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The origin of ciliated cell cysts of the anterior pituitary

An experimental study in the rat

Gotetsu Gon
Department of Anatomy, Jikei University School of Medicine, 3-25-8 Nishi-Shinbashi, Minato-ku, Tokyo 105, Japan

Summary. Rats were decapitated and the heads were stored at 4° C for 24 h. The anterior pituitaries were then removed and incubated for 5 days. On the 1st, 3rd and 5th days of incubation, explants were studied by electron microscopy and immunohistochemistry using antiserum against S-100 protein. In the explant many granulated cells underwent necrosis; folliculo-stellate (FS) cells formed many cyst-like structures (CLSs) and became squamous epithelioid cells (CLS-forming cells). After incubation for 5 days the explants were isotransplanted under the renal capsules of male rats in order to observe morphological changes in the CLSs. Immediately after transplantation, the CLSs were encircled by a basement membrane, but from the 8th to 14th day, ciliation occured in CLS-forming cells and "ciliated cell cysts" were formed. The ciliated cells were immunostained with antiserum against S-100 protein. The present study suggests that FS cells are related to CLS formation and have the potential to trans-differentiate to ciliated cells.

Key words: Anterior pituitary – Organ culture – Cyst – Folliculo-stellate cell – Cilia

Introduction

The presence of cyst-like structures (CLSs) has been described in anterior pituitaries of many higher vertebrates such as fowl (Campbell 1962), guinea pig (Chadwick 1937), rat (Opper 1940; Ferrer 1956), dog (Rajan and Mohiyuden 1973) and man (Shanklin 1951). It is also well known that cystic pituitary tumours such as Rathke's cyst (Ringel and Bailey 1972; Yoshida et al. 1977) and craniopharyngioma (Gathak et al. 1971; Banna 1976) occur in the human pituitary gland. The aetiology and physiological significance of these cystic tumours and the relationships with CLSs found in normal pituitaries is not known, because previous studies used ordinary histological techniques and few experimental approaches have been made to the study of CLSs in the anterior pituitary gland.

Some studies have described that CLSs arise after the degeneration of glandular cells in the anterior pituitary under physiological (Fernholn and Olsson 1969; Benjamin 1981) and experimental conditions (Selye 1943; Gon et al. 1987). Previous morphological studies of pituitary grafts revealed that folliculo-stellate (FS) cells formed CLSs after degeneration of glandular cells (Gon et al. 1987). In addition, other morphological studies of pituitary explants in organ cultures have indicated that CLSs arose after degeneration of glandular cells (Gaillard 1937; Petrovic and Porte 1961; Pathak and Fisk 1974).

Organ culture seems to be a useful experimental method for studying the origin, the aetiology and the physiological function of CLS, and was therefore used in this study. The methods of forming CLSs and the morphological changes in CLSs after transplantation under the renal capsule are described.

Materials and methods

Wistar-Imamichi male rats (weighing about 300–400 g) were used. The animals were divided into six groups (Table 1). Group 2 contained 21 rats, and the remaining groups (1, 3, 4, 5 and 6) contained 3 rats each. Group 1 was used as control for organ culture and group 2 was used for organ culture and transplantation. The remaining

Offprint requests to: G. Gon

Table 1. Experimental design

Group	n[a]	Storage[b]	Organ[c] culture	Trans-plantation	Host[d] rat
1	3	+	–	–	–
2	9	+	+	–	–
	12	+	+	+	–
3	3	–	–	–	+
4	3	–	–	–	+
5	3	–	–	–	+
6	3	–	–	–	+

[a] Number of rats
[b] At 4° C for 24 h
[c] In serum-free Ham's F-10 medium for 5 days
[d] Groups 3, 4, 5 and 6 were used as hosts for transplantation

four groups (3–6) were used as hosts for transplantation.

In order to cause severe degeneration of glandular tissues, anterior pituitary glands were incubated in serum-free medium after storage at 4° C for 24 h without normal blood supply. The rats of groups 1 and 2 were decapitated, and the heads were put in a vinyl bag. After storage at 4° C for 24 h, the pituitaries were removed aseptically. The anterior pituitaries of group 1 were immediately sampled for morphological observation. The pituitaries of groups 2 were rinsed three times in Hanks' balanced salt solution (buffered with bicarbonate, pH 7.4), containing penicillin (50 U/ml) and streptomycin (50 µg/ml). The pituitaries were then plated into seven 60 mm Primaria culture dishes (Falcon Products, Oxford, CA, USA) each containing 3 glands. The incubation medium consisted of serum-free Ham's F-10 medium (buffered with sodium bicarbonate, pH 7.4), supplemented with penicillin (50 U/ml) and streptomycin (50 µg/ml).

