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Topography of nerve terminals in Merkel nerve endings in mammals

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Abstract. Merkel nerve endings are found in the skin as well as oral and anal mucosa of all mammals. In the two types of glabrous skin, individual or groups of Merkel nerve endings are found in the basal layer of the epidermal ridges close to the excretory ducts of sweat glands or in the basal layer of the epithelial pegs, respectively. Here, Merkel cells are oval in shape and their long axis runs parallel to the surface. The nerve terminals have discoid form and are in close contact with the basal part of the Merkel cells.

In the hairy skin, Merkel cells are found in the epithelial thickenings between hair follicles ("Tastscheiben") as well as in the basal layer of all types of hair follicles. While the "Tastscheiben"-structure is mainly identical to the arrangement in the glabrous skin, in sinus hair follicles Merkel cells (up to several thousand) form a cuff around the thicker part of the hair follicle below the sebaceous gland. The discoid nerve terminals are located on the side of the Merkel cell opposite to the basal lamina. Their longitudinal axis runs parallel to the hair shaft.

In the anal mucosa the epithelium forms similar thickenings as seen in the epithelial pegs with the same arrangement of the nerve terminals. In the oral mucosa Merkel nerve endings are found mainly in the masticatory mucosa of the gingiva and hard palate. In most species, the arrangement is comparable to "Tastscheiben". However, in the monkey papilla incisiva we found Merkel cells arranged with their longitudinal axis perpendicular to the surface and the nerve terminal facing their labial side.

In conclusion, the location of the nerve terminal obviously depends on the direction of the main mechanical stimulus in the way that the Merkel cell is placed between the mechanical stimulus and the nerve terminal.

Introduction

The original discovery of the Merkel nerve ending in mammals was preceded by the description of so called "Tastzellen" (touch cells) in the tongue and beak skin of some aquatic birds [1]. Obviously, Merkel trained his eye by looking at the structure of the much larger Grandry cells in birds [2] before recognising the "real" Merkel nerve endings in the dermis of pidgeon and chick and in the epidermis of various mammals including man. Around the turn of the century, these receptors were generally termed "Merkel'sche Tastzellen" and "Merkel'sche Tastkörperchen" [3,4].

Since the introduction of electronmicroscopy, details of the structure have been looked at in detail [5] and related functionally to the slowly adapting type I mechanoreceptor [6]. In contrast to Merkel and his successors (for review see

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[7,8]), the original assumption of the Merkel cell as mechanotransducer has been put in question by [9,10]. Thus, the present study examined the relationship between Merkel cell and nerve terminal in relation to the direction of physiological application of pressure.

Materials and Methods

Samples of skin and ectoderm derived mucosa from various mammals were fixed in glutaraldehyde. After osmification and embedding in epon 812 semithin sections were stained according to [11]. Selected sections were re-embedded and cut in ultrathin sections for electronmicroscopy. For further details of the method see [12].

Results

Merkel nerve endings are seen in hairy and glabrous skin as well as in ectoderm derived mucosa (oral cavity and anus). Table 1 lists the relevant characteristic criteria as number of Merkel cells per receptor in the various locations. In general, specialization of the skin and mucosa surrounding the Merkel nerve endings are found. Some have their own names like "Eimer's organ" or "touch dome" (Figs. 1

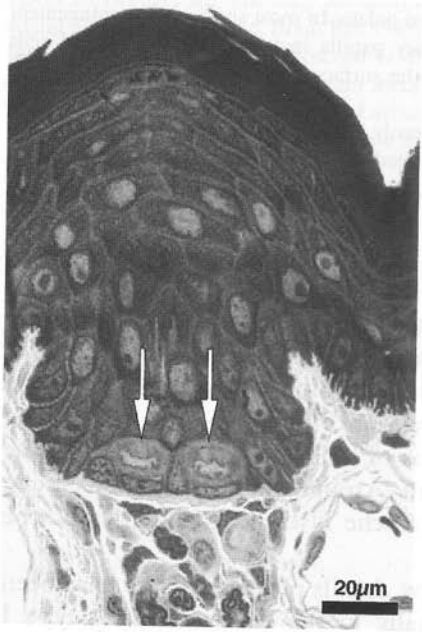

Fig. 1. Vertical semithin section through an epithelial peg of the mole snout. Merkel cells in the basal layer of the epidermis are marked by arrows. Small lamellated corpuscles are seen in the underlying dermis. Pressure from the skin surface has to penetrate all layers of the epidermis before reaching the receptors (indicated by the direction of the arrows). Staining according to Laczko and Levai.

