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Merkel Cells as Human Cutaneous Neuroreceptor Cells

Their Presence in Dermal Neural Corpuscles and in the External Hair Root Sheath of Human Adult Skin

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Summary. Merkel cells were found in the dermis closely associated with non-myelinated axons in human adult hairy skin. They were enclosed in a neural corpuscle formed by Schwann cells, myelinated and non-myelinated axons, and surrounded by flattened laminar cells. The neural corpuscle was attached to the basal lamina of the hair external root sheath.

Additionally, Merkel cells were found in the outermost cell layer of the follicular epithelium, not covered by the neural corpuscle. They were in close contact with a surrounding axonal network, forming epithelio-neural junctions.

In conclusion, this study confirms the significance of the Merkel cells as an important neuroreceptor cell enabled to register and to transform peripheral stimuli into axonal impulses from the dermis, the epidermis and the follicular epithelium as well.

Zusammenfassung. Diese Untersuchung zeigt das Vorkommen *dermaler Merkel-Zellen* in der behaarten Haut des Erwachsenen. Die dermalen Merkel-Zellen sind assoziiert mit nicht myelinisierten Axonen und bilden Merkelzell-axonale Komplexe. Diese sind eingeschlossen in einem von schmalen Hüllzellen umschlossenen Nervenkörperchen, welches neben den nicht myelinisierten Axonen auch myelinisierte Axone und Schwann-Zellen enthält. Das Nervenkörperchen liegt dicht an der äußeren Wurzelscheide des Haarfollikels.

Darüber hinaus finden sich außerhalb des Nervenkörperchens *Merkel-Zellen auch im Follikelepithel*, die mit dem dermalen Nervengeflecht epithelio-neurale Verbindungen bilden.

Unsere Untersuchungen belegen, daß Merkel-Zellen nicht nur in der Epidermis, sondern auch in der Dermis und im Follikelepithel vorkommen. Sie stellen offenbar die *spezialisierten Neuroreceptorzellen der Haut dar*, die in der Lage sind, periphere Reize zu registrieren und in axonale Impulse umzusetzen.

Merkel cells in the basal epidermal layer were described as neuroreceptor cells of human epithelio-neural junctions [6, 9, 12]. They were never found in the dermis or in the follicular epithelium of human adult skin [13, 15]. In this study we report our observations on dermal Merkel cells situated in an encapsulated sensory corpuscle and on Merkel cells of the external hair root sheath. These findings suggest, that Merkel cells have a major significance as neuroreceptor cells in skin innervation.

Material and Method

The skin specimen was obtained from the upper leg of a 57 year old woman, which suffered from pityriasis lichenoides chronica. 4 mm punch biopsy was taken under local anesthesia with Scandicain® from a typical lesion. After prefixation in a paraformaldehyde/glutaraldehyde solution (4:2.5%, buffered with cacodylate buffer, pH 7.2) for 18 hrs, the specimen was cut in small flakes, rinsed briefly in cacodylate buffer (pH 7.2), fixed in osmic acid for 1 hr, dehydrated in rising concentrations of acetone, and embedded in Araldite®. Thin sections were stained with uranyl acetate and lead citrate and examined with a Zeiss 9 A electron microscope.

Results

In the middermis we found multiple cup-shaped laminar cells forming a neural corpuscle associated with a hair follicle (Fig. 1). The laminar cells approached the basal lamina of the follicular epithelium and attached the corpuscle to the external root sheath of the hair. The follicular basal lamina was intact and no direct contact between laminar cells and epithelial cells was observed.

Between the laminar cells myelinated and non-myelinated axons were arranged, totally enclosed or partly surrounded by cytoplasmic seams of Schwann cells. Furthermore, three dermal Merkel cells were found in the periphery of the neural corpuscle closely associated with non-myelinated axons (Fig. 2).

