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Secretory granules of pituitary adenomas: quantitative study of hormonal antigenicity

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Abstract Ultrastructurally, the antigenicity of major pituitary hormones in secretory granules was quantitatively investigated in five growth hormone (GH)-secreting adenomas, five prolactin (PRL)-secreting adenomas and eight clinically non-functioning (CN-F) adenomas. Sparsely granulated cells with a few or several small secretory granules (60–100 nm) exhibiting little or only weak antigenicity of various biochemically unrelated hormones were commonly observed in CN-F adenomas and occasionally in GH- and PRL-secreting adenomas. GH- or PRL-secreting adenomas consisted of many densely granulated cells with medium-sized (200–250 nm) or large (over 250 nm) secretory granules and a few or several sparsely granulated cells with small secretory granules. The densely granulated cells showed intense GH or PRL antigenicity and slight to moderate antigenicity for other hormones in large secretory granules and little or only weak antigenicity for various hormones including GH or PRL in small secretory granules. Their secretory granules larger than 160 nm or 140 nm significantly exhibited intense GH or PRL antigenicity (Fisher's exact test; $P < 0.05$ and < 0.01, respectively). Two CN-F adenomas showed sparsely and densely granulated cells as well as intermediate cells. The densely granulated cells closely resembled GH-secreting cells. The intermediate cells simultaneously included small and medium-sized or large secretory granules exhibiting little/slight and intense GH-antigenicity, respectively. This study indicates that sparsely granulated cells of different categories showing slight antigenicity for various hormones, antigenically share the same origin, and that their hormonality, single or multiple, may be selectively activated in the developmental course of secretory granules.

Key words Pituitary adenomas · Hormonal antigenicity · Immunoelectron microscopy

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Introduction

The size and number of secretory granules of normal or neoplastic pituitary cells have been considered to be morphologically specific for certain hormones. Hormonality of secretory granules is believed to be determined at the time of differentiation from progenitor cells to hormone secreting cells through stem cells [10–14, 17, 18, 26, 29, 31–33, 35]. Recent immunological and gene technology enables us to detect multihormonality of different cell lines in the same secretory granules [5, 15, 21, 29]. The stem cell theory has difficulty in explaining the multihormonal character. Recently, it has been proposed [5, 21, 29, 35] that pituitary adenomas secreting multiple biochemically unrelated hormones may arise directly from multidirectional progenitor cells or stem cells. These new interpretations appear complicated and somewhat sophistical. Using immunoelectron microscopy, this study quantitatively demonstrates hormonal antigenicity in secretory granules of pituitary adenomas and discusses the cytological significance of the antigenicity.

Materials and methods

This study is based on 5 growth hormome (GH)-secreting adenomas (cases 1–5), 5 prolactin (PRL)-secreting adenomas (cases 6–10) and 8 clinically non-functioning (CN-F) adenomas (cases 11–18) obtained at surgery. Preoperative serum hormonal levels of these 18 cases, as determined by radioimmunoassay, are shown in Table 1. According to Karnovsky' s method [16], tumor tissues were fixed with paraformaldehyde-glutaraldehyde for 2 h at room temperature and post-fixed with osmium-tetroxide for 2 h at 4 °C. After dehydration in a series of graded ethanols and propylene oxide, the fixed materials were embedded in Epon 812. For routine electron microscopic study, ultrathin sections were stained with uranyl acetate and lead citrate, and their ultrastructures were observed in a Japan Electron Optics Laboratory (JEOL) 100 CX microscope.

For immunoelectron microscopy using the protein A-gold method of Bendayan and Zollinger [4], ultrathin sections were incubated overnight with the primary antibody diluted 1:500 at 4 °C. The rabbit polyclonal antibody to human GH, PRL and major glycoprotein hormones (LH, luteinizing hormone; FSH follicle stimulating hormone; TSH thyroid stimulating hormone) (Dako Japan,

Table 1 Serum hormonal levels of patients with pituitary adenomas Normal ranges of pituitary hormones: GH, 0–5 ng/ml; PRL, 0–25 ng/ml; TSH, 0–10 mU/ml; LH, 6.5–34.5 (M)/3.0–44.5 (F) mIU/ml; FSH, 2.0–22.0 (M)/3.5–37.7 (F) mIU/ml; ACTH, 9.6–31.2 (M)/5.7–19.9 (F) pg/ml (*GH* growth hormones, *PRL* prolactin, *ACTH* adrenocorticotropic hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *TSH* thyroid-stimulating hormone, *NE* not examined)