The pituitaries were kept in a humidified incubator at 37° C in 95% air-5% CO_2, and the medium was not changed for 5 days. At the 1st, 3rd and 5th day of incubation, three pituitary glands were used for morphological observation and the remaining twelve pituitary glands were used for transplantation (Table 1).

After incubation for 5 days, pituitary glands were iso-transplanted under the right renal capsules of male rats (groups 3–6) under Nembutal anesthesia. The host rats were housed three per cage, and kept at 20–24° C. They were given food and water ad libitum. At the 2nd day (group 3), the 4th day (group 4), the 8th day (group 5) and the 14th day (group 6) of transplantation, the grafts were removed and studied.

Each explant and graft were divided midsagittally with a razor blade and each hemipituitary was fixed for light and electron microscopical observations. For light microscopy explant and graft halves of each group were fixed with formol-sublimate for 12 h at 4° C. After dehydration with ethanol the grafts were embedded in paraplast and 3 µm serial sections were cut and stained with haematoxylin-eosin. For electron microscopy, the remaining explant and graft halves were cut into small pieces with razor blades. These pieces were fixed with 1% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, for 2 h at 4° C. After washing twice with the above buffer supplemented with 2% sucrose, they were post-fixed with 1% osmic acid in Millonig's buffer (Millonig 1962), pH 7.4, for 2 h at 4° C, and embedded in Epon-Araldite resin. Ultrathin sections were cut, stained with uranyl acetate and lead citrate and observed with a JEOL 100B electron microscope.

Sections were treated with 0.3% H_2O_2 in methanol for 30 min to block endogenous peroxidase activity and then immersed in 5% normal goat serum in phosphate buffered saline (154 mM sodium chloride in 50 mM sodium phosphate buffer, pH 7.4) for 30 min to eliminate the non-specific binding of antibodies. Anti-bovine S-100 protein serum (1:1000), prepared in this laboratory (Shirasawa and Yoshimura 1983), was used for the first antibody, because S-100 protein is a marker protein of the FS cell of the rat anterior pituitary gland (Nakajima et al. 1980; Cocchia and Miani 1980).

Immunostaining was carried out by the avidin-biotin-peroxidase complex method by Hsu et al. (1981). The specificity of the antiserum against bovine S-100 protein was demonstrated by a preabsorption test and a direct binding assay using isotope-labelled antigen (Shirasawa and Yoshimura 1983; Shirasawa et al. 1984). In the present study, the immunostainability could be abolished by preabsorption of antiserum (1:1000) with S-100 protein (10 µg/ml) (Wako Pure Chemical Industries. LTD. Osaka Japan).

Results

The histological features of rat pituitaries after storing at 4° C for 24 h were similar to those of normal rat pituitaries. However, many pyknotic nuclei were observed due to anoxia (Fig. 1a). Immunohistochemical staining with anti S-100 protein serum showed folliculo-stellate (FS) cells intervening with glandular cells. The FS cells were stellate in shape and occasionally formed cell clusters in the center of the lobules. They had spherical nuclei and narrow cytoplasm, both of which were immunostained with antiserum (Fig. 1b). Their