Table 1. Merkel nerve endings.

Discovery	Merkel 1875 [1]
Electronmicroscopy	Cauna 1962 [5]
Physiology	Iggo/Muir 1969 [6]
Hairy skin – Hair follicles	
Sinus hair	
Localisation	Basal layer of the hair follicle below the sebaceous gland
Density	1000–2000
Guard hair	
Localisation	Basal layer of the hair follicle below the sebaceous gland
Density	Several dozens
Velsus hair	
Localisation	Basal layer of the hair follicle below the sebaceous gland
Density	Up to five
Hairy skin – Epidermis between hair follicles	
Touch dome (Tastscheibe)	
Localisation	Basal layer
Density	Up to twenty
Nonhairy skin	
Primates and marsupials	
Localisation	Basal layer of sweat gland ridges in fingers, palms, toes and soles
Density	Up to ten
Other mammals	
Localisation	Basal layer of rete pegs in nose, fingers, palms, toes and soles
Density	Up to twenty
Ectoderm derived mucosa	
Localisation	Basal layer rete pegs in incisival papilla, palatinal rugae, gingva, lips and anus
Density	Up to twenty

and 2). The epithelium in those organs is arranged in a way allowing optimum transfer of pressure to the Merkel nerve ending. Merkel cells are oval in shape and contain only few tonofilaments compared with the surrounding epithelial cells. Also the cytoplasmic membrane of the Merkel cell has characteristic features (Figs 3 and 4). Facing the epithelium are finger-like protrusions enlarging the surface. Contacts with epithelial cells are firmly arranged through desmosomes in the areas of the cytoplasmic membrane between those protrusions. On the opposite site towards the nerve terminal, typical osmiophilic granules are found in the cytoplasm and the cell membrane is flat with several synapse-like contacts.

The orientation of this arrangement is not aligned to the surface but depends on the direction of the pressure acting under physiological conditions. In rete ridges, rete pegs and touch domes the long axis of the Merkel cells runs parallel

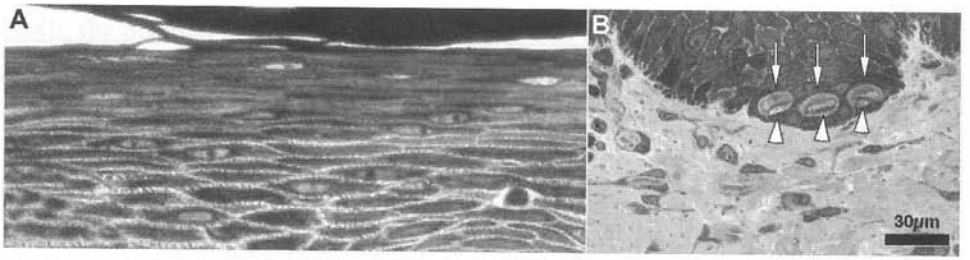

Fig. 2. Epithelial peg from the incisive papilla of the domestic goat. **A:** Keratinized surface of the stratified flat epithelium. **B:** Basal part of the same peg. It is about three times as high as the one from the mole in Fig. 1. A group of Merkel cells in the basal layer of the epithelium is marked by arrows. The corresponding nerve terminals are located below the Merkel cells. Pressure is exerted perpendicularly to the epithelial surface (indicated by the direction of the arrows). Staining according to Laczko and Levai.

