

Morphology, Development, and Evolution of the Adenohypophysis

Corey S. Johnson*

Department of Biology, University of North Carolina at Chapel Hill, North Carolina, USA

Abstract

The pituitary gland is an essential component of the endocrine system of vertebrates. It is responsible for the control of various processes, including metabolism, reproduction, lactation, the response to stress, growth, and morphological color change. Though having some variation, jawed vertebrates possess many shared features of pituitary development, morphology, and function. In this review, the evolutionary origins of these characteristics are traced with a focus on the origins of the relationship between the hypothalamus and the adenohypophysis. Recent research into the developmental biology of chordates and the hormones of hagfish and lampreys have shed light upon the evolutionary novelties of jawed vertebrates.

Keywords: Morphology • Developmental biology • Adenohypophysis

Introduction

The pituitary gland is a peculiar structure, having several unique features. It is a composite structure made of glandular epithelium, the adenohypophysis (AH), and an extension of the hypothalamus, the neurohypophysis (NH). The AH is responsive to hypothalamic neurohormones transported through a portal system. The evolutionary history of these structures, their function, and their morphological elaboration has become more apparent in recent years as modern developmental gene expression techniques and traditional descriptive embryology has been applied to non-model organisms.

Morphology of the Gnathostome Pituitary

Humans, mammals, and nearly all extant vertebrates are gnathostomes, descendants of jawed fish. The well-characterized physiological functions of the AH in these organisms include control of reproduction, lactation, metabolic function and rate, growth, and pigmentation. Much of this understanding is derived from studies in mammals, although studies in other vertebrates have provided relevant comparative data. The axon terminals of the hypothalamic nuclei are concentrated in two loci of the NH: the pars nervosa (PN) and the median eminence (Figure 1).

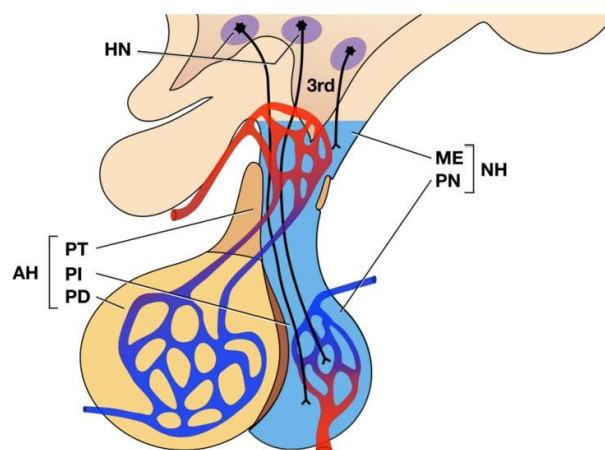


Figure 1: Generalized anatomy of the mammalian adenohypophysis and neurohypophysis, anterior to the left. Hypothalamic neurosecretory neurons terminate in the median eminence and pars nervosa. The circulation is shown in schematic to illustrate the portal circulation with primary and secondary capillary beds in the median eminence and pars distalis.

In agnathans, chondrichthyans, and some actinopterygian fish, the functionally equivalent region of the NH has been called the proximal neurosecretory contact region [1-3]. Regardless of slight differences in morphology across gnathostome taxa, the hormones of the median eminence regulate the secretions of the AH, while the hormones of the PN find their targets at more distant targets: the blood vessels, kidneys, and mammary glands.

*Address for Correspondence: Dr. Corey S. Johnson, Department of Biology, University of North Carolina at Chapel Hill, North Carolina, USA; Tel: 9197245429; E-mail: johnsonc@bio.unc.edu

Copyright: © 2020 Johnson CS. This is an open-access article distributed under the terms of the creative commons attribution license which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Received: 10 August, 2020; Accepted: 25 August, 2020; Published: 1 September, 2020

Hypophyseal arteries branch directly or indirectly from the internal carotid arteries. These vessels supply capillary beds to the median eminence [4]. Interestingly, early investigators working in mammalian systems suggested that blood flow was from the AH toward the brain [5]. However, the hypothalamic-hypophyseal portal system was eventually described correctly by Wislocki and King [6]. The capillary blood of the median eminence flows to a secondary capillary bed in the AH by the long portal vessels. While understanding of the venous drainage eluded researchers for some time (reviewed in Page 1982), the modern understanding eventually emerged wherein blood flows into a primary capillary bed in the median eminence to a secondary capillary bed in the AH, and finally is drained via hypophyseal veins to the cavernous sinuses. Comparative studies of portal vasculature among non-mammals have received little attention, but the anatomical arrangement of vessels appears to imply a similar portal circulation in most gnathostomes.

Three subdivisions are found within the gnathostome AH, with three endocrine profiles: the pars distalis, pars tuberalis, and pars intermedia. The pars distalis is the largest and anterior-most region of the AH and contains several hormone-specific cell types: corticotrophs, melanotrophs, somatotrophs, lactotrophs, gonadotrophs, and thyrotrophs. Folliculostellate cells are also present in the AH [7]. Although their role has not been fully understood, they do function in the paracrine regulation of hormone secretion and in immune system interactions with dendritic cells and macrophages of the AH [8,9]. The pars tuberalis is a region that surrounds the infundibulum of the hypothalamus. Like the pars distalis, it contains thyrotropes. However, no other hormone-producing cells appear to be present [10]. Recent evidence has accumulated that implicates the pars tuberalis as a significant site of regulation for circannual rhythm, especially in organisms with distinct seasonal adaptations regarding feeding, metabolism, and reproduction [11]. The pars intermedia (PI) is found adjacent to the PN. The always diminutive PI is comprised of melanotropes that secrete Melanocyte stimulating hormone (MSH). Although found in the human fetus, the PI is absent in postnatal life. Evidence indicates that its cells migrate into the pars distalis and PN [12]. In many other mammalian species, the pars intermedia persists throughout postnatal life. Not all gnathostomes possess all of the regions above, and their absence is considered secondary. For example, birds, cetaceans, and some squamates do not have a pars intermedia; snakes and lungfish lack a pars tuberalis. Such details are beyond the scope of this review, and the reader is directed to Norris and Carr for an excellent review of the literature describing unique examples of variation among gnathostome fish and tetrapods [13].

