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12

Developmental disorders of the hypothalamus and pituitary gland associated with congenital hypopituitarism

Ameeta Mehta MBBS, DCH, MD, DNBE, MRCP, MSC, MD
Clinical Research Fellow, Developmental Endocrinology Research Group
Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

Mehul T. Dattani* MBBS, DCH, FRCPCH, FRCP, MD
Professor and Consultant in Paediatric Endocrinology, Developmental Endocrinology Research Group
Paediatric Endocrinology, Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

The pituitary gland is a complex organ secreting six hormones from five different cell types. It is the end product of a carefully orchestrated pattern of expression of signalling molecules and transcription factors. Naturally occurring and transgenic murine models have demonstrated a role for many of these molecules in the aetiology of congenital hypopituitarism. These include the transcription factors *HESX1*, *PROP1*, *POU1F1*, *LHX3*, *LHX4*, *PITX1*, *PITX2*, *SOX2* and *SOX3*. The expression pattern of these transcription factors dictates the phenotype that results when the gene encoding the relevant transcription factor is mutated. The highly variable phenotype may consist of isolated hypopituitarism or more complex disorders such as septo-optic dysplasia and holoprosencephaly. However, the overall incidence of mutations in known transcription factors in patients with hypopituitarism is low, indicating that many genes remain to be identified; characterization of these will further elucidate the pathogenesis of this complex condition and also shed light on normal pituitary development and function.

Key words: pituitary; septo-optic dysplasia; isolated GHD; combined pituitary hormone deficiency; transcription factors.

* Corresponding author. Tel.: +44 20 79052657; Fax: +44 20 74046191.
E-mail address: mdattani@ich.ucl.ac.uk (M.T. Dattani).

The adult pituitary gland consists of the adenohypophysis (anterior and intermediate lobes) and neurohypophysis (posterior lobe). The anterior pituitary consists of five different cell types secreting six hormones: growth hormone (GH) secreted by somatotrophs, prolactin secreted by lactotrophs, thyrotrophin (TSH) secreted by thyrotrophs, gonadotrophins (follicle-stimulating hormone, FSH, and luteinizing hormone, LH) secreted by gonadotrophs, and adrenocorticotrophin (ACTH) secreted by corticotrophs. The intermediate lobe secretes pro-opiomelanocortin (POMC), which is a precursor to melanocyte-stimulating hormone (MSH) and endorphins, and involutes in the adult. The posterior lobe secretes arginine vasopressin (AVP) and oxytocin. The hypothalamus secretes stimulatory and inhibitory hormones and is critical for normal pituitary gland function. Hormones secreted by the posterior lobe of the pituitary gland are synthesized in magnocellular neurones of the paraventricular and supraoptic nuclei within the hypothalamus. The hormones secreted from the anterior pituitary regulate growth, puberty, metabolism, response to stress, reproduction, and lactation, while those from the posterior pituitary are required during parturition and lactation, and regulate water balance. The infundibulum or pituitary stalk carries both the portal blood delivering hypothalamic hormones to the anterior pituitary and neural tracts from the hypothalamic nuclei to the posterior pituitary.

EMBRYOLOGY OF THE PITUITARY GLAND

Pituitary development is similar in all vertebrates, and human pituitary development would appear to mirror that of the rodent. The anterior and intermediate lobes of the pituitary gland are derived from oral ectoderm, while the posterior pituitary is derived from neural ectoderm.[1,2] The development of the pituitary gland in the rodent occurs in four distinct stages (Figure 1).

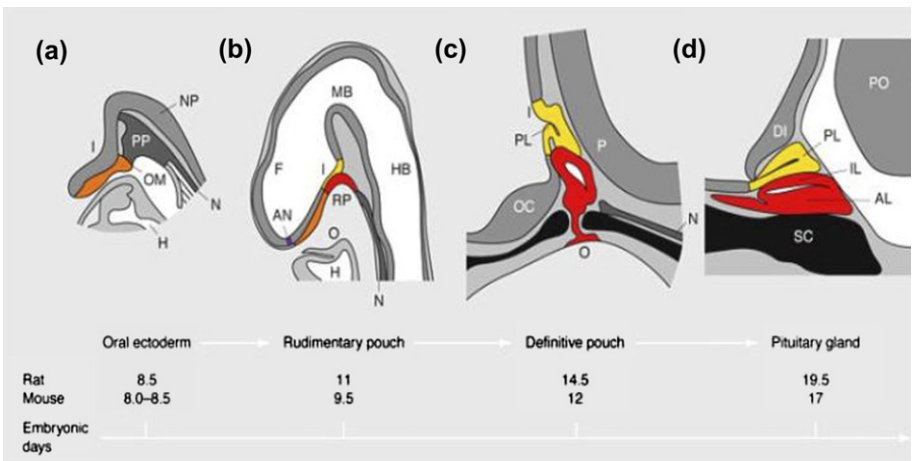

Figure 1. Stages of rodent pituitary development. (a) Oral ectoderm. (b) Rudimentary pouch. (c) Definitive pouch. (d) Adult pituitary gland. I, infundibulum; NP, neural plate; N, notochord; PP, pituitary placode; OM, oral membrane; H, heart; F, forebrain; MB, midbrain; HB, hindbrain; RP, Rathke's pouch; AN, anterior neural pore; O, oral cavity; PL, posterior lobe; OC, optic chiasm; P, pontine flexure; PO, pons; IL, intermediate lobe; AL, anterior lobe; DI, diencephalon; SC, sphenoid cartilage. From Sheng and Westphal (1999 *Trends in Genetics* 15: 236–240) with permission.