Case	Age (years), sex	GH	PRL	ACTH	LH	FSH	TSH
1	40, M	23.9	84.4	13	6.6	7.9	1.6
2	50, F	28.5	16.4	54	82.3	61.5	1.2
3	38, M	57.2	15.0	31	5.0	11.8	3.4
4	41, F	96.0	2.6	16	12.8	9.8	2.5
5	45, M	8.3	11.4	53.0	3.7	8.2	0.5
6	45, F	1.2	16750	< 10	4.3	2.0	1.6
7	56, M	0.9	25100	25	6.4	9.9	2.5
8	35, M	0.8	1052	14	11.4	11.1	3.1
9	47, M	1.7	3640	37	19.5	5.2	3.7
10	25, F	1.9	1120	< 10	4.8	21.9	2.1
11	40, M	1.6	5.1	< 10	11.4	8.3	2.9
12	51, M	0.6	13.6	< 10	10.4	11.8	2.2
13	34, F	0.5	53.0	NE	6.5	12.0	3.8
14	66, F	0.6	94.5	< 10	7.2	14.4	6.6
15	56, F	0.7	8.6	51	54.6	67.2	4.7
16	53, F	0.5	70.0	23	11.2	29.6	4.5
17	40, F	0.3	44.9	< 10	7.6	16.3	0.4
18	57, F	0.5	20.0	76	0.5	0.8	5.0

Kyoto, Japan), and the mouse monoclonal antibody to human adrenocorticotropic hormone (ACTH; Biostride, Calif.) were employed for the primary antibody. After adequate washing with phosphate-buffered saline, the sections were incubated with goat anti-rabbit or anti-mouse IgG F(ab')$_2$ fragment-specific-gold particles (5 or 15 nm; E-Y Laboratory, San Meteo, Calif.) diluted 1 : 20 at room temperature for 1 h. The specificity of the immunostaining was tested by substituting normal rabbit serum for antisera, absorbing each antiserum with its corresponding antigen or omitting one component of the reaction. After immunolabeling, the sections were also subjected to staining with uranyl acetate and lead citrate. This single immunolabeling method identified the number of gold-immunolabeling particles in secretory granules, showing the intensity of hormonal antigenicity. In each case, secretory granules measuring from 60 to 350 nm were divided according to size into 10-nm subgroups. The number of investigated secretory granules ranged from 118 to 248 for GH, from 69 to 170 for PRL, from 59 to 122 for ACTH and from 39 to 123 for glycoprotein hormones. Average values (± SD) for gold immunolabeling particles to individual hormones in the size subdivisions of secretory granules are shown in Figs. 2–5. Correlation between sizes of secretory granules and antigenic intensity of GH and PRL was statistically analyzed. We also discuss the significance of multihormonality in pituitary adenomas.

Results

Moderately elevated serum ACTH levels were observed in patients with GH-secreting (case 2), PRL-secreting (case 9) and CN-F (cases 15 and 18) adenomas. Patients with GH-secreting (case 1) and CN-F (cases 13, 14, 16 and 17) adenomas showed moderately elevated levels of PRL, which appeared to result from suppression of the hypothalamic prolactin inhibitory factor or actual secretion by the tumors themselves. In cases 2 and 15, the elevated LH and FSH levels were regarded as a matter of course in postmenopausal females (Table 1).

Immunoelectron microscopy in this study generally showed a few immunolabeling particles outside secretory granules. The particles in the Golgi apparatus, rough endoplasmic reticulum and mitochondria appeared to be related to hormone synthesis. In contrast, particles unrelated to such organelles were extremely rare.