Development of the Gnathostome Adenohypophysis

The pre-placodal ectoderm (PPE) is a region of placode and neural crest forming tissue that forms along the anterior border of the anterior neural plate. It is from this region that five placodes form: the single median adenohypophyseal placode and paired bilateral olfactory and lens placodes [14-16]. Later in embryogenesis, the adenohypophyseal placode is found forming among cells of the oral ectoderm, the stomodeum. Invagination of the placode towards the developing brain forms Rathke's pouch. Various transcription factors are known to be important to the specification of the

adenohypophyseal placode and Rathke's pouch, including Six1/2, Eya, and Pitx [17]. In close proximity, the hypothalamus forms in the ventral floor of the diencephalon [18]. A portion of the developing hypothalamus, the infundibulum, is responsible for the induction of Rathke's pouch from the stomodeal ectoderm through its release of BMP and FGF signals [19]. The infundibulum and Rathke's pouch remain in close contact throughout their continued development. The neuroectoderm-derived infundibulum forms the hypothalamus, and its axons project to the eventual sites of hormone release in the median eminence and PN.

Rathke's pouch develops several distinct lobes. The posterior portion in contact with the hypothalamus forms the pars intermedia. Two lateral lobes form the pars tuberalis, and the anterior lobe forms the pars distalis [20,21]. Depending on the species and developmental stage, the lumen between the pars intermedia and pars distalis may be lost or persist as a narrow cleft. In normal human development, the connection to the stomodeum is lost, although remnants of Rathke's pouch commonly persist outside the AH proper as a pharyngeal hypophysis in the roof of the nasopharynx. The cell types present have been determined to be the same as that of the pars distalis [22].

Chordate Development

Jawed vertebrates, along with the jawless cyclostomes, make up the living vertebrates. The wider group to which vertebrates belong is the chordates. There are morphological, developmental, and physiological features among the non-vertebrate chordates that may provide clues to the evolution of the vertebrate condition. All chordates (cephalochordates, urochordates, vertebrates) at some time in their development possess a notochord, for which they are named. They also possess a post-anal tail, a dorsal hollow nerve cord, and pharyngeal slits. Model chordates include the tunicates (*Halocynthia* and *Ciona*) and amphioxus. Amphioxus is a filter-feeding cephalochordate with a highly conserved genomic structure and morphology [23,24]. It superficially resembles the lamprey ammocoetes larva as well as *Pikaia gracilens*, a putative chordate from the Cambrian [25,26]. The model tunicate species are filter-feeding urochordates that have a motile larval stage and metamorphose into sessile adults. Although tunicates do not share a strong resemblance to vertebrates and cephalochordates, they do share some vertebrate-like features of early development. Unlike amphioxus, some tunicates have a migratory cell population arising from the margins of the neural tube during its development. Like neural crest cells in vertebrates, these cells form melanophores [27]. Aspects of tunicate development, however, are quite divergent from what is found in vertebrates and amphioxus. As reviewed by Holland, tunicates have evolved a more mosaic paradigm of development based on the use of operons [28]. Despite the limited morphological similarity between urochordates and vertebrates, they are considered the most likely sister group to vertebrates [29]. Although more distantly related, cephalochordates such as amphioxus have more in common with vertebrates morphologically, making them essential models for understanding the roots of the chordate and vertebrate lineages.

Amphioxus has an evagination of its rostral gut, Hatschek's pit, that is in contact with the ventral brain. Such an arrangement has, for obvious reasons, given the impression that these are the rudiments

of a primitive hypothalamus-AH association, beginning with Berthold Hatschek himself and extending to modern times [28,30-32]. From a morphogenetic standpoint, the question of homology between Hatschek's pit and the vertebrate AH is complicated due to the convoluted embryological formation of the cephalochordate structure. As reviewed in Glardon, et al. (1998), the developmental events that lead to Hatschek's pit formation begin in the neurula and are not completed until metamorphosis. From an evagination of the left rostral gut, Hatschek's left diverticulum (HLD) is formed. Separating from this layer, HLD fuses with an invagination of the ectoderm to form the preoral pit. The preoral pit, with its ectodermal and HLD-derived components, establishes continuity with the pharyngeal cavity. During metamorphosis, it is from the derivatives of the preoral pit that Hatschek's pit evaginates dorsally. Accurate lineage tracing will be required to discern which germ layer(s) form Hatschek's pit and provide definitive evidence for homology.

In the tunicate, like in amphioxus, a pair of tissues are juxtaposed in a similar developmental and spatial relationship. From the rudiment of the central nervous system, an evagination develops that proceeds toward the stomodeum. As contact is made with the stomodeum, the two structures fuse, and their lumens become continuous. In time, the neural component differentiates to form the neural gland. The oral component maintains its continuity with the stomodeum and contributes to the ciliated funnel (buccal funnel) found at the stomodeal roof. Together, the tunicate neural complex is likely an organ for osmotic balance and was implicated by early investigators as containing the AH homolog [33-36].

While revealing no definitive evidence of endocrine function, Hatschek's pit and the ciliated funnel are suggestive of early homologs to the AH. Despite not having the same endocrine structures as vertebrates, tunicates and amphioxus have a variety of individual cells located elsewhere in their epidermal tissues with the characteristics one would expect in the evolutionary precursors to the hypothalamic-AH axis. That is, some cells act as chemoreceptors to respond to the environment, and other cells secrete substances to affect internal systems [37]. Evidence suggests these functions are linked such that stimuli within the environment can affect internal physiology [38,39]. More investigation into a putative endocrine function within these organisms is needed to complement our growing developmental understanding of these organisms. Thus, the morphological forerunners of the hypothalamus-AH are present, and the sensory-secretory building blocks of an endocrine seem to be present, but these features are not found within the same part of the cephalochordate or urochordate body as they are in vertebrates.

