

## Postnatal maturation of the parenchymal cell types in the rabbit pineal gland

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**Summary.** An ultrastructural study on the maturation of the parenchymal rabbit pineal cell types from the first postnatal day up to 120 days is presented. Two main cell types are distinguished from the first 24h of postnatal life. Pinealocytes of the types I and II display different developmental degrees. Both immature cell types are arranged in groups. In addition, type II pinealocytes form rosette-like structures. Both cell types progressively become isolated and display cell processes. The nucleus and the cytoplasm of type I pinealocytes are barely electron-dense. During the postnatal period, the number of cytoplasmic organelles, cell processes and terminal clubs increase progressively. Terminal clubs are frequently seen near blood vessels. After 30 days, type I pinealocytes show characteristics of adult pinealocytes. However, the maturation of most type I pinealocytes does not complete until the 90th postnatal day. Type II pinealocytes present a fairly electron-dense nucleus and cytoplasm. Mature forms can be seen after the 5th postnatal day. During the postnatal period, a close relationship is determined among type II pinealocytes and cell processes and terminal clubs of type I pinealocytes.

**Key words:** Pinealocyte, Rabbit, Postnatal development, Ultrastructure

### Introduction

Most studies on the pineal gland of mammals have been performed on rodents, with very few in other species. On the rabbit the scarce ultrastructural descriptions reported were based on the adult pineal gland (Wartenberg and Gusek, 1965; Leonhardt, 1966,

1967; Romijn, 1973a), and most of them focused particularly on the gland innervation (Romijn, 1973b, 1975a,b, 1976; Romijn and Gelsema, 1976; Romijn et al., 1976, 1977).

Two main cell types are distinguished in the rabbit pineal gland parenchyma: light pinealocytes (Romijn, 1973a) (Type I pinealocytes according to Pevet, 1977), and dark pinealocytes (Romijn, 1973a) (Type II pinealocytes according to Pevet, 1977). Few astrocytes have also been described in the rabbit pineal gland (Romijn, 1973a).

No further ultrastructural reports on the postnatal development of the rabbit pineal gland have succeeded the first light microscopical description from Kerenyi and von Westarp (1971).

In our work we shall study the ultrastructural maturation of the parenchymal cell types on the rabbit pineal gland.

### Materials and methods

24 New Zealand White albino rabbits were used in the study. The animals were kept under artificial light cycles (16L:8D) (100W light bulbs). Food and water was administered ad libitum.

Animals used were aged 1 day to 120 days old, when rabbits become fertile and are considered adults. Two animals from each age group (1, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, and 120 days old) were sacrificed. Tissue blocks were sampled between 17 and 20 hours through the months of October to the next February. Animals previously anesthetized were sacrificed by decapitation. In the first stages, animals were anesthetized with ether and older animals with 3-10 cc of 10% chloral hydrate intraperitoneally, depending on the age of the animal.

For the electron microscope study, tissue blocks were fixed by immersion in cold 2% glutaraldehyde-2% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4, postfixed in osmium tetroxide, dehydrated in

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acetone and embedded in Vestopal. Ultrathin sections obtained with a LKB ultramicrotome were stained with uranyl acetate and lead citrate. Ultrathin sections were studied under a Philips EM 201 electron microscope.

## Results

No differences could be found between sexes during the postnatal evolution of the rabbit pineal gland, whereby no references are mentioned in the results.

*Day 1.* After 24 hours of postnatal life, two parenchymal cell types could be identified in the rabbit pineal gland: types I and II pinealocytes. Type I pinealocytes showed a rounded or ovoid nucleus with slight contour irregularities. Chromatin was loose with small peripheric densifications (Fig. 1). Frequently one or two nucleoli of compact appearance were observed. The hyaloplasm was lightly electrondense, though variations existed among type I pinealocytes. The clearest showed a more extensive development of the organoids (Fig. 1). However, the darker ones showed less cytoplasm and tended to locate forming small irregular, vaguely-defined clusters (Fig. 2). In both cases, diplosomes were frequently found. Occasionally, type I pinealocytes showed short, thick cell processes free of terminal club (Fig. 3).