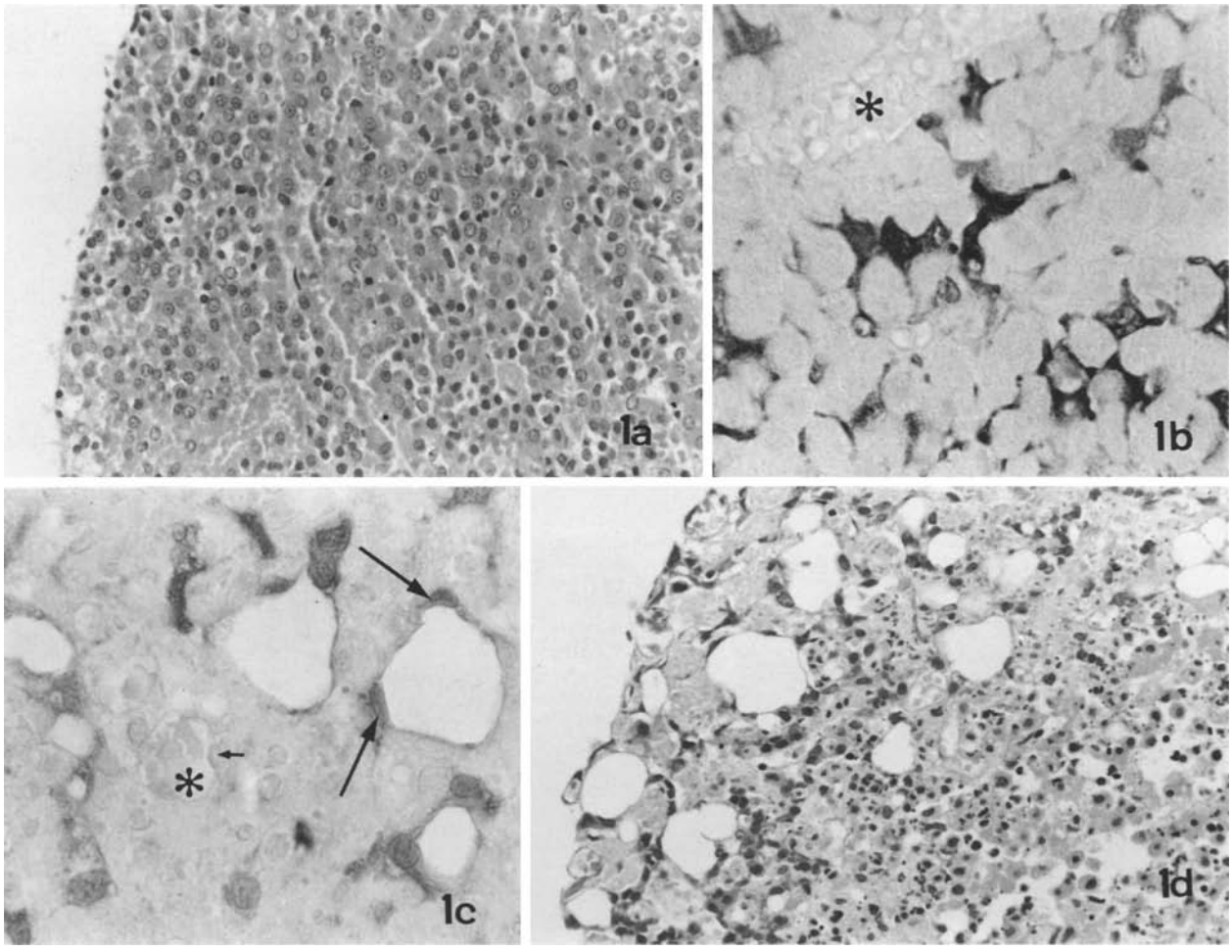

Fig. 1 a–d. Light microscopy of pituitary explants after storage at 4° C for 24 h (**a, b**), and after incubation (**c, d**). *Asterisks* indicate blood vessels. **a** Histology of pituitary gland after storage is well preserved as seen in vivo. HE staining. ×330. **b** Immunohistochemical staining for S-100 protein indicates that stellate cells occasionally form cell clusters, and their slender cell projections encircle adjacent glandular cells. ×870. **c** On the 3rd day of incubation, CLSs are lined by immunostained squamous cells (*large arrows*). The endothelium of blood vessel does not immunostain (*small arrow*). ×900. **d** On the 5th day of incubation, necrosis of the central area is seen. In the periphery many CLSs are formed. HE staining. ×330

slender cell projections encircled adjacent oval or spherical glandular cells which did not immunostain with antiserum against S-100 protein (Fig. 1b).

Incubation with serum-free medium caused cyst-like structure (CLS) formation by FS cells and the degeneration of many glandular cells. From the 1st to 3rd day of incubation, non-immunostained glandular cells began to degenerate, but FS cells remained viable and formed small cavities (Fig. 1c). From the 3rd day to the 5th day of incubation, the number of cavities increased. Each cavity enlarged and formed CLS. FS cells which formed CLSs transformed to squamous cells (Fig. 1c). The CLSs were easily distinguished from blood capillaries, because the endothelial cells of blood capillaries did not immunostain with antiserum (Fig. 1c). Although the cavity of CLSs appeared to be empty, blood capillaries contained many red blood cells (Figs. 1b and 1c). At the 5th day of incubation, explants were composed of peripheral glandular tissue and a large central necrotic area, but the glandular tissues were also severely damaged and many CLSs formed (Fig. 1d). Viable glandular cells decreased in the periphery of explants, and a few cells remained around the CLSs (Fig. 1d). CLSs were variable in size, but the average was about 30–50 μm in diameter.

Ultrastructural observation indicated that after storing pituitaries at 4° C for 24 h FS cells were connected by junctional complexes and lined small cavities, the so called follicles (Fig. 2a). On the

