DEVELOPMENT OF THE PITUITARY GLAND

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Abstract

The pituitary gland develops from the two parts: the glandular primordium (Rathke’s pouch) and the neural primordium (the infundibulum). Rathke’s pouch forms as an invagination of oral epithelium and later develops into the adenohypophysis. The infundibulum originates from the base of the diencephalon and becomes the neurohypophysis. An interplay between both structures is essential for adequate pituitary development. A variety of signaling molecules and genes are involved in the precise regulation of pituitary organogenesis. Developmental anomalies of the sellar region occur as a result of disruption of this rather complex process.

KEYWORDS: development, infundibulum, pituitary disorders, pituitary gland, Rathke’s pouch

INTRODUCTION

The pituitary gland (or hypophysis) is an endocrine structure composed of two sets of tissue which differ both in their origin and anatomy. The neural tissue forms the neurohypophysis, while the glandular part forms the adenohypophysis. The latter can be further subdivided into pars distalis, pars intermedia and pars tuberalis, which all exhibit some peculiarities regarding their developmental origin.

The entire structure is derived from the ectodermal tissue originating from the two sites: the oral epithelium from the roof of the stomodeum (primitive oral cavity) and neuroectoderm from the base of the third ventricle. These two pituitary rudiments grow toward each other to eventually form the single pituitary gland during the week 7 of embryonic development. Interaction between these two rudiments is considered to be a primary driver of pituitary development. Any disturbances in the developmental process might lead to congenital anomalies or tumors, which will be briefly discussed later.

Distinct types of adenohypophysal hormones-secreting cells start to differentiate from the single cell population at month 4 of gestation, influenced by the surrounding mesoderm. The processes of cell proliferation and differentiation are influenced by the sequential expression of homeobox genes, including Hesx1, Lhx3, Lhx4, Prop1, Pit1/2, and Pit1 among others. The cells start to express specific hormone encoding genes ranging from week 9 (GH, FSH/LH, ACTH) to week 13 (TSHB, PRL) of gestation. Mutations in these genes might lead to specific pituitary hormone deficits. For example, mutation in Pit1 results in growth hormone, prolactin, and occasionally TSH deficiency.³ The cells are finally distributed unevenly throughout the gland: basophil cells (corticotrophs, gonadotrophs, and thyrotrophs) are more numerous in anteromedial, while acidophil cells (somatotrophs and mammatrophs) are more present in posterolateral parts of the pituitary. Oppositely, the chromophobe cells (melanotrophs) are scattered equally throughout the gland.

DEVELOPMENT OF THE ADENOHYPOPHYSIS

The formation of the pituitary gland starts at approximately the same time as neurulation (development of the nervous system). Firstly, at day 21 of gestation, the oral epithelium just anterior to the buccopharyngeal membrane becomes thicker, thus forming a placode (Figure 1). At days 25-26, flexure of the anterior end of the neural tube (which later develops into brain) causes placode cells to fold upwards towards the diencephalon.² This invagination of oral epithelium from the roof of the stomodeum towards the diencephalon is known as Rathke’s pouch (Figure 1). At week 5 of gestation, further elongation of Rathke’s pouch will eventually reduce its attachment with the oral epithelium only to form the pharyngohypophyseal stalk. Finally, the stalk regresses sometimes leaving only remnants of tissue in the pharyngeal roof named pharyngeal hypophysis.¹²³ Endocrine cells of the adenohypophysis develop from the cells of the Rathke’s pouch. The pouch has its lumen partially encircled by anterior and posterior wall. The two walls exhibit different developmental fates and thus give rise to distinct parts of the gland. The cells of the anterior wall proliferate and will eventually form both the pars distalis and the pars tuberalis of the adenohypophysis. Contrary to the anterior wall, the cells of the posterior one do not proliferate. Consequently, the posterior wall forms only a thin zone of tissue between the anterior and posterior pituitary lobes (hence it is called pars intermedia). The lumen of the Rathke’s pouch becomes obliterated as cells substantially proliferate; leaving only narrow cleft in the pars intermedia.¹²³

DEVELOPMENT OF THE NEUROHYPOPHYSIS

At day 40 of the embryonic development, the neurohypophysis primordium, or infundibulum, starts to develop as a depression at the floor of the third ventricle. The depression extends towards and posterior to Rathke’s pouch and will
Figure 1. Developmental stages of pituitary development from day 24 to adult stage.