Type II pinealocytes presented a narrow electron-dense cytoplasm poor in organoids (predominantly polyribosomes and rough endoplasmic reticulum), and an elongated nucleus with dense homogeneous chromatin. Frequently a nucleolus was observed (Figs. 3, 4). These type II pinealocytes could be found isolated or forming clusters of variable cell number (Fig. 5). In this first postnatal day we observed cell processes in the type II pinealocytes, particularly in those not forming large groups (Fig. 6).

Frequently, type II pinealocytes formed rosette-like structures, extending apical cilia towards a narrow central lumen (Fig. 7). Complex interdigitations existed at the lateral faces along with frequent intercellular adherens and gap-like junctions (Fig. 8).

*Day 3.* At this stage, type I pinealocytes developed thin cell processes rich in microtubuli (Fig. 9). Sometimes, these cell processes tues. Assuming duration of M phase to be 1/2 hour,  $G_1$  values ranged from 2.8 to 5.4 hours.

Minimal percentage values of labelled mitoses occurred at the 24, then 48 hour post pulse-chase time points in all cell lines. A second peak of labelled dings were located near blood vessels and among the somata of pinealocytes.

*Day 5.* Numerous type I pinealocytes showed a relatively wide cytoplasm rich in polyribosomes and mitochondria. The rough endoplasmic reticulum was organized in small groups of parallel cisterns. Golgi dictyosomes, dense bodies and microtubuli were

also observed (Fig. 11). Frequently, cell processes from type I pinealocytes related with type II pinealocytes (Fig. 11). Bulbous endings of the type I pinealocytes, located near blood vessels, were progressively more numerous (Fig. 12). Type II pinealocytes showed a larger organoid development, particularly the Golgi apparatus. Their cell processes were more abundant and frequently closely related to blood capillaries, abutting on their basement membrane (Fig. 13).

