiments with Dio2 knockout mice contributed to elucidate the relative importance of the multiple cell sources of D2 for HPT axis regulation. Global Dio2 knockout mice have elevated serum T4 and TSH concentrations, consistent with the necessity of this enzyme for negative feedback. However, Trh expression in the hypothalamus is decreased, indicating that remaining D2 tanyocyte expression is critical for normal HPT axis function (96). In addition, Dio3-KO studies support the proposal that this enzyme is necessary for normal HPT axis function 

with a deletion of Dio2 expression specific for the pituitary gland show high serum T4 and TSH concentrations, with unchanged Dio2 activity in the hypothalamus. However, Trh expression in the hypothalamus is decreased, indicating that remaining Dio2 expression is critical for normal HPT axis function (96). In addition, immunohistochemical studies show a high expression of Dio3 in the hypothalamus; although mostly in GnRH axon terminals (97), Dio3-KO studies support the proposal that this enzyme is necessary for normal HPT axis function, in part through hypothalamic mechanisms (98–100).

TH bioavailability in the cytosol may also be under the control of µ-crystallin (CRYM), which binds with high affinity to T3 and T4 and functions similarly to serum TH transporters (101). The transfection of a plasmid expressing CRYM in cells expressing MCT8 or MCT10 TH transporters increases the permanence...
of T3 in the cytosol (102, 103). Interestingly, Crym relative expression is higher in all subtypes of MBH tanycytes than in other cellular elements of the ARC/ME (69, 104), with a lower expression in β2-tanycytes. Differences in expression of Crym could adjust the time-course of T3 interaction with TR or the efflux of T3, and thus of target gene transcription. Figure 4 illustrates genes related with HPT axis regulation expressed in tanycyte subtypes.

The pathway that TH use to feedback on Trh expression in the PVN is still a puzzling matter. Although TH most probably reach the PVN cells through the BBB and Dio2 mRNA is expressed in the PVN (105), possibly by astrocytes, early studies indicated that D2 is absent from PVN neurons (91, 92), and peripheral administration of a dose of T3 restituting its physiological levels is not enough to reduce Trh expression in the PVN in hypothyroid rats, unless larger doses are used (47). It was therefore put forward that after T4 entrance and T3 production by D2 in tanycytes, a route of T3 transport from tanycytes to the PVN was necessary for feedback regulation of TRH neurons. One proposal is that T3 could be transported from tanycytes to the third ventricle or parenchyma and bound to Transthyretin (106) diffuse, and/or move by bulk flow, to parvocellular PVN neuronal cell bodies. While ependymal cells proximal to the PVN have intercellular spaces that allow entry into parenchyma of practically all molecules from the ventricle, significant entry of T3 generated by tanycytes through this route seems unlikely. Tanycytes have 2 cilia (α-tanycytes) or 1 cilium (β-tanycytes), in contrast with the multiciliate ependymal cells in contact with the cerebrospinal fluid of the ventricles (109). Tanycytes are poor contributors of cerebrospinal flow, as ciliary beat is involved with pulsatile motion of the cerebrospinal fluid from the ventricles (109). This observation suggests that in tanycyte-rich regions the CSF proximal to the ventricular walls is more static than in the upper ventricular wall, which is enriched with multiciliate ependymal cells; thus, molecules transported or generated by tanycytes may have a paracrine impact limited to proximate hypothalamic nuclei.

An alternate hypothesis takes into account that T3 exert feedback effects exclusively in the hypophysiotropic TRH neurons of the PVN located in middle and caudal zones, which send their axons to the ME, but not in nearby TRH neurons of the anterior PVN or lateral hypothalamus of the rat (15, 110). Since MCT8 and OATP1c1 are present in β2-tanycyte processes (95) and MCT8 is detected on axon varicosities of TRH neurons contacting tanycytes (97), these varicosities may be a preferential site of uptake for T3 by hypophysiotropic TRH neurons, followed by retrograde axonal transport to the PVN (10). Whether T3 is indeed retrogradely transported in TRH neurons requires further studies.

T3 generated from α-tanycytes may also interact with hypothalamic nuclei that regulate energy balance. D2 expressing α2-tanycytes may be in close relationship with AgRP neurons, and T3 increases the mitochondrial density and uncoupling activity in NPY/AgRP neurons of the ARC, actions related with their firing frequency. This may contribute to the feedback inhibition of TRH neuron activity, through the monosynaptic ARC-PVN pathway (5, 93) but also to TH-induced increase in food intake (111).

**TANCYTES, THYROID HORMONES FEEDBACK AND THE CONTROL OF MEDIAN EMINENCE TRH FLUX INTO PORTAL VESSELS**

Another actor of HPT axis regulation expressed in tanycytes is pyroglutamyl peptidase II or TRH-degrading ectoenzyme (TRH-DE), a membrane-bound omega zinc-dependent metallopeptidase which catalyzes the hydrolysis of the pGlu-His bond of TRH in the extracellular space. Multiple evidences support the role of TRH-DE as the main regulator of TRH turnover in the extracellular space. TRH-DE specificity is narrow, hydrolysis being limited to pGlu-X-Y peptides (in which X is an uncharged residue and Y Pro, Ala, Trp, Pro-Gly, Pro-NH2, Pro-naphthylamide, or Pro-7-amino-4-methyl coumarin), being TRH the only biological substrate (112, 113). Trhde expression is mainly restricted to various brain regions,
being particularly rich at ME site (114). Vimentin-expressing β2-tanyocytes express *Trhde* in the cell body but possibly also along their basal process; moreover, *Trhde* expression is more intense in the external zone of the ME, where TRH neurons release their contents close to portal capillaries, than in other tanyocytes domains (63). Single cell transcriptome analysis of MBH confirms *Trhde* is particularly enriched in β2-tanyocytes (69) (Figure 4). The localization of *Trhde* mRNA to β2-tanyocyte processes suggests that local translation of TRH-DE is a major source of TRH-DE activity in the intermediate and/or external layers of the median eminence. However, although TRH-DE activity is high in median eminence, coincident with *Trhde* mRNA levels (63), it should be noted that there are at least 2 isoforms of TRH-DE, one of them being a shorter, dominant-negative form; these isoforms are expressed in brain (115). Thus, clarification of the precise localization of TRH-DE activity in the β2-tanyocyte domain awaits additional studies.

Functional evidence for TRH-DE relevance in regulating TSH secretion comes from experiments showing that inhibition of this enzyme enhances TRH recovery from incubation medium of median eminence explants (63), or in which the intra peritoneal (ip) injection of a brain-permeant inhibitor of TRH-DE (116) enhances serum TSH concentration in response to a cold stress or ip TRH (63). However, since the ip administration of the brain-permeant TRH-DE inhibitor may have altered TRH-DE activity in various tissues, definitive evidence for the importance of TRH-DE activity in tanyocytes *in vivo* is lacking. For example, a soluble TRH-DE isofrom generated in liver, termed Thryroliberinase (117), circulates in serum and may contribute to regulation of TSH secretion (118, 119). A link between TRH-DE and metabolism was first noted when it was shown that the activity of Thyroliberinase is positively correlated with body weight in man (120). More recently, single nucleotide polymorphisms of *Trhde* have been associated with differences in body weight and chest girth in sheep (121), but the phenotypic relevance of tanyocyte *Trhde* is unknown.

TRH-DE activity is highly sensitive to TH levels in the median eminence, as previously demonstrated for pituitary and serum TRH-DE (122, 123). An ip injection of T4 to adult euthyroid rats enhances the expression of *Trhde* in tanyocytes and of TRH-DE activity in the median eminence (63). Deiodination of T4 from D2 is necessary to change *Trhde* expression in response to short-term exposition (hours) to TH: in D2 knockout mice *Trhde* is upregulated by T3 administration but not by T4 (124). Changes in *Trh* mRNA levels in response to T3 are not as rapid as those observed for ME *Trhde* expression, suggesting that the regulation of *Trhde* expression in the median eminence by feedback may be critical for short term adjustment of TRH output (124). TH effects on *Trhde* expression are likely direct on tanyocytes since they express *Thra* ([69], Figure 4).