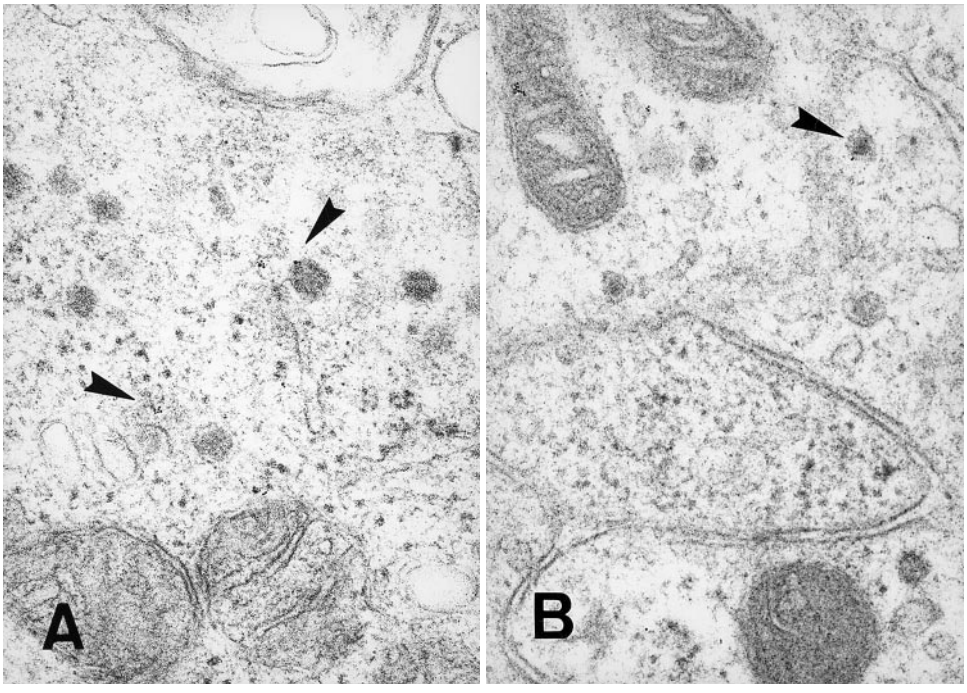


Fig. 1 Weak hormonality *(arrowheads)* in small secretory granules of sparsely or slightly granulated cells. **A** PRL antigenicity in a clinically non-functioning adenoma (case 12). **B** ACTH antigenicity in a GH-secreting adenoma (case 2) (*PRL* prolactin, *ACTH* adrenocorticotropic hormone, *GH* growth hormone). **A, B** × 48,000

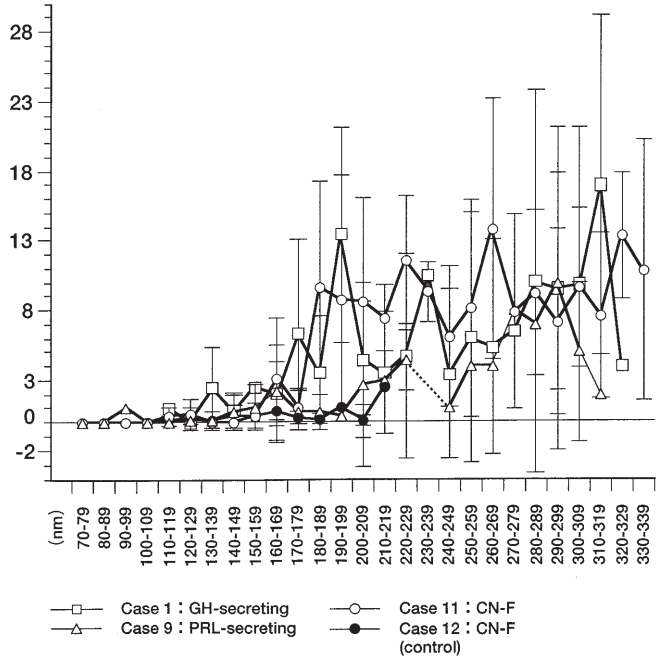


Fig. 2 GH immunolabeling. Small secretory granules of less than 160 nm in various cases show only a few or rare GH immunolabeling particles. A significant increase in the number of the particles is demonstrated in secretory granules larger than 180 nm of cases 1 and 11 ($P < 0.05$). Case 9 exhibits a slight or moderate increase in particles in secetory granules larger than 200 nm

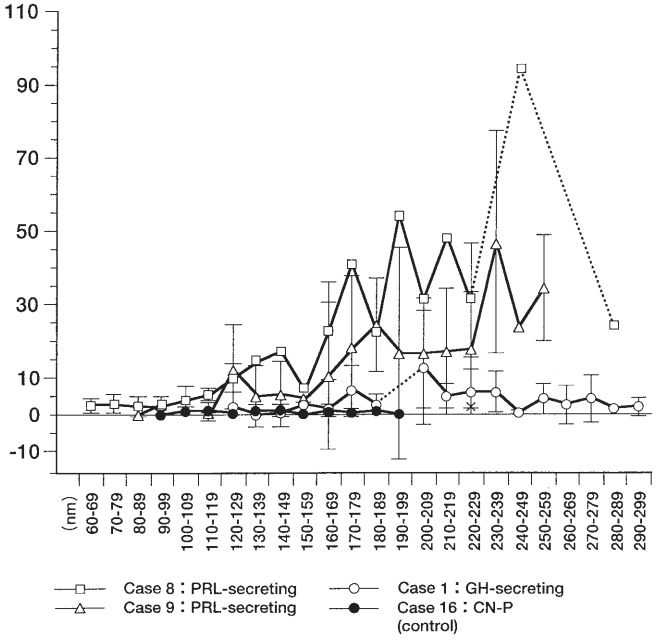


Fig. 3 PRL immunolabeling. Only a few or rare PRL immunolabeling particles are demonstrated in small secretory granules of various cases. Cases 8 and 9 exhibit a significant increase of the particles in secretory granules larger than 140 nm ($P < 0.01$). Case 1 also shows a slight increase of the particles in secretory granules larger than170 nm

