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DEVELOPMENT OF PITUITARY ACTH AND GH CELLS IN NEAR TERM RAT FETUSES

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Abstract – This study describes the development of ACTH and GH cells in 19- and 21-day-old rat fetuses using immunohistochemistry and morphometric measurements. Between days 19 and 21 of pregnancy, the total volume of fetal ACTH cells was unchanged, while their volume density and number per unit of area decreased significantly. ACTH-like immunopositivity in the pars intermedia increased during the examined period. The cell volume, volume density and number of GH cells per unit of area all markedly increased in parallel with fetal development, i.e., from gestational days 19 to 21. GH-like immunopositivity is demonstrated in the pars intermedia of 21-day-old fetuses for the first time.

Key words: ACTH cells, GH cells, fetuses, rat

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INTRODUCTION

The epithelial component of the pituitary gland, the adenohypophysis, is organized in a glandular pattern. During fetal development, an oral pouch is formed from an upward evagination from the epithelium of the primary oral cavity known as Rathke's pouch. This pouch grows disproportionally and develops into the adenohypophysis which consists of a pars tuberalis, pars distalis, and pars intermedia (P a g e, 1994). The neurohypophysis or neural portion of the pituitary is derived from the neural ectoderm associated with third-ventricle development. Neuroepithelial cells lining the third ventricle floor mature into magnocellular and parvicellular neurons whose axon tracts terminate in the pars neuralis. The neurohypophysis includes the infundibular stalk and median eminence besides the pars neuralis (P a g e, 1994; S a v a g e et al., 2003).

The pars intermedia originates from the part of Rathke's pouch which is in contact with the developing pars neuralis. The posterior part of Rathke's pouch closes and makes intimate contact with the primordium of the pars neuralis generating the primordium of the pars intermedia on the 13th day of fetal development. The pars intermedia remains as a thin band of glandular tissue separated from the expanded pars distalis by the residual lumen. On day 16 of fetal development, the developing pars intermedia consists of 2-3 rows of tall, cylindrical cells with well-demarcated cell borders (S v a l a n d e r, 1974). The epithelium here grows slowly and the cells retain their cylindrical shape. The characteristic histology, synthetic activity and physiological control of the pars intermedia remain throughout the life span (L u g o and P i n t a r, 1996).

In rats, the earliest detectable cells with adrenocorticotrophic hormone (ACTH) appear in the pars tuberalis *anlage* on day 13 of fetal development. One day later, ACTH immunoreactivity is displayed in the pars distalis. The pars intermedia is the last area where ACTH immunostaining was observed (N e m e s k e r i et al., 1988). Initial pituitary growth hormone (GH) expression was detected on day 15 of gestation using a sensitive method, namely, the reverse transcriptase-polymerase chain reaction (RT-PCR) (R o d r i g u e z - G a r c i a et al., 1995). The quantity of GH transcripts remains at an extremely low level in the following phase of GH cell development. However, a marked increase in GH production and immunopositivity occurs between days 18 and

19 of fetal development (T a n i g u c h i et al., 2001).

The aim of this study was to illustrate the development of pituitary ACTH and GH cells in near term, i.e., 19- and 21-day-old, rat fetuses using immunohistochemical and morphometrical methods. Also, we monitored ACTH and GH-like immunopositivity in the developing pars intermedia.

MATERIAL AND METHODS

Experimental design

Adult virgin Wistar female rats weighing approximately 250 g were housed in groups (three rats per cage) in the presence of a sexually-experienced male rat weighing 400 g for one night (24 h or less). The day when females were sperm-positive was designated gestational day 1. Pregnant rats were individually housed in plastic breeding cages, allowed *ad libitum* access to food and water, and maintained on a 12:12 light/dark cycle at constant room temperature. On days 19 and 21 of pregnancy, the dams and their fetuses were sacrificed under ether anesthesia, the fetuses being referred to as 19- and 21-day-old fetuses.