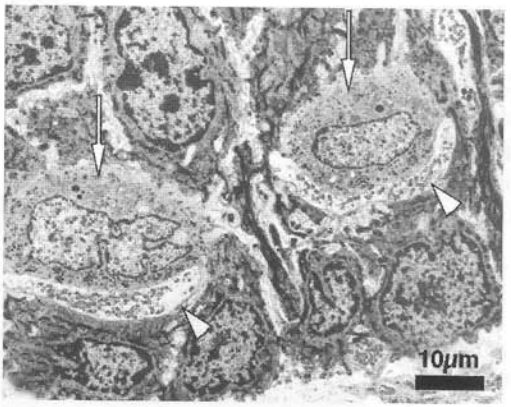

Fig. 3. Electronmicrograph of an epithelial peg from the cat nose. Two Merkel nerve endings are shown consisting of Merkel cells (arrows) and discoid nerve terminals (arrowheads). Both nerve terminals originate from the same axon. The direction of the pressure is indicated by the arrows.

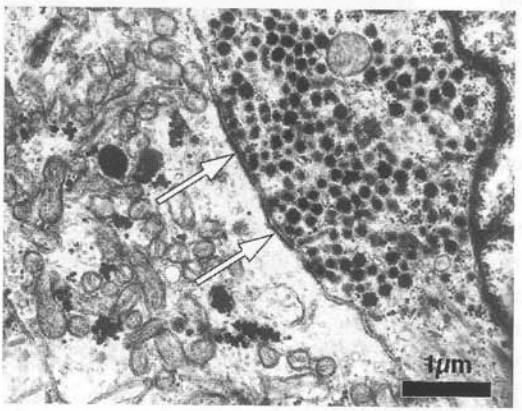

Fig. 4. Electronmicrograph showing details of the contact area between Merkel cell and nerve terminal. The axolemn of the nerve terminal and the cytoplasmic membrane of the Merkel cell form synapse-like contacts (arrows).

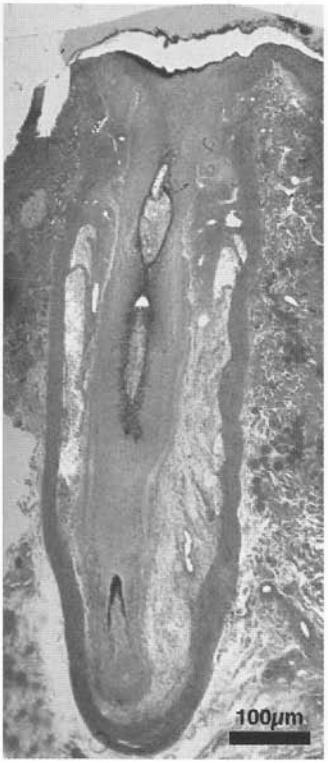

Fig. 5. Longitudinal semithin section of a sinus hair from the upper lip of a rhesus monkey. The entire hair follicle is embedded in a blood sinus. Staining according to Laczko and Levai.

to the surface while the applied pressure hits the surface perpendicularly (Figs. 1–4). In contrast, in hair follicles pressure is exerted through bending of the hair shaft squeezing the basement membrane on the concave side against the Merkel cells (Figs. 5–8). In the incisive papilla the position depends on the feeding behaviour of the animal. In rhesus monkey, food is moved by the tongue against the palate and incisive papilla from the labial to the aboral side. The long axis of Merkel cells are arranged perpendicularly to the surface with the nerve terminals on the aboral side in line with the direction of the pressure coming from the labial side (Fig. 9). On the other hand, in the goat food is pressed between tongue and incisive papilla before being pulled off. Thus, physiologically the pressure is applied perpendicularly to the surface and the arrangement of Merkel cell and nerve terminal reflects this situation, placing the Merkel cell above the nerve terminal towards the surface (Fig. 10).

