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A lamprey view on the origins of neuroendocrine regulation of the thyroid axis

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ABSTRACT

This mini review summarizes the current knowledge of the hypothalamic-pituitary-thyroid (HPT) endocrine system in lampreys, jawless vertebrates. Lampreys and hagfish are the only two extant members of the class of agnathans, the oldest lineage of vertebrates. The high conservation of the hypothalamic-pituitary-gonadal (HPG) axis in lampreys makes the lamprey model highly appropriate for comparative and evolutionary analyses. However, there are still many unknown questions concerning the hypothalamic-pituitary (HP) axis in its regulation of thyroid activities in lampreys. As an example, the hypothalamic and pituitary hormone(s) that regulate the HPT axis have not been confirmed and/or characterized. Similar to gnathostomes (jawed vertebrates), lampreys produce thyroxine (T4) and triiodothyronine (T3) from thyroid follicles that are suggested to be involved in larval development, metamorphosis, and reproduction. The existing data provide evidence of a primitive, overlapping yet functional HPG and HPT endocrine system in lamprey. We hypothesize that lampreys are in an evolutionary intermediate stage of hypothalamic-pituitary development, leading to the emergence of the highly specialized HPG and HPT endocrine axes in jawed vertebrates. Study of the ancient lineage of jawless vertebrates, the agnathans, is key to understanding the origins of the neuroendocrine system in vertebrates.

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1. Introduction

Modern vertebrates are classified into two major groups, the gnathostomes (jawed vertebrates) and the agnathans (jawless vertebrates). There are only two surviving agnathan lineages: the

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hagfishes (order Myxiniformes) and lampreys (Petromyzontiformes). Gnathostomes constitute all other living vertebrates including the bony and cartilaginous fishes and the tetrapods. In this review, lampreys and hagfishes will be considered to be monophyletic, although the phylogenetic relationship between hagfishes, lampreys and the jawed vertebrates is still not completely resolved (Forey and Janvier, 1994; Heimberg et al., 2010; Janvier, 2010; Near, 2009; Ota et al., 2007). It is generally believed that two large-scale genome duplications (2R) occurred during the evolution of early vertebrates, although there is controversy on whether the 2R duplications occurred in the lineage leading to all extant vertebrates (including the hagfishes and lampreys) or whether there was one round of duplication (1R) prior to and a second round of duplication after divergence of the jawless vertebrates (Holland et al., 1994; Ohno, 1970; Smith et al., 2013; Vandepoele et al., 2004). Recently, Smith and Keinath (2015) provide evidence that there was only one 1R prior to the divergence of lampreys and gnathostomes. The occurrence(s) of 1R and/or 2R in basal vertebrates allowed for specialization and diversification of the hypothalamic-pituitary (HP) endocrine axes.

The hypothalamic-pituitary system, which is specific to vertebrates, is considered to be an evolutionary innovation that emerged prior to or during the differentiation of the ancestral jawless vertebrates coinciding with 1R (Sower et al., 2009). Such an innovation is one of the key elements leading to physiological divergences, including reproduction, growth, metabolism, stress, and osmoregulation in the subsequent evolution of jawed vertebrates. Reproduction in vertebrates is controlled by a hierarchically organized endocrine system (Sower et al., 2009; Sower, 2015a). In spite of the very diverse patterns of life cycles, reproductive strategies, and behaviors, this endocrine system is remarkably conserved throughout the vertebrate lineages (Sower, 2015a). It is now well established that lampreys, similar to jawed vertebrates, have a hypothalamic-pituitary-gonadal (HPG) axis and that there is high conservation of the mechanisms of gonadotropin-releasing hormone (GnRH) action, reviewed in Sower (2015a).