Light microscopy and immunohistochemistry

The pituitary glands were excised with part of the sphenoid bone, fixed in Bouin's solution for 48 h, and embedded in paraffin. Pituitary hormones were localized immunohistochemically using the peroxidase-anti-peroxidase complex (PAP) method of S t e r n b e r g e r et al. (1970). Specific rabbit anti-human ACTH antibodies (Dako, Glostrup, Denmark) and rabbit anti-human GH antibodies, (Dako, Glostrup, Denmark) in the dilution appropriate for 24 h at room temperature (1:300) were employed. Antibody localization was visualized by immersing the sections in Tris-HCl-buffered saline (0.5 mol/l; pH 7.4) supplemented with 3, 3-diaminobenzidine tetrachloride (DAB; Serva, Heidelberg, Germany).

Morphometry

Volume densities (Vv) of nuclei and cytoplasm of ACTH and GH-immunopositive cells, as well as the numerical density (Na) of their nuclei per μm^3, were measured in 50 test areas per pituitary gland at a magnification of X1000 using the M_{42} multipurpose test system (W e i b e l, 1979).

The number of nuclei of immunostained ACTH and GH cells per mm^3 was estimated according to W e i b e l (1979). Since rat ACTH and GH cells are mononuclear, the numerical density of nuclei (Nv) corresponded to the number of cells per cubic millimeter in accordance with the formula:

$$Nv = (k/\beta) \times (Na^{3/2}/Vv^{1/2})$$

On the basis of earlier karyometric studies (M a l e n d o w i c z, 1974), the shape coefficient β for pituitary cells was estimated to be 1.382. It relates Nv (number of cells counted per unit of volume) to Na (number of cells counted per square millimeter) and Vv (volume density) and depends on the axial ratio of nuclei. The volume density of ACTH and GH cells was expressed as the percentage of total pituitary cell volume in μm^3.

Digital images were made on a Leica DM RB Photo Microscope (Leica, Wetzlar, Germany) with a JVC TK 1280E Video Camera (Leica) using the Qwin program (Leica) for acquisition and analysis of images.

Statistical analysis

All results are expressed as means for eight to 10 animals per group ± standard deviation (SD). Data were tested for normality of distribution by the Kolmogorov-Smirnov test, whereas the homogeneity of variances was evaluated by the F-test. Student's t test was used to compare mean values. The minimum level of statistical significance was set at $p < 0.05$.

RESULTS

Histological analysis of ACTH and GH cells in 19- and 21-day-old fetuses

Frontal sections of the pituitary gland of 19-day-old fetuses showed completely differentiated pars distalis and pars intermedia of the adenohyphophysis and pars neuralis of the neurohypophyisis. The adenohypophyseal pars distalis had a dense network of capillaries and was composed of cells arranged in follicular structures with rounded or polygonal cells in between forming cords or trabecular structures in places. The marginal cell layer surrounding the residual lumen had an epithelial structure. The pars intermedia was several cell layers thick (Fig. 1A).

Numerous ACTH cells were present in all regions of the pars distalis in both examined groups of near term fetuses. They were positioned as single cells among

parenchymal cells of the pars distalis and around the capillary network or organized in groups. Immunocytochemically labeled ACTH cells had different shapes, polygonal or with cytoplasmic processes, and rounded eccentric nuclei. Immunopositivity was intensive and diffusely distributed throughout the cytoplasm. In 21-day-old fetuses, ACTH cells were less numerous than in 19-day-old fetuses (Figs. 1B and 1D). Adenocorticotrophic hormone immunopositivity was detected in the pars intermedia of 19-day-old fetuses, being localized in single cells or small groups of cells. A significant increase of ACTH-like immunostaining occurred during the next 48 h, i.e., in 21-day-old rat fetuses ACTH immunopositive cells were more numerous and grouped together forming clusters which protruded into the neural lobe (Figs. 1C and 1E).

