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Regulation of pituitary somatotroph differentiation by hormones of peripheral endocrine glands

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Abstract

Anterior pituitary somatotroph differentiation occurs during chick embryonic and rat fetal development. A number of findings support the hypothesis that differentiation of these growth hormone (GH) producing cells in the chick and the rat is regulated by adrenal glucocorticoids and thyroid hormones. Somatotroph differentiation can be induced in cultures of chick embryonic and rat fetal pituitary cells with adrenal glucocorticoids and this effect can be modulated by concomitant treatment with thyroid hormones. Plasma levels of thyroid hormones, corticosterone and adrenocorticotropic hormone increase during development, consistent with the ontogeny of somatotrophs. Treatment of chick embryos or rat fetuses with glucocorticoids in vivo induces premature somatotroph differentiation, indicating that the adrenal gland, and ultimately anterior pituitary corticotrophs, may function to regulate pituitary GH cell differentiation during development. Administration of thyroid hormones in vivo also increases somatotrophs prematurely, and administration of the thyroid hormone synthesis inhibitor methimazole inhibits somatotroph differentiation in vivo, suggesting that endogenous thyroid hormone synthesis contributes to normal somatotroph differentiation. Our working model for the regulation of somatotroph differentiation during normal development includes modulation by elements of the hypothalamo–pituitary–adrenal and hypothalamo–pituitary–thyroid axes. Additional research is reviewed defining the mechanism of action for these peripheral hormones in induction of pituitary GH gene expression during development.

Keywords: Adenohypophysis; Embryo; Fetal; Somatotropin; Glucocorticoid; Thyroid; Chicken; Rat

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1. Introduction

Five major cell types comprise the anterior pituitary gland. Each cell type possesses a distinctive function, and somatotrophs are one of the more abundant cell types within the pituitary. Their function is the secretion of growth hormone (GH). This review summarizes evidence that hormones of peripheral endocrine glands regulate differentiation of somatotrophs during chick embryonic and rat fetal development. A working model linking the actions of peripheral hormones with initiation of GH gene expression is presented.

2. Somatotroph ontogeny and regulation

Somatotrophs differentiate during the last half of chick embryonic and rat fetal development. In the rat, GH cells differentiate around day 18 or 19 of fetal development [1,2]. In the chick, the abundance of GH cells increases dramatically between embryonic day (e) 12 and e16 [3]. Somatotrophs are rare on e12 and earlier, although immunoreactive GH has been reported shortly after the formation of the pituitary gland on e4.5 [4]. Parallel to somatotroph abundance, serum GH levels become detectable after e16 [5]. Nearly all somatotrophs respond to GH releasing hormone (GHRH), somatostatin and insulin-like growth factor-I on e16 [3,6,7], but responsiveness to the other major GH regulating hormone in the chicken, thyrotropin-releasing hormone, is delayed toward the end of embryonic development [6,8].

The process of somatotroph differentiation likely involves a number of intracellular and extracellular signals [9–11]. In the chick, somatotrophs reside in the caudal lobe of the anterior pituitary gland [12,13], indicating that local morphogenic signals restrict the differentiation and/or migration of the somatotroph precursor population. Evidence from mammals clearly shows an absolute requirement for the pituitary-specific transcription factor Pit-1 in GH gene expression [14–17]. Expression of Pit-1 induces transcription of the GH gene in birds [18]. However, Pit-1 is expressed days before GH [19], indicating that factors other than Pit-1 are involved in the initiation of GH gene expression during development. Furthermore, GH cells fail to differentiate spontaneously among chick embryonic pituitary cells or within rat fetal pituitary glands isolated prior to somatotroph differentiation [20–23], indicating a requirement for an extrapituitary signal or factor in induction of GH gene expression.

3. Serum GH cell differentiating activity

At least one of the extracellular/extrapituitary signals regulating somatotroph differentiation may circulate in the blood. Chick embryonic pituitary cells isolated from e10 to e16 will not differentiate spontaneously into GH-producing cells in serum-free medium [20]. Interestingly, addition of embryonic serum to the cultured cells increases the abundance of GH-secreting cells in the cultures, and the capacity of embryonic serum to induce GH cells in vitro follows a similar pattern during development as the ontogeny of somatotrophs. Treatment of e12 pituitary cells with serum from e16 increased the number of GH-secreting cells more than 10-fold, from less than 1% to greater than 12% of all pituitary cells in