Sparsely granulated cells, showing a few or several small (60–100 nm) secretory granules and poorly developed cytoplasmic organelles, were commonly observed in CN-F adenomas and occasionally in GH- and PRL-secreting adenomas (Fig. 1). The small secretory granules of individual adenomas exhibited a few gold immunolabeling particles for various biochemically unrelated hormones, signifying slight antigenicity (Figs. 2–5). In CN-F adenomas, secretory granules of slightly granulated cells appeared somewhat larger (100–150 nm) and more frequent. Most of these secretory granules also showed slight antigenicity for various hormones (Figs. 2–5). Oncocytic transformation and mitochondrial abnormality were demonstrated in sparsely granulated cells, especially in CN-F adenomas. Interestingly, two CN-F adenomas (cases 11 and 17) additionally included densely granulated cells, closely resembling GH-secreting cells and cells intermediate between the sparsely and the densely granulated cells. The densely granulated cells showed numerous large (over 200 or 250 nm) and a few small secretory granules. The large secretory granules exhibited 5–15 GH-immunolabeling gold particles and small secretory granules less than 5 (Fig. 2). The intermediate cells simultaneously included several small and large secretory granules (Fig. 6). Although their secretory granules of under 150 nm only showed a few GH-immunolabeling gold particles, those of 160–180 nm showed more GH- immunolabeling gold particles, while those of 300–350 nm showed peak levels (Fig. 2). For secretory granules larger than 180 nm, the finding of more than 5 GH-immunolabeling gold particles

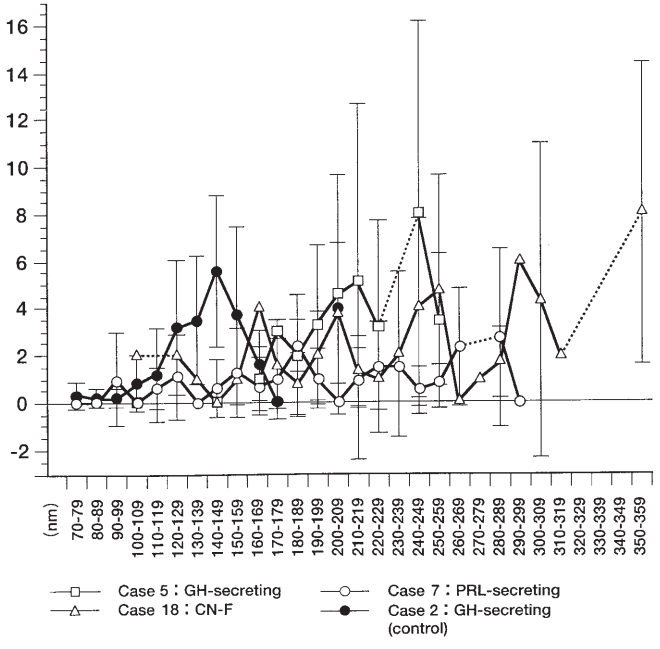


Fig. 4 ACTH immunolabeling. Secretory granules smaller than 120 nm in various cases show only a few or rare ACTH immunolabeling particles. Cases 5, 7 and 18 exhibit a slight or moderate increase of the particles in secretory granules larger than 120 or 160 nm

was significant (Fisher's exact test: $P < 0.05$). In secretory granules ranging from 130 to 180 nm, four CN-F adenomas exhibited slightly or moderately increased antigenic-