Growth hormone cells of the pars distalis were scattered throughout it in both fetal groups. Immunopositive cells were usually rounded or ellipsoid. In 19-day-old fetuses the number of GH cells was modest. The intensity of staining varied between cells: numerous GH cells were weakly immunoreactive, while only a few GH cells showed intense immunostaining (Fig. 2A). An apparent increase in fetal GH cell number and size was seen in near term fetuses from day 19 to day 21 of pregnancy. In

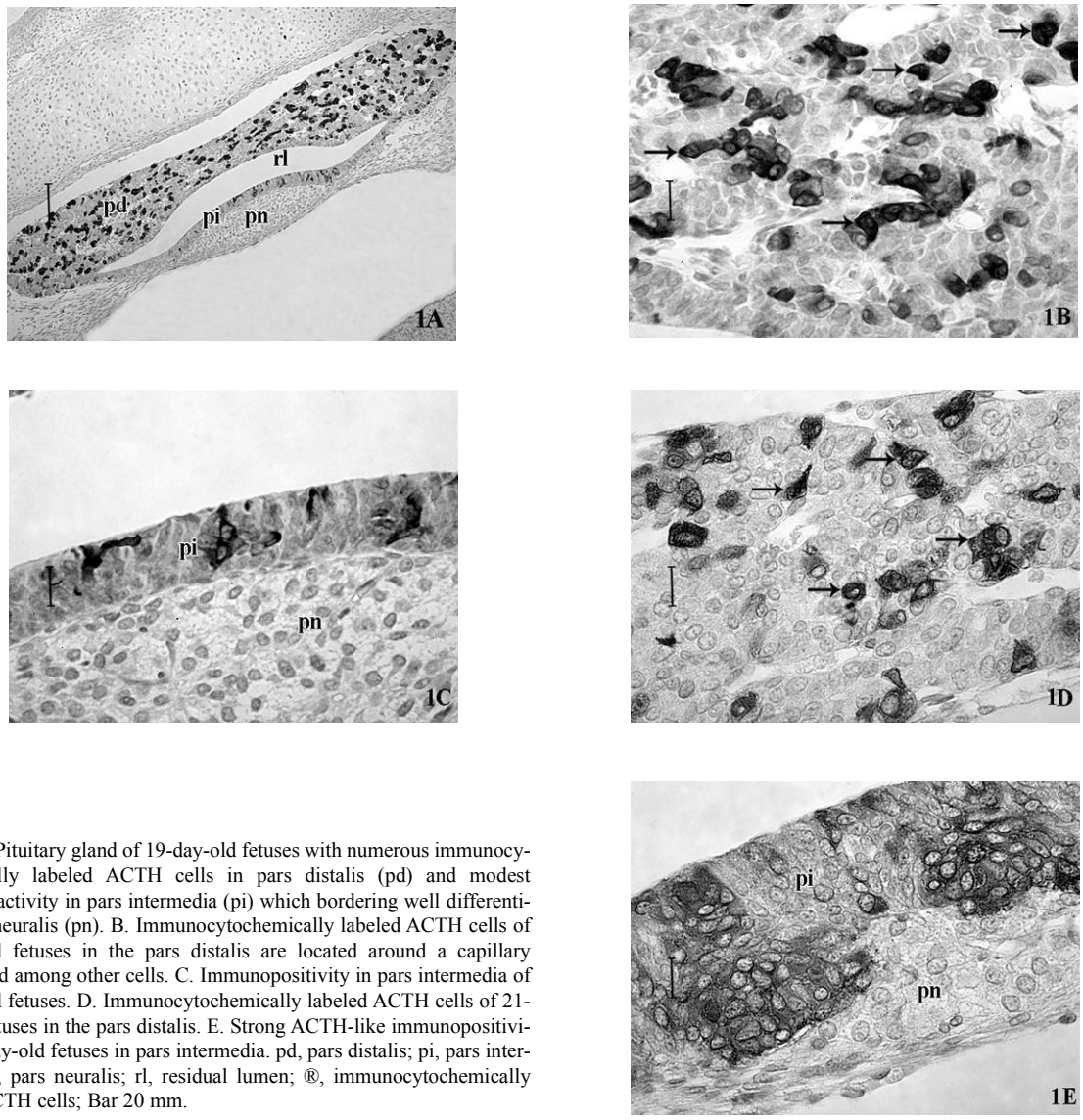

Fig. 1. A. Pituitary gland of 19-day-old fetuses with numerous immunocytochemically labeled ACTH cells in pars distalis (pd) and modest immunoreactivity in pars intermedia (pi) which bordering well differentiated pars neuralis (pn). B. Immunocytochemically labeled ACTH cells of 19-day-old fetuses in the pars distalis are located around a capillary (arrow) and among other