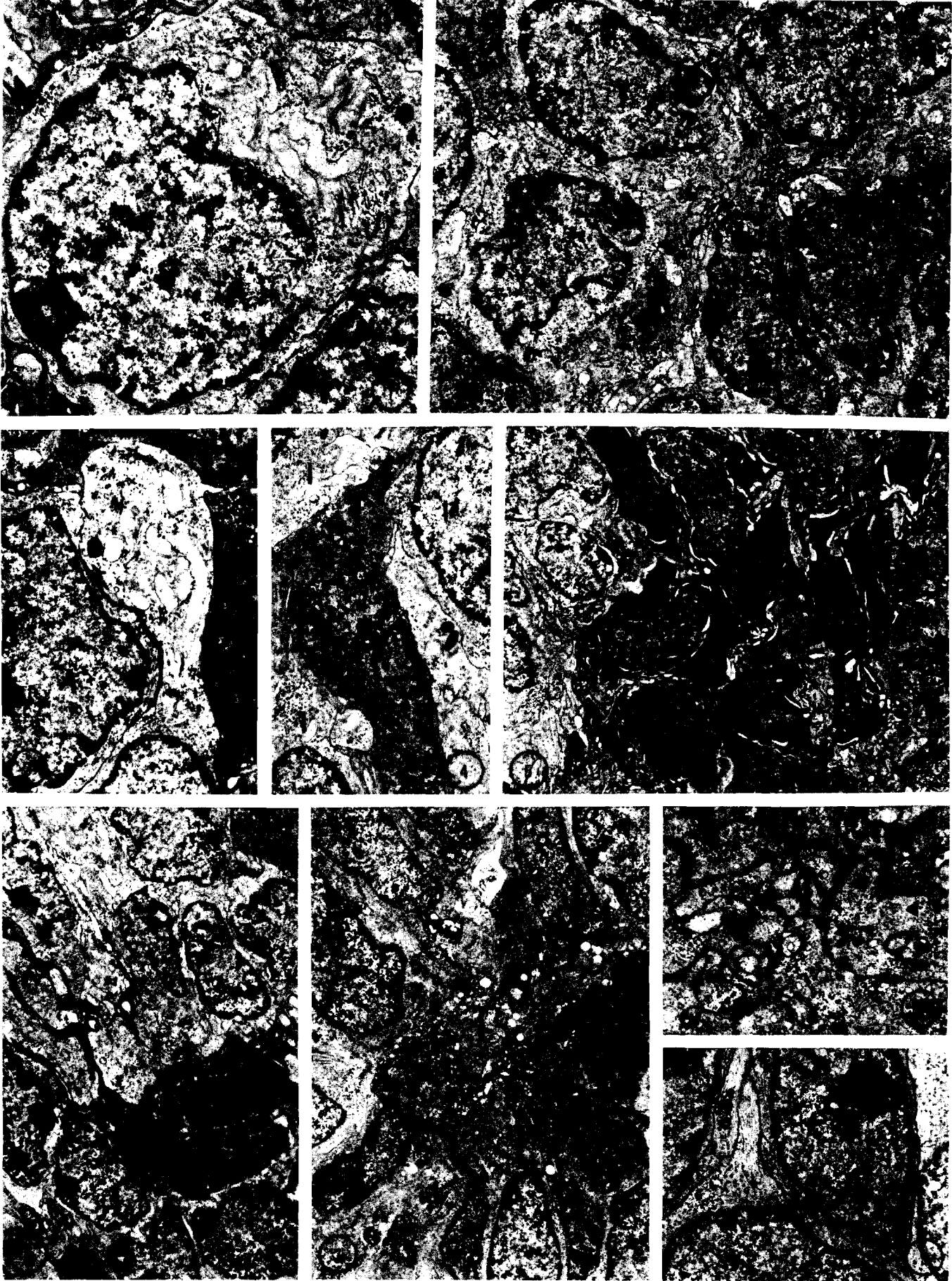
*Day 7-15.* The nucleus of the type I pinealocyte showed an eccentric position. Numerous mitochondria were found grouped in a juxtannuclear position around a Golgi zone centred by a diplosome. Clear, dense core and coated vesicles were also found near the dictyosomes. Microtubuli and dense bodies were abundant. Polyribosomes appeared to be less abundant than in former stages. Cilia, apparently originating in deep cytoplasmic regions, were occasionally observed (Fig. 14). Type I pinealocyte cell processes were somewhat more complex. Frequently they stemmed from a thick trunk located on the side opposite to the nucleus (Fig. 15). In the terminal clubs of the cell processes a few dense core vesicles began to appear among the clear vesicles.

*Day 20-30.* At the 20th postnatal day, within the terminal clubs, structures formed by concentrically smooth cisterns, named nebenkern or whorls, were first seen (Fig. 16). At the 30th postnatal day, type I pinealocytes ultrastructurally similar to adult cells were identified. Their nucleoli acquired a reticulated appearance. Rough endoplasmic reticulum organized in groups of short parallel cisterns were found preferentially at the periphery of the soma (Fig. 17). A well-developed smooth endoplasmic reticulum was also regularly found. Subsurface cisterns were detected along all the surface of type I pinealocytes (Fig. 18). Cilia could still be seen in these cells.