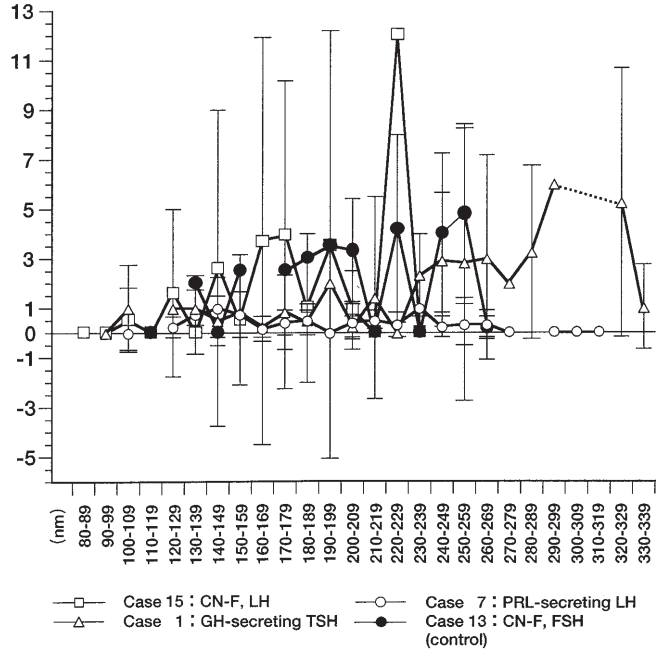


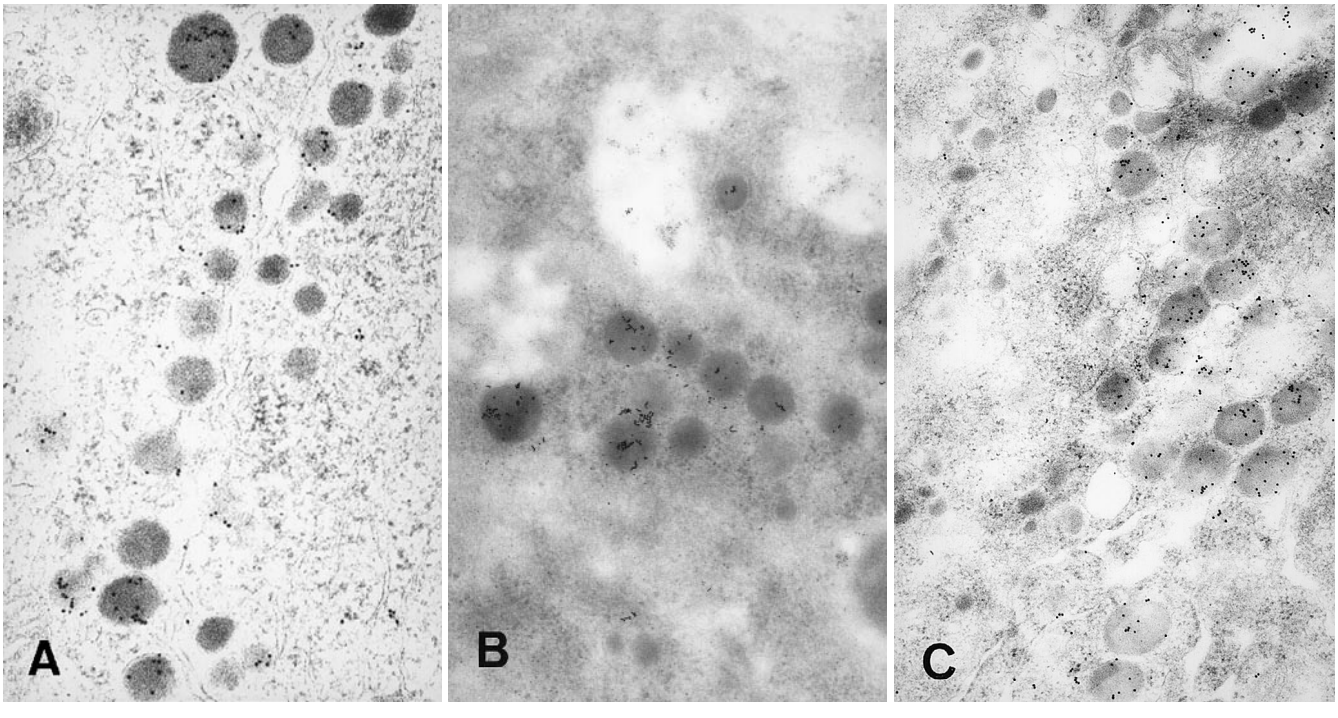
Fig. 5 Glycoprotein hormone immunolabeling. Secretory granules smaller than 120 nm in various cases exhibit only a few or rare immunolabeling particles of glycoprotein hormones. A slight increase of the particles is demonstrated in secretory granules 130 or 150 nm of cases 1 and 15

Fig. 6 A–C Weak and intense GH or PRL antigenicity are demonstrated in small and large secretory granules, respectively. **A** GH antigenicity in a GH-secreting adenoma (case 2). **B** PRL antigenicity in a PRL-secreting adenoma (case 6). *C* GH antigenicity in a clinically non-functioning adenoma (case 16). **A** × 36,000; **B** × 34,350; **C** × 18,000

ity of ACTH, and one showed antigenicity for the major glycoprotein hormones (Figs. 4, 5).

The GH- and PRL-secreting adenomas consisted of many densely and a few sparsely granulated cells. The densely granulated cells showed abundant large (over 250 nm) or medium-sized (200–250 nm) and a few small secreory granules. Cytoplasmic organelles, especially Golgi apparatus, rough endoplasmic reticulum and free ribosomes, appeared well developed in the densely granulated cells and poorly developed in the sparsely granulated cells. In PRL-secreting adenomas, well-developed rough endoplasmic reticulum, known as Nebenkern, was occasionally seen. There were few morphological differences between sparsely granulated cells in GH- and PRL-secreting adenomas and those in CN-F adenomas. Their small secretory granules similarly showed only weak antigenicity for various hormones (Figs. 2–5). The medium-sized or large secretory granules contained abundant GH- (more than 10) or PRL- (more than 20) immunolabeling gold particles (Figs. 2, 3).

Even in GH-secreting adenoma cells, secretory granules smaller than 150 nm usually had less than five GH-immunolabeling gold particles. Larger granules of 150 or 180 nm showed more than five GH-immunolabeling gold particles, with maximal GH labeling in granules of 300 nm or larger (Fig. 2). Secretory granules larger than 180 nm significantly exhibited intense GH antigenicity (Fisher's exact test; $P < 0.05$). Two GH-secreting adenomas (cases 1 and 5) showed antigenicity of PRL and ACTH, with an immunolabeling pattern similar to that of GH (Figs. 3, 4, 7 A). Their secretory granules smaller than 150 nm showed only a few PRL- and ACTH-immunolabeling gold particles; however, those of 150–200 nm showed five or more PRL-and over ten ACTH-immunolabeling gold particles. Secretory granules larger than 150 nm in GH-secreting