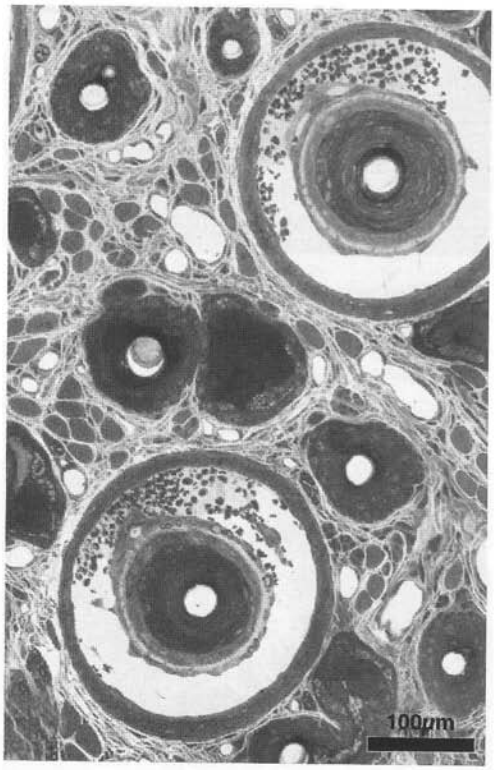

Fig. 6. Semithin cross-section of two sinus hairs and several lanugo hairs from the hairy skin of the mole snout. The hair follicles of the sinus hairs are embedded in blood sinus. The hair follicles of the lanugo hairs are located in the dermis between the sinus hairs. The section shows also parts of the sebaceous glands and fibres of mimic muscles associated with these hairs. Staining according to Laczko and Levai.

Discussion

To the best of our knowledge, this is the first report looking systematically at the arrangement of Merkel cell and nerve terminal in a variety of mammals and different locations in relation to the physiological pressure applied to these receptors. These results can only be obtained by combining serial semithin sectioning followed by electronmicroscopy of selected semithin sections for detailed analysis of the topography of the receptors under investigation. A consistent finding of this study is the observation that the Merkel cell is always located at the side of the applied pressure while the nerve terminal is on the opposite side (see also [12–14]). In addition, the anchoring of the Merkel cells among the epithelial cells with desmosomes and arrangement of cytoplasmic processes invaginating the keratinocytes allows the optimal transfer of mechanical stimuli from this direction. Particularly in those cases, where special touch organs are formed, a large number of Merkel nerve endings are seen, depending on the size of the

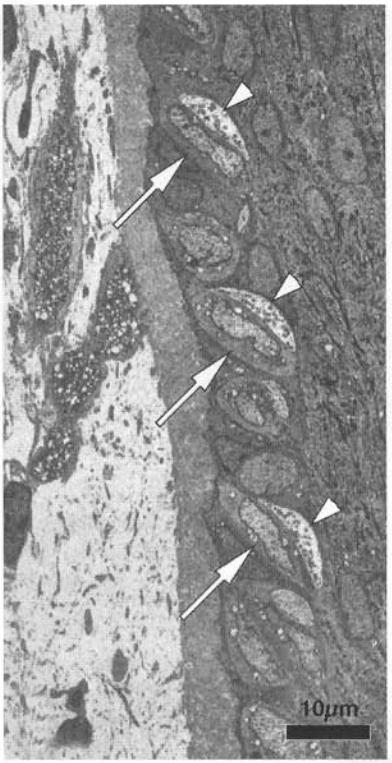

Fig. 7. Electronmicrograph of a longitudinal section through a sinus hair from the upper lip of a cat. In the basal layer of the hair follicle are Merkel cells arranged like roof tiles. The Merkel cells (arrows) are facing the basement membrane for the hair follicle with the nerve terminal (arrowhead) on the inner side of the Merkel cell. Pressure is applied by bending the hair follicle within the blood sinus. The direction of the pressure is indicated by the arrows.

organ (4 to 2000). In view of these findings, it is difficult to argue that the Merkel cell only serves as an abutment, while the mechano-electric transduction process occurs in the nerve terminal as postulated by [9,10,15]. Thus, the present findings are in support of functional studies showing increase in cytosolic calcium concentrations during mechanical stimulation of Merkel cells [16–19], which would be a prerequisite for the release of neurotransmitter.

