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Functional maturation of growth hormone cells in the anterior pituitary gland of the fetus

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Abstract

Recent studies have disclosed the molecular mechanisms responsible for the phenotype determination of the anterior pituitary cell types. However, as far as growth hormone (GH) cells are concerned, particular extra-cellular cues are required for the initiation of GH and GH-releasing hormone (GHRH)-receptor gene production in addition to the expression of the cell type specific transcription factor, pit-1. The glucocorticoids play a principal role in the functional maturation of nascent GH cells in the fetal pituitary glands in rodents, inducing GH and GHRH-receptor gene expression, and establish the GH secretory system regulated by the brain in late gestation. Research supporting this role for glucocorticoid in the development of GH cells is discussed.

Keywords: Growth hormone; Growth hormone-releasing hormone receptor; Fetus; Glucocorticoids; Pituitary gland

1. Introduction

Growth hormone (GH) is secreted from the anterior pituitary gland, and plays principal roles not only in longitudinal bone growth at the pubertal growth spurt, but also in the regulation of carbohydrate and lipid metabolism throughout life. While GH is produced in the extra-pituitary tissues including the immune system [1] and central nervous systems [2,3], the serum GH level is regulated by the anterior pituitary gland, and a deficiency in pituitary GH results in severe growth retardation [4]. GH-producing cells in the anterior pituitary gland develop on embryonic day 19 (E19) in rats [5–7], and accordingly, GH secretion starts before birth [8]. The expression of the GH-releasing hormone (GHRH)-receptor, another GH cell-specific gene, also occurs on E19 [9,10]. These data suggest that the functional maturation of GH cells in rats is achieved by E19. On the other hand, the onset of pit-1 [11] (also termed GHF-1 [12], or PUF-1 [13]), a pituitary specific transcription factor that is a prerequisite for GH gene transcription, occurs on E15 [14]. Thus, several days are required for the functional maturation of nascent GH cells after the onset of pit-1 expression. Little is known about the changes in the cellular function that occur in GH cells during these four days. We will discuss here the ontogeny of GH cells in the fetal pituitary gland, the factors that trigger the activation of GH cell-specific gene expression, such as the GH and GHRH-receptor genes in nascent GH cells.

2. Differentiation of the anterior pituitary cells

The mechanisms responsible for the phenotype determination of the anterior pituitary cells have been proposed by Rosenfeld and his co-workers [15,16]. Organogenesis of the pituitary gland starts with the

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invagination of oral ectoderm to form Rathke's pouch. The cells that compose Rathke's pouch are the progenitors of anterior pituitary cells. The dorsoventral gradient of the concentration of FGF 8 produced by the ventral diencephalon and the opposing gradient of BMP2 emanates from the ventral pituitary organizing center results in the overlapping expression patterns of specific transcription factors, the dorsal pit-1 and the ventral GATA2. Pit-1-expressing cells differentiate into GH cells, some of which are believed to differentiate into prolactin (PRL) cells. The mechanisms for PRL cell differentiation have not yet been elucidated. The cells expressing GATA2 differentiate into gonadotropic hormone (GTH) cells that secrete both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The cells expressing both GATA2 and pit-1 differentiate into thyroid-stimulating hormone (TSH) cells. Adrenocorticotropic hormone (ACTH) cells belong to neither of the cell lineages that express pit-1 or GATA2, and are considered to be specified by the expression of T-pit [17,18].