cells. C. Immunopositivity in pars intermedia of 19-day-old fetuses. D. Immunocytochemically labeled ACTH cells of 21-day-old fetuses in the pars distalis. E. Strong ACTH-like immunopositivity in 21-day-old fetuses in pars intermedia. pd, pars distalis; pi, pars intermedia; pn, pars neuralis; rl, residual lumen; ®, immunocytochemically labeled ACTH cells; Bar 20 mm.

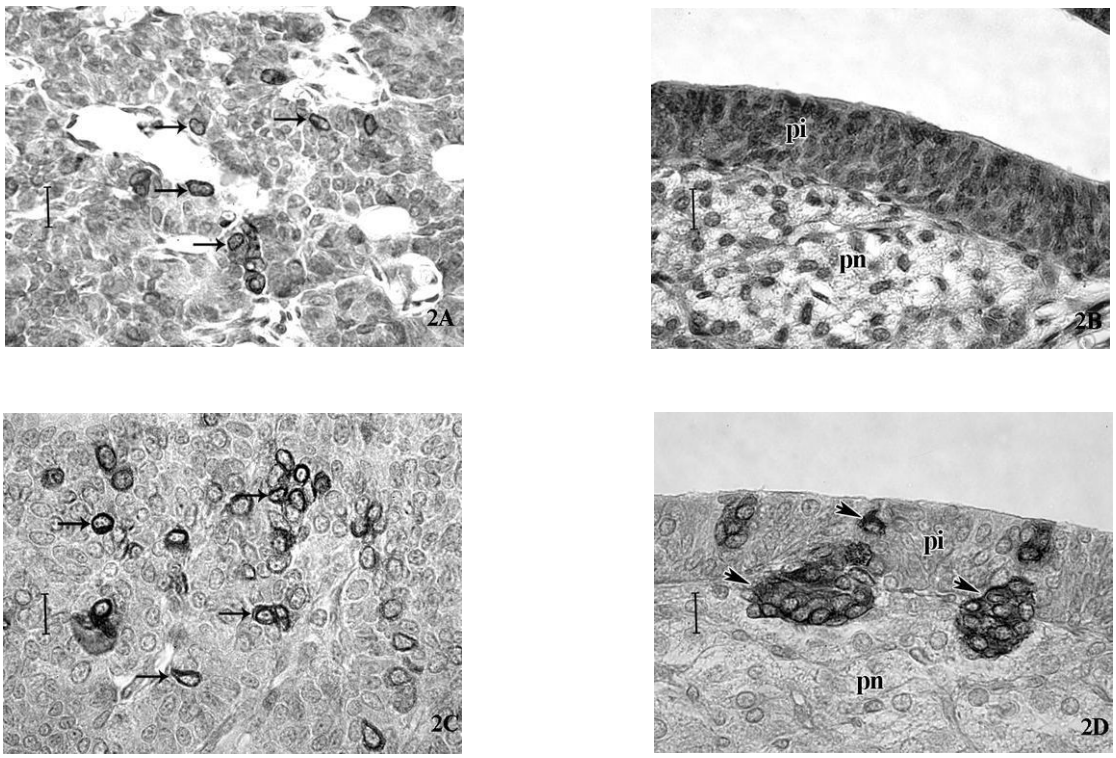

Fig. 2. A. A small number of GH cells of 19-day-old fetuses in the pars distalis with a little amount of citoplasmic immunopositivity. B. Pars intermedia of 19-day-old fetuses is with no immunopositive labeling. C. Numerous GH cells with strong immunoreactivity are characteristic for pituitary gland in 21-day-old fetuses. D. In pars intermedia of 21-day-old fetuses GH-like immunopositivity is present. pi, pars intermedia; pn, pars neuralis; ®, immunocytochemically labeled GH cells; Bar 20 mm.