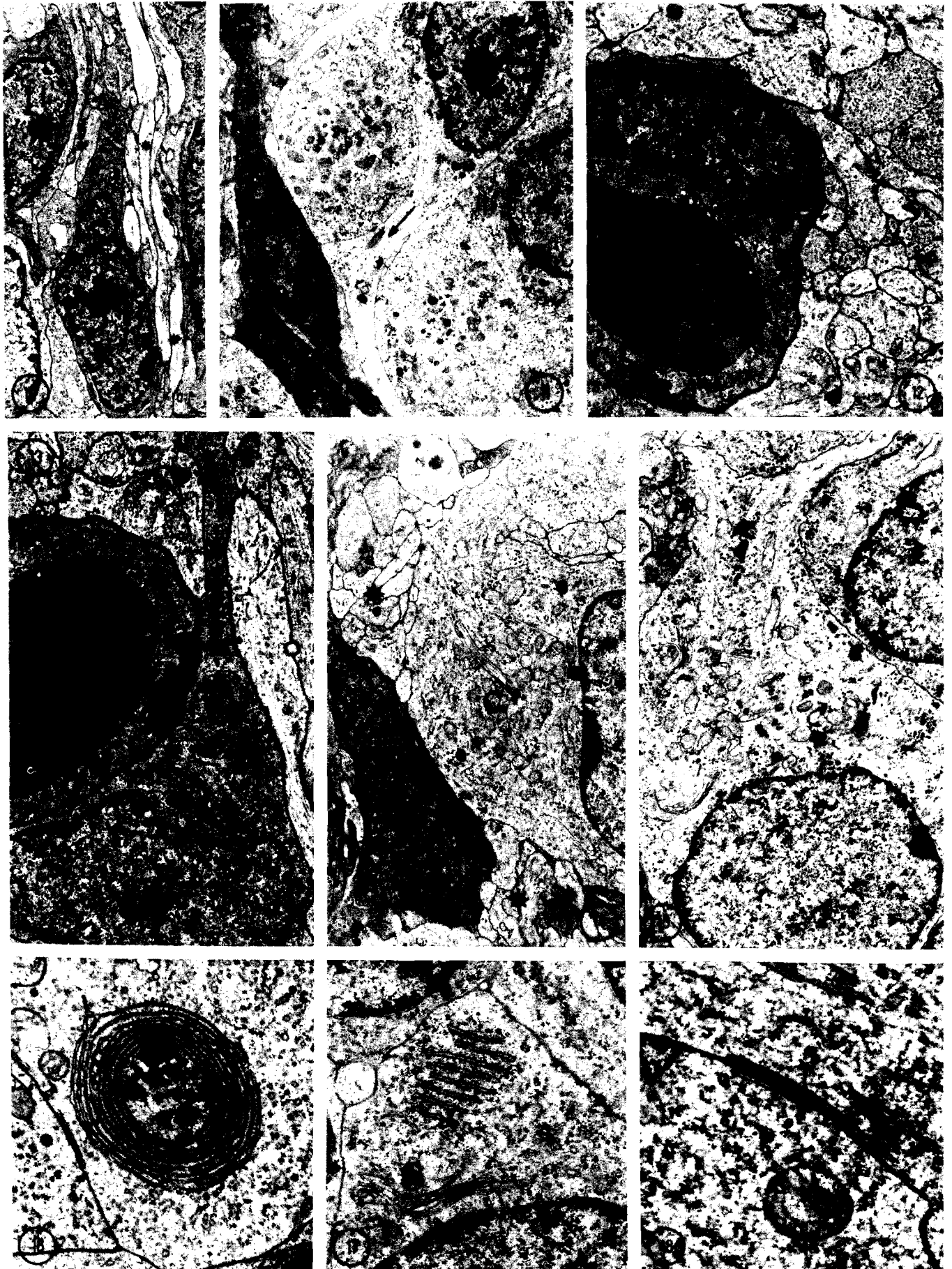
*Day 90 (Adult).* Almost all type II and I pinealocytes exhibited cell characteristics similar to adult cells. It was at this age when histological maturation was attained. A wider development of the smooth endoplasmic reticulum was detected on the bulbous endings of type I pinealocytes. Subsurface cisterns were much more frequent. Centrioli persisted in the adult type I pinealocyte, though cilia tended to disappear. Nebenkern were also frequent in the terminal bulbs.