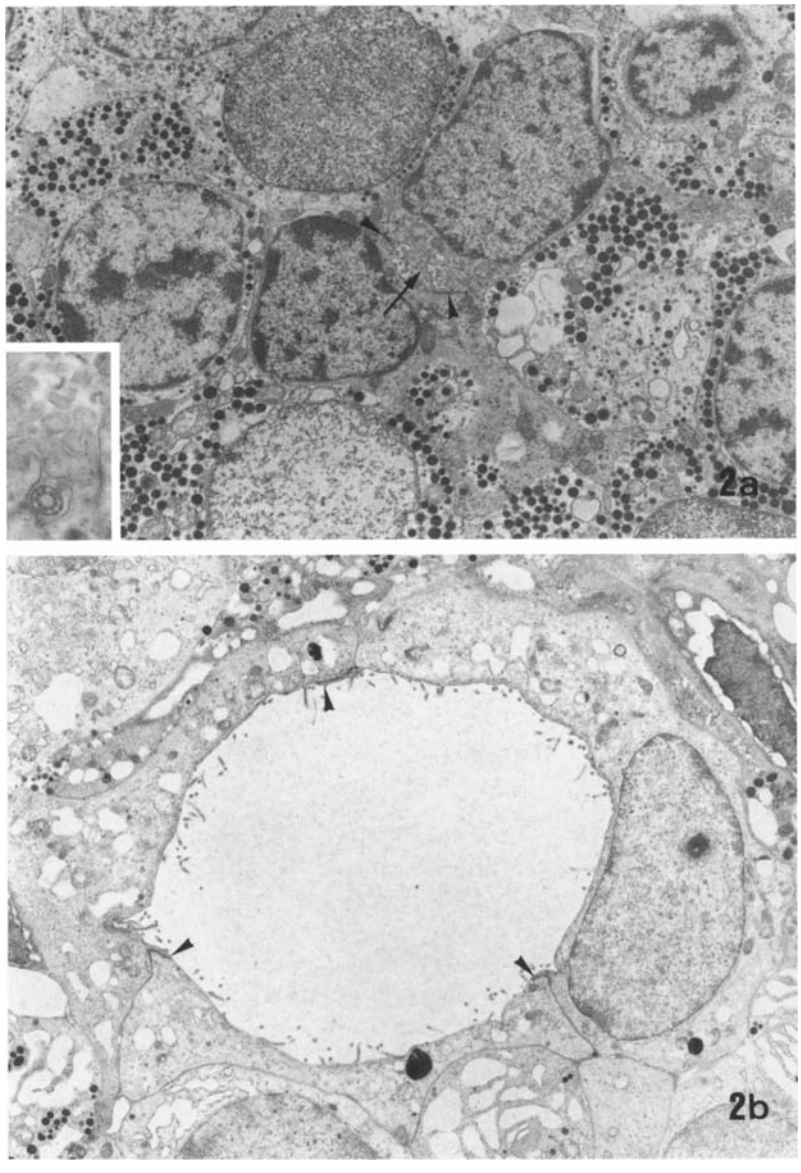

Fig. 2a, b. Electron microscopy of pituitary explants after storage (**a**) and after incubation for 5 days (**b**). **a** FS cells of the pituitary gland after storage at 4° C for 24 h. The slender cell projections encircle adjacent granulated cells. *arrow*: follicle. *arrowheads*: intercellular junctions. ×4050; *inset*: primary cilium. ×15300. **b** A CLS lined by squamous epithelioid cells (CLS-forming cells). Microvilli are seen on the free surface. CLS-forming cells are connected by intercellular junctions (*arrowheads*). ×5670

apical surface of the cells many microvilli and occasionally cilia of the 9+0 type (which had no central pair of microtubules, Fig. 2a inset), were seen. Slender projections of FS cells encircled adjacent granulated cells. FS cells contained a few mitochondria, scattered rough endoplasmic reticulum (RER) cisternae, small Golgi apparatus, lysosome-like dense bodies, occasional lipid droplets, and dark-colored cytoplasm which was rich in free polysomes (Fig. 2a). Although squamous epithelioid cells (CLS-forming cells), derived from FS cells after incubation, were connected by intercellular junctions, desmosomal junctions were not observed. Microvilli appeared on the apical surfaces (Fig. 2b). Cilia were seldom observed. CLS-forming cells contained a few mitochondria, RER cisternae, small Golgi apparatus and no secretory granules (Fig. 2b).

On the 2nd day of transplantation, the center of the graft was necrotic, and many red blood cells were present due to bleeding in the renal capsule at transplantation. CLSs were not damaged by transplantation (Fig. 3). Many mitotic figures in CLS-forming cells were observed. Ultrastructurally, the spaces were not encircled by a basement membrane. Intercellular spaces among CLSs were filled by remnants of necrotic cells, and mononuclear phagocytes actively ingested these.

On the 4th day of transplantation, the necrotic area disappeared. Grafts were filled by many CLSs