21-day-old fetuses, GH cells became well differentiated with the characteristic cytoplasmatic ring-shaped area around the nuclei. The intensity of GH cell immunostaining increased notably throughout the duration of the examined period (Fig. 2C). In 21-day-old fetuses, GH-like immunopositivity was uniformly distributed throughout the cytoplasm in some cells of the pars intermedia that formed clusters, positioned beside unlabeled cells (Fig. 2D). There was no GH-like immunopositivity in 19-day-old fetuses (Fig. 2B).

Morphometric parameters

Morphometric parameters such as volume density and the number of ACTH cells per unit of area signifi-

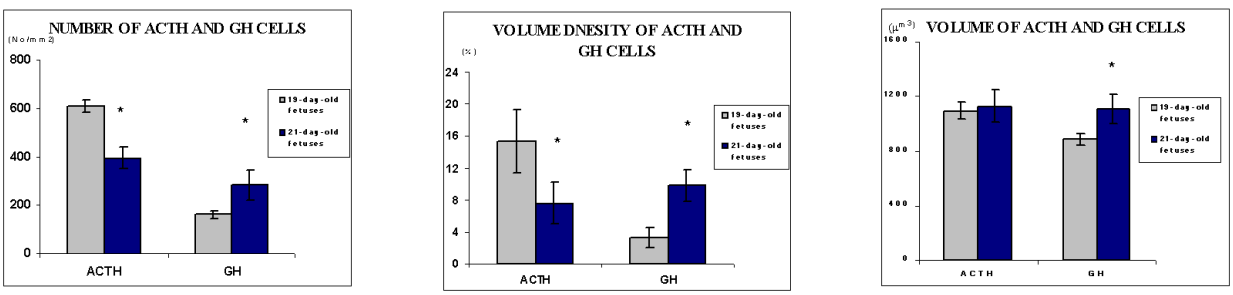

Fig. 3. Morphometric parameters of 19- and 21-day-old fetal ACTH and GH cells. A. Volume of ACTH and GH cells. B. Volume density of ACTH and GH cells. C. Number of ACTH and GH cells per unit area. Results are presented as means ± S.D. (n = 8); *, p <0.05 *vs.* 19-day-old.

cantly declined from 51% to 35% between days 19 and 21 of fetal development. There were no significant changes in the volume of fetal ACTH cells during the examined period (Fig. 3).

Growth hormone cell volume, volume density, and the number of GH cells per unit of area markedly increased in parallel with fetal development, i.e., from gestational days 19 to 21 (Fig. 3).

DISCUSSION

The results presented in this study demonstrate that in 19- and 21-day-old rat fetuses strong immunoreactivity is characteristic of ACTH cells in the pars distalis, while a significant increase of ACTH-like immunostaining was noticed in the pars intermedia during the examined time period. The size of fetal ACTH cells did not change, while their volume density and number per unit of area significantly decreased from day 19 to day 21 of pregnancy. On the other hand, GH cells started to appear in 19-day rat fetuses. During the next 48 h, the intensity of GH cell immunostaining was augmented, while GH cell volume, GH cell volume density, and the number of GH cells significantly increased. Thus, GH-like immunoreactivity is demonstrated in the pars intermedia of 21-day-old fetuses for the first time.

