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a0005

5.02 Merkel Cells

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AU1

Abbreviation

CGRP calcitonin gene related peptide

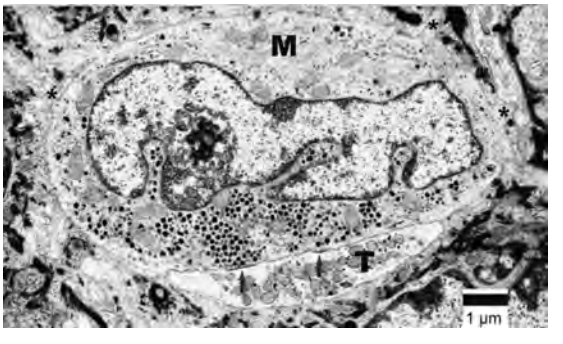
s0005

5.02.1 Localization and Ultrastructure of Merkel Nerve Endings

p0005 Merkel cells are usually associated with nerve endings located in the skin and some parts of the mucosa in all vertebrates. They function as mechanoreceptors and are found in mammalian epidermis as well as the epithelium of ectoderm-derived mucosa (Merkel, F., 1875; Iggo, A. and Muir, A. R., 1969; Halata, Z. *et al.*, 2003). However, in birds they are located in the superficial layer of the dermis (Saxod, R., 1978). Occasionally, dermal Merkel cells are also found in mammals especially in man (Mahrle, G. and Orfanos, C. E., 1974).

p0010 Light microscopically, Merkel cells can be best seen using their characteristic immunohistochemical staining for cytokeratins CK8, CK18, and CK20 (Moll, R. *et al.*, 1984; 1995). In addition, Merkel cells show immunoreactivity to neuron-specific enolase, chromogranin, vasoactive intestinal polypeptide, met-enkephalin, serotonin, substance P, calcitonin gene-related peptide (CGRP), somatostatin, calcitonin protein gene product 9.5, and bombesin (Hartschuh, W. *et al.*, 1979; Hartschuh, W. and Weihe, E., 1988; Cheng Chew, S. B. and Leung, P. Y., 1991; English, K. B. *et al.*, 1992).

p0015 Electron microscopically, Merkel cells (Figure 1) can be identified by their characteristic disk-shape, large lobulated nuclei and close contact with nerve terminals. Merkel cells bear spike-like protrusions that interdigitate with the surrounding keratinocytes and are attached by desmosomes. The cytoplasm contains intermediate cytokeratin filaments and many large (50–110 nm) dense-core granules, particularly accumulated near the junction with the nerve fiber (Iggo, A. and Muir, A. R., 1969). The cytoplasmic membrane forms areas of synaptic membrane specialization with the membrane of an axonal terminal (Iggo, A. and Findlater, G. S., 1984). The nerve

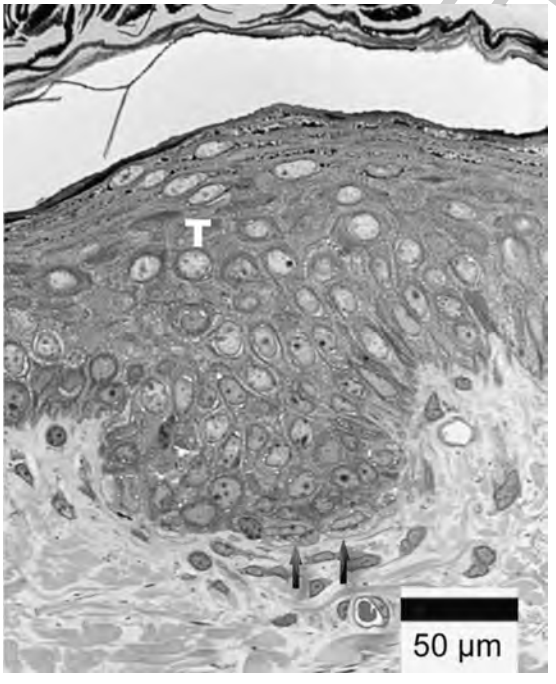


f0005 **Figure 1** Ultrathin section from the planum nasale of a domestic cat. The typical Merkel nerve ending consists of a Merkel cell (M) with characteristic finger-like protrusions (*) and a discoid nerve terminal (T) containing a large number of mitochondria. Synapse-like contacts between Merkel cells and nerve terminal are marked by arrows. The cytoplasm of the Merkel cell facing the nerve terminal is packed with dense-core granules.

terminal is packed with mitochondria and optically clear vesicles.

s0010 ## 5.02.2 Merkel Nerve Endings in Mammalian Glabrous Skin

p0020 Merkel cells in the mammalian glabrous skin are always in the basal layer of the epidermis (Figures 1 and 2). Pegged skin has solid epidermal pegs of different size anchoring the epidermis in the dermis containing blood sinus separating the epithelial pegs. Typical examples are the pig snout and planum nasale of mole and cat. Clusters of up to 40 Merkel cells are found in the basal layer of the epidermis at the base of these pegs. All Merkel cells are in synaptic contact with discoid terminals of branches of one myelinated axon (3–5 μm), losing the myelin sheath on entering the epidermis. In ridged skin (typically found in the tips of fingers and toes of primates and marsupials) clusters of up to 10 Merkel nerve endings are found at the base of the epidermal ridges near the ducts of sweat glands (Halata, Z., 1975).



f0010 **Figure 2** Semithin section of a touch dome (T) from the eyelid of a rhesus monkey. Merkel cells in the basal layer of the rete peg are marked by arrows.

