Breaking Dogma on the Hypothalamic-Pituitary Anatomical Relations in Vertebrates

Stacia A. Sower

Center for Molecular and Comparative Endocrinology, Department of Molecular, Cellular and Biomedical Sciences, University of New Hampshire, Durham, New Hampshire 03824

The hypothalamus and pituitary are present in all vertebrates from agnathans (jawless fishes) to mammals. The hypothalamus is located below the thalamus, just above the brain stem and forms the ventral part of the diencephalon. The appearance of the pituitary was a seminal event in the evolution of vertebrates (1, 2). The pituitary is not present in protochordates or other invertebrates. The pituitary consists of the same 2 principal divisions, the neurohypophysis and adenohypophysis. The neurohypophysis develops from the floor of the diencephalon as an infundibular extension, whereas the adenohypophysis develops from the oral epithelium that comes in contact with this infundibulum. In vertebrates, the evolution of a complex pituitary with dual developmental origin along with the more highly developed tripartite brain added another layer of control leading to the neuroendocrine control of many complex physiological functions such as growth, reproduction, development and metabolism among others. These functionally adaptive conditions may then have contributed to the expansion of vertebrates into new environments. The acquisition of the vertebrate pituitary probably resulted from whole-genome duplications that occurred early in vertebrate evolution (3).

The adenohypophysis of the pituitary gland secretes a number of protein hormones that regulates a variety of the physiological processes of vertebrates. The adenohypophysial hormones can be classified, on the basis of structural and functional similarity, into 3 groups, the proopiomelanocortin family, the GH/prolactin/somatolactin family, and the glycoprotein hormone family (gonadotropins, thyroid-stimulating hormone, and a novel hormone called thyrostimulin). Somatolactin is only found in teleosts. Each family is believed to have evolved from an ancestral gene by duplication and subsequent mutations (4).

During the evolution of the vertebrates, structural features of the pituitary and hypothalamus also evolved that perhaps optimized the communication between these tissues as vertebrates became larger and more complicated in form and distance between the hypothalamus and pituitary increased significantly (5). Classically, in vertebrates, there are generally 3 models for anatomical control of the pituitary: portal system via the median eminence (tetrapods); direct innervation (teleosts) and diffusion (agnathans). In mammals, releasing hormones are secreted from the terminal boutons in the median eminence and enter the vascular portal network through capillary beds (6). The releasing hormones subsequently act on the glandular tissue of the adenohypophysis, or anterior pituitary, inducing the synthesis and release of the anterior pituitary hormones (6). Of all vertebrates, only the agnathan and teleosts lack a portal vascular system (median eminence) for transferring neurohormones from the hypothalamus to the adenohypophysis (7). The adaptive importance of such a portal system is that it makes possible central nervous regulation of such vital processes as reproduction by external (and internal) cycling environmental conditions. As extensively reported in the literature, the teleosts have solved this structural problem by direct innervation of the pars distalis by appropriate neurosecretory neurons from the adjacent hypothalamus (8). The agnathans (basal vertebrates), however, have no nervous or vascular communication between the brain and neurohypophysis (9). This had led to speculation that nervous regulation of the agnathan pars distalis is by diffusion of brain peptides from

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in USA

Received September 4, 2015. Accepted September 8, 2015.

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Abbreviation: GnRH3, type 3 GnRH.

the adjacent neurohypophysis, across the thin connective tissue layer that separates the neural from the glandular tissues. Anatomical and experimental studies provided evidence to support the concept of hypothalamic control of adenohypophysial function by diffusion of the neurohormones from the neurohypophysis to the pars distalis of the adenohypophysis (10–12). In the lamprey, GnRH-like neurons identified by immunocytochemistry project their fibers primarily into the neurohypophysis from the preoptic region (10, 13–15). In addition, Crim (16) and King et al (10) showed that GnRH neurons project into the third ventricle. These authors proposed an additional route of GnRH via secretion into the third ventricle and transport by tanycytes to the adenohypophysis (10). Nozaki et al (11) concluded that in the evolutionary sense there have been 3 types of regulation of the adenohypophysis developed in the vertebrates: the agnathan diffusional type, the teleostean direct innervational type, and the vascular type seen in all other vertebrates. As stated by these authors, perhaps the principal advantage of the vascular median eminence type of control by the brain is that it permitted development of larger and thicker glands as vertebrates became larger and more complicated in form and the distance between the hypothalamus and pituitary increased significantly (11).