However, compared to jawed vertebrates, there is very little known of the hypothalamic-pituitary axis in its regulation of thyroid activities in either hagfish or lampreys. Relatively little is known about the actions of thyroid hormones in lampreys. In general, with some exceptions, the major features of the hypothalamic-pituitary-thyroid (HPT) axis in jawed vertebrates include the hypothalamic thyrotropin releasing hormone (TRH) and/or corticotropin releasing hormone (CRH), the pituitary hormone, thyrotropin (TSH), and the thyroid hormones thyroxine (T4) and triiodothyronine (T3). In mammals, TRH is the major hypothalamic neurohormone stimulating release of TSH from the pituitary. TRH is a tripeptide (p-Glu-His-Pro-NH_2) whose structure is highly conserved across all vertebrate classes (Wallis, 2010). TSH is a member of the pituitary glycoprotein hormone family that is found in all gnathostomes (Maugars et al., 2014). TSH in turn acts on the thyroid gland to stimulate the synthesis and/or release of the thyroid hormones, T4 and T3. In contrast, the hypothalamic and pituitary hormones that may be involved in thyroid activities have not been identified in lampreys. This brief review summarizes the current status of the hypothalamic-pituitary-thyroid endocrine system in lampreys.

2. Glycoprotein hormone evolution and the overlap between the HPG-HPT axes

Extensive biochemical, molecular, immunocytochemical, and functional studies have established that lampreys have a conserved HPG axis with some unique differences, such as three hypothalamic GnRHs, and two nontraditional coevolved GpHs and receptors (reviewed in Sower, 2015a). Generally, jawed vertebrates have one or two hypothalamic GnRHs, and two gonadotropic pituitary hormones (luteinizing hormone, LH and follicle stimulating hormone, FSH) with two corresponding gonadal receptors (luteinizing hormone receptor, LH-R and follicle stimulating hormone, FSH-R). In comparison, lampreys have three hypothalamic GnRHs (lamprey GnRH-I, -II and −III), at least one, but likely two glycoprotein hormones (lamprey glycoprotein hormone (lGpH) and thyrostimulin), and two gonadal glycoprotein receptors (lGpH-R I and II) (Sower et al., 2009; Sower, 2015a).

In jawed vertebrates, the classical pituitary heterodimeric GpHs belong to the cystine knot-forming glycoprotein hormone family, consisting of two non-covalently bound, chemically distinct α- and β-subunits (Kawauchi and Sower, 2006). The α-subunit is common among the GpHs within a single species, whereas the β-subunit is specific for each hormone and thus confers receptor specificity (Kawauchi and Sower, 2006). The jawed vertebrate GpH family consists of two pituitary gonadotropins (GTHs; LH and FSH) and a thyrotropin (TSH) that each consists of a common α-subunit (GpH-α or GPA1) and unique β−subunits (FSHβ/LHβ/TSHβ). In general, FSH and LH regulate gonadal activity, and TSH regulates thyroidal activity (Sower et al., 2015). These classical vertebrate LH, FSH, and TSH subunits are not found in invertebrates. In recent years, another pituitary GpH was identified and named thyrostimulin because it activated the TSH receptor (Nakabayashi et al., 2002) but its function has not been established (Nakabayashi et al., 2002; Dos Santos et al., 2009; Park et al., 2005). Compared with other GpHs, thyrostimulin has distinct subunits called GpA2 (α-subunit) and GpB5 (β-subunit) and are found both in invertebrates and vertebrates. Based on phylogenetic and synteny analyses, the thyrostimulin subunits are considered ancestral to the vertebrate GpHs subunits (Dos Santos et al., 2009; Sudo et al., 2005).

In contrast to jawed vertebrates, lampreys only have two heterodimeric pituitary GpHs consisting of α and β subunits, lamprey GpH (lGpH) (lGpA2/lGpHβ) (Sower, 2015a; Sower et al., 2006) and thyrostimulin (lGpA2/lGpB5) (Dos Santos et al., 2009; Marquis et al., 2017) (Table 1). Similar to jawed vertebrates, the primary amino acid sequence of the alpha subunit, lGpA2, is identical for the two GpHs in lampreys but it is not the classical alpha (α)-subunit found in LH, FSH and TSH of jawed vertebrates. Therefore, we propose that the lamprey GpH represents an ancestral type GpH not found in gnathostomes. In addition, the lamprey pituitary lacks a classical vertebrate TSH (Marquis et al., 2017). The existing data suggest the existence of primitive, overlapping yet functional HPG and HPT endocrine systems in lamprey, involving at least one, but probably two pituitary glycoprotein hormones and two glycoprotein hormone receptors, reviewed in Sower, 2015a, Sower et al., 2015. Hagfish, the only other extant agnathan, also has one non-typical GpH consisting of GpA1 and GpHβ (Uchida et al., 2010). This is in contrast to the three glycoprotein hormones (LH, FSH and TSH) interacting specifically with three receptors in jawed vertebrates (LH-R, FSH-R, and TSH-R, respectively) (Sower, 2015a). Since the pituitary gland and its hormones arose with the vertebrates coinciding with 1R, we hypothesize that lampreys are in an evolutionary intermediate stage of hypothalamic-pituitary development, leading to the emergence of the highly specialized gnathostome neuroendocrine axis.