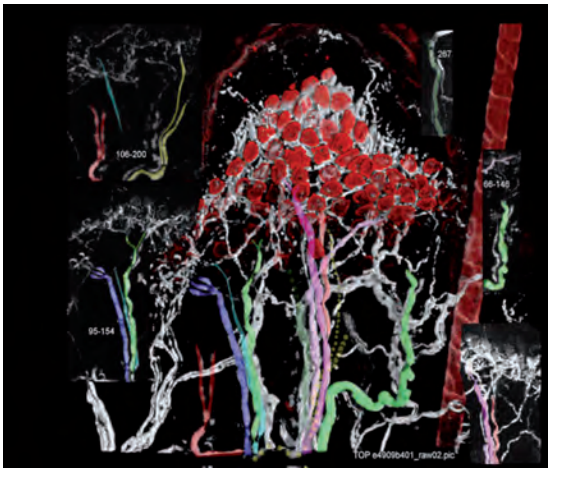
s0015 ## 5.02.3 Merkel Nerve Endings in Mammalian Hairy Skin

p0025 In hair follicles of velus hairs and guard hairs, Merkel nerve endings are found at the thickening of the follicle – the so-called bulge region – below the sebaccous gland. This part of the hair follicle does not change its form during the hair cycle and the bulge region is also a stem cell niche of the epidermis (Oshima, H. *et al.*, 2001).

p0030 Between hair follicles of the hairy skin, the epidermis forms epithelial pegs of different size and density, often referred to as touch dome (Haarscheibe; Figure 2). These are basically similar to the epithelial pegs in glabrous skin (see above), containing up to 150 Merkel nerve endings (Figure 3) supplied by one trunk nerve fiber.

s0020 ## 5.02.4 Merkel Nerve Endings in Sinus Hairs of Mammals

p0035 Specialized large hairs (vibrissae, whiskers, or sinus hairs) are found in all mammals apart from man, arranged in groups especially in the face and innervated by the trigeminal nerve. They are large hair follicles embedded in blood sinus with strong sturdy hairs. Fibers of mimic muscles are inserted into the



f0015 **Figure 3** Touch dome from the interdigital skin of the cat paw reconstructed from confocal microscopic images. The trunk nerve fiber branches below the level of this figure into several preterminal nerve fibers (marked in different colors) before branching further into terminal nerve fibers, each making contact with 5–10 Merkel cells. In this touch dome a total of 137 Merkel cells (red) were counted. Figure kindly provided by Dr. Satomi Ebara, Kyoto, Japan from Ebara *et al.* (in preparation). AU3

capsule of the blood sinus. The hair follicles are richly innervated with free nerve endings and a variety of different mechanoreceptors especially Merkel nerve endings. Sinus hairs of land mammals contain up to 2000 Merkel cells (Gottschaldt, K.-M. *et al.*, 1973; Ebara, S. *et al.*, 2002) while marine mammals can have up to 20 000 Merkel cells in one follicle (Dehnhardt, G. *et al.*, 2003). They have large cortical representations in somatotopically organized barrels (Woolsey, T. A. and van der Loos, H., 1970).

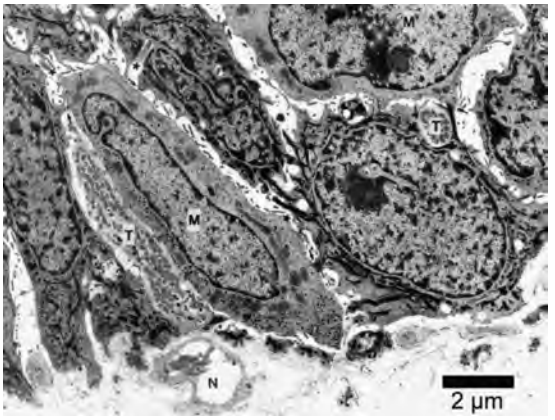
p0040 Merkel cells are located in the basal layer of the epithelium of the hair follicle in the thickened part below the sebaceous gland arranged like scales in a pine cone, oblique to the basal lamina (glassy membrane) sending cytoplasmic processes of about 3 μm through the glassy membrane. This area is surrounded by the ring sinus. All Merkel cells are in contact with discoid nerve terminals on the opposite side (Figure 4). The part of Merkel cells facing nerve terminals contains the typical dense-core (osmiophilic) granules. The myelinated axons (diameter about 5 μm) lose their myelin sheath and Schwann cells on penetrating the basal lamina, branching intensively supplying up to 50 Merkel cells (Ebara, S. *et al.*, 2002). Other Merkel nerve endings are found in the epidermis close to the penetration of the hair shaft in the rete pegs of the epidermis similar to the description above.