In adult rats specific topographic affinities between ACTH and GH cells make possible paracrine interaction, which has a great influence on the functions of both types of hormone-producing cells (N o d a et al., 2003). Even during fetal development, an indirect functional relationship commences between ACTH and GH cells. As the first differentiated hormone-producing cells in the pituitary, ACTH cells stimulate adrenal glucocorticoid production, which exerts a positive influence on GH cell appearance and development.

Recent results demonstrate that ACTH cells in near term fetuses are highly differentiated hormone producing cells. The histological analysis in this study showed that strong ACTH immunoreactivity is indicated by the presence of numerous immunopositive secreatary granules in the cytoplasm, reflecting high synthetic activity and significant storage capacity of these cells. Values for plasma ACTH concentration obtained in an earlier study demonstrated that intensive ACTH synthesis and release occur in near term fetuses and continue during the neonatal period (K a l a f a t i ć et al., 2000). Our present results show that the number of ACTH cells expressed per volume and area unit markedly declined between fetal days 19 to 21, this increase occuring as a consequence of rapid pituitary growth and intensive differentiation of other hormone-producing cells before birth. Adrenocorticotropic hormone cells are the first immunopositive cells to appear in ontogenesis of the pituitary gland. The later differentiation of thyrotrophs, gonadotrophs, somatotrophs, and finally lactotrophs, and their intensive multiplication (N e m e s k e r i et al., 1988), then lead to a decrease of ACTH volume density and number per mm^2, although their number expressed per pituitary gland increases during this period (T a n i g u c h i et al., 2000).

Analyzing the histological picture of ACTH immunopositivity in 19-day-old fetuses, we can conclude that the pars distalis contains numerous well differentiated immunopositive ACTH cells, whereas ACTH-like immunopositivity is weakly expressed in the pars intermedia. Although immunopositivity rose significantly during the next 48 h, it did not reach the adult level, with characteristic strong ACTH-like immunopositivity throughout the whole pars intermedia. Inasmuch as CRH receptors are less abundant in cells of the pars intermedia than in ACTH-producing cells of the pars distalis (V a l e et al., 1983), a decline of CRH stimulatory effects on proopiomelanocortin (POMC)-derived peptide synthesis and secretion can explain why the pars intermedia is the last pituitary part where ACTH-like immunopositivity appears. Also, it has been established that a 10-fold higher CRH concentration is needed to stimulate secretion of POMC-derived peptides from the pars intermedia compared to ACTH cells in the pars distalis (L u g o a n d P i n t a r, 1996).

Initiation of ACTH synthesis occurs on day 13 of fetal development (N e m e s k e r i et al., 1988), and by day 19 ACTH cells have become highly functional and able to operate in a regulated manner. On day 19 of fetal development, maximal plasma ACTH concentration (C h a t e l a i n a n d C h e o n g, 1986), the most rapid proliferation of ACTH cells (T a n i g u c h i et al., 2001), and their greatest volume and highest numerical density were demonstrated. These results, obtained by different approaches, confirmed that day 19 of fetal development represents a time of very intensive ACTH trophic support for steroidogenic maturation of the fetal adrenal gland cortex. As the main trophic factor, ACTH stimulates proliferation and growth of fetal adrenocortical cells and glucocorticoid production (W o t u s et al.,

1998). Secreted glucocorticoids make possible active homeostasic regulation in near term fetuses and negative feedback control of ACTH secretion in response to different maternal stressors (Reichardt and Schutz, 1996). Furthermore, due to glucocorticoid influence metabolic, cardiovascular, and immune adaptations take place near term, enabling birth-related stress to be overcome and promoting successful postnatal adaptation of the newborn to environmental challenges (Ducsay, 1998). In addition, glucocorticoids are indispensable for proper differentiation, expansion, and functioning of certain pituitary cell lineages, especially GH cells (Nogami et al., 1995).