3. Anatomical connections of the lamprey hypothalamic-pituitary-axis

All vertebrate brains contain a hypothalamus that forms the ventral part of the diencephalon. In lampreys, the hypothalamus comprises the largest part of the diencephalon (Butler and Hodos, 2005). The hypothalamus is then further divided into the preoptic

Table 1
Snapshot of Occurrence of Selected Factors of Hypothalamic-Pituitary-Thyroid Axis in Vertebrates. Functions represent known/possible functions (either stimulatory or inhibitory) of thyroid system. (?), hormones and receptors are identified, but thyroid-related functions are not established.

Vertebrate	Hypothalamic factor(s)	Pituitary hormone(s)	Thyroid hormones	Hormone receptors	Functions
Agnathans (Jawless Vertebrates)					
Lamprey	TRH (?) CRH (?) lGnRH-I (?) lGnRH-II (?) lGnRH-III (?)	lGpH (?) Thyrostimulin (?)	T4, T3	lGpH-R I (?) lGpH-R II (?) PmTR1 PmTR2	Correlative studies associated with metamorphosis and reproduction
Gnathostomes (Jawed Vertebrates)					
Sharks	(?)	TSH	T4, T3	TSHR	Reproduction Neural behavior Neural differentiation
Teleosts	(?)	TSH	T4, T3	TSHR-a TSHR-b TRa-A, TRa-B TRb	Development Growth Reproduction Neural behavior
Amphibians	CRH	TSH	T4, T3	TSHR	Development Neural behavior Reproduction Growth
Birds	CRH TRH (?)	TSH	T4, T3	TSHR	Development Molting Growth Metabolism Reproduction Neural behavior
Mammals	TRH	TSH Thyrostimulin (?)	T4, T3	TSHR TRa TRb	Development Molting Growth Metabolism Reproduction Neural behavior Neural differentiation Thermogenesis

CRH, corticotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; lGnRH, lamprey gonadotropin-releasing hormone; lGpH, lamprey glycoprotein hormone; lGpH-R, lamprey glycoprotein hormone receptor; pmTR, *Petromyzon marinus* thyroid hormone nuclear receptor; T3, triiodothyronine; T4, thyroxine; TRs, thyroid hormone nuclear receptors; TRH, thryotropin releasing hormone; TSH, thyrotropin/thyroid stimulating hormone; TSHR, thryotropin receptors/thyroid stimulating hormone receptor. Summarized from reviews: Sower, 2015a; Manzon et al., 2015; Norris and Carr, 2013.

area, dorsal, and ventral regions. Although there is a considerable body of reported information on the neuroendocrinology of the lamprey hypothalamus, there are relatively few modern reports on its cytoarchitecture or connections, reviewed in Sower, 2015a.