## Discussion

In the rabbit pineal gland two parenchymal cell types can be identified from the first 24 hours of postnatal life that will undergo a series of modifications during the postnatal life. During the first postnatal phases, type I pinealocytes could be seen at different developmental stages. The most immature



*Postnatal maturation of rabbit pineal gland*



**Fig. 1.** Female rabbit pineal gland. 1st postnatal day. Type I pinealocyte with a large nuclear development showing loose chromatin and lightly electrondense hyaloplasm. Moderate organelle development.  $\times 15,400$

**Fig. 2.** Female rabbit pineal gland. 1st postnatal day. Cluster of dense type I pinealocytes with scant cytoplasmic development.  $\times 7,500$

**Fig. 3.** Female rabbit pineal gland. 1st postnatal day. Clear type I pinealocyte with a thick cell process showing an accumulation of organelles. Not to be considered yet as a terminal club. (\*). Type II pinealocyte.  $\times 9,200$

**Fig. 4.** Male rabbit pineal gland. 1st postnatal day. Type II pinealocyte with strongly electrondense cytoplasm among type I pinealocytes (I).  $\times 9,200$

**Fig. 5.** Female rabbit pineal gland. 1st postnatal day. Type II pinealocyte among type I pinealocytes. Note the stronger electrondensity of the former.  $\times 4,300$

**Fig. 6.** Male rabbit pineal gland. 1st postnatal day. Type II pinealocytes showing fine cytoplasmic processes snaking among adjacent type I pinealocytes (arrows).  $\times 5,700$

**Fig. 7.** Male rabbit pineal gland. 1st postnatal day. Type II pinealocytes forming rosette-like structures.  $\times 16,000$

**Fig. 8.** Male rabbit pineal gland. 1st postnatal day. Adherens-type junction mechanisms (arrows) and gap-like junctions (arrowheads) between type II pinealocytes forming the rosette-like structure.  $\times 16,000$

**Fig. 9.** Male rabbit pineal gland. 3rd postnatal day. Type I pinealocytes showing scant cytoplasm and the outset of a small cell process rich in microtubuli.  $\times 10,300$

**Fig. 10.** Male rabbit pineal gland. 3rd postnatal day. Group of type I pinealocyte cell processes (\*) related to type II pinealocyte somata (II). M: terminal club.  $\times 7,500$

**Fig. 11.** Female rabbit pineal gland. 5th postnatal day. Wide cytoplasm of type I pinealocytes with a broad organelle development. Note the cell process stemming from one of them (arrow), related to an adjacent type II pinealocyte (II).  $\times 18,600$

**Fig. 12.** Female rabbit pineal gland. 5th postnatal day. Abundant perivascular type I pinealocyte terminal clubs. L: capillary lumen. P: Pericyte.  $\times 11,200$

**Fig. 13.** Male rabbit pineal organ. 5th postnatal day. Type II pinealocyte leaning on the basal membrane of a blood capillary. A fine cell process (arrow) is seen extending from the soma and lying among the bulbous endings and processes of type I pinealocytes.  $\times 12,000$

**Fig. 14.** Male rabbit pineal gland. 7th postnatal day. Type I pinealocyte with an eccentric nucleus and a wide, moderately dark cytoplasm rich in organoids. Next to it, abundant processes of type I pinealocyte (\*) and a type II pinealocyte containing a strong-dark hyaloplasm.  $\times 9,000$

**Fig. 15.** Male rabbit pineal gland. 7th postnatal day. Type I pinealocyte with wide cytoplasm an eccentric nucleus. Cell processes (arrow) emerging from the side opposite to the nucleus. Note the numerous organelles in the cytoplasm.  $\times 9,400$

**Fig. 16.** Male rabbit pineal gland. 30th postnatal day. Nebenkern on the bulbous endings.  $\times 21,000$

**Fig. 17.** Male rabbit pineal gland. 20th postnatal day. Characteristic groups of rough endoplasmic reticulum cisterns on the cytoplasm of a type I pinealocyte (G: Golgi complex).  $\times 15,000$