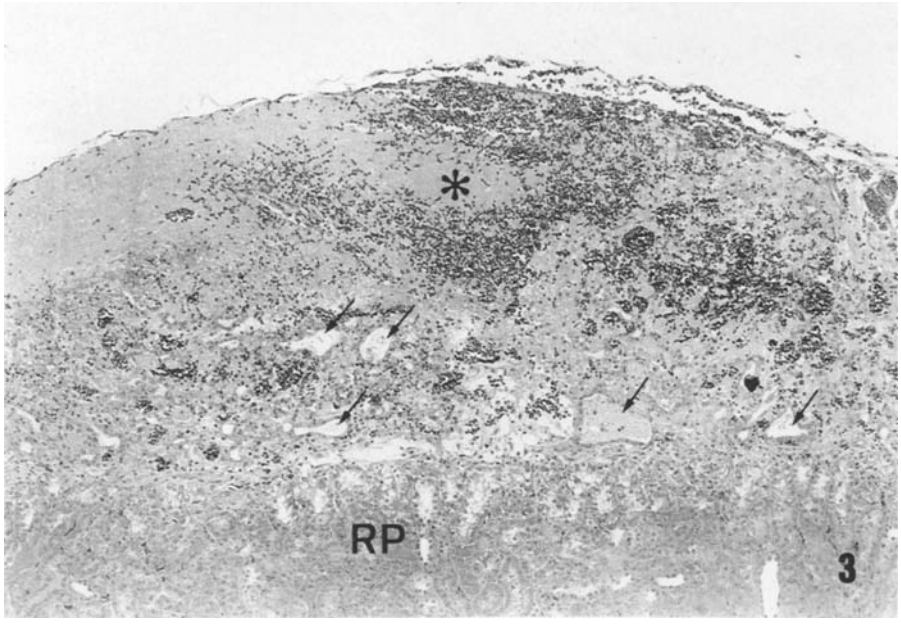

Fig. 3. Pituitary grafts on the 2nd day of transplantation. Central necrotic area (*asterisk*) and peripheral CLSs (*arrows*) are seen. *RP*: renal parenchyma. HE staining. × 72

and viable cells (Fig. 4a). Ultrastructurally, CLSs were lined by dark-colored, agranular cells. The cells had small cytoplasm and were irregular-shaped (Fig. 4b). The cavities were filled by an electron dense, amorphous material and contained some mononuclear cells of unknown origin, while the basal side was surrounded by a basement membrane (Fig. 4b). Remnants of necrotic cells disappeared both from the intercellular spaces and the cavities of CLSs.

On the 8th day of transplantation, the spaces were encircled by loose connective tissue. Mitotic figures in CLS-forming cells were not seen; however, the most prominent finding was that ciliation occurred in them.

Ultrastructurally, variable stages of ciliation from non-ciliated cells to complete ciliation could be observed (Figs. 5 and 6). CLS-forming cells were connected by junctional complexes (Fig. 5). Some CLS-forming cells contained much cytoplasm, developed Golgi apparatus, many mitochondria and free polysomes. Lipid droplets were frequently found in the cytoplasm of ciliated cells, and replication of centrioles and basal bodies occurred in their cytoplasm (Fig. 5). In some cases ciliation appeared to occur in small intracellular cavities initially. Basal bodies migrated to the edge of the intracellular cavities and initiated the formation of cilia (Fig. 6). The intracellular cavities containing cilia then opened to intercellular cavities of CLSs. In other cases, basal bodies migrated to the apical surfaces of intercellular cavities and initiated formation of cilia. These cilia had a central pair of microtubules (9+2 type) (Fig. 6). Some CLSs appeared to be lined by only ciliated cells, which were morphologically well differentiated. They had oval nuclei and large, cuboidal or columnar cytoplasm which contained many mitochondria accumulating in the apical and basal cytoplasm, supra-nuclear Golgi apparatus, scattered RER, many free polysomes, a few lysosome-like dense bodies and lipid droplets (Fig. 6).

On the 14th day of transplantation, grafts became a half or one third thinner when compared with grafts on the 2nd and the 4th day of transplantation. Ciliated cells were found in the majority of CLSs and the number of ciliated cells in each CLS increased (Fig. 7a). Ultrastructurally each ciliated cell was morphologically well differentiated as shown in Figure 6. Although from the 2nd to the 4th day of transplantation there were no immunostained cells in CLSs, from the 8th to 14th day ciliated and non-ciliated CLS-forming cells were immunostained with antiserum against S-100 protein (Fig. 7b).

Discussion

Some morphological studies of pituitary explants in organ culture indicated that many empty cavities or CLSs appeared among glandular cells at early stages of culture (Gaillard 1937; Petrovic and Porte 1961; Pathak and Fisk 1974). These CLSs were lined by agranular, squamous epithelioid cells