Classically, there are generally three models for anatomical control of the pituitary in vertebrates: portal system via the median eminence (tetrapods), direct innervation (teleosts), and diffusion (agnathans) (Sower, 2015b). In mammals, releasing hormones are secreted from the hypothalamus into the median eminence and reach the pituitary via a vascular portal network. The releasing hormones subsequently act on the specific cell types of the adenohypophysis inducing the synthesis and/or release of the anterior pituitary hormones. Recently, the dogma of the known anatomical relationship has been challenged in teleosts and hagfish (Golan et al., 2015; Nozaki and Sower, 2016). An alternative view of pituitary control was provided by studies in zebrafish (a teleost fish) that showed that there was a neurovascular route along with the classical direct innervation by hypothalamic neurons to the pituitary (Golan et al., 2015). These authors provided evidence by elegant studies that the anatomical aspects of gonadotropin regulation by a type 3 GnRH suggested neurovascular control of gonadotropins in this teleost fish. New immunohistochemical studies with a neuropeptide called Pro-Gln-Arg-Phe (PQRF) amide also indicated that hagfish may have a primitive type neurovascular system along with the classical diffusion route (Nozaki and Sower, 2016). Lampreys have been considered to have a diffusional type of hypothalamic regulation of the adenophypophysis (Nozaki et al., 1994) as supported by anatomical and experimental data demonstrating diffusion of the neurohormones from the neurohypophysis to the adenohypophysis, regulating its secretory activity in lampreys (Nozaki et al., 1994; King et al., 1988; Tsuneki, 1988). Whether lampreys have a primitive neurovascular system along with diffusion has not been studied. During the evolution of vertebrates, structural features of the pituitary and hypothalamus also evolved along with the molecular evolution of the structure and function of the hormones and receptors. The study of basal vertebrates provides promising models for understanding the evolution of the hypothalamic-pituitary-thyroidal and gonadal axes.

4. Hypothalamic neurohormones

While TRH is considered the major neurohormone regulating the pituitary in mammals, the role of TRH in non-mammalian vertebrates is much less established, reviewed in De Groef et al., 2006, Denver, 2013. In amphibians, reptiles, and birds, CRH rather than TRH seems to be the major regulator of TSH (De Groef et al., 2006; Denver, 2013; Okada et al., 2009). In teleost fish, it is proposed that the fish thyroidal system is not under central control but rather under peripheral control by deiodinases, reviewed in Blanton and Specker, 2007. Hypothalamic control of the pituitary-thyroid axis is unknown in lampreys. To date, there are only two reports on TRH in lampreys and neither of these reports shows that TRH regulates the pituitary gland (Del Carmen De Andres et al., 2002; Youngs et al., 1985). Youngs et al. (1985) demonstrated that TRH was present in the pituitary, brain, and spinal cord of larval and adult sea lamprey and adult European river lamprey. A more extensive immunocytochemistry study was done, in which the distribution of TRH mainly occurred in the preoptic region and the hypothalamus in large larvae and adult upstream migrating sea lamprey (Del Carmen De Andres et al., 2002). Sower et al. (1985) reported that treatment of adult lamprey with a partly purified salmon gonadotropin or a GnRH analog significantly elevated plasma thyroxine. In later studies, brain concentrations of lamprey gonadotropin-releasing hormones (GnRH-I and -III) were shown to increase as the seven stages of metamorphosis progressed with significant elevation occurring between stages 6 and 7 (Youson and Sower, 1991). It is hypothesized from these studies that hypothalamic GnRH stimulates both the pituitary-thyroid and pituitary gonadal axes.

CRH was recently identified in the lamprey (Endsin et al., 2017). These authors showed that the expression of CRH was elevated prior to and at the onset of metamorphosis, however, these changes were not significant. Whether CRH is involved in the HPT axis is unknown. The identity of potential hypothalamic neurohormones that may be involved in regulating pituitary-thyroid activity is an exciting area ripe for study in lampreys.

5. Pituitary cell types

In the adenohypophysis (anterior pituitary) of all gnathostomes, there are six tropic cell types: corticotropes, melanotropes, somatotropes, lactotropes, gonadotropes, and thyrotropes; each cell type produces specific tropic hormones. In contrast, it has been shown by comprehensive histological and immunological studies that there are only four tropic cell types including corticotropes, somatotropes, melanotropes and a novel proto-glycotrope in the sea lamprey (*Petromyzon marinus*) anterior pituitary (Marquis et al., 2017). There are very limited reports on examination of the cell type that produces the thyrostimulin subunits in gnathostomes. In the rat, thyrostimulin expression was shown in the pituitary (Li et al., 2004) but the cell type was not identified. In another study in humans, the subunits of thyrostimulin (also called corticotroph-derived glycoprotein hormone), were surprisingly expressed in the corticotropes and not the gonadotropes or thyrotropes (Okada et al., 2006). Whether this is a general pattern in mammals is not known. In lampreys, the proto-glycotrope was shown to produce the subunits (GpA2, GpB5, GpHβ) of lGpH and thyrostimulin and that it is the predominant cell type throughout all of the regions of the anterior pituitary at all major life stages of the sea lamprey. The production of both lamprey GpHs by one cell type reinforces the concept of a less developed and refined pituitary compared to later evolved vertebrates. In an evolutionary sense, these data lend further support to the working hypothesis that lampreys are in an evolutionary intermediate stage of pituitary development, leading to the more highly specialized tropic hormones and tropic cells founds in gnathostomes (Sower et al., 2009; Sower, 2015a).