Since recent evidence suggests that control of β2-tanyocyte end-feet morphology impacts serum TSH concentration (see section “Interactions between β2-tanyocytes and hypophysiotropic TRH neurons directly control the output of TRH into portal vessels”), it seems appropriate to test whether morphological changes in the end feet of tanyocytes occur in response to TH, and contribute to the feedback control of the HPT axis in mammals.

Finally, because TH control proliferation and differentiation of progenitor cells to a neuronal phenotype in adult rodents...
(125–127), and tanycytes have the molecular machinery needed to integrate TH signaling, testing whether fluctuations in local TH levels in the MBH may control the neuron precursor potential of tanycytes is warranted (128). Apart from negative feedback, other energy-related cues regulating HPT axis activity implicate tanycytes.

**COLD EXPOSURE, HPT AXIS, AND TANYCYTES**

In response to cold exposure, catecholaminergic pathways from the brainstem activate a large subpopulation of hypophysiotropic TRH neurons leading to enhanced secretion of TRH and TSH secretion, and TH synthesis (11, 18, 19, 51, 63, 129–131), contributing to facultative thermogenesis, a critical event for body thermoregulation. Although responses of the HPT axis to cold have been attributed to regulation of TRH neurons activity, additional events occurring in the median eminence have also been detected, including evidence that during a cold stress an interaction between NA and TRH terminals (132) plays a permissive role for TRH secretion (23, 133). Tanycytes may also regulate the dynamics of TRH entry into portal capillaries during a cold stress since the ip administration of a TRH-DE inhibitor enhances serum TSH concentration induced by cold exposure (63).

**NEGATIVE ENERGY BALANCE, HPT AXIS, AND TANYCYTES**

The ARC exerts a well-known and critical influence on homeostatic mechanisms of energy intake and expenditure. The activity of ARC neurons expressing POMC/CART or NPY/AgRP/GABA is regulated in opposite direction according to nutritional status and energy balance, in direct response to signals such as leptin, ghrelin, insulin, and glucose. ARC neurons provide direct inputs onto hypophysiotropic TRH neurons, and their messengers directly up- (αMSH, CART) or down-regulate (NPY, AgRP) TRH neurons activity (10, 17, 134).

**Fasting, Food Restriction, and Voluntary Exercise**

Fasting promotes a profound down regulation of HPT axis activity, sparing energy use. This is driven by a reduction of PVN Trh mRNA levels and TRH concentration in portal vessels, leading to decreases in serum TSH and TH concentrations (10). In this model, the reduction of TRH neurons activity has been attributed in part to the effect of a decrease of circulating lepin concentration (135), mediated by inhibition of the POMC/CART neurons of the ARC and stimulation of the NPY/AgRP/GABA neurons (10, 136, 137), and also by reduction of direct lepin stimulation of TRH neurons (138, 139). On the other hand, high levels of circulating ghrelin in fasted animals may also indirectly inhibit the activity of TRH neurons (140, 141), although this is not settled.

Leptin effects on the central arm of the HPT axis depend on access to the hypothalamic parenchyma. Although the ventromedial ARC has vessels whose permeability is regulated by energy status (142), making part of this nucleus sensitive to circulating peptides during fasting, peptide hormones do not generally pass the BBB, suggesting additional mechanisms of transport must operate (143). Thus, leptin enters the brain bypassing the BBB across the choroid plexus (144), and through median eminence tanycytes. Transport of leptin through tanycytes into the CSF depends on Extracellular Regulated Kinase induction in tanycytes (145). Tanycytes may also transport ghrelin from the median eminence into the CSF (146, 147). Peptide hormones can easily diffuse from the ventral part of the third ventricle, into the adjacent dorsomedial ARC, and possibly via the parenchyma to the PVN. Thus, the function of critical regulators of HPT axis activity likely depends, at least in part, on the transport function of tanycytes.

During fasting, Dio2 mRNA expression and activity is upregulated in tanycytes (148), in parallel with a local increase in T3 concentration (3), albeit this increase is transitory, it coincides with the lowest levels of Trh expression in the PVN (119), consistent with a role of tanycyte D2 in the local regulation of the HPT axis. Possibly because of this induction, an increase of ME TRH-DE activity is detected in response to a prolonged (72 h) fast in male rats; that may strengthen the reduction of HPT axis activity (119).

Therefore, tanycyte D2, and TRH-DE coordinated regulation during prolonged fasting likely contributes to maintain inhibition of HPT axis activity (119). The increase in D2 activity raises the local levels of T3 which feedbacks on TRH synthesis, while up regulation of the expression of Trhde and its activity in the tanycyte may reduce TRH access into the portal blood. Fasting-induced increase in D2 activity could also regulate the activity of ARC neurons, thus indirectly controlling the HPT axis (5). However, since Dio2 expression in the PVN is upregulated by fasting (105), other hypothalamic sources of T3 may also contribute to regulate the activity of TRH neurons when energy balance is negative.

Food reduction or restriction can also reduce the activity of the HPT axis (149–152). Contrary to fasting, a strong food restriction (gradually from 35 to 75% for 7 days) decreases Trhde expression, but not TRH-DE activity, although D2 expression and activity are increased in the MBH (152).

Compared to sedentary animals, 2 weeks of voluntary exercise in male rats diminish food intake by 18% and markers of the central activity of the HPT axis, increase the activity of D2 in MBH but have no effect on Trhde expression in the median eminence (153). Thus, as occurs during food restriction, sustained but limited negative energy balance does not increase the expression of Trhde in the ME, implying changes in Trhde expression in the ME may depend on intensity and/or duration of negative energy balance.

**Non-thyroidal Illness Syndrome**

Pathological conditions, as chronic infection or cachexia produce the non-thyroidal illness syndrome (NTIS) generally
characterized by normal basal TSH concentration, and low thyroid hormone serum concentrations (154). Experimental evidences indicate central and peripheral changes. The injection of bacterial Lipopolysaccharide in animals, which mimics a bacterial infection, suppresses hypophysiotropic Trh expression and serum TH concentrations (10, 84, 148, 155). Unlike fasting, endotoxin injection has a pronounced positive effect on Dio2 expression in the α-tanycytes (84, 156), the peak in Dio2 expression coincides with the maximum decrease of Trh mRNA level in the PVN, suggesting that, apart from the β-tanycytes, α-tanycyte T3 production is also critical for HPT axis regulation (84, 148, 155).

INTERACTIONS BETWEEN β2-TANCYTES AND HYPOPHYSIOTROPIC TRH NEURONS AND THE FLUX OF TRH INTO PORTAL VESSELS

The previous sections have shown that tanycytes determine local concentrations of TH, sense and transport energy related cues, and may control TRH turnover in the extracellular space of the ME, all of which influence directly or indirectly TRH neurons activity and output into portal vessels. New evidences suggest TRH neurons control tanycyte properties defining the output of TRH into the portal capillaries, through mechanisms which operate in the external layer at post-secretory levels. While a hybridization signal for TRH receptors was not initially detected in the median eminence (26), more recent evidence indicates β2-tanycytes do express low levels of Trhr [(64, 69, Figure 4]. Activation of TRH-R1 in β2-tanycytes induces Ca\(^{+}\) entry and an increase of TRH-DE activity in the median eminence. This may enhance TRH hydrolysis before entry into the portal vessels, a decrease in bioavailability which may limit desensitization and/or downregulation of TRH-R1 in the thyrotropes, and/or contribute to transient pulses of TRH. These experiments also showed that TRH binding to TRH-R1 promotes the extension of tanycyte basal processes between TRH terminals and portal vessels, which may also reduce the flux of TRH into the portal vessels. Therefore, TRH seems to have the capacity to modulate its own entry into portal vessels by two complementary mechanisms: modulation of TRH-DE activity and end-feet contacts of β2-tanycytes with portal capillaries (64). These evidences were obtained in part in models in which Go_{q/11} proteins were made inactive; however, the functional demonstration that TRH-DE activity and/or end-feet contacts of β2-tanycytes with portal capillaries are critical is still lacking.