A comparison of the development of Hatschek's pit and ciliated funnel with the AH has another notable difference. The developmental forerunner of Rathke's pouch, the adeno-hypophyseal placode, is absent from non-vertebrate chordates. In fact, there are no placodes of any kind in the development of these organisms. In the early stages of vertebrate development, the PPE expresses Six1/2, Eya, and Pitx gene family members. These genes play a role in defining the anterior placode-forming region, including the adeno-hypophyseal placode [40-42]. Amphioxus does not exhibit Six1/2 and Eya expression in this region, and Pitx is present only briefly [37]. These results are consistent with the lack of placode formation in amphioxus since these are transcription factors associated with placode and cell shape changes. However, at later

stages of development, Six and Eya family members are found in HLD. Still later, during metamorphosis Six, Eya, and Pitx genes are found in Hatschek's pit [28]. Despite differences in developmental timing, the same network of genes does seem to be involved in the formation of Hatschek's pit and the vertebrate AH. This evidence is only correlative, yet it does provide an intriguing possibility of either direct homology of structures or the co-option of the gene network.

In tunicates, like amphioxus, placodes and the discrete gene expression subdomains that would prefigure them are not observed. Examination of embryos prior to neural gland formation has shown that an ectodermal developmental regulatory domain containing Six1/2 and Eya genes is present in tunicates [43]. This "proto-placodal ectoderm" is found directly anterior to the tunicate neural plate, just as is the case with the vertebrate PPE. Although it does not form placodes, it does bear the characteristic regulatory network of the vertebrate PPE, and its cells exhibit gene expression characteristic of vertebrate placodal cell populations. Portions of the proto-placodal ectoderm later form the ciliated funnel, which continues to express Six1/2 and Eya genes as well as Pitx [32,44,45]. These data indicate that the genetic regulatory network that compartmentalizes and then specifies the vertebrate AH was present in the common ancestor of tunicates and vertebrates, even if placodes per se were not present. The steps that would result in the gathering of ectoderm-derived neurosecretory or sensory cells into placodes would only occur after the split between tunicates and their last common ancestor with the vertebrates.

Cyclostome Development

The curious developmental sequence, the physical proximity of the AH and NH, and the portal circulation beg for an explanation of the evolutionary roots and adaptive value of this system. To understand the earliest vertebrate patterns of development and evolution, studies in cyclostomes have been very insightful. The two extant lineages include the Myxini (hagfishes) and the Petromyzontiformes (lampreys). Although vertebrates, these are jawless fish with many simple anatomical features that have been elaborated in the gnathostome lineages: the Chondrichthyes (cartilaginous fish), the Actinopterygii (ray-finned fish), and the Sarcopterygii (lobe-finned fish and tetrapods; Figure 2). The morphological features of the hagfish are, in many ways, more simplistic than that of the lamprey. However, the most recent developmental and genomic evidence suggests that the cyclostomes are indeed monophyletic [46-48].

Hormones of the Gnathostome Adenohypophysis

The gnathostome AH produces three families of hormones. The Pro-opiomelanocortin (POMC) hormones include several cleavage variants of a single peptide, including adrenocorticotropin (ACTH), which contains α -melanotropin (also called α -melanocyte-stimulating hormone (α -MSH)). Additionally, β -MSH, γ -MSH, and β -endorphin are contained within the POMC peptide. Uniquely, Chondrichthyan have an additional, MSH [52]. The single-protein hormones include growth hormone (GH) and prolactin (PRL). The glycopeptides FSH, LH, TSH, and thyrostimulin are dimers with α and β subunits. FSH, LH, and TSH share a common α subunit, GpA1, and they are differentiated from one another by the presence of a unique β subunit: FSH β , LH β , or TSH β . Thyrostimulin has unique α and β subunits, GpA2/GpB5.

The regulation of all hormones of the AH occurs primarily through releasing and inhibiting hormones of the hypothalamus. Such hypothalamic hormones include corticotropin-releasing hormone, growth hormone-releasing hormone, somatostatin, dopamine, gonadotropin-releasing hormone (GnRH), and thyrotropin-releasing hormone. Extensive paracrine activity and some direct innervation play a role in the regulation of AH hormone secretion [53-55].

Chordate Hormones

The homologs to vertebrate hormones in chordates are few in number. Genes encoding forms of the hypothalamic hormone GnRH and GnRH receptors have been identified in the amphioxus and tunicate genomes [56-61]. It is important to note, however, that GnRH does not function exclusively to control gonadotropins; it has many well known neural functions independent of its control over the AH. An initial report that amphioxus has a gonadotropin localized to Hatschek's pit provided intriguing evidence for the functional homology of Hatschek's pit to the vertebrate AH [62]. Likewise, PRL immunoreactivity in Hatschek's pit has been reported. However, these antibody-based approaches have since been refuted by more definitive genomic studies indicating that there are no adenohypophyseal hormones in chordates. Additionally, there is no definitive evidence for GH family peptides [58,63,64]. Also, not present are genes encoding POMC hormones or TSH [56,58,63,64]. The lack of a POMC gene or sequences for its subcomponents is somewhat surprising. Several invertebrate groups have proteins with high sequence similarity to the gnathostome POMC. Leech and mollusk genomes contain the POMC gene components in the same sequential order as in gnathostomes. The absence of these genes in chordates is puzzling. It opens the door to the possibility of horizontal gene transfer from parasite to host, or less parsimoniously, the chordate inheritance of the gene, followed by its loss in both urochordate and cephalochordate lineages after the divergence of the vertebrate lineage.

Although there is no gonadotropin in either chordate genome, the α and β components of Thyrostimulin have been identified [23]. It remains to be determined whether GnRH has influence over Thyrostimulin in amphioxus, or whether its expression is localized to Hatschek's pit or the ciliated funnel. The remarkable scarcity of hormones in chordates indicates that POMC family hormones and

single-protein hormones like GH are vertebrate innovations. GnRH and Thyrostimulin are the sole representatives of vertebrate hypothalamic-AH hormones that are found among non-vertebrate chordates.