6. Lamprey glycoprotein hormone receptors

GTHs (LH and FSH) and TSH hormone actions are mediated through a subfamily of G-protein coupled receptors (GPCR), the GpH receptors (GpH-R) (Combarnous, 1992). Known GpH-Rs share a number of unique features. They are composed of a characteristically large N-terminal extracellular domain followed by a typical GPCR transmembrane domain, and an intracellular domain that interacts with G-proteins. In mammals, the GpH/GpH-receptor system exhibits two characteristics tightly related to their proper function under normal physiological conditions: the specificity of their temporal and tissue expression profiles, and selectivity in the interaction with their ligands (Freamat and Sower, 2010). These characteristics evolved during divergent evolution of the ancestral duplicated genes that were inherently neither specific in their expression nor selective in their ligand affinities. While thyrostimulin can activate the mammalian TSH receptor (Okada et al., 2006), a specific (cognate) receptor has not been identified for thyrostimulin in vertebrates.

Two functional GpH-Rs (lGpH-R I and lGpH-R II) have been identified and described in the sea lamprey and are the only members of the GpH-R subfamily in lampreys (Freamat et al., 2006; Freamat and Sower, 2008a). Based on phylogenetic analysis (Freamat and Sower, 2008a), these receptors are descendants of the TSH receptor-like molecular ancestors of the GpH-Rs in gnathostomes and are likely the result of the genome duplication event hypothesized to have taken place before the divergence of agnathans (Smith et al., 2013). The key motifs, sequence comparisons, and characteristics of the identified lamprey GpH-Rs reveal a mosaic of features common to all other classes of GpH-Rs in vertebrates. Both lGpH-R I and II were shown to activate the cAMP signaling system using COS7 cells when tested with heterodimeric-chimeric GpHs (Freamat et al., 2006; Freamat and Sower, 2008a, 2008b, 2010). A recombinant lamprey GpH was constructed as a single-chain polypeptide in the methylotropihic yeast, *Pichia pastoris*, and tested in a functional expression system (Sower et al., 2015). This recombinant lamprey GpH activated lGpH-R I but not lGpH-R II as measured by increased cAMP/luciferase activity (Sower et al., 2015). Further studies will be required to determine whether there is a specific receptor for each of lamprey GpH and thyrostimulin or whether both GpHs can differentially activate the GpH-R receptors. In addition, functional and signaling mechanisms of the lamprey GpH and thyrostimulin will be needed to examine and understand the role of each of the GpHs in regulating reproduction, development and/or metabolism via its receptor(s). Such studies are important in understanding each of their roles in regulating reproductive and/or thyroidal activities during key life cycle stages. Therefore, at this point, a comparative perspective on the HPT/HPG in lampreys suggests the involvement of lGpH and thyrostimulin with two GpH-Rs, as opposed to the well-established paradigm of three GpHs, LH, FSH and TSH, with three respective receptors, LH-R, FSH-R and TSH-R in jawed vertebrates. Sower and colleagues hypothesize that there is lower specificity of GpH/GpH-R interactions in agnathans, and that specific interactions of each gnathostome GpH (TSH, LH, and FSH) with its receptor increased during co-evolution of the ligand/receptor pair (Sower et al., 2009).