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eventually attach to it (Figure 1). Thus, the infundibulum will finally give rise to all three parts of the neurohypophysis (pars nervosa, infundibular stem and median eminence). During the fourth month, the cells of infundibulum differentiate into the specific type of the neuroglial cells, known as the pituicytes. Axon fibers from the hypothalamic nuclei above the pituitary grow through the infundibular stalk and into the neurohypophysis to form the hypothalamic-hypophysial tract. The latter serves as a pathway through which neurosecretory granules released from the hypothalamus are transported to the pituitary.

**MOLECULAR BASIS OF THE PITUITARY DEVELOPMENT**

Development of the pituitary gland, similarly to other organs, is orchestrated by the spatially and temporally regulated extrinsic signals released from the organizing signaling centers. This includes the ventral diencephalon and the oral epithelium, but also the notochord situated posterior to the developing pituitary. The whole variety of morphogens, including FGF, TGFβ/BMP, SHH, WNT and Notch signaling pathways/molecules are required for adequate pituitary organogenesis. For example, Bmp4 is considered to be an early dorsal signal required for the Rathke’s pouch formation. Furthermore, Wnt4 and Wnt5, in addition to Bmp2 and Bmp, are shown to be implicated in the development of the anterior pituitary. The intensive research on this complex network of signaling pathways promises novel insight into the pituitary development and hormonal deficiencies.

**EMPTY SELLA SYNDROME**

Empty sella syndrome states for the appearance of an empty sella turcica on radiographic images (Figure 2). It is thought to arise from a communication between the sellar diaphragm and the subarachnoid space, which results in leakage of cerebrospinal fluid into the sella. As a consequence, the tissue of the pituitary becomes compressed alongside the walls of the sella. This radiographic finding may appear as a result of surgery, radiotherapy or apoplexy, but also develops without previously known conditions, possibly due to inherent weakness of sellar diaphragm and/or intracranial hypertension. In adults, it is common among obese, multiparous women. The finding is usually asymptomatic in adults but may be associated, especially in children, with endocrine disorders.

**RATHKE’S CLEFT CYST**

Rathke’s cleft cyst is a benign pituitary mass which develops as a result of incomplete obliteration of the lumen of the Rathke’s pouch (Figure 3). These cysts are common in general population. Although often asymptomatic, Rathke’s cleft cysts might occasionally produce symptoms resulting from compression of surrounding structures. The most common include headache, galactorrhea, visual field loss and hypopituitarism. Regarding treatment, the aspiration and partial removal of the cyst are usually performed.

**CRANIOPHARYNGIOMA**

Craniopharyngioma is a rare low-grade tumor occurring both in children and adults (Figure 4). The tumor is considered to arise from the remnants of the craniopharyngeal duct (neck of the Rathke’s pouch) and/or the Rathke’s cleft. It commonly presents with hypotalamic/pituitary deficiencies, visual disturbances and elevated intracranial pressure. The treatment requires surgery and occasionally irradiation, but yields high survival rates.
ECTOPIC PITUITARY, AGENESIS AND DUPLICATION OF PITUITARY

Ectopic posterior pituitary lobe is seen on MRI images as a lack of a “bright spot” in its normal location (i.e. posterior aspect of pituitary fossa), but present at the median eminence or along the pituitary stalk (Figure 5). It is commonly associated with pituitary dwarfism as well as other brain anomalies. It is considered to result from perinatal brain injury principally to infundibular stem, but genetic causes have been implicated as well.\textsuperscript{13,14} Agenesis of the pituitary and duplication of the pituitary are rare conditions commonly present with other brain anomalies.\textsuperscript{13}

References:

Sažetak


**KLJUČNE RIJEČI:** hipofiza, infundibulum, poremećaji hipofize, Ratkeova vreća, razvoj

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