Cyclostome Hormones

Until recent decades, it was unknown whether the morphologically simplistic hagfish AH had any functioning hormones. Studies have since revealed that all three gnathostome hormone families have at least a single representative in cyclostomes. These include a glycopeptide hormone (GpH) with gonadotropin function. This hormone is comprised of GpA1/GpH β subunits, which contain the α subunit common to FSH, LH, and TSH of higher vertebrates but having a unique β subunit [65,66]. Lampreys likewise have a gonadotropin with a homologous GpH β subunit but do not possess the hagfish and gnathostome GpA1 subunit. Instead, lamprey gonadotropin utilizes the same α subunit as in thyrostimulin, GpA2 [67]. Interestingly, the thyrostimulin subunits (GpA2/GpB5) have not been identified in hagfish, but they are present in gnathostomes, lampreys, as well as in non-vertebrate chordates [23,56,68]. One evolutionary scenario would place GpA1, GpA2, and GpB5 at the last common ancestor of all vertebrates, with the subsequent loss of GpA1 from the lamprey lineage and GpA2/GpB5 from the hagfish lineage. Neither cyclostome group has the β subunits for TSH, FSH, or LH. These are gnathostome novelties that have likely arisen from gene duplication and divergence events from their respective hormone families.

The single-protein family member GH is found in the lamprey genome and evidence supports its presence in hagfish [69,70]. PRL is not present, except in gnathostomes. The third hormone family, the hormones, is present in parts. Rather than being found as a single gene sequence as in gnathostomes, the hormone-encoding sequences are found on two genes, pro-opiomelanocortin (POC) and pro-opiomelanotropin (POM) [71]. Genetic data from hagfish is lacking. Immunohistochemical binding assays indicate the likelihood of a pro-opiomelanocortin similar to that of lampreys, but there is little evidence to suggest the presence of MSH-like molecules [70,72]. The hypothalamic control of the identified cyclostome hormones, GpH, thyrostimulin, ACTH, and GH, has not been thoroughly investigated. Nonetheless, initial evidence indicates the presence of GnRH and corticotropin-releasing hormone [73,74]. These hypothalamic hormones may regulate glycopeptides and POC, respectively. A hypothalamic regulator of GH in hagfish has not been identified.

Research in lampreys has shed light on the regulation of gonadal and thyroid function. Interestingly, exogenous GnRH raises both thyroxine and estradiol levels, indicating that both GpH and Thyrostimulin may be under the control of the same hormone [75,76]. In lampreys, reproductive function and increased metabolic activity are coincidental with metamorphosis; thus, the overlapping regulation of ovarian and thyroid endocrine activity is not surprising. In the course of gnathostome evolution, FSH and LH would functionally replace the single gonadotropin, the regulation of the gonadotropins and thyrostimulin would become independent, and TSH would be added to the AH-thyroid axis of control.

Evolutionary Connections and Conclusions

Examining the origins of the AH among the non-vertebrate chordates shows that the building blocks of these systems are present. First, although there are few hormones present in chordates, homologs to those that would form a hypothalamic-AH axis are present within the genome. The expression patterns of GnRH and thyrostimulin in cephalochordates or urochordates are unknown. Secondly, Hatschek's pit and the ciliated funnel appear to be homologs to the AH of vertebrates; that is, they form like the vertebrate AH and from the expected tissue layers, even if they do not share common function. Lastly, it is also clear that chordates possess homologous cell types, sensory cells sensitive to olfactory, gustatory, or otherwise chemoreceptive stimuli in the environment. Also, chordates possess secretory cells capable of releasing chemical messengers to the blood for long-range communication. The juxtaposition of two such cell types in the ancestors of vertebrates would allow important physiological coordination in response to environmental cues.

If cyclostome ontogeny is indicative of an ancestral morphological condition, the single nasohypophyseal placode was the anlagen of both chemoreceptive and secretory adenohypophyseal cells. These cells would have had a close functional relationship, much like the enterocytes and enteroendocrine cells of the intestinal wall in higher vertebrates. How the hormones came to be expressed in the sensory and secretory cell types, and how the secretory cell types organized into placodes and became incorporated into evaginating stomodeal ectoderm, remains a central question in the evolution of vertebrates.

However, it should be noted that the separation of the olfactory and AH placodes found in the course of vertebrate development and evolution is only apparent. Cells originating in the olfactory placode migrate during ontogeny to take up residence in hypothalamic nuclei, not far from the AH. These migratory cells from the olfactory placode become GnRH-secreting hypothalamic neurons [77-79]. From this destination in the hypothalamus, GnRH neurons were sufficiently close to control the AH in a diffusional manner as seen in cyclostomes or an endocrine manner as in gnathostomes. Such an evolutionary step, where GnRH secreting cells undergo epithelial-mesenchymal transition and migrate to retain their developmental and ancestral proximity to the AH, would allow for the rearrangement and expansion of tissues in the head. Freeing the olfactory epithelium from the AH would have been an essential step in permitting the evolution of morphologically diverse patterns of tissues within the head.

Despite minor differences in overall morphological proportions of their components, all gnathostome vertebrates retain similar developmental and morphological relationships between the hypothalamus and the AH. These similarities extend to the regulation of the AH by way of the portal circulation. Portal circulations are found in birds and reptiles, amphibians, lobe-finned fish and cartilaginous fish [80-84]. In apparent deviation from the norm, teleost fish, a highly derived clade of actinopterygians, have an extensive innervation of the AH by hypothalamic neurons. Although extensive, the innervation of the AH in teleosts is not completely without a portal circulation [85]. Thus, the regulation of the AH in all examined vertebrate groups involves a portal system.

The portal circulation that most gnathostomes depend upon for direct hormonal communication between the median eminence and the AH is not present in cyclostomes. Instead, the hypothalamus of cyclostomes exerts its influence over the AH by paracrine signaling. Studies in hagfish have demonstrated that substances injected into the third ventricle can diffuse quickly to the AH [86]. Dyes and even the large protein, horseradish peroxidase, eventually travel to the AH through the intervening connective tissue. Although there is no portal system, the anatomical proximity of the hypothalamus and AH allows the physiologically relevant exchange of substances. It should be noted that in one hagfish species, several small blood vessels have been identified within the connective tissue between AH and the hypothalamus. The authors conjecture that these vessels may allow a more efficient communication in the manner of a primitive portal system [87]. No studies have yet been conducted to indicate the precise anatomical arrangement of these vessels nor the direction of blood flow. The lack of similar vessels in other hagfish species and lampreys suggests their appearance may be an evolutionary novelty if indeed the vessels function in a manner analogous to the portal system found in higher vertebrates.