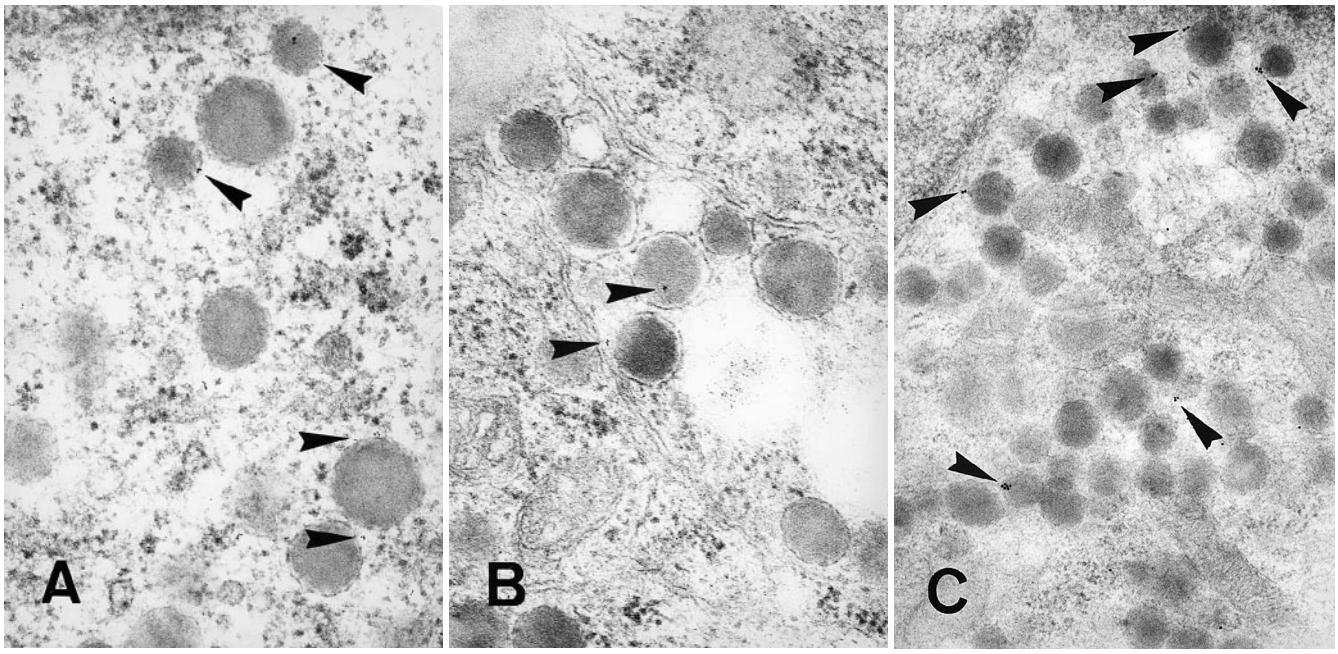


Fig. 7 A–C Weak or moderate hormonal antigenicity *(arrowheads)* in large secretory granules. A ACTH antigenicity in a GH-secreting adenoma (case 5). B GH-antigenicity in a PRL-secreting adenoma (case 6). C TSH-antigenicity in a GH-secreting adenoma (case 1) (*TSH* thyroid-stimulating hormone). **A** × 44,300; **B** × 42,280; **C** × 22,150

adenoma cells also exhibited slight or moderate antigenicity of major glycoproteins (Figs. 5, 7C).

Secretory granules smaller than 100 nm in both sparsely and densely granulated cells in PRL-secreting adenomas showed only a few immunolabeling gold particles for various hormones including PRL (Figs. 2–5). Larger granules of 120–160 nm showed more than ten PRL-immunolabeling gold particles, with a maximal number being found in secretory granules measuring over 190 nm (Figs. 3, 6B). Secretory granules larger than 140 nm significantly exhibited intense PRL antigenicity with more than 10 immunolabeling gold particles (Fisher's exact test; $P < 0.01$). One PRL-secreting adenoma (case 9) exhibited slight to moderate GH antigenicity in secretory granules larger than 200 nm (Figs. 2, 7B). In one PRL-secreting adenoma (case 7), slightly increased number of particles immunolabeling ACTH and major glycoprotein hormones were demonstrated in secretory granules larger than 200 or 230 nm (Figs. 4, 5).

Discussion

Advanced diagnostic techniques enable us to detect hormonality in CN-F adenomas and multihormonality of different cell lines in hormone-secreting adenomas far more effectively than had been previously possible [1, 5, 6, 9, 12, 17, 21, 24–26, 28, 29, 31, 32, 35]. This multihormonal character has raised an important question regarding the stem cell theory, which has been believed to be essential to cyto-differentiation of normal and neoplastic pituitary cells. Normal and neoplastic pituitary cells are considered to be derived from multipotential or multidirectional progenitor cells through acidophilic or basophilic stem cells [5, 10–14, 17, 18, 21, 24–26, 29, 31, 32, 35]. The stem cell theory, however, has difficulties in explaining how well differentiated hormone-secreting adenoma cells produce multiple, biochemically unrelated, hormones. Many authors cited above have explained the multihormonal character based on the stem cell theory. Their explanations, however, appear somewhat complicated and sophistical.