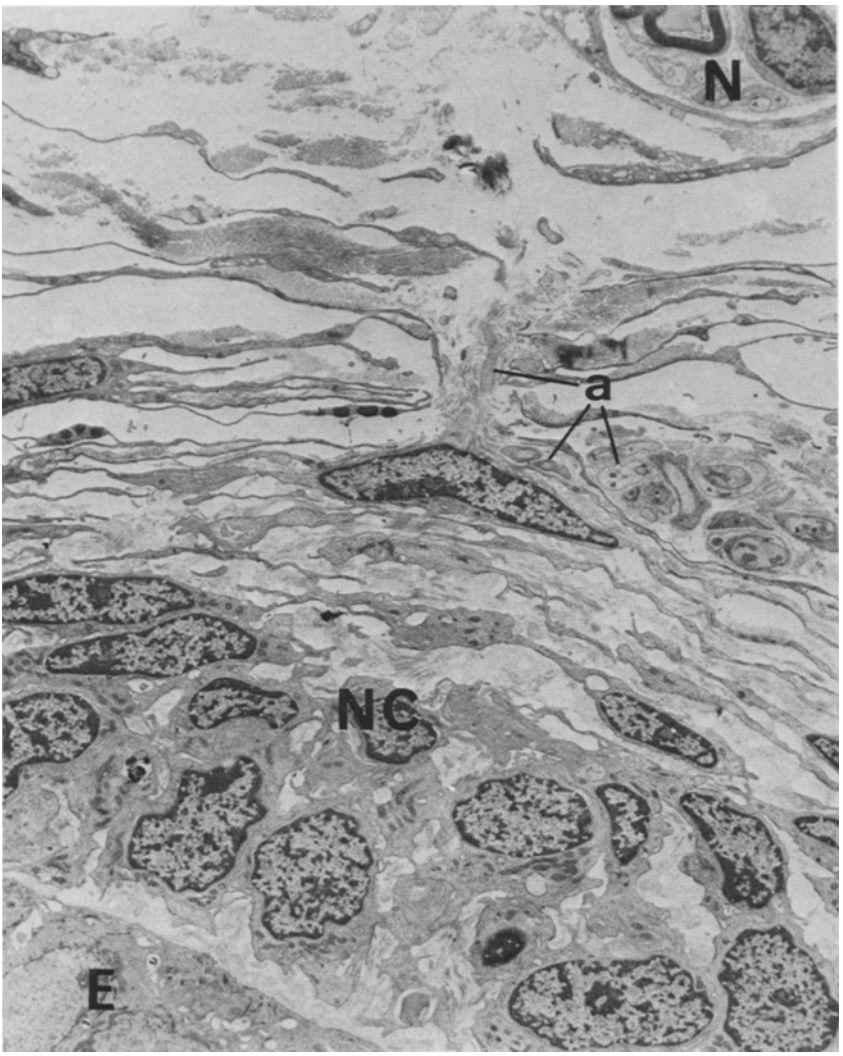

Fig. 1. *Dermal neural corpuscle* (*NC*), formed by laminar cells and attached to the follicular epithelium (*E*). Dermal nerve trunk (*N*). Axons entering the neural corpuscle (*a*). ×5150