If paracrine factors can efficiently diffuse from the NH to the AH, one might wonder why a portal system is necessary. Lampreys, with many of the same neuroendocrine signaling systems seen in gnathostomes, are seemingly not limited by the lack of a hypothalamic-hypophyseal portal system. The morphology of the cyclostome AH provides a clue. Its thin, flat appearance may be an optimization for surface area. In order for paracrine communication from the NH to be efficient, the responding cells must be within proximity. The evolutionary acquisition of jaws and a more active predatory lifestyle coincide with the increase in body size in gnathostome fishes [88]. The pituitary gland would be expected to enlarge with vertebrate body size, and perhaps a reliance upon paracrine signaling became size-limiting for vertebrates.

A more significant explanation for the portal circulation may lie within the morphological changes that occurred in the vertebrate head throughout evolution. As has been discussed, cyclostomes possess a single nasohypophyseal duct. Fossil agnathans such as the anaspids also exhibit a single nasohypophyseal duct but the Galeaspids appears to be one of the earliest lineages of vertebrates to have bilateral nasal organs [89]. In these well preserved endocranial specimens, it is evident that the hypophyseal duct retains its connection to the exterior environment. Unlike cyclostomes, which have an antero-dorsally located opening to their duct, galeaspids have a hypophyseal duct that opens ventrally within the oral cavity. Gai et al. suggest that these changes removed the barrier to the expansion of tissues to form the upper jaw in the ancestors of gnathostomes [90]. This evolutionary repositioning of the adenohypophyseal duct and the formation of bilateral nasal sacs was a significant rearrangement of tissues in the head. Such changes may have played a role in distancing the AH from the hypothalamus in gnathostome ancestors. A portal circulation would ensure continuity of function between these organs, despite changes in their proximity. While it is impossible to know whether a functional portal system in galeaspids was present, their fossils indicate the presence of hypophyseal arteries, branches of the internal carotid arteries that serve the hypothalamus and AH in extant organisms that possess portal circulations [90].

Connections drawn from physiology, development, and morphology of extinct and extant organisms reveal a picture of the evolutionary cohesion of endocrine cells of the AH and their GnRH-secreting regulators. This morphological and functional relationship has not been identified among modern urochordates or cephalochordates, but it must have formed among the ancestors of vertebrates [91]. While their physical proximity is present embryologically in cyclostomes, the apparent separation of olfactory and AH cells during development would leave the AH without its physiological regulator. The migration of a subset of olfactory cells to take up residence in the hypothalamus allows continuity of function despite evolutionary changes to the relative position of olfactory organs and the AH [92]. Further changes early in the vertebrate lineage would include the expansion of the head region and the increase of body size. Concomitantly, the position of the adenohipophyseal placode underwent a significant ventral relocation. Together, these factors may have been responsible for further distancing the AH from its regulators in the hypothalamus [93]. The acquisition of a portal circulation allowed for the maintenance of a physiological connection despite the morphological distancing that occurred throughout the evolution of gnathostome ancestors.