Apart from TRH, hypophysiotropic TRH neurons use glutamate as a transmitter (157). The role of this pool of glutamate is still under investigation, but it is interesting to note that mRNA coding for 2 ionotropic glutamate receptors, including the Glutamate Receptor Ionotropic Kainate Type Subunit 3, are expressed by tanycytes [(69, 158, 159, Figure 4], and that glutamate regulates TRH-DE activity in the hippocampus (160), making it tempting to speculate glutamate regulates TRH-DE activity in the ME.

PROGRAMMING OF HPT AXIS AND TANCYTE Trhde EXPRESSION

In the rat, the development of median eminence tanycytes, which are first detected before birth (87) occurs in parallel with multiple aspects of HPT axis ontogeny. Since tanycytes control the local (hypothalamic) bioavailability of TH, the postnatal development of tanycytes is probably critical for HPT feedback development, as has been suggested in chicken (161).

Multiple determinants, which include nutrition, stress and toxics exposure, during pre- or post-natal development can program adult HPT axis function (162, 163). Some impacts have been linked to hypophysiotropic TRH neurons and tanycytes, although the mechanistic insights are still limited (163). One of the best understood models of post-natal stress is repeated maternal separation (MS) during lactation. MS causes multiple long-term endocrine perturbations (164), including the functional state of the HPT axis in adult rats in a sex related manner. Pups separated from their mother for 3 h daily during lactation have altered HPT axis activity. As adults, male rats have decreased TSH and T3 serum concentrations and a higher expression of Trhde in tanycytes of ME, compared to undisturbed pups. MS males do not respond to fasting as expected: Trhde expression is not enhanced and HPT axis activity inhibition is blunted. These changes are not detected in MS females who have higher (compared to undisturbed animals) fat mass and Trh expression in PVN but normal serum concentrations of TH and no changes in their reaction to fasting (165). The higher susceptibility to MS of males compared to females has been observed in other paradigms (166), but it is interesting that the more intense change is in Trhde expression and is long-lasting (165). The sex–specific programing of Trhde expression together with TSH and T3 serum concentrations in this MS paradigm reinforces the hypothesis that alterations in tanycyte properties can have short- and long-term consequences on thyroid status. Understanding the mechanisms programing tanycyte functions, including Trhde expression, in response to stressors, nutrition and toxic substances is warranted.

TANCYTES AND HPT AXIS IN NON-MAMMALIAN VERTEBRATES

The evolutionary origin of the TRH neuron-tanycyte interaction is poorly understood. Except for teleosts, hypothalami of vertebrates have a median eminence whose external layer connects hypothalamus and pituitary via a portal system. As in mammals, in most non-mammalian vertebrates, the external layer also contains end-feet of glial-like cells, which cell body is localized in the floor of the third ventricle (167). These glial-like cells express vimentin and GFAP (therefore denominated tanycytes) and contact portal vessels in most vertebrates (168–170). Moreover, in non-mammalian vertebrates, tanycytes of the median eminence have an anatomical position akin to that seen in mammals, although their molecular signatures are unknown. Since most non-mammalian vertebrates possess a median eminence with tanycytes analogous to β2-tanycytes, they
are probably fundamental to create an appropriate physical, molecular and anatomical link between brain and pituitary, and regulate the HPT axis. Although Trh, and Trhr genes are detected in most non-mammalian vertebrates, their functional roles are not always related to the regulation of TSH secretion (171), and therefore to the control of TH secretion. Thus, for example, the thyroid status does not regulate TRH synthesis in the hypothalamus of the fish brain (172, 173), in a site homologous to the mammalian PVN. On the contrary, Corticotropin Releasing Hormone (CRH) is a major Thyrotropin-Releasing Factor (TRF) in non-mammalian vertebrates (174). Among the many unknowns about non-mammalian vertebrates tanycytes and HPT axis, we can pinpoint the following: could the local production of T3 regulate hypothalamic CRH synthesis, as it does for TRH in mammals? Are morphological changes of tanycytes regulating TRF availability? Is an hydrolase analogous to TRH-DE operating for another TRF?

PHOTOPERIOD AND THE CONTROL OF TANCYTE-DERIVED T3

In avian and mammalian species sensible to photoperiod, photoperiod effects on neuroendocrine axes critically depend on tanycytes. Melatonin, which transduces photoperiod, interacts with the melatonin 1 receptor expressed in secretory pars distalis specific thyrotropes, a cell phenotype different from the pars distalis thyrotropes, and induces rhythmic TSH secretion from the pars distalis linked to the regulation of seasonal breeding (175, 176). Exposure to long days enhances TSH secretion from the pars distalis (177–179), followed by a later stimulation of Dio2 and a decrease of Dio3 expression in tanycytes (180, 181). Although all tanycyte subtypes express Tshr (Figure 4), TSH-induced expression of Dio2 occurs mostly in α1-, α2-, and β1-tanycytes (177–179). As a result, MBH T3 levels are raised in long day seasons (180). This in turn influences the morphology of tanycytes end-feet in the lateral median eminence, increasing GnRH terminals access to the basal lamina and release into the portal circulation (182, 183). Pars tuberalis thyrotrope interaction with MBH tanycytes and reproductive axis consequences have been reviewed recently (184).

Although TSH-induced expression of Dio2 during seasonal cycles is limited to α- and β1-subtypes, it may still influence Trh transcription in the PVN if β2-tanycytes are not critical for T3 effects on the HPT axis (see for example sub section “Non-thyroidal illness syndrome”). Nevertheless, photoperiod has no effect on Trh expression in Siberian hamster or F344 rats (185, 186). Furthermore, TSH production from the pars tuberalis is not affected by thyroid hormones nor TRH (175) and even if pars tuberalis-derived TSH can bind to TSH receptors, it is not active in the thyroid gland (187). Thus, TSH released from the pars tuberalis has only a local action in the MBH, and there is no evidence that it regulates the HPT axis activity according to photoperiod. The lack of coupling between TSH receptor activation and Dio2 expression in β2-tanycytes may result in uncoupling of the HPT axis from photoperiod information (184).

CONCLUSIONS

In the external layer of the median eminence, various imbricated inter- and intra-cellular processes may coordinate the flux of TRH into the portal capillaries, down-stream of the enhancement of TRH release by action potentials arrival. Tanycytes are critical cells that link HPT axis activity to physiological status through molecular and cellular and adaptations. Thus, although TH negatively regulate hypothphysiotropic TRH neurons activity, this role depends on biotransformation of T4 in tanycytes. Furthermore, the post-secretory availability of TRH may also be TH dependent, regulated by tanycyte TRH-DE activity and
possibly the physical barrier that the end-feet make near the portal vessels. These advances suggest that tanycytes, in particular β2-tanyctyes, are critical for feedback control of the HPT axis (Figure 5). An interesting question remaining to be solved is the relative importance for TRH output in mammals of the barrier function of the end-feet and of TRH-DE activity.

Another remarkable aspect is that TRH, and possibly glutamate, released from TRH terminals, regulates TRH accessibility to portal vessels through a dynamic and reciprocal interaction with tanycytes. This interaction rapidly regulates the activity of the TRH-DE and the end-feet contacts with median eminence capillaries. On the other hand, tanycytes may also feedback on TRH secretion, interactions that together may contribute to generate cycles of TRH release, and/or may rapidly regulate it in response to physiological stimuli, such as during cold exposure. Median eminence tanycytes are thus an additional critical level of control of the HPT axis, sensitive to energy balance clues, and impacting on TRH output. The efficiency of this control point may be programmed by developmental challenges.

Other aspects of HPT axis control at median eminence level still requiring investigation are putative interactions of SRIF terminals and tanycytes, since there is an ample rostro-caudal distribution of SRIF varicosities that terminates in the infundibular stalk (30). These and other local mechanisms may also have a significant effect on the control of the thyroid axis.