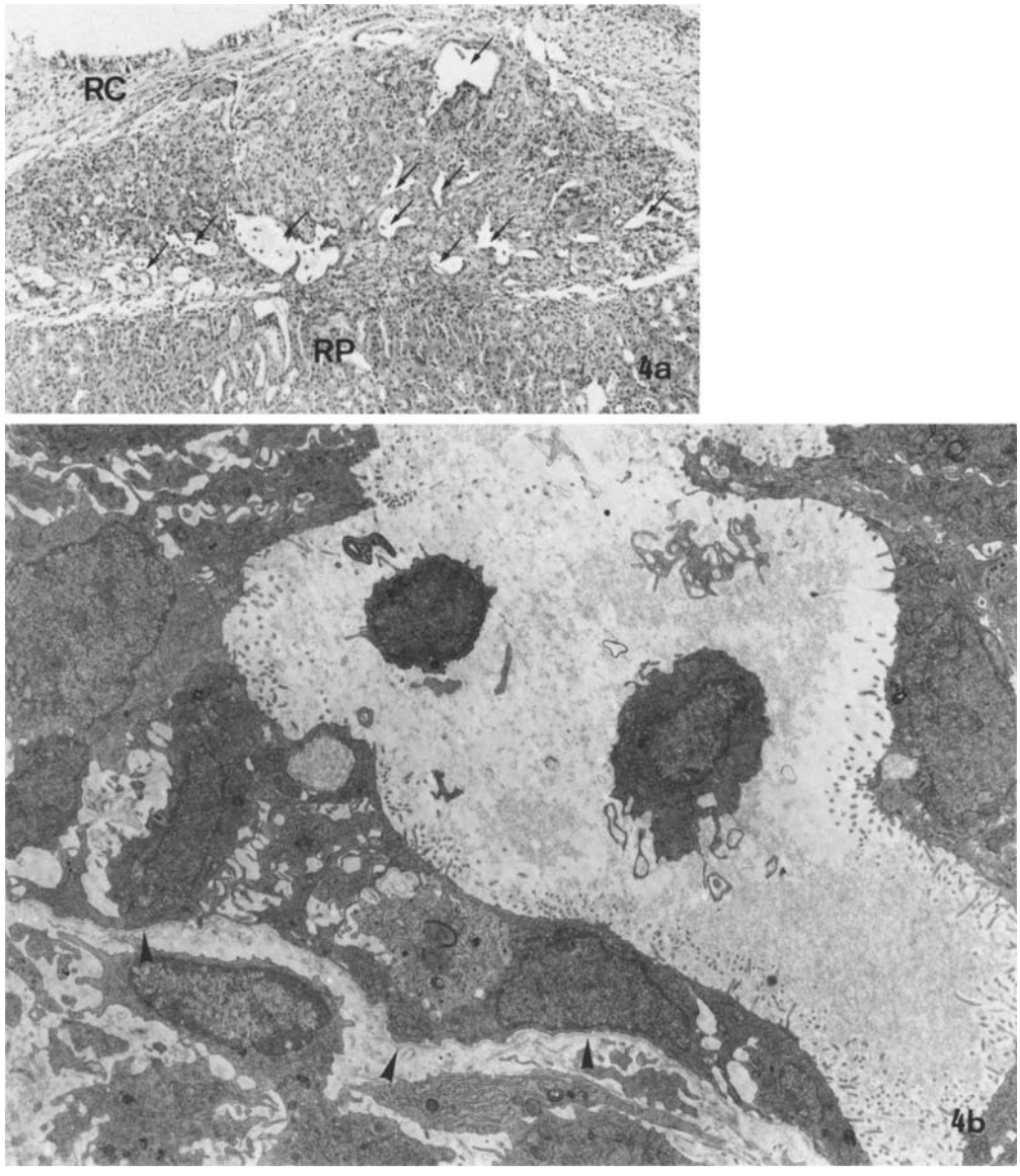

Fig. 4a, b. Pituitary grafts on the 4th day of transplantation. **a** Pituitary graft contains many CLSs (*arrows*) and other variable cells. *RP*: renal parenchyma. *RC*: renal capsule. HE staining. ×72. **b** Ultrastructural feature of CLS. Basement membrane (*arrowheads*) encircles the CLS. Electron dense material fills the cavity of CLS, in which one can observe two mononuclear cells of unknown origin. ×3840

(Petrovic and Porte 1961; Pathak and Fisk 1974), but their origin and physiological significance has been unknown. The present study, using immunohistochemistry and electron microscopy, revealed that these CLSs were derived from the FS cells of the anterior pituitary gland.

There is little information on morphological changes of FS cells in culture. Yamashita (1972) described that the cytoplasm of FS cells hypertrophied after a short-term incubation, and Farquhar (1975) suggested that FS cells could resist lower oxygen tension. Thus the experimental conditions used in this study, such as storing at 4° C for 24 h and incubation in serum-free medium, probably caused selective degeneration of granulated cells while preserving FS cells in the explant. Although the mechanism of CLS formation is not clear, several studies have indicated that CLS formation is related to glandular cell degeneration in the pituitary gland (Selye 1943; Fernholn and Olsson 1969; Benjamin 1981; Gon et al. 1987).