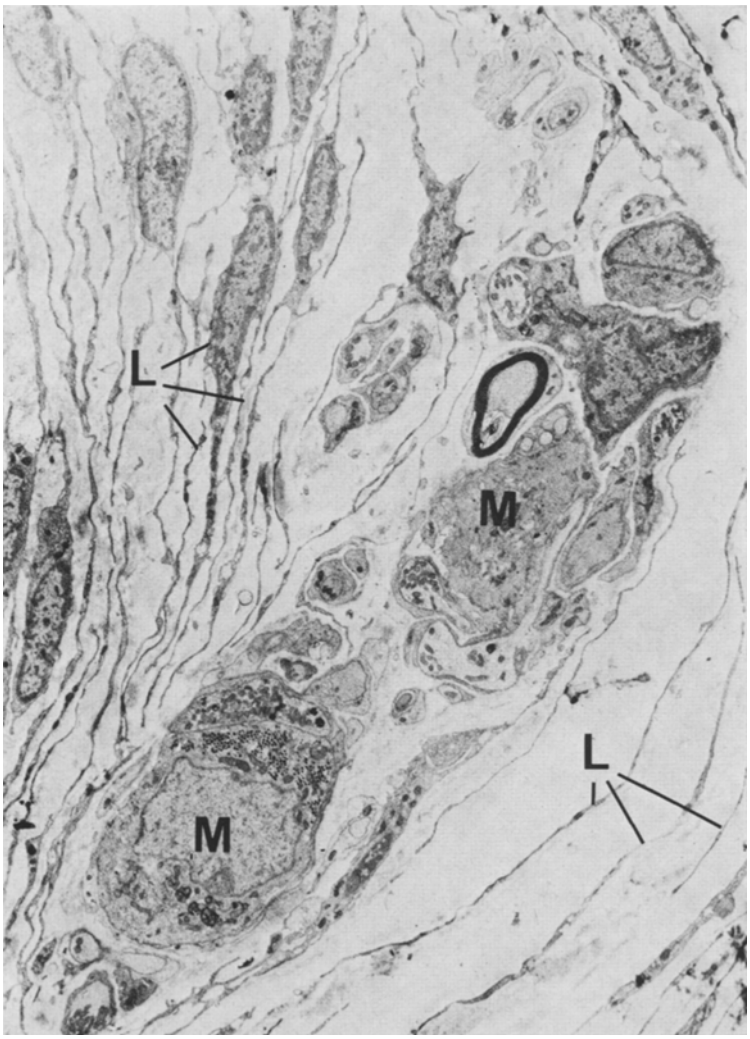

Fig. 2. *Dermal Merkel cell-axon junctions* in the periphery of the neural corpuscle. Merkel cells (*M*). Laminar cells (*L*). ×5150

The Merkel cells were characterized by accumulations of typical 100—140 nm sized dense-core granules (Fig. 3). These granules were concentrated in the cytoplasmic area opposite to the adjacent axons, which contained numerous mitochondria. Each Merkel cell possessed its own basal lamina and was, as a rule, isolated from the axonal Schwann cells and from the laminar cells of the corpuscle. However, in the Merkel cell-axon junction the concomitant Schwann cell was partly in close apposition to the Merkel cell and the basal lamina of the two cells fused together. In some areas cytoplasmic protrusions of the two cell types were highly intermingled and the differentitation between Schwann cell and Merkel cell was difficult.