Finally, although knowledge about the relation of tanycytes and HPT axis function is still limited, it is tempting to think that clinical applications may be considered in the future, since the ME compartment is outside the BBB. Sex dimorphism should be investigated, because of its physiological and clinical relevance.

AUTHOR CONTRIBUTIONS

AR-R and J-LC conceived and wrote the manuscript. IL, ES-J, RU, LJ-H, and PJ-B wrote selected portions and edited the manuscript. All authors read and approved the final manuscript. Figures were made by AR-R with open source software, including Inkscape (www.inkscape.org) and Matplotlib (188).

FUNDING

Partially funded by grants from CONACYT (CB154931, CB254960, and PN562) to J-LC, CONACYT (CB284883) and DGAPA-UNAM (PAPIIT IN204316) to PJ-B. AR-R is a fellow of the Postgraduate Program in Biochemistry, UNAM; his fellowship was granted by CONACYT.

ACKNOWLEDGMENTS

We acknowledge the contributions of Miguel Cisneros, Fidelia Romero, Antonieta Cote-Vélez, Karina Hernández-Ortega, Mariana Gutierrez-Mariscal and Nashiely Yáñez-Recéndis, that aided the efforts of the authors in research related to the review subject.

REFERENCES

1. Bernal J. The significance of thyroid hormone transporters in the brain. Endocrinology. (2005) 146:1698–700. doi: 10.1210/en.2005-0134

2. Raymond J, LaFranchi SH. Fetal and neonatal thyroid function: review and summary of significant new findings. J Clin Endocrinol Metab. (2010) 19:171–7. doi: 10.1210/jc.2009-1903.2010

3. Mullur R, Liu Y-Y, Brent GA. Thyroid hormone regulation of metabolism. Annu Rev Med. (2003) 54:205–13. doi: 10.1146/annurev.med.54.013102.134103

4. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. Ann Intern Med. (2005) 143:190–5. doi: 10.7326/0003-4819-139-3-20030805-00010

5. Coppola A, Liu Z-W, Andrews ZB, Paradis E, Roy M-C, Friedman JM, et al. A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. Cell Metab. (2007) 5:21–33. doi: 10.1016/j.cmet.2006.12.002

6. Decherf S, Seugnet I, Koudial S, Lopez-Juarez A, Clerget-Froidevaux M-S, Demeneix BA. Thyroid hormone exerts negative feedback on hypothalamic type 4 melanocortin receptor expression. Proc Natl Acad Sci USA. (2010) 107:4471–6. doi: 10.1073/pnas.0905190107

7. López M, Varela L, Vázquez MJ, Rodríguez-Cuenca S, González CR, Velagapudi VR, et al. Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. Nat Med. (2010) 16:1001–8. doi: 10.1038/nm.2207

8. Hameed S, Patterson M, Dhillo WS, Rahman SA, Ma Y, Holton C, et al. Thyroid hormone type 4 melanocortin receptor expression. Proc Natl Acad Sci USA. (2010) 107:4471–6. doi: 10.1073/pnas.0905190107

9. Roelfsema F, Boelen A, Kalsbeek A, Flors E. Regulatory aspects of the human hypothalamic-pituitary-thyroid axis. Best Pract Res Clin Endocrinol Metab. (2017) 31:487–503. doi: 10.1016/j.bepo.2017.09.004

10. Fekete C, Lechan RM. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr Rev. (2014) 35:159–94. doi: 10.1210/er.2013-1087

11. Joseph-Bravo P, Jaimez-Hoy L, Uribe R-M, Charli J-L. 60 years of neuroendocrinology: TRH, the first hypophysiotropic releasing hormone isolated: control of the pituitary–thyroid axis. J Endocrinol. (2013) 226:T85–100. doi: 10.1530/JOE-15-0124

12. Swanson LW, Kuypers HGJM. The paraventricular nucleus of the hypothalamus: Cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. J Comp Neurol. (1980) 194:555–70. doi: 10.1016/cne.901940306

13. Kawano H, Tsuruo Y, Bando H, Daikoku S. Hypophysiotropic TRH-producing neurons identified by combining immunohistochemistry for pro-TRH and retrograde tracing. J Comp Neurol. (1991) 307:531–8. doi: 10.1002/cne.903070402

14. Fekete C, Mihály E, Herscovici S, Salas J, Tu H, Larsen PR, et al. DARPP-32 and CREB are present in type 2 iodothyronine deiodinase-producing tanycytes: implications for the regulation of type 2 deiodinase activity. Brain Res. (2000) 862:154–61. doi: 10.1016/S0006-8993(00)02105-3

15. Kadar A, Sanchez E, Wittmann G, Singru PS, Fuzesi T, Marsili A, et al. Distribution of hypophysiotropic thyrotropin-releasing hormone (TRH)-synthesizing neurons in the hypothalamic paraventricular nucleus of the mouse. J Comp Neurol. (2010) 518:3948–61. doi: 10.1002/cne.22432

16. Joly J-S, Osório J, Alunni A, Auger H, Kano S, Rétaux S. Windows of the brain: towards a developmental biology of circumventricular and other neurohemal organs. Semin Cell Dev Biol. (2007) 18:512–24. doi: 10.1016/j.semcdb.2007.06.001

17. Ghamari-Langroudi M, Vella KR, Sriasi D, Sugrue ML, Hollenberg AN, Cone BD. Regulation of thyrotropin-releasing hormone-expressing neurons...
in paraventricular nucleus of the hypothalamus by signals of adiposity. Mol Endocrinol. (2010) 24:2366–81. doi: 10.1210/me.2010-0203

18. Uribe M, Redondo L, Charli J-L, Joseph-Bravo P. Sucking and cold stress rapidly and transiently increase TRH mRNA in the paraventricular nucleus. Neuroendocrinology. (1993) 58:140–5. doi: 10.1159/000126523

19. Zoeller RT, Kaehler N, Albers HE. Cold exposure elevates cellular levels of messenger ribonucleic acid encoding thyrotropin-releasing hormone in paraventricular nucleus despite elevated levels of thyroid hormones. Endocrinology. (1990) 110:2955–62. doi: 10.1210/endo-110-7-2955

20. Sánchez E, Uribe RM, Corkidi G, Zoeller RT, Cisneros M, Zacarias M, et al. 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. (2001) 74:807–22. doi: 10.1159/000054707

21. Soto-Rivera I, Cote-Vélez A, Uribe R-M, Charli J-L, Joseph-Bravo P, Glucocorticoids curtail stimuli-induced CREB phosphorylation in TRH neurons through interaction of the glucocorticoid receptor with the catalytic subunit of protein kinase A. Endocrine. (2017) 55:861–71. doi: 10.1007/s12020-016-1223-z

22. Uribe M, Joseph-Bravo P, Pasten J, Ponce G, Méndez M, Covarrubias L, et al. Some events of thyrotropin-releasing hormone metabolism are regulated in lactating and cycling rats. Neuroendocrinology. (1991) 54:493–8. doi: 10.1159/000125943

23. Arancibia S, Tapia-Arancibia L, Astier H, Assenmacher I. Physiological evidence for α1-adrenergic facilitatory control of the cold-induced TRH release in the rat, obtained by push-pull cannulation of the median eminence. Neurosci Lett. (1989) 100:169–74. doi: 10.1016/0304-3940(89)90679-4

24. Rondeel JMM, de Greef WJ, Hop WCJ, Rowland DL, Visser TJ. Effect of cold exposure on the hypothalamic release of thyrotropin-releasing hormone and catecholamines. Neuroendocrinology. (1991) 54:477–81. doi: 10.1159/000125940

25. Rondeel JMM, Heide R, de Greef WJ, van Toor H, van Haasteren GAC, et al. Effect of starvation and subsequent refeeding on the hypothalamic release of thyrotropin-releasing hormone. Neuroendocrinology. (1992) 56:348–53. doi: 10.1159/000126248