One may consider that the polyclonal antibodies to human pituitary hormones employed in this study are inappropriate for examination of multihormonal character in pituitary adenomas. The major glycoprotein hormones (TSH, LH and FSH) consist of a common α-subunit and individual β-subunits. This study, indeed, does not define whether immunolabeling reaction to such major glycoprotein hormones result from the common α-subunit or individual β-subunits or both. These constituents, nevertheless, are biochemically unrelated to GH, PRL and ACTH. Our results demonstrate the value of examining the multihormonality of different cell lines or biochemically unrelated hormones in pituitary adenomas.

Morphologically and hormonally, Horvath and Kovacs [10], and Kovacs and Horvath [18] divided GH-, PRL-, and ACTH-secreting adenomas into two subgroups (sparsely granulated and densely granulated or endocrinologically active and clinically silent). They also classified oncocytomas and null cell adenomas as distinct entities of undifferentiated pituitary adenomas. Their classification appears easy to understand but puts too much emphasis on morphology. Recently, they have proposed a five-tier classification of adenohypophysial neoplasms based on

clinical and biochemical results, imagings, operative findings, histology, immunocytochemistry, and electron microscopy [20]. They did not, however, address the morphological and hormonal relationships between sparsely and densely granulated cells in the same adenomas or those among sparsely granulated cells of different cell-lined tumors. Such relationships appear most significant for the identification of pituitary adenoma cells.

Morphologically, pituitary adenomas may be classified as monomorphous, bimorphous and trimorphous by the size and the number of their secretory granules [5, 12, 25, 31, 32, 35]. Horvath et al. [12] emphasized that morphology and hormonality of pituitary adenomas might depend upon the degree and direction of the cellular differentiation of multidirectional progenitor cells. In this study, we highlight the hormonality of small secretory granules. Small secretory granules measuring from 60 to 100 nm were found in both sparsely and densely granulated cells of various types of adenomas. Careful electron microscopic observations enabled us to detect common hormonal antigenicity in small and large secretory granules. As noted by Horvath and Kovacs [10], we found sparsely granulated cells scattered among densely granulated cells in GH- and PRL-secreting adenomas. This study also showed intermediate cells between the sparsely and densely granulated cells in GH- and PRL-secreting adenomas and even in CN-F adenomas. The co-existence of cells exhibiting different morphology and hormonality in the same tumors led us to regard their differences as the consequence of developmental changes in pituitary adenoma cells.

Small secretory granules showed an approximately similar slight or weak antigenicity for biochemically unrelated hormones at the ultrastructural level. In slightly granulated cells, secretory granules appearing somewhat larger in size (100–150 nm) and increased in number exhibited hormonal antigenicity similar to that of small secretory granules. At the ultrastructural level, large secretory granules (over 200 nm) of our GH- or (over 250 nm) PRL-secreting adenoma cells also exhibited weak or moderate antigenicity of other hormones biochemically unrelated to GH or PRL. Secretory granules of 160–180 nm and 140–160 nm showed increased antigenicity for GH and PRL, respectively, and those of 250 or 330 nm revealed peak levels of hormonal antigenicity. The antigenicity of GH in GH-secreting adenomas and PRL in PRL-secreting adenomas was significantly increased in secretory granules of over 180 and 160 nm, respectively (Fisher's exact test: $P < 0.05$ and $P < 0.01$, respectively). The retention of antigenicity for other hormones at low levels in secretory granules of 160–180 nm in GH-secreting adenoma cells and those of 140–160 nm in PRL-secreting adenoma cells may indicate a selective activation of GH and PRL, respectively, in the course of growth. Our two CN-F adenomas, in which transitional cells to GH-secreting cells included small and large secretory granules simultaneously, clearly exhibited size-dependent GH hormonality. These findings are partly in accordance with LH and FSH hormonality in mice gonadotroph cells as reported by Watanabe et al. [36]. Demonstrating antigenicity of LH in small and LH and FSH in large secretory granules, they proposed two different systems for secreting LH and FSH, which closely related to the size of secretory granules.

Many authors have supposed that pituitary adenomas secreting multiple, biochemically unrelated hormones do not arise from well-differentiated hormone-secreting cells but from multipotential or multidirectional progenitor cells or stem cells. Previously, McComb et al. [25] and recently others [21, 24, 29] offered an explanation or interpretation of the multihormonal character of pituitary adenomas. Their interpretations, essentially based on the stem cell theory, appear to overlook the low antigenicity of multiple biochemically unrelated hormones in small and even in large secretory granules of hormone-secreting adenoma cells. Focusing on a finding that GH-secreting adenoma cells tend to produce multiple hormones, while PRL-secreting adenoma cells secrete PRL only or predominantly, Matsuno et al. [24] have recently suggested that some GH-secreting adenomas are derived from plurihormonal primordial stem cells and PRL-secreting adenomas from lactotropic cells of well differentiated acidophilic stem cells. At the ultrastructural level, however, this study showed a general weak antigenicity for multiple hormones in small and large secretory granules of PRL-secreting adenoma cells. The hormonality of the small secretory granules especially in sparsely granulated cell may hold the key to the multihormonal character of pituitary adenomas.