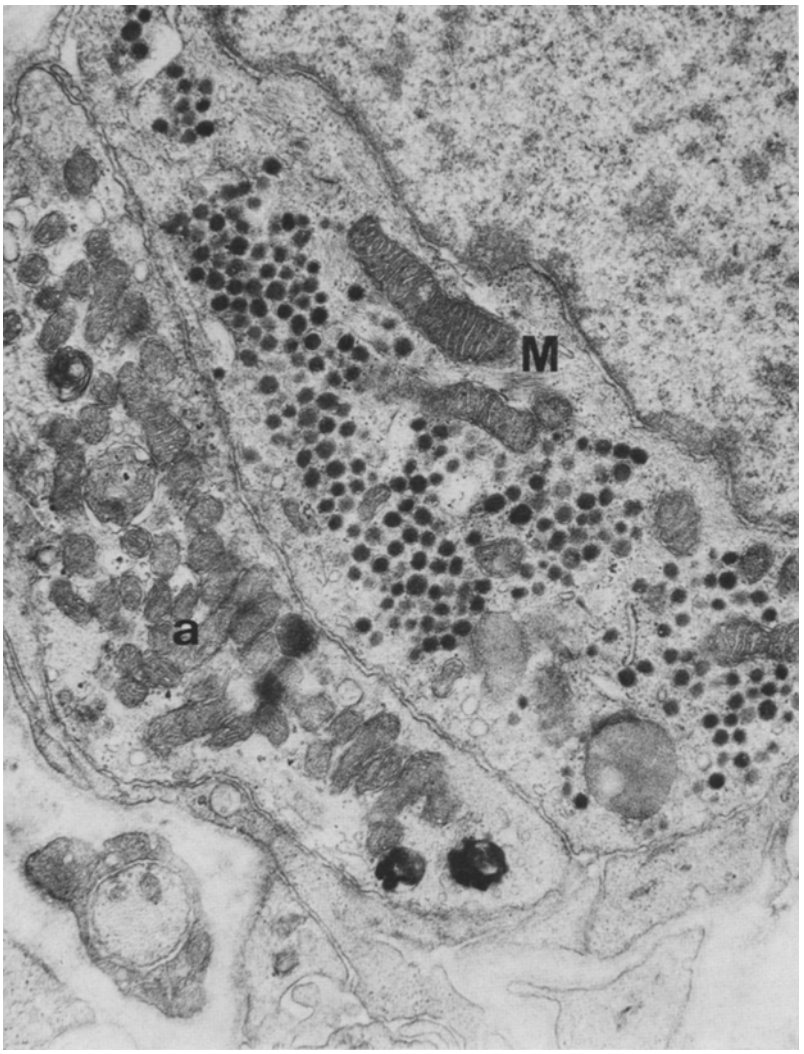

Fig. 3. *Dermal Merkel cell* (*M*) containing typical large dense-core granules in close contact with an axonal disque (*a*) rich in mitochondria. ×30000

Although cytofilaments were found within the dermal Merkel cells, no desmosomes could be detected on their surface, in contrast to epidermal Merkel cells. All other ultrastructural features of the dermal Merkel cells were similar to those described in epidermal Merkel cells.

Occasionally, neurites with myelinated axons passed nearby the dermal Merkel cells (Fig. 4). In all these cases the Merkel cell was separated from the neurite by an interspace measuring ca. 150 nm between their basal lamina. No direct contact was found between dermal Merkel cells and myelinated axons.

At the dermal site of the follicular epithelium not covered by the neural corpuscle an axonal network was found. Though we did not detect any connections

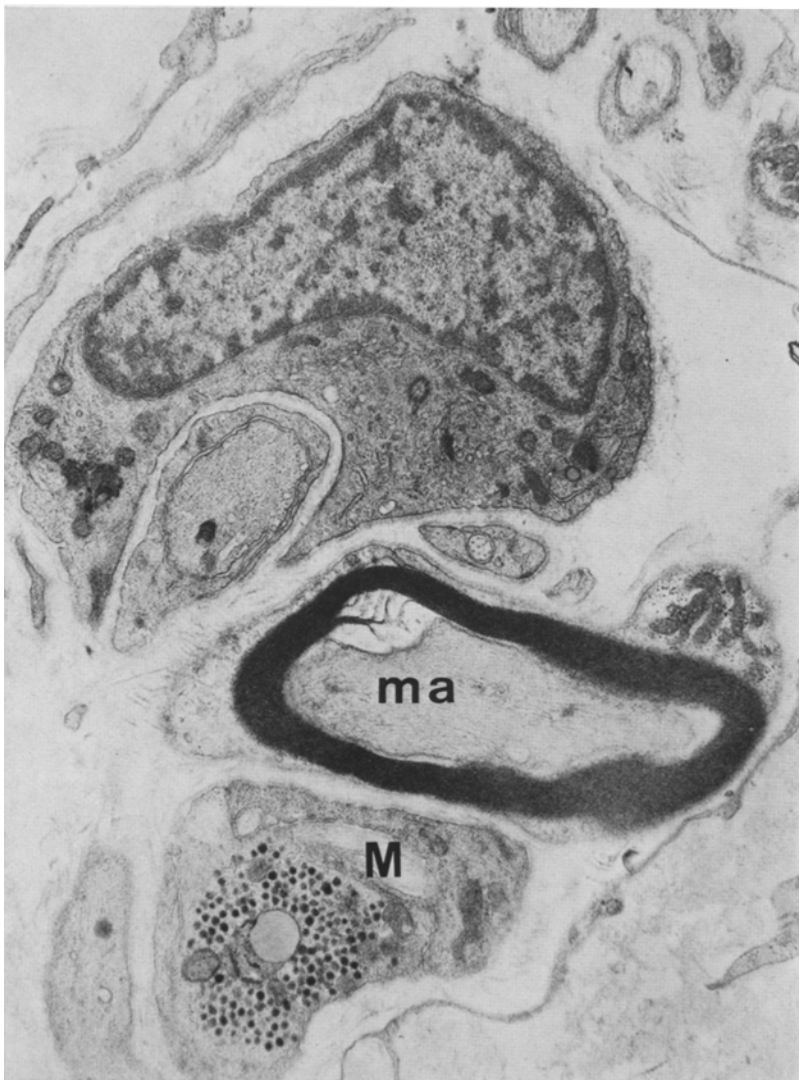

Fig. 4. *Dermal Merkel cell* (*M*) with dense-core granules. A neurite with a myelinated axon (*ma*) pass nearby the dermal Merkel cell. ×14400