26. Heuer H, Schäfer MKH, O’Donnell D, Walker P, Bauer K. Expression of thyrotropin-releasing hormone receptor 2 (TRH-R2) in the central nervous system of rats. J Comp Neurol. (2000) 428:319–36. doi: 10.1002/1096-9861(20001121)428:2<319::AID-CNE10>3.0.CO;2-9

27. Hinkle PM, Gehret AU, Jones BW. Desensitization, trafficking, and resensitization of the pituitary thyrotropin-releasing hormone receptor. Front Neurosci. (2012) 6:180. doi: 10.3389/fnins.2012.00180

28. Chimadorla MI, Sidhaye AR, Matsumoto S, He Q, Hashimoto K, Ortiga MD, et al. Multiple types of α2-adrenergic receptors in the hypothalamic paraventricular nucleus. Anatom Rec. (2006) 289:1260–71. doi: 10.1002/ar.20794

29. Kakucska I, Rand W, Lechan RM. Thyrotropin-releasing hormone gene expression in the hypothalamic paraventricular nucleus is dependent upon feedback regulation by both triiodothyronine and thyroxine. Endocrinology. (1992) 130:2845–50. doi: 10.1210/endo.130.5.1572297

30. Perello M, Friedman T, Pavez-Espinoa V, Shen Y, Stuart BC, Nilini EA. Thyroid hormones selectively regulate the posttranslational processing of prothyrotropin-releasing hormone in the paraventricular nucleus of the hypothalamus. Endocrinology. (2006) 147:2705–16. doi: 10.1210/en.2005-1609

31. Yamada M, Rogers D, Wilber JF. Exogenous triiodothyronine lowers thyrotropin-releasing hormone concentrations in the specific hypothalamic nucleus (paraventricular) involved in thyrotropin regulation and also in posterior nucleus. Neuroendocrinology. (1989) 50:560–3. doi: 10.1159/000125281

32. Rondeel JMM, De Greef WJ, Van Der Schoot P, Klootwijk W, Visser TJ. Regulation of hypothalamic TRH production and release in the rat. Acta Med Austriaca. (1992) 19(Suppl 1):77–9.

33. Dumitrescu AM, Liao X-H, Weiss RE, Millen K, Refetoff S. Tissue-specific thyroid hormone deprivation and excess in monocarboxylate transporters: the knowns and the unknowns. Mol Endocrinol. (2011) 25:1–14. doi: 10.1210/me.2010-0099

34. Davis PJ, Leonard JL, Lin HY, Leinung M, Mousa SA. Molecular basis of nongenomic actions of thyroid hormone. Vitam Horm. (2018) 106:67–96. doi: 10.1016/bs.vh.2017.06.001

35. Toth G, Mazák K, Hosztai S, Kókosi J, Noszlá B. Species-specific lipophilicity of thyroid hormones and their precursors in view of their membrane transport properties. J Pharm Biomed Anal. (2013) 76:112–8. doi: 10.1016/j.jpba.2012.12.010

36. Visser WE, Friesema ECH, Visser TJ. Minireview: thyroid hormone transporters: the knowns and the unknowns. Mol Endocrinol. (2011) 25:1–14. doi: 10.1210/me.2010-0099

37. Segerson TP, Kauer J, Wolfe HC, Mobtaker H, Wu P, Jackson JM, et al. Thyroid hormone regulates TRH biosynthesis in the paraventricular nucleus of the rat hypothalamus. Science. (1987) 238:78–80. doi: 10.1126/science.3116669

38. Koller KJ, Wolff RS, Warden MK, Zoeller RT. Thyroid hormones regulate levels of thyrotropin-releasing-hormone mRNA in the paraventricular nucleus. Proc Natl Acad Sci USA. (1987) 84:7329–33. doi: 10.1073/pnas.84.20.7329

39. Kakucска I, Rand W, Lechan RM. Thyrotropin-releasing hormone gene expression in the hypothalamic paraventricular nucleus is dependent upon feedback regulation by both triiodothyronine and thyroxine. Endocrinology. (1992) 130:2845–50. doi: 10.1210/endo.130.5.1572297

40. Perello M, Friedman T, Pavez-Espinoa V, Shen Y, Stuart BC, Nilini EA. Thyroid hormones selectively regulate the posttranslational processing of prothyrotropin-releasing hormone in the paraventricular nucleus of the hypothalamus. Endocrinology. (2006) 147:2705–16. doi: 10.1210/en.2005-1609

41. Yamada M, Rogers D, Wilber JF. Exogenous triiodothyronine lowers thyrotropin-releasing hormone concentrations in the specific hypothalamic nucleus (paraventricular) involved in thyrotropin regulation and also in posterior nucleus. Neuroendocrinology. (1989) 50:560–3. doi: 10.1159/000125281

42. Rondeel JMM, De Greef WJ, Van Der Schoot P, Klootwijk W, Visser TJ. Effect of thyroid status and paraventricular area lesions on the release of thyrotropin-releasing hormone and catecholamines into hypophysial portal blood. Endocrinology. (1988) 123:523–7. doi: 10.1210/endo-123-1-523

43. de Greef WJ, Rondeel JM, Van Haasteren GA, Klootwijk W, Visser TJ. Regulation of hypothalamic TRH production and release in the rat. Acta Med Austriaca. (1992) 19(Suppl 1):77–9.

44. Dumitrescu AM, Liao X-H, Weiss RE, Millen K, Refetoff S. Tissue-specific thyroid hormone deprivation and excess in monocarboxylate transporter (Mct) 8-deficient mice. Endocrinology. (2006) 147:4036–43. doi: 10.1210/en.2006-0390

45. Trakovic M, Visser TJ, Mittag J, Horn S, Lukas J, Darras VM, et al. Abnormal thyroid hormone metabolism in mice lacking the monocarboxylate transporter. J Clin Investigat. (2007) 117:627–35. doi: 10.1172/JCI28253
Rodríguez-Rodríguez et al. Tanyocytes and Hypophysiotropic TRH Neurons

68. Chen R, Wu X, Jiang L, Zhang Y. Single-cell RNA-seq reveals hypothalamic enkephalinergic organizations of the hypothalamic paraventricular nucleus. Endocrinology. (1994) 135:92–100. doi: 10.1210/en.135.1.7516871

69. Chatzitomaris A, Hoermann R, Midgley JE, Hering S, Urban A, Dietrich B, et al. A molecular census of arcuate hypothalamus and median eminence cell types. Cell Rep. (2017) 12:e1001808. doi: 10.1016/j.celrep.2017.03.004

70. Langlet F. Tanyocyte gene expression dynamics in the regulation of energy homeostasis. Front. Endocrinol. (2019) 10:226. doi: 10.3389/fendo.2019.00286

71. Chatzitomaris A, Hoermann R, Midgley JE, Hering S, Urban A, Dietrich B, et al. A molecular census of arcuate hypothalamus and median eminence cell types. Cell Rep. (2017) 12:e1001808. doi: 10.1016/j.celrep.2017.03.004

72. Muller A, Bouret SG, Prevot V, Dehouck B. Differential distribution of tight junction proteins suggests a role for tanyocytes in blood-hypothalamus barrier regulation in the adult mouse brain. J Comp Neurol. (2010) 518:943–62. doi: 10.1002/cne.22273

73. Altman J, Bayer SA. Development of the diencerehonal in the rat. I autoradiographic study of the time of origin and settling patterns of neurons of the hypothalamus. J Comp Neurol. (1978) 182:945–71. doi: 10.1002/cne.901820511

74. Bennett L, Yang M, Enikolopov G, Iacovitti L. Circumventricular organs: a novel site of neural stem cells in the adult brain. Mol Cell Neurosci. (2009) 41:337–47. doi: 10.1016/j.mcn.2009.04.007

75. Meister B, Höftel T, Tetzlaff Y, Hemmings H, Oumiet C, Greengard P, et al. DARPP-32, a dopamine- and cyclic AMP-regulated phosphoprotein in tanyocytes of the mediobasal hypothalamus: distribution and relation to dopamine and luteinizing hormone-releasing hormone neurons and other glial elements. Neuroscience. (1988) 27:607–22. doi: 10.1016/0306-4522(88)90292-8