7. Thyroid hormones and functions

In all vertebrates, thyroid follicles are considered the functional unit of the thyroid, which may be organized as a gland or as follicular clusters embedded in connective tissue (Blanton and Specker, 2007; Power et al., 2001). These follicles surround an extracellular space, called the lumen, where thyroglobulin is secreted and stored. Thyroid follicles uptake inorganic iodide from the blood, then through a series of processes involving thyroglobulin eventually produce T4. In gnathostomes, functions of thyroid hormones have been well established. The major thyroid hormones, T4 and T3, are found in all vertebrates. T4 is considered to act primarily as a precursor for T3, which is considered the biologically active form of this hormone. Thyroid hormones are known to regulate several major physiological processes including development, differentiation, and metabolism. While the functions of thyroid hormones have not been confirmed in lampreys, several studies suggest that thyroid hormones are involved in larval development, metamorphosis and reproduction (Sower, 2015a; Manzon et al., 2015).

The endostyle of larval lampreys produces thyroid hormones and changes during metamorphosis into the thyroid in adult lampreys (Blanton and Specker, 2007). The endostyle is found ventral to the pharynx of protochordates and larval lampreys and produces mucus to obtain food particles (Barrington and Sage, 1972). Lampreys are the only vertebrates to have an endostyle. The thyroid in lampreys is not a distinct gland but rather a group of follicles embedded in connective tissue near the ventral aorta (Barrington and Sage, 1972).

In relation to lamprey metamorphosis, thyroid hormones have been extensively studied and compared to other vertebrates, presenting a paradoxical picture (Manzon et al., 2015). Metamorphosis in lampreys is an extensive transformation from larval to the young adult via dramatic morphological, cellular, and biochemical changes. These changes include the development and appearance of the mouth, eyes, and teeth, restructuring of the branchial region, and many other major internal and external changes. Metamorphosis in sea lamprey is characterized by a significant decline in thyroid hormones, changes in lipid metabolism, and elevated GnRH (Youson and Sower, 1991; Manzon et al., 2015). Several studies have shown that goitrogens (chemicals that disrupt the production of thyroid hormones) suppress thyroid hormone synthesis and induce partial or complete metamorphosis, yet exogenous thyroid hormone treatment inhibits metamorphosis (Manzon et al., 2015).

Deiodinases are an important regulator of thyroid hormone metabolism. Thyroid hormones are activated or deactivated by peripheral deiodination, catalyzed by thyroid hormone deiodinases. It is considered that peripheral regulation via deiodinases is more important in teleost fish than other vertebrates (Blanton and Specker, 2007; Eales and Brown, 1993). Various studies in lampreys showed that deiodinase activity functions to lower the availability of circulating thyroid hormones during metamorphosis, supporting that a decline of thyroid hormones is necessary for such a transformation (Manzon et al., 2015).

Thyroid hormones exert their effects by activating thyroid hormone receptors (TRs). Two functional TRs (PmTR1 and PmTR2) were identified in lampreys (Manzon et al., 2014). PmTR1 showed dynamic changes of expression during metamorphosis suggesting that thyroid hormones may function to modulate changes at the cellular or tissue level during lamprey metamorphosis (Manzon et al., 2014). In summary, Manzon et al. (2015) proposed that thyroid hormones have a dual role in lampreys in which high levels of thyroid hormones promote larval growth and a subsequent sharp decline is important for development and metamorphosis. In all other vertebrates that undergo metamorphosis, the thyroid hormones are considered the driver for these extensive changes at the cellular and tissue levels (Laudet, 2011). Further studies are required to understand the role of the thyroid system during larval growth and metamorphosis in the basal vertebrate of lampreys.

8. Summary

As just reviewed, there are many unresolved questions concerning the regulatory role of the hypothalamic-pituitary-thyroid axis in lampreys. To what extent is there hypothalamic control? What hypothalamic and/or pituitary hormones are involved? How do the two identified pituitary GpHs differentially regulate gonadal and thyroidal activity via two receptors, and do these dynamics change during the lamprey life cycle? We lack a basic understanding of the hypothalamic/pituitary hormones that regulate thyroid activity and the actions of thyroid hormones during the three major life stages of the lamprey. The existing data suggest the existence of a primitive, overlapping yet functional HPG and HPT endocrine system in lampreys, one of the two extant basal vertebrates of the class of agnathans. Our working hypothesis is that lampreys are in an evolutionary intermediate stage of hypothalamic-pituitary development, leading to the more highly specialized neuroendocrine control of tropic cells and their hormones found in the later evolved jawed vertebrates. The reproductive and thyroid endocrinology of lamprey can be considered a