Acknowledgements

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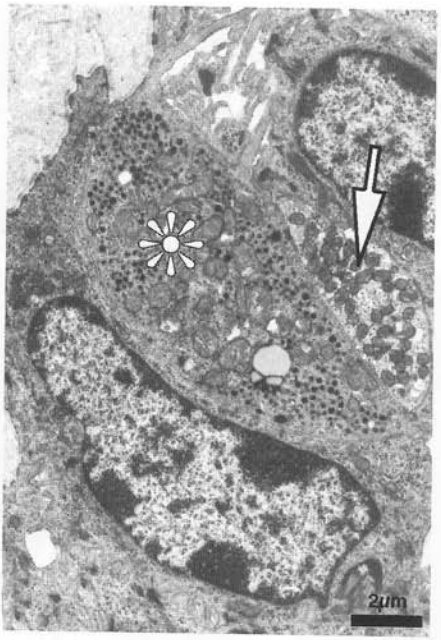

Fig. 8. Electronmicrograph showing details of a Merkel nerve ending from a sinus hair of rhesus monkey. The cytoplasm of the Merkel cell (asterix) contains osmiophilic granules. Opposite to the basement membrane is the discoid nerve terminal filled with mitochondria.

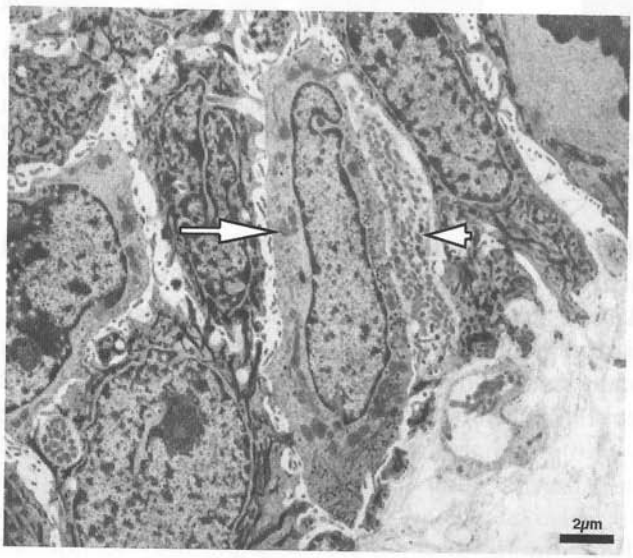

Fig. 9. Electronmicrograph of a Merkel nerve ending from an epithelial peg of the incisive papilla of rhesus monkey. The longitudinal axis of the Merkel cell (arrow) is arranged perpendicular to the epithelial surface (horizontally far outside the picture) and the basement membrane. Also the discoid nerve terminal has this perpendicular arrangement. The direction of pressure applied to the Merkel cell by the tongue is indicated by the arrow.

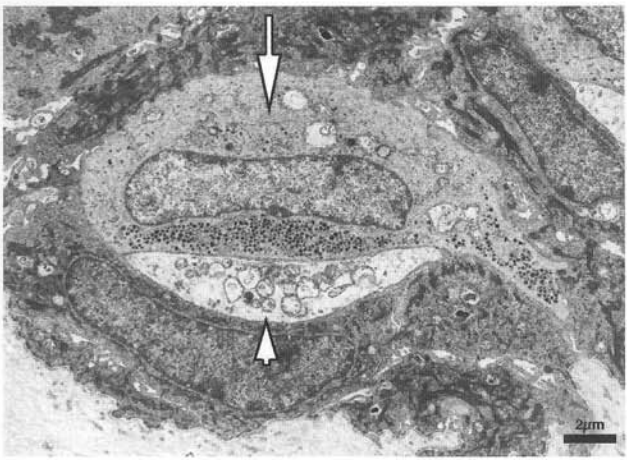

Fig. 10. Electronmicrograph of a Merkel nerve ending from an epithelial peg of the incisive papilla of a domestic goat. The longitudinal axis of the Merkel cell is arranged parallel to the surface of the mucosa (horizontally far outside the picture). The nerve terminal is positioned below the Merkel cell. The direction of pressure is indicated by the arrow.