76. Yin W, Gore AC. The hypothalamic median emience and its role in reproductive aging: Yin & Gore. Ann N Y Acad Sci. (2010) 1204:113–22. doi: 10.1111/j.1749-6632.2010.05518.x

77. Djogo T, Robins SG, Schneider S, Krizskayza D, Liu X, Mingay A, et al. Adult NG2-glia are required for median emience-mediated leptin sensing and body weight control. Cell Metab. (2016) 23:797–810. doi: 10.1016/j.cmet.2016.04.013

78. Russell JA. Fifty Years of Advances in Neuroendocrinology. Brain Neurosci. Adv. (2018) 2:239821281881201. doi: 10.1177/2398212818812014

79. Giacobini P, Parkash J, Campagne C, Messina A, Casoni F, Vanacker et al. Brain endothelial cells control fertility through ovarian-steroi-d-dependent release of semaphorin 3A. PLoS Biol. (2014) 12:e1001808. doi: 10.1371/journal.pbio.1001808

80. Parkash J, Messina A, Langlet F, Cimino I, Loyens A, Mazur D, et al. Semaphorin3A regulates neurological plasticity in the adult hypothalamic median emience. Nat Commun. (2015) 6:6385. doi: 10.1038/ncomms7385

81. Prevot V, Dehouck B, Sharif A, Ciofi P, Giacobini P, Clasadonte J. The versatile tanyocyte: a hypothalamic integrator of reproduction and energy metabolism. Endocrin. (2018) 39:333–68. doi: 10.1016/er/2017.00235

82. Johansson O, Höftel T. Thyrotropin releasing hormone, somatostatin, and enkephalin: distribution studies using immunohistochemical techniques. J Histochem Cytochem. (1980) 28:364–6. doi: 10.1177/28.4.6103014

83. Shioda S, Nakai Y. Immunocytochemical localization of TRH and autorigaphic determination of TRH-binding sites in the arcuate nucleus-median emience nucleus of the rat. Cell Tissue Res. (1983) 228:475–87. doi: 10.1007/BF00211469

84. Fekete C, Gereben B, Doleschall M, Harney JW, Dora JM, Bianco AC, et al. Lipopolysaccharide induces type 2 iodothyronine deiodinase in the mediobasal hypothalamus: implications for the nonthyroidal illness syndrome. Endocrinology. (2004) 145:1649–55. doi: 10.1210/endo-110-2-367

85. Wittmann G, Farkas E, Szilvásy-Szabó A, Gereben B, Fekete C, Léchan D, et al. Type II iodothyronine deiodinase mRNA expression and protein distribution in the hypothalamic paraventricular nucleus. J Comp Neurol. (1992) 323:1–14. doi: 10.1002/cne.903230224

86. Meister B, Höftel T, Tetzlaff Y, Hemmings H, Oumiet C, Greengard P, et al. DARPP-32, a dopamine- and cyclic AMP-regulated phosphoprotein in tanyocytes of the mediobasal hypothalamus: distribution and relation to dopamine and luteinizing hormone-releasing hormone neurons and other glial elements. Neuroscience. (1988) 27:607–22. doi: 10.1016/0306-4522(88)90292-8

87. Yim W, Gore AC. The hypothalamic median emience and its role in reproductive aging: Yin & Gore. Ann N Y Acad Sci. (2010) 1204:113–22. doi: 10.1111/j.1749-6632.2010.05518.x

88. Crantz FR, Silva JE, Larsen PR. An analysis of the sources and quantity of 3,3′,5′-Triiodothyronine in the hypothalamic paraventricular nucleus. J Neuroendocrinol. (1994) 5:3389–405. doi: 10.1111/j.1365-2826.1994.tb00401.x

89. Obregon M-J, Larsen PR, Silva JE. The role of 3,3′,5′-Triiodothyronine in the hypothalamic paraventricular nucleus. J Neuroendocrinol. (1994) 5:3389–405. doi: 10.1111/j.1365-2826.1994.tb00401.x

90. Parkash J, Messina A, Langlet F, Cimino I, Loyens A, Mazur D, et al. Semaphorin3A regulates neurological plasticity in the adult hypothalamic median emience. Nat Commun. (2015) 6:6385. doi: 10.1038/ncomms7385

91. Riskind PN, Kolodny JM, Reed Larsen P. The regional hypothalamic regulation of type II iodothyronine deiodinase in euthyroid and hypothyroid rats. Brain Res. (1987) 392:190–9. doi: 10.1016/0006-8993(87)90296-0

92. Tu HM, Kim S-W, Salvatore D, Bartha T, Legradi G, Larsen PR, et al. Regional Distribution of type 2 thyroxine deiodinase messenger ribonucleic
acid in rat hypothalamic and pituitary and its regulation by thyroid hormone. Endocrinology. (1997) 138:3359–68. doi: 10.1210/endo.138.8.5318

93. Diano S, Naftolin F, Goglia F, Csernus V, Horvath TL. Monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5'-deiodinase mRNA and the median eminence-projective TRH cells of the rat paraventricular nucleus: monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5'-deiodinase mRNA and the median eminence-projective TRH cell. J Neuroendocrinol. (1998) 10:731–42. doi: 10.1046/j.1365-2826.1998.00204.x

94. Heuer H, Maier MK, Iden S, Mittag J, Friesema ECH, Visser TJ, et al. The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. Endocrinology. (2005) 146:1701–6. doi: 10.1210/en.2004-1179

95. Roberts LM, Woodford K, Zhou M, Black DS, Haggerty JE, Tate EH, et al. Expression of the thyroid hormone transporters monocarboxylate transporter-8 (SLC16A2) and organic ion transporter-14 (SLCO1C1) at the blood-brain barrier. Endocrinology. (2008) 149:6251–61. doi: 10.1210/en.2008-0378

96. Fonseca TL, Correa-Medina M, Campos MPO, Wittmann G, Werneck-de Castro JP, Arrojo e Drigo R, et al. Coordination of hypothalamic and pituitary T3 production regulates TSH expression. J Clin Investig. (2013) 123:1492–500. doi: 10.1172/JCI61231

97. Kallo I, Mohácsik P, Vida B, Zeöld A, Bardóczi Z, Zavacki AM, et al. Regional thyroid hormone dynamics during non-thyroidal illness syndrome triggered by fasting or hypoglycemia. Front Physiol. (2017) 8:628. doi: 10.3389/fphys.2017.00699

98. Hernandez A, Martinez ME, Fiering S, Galton VA, Refetoff S, Galton V, et al. Type 3 deiodinase is critical for the maturation and function of the thyroid axis. J Clin Invest. (2006) 116:476–84. doi: 10.1172/JCI26240

99. Hernandez A, Martinez ME, Liao X-H, Souza LL, Wilieman AF, et al. Differential regulation of thyroid hormone metabolism target genes during non-thyroidal illness syndrome triggered by fasting or sepsis in adult mice. Front Physiol. (2017) 8:828. doi: 10.3389/fphys.2017.00995

100. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, et al. Genome-wide atlas of gene expression in the adult mouse brain. Nature. (2007) 445:168–76. doi: 10.1038/nature05433

101. Fontes KN, Cabanelas A, Bloise FE, Andrade CBV de, Souza LL, Wilieman M, et al. Differential regulation of thyroid hormone metabolism target genes during non-thyroidal illness syndrome triggered by fasting or sepsis in adult mice. Front Physiol. (2017) 8:482. doi: 10.3389/fphys.2017.00995

102. Visser WE, Wormald WS, van Mullem AAA, Friesema ECH, Geyer J, et al. Transport of thyroid hormones via the choroid plexus into the brain: the roles of transthyretin and thyroid hormone transmembrane transporters. Front Neurosci. (2015) 9:66. doi: 10.3389/fnins.2015.00066

103. Bruni JE. Ependymal development, proliferation, and functions: a review. Microsc Res Tech. (1998) 41:12–13. doi: 10.1002/(SICI)1097-0282(19980401)41:1<1::AID-JEMT2>3.0.CO;2-Z