**Fig. 18.** Female rabbit pineal gland. 30th postnatal day. Typical subsurface cisterns located at cytoplasmic periphery of type I pinealocyte.  $\times 36,400$

forms were grouped in irregular clusters. In these cases their cytoplasm was scarce and polyribosomes predominated. However, those more developed showed a wider cytoplasm richer in organoids. In addition, these cells tended to display cell processes, though at this age no terminal clubs could be seen in the distal stumps. After 30 days, some type I pinealocytes were fully developed. Nevertheless, the maturation of the major part of this cell type is completed at the 90 postnatal day, an observation largely overlapping those of Kerenyi and von Westarp (1971).

During postnatal life, the nucleus of the type I pinealocyte undergoes transformations similar to those observed in the hamster pineal gland (Hewing, 1979). The contour becomes more regular with the cellular maturation. Kerenyi and von Westarp (1971) obtained opposite results in their light microscope study. Romijn (1973a) describes the nuclear ultrastructure of the type I pinealocyte as lobated. The compact nucleolus observed in the first stages of the postnatal period, transforms into a reticulated nucleolus, as has been described in the nucleoli of the adult type I pinealocyte of different mammal species (Lew et al., 1982; Banks et al., 1985; López-Iglesias et al. 1986).

Throughout the developmental process, cytoplasmic organoids of the type I pinealocyte varied in number, organization and distribution. At the first postnatal day isolated cisterns of rough endoplasmic reticulum were found. During the maturation process of the type I pinealocyte, the cisterns tended to form small groups of parallel cisterns preferentially located at the periphery of the soma. This organization of the rough endoplasmic reticulum can be a sign of maturation of the type I pinealocyte. In the adult rabbit, the rough endoplasmic reticulum is described as abundant (Leonhardt, 1967) and concentrated at the periphery of the type I pinealocyte. However, Wartenberg and Gusek (1965) do not refer to its peculiar disposition in small groups. The abundance of rough endoplasmic reticulum can reflect an intensive protein synthesis in the type I pinealocyte.

The smooth endoplasmic reticulum has been described in the type I pinealocyte of the adult rabbit by Wartenberg and Gusek (1965), Leonhardt (1967) and Romijn (1973a). According to our results, it appears at the 30th postnatal day. The Golgi complex is seen from the first postnatal day, with a greater development with age. Clear, dense core and coated vesicles are found close to Golgi dictyosomes in the adult rabbit (Romijn, 1973a). In the first postnatal stages, only clear vesicles were seen. From the 7th postnatal day onwards dense core and coated vesicles appeared. In most mammals, clear vesicles are located frequently at the type I pinealocyte bulbous endings, suggesting that some secretion products could be contained inside (Romijn, 1973a; Welsh et al., 1979;



Karasek, 1981). The number of dense core vesicles follows a circadian rhythm (Romijn et al., 1976), decreasing after the sympatectomy (Romijn et al., 1975a). It has been suggested that the content of the dense core vesicles corresponds to peptides and indolamines (Romijn and Gelseman, 1976; Juillard, 1979; Juillard and Collin, 1980; Masson-Pevet et al., 1987). The significance of coated vesicles described at the type I pinealocyte of the adult rabbit by Leonhardt (1967) and Romijn (1973a) is unclear, though Romijn (1973a) considers their potential for transformation into dense core vesicles.

The juxtannuclear position of the mitochondrial accumuli, also described in the adult rabbit type I pinealocyte by Wartenberg and Gusek (1965), Leonhardt (1967) and Romijn (1973a), became evident from the 7th postnatal day. The juxtannuclear localization of mitochondria in pinealocytes of different mammals, recalls that seen in photoreceptor cells (Vollrath, 1981). According to Romijn et al. (1977), mitochondria of rabbit type I pinealocytes will intervene in the synthesis of indolamines. Tryptophan 5-hydroxylase, an enzyme involved in the synthesis of serotonin, is found in these mitochondria.