References

- 1 Polenov AL. "On the evolution of the median eminence--the proximal neurosecretory contact region in some fishes (Elasmobranchii, Chondrosteoidei)." *Arch Anat Histol Embryol* 51 (1968): 551-561.
- 2 Garlov, PE. "Electron microscope study of neurosecretory elements of the proximal neurosecretory contact region in the sturgeon." *Dokl Akad Nauk SSSR* 188 (1969): 245-248.
- 3 Belenky, Michael A, Konstantinova MS and Polenov AL. "The hypothalamo-hypophysial system of the lamprey, *Lampetra fluviatilis* L. II." *Cell Tissue Res*. 204 (1979): 319-331.
- 4 Antunes, Lobo J and Muraszko K. "The vascular supply of the hypothalamus-pituitary axis." *Acta Neurochir Suppl (Wien)* 47 (1990): 42-47.
- 5 Popa, Gregor and Fielding U. "A Portal Circulation from the Pituitary to the Hypothalamic Region." *J Anat* 65 (1930): 88-91.
- 6 Wislocki, George B and King LS. "The permeability of the hypophysis and hypothalamus to vital dyes, with a study of the hypophyseal vascular supply." *Am J Anat* 58 (1936): 421-472.
- 7 Farquhar, Marilyn Gist and Rinehart JF. "Electron microscopic studies of the anterior pituitary gland." *J Histochem Cytochem* 1 (1953): 93-113.
- 8 Sato, Tetsuji and Inoue K. "Dendritic cells in the rat pituitary gland evaluated by the use of monoclonal antibodies and electron microscopy." *Arch Histol Cytol* 63 (2000): 291-303.
- 9 Herkenham, Miles. "Folliculo-Stellate (FS) Cells of the Anterior Pituitary Mediate Interactions between the Endocrine and Immune Systems." *Endocrinology* 146 (2005): 33-34.
- 10 Wood, Shona H, Christian HC, Miedzinska K and Saer BRC, et al. "Binary Switching of Calendar Cells in the Pituitary Defines the Phase of the Circannual Cycle in Mammals." *Curr Biol* 25 (2015): 2651-2662.
- 11 Wood, Shona and Loudon A. "The pars tuberalis: The site of the circannual clock in mammals?." *Gen Comp Endocrinol* 258 (2018): 222-235.
- 12 Horvath, Eva, Kovacs K and Lloyd RV. "Pars intermedia of the human pituitary revisited: Morphologic aspects and frequency of hyperplasia of POMC-peptide immunoreactive cells." *Endocrine Pathol* 10 (1999): 55-64.
- 13 Norris, David O and Carr JA. The Hypothalamus-Pituitary System in Non-Mammalian Vertebrates. In: Norris, DO, Carr JA (Eds). *Vertebrate Endocrinology* (5th Edn). San Diego: Academic Press, USA, 2013: 151-205.
- 14 Couly, Gérard F and Le Douarin NM. "Mapping of the early neural primordium in quail-chick chimeras: I. Developmental relationships between placodes, facial ectoderm, and prosencephalon." *Dev Biol* 110 (1985): 422-439.
- 15 Streit, Andrea. "Extensive cell movements accompany formation of the otic placode." *Dev Biol* 249 (2002): 237-254.
- 16 Bhattacharyya, Sujata, Bailey AP, Bronner-Fraser M and Streit A. "Segregation of lens and olfactory precursors from a common territory: cell sorting and reciprocity of *Dlx5* and *Pax6* expression." *Dev Biol* 271 (2004): 403-414.
- 17 Schlosser, Gerhard. "Evolutionary origins of vertebrate placodes: insights from developmental studies and from comparisons with other deuterostomes." *J Exp Zool B Mol Dev Evol* 304 (2005): 347-399.
- 18 Schwind, Joseph L. "The development of the hypophysis cerebri of the albino rat." *Am J Anat* 41 (1928): 295-319.
- 19 Takuma, Naoyuki, Sheng HZ, Furuta Y and Ward JM, et al. "Formation of Rathke's pouch requires dual induction from the diencephalon." *Development* 125 (1998): 4835-4840.
- 20 Atwell, Wayne J. "The development of the hypophysis cerebri in man, with special reference to the pars tuberalis." *The American Journal of Anatomy* 37 (1926): 159-193.
- 21 Schwind, JL. "The development of the hypophysis cerebri of the albino rat." *Am J Anat* 41 (1928): 295-319.
- 22 Ciocca, DR, Puy LA and Stati AO. "Identification of seven hormone-producing cell types in the human pharyngeal hypophysis." *J Clin Endocrinol Metab* 60 (1985): 212-216.
- 23 Dos Santos, S, Bardet C, Bertrand S and Escriva H, et al. "Distinct expression patterns of glycoprotein hormone-alpha2 and -beta5 in a basal chordate suggest independent developmental functions." *Endocrinology* 150 (2009): 3815-3822.
- 24 Holland, Linda Z. "Genomics, evolution and development of amphioxus and tunicates: The Goldilocks principle." *J Exp Zool B Mol Dev Evol* 324 (2014): 342-352.
- 25 Morris, Simon Conway, and Caron JB. "Pikaia gracilens Walcott, a stem-group chordate from the Middle Cambrian of British Columbia." *Biol Rev Camb Philos Soc* 87 (2012): 480-512.
- 26 Mallatt, Jon and Holland N. "Pikaia gracilens Walcott: stem chordate, or already specialized in the Cambrian?." *J Exp Zool B Mol Dev Evol* 320 (2013): 247-271.
- 27 Jeffery, William R. "Ascidian neural crest-like cells: phylogenetic distribution, relationship to larval complexity, and pigment cell fate." *J Exp Zool B Mol Dev Evol* 306 (2006): 470-480.
- 28 Kozmik, Zbynek, Holland ND, Kreslova J and Oliveri D, et al. "Pax-Six-Eya-Dach network during amphioxus development: Conservation in vitro but context specificity in vivo." *Dev Biol* 306 (2007): 143-159.
- 29 Delsuc, Frédéric, Brinkmann H, Chourrout D, and Philippe H. "Tunicates and not cephalochordates are the closest living relatives of vertebrates." *Nature* 439 (2006): 965-968.
- 30 Hatschek, Berthold. Studien über entwicklung des amphioxus. Michigan: Michigan Publishing, USA, 1881.
- 31 Yasui, Kinya, Zhang S, Uemura M and Saiga H. "Left-right asymmetric expression of *BbPtx*, a *Ptx*-related gene, in a lancelet species and the developmental left-sidedness in deuterostomes." *Development* 127 (2000): 187-195.
- 32 Boorman, Clive J and Shimeld SM. "Ptx homeobox genes in *Ciona* and amphioxus show left-right asymmetry is a conserved chordate character and define the ascidian adenohipophysis." *Evol Dev* 4 (2002): 354-365.
- 33 Ruppert, Edward E. "Structure, Ultrastructure and Function of the Neural Gland Complex of *Ascidia interrupta* (Chordata, Ascidiacea): Clarification of Hypotheses Regarding the Evolution of the Vertebrate Anterior Pituitary." *Acta Zool* 71 (1990): 135-149.
- 34 Julin, C. "Recherches sur l'organisation des Ascidiées simples. Sur l'hypophyse et quelques organes qui s'y attachent, dans les genres *Corella*, *Phallusia*, et *Ascidia*." *Arch Biol* 1881 (2): 59-126.
- 35 Willey, A. "Studies on the Protochordata. I. On the origin of the branchial stigmata, praeoral lobe, endostyle, atrial cavities, etc. in *Ciona intestinalis*, Linn., with remarks on *Clavelina lepadiformis*." *Q J Micr Sci* 34 (1893): 317-360.