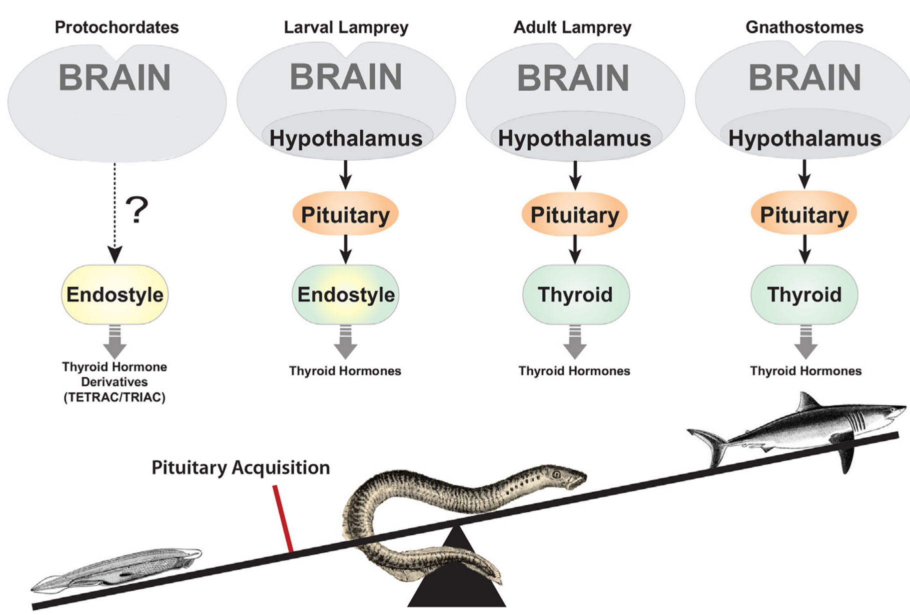

Fig. 1. Schematic representation of the evolution of the hypothalamic-pituitary-thyroid axis in chordates. Protochordates (invertebrates) lack a hypothalamic-pituitary axis and thyroid gland. Instead, protochordates produce mucous and thyroid hormone derivatives through the endostyle, the vertebrate thyroid homolog. The endostyle of larval lampreys produces thyroid hormones and becomes the thyroid of adult lampreys during metamorphosis, representing a transitional state of thyroid control, morphogenesis, and function. Lampreys are the only vertebrates to have an endostyle. The acquisition of the hypothalamic-pituitary axis allowed vertebrates to coordinate thyroid hormone synthesis and secretion. Abbreviations: TETRAC/TRIAC, tetraiodothyroacetic/triiodothyroacetic acids.

picture in time when these two systems were emerging, i.e. a picture modified during the hundreds of millions of years of independent evolution of the modern vertebrates (Fig. 1). Understanding the exquisite architecture and functional precision of these two systems from an evolutionary point of view are important in the study of the mechanisms of evolutionary change of the sequences of the protein components of these pathways. In addition, understanding regulatory mechanisms that lead to the spatial and temporal specificity of their expression as well as their relationships with other endocrine systems are key to understanding the origins of the neuroendocrine system in vertebrates.

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Abbreviations and acronyms

CRH	corticotropin-releasing hormone
GnRH	gonadotropin-releasing hormone
GpH	glycoprotein hormone
lGpH	lamprey glycoprotein hormone
GTH	gonadotropin
HPG	hypothalamic-pituitary-gonadal
HPT	hypothalamic-pituitary-thyroid
lGpH-R	lamprey glycoprotein hormone receptor
LH	luteinizing hormone
FSH	follicle stimulating hormone
TETRAC/TRIAC	tetraiodothyroacetic/triodothyroacetic acids
pmTR	*Petromyzon marinus* thyroid hormone nuclear receptor
T3	triiodothyronine
T4	thyroxine
TRs	thyroid hormone nuclear receptors
TRH	thyrotropin releasing hormone
TSH	thyrotropin/thyroid stimulating hormone
TSHR	thyrotropin receptors/thyroid stimulating hormone receptor

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