Thus, for the past 30–40 years, these 3 types of regulation have been the dogma in hypothalamic regulation of the pituitary gland. In this issue of Endocrinology, Golan et al (17), performed elegant studies examining the anatomical aspects of the gonadotropin regulation by a type 3 GnRH (GnRH3) in zebrafish. The studies were well described and build upon the use of a transgenic zebrafish model. The authors have provided with stunning clarity an alternative view of pituitary control in teleosts that along with direct innervation by hypothalamic neurons to the pituitary, they show that there may be neurovascular control of gonadotropes in a teleost fish via GnHR3. By using a transgenic zebrafish model, Golan et al (17) studied the functional and anatomical aspects of FSH and LH regulation. They showed a close association between FSH cells and GnRH boutons, but only a fifth of the LH cells was in direct contact with the GnRH terminals. Although most GnRH3 terminals were not located next to gonadotropes, a strong association was observed between the GnRH3 terminals and the permeable blood vessels entering the pituitary, suggesting the uptake of GnRH peptides by the afferent circulation. These findings have broad implication in the regulation of a teleost pituitary by the hypothalamus because they present a significant difference between the regulation modes of the 2 gonadotrope types and highlight the circulation as a potentially important component in gonadotrope regulation.

Importantly, in nonmammalian vertebrates and unlike mammals, the hypothalamus releases typically more than one GnRH up to 3 GnRHs in control of the pituitary. Although GnRH3 is considered the major GnRH hypothalamic hormone in zebrafish, it has been shown that GnRH2 can also innervate the zebrafish pituitary and is involved in some regulation of the pituitary (18). Thus, further studies will need to be done on the possible mode of regulation of GnRH2 in zebrafish. In a basal vertebrate, hagfish, it has been assumed along with lampreys, that it has a diffusional type regulatory system. However, more recent information, reviewed in Nozaki and Sower (19), suggests that the hagfish may have both a diffusional model of regulation of the pituitary as well as a "premedian eminence." This is in part based on studies showing a pair of small blood vessels along with some Pro-Gln-Arg-Phe (PQRF)amide neuronal fibers terminating on the blood vessels within the hypothalamus (20). Nozaki and Sower (19) suggested that hagfish may represent an intermediate stage in the hypothalamic-pituitary anatomical relations in vertebrates. Therefore, it is highly likely that a neurovascular connection may also be found in other later evolved nonmammalian vertebrates. Thus, many more studies will need to be done to fully examine the extent of a neurovascular connection vs directed innervation not only in this fish species but also along with other fish species. Although a neurovascular mode of delivery has not been shown in other teleost fish, it is expected that this type of regulation may be found in other fish with the advent of transgenic models and more sophisticated microscopic techniques. Golan et al (17) certainly open up many avenues of investigation into hypothalamic-pituitary relations of vertebrates.

During the evolution of the vertebrates, structural features of the pituitary and hypothalamus also evolved that perhaps optimized the communication between these tissues as vertebrates became larger and more complicated in form and distance between the hypothalamus and pituitary increased significantly (5). Golan et al (17) paper provides an exciting groundbreaking approach using novel genetic techniques and microscopy. These authors have provided a promising model for further investigations on the anatomical relations between the hypothalamus and pituitary that can provide important clues for understanding the organization and evolution of this system as essential regulatory systems in all vertebrates.

Acknowledgments

Address all correspondence and requests for reprints to: Stacia A. Sower, Department of Molecular, Cellular and Biomedical Sciences, UNH, 46 College Road, Durham, NH 03824. E-mail: sasower@unh.edu.

This work was supported by the National Science Foundation Grant IOS-1257476. Partial funding was also provided by the New Hampshire Agricultural Experiment Station. This is Scientific Contribution Number 2629. This work is also supported by the US Department of Agriculture National Institute of Food and Agriculture (Hatch) Project NH00624.

Disclosure Summary: The author has nothing to disclose.

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