- 36 Manni, Lucia, Agnoletto A, Zaniolo G and Burighel P. "Stomodaeal and neurohypophysial placodes in *Ciona intestinalis*: insights into the origin of the pituitary gland." *J Exp Zool B Mol Dev Evol* 304 (2005): 324-339.
- 37 Schlosser, Gerhard. "From so simple a beginning – what amphioxus can teach us about placode evolution." *Int J Dev Biol* 61 (2017): 633-648.
- 38 Tjoa, Loan T and Welsch U. "Electron microscopical observations on Kölliker's and Hatschek's pit and on the wheel organ in the head region of *Amphioxus* (*Branchiostoma lanceolatum*)." *Cell Tissue Res* 153 (1974): 175-187.
- 39 Sahlin, Karin and Olsson R. "The wheel organ and Hatschek's groove in the lancelet, *Branchiostoma lanceolatum* (Cephalochordata)." *Acta Zool* 67 (1986): 201-219.
- 40 Grocott, Timothy, Tambalo M and Streit A. "The peripheral sensory nervous system in the vertebrate head: a gene regulatory perspective." *Dev Biol* 370 (2012): 3-23.
- 41 Schlosser, Gerhard. "Making senses development of vertebrate cranial placodes." *Int Rev Cell Mol Biol* 283 (2010): 129-234.
- 42 Tadjuidje, Emmanuel and Hegde RS. "The Eyes Absent proteins in development and disease." *Cell Mol Life Sci* 70 (2013): 1897-1913.
- 43 Abitua, Philip Barron, Gainous TB, Kaczmarczyk AN and Winchell CJ, et al. "The pre-vertebrate origins of neurogenic placodes." *Nature* 524 (2015): 462-465.
- 44 Mazet, Françoise, Hutt JA, Milloz J and Millard J, et al. "Molecular evidence from *Ciona intestinalis* for the evolutionary origin of vertebrate sensory placodes." *Dev Biol* 282 (2005): 494-508.
- 45 Christaen, Lionel, Burighel P, Smith WC and Vernier P, et al. "Pitx genes in Tunicates provide new molecular insight into the evolutionary origin of pituitary." *Gene* 287 (2002): 107-113.
- 46 Kuraku, Shigehiro. "Insights into cyclostome phylogenomics: pre-2R or post-2R." *Zool Sci* 25 (2008): 960-968.
- 47 Oisi, Yasuhiro, Ota KG, Kuraku S and Fujimoto S, et al. "Craniofacial development of hagfishes and the evolution of vertebrates." *Nature* 493 (2013): 175-180.
- 48 Ota, Kinya G, Oisi Y, Fujimoto S and Kuratani, S. "The origin of developmental mechanisms underlying vertebral elements: implications from hagfish evo-devo." *Zoology (Jena)* 117 (2014): 77-80.
- 49 Gorbman, Aubrey. "Early Development of the Hagfish Pituitary Gland: Evidence for the Endodermal Origin of the Adenohypophysis." *Am Zool* 23 (1983): 639-654.
- 50 Nozaki, Masumi, Oshima Y, Shimotani T and Sower SA. "Immunohistochemical detection of gonadotropin-like material in the hagfish pituitary, correlated with their gonadal conditions." *Fish Physiol Biochem* 28 (2003): 85-87.
- 51 Sterba, G. "Endocrinology of the lampreys." *Gen Comp Endocrinol* 2 (1969): 500-509.
- 52 Dores, Robert M, Cameron E, Lecaude S and Danielson PB. "Presence of the delta-MSH sequence in a proopiomelanocortin cDNA cloned from the pituitary of the galeoid shark, *Heterodontus portusjacksoni*." *Gen Comp Endocrinol* 133 (2003): 71-79.
- 53 Ju, Gong. "Innervation of the mammalian anterior pituitary: A mini review." *Microsc Res Tech* 39 (1997): 131-137.
- 54 Liu, Shaojun. "Peptidergic innervation in pars distalis of the human anterior pituitary." *Brain Res* 1008 (2004): 61-68.
- 55 Deneff, C. "Paracrinicity: the story of 30 years of cellular pituitary crosstalk." *J Neuroendocrinol* 20 (2008): 1-70.
- 56 Holland, Linda Z, Albalat R, Azumi K and Benito-Gutiérrez È, et al. "The amphioxus genome illuminates vertebrate origins and cephalochordate biology." *Genome Res* 18 (2008): 1100-1111.
- 57 Mirabeau, Olivier and Joly JS. "Molecular evolution of peptidergic signaling systems in bilaterians." *Proc Natl Acad Sci U S A* 110 (2013): E2028-2037.
- 58 Putnam, Nicholas H, Butts T, Ferrier DEK and Furlong RF, et al. "The amphioxus genome and the evolution of the chordate karyotype." *Nature* 453 (2008): 1064-1071.
- 59 Roch, Graeme J, Tello JA and Sherwood NM. "At the transition from invertebrates to vertebrates, a novel GnRH-like peptide emerges in amphioxus." *Mol Biol Evol* 31 (2014): 765-778.
- 60 Adams, Bruce A, Tello JA, Erchegyi J and Warby C, et al. "Six novel gonadotropin-releasing hormones are encoded as triplets on each of two genes in the protochordate, *Ciona intestinalis*." *Endocrinology* 144 (2003): 1907-1919.
- 61 Tello, Javier A, Rivier JE and Sherwood NM. "Tunicate Gonadotropin-Releasing Hormone (GnRH) Peptides Selectively Activate *Ciona intestinalis* GnRH Receptors and the Green Monkey Type II GnRH Receptor." *Endocrinology* 146 (2005): 4061-4073.
- 62 Nozaki, Masumi, and Gorbman A. "The Question of Functional Homology of Hatschek's Pit of *Amphioxus* (*Branchiostoma belcheri*) and the Vertebrate Adenohypophysis." *Zool Sci* 9 (1992): 387-395.
- 63 Paramvir, Dehal, Satou Y, Campbell RK and Chapman J, et al. "The draft genome of *Ciona intestinalis*: insights into chordate and vertebrate origins." *Science* 298 (2003): 2157-2167.
- 64 Campbell, Robert K, Satoh N, and Degnan BM. "Piecing together evolution of the vertebrate endocrine system." *Trends Genet* 20 (2004): 359-366.
- 65 Miki, Makoto, Shimotani T, Uchida K and Hirano S, et al. "Immunohistochemical detection of gonadotropin-like material in the pituitary of brown hagfish (*Paramyxine atami*) correlated with their gonadal functions and effect of estrogen treatment." *Gen Comp Endocrinol* 148 (2006): 15-21.
- 66 Uchida, Katsuhisa, Moriyama S, Chiba H and Shimotani T, et al. "Evolutionary origin of a functional gonadotropin in the pituitary of the most primitive vertebrate, hagfish." *Proc Natl Acad Sci U S A* 107 (2010): 15832-15837.
- 67 Sower, Stacia A, Decatur WA, Hausken KN and Marquis TJ, et al. "Emergence of an Ancestral Glycoprotein Hormone in the Pituitary of the Sea Lamprey, a Basal Vertebrate." *Endocrinology* 156 (2015): 3026-3037.
- 68 Tando, Yukiko and Kubokawa K. "Expression of the gene for ancestral glycoprotein hormone β subunit in the nerve cord of amphioxus." *Gen Comp Endocrinol* 162 (2009): 329-339.
- 69 Kawauchi, Hiroshi, Suzuki K, Yamazaki T and Moriyama S, et al. "Identification of growth hormone in the sea lamprey, an extant representative of a group of the most ancient vertebrates." *Endocrinology* 143 (2002): 4916-4921.
- 70 Nozaki, Masumi, Oshima Y, Miki M and Shimotani T, et al. "Distribution of immunoreactive adenohypophysial cell types in the pituitaries of the Atlantic and the Pacific hagfish, *Myxine glutinosa* and *Eptatretus burgeri*." *Gen Comp Endocrinol* 143 (2005): 142-150.
- 71 Takahashi, A, Amemiya Y, Sarashi M and Sower SA, et al. "Melanotropin and corticotropin are encoded on two distinct genes in the lamprey, the earliest evolved extant vertebrate." *Biochem Biophys Res Commun* 213 (1995): 490-498.
- 72 Nozaki, Masumi, Shimotani T and Uchida K. "Gonadotropin-like and adrenocorticotropin-like cells in the pituitary gland of hagfish, *Paramyxine atami*; immunohistochemistry in combination with lectin histochemistry." *Cell Tissue Res* 328 (2007): 563-572.
- 73 Kavanaugh, Scott I, Powell ML and Sower SA. "Seasonal changes of gonadotropin-releasing hormone in the Atlantic hagfish *Myxine glutinosa*." *Gen Comp Endocrinol* 140 (2005): 136-143.
- 74 Amanoa, Masafumi, Amiya N, Yokoyama T and Onikubo K, et al. "Immunohistochemical detection of corticotropin-releasing hormone (CRH) in the brain and pituitary of the hagfish, *Eptatretus burgeri*." *Gen Comp Endocrinol* 236 (2016): 174-180.
- 75 Hausken, Krist N, Marquis TJ and Sower SA. "Expression of two glycoprotein hormone receptors in larval, parasitic phase, and adult sea lampreys." *Gen Comp Endocrinol* 264 (2018): 39-47.
- 76 Sower, Stacia A, Plisetskaya E and Gorbman A. "Changes in plasma steroid and thyroid hormones and insulin during final maturation and spawning of the sea lamprey, *Petromyzon marinus*." *Gen Comp Endocrinol* 58 (1985): 259-269.
- 77 Schwanzel-Fukuda, Marlene and Pfaff DW. "Origin of luteinizing hormone-releasing hormone neurons." *Nature* 338 (1989): 161-164.
- 78 Yamamoto, Naoyuki, Uchiyama H, Ohki-Hamazaki H and Tanaka H, et al. "Migration of GnRH-immunoreactive neurons from the olfactory placode to the brain: a study using avian embryonic chimeras." *Brain Res Dev Brain Res* 95 (1996): 234-244