3. Ontogeny of GH cells in embryonic pituitary gland

Early immunohistochemical studies [6,7] have revealed that the ACTH cells are those that appear first in the developing anterior pituitary gland in the rat fetus. ACTH cells are detected first on embryonic day 15 (E15) in rats, followed by TSH cells on E16. The LH cells appear on E17 and FSH cells develop on E19. PRL cells have been reported to appear only after birth. A small number of GH cells were detectable in the anterior pituitary gland as early as E18 in rats, and they had increased remarkably in number by E19 (Fig. 1). The GH cell number showed a moderate increase by E20 but showed no marked increase thereafter. The age at which each pituitary cell type is first detectable differs to a certain extent among investigations, probably due to the sensitivity of the immunohistochemistry utilized [19,20]. However, the sequential order of the differentiation of pituitary cells is consistent. Using in situ hybridization, The GH mRNA has not been detected on E18 or earlier in rats, but a number of GH mRNA positive cells have been detected on E19 [21] (Fig. 1). By reverse hemolytic plaque assay, Frawley et al. [22] revealed that cells that secrete GH comprised less than 1% of pituitary cells at E18, but increased to 13.6% and 22.4% in cultures of E19 and E20, respectively. GH is detectable in the fetal circulation by radioimmunoassay as early as E19 [8].

In mice, GH cells are scarce until E15, increasing rapidly on E16 [23]. The number of GH cells increases sharply between E14 and E16 in chicken pituitary gland [24,25]. Thus, the rapid increase in the number of GH cells in the developing pituitary gland is seen in several

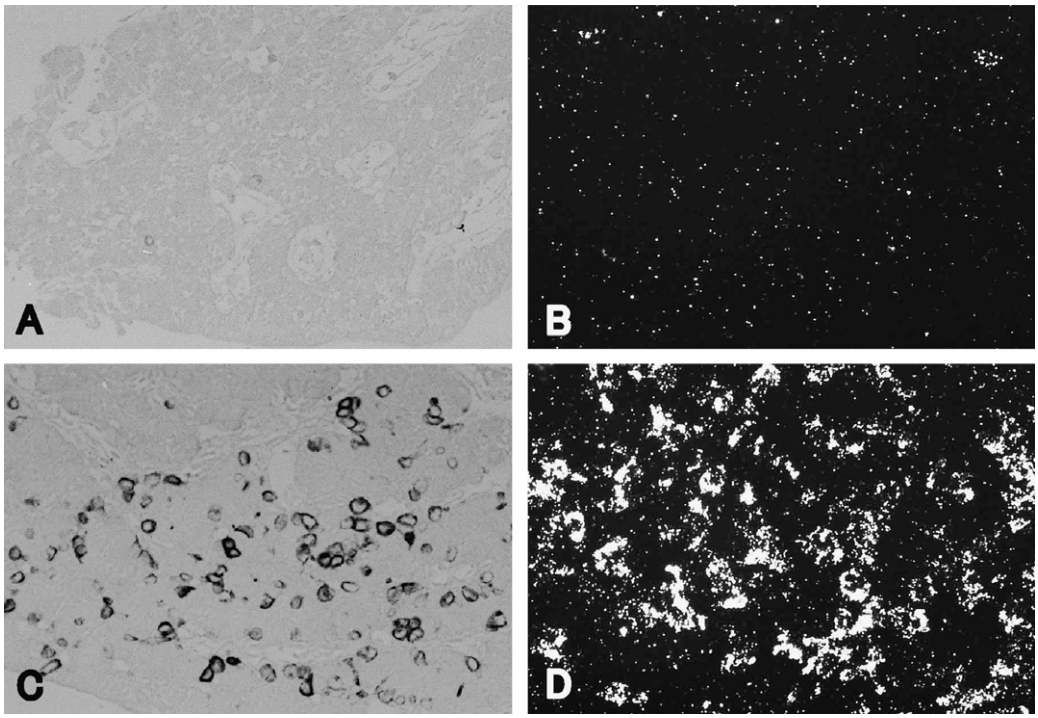

Fig. 1. Immunocytochemical staining for GH (A and C) and in situ hybridization for GH mRNA (B and D) of fetal rat pituitaries on E18 (A and B) or E19 (C and D). Only a few GH or GH mRNA positive cells are encountered in the E18 pituitary gland, but they rapidly increase in number by E19.