Subsurface cisterns have not been described in the rabbit type I pinealocyte. They appeared at the 30th postnatal day, being particularly abundant in adults. It has been suggested that they may intervene in a possible interchange of substances (Wartenberg, 1968; Pevet, 1979; Karasek, 1983).

In the rabbit, centrioles are frequently observed throughout the postnatal development of the type I pinealocyte and persist in the adult, as was pointed out by Romijn (1973b). With respect to the cilia, most authors found them in the rat pinealocytes in the first stages of postnatal development (Zimmerman and Tso, 1975; Steinberg et al., 1981; Calvo and Boya, 1983). We observed similar features in the adult rabbit type I pinealocyte.

The type I pinealocyte of the adult rabbit has been described as a cell poor in cell processes (Wartenberg and Gusek, 1965; Leonhardt, 1967; Kappers, 1976). However, Romijn (1973a), described them as abundant. On the other hand, we observed long, but scarce cell processes. From the 3rd postnatal day onwards, cell processes of type I pinealocytes showed signs of a more extensive development displaying terminal clubs. With age, cell processes became more numerous, ramifying from the main stem. Their abundant microtubular content may participate in the transport of both clear and dense core vesicles from the Golgi apparatus towards the terminal clubs as suggested by Romijn (1973a) and Romijn et al. (1976). During postnatal development and in the adult, cell processes of type I pinealocytes followed a conjoint trajectory. Bearing in mind the close proximity among pinealocytes, this disposition would facilitate the access of the cell processes to the vessels. These hypothetical paths

could be determined in part by type II pinealocytes. This is suggested by the fact that, from the third day, a close and constant relationship was determined between the bundles of cell processes of type I and type II pinealocytes.

At the 3rd postnatal day, terminal clubs appeared in type I pinealocytes, easily identified by their clear vesicular content. Terminal clubs became more numerous with cell maturation. At the 7th postnatal day, dense core vesicles began to appear. In the terminal clubs of adult type I pinealocyte, mitochondria and smooth endoplasmic reticulum are present in addition to vesicles (Romijn, 1973a). In these terminal clubs we also found nebenkern from day 20. Present in small amounts, they were described and named as «whorls» by Leonhardt (1967) and Romijn (1973a) in the adult rabbit. However, we have observed them frequently, particularly in the adult type I pinealocyte. Their almost exclusive presence in the terminal clubs suggests that they may be involved in the secretion process of type I pinealocytes. Karasek (1983) considers that these «whorls» are related to an increase in the secretory activity. Conversely, Romijn (1975a) observes an increase of these structures in the terminal clubs after sympathetic and parasympathetic denervation of the rabbit pineal gland.

Our results confirm the ultrastructural features of type II pinealocytes described by Wartenberg and Gusek (1965) and Romijn (1973a). Obviously, we do not find pigment grains in this cell type, since we used albino rabbits.

In the first phases and throughout the postnatal period, immature type II pinealocytes were arranged in groups or cellular cords, also forming rossete-like structures. With maturation, they became independent, being located among type I pinealocytes or forming small groups of 2-3 cells. At the same time, there was an increase in organoids and in the number of long cell processes, as described in the rat (Calvo and Boya, 1983). At the 5th postnatal day, we found differentiated forms of type II pinealocytes. In the pineal gland of the adult rabbit and during development, a close relationship is found among the cell processes and the terminal clubs of type I pinealocytes with type II pinealocytes. This suggests that type II pinealocytes could facilitate in some way the access of the cell processes of type I pinealocytes to the vessels. Therefore, we may consider that at least during postnatal development, type II pinealocytes will have in part a support function facilitating the development of type I pinealocytes, particularly their cell processes and the bulbous endings. Romijn (1973a, 1975a), considers that type II pinealocytes will participate directly in the pineal secretion. In other species, e.g. the rat, a glial nature has been suggested for these cells (Calvo et al., 1988; Krstic and Nicolas, 1990).

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