In the rat anterior pituitary gland, the presence of two types of epithelium-lined CLSs was described (Opper 1940; Ferrer 1956). One is a ciliated

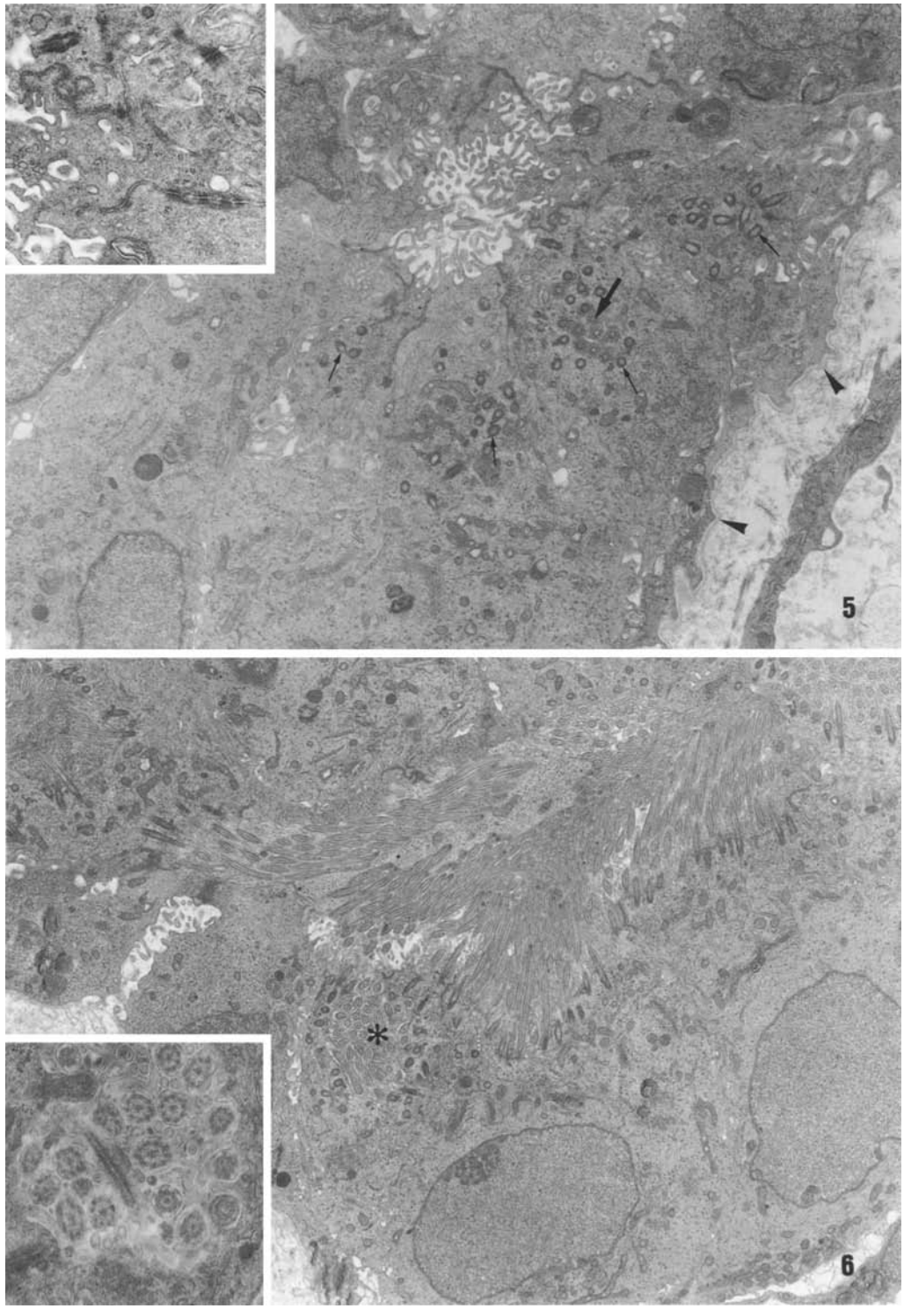

Fig. 5. Pituitary graft on the 8th day of transplantation. Ciliated cells in variable stage of ciliation are seen in one CLS. *large arrow*: cilia. *small arrows*: basal bodies. *arrowheads*: basement membrane. × 5800; *inset*: junctional complexes. × 10400

Fig. 6. Ultrastructural features of "ciliated cell cysts" on the 8th day of transplantation. Ciliation occurrs in intracellular cavities (*asterisk*). The cavity of CLS are filled by many cilia. × 4480 *inset*: cilia of the 9 + 2 type. × 16000