The hormonality of small secretory granules has been demonstrated in sparsely granulated cells of hormone-secreting adenomas [19] and even in oncocytomas and null cell adenomas [1, 37]. Using immunocytochemistry and in situ hybridization, Jin et al. [15] demonstrated PRL receptor mRNA in various types of normal and neoplastic pituitary cells. Their findings appear compatible with our results, showing that not only small but also large secretory granules of pituitary adenoma cells exhibit antigenicity for various hormones, even though of a weak level. Thus, antigenically, sparsely granulated cells of different categories appear to have the same origin.

Another important finding in this study is that the size and number of secretory granules co-ordinate with the development of Golgi apparatus, rough endoplasmic reticulum and free ribosomes. Cytoplasmic organelles appeared poorly developed in sparsely granulated cells and well developed in moderately or densely granulated cells. Kovacs et al. [19] considered silent corticotrophic adenomas to be a distinct entity. On electron micrographs [22], developmental sequences of secretory granules and cytoplasmic organelles between endocrinologically active and clinically silent corticotropic adenomas can be found. It remains open to debate as to whether distinct morphological and hormonal differences exist between endocrinologically active and clinically silent (especially subtype 3) corticotropic adenomas. This study also showed sparsely granulated cells among GH-, PRL-secreting and CN-F adenomas, whose small secretory granules exhibited sim-

ilar morphology and hormonal antigenicity. As far as we know, sparsely granulated cells including oncocytes and null cells appear to be the most primitive or undifferentiated among actually existing pituitary cells. Small secretory granules of sparsely and densely granulated cells of different types of tumors similarly showed weak antigenicity of multiple hormones.

Together with cytoplasmic organelles, the size and number of secretory granules signify the development of GH- and PRL-secreting adenoma cells. The selective activation of certain hormones may be stimulated during the developmental course of secretory granules. Felix et al. [7] reported a silent corticotrophic adenoma which subsequently showed LH-, FSH- and α-subunit-immunoreactive cells in recurrent specimens. They postulated that irradiation therapy following the first surgery might play a role in the alteration of tumor phenotype. Implying their convertibility to mammosomatotrophs and possibly lactotrophs, Stefaneanu et al. [34] demonstrated PRL production of mature somatotrophs in pregnancy. We, on the other hand, think that the multiple hormones of their cases may have been activated at different times, ACTH or GH initially and glycoprotein hormones or PRL subsequently, under particular circumstances such as irradiation or pregnancy.

It is well known that hormone secretion and tumorigenesis of pituitary cells are regulated by the hypothalamic hormones such as GH-releasing hormone (GRH), thyrotropin-releasing hormone and somatotrophin-releasing inhibiting hormone and bromocriptine. According to Asa et al. [2], protracted GRH stimulation may result in proliferation, hyperplasia and adenomas of adrenohypophyseal cells in mice.

By contrast, several authors have recently noted mRNAs in pituitary adenomas, which are related to hormone secretion [3, 8, 15, 19, 21–24, 27, 28, 30, 34]. Among them, Pit-1 mRNA is noteworthy. In these studies, the POU domain protein Pit-1, a pituitary-specific transcription factor, is thought to play an important role in the generation, differentiation and proliferation of GH-, PRL- and TSH-secreting cells. Several of the authors mentioned above noted that ACTH-secreting or gonadotroph cell adenomas did not express the Pit-1 gene but that it was expressed in GH-, PRL-secreting, mixed GH- and PRL-secreting and TSH secreting adenomas, thus signifying their multihormonal character. Lloyd et al. [23], however, showed Pit-1 mRNA in null cell adenoma cells, GH-, PRL-, and even in ACTH-immunoreactive tumors. Obtaining results similar to those of Lloyd et al. [23], Friend et al. [8] suggest certain subtypes of corticotrophs and gonadotrophs that contain Pit-1 mRNA. Sanno et al. [30] demonstrated high-rated co-localization of Pit-1 mRNA with GH-, PRL-, TSHb- and α-subunit-immunoreactive cells in GH-secreting, PRL-secreting, TSH-secreting and CN-F adenomas, and speculated that these adenomas might be derived from multipotential progenitor or stem cells. Thus, the occurrence of Pit-1 mRNA in various tumor cells of different cell lines may provide a new interpretation of the multihormonal character of pituitary adenomas, differing from the stem cell theory. Further investigations are required to ascertain such multihormonal character.

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