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Review

A journey through the pituitary gland: Development, structure and function, with emphasis on embryo-foetal and later development

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ABSTRACT

The pituitary gland and the hypothalamus are morphologically and functionally associated in the endocrine and neuroendocrine control of other endocrine glands. They therefore play a key role in a number of regulatory feedback processes that co-ordinate the whole endocrine system. Here we review the neuroendocrine system, from the discoveries that led to its identification to some recently clarified embryological, functional, and morphological aspects. In particular we review the pituitary gland and the main notions related to its development, organization, cell differentiation, and vascularization. Given the crucial importance of the factors controlling neuroendocrine system development to understand parvocellular neuron function and the aetiology of the congenital disorders related to hypothalamic–pituitary axis dysfunction, we also provide an overview of the molecular and genetic studies that have advanced our knowledge in the field. Through the action of the hypothalamus, the pituitary gland is involved in the control of a broad range of key aspects of our lives: the review focuses on the hypothalamic–pituitary–gonadal axis, particularly GnRH, whose abnormal secretion is associated with clinical conditions involving delayed or absent puberty and reproductive dysfunction.

Abbreviations: 7B2, neuroendocrine protein; ACTH, adrenocorticotropic hormone; ADH, vasopressin or antidiuretic hormone; αGSU, α-glycoprotein subunit; ARK, tyrosine kinase receptor; AVP, arginine vasopressin; BMP, bone morphogenetic protein; BDNF, brain-derived neurotrophic factor; CC2, cell surface glycoprotein; CGRP, calcitonin gene-related peptide; CNS, central nervous system; CRH, corticotropin-releasing hormone; DA, dopamine; DCC, deleted in colorectal cancer-netrin receptor; Eph, ephrin receptor; FGF, fibroblast growth factor; FN, fibronectin; FSH, follicle-stimulating hormone; GH, growth hormone; GDNF, glial cell line-derived neurotrophic factor; GHIH, growth hormone-inhibiting hormone; GHRH, growth hormone-releasing hormone; GnIH, gonadotropin-inhibiting hormone; GnRH, gonadotropin-releasing hormone; HSPG, heparan sulphate proteoglycan; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IL6, interleukin 6; L1, neural cell adhesion molecule; LCG, lactosamine-containing glycans; LH, luteinizing hormone; MEK, MAP kinase ERK; MSH, melanocyte-stimulating hormone; NELF, nasal embryonic luteinizing hormone-releasing hormone factor; NmB, neuromedin B; NmU, neuromedin U; NPY, neuropeptide Y; OCAM, olfactory cell adhesion molecule; OT, oxytocin; PA-CAP, pituitary adenylate cyclase-activating polypeptide; PHDA, periventricular hypophyseal dopaminergic neurons; POMC, pro-opiomelanocortin; PRL, prolactin; PSA-NCAM, polysialyated form of neural cell adhesion molecule; PVN, paraventricular nucleus; Robo, roundabout-slit receptor; SON, supraoptic nucleus; SST, somatostatin; THDA, tuberohypophyseal dopaminergic neurons; TIDA, tuberoinfundibular dopaminergic neurons; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; VEGF, endothelial growth factor; VIP, vasoactive intestinal peptide.

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Introduction

The easiest approach to the adult hypothalamus, which is found in the diencephalon (3rd ventricle), is to subdivide it into four rostrocaudal levels: preoptic, anterior, tuberal, and mammillary; each level involves a lateral, a medial, and a periventricular area.

The anterior area, which forms where the optic chiasm and the supraoptic commissure become clearly distinct, lies caudal to the preoptic area; the tuberal area forms at the level of the median eminence and the infundibulum, and the mammillary region forms caudal to the infundibulum.

It is virtually impossible to address the subject without a brief overview of the scholars and discoveries that have marked its history. Interest in the hypothalamus and the pituitary gland (or hypophysis) dawned in the last two decades of the 19th century. In 1886, Pierre Marie (de Herder, 2009) introduced the term acromegaly and associated it with hyperpituitarism, although he was unaware of their causal relationship. In 1893, Oliver and Schäfer (Welbourn, 1992) first hypothesized that the pituitary gland might have distinctive functions, since parenteral administration of pituitary extracts had a hypertensive effect on the animal. They subsequently found that the treatment also induced several other effects, including uterine wall contraction, milk secretion by mammary glands, and an antidiuretic action.