References

1. Merkel F. Tastzellen and Tastkoerperchen bei den Hausthieren und beim Menschen. Arch Mikr Anat 1875;11:636–652.
2. Grandry M. Recherches sur les corpuscles de Pacini. J Anat Physiol 1869;6:390–395.
3. Szymonowicz L. Beitraege zur Kenntnis der Nervenendigungen in Hautgebilden. Arch Mikr Anat 1895;45:624–653.
4. Szymonowicz L. Ueber den Bau und Entwicklung der Nervenendigungen im Entenschnabel. Arch Mikr Anat 1897;48:329–358.
5. Cauna N. Functional significance of the submicroscopical, histochemical and microscopical organisation of the cutaneous receptor organs. Anat Anz 1962;111(Suppl):181–197.
6. Iggo A, Muir AR. The structure and function of a slowly adapting touch corpuscle in hairy skin. J Physiol (Lond) 1969;200:763–796.
7. Halata Z. Die Sinnesorgane der Haut und der Tiefensensibilität. In: Niethammer, J Schliemann, H Starck D et al. (eds) Handbook of Zoology. Berlin, New York: de Gruyter, 1993;18:Part 57.
8. Zelena J. Nerves and mechanoreceptors. London, New York, Tokyo: Chapmann & Hall, 1994.
9. Diamond J, Holmes M, Nurse CA. Are Merkel cell-neurite reciprocal synapses involved in the initiation of tactile responses in salamander skin? J Physiol (Lond) 1986;376:101–120.
10. Gottschaldt K-M, Vahle-Hinz C. Merkel cell receptors: structure and transducer function. Science 1981;214:183–186.
11. Laczko J, Levai G. A simple differential staining method for semithin sctions of ossyfying cartilage and bone tissue embedded in epoxy resin. Mikr 1975;31:1–4.
12. Halata Z, Baumann KI. Sensory nerve endings in the hard palate and papilla incisiva of the rhesus monkey. Anat Embryol 1999;199(5):427–437.
13. Halata Z, Cooper BY, Baumann KI, Schwegmann C, Friedman RM. Sensory nerve endings in the hard palate and papilla incisiva of the goat. Exp Brain Res 1999;129:218–228.
14. Rettig T, Halata Z. Structure of the sensory innervation of the anal canal in the pig. A light- and electron-microscopical study. Acta Anat 1990;137(3):189–201.
15. Diamond J, Mills LR, Mearow KM. Evidence that the Merkel cell is not the transducer in the

mechanosensory Merkel cell-neurite complex. In: Hamann W, Iggo A (eds) Progress in Brain Research 74. Transduction and Cellular Mechanisms in Sensory Receptors. Amsterdam, New York: Elsevier, 1988;51–56.

16. Baumann KI, Senok SS, Chan E, Yung WH. Calcium influx and calcium-induced calcium release in mechanically stimulated Merkel cells of rat sinus hair type I mechanoreceptors. In: Suzuki H, Ono T (eds) Merkel Cells, Merkel Cell Carcinoma and Neurobiology of the Skin. Amsterdam: Elsevier, 2000;73–81 (these proceedings).
17. Chan E, Yung WH, Baumann KI. Cytoplasmic Ca^{2+} concentrations in intact Merkel cells of an isolated, functioning rat sinus hair preparation. Exp Brain Res 1996;108(3):357–366.
18. Senok SS, Baumann KI. Functional evidence for calcium-induced calcium release in isolated rat vibrissal Merkel cell mechanoreceptors. J Physiol (Lond) 1997;500(1):29–37.
19. Tazaki M, Tazaki Y, Inoue T, Shimono M. Calcium inflow of single Merkel cell in response to direct mechanical stimulation. In: Suzuki H, Ono T (eds) Merkel Cells, Merkel Cell Carcinoma and Neurobiology of the Skin. Amsterdam: Elsevier, 2000;63–71 (these proceedings).