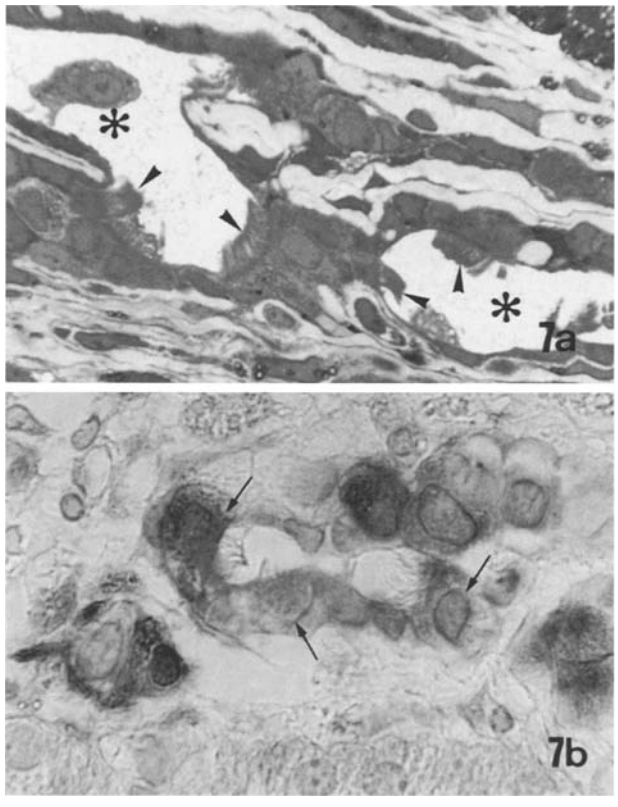

Fig. 7a, b. CLSs on the 14th day of transplantation. **a** 1 μm epon section, stained with 1% toluidine blue. *asterisks*: cavities of CLSs. *arrowheads*: ciliated cells. ×1000. **b** Ciliated cells are immunostained with antiserum against S-100 protein (*arrows*). Counterstained with haematoxylin. ×1080

epithelium with or without mucous cells ("ciliated cell cyst"). The other is a squamous epithelium similar to that forming the anterior lining of the Rathke's cleft ("squamous cell cyst"). CLSs lined by both kinds of epithelium were also described. Opper (1940) indicated that CLSs have been found in 10% of rat anterior pituitaries under normal conditions. The "ciliated cell cysts" are also found in normal anterior pituitaries of other species such as guinea pig (Chadwick 1937), dog (Rajan and Mohiyuddeen 1973), and human (Shankling 1951). The CLSs are believed to be remnants of Rathke's pouch during the development of the pituitary gland.

In the present study CLSs derived from FS cells were very similar to the "squamous cell cyst". Moreover, ciliated cells appeared in the CLSs. Therefore it is suggested that both "squamous cell cysts" and "ciliated cell cysts" are derived not only from Rathke's pouch remnants but also by trans-differentiation of FS cells even in the mature rat anterior pituitary. As described earlier, "ciliated cell cysts" occasionally contain mucous cells among ciliated cells (Opper 1940; Ferrer 1956) but in the present study the mucous cells were not found.

It has been described that FS cells have isolated cilia of 9+0 type called "solitary cilia" or "primary cilia" (Vila-Porcile 1972; Girod and Lheritier 1986). Granulated cells of the anterior pituitary have also been described to have cilia of the 9+0 type (Barnes 1961; Wheatley 1967). Some studies have indicated the presence of FS cells with cilia of 9+2 type (Dingemans and Feltkamp 1972; Yoshimura et al. 1977, Fig. 2). According to the previous and present studies, it is suggested that cilia of normal FS cells are of the 9+0 type, and "FS cells with cilia of the 9+2 type" are ciliated cells which differenciated from FS cells under unknown physiological conditions.

Cystic tumours occur within the sella turcica, such as Rathke's cleft cyst (Ringel and Bailey 1972; Yoshida et al. 1977) and craniopharyngioma (Gathak et al. 1971; Banna 1976). Rathke's cleft cyst is lined by ciliated or non-ciliated epithelium, but craniopharyngioma is morphologically variable, being mainly composed of stratified squamous epithelium. In 1985, Goodrich et al. described an intermediate type of tumour, "ciliated craniopharyngioma". Cystic tumours are commonly assumed to arise from Rathke's pouch remnants, but the exact origin is unknown. From the present findings, we suggest that cystic tumours within the sella turcica might be also derived from FS cells. This suggestion seems to be supported by evidence that FS cells can proliferate (Wilson 1986; Gon et al. 1987) but there are few reports on pituitary tumours composed of FS cells (Yagishita et al. 1984).

The FS cells are primitive cells which do not contain secretory granules and line small follicles in the anterior pituitary (Dingemans and Feltkamp 1972; Vila-Porcile 1972; Yoshimura et al. 1977). It is supposed that FS cells from a continuous intercellular "cavity" system and act as a scavenger system in the rat anterior pituitary (Dingemans and Feltkamp 1972; Vila-Porcile 1972; Giocca and Gonzalez 1978). Some authors have suggested that FS cells have potential to differentiate into granulated cells (Yoshimura et al. 1977; Leatherland and Renfree 1982). The present study has revealed that CLS-forming cells can be derived from FS cells, but differentiate only into ciliated cells. Further studies are necessary to decide whether FS cells have the potential to trans-differentiate to granulated cells.

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