between the axons of the corpuscle and the follicular epithelium, epithelio-axonal junctions occurred between the extracorpuscular neural network and the follicular cells (Fig. 5). These junctions consisted of non-myelinated axons adjoining follicular cells or typical Merkel cells of the outermost follicular cell layer. Epithelio-axonal junctions with non-specialized receptor cells of the external hair root sheath were described earlier [13] and will not be discussed here. The epithelio-axonal junctions with specialized receptor cells in the follicular epithelium were similar to those of Merkel-Ranvier in the epidermis. Fig. 6 visualizes the complex innervation of hair

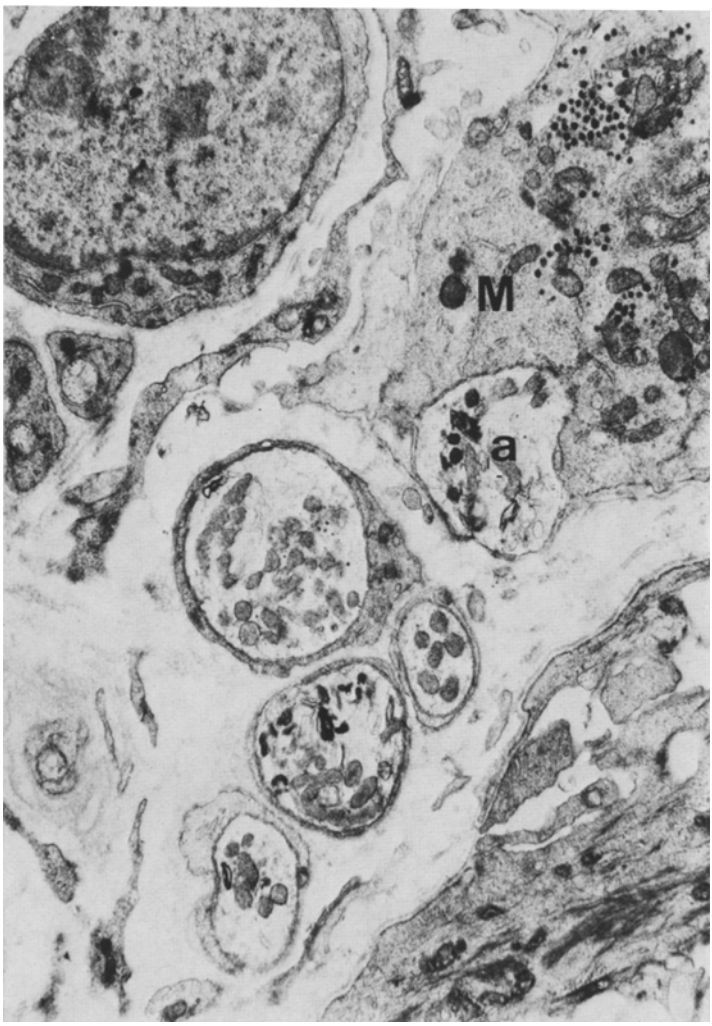

Fig. 5. *Epithelial Merkel cell* (*M*) in the external hair root sheath. A non-myelinated axon (*a*) is observed above the basal lamina in apposition to the Merkel cell. ×12000

follicle including encapsulated dermal Merkel cell-axon junctions and non-encapsulated epithelial Merkel cell-axon junctions, as described above.