- 79 Biju KC, Gaikwad A, Sarkar S and Schreiber MP, et al. "Ontogeny of GnRH-like immunoreactive neuronal systems in the forebrain of the Indian major carp, *Cirrhinus mrigala*." *Gen Comp Endocrinol* 141 (2005): 161-171.
- 80 Wingstrand, KG. "The structure and development of the avian pituitary from a comparative and functional viewpoint." C. W. K. Gleerup, Lund, 1951.
- 81 Enemar, Anders. "The development of the hypophysial vascular system in the lizards *Lacerta a. agilis* Linnaeus and *Anguis fragilis* Linnaeus and in the snake *Natrix n. natrix* (Linnaeus), with comparative remarks on the Amniota." *Acta Zool* 41 (1960): 141-237.
- 82 Rodríguez, Esteban M and Piezzi RS. "Vascularization of the hypophysial region of the normal and adeno-hypophysectomized toad." *Z Zellforsch Mikrosk Anat* 83 (1967): 207-218.
- 83 Lagios, Michael D. "Evidence for a hypothalamo-hypophysial portal vascular system in the coelacanth *Latimeria chalumnae* Smith." *Gen Comp Endocrinol* 18 (1972): 73-82.
- 84 Knowles, Francis, Vollrath L and Meurling P. "Cytology and neuroendocrine relations of the pituitary of the dogfish, *Scyliorhinus canicula*." *Proc R Soc Lond B Biol Sci* 191 (1975): 507-525.
- 85 Golan, Matan, Zelinger E, Zohar Y and Levavi-Sivan B. "Architecture of GnRH-Gonadotrope-Vasculature Reveals a Dual Mode of Gonadotropin Regulation in Fish." *Endocrinology* 156 (2015): 4163-4173.
- 86 Tsukahara, Tetsuo, Gorbman A and Kobayashi H. "Median eminence equivalence of the neurohypophysis of the hagfish, *Eptatretus burgeri*." *Gen Comp Endocrinol* 61 (1986): 348-354.
- 87 Kobayashi, Hideshi and Uemura H. "The neurohypophysis of the hagfish, *Eptatretus burgeri* (Girard)." *Gen Comp Endocrinol* 3 (1972): 114-124.
- 88 Louis Payne, Jonathan, Boyer AG, Brown JH and Finnegan S, et al. "Two-phase increase in the maximum size of life over 3.5 billion years reflects biological innovation and environmental opportunity." *Proc Natl Acad Sci USA* 106 (2009): 24-27.
- 89 Janvier, Philippe. "Early Jawless Vertebrates and Cyclostome Origins." *Zoolog Sci* 25 (2008): 1045-1057.
- 90 Gai, Zhikun, Donoghue PCJ, Zhu M and Janvier P, et al. "Fossil jawless fish from China foreshadows early jawed vertebrate anatomy." *Nature* 476 (2011): 324-327.
- 91 Bertrand, Stephanie and Escriva H. "Evolutionary crossroads in developmental biology: amphioxus." *Development* 138 (2011): 4819-4830.
- 92 Page, RB. "Pituitary blood flow." *Am J Physiol Endocrinol Metab* 243 (1982): E427-E442.
- 93 Popa, Gregor and Fielding U. "The vascular link between the pituitary and the hypothalamus." *Lancet* 216 (1930), 238-240.

How to cite this article: Johnson, Corey S. "Morphology, Development, and Evolution of the Adeno-hypophysis". *J Morphol Anat* 4(2020): 133.