Indeed, the time of the GH cell onset overlaps with the glucocorticoid rise in circulation (Wotus et al., 1998) and with the initial expression of glucocorticoid receptors (GR) in these cells on day 19 of fetal development (Nogami et al., 1999). Our results demonstrated moderate immunopositivity and scarcity of GH cells in 19-day-old fetuses, indicating that the synthetic activity of GH cells was weak. The significant increase of GH cell immunopositivity, size, and number per volume and unit of area indicated that synthetic activity, storage, and proliferation rose markedly during the next 48 h. This corresponded with a further increase of plasma corticosterone concentration in near term rat fetuses (Hristić et al., 1997). Under the influence of circulating glucocorticoids, GH production started in undifferentiated cells and was maintained (Nogami et al., 1989). Glucocorticoids strongly enhance GH gene expression, resulting in increased GHmRNA levels (Sato and Watanabe, 1998; Nogami et al., 1995). In addition, hypothalamic GH-releasing hormone (GHRH) had a stimulatory effect on GH cell activity and proliferation. Moreover, glucocorticoids induced GHRH receptor mRNA expression and accumulation in GH cells of the fetal rat pituitary gland, amplifying the stimulatory influence of GHRH (Nogami et al., 1999).

There are two routes that lead to an increase in the number of GH cells during fetal development. Firstly, the appearance of GH mRNA in immature cells that do not yet produce any hormones contributes to increase of GH cell number and volume density (Porter et al., 2001). Secondly, intensive proliferation of existing GH cells leads to increased numbers throughout the period studied and enables GH cells to become the predominant cells in the pituitary during the neonatal period (Nogami et al., 1989).

This is the first report indicating GH-like immunopositivity in the pars intermedia of 21-day-old rat fetuses, and it is difficult to explain. On the basis of the study presented here, it could be proposed that cells in the pars intermedia with GH-like immunoreactivity possess GH molecules identical to those in GH cells of the pars distalis. The second possibility is that proteins with similar amino-acid fragments, complementary with the specific antibodies used in this study, provided for positive immunoreactions in some cells of the pars intermedia. It has been shown that proteins with GH-like immunoreactivity are also present in many extrapituitary tissues, indicating translation of GH transcripts in neural, reproductive, and lymphoid tissues (Harvey et al., 2000). Different experimental approaches will have to be used to confirm or reject the presence of GH or GH-like molecules in the pars intermedia during fetal development.

On the basis of the immunopositivity, size, and number of ACTH cells in 19- and 21-day-old rat fetuses, it can be concluded that they represent differentiated and active hormone producing pituitary cells before delivery. On the contrary, GH cells made their appearance in 19-day-old fetuses, and increase of their immunopositivity and morphometric features was established in 21-day-old fetuses, indicating that they became functional hormone producing cells during the examined time. It can be concluded that early ACTH cell differentiation, timely activation of fetal glucocorticoid synthesis, and GH cell appearance and development were probably mutually dependent and connected processes.

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РАЗВОЈ ACTH И GH ЋЕЛИЈА ХИПОФИЗЕ ФЕТУСА ПАЦОВА ПРЕД РОЂЕЊЕ

МИЛИЦА МАНОЈЛОВИЋ-СТОЈАНОСКИ, НАТАША НЕСТОРОВИЋ, НАТАША НЕГИЋ, СВЕТЛАНА ТРИФУНОВИЋ, М. СЕКУЛИЋ и В. МИЛОШЕВИЋ

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Презентовано истраживање описује развој ACTH и GH ћелија хипофизе фетуса пацова, непосредно пред рођење коришћењем имунохистохемије и морфометријских мерења. Од 19. до 21. дана гестације волумен ACTH ћелија фетуса био је непромењен, док су волуменска густина и број ћелија по јединици површине значајно смањени. Интензитет ACTH имунопозитивности у парс интермедиа повећавн је током испитиваног периода. Волумен GH ћелија, волуменска густина и бројност по јединици површине значајно су повећани током завршног периода феталног развоја, тј. од 19. до 21. дана гестације. GH имунопозитивност први пут је демонстрирана у ћелијама парс интермедиа код фетуса старих 21 дан.