Discussion

Merkel cells are rarely found isolated or multiple in the basal epidermal layer of human skin, forming endings of Merkel-Ranvier or tactile hair disks respectively [14, 15]. Occasionally, they project downward from the basal layer into the dermis, imitating dermal Merkel cells [4, 7]. Dermal Merkel cells have only been described in fetal human skin, most likely representing cells migrating into the epidermis [5]. Furthermore, a Merkel cell has been noted by McGavran [11] in the

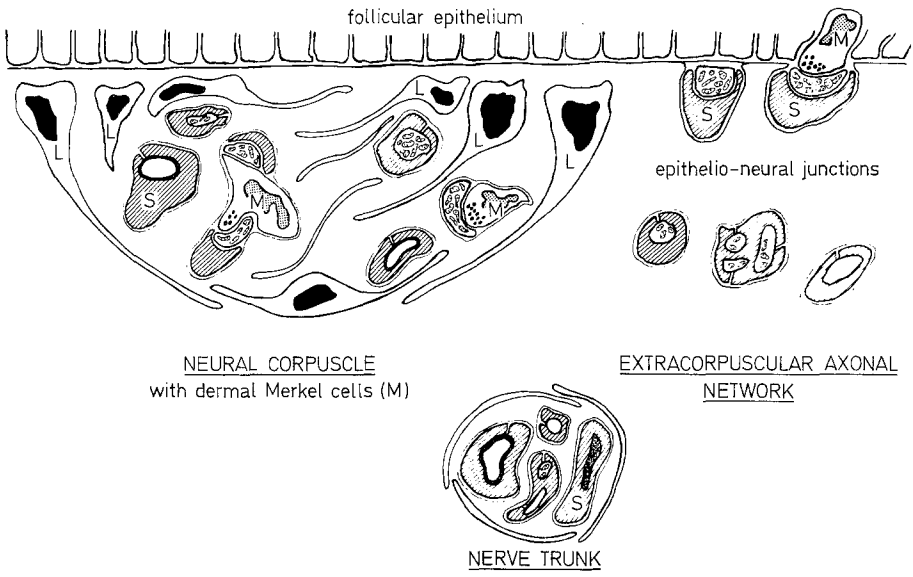

Fig. 6. *The complex innervation of hair follicle with dermal and epithelial Merkel cells (M)*, shown schematically. The laminar cells (*L*) posses their own basal lamina, not drawn in this figure. Schwann cells (*S*)

dermis of the axillary skin of an 11-month-old boy with xanthogranuloma. To our knowledge no dermal Merkel cells have yet been described in human adult skin, neither isolated nor in encapsulated neural corpuscles. For our study it seems unlikely that pityriasis lichenoides chronica contributes to the formation of such a specialized neural corpuscle. Therefore, we regard their presence as a general feature of human adult skin.

Merkel cells can not be identified with certainty at the light microscopic level [10]. Particularly their differentiation from other epidermal clear cells, such as Langerhans cells and melanocytes, is difficult. To date no specific histochemical techniques have been developed to demonstrate Merkel cells. It seems, that the only definite identification of Merkel cells is possible by ultrastructural criteria, i.e. the accumulation of typical large dense-core granules, the fine intracytoplasmic filaments, the desmosomes with adjacent keratinocytes, the lobulated nucleus, and the presence of closely associated axons filled with mitochondria. The dermal Merkel cells described in this study had the same structural features except for the absence of desmosomes on their plasma membrane.

Remarkably enough, the observed dermal Merkel cells occurred in groups, were surrounded by flattened laminar cells together with non-myelinated and myelinated axons and their Schwann cells and gave to us, as a whole, the impression of a dermal neural corpuscle. Some similarities to Meissner corpuscles were obvious. However, Meissner corpuscles are found in glabrous skin and contain no Merkel cells [3, 8]. Additionally, the axons lose their myelin sheaths when they enter the Meissner corpuscle, whereas myelinated axons were clearly demonstrated in the corpuscle described in this study. On the other hand, in their review on

Merkel cells Winkelmann and Breathnach [15] quoted the work of Grandry, who described a similar specialized corpuscle in the skin of the duck and goose bill. It was shown by Andersen and Nafstad, that Grandry corpuscles also found in the hard palate region of the hen contain Merkel cells [1].

Another striking result of this investigation was the presence of Merkel cells in the adult common hair external root sheath, to date exclusively related to vibrissal or sensory hairs of mammals [2]. It seems, therefore, that in human skin, too, hairs exist with specialized receptor functions.

In conclusion this study underlines the importance of the Merkel cells as specialized neuroreceptor cells not only in epidermal, but also in dermal and adnexal skin innervation.

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