In 1894, Ramon and Cajal first demonstrated a neural pathway from the SON of the hypothalamus to the posterior pituitary (Sotelo, 2011). But the first researcher to conceive the notion of a neuroendocrine system was Wolfang Bargmann (Bargmann, 1949; Bargmann and Hild, 1949; Bargmann et al., 1950; Watts, 2011), who in 1949 demonstrated that the neurons of the hypothalamic SON and PVN and their axons stained selectively for the Gomori method, which had previously been used to stain colloidal material secreted by endocrine cells. This key finding suggested to Bargmann that those neurons produce neurosecretion, which is transported through their axons to the vessels of the posterior pituitary. In 1955 Vincent du Vigneaud was awarded the Nobel prize for isolating and synthesizing the two neurosecretory peptides, OT and ADH, that are responsible for the hypertensive, antidiuretic, uterine, and mammotropic effects (den Hertog et al., 2001). du Vigneaud also demonstrated that they are secreted by SON and PVN magnocellular neurons (Du Vigneaud, 1954–1955; Iovino et al., 2014).

In the mid 1950s, Guillemin and Rosenberg described the neurohumoral control of the pituitary gland; in the same period (Saffran and Schally, 1955) independently reported that hypothalamus and median eminence extracts contained a factor that induced the release of an ACTH by the pituitary gland. Guillemin and Rosenberg received the Nobel prize for research on the peptide structure of some neurotransmitters and the hypothalamic parvocellular neurons.

The neuroendocrine system

The hypothalamus contains magnocellular and parvocellular neurons. The former cells produce ADH and OT and convey them through their axons to the neurohypophysis, whence they enter the systemic circulation (Figs. 1 and 2).

Parvocellular neurons control a variety of key physiological processes. The parvocellular neuroendocrine system consists of six neuron types that project to the median eminence. They secrete releasing hormones and release-inhibiting hormones into the vessels of the hypophyseal portal system, which connects the hypothalamus to the pituitary gland. These hypophysiotropic hormones control six well-described cell populations in the anterior pituitary, which express their receptors. The production of hypothalamic hypophysiotropic hormones by parvocellular neurons is neurally mediated (Kordon et al., 2005; Zhao et al., 2010). The hormones control the anterior pituitary, which in turn modulates

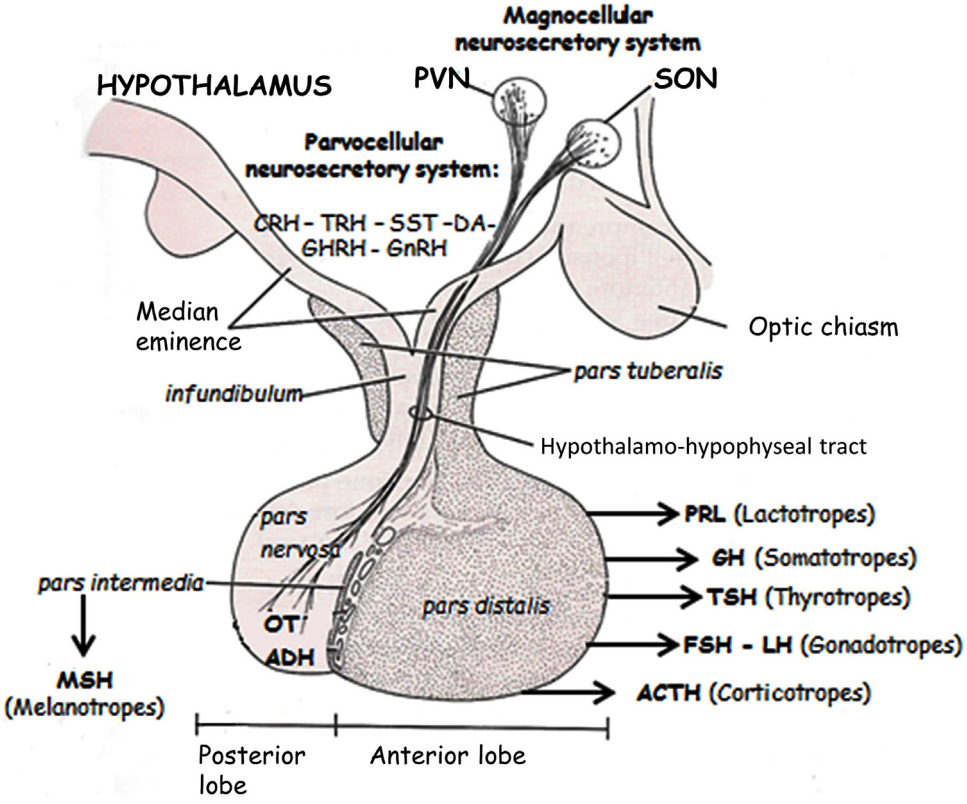

Fig. 1. The hypothalamic–pituitary axis.

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