104. Mizraadeh Z, Kusne Y, Duran-Moreno M, Cabales E, Gil-Geron S, Ortiz C, et al. Bi- and uniciliated ependymal cells define continuous floor-plate-derived tanyctic territories. Nat Commun. (2017) 8:13759. doi: 10.1038/s41467-017-01379

105. Richardson SJ, Wormald WS, van Mullem AAA, Friesema ECH, Geyer J, Visser TJ. Study of the transport of thyroid hormone by transporters of the SLC10 family. Mol Cell Endocrinol. (2010) 315:138–45. doi: 10.1016/j.mce.2009.08.003

106. Reiner J, Ehrchen J, Bauer K, Taché Y. Thyroid hormone binding in the paraventricular nucleus: monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5'-deiodinase mRNA and the median eminence-projective TRH cells of the rat paraventricular nucleus: monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5'-deiodinase mRNA and the median eminence-projective TRH cell. J Neuroendocrinol. (1998) 10:731–42. doi: 10.1046/j.1365-2826.1998.00204.x

107. Chávez-Gutiérrez L, Bourdais J, Aranda G, Vargas MA, Mata-Camacho E, Ducancel F, et al. A truncated isoform of pyroglutamyl aminopeptidase II produced by exon extension has dominant-negative activity. J Neurochem. (2005) 92:807–17. doi: 10.1111/j.1471-4159.2004.02968.x

108. Sánchez E, Charli J-L, Lecan RM. Pyroglutamyl-Peptidase II. In: Rawlings ND, Salvesen G, editors. Handbook of Proteolytic Enzymes. Oxford, UK: Academic Press (2013). p. 414–9.

109. Yamadori T, Nara K. The directions of ciliary beat on the wall of the lateral ventricle and the currents of the cerebrospinal fluid in the brain ventricles. Scan Electron Microsc. (1976) 259:591–3. doi: 10.1038/259591a0

110. Lazcano I, Cabral A, Uribe RM, Jaimez-Hoy L, Perello M, Joseph-Bravo P, et al. Fasting enhances pyroglutamyl peptidase II activity in tanyctyes of the mediobasal hypothalamus of male adult rats. Endocrinology. (2015) 156:2713–23. doi: 10.1210/en.2014-1885

111. Friedman TC, Yanovski JA, Jayasvasti V, Yanovski SZ, Koenig RJ, Wilk S. Pyroglutamyl peptidase-II (“thyroliberinase”) activity in human serum: influence of weight and thyroid status. J Clin Endocrinol Metab. (2005) 88:1086–9. doi: 10.1210/jcem.2004-1273

112. Charli J-L, Vargas MA, Cisneros M, de Gortari P, Baeza MA, Jasso P, et al. TRH-DE from serum and liver. Euro J Biochem. (2002) 269:1278–86. doi: 10.1046/j.1432-1033.2002.02768.x

113. Schmitteiner S, Thole H, Bader A, Bauer K. Purification and characterization of the thyrotropin-releasing hormone (TRH)-degrading serum enzyme and its identification as a product of liver origin: characterization of the TRH-DE from serum and liver. Euro J Biochem. (2002) 269:1278–86. doi: 10.1046/j.1432-1033.2002.02768.x

114. Heuer H, Ehren J, Bauer K, Schäfer MKH. Region-specific expression of thyrotrophin-releasing hormone-degrading ectoenzyme in the rat central nervous system and pituitary gland: distribution of the TRH-degrading ectoenzyme. Eur J Neurosci. (1997) 10:1465–78. doi: 10.1111/j.1460-9568.1997.00158.x

115. Charli J-L, Vargas MA, Mata-Camacho E, Ducancel F, et al. A truncated isoform of pyroglutamyl aminopeptidase II produced by exon extension has dominant-negative activity. J Neurochem. (2005) 92:807–17. doi: 10.1111/j.1471-4159.2004.02968.x

116. Sánchez E, Charli J-L, Lecan RM. Pyroglutamyl-Peptidase II. In: Rawlings ND, Salvesen G, editors. Handbook of Proteolytic Enzymes. Oxford, UK: Academic Press (2013). p. 414–9.

117. Reiner J, Ehrchen J, Bauer K, Taché Y. Thyroid hormone binding in the paraventricular nucleus: monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5'-deiodinase mRNA and the median eminence-projective TRH cells of the rat paraventricular nucleus: monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5'-deiodinase mRNA and the median eminence-projective TRH cell. J Neuroendocrinol. (1998) 10:731–42. doi: 10.1046/j.1365-2826.1998.00204.x
127. Kapoor R, Desouza LA, Nanavaty IN, Kernie SG, Vaidya VA. Thyroid hormone accelerates the differentiation of adult hippocampal progenitors: T3 accelerates hippocampal progenitor differentiation. J Neuroendocrinol. (2012) 24:1259–71. doi: 10.1111/j.1600-0522.2012.02329.x

128. Remaud S, Gothié J-D, Morvan-Dubois G, Demeneix BA. Thyroid hormone signaling and adult neurogenesis in mammals. Front Endocrinol. (2014) 5:62. doi: 10.3389/fendo.2014.00062

129. Arancibia S, Rage F, Astier H, Tapia-Arancibia L. Neuroendocrine and autonomous mechanisms underlying thermoregulation in cold environment. Neuroendocrinology. (1996) 64:257–67. doi: 10.1159/000127126

130. Füzesi T, Wittmann G, Lechan RM, Liposits Z, Fekete C. Noradrenergic innervation of hypophyseotropic thyrotropin-releasing hormone-synthesizing neurons in rats. Brain Res. (2009) 1294:38–44. doi: 10.1016/j.brainres.2009.07.094

131. Perello M, Staurt RC, Vaslet CA, Nillni EA. Cold exposure increases the biosynthesis and proteolytic processing of prothyrotropin-releasing hormone in the hypothalamic paraventricular nucleus via β-adrenoreceptors. Endocrinology. (2007) 148:4952–64. doi: 10.1210/en.2007-0522

132. Nakai Y, Shioda S, Ochiai H, Kudo J, Hashimoto A. Ultrastructural distribution of leptin into and out of the rat brain. J Neuroendocrinol. (2001) 13:232–9. doi: 10.1046/j.1365-2833.2001.01001.x

133. Tapia-Arancibia L, Arancibia S, Astier H. Evidence for a 1-adrenergic stimulatory control of in vitro release of immunoreactive thyrotropin-releasing hormone from rat median eminence: in vivo corroboration. Endocrinology. (1985) 116:2314–9. doi: 10.1210/endo-116-6-2314

134. Ghamari-Langroudi M, Srisai D, Cone RD. Multinodal regulation of the hypothalamic pathways controlling food intake. J Comp Neurol. (2010) 518:2250–9. doi: 10.1002/cne.22437

135. Légrádi G, Emerson CH, Ahima RS, Flier JS, Lechan RM. Leptin signaling and adult neurogenesis in mammals. Front Endocrinol. (2014) 5:62. doi: 10.3389/fendo.2015.00044

136. Mihaly E. Hypophysiotropic thyrotropin-releasing hormone-synthesizing neurons in rats. J Neuroendocrinol. (2015) 27:503–9. doi: 10.1111/jene.12516

137. Elmqvist JK, Coppari R, Balthasar N, Ichinose M, Lowell BB. Identifying hypothalamic pathways controlling food intake, body weight, and glucose homeostasis. J Comp Neurol. (2005) 493:653–70. doi: 10.1002/cne.20786

138. Herris A, Aschkenasi C, Elias CF, Chandrakannel A, Nillni EA, Bjerbeck C, et al. Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling. J Clin Invest. (2001) 107:111–20. doi: 10.1172/JCI10741

139. Perello M, Çakir I, Cyr NE, Romero A, Stuart RC, Chiappini F, et al. Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin: differential trh expression in anterior and caudal pvn. role of type 2 deiodinase and pyroglutamyl aminopeptidase ii. Endocrinology. (2012) 153:4067–76. doi: 10.1210/jc.2011-2011

140. Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S, et al. Evidence supporting a role for the blood-cerebrospinal fluid barrier transporting ghrelin into the brain. Mol Neurobiol. (2018). 56:4120–34. doi: 10.1007/s12053-018-1362-8

141. dos-Santos RC, Grover HM, Reis LC, Ferguson AV, Mecawi B, et al. Fast-induced increase in type II iodothyronine deiodinase activity and messenger ribonucleic acid levels is not reversed by thyroxine in the rat hypothalamus. Endocrinology. (1998) 139:2879–84. doi: 10.1210/en.139.6.2879

142. Armario A, Montero JL, Jolin T. Chronic food restriction and the circadian rhythms of pituitary-adrenal hormones, growth hormone and thyroid-stimulating hormone. Ann Nutr Metab. (1987) 31:81–7. doi: 10.1159/0001277254

143. van Haastereen GA, Links L, van Toor H, Klootwijk W, Kaptein E, de Jong FH, et al. Effects of long-term food restriction on the hypothalamus-pituitary-thyroid axis in male and female rats. J Endocrinol. (1996) 156:169–78. doi: 10.1677/joe.0.1500169

144. Uriarte M, De Francesco PN, Fernandez G, Cabral A, Castrogiovanni D, et al. Transcriptional regulation of the thyrotropin-releasing hormone gene in the hypothalamic paraventricular nucleus of the human hypothalamus. Cell Tissue Res. (2014) 27, 2019. doi: 10.1159/000348010

145. Balland E, Dam J, Langlet F, Caron E, Steculorum S, Messina A, et al. Tanycytic VEGF-A boosts blood-hypothalamus barrier plasticity and hypophysiotropic TRH Neurons. Front Endocrinol. (2014) 5:1169. doi: 10.3389/fendo.2015.00044

146. Eyigor O, Jennes L. Identification of kainate-preferring glutamate receptor subunit-immunoreactivities in the median eminence of the hypothalamic paraventricular nucleus (PVN) in female animals submitted to food-restriction or dehydration-induced anorexia and cold exposure. Horm Behav. (2008) 53:366–77. doi: 10.1016/j.yhbeh.2007.11.003

147. Perello M, Zhao L, Saez LM, Chiappini F, et al. Maintenance of the thyroid axis during diet-induced obesity in rodents is not reversed by thyroxine in the rat hypothalamus. J Endocrinol. (2014) 27:2019. doi: 10.1210/joe.2013-1724

148. DeGroot LJ. (2015). The Non-thyroidal illness syndrome. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al. editors. Endocrinology and Metabolism: Principles and Practice. Lippincott Williams & Wilkins. Available online at: http://www.ncbi.nlm.nih.gov/books/NBK285570/ (accessed February 27, 2019).

149. Eyigor O, Jennes L. Identification of kainate-preferring glutamate receptor subunit-immunoreactivities in the median eminence of the hypothalamic paraventricular nucleus (PVN) in female animals submitted to food-restriction or dehydration-induced anorexia and cold exposure. Horm Behav. (2008) 53:366–77. doi: 10.1016/j.yhbeh.2007.11.003
in the rat hippocampus. *Neurosci Lett.* (2009) 449:211–4. doi: 10.1016/j.neulet.2008.11.005

161. Mohácsik P, Füzesi T, Doleschall M, Szilvásv-Szabó A, Vancamp P, Hadadi E, et al. (2016). Increased thyroid hormone activation accompanies the formation of thyroid hormone-dependent negative feedback in developing chicken hypothalamus. *Endocrinology.* 157:1211–21. doi: 10.1210/endo.2015-1496

162. Duntas LH, Statthatos N. Toxic chemicals and thyroid function: hard facts and lateral thinking. *Rev Endocrine Metab. Disorders.* (2015) 16:311–8. doi: 10.1007/s11154-016-9331-x

163. Joseph-Bravo P, Jaimes-Hoy L, Charli J-L. Advances in TRH neuroendocrine systems. *Front Neuroendocrinol.* (2013) 34:190–7. doi: 10.1016/j.yfrne.2013.05.003

164. Auger CJ, Auger AP. Permanent and plastic epigenesis in non-mammalian vertebrates. *Dialogues Clin Neurosci.* (2014) 16:321–33.

165. Jaimes-Hoy L, Gutiérrez-Mariscal M, Vargas Y, Pérez-Maldonado A, Romero F, Sánchez-Jaramillo E, et al. Neonatal maternal separation alters, in a sex-specific manner, the expression of TRH, of TRH-degrading ectoenzyme in the rat hypothalamus, and the response of the thyroid axis to starvation. *Endocrinology.* (2016) 157:2325–65. doi: 10.1210/endo.2016-1239

166. Anacker C, O’Donnell KJ, Meaney MJ. Early life adversity and the epigenetic programming of hypothalamic-pituitary-adrenal function. *Dialogues Clin Neurosci.* (2016) 18:605–12. doi: 10.1016/j.jycne.2016.05.003

167. Kobayashi H, Matsui T, Ishii S. Functional electron microscopy of the hypothalamic median eminence. *Int Rev CytoL.* (1970) 29:281–381.

168. Kalmán M, Székely AD, Cailll A. Distribution of glial fibrillary acidic protein-immunopositive structures in the brain of the domestic chicken (*Gallus domesticus*): GFAP in chicken brain. *J Compar Neurol.* (1993) 330:221–37. doi: 10.1002/cne.903300206

169. Lazzari M, Franceschini V, Ciani F. Glial fibrillary acidic protein and vimentin in radial glia of ambystoma mexicanum and triturus carnifex: an immunocytochemical study. *J Hirnforsch.* (1997) 38:187–94.

170. Lazzari M, Franceschini V. Glial fibrillary acidic protein and vimentin immunoreactivity of astroglial cells in the central nervous system of the African lungfish, *Protopterus annectens* (*Dipnoi: Lepidosirenidae).* I. *J Morphol.* (2004) 262:741–9. doi: 10.1002/jmor.10274

171. Galas L, Raoul E, Tonon M-C, Okada R, Jenks BG, Castaño JP, et al. TRH acts as a multifunctional hypophysiotropic factor in vertebrates. *Gen Comp Endocrinol.* (2009) 164:40–50. doi: 10.1016/j.ygcen.2009.05.003

172. Campinho MA, Silva N, Roman-Padilla J, Ponce M, Manchado M, Power DM. Flatfish metamorphosis: a hypothalamic independent process? *Mol Cell Endocrinol.* (2015) 404:16–25. doi: 10.1016/j.mce.2014.12.025

173. Ogawa S, Ng KW, Xue X, Ramadasan PN, Sivalingam M, Li S, et al. Thyroid hormone upregulates hypothalamic kiss2 gene in the male nile tilapia, *oreochromis niloticus.* *J Neuroendocrinol.* (2008) 20:576–86. doi: 10.1111/j.1365-2826.2008.01702.x

174. Hanon EA, Lincoln GA, Fustin J-M, Dardente H, Masson-Pévet M, Morgan PJ, et al. Ancestral TSH mechanism signals summer in a photoperiodic mammal. *Carr. Biol.* (2008) 18:1147–52. doi: 10.1016/j.cub.2008.06.076

175. Bockmann J, Böckers TM, Winter C, Wittkowski W, Winterhoff H, Deufel T, et al. Thyrotropin expression in hypophyseal pars tuberalis-specific cells is 3,5,3′-triiodothyronine, thyrotropin-releasing hormone, and pit-1 independent. *Endocrinology.* (1997) 138:1019–28. doi: 10.1210/endo.138.3.5007

176. Klosen P, Bienvenu C, Demarteau O, Dardente H, Guererro H, Pévet P, et al. The mT1 melatonin receptor and ROB receptor are co-localized in specific TSH-immunoreactive cells in the pars tuberalis of the rat pituitary. *J Histochem Cytochem.* (2002) 50:1647–57. doi: 10.1177/002215540205001209

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.