s0025 5.02.5 Merkel Nerve Endings in the Mucosa of Mammals

p0045 In mucosa derived from the ectoderm (mouth, lips, and anal canal), Merkel cells can be found in many mammalian species. In the mouth, the so-called surrounding mucosa is not cornified and covers the surface of lips, cheeks, and the soft palate forming epithelial pegs containing numerous Merkel nerve endings at their base. Masticatory mucosa with cornified epithelium covering the hard palate and forming the surface of the gingiva has to withstand heavy mechanical loads during chewing of food. The basal layer of the epithelium forms rete ridges or rete pegs containing many Merkel nerve endings in the basal layer with identical structure as found in glabrous skin (Figure 5; Halata, Z. and Baumann, K. I., 1999). In contrast, the specialized mucosa covering the surface of the tongue with typically structured papillae and gustatory organs is free of Merkel nerve endings.

f0020 **Figure 4** Ultrathin longitudinal section through the thickened portion below the sebaceous gland of a sinus hair from the upper lip of a rhesus monkey. Merkel cells (M) and nerve terminals (T) are arranged obliquely to the glassy membrane (*) like scales of a pine cone. The Merkel cell is always facing the glassy membrane. A lanceolate nerve terminal (L) in close contact with the glassy membrane is seen on the outer side.

p0050 In the mucosa of the anal canal, Merkel nerve endings can be found in nonkeratinized and keratinized parts. In the nonkeratinized part, the epithelium is a flat stratified epithelium with rete pegs. In basal



f0025 **Figure 5** Ultrathin cross section through the papilla incisive of a rhesus monkey. Merkel cells (M) with cytoplasmic protrusions (*) and desmosomal contacts (arrows) with epithelial cells of the basal epithelial layer. Nerve terminals (T) from the afferent axon (N) covered by a Schwann cell.

parts of rete pegs typical Merkel nerve endings are present. Also the keratinized part shows rete pegs with numerous Merkel nerve endings (Rettig, T. and Halata, Z., 1990).

s0030 5.02.6 Merkel-like Cells with Suggested Neuroendocrine Function

p0055 Structurally, Merkel cells resemble cells of the diffuse endocrine system found mainly in the epithelium of the gut and bronchial mucosa. Various substances were found in the osmiophilic granules of Merkel cells (see above), resulting in the classification of Merkel cells as part of the family of the APUD system (Pearse, A. G. E., 1968; Fujita, T., 1977). These cells are believed to release neurotransmitters with paracrine function. Also in those areas where Merkel cells are usually found, pale oval cells with dense-core granules are occasionally found in the basal layer of the epidermis or mucosa of ectodermal origin. But these cells lack any contact with nerve terminals. In contrast to normal Merkel cells, these cells have oval nuclei with many nuclear pores. So far there is no evidence for exocytosis of substances from Merkel cells to support the assumption of a paracrine (Fujita, T., 1977) or neuroendocrine role (Boot, P. M. *et al.*, 1992), leaving the question about the functional role of those substances in the dense-core granules of Merkel cells widely open.

5.02.7 Merkel Cell Carcinoma s0035

p0060 In a highly malignant type of skin tumor, cells were found with osmiophilic granules and positive immunohistochemical reaction with neuron-specific enolase (Tang, C. K. and Toker, C., 1978; Johannessen, J. V. and Gould, V. E., 1980). It is widely assumed that these tumors originate from Merkel cells, giving rise to the name Merkel cell carcinoma. However, direct evidence for this assumption is still lacking (Gould, V. E. *et al.*, 1985; Moll, R. *et al.*, 1992). Another assumption is that this tumor may originate from dermal neuroendocrine cells (Hoefler, H. *et al.*, 1985).

5.02.8 Developmental Origin of Merkel Cells s0040

p0065 There has been a long controversy about the developmental lineage of Merkel cells. One view is that Merkel cells arise from a common ectodermal stem cell (English, K. B., 1974; Moll, I. *et al.*, 1986). This hypothesis is mainly supported by the finding of low molecular cytokeratin (CK8, CK18, and CK20) in Merkel cells of mammals (Moll, R. *et al.*, 1984; Moll, I. *et al.*, 1995; Kim, D. K. and Holbrook, K. A., 1995). In contrast, several studies suggested that they originate from the neural crest and migrate into the mammalian epidermis during the embryonic period (Hashimoto, K., 1972; Breathnach, A. S., 1978). Using the chick/quail marking system, it was shown that avian Merkel cells do not develop from ectodermal or mesodermal cells, but that they originate from the neural crest (Grim, M. and Halata, Z., 2000). In mammals, Szeder V. *et al.* (2003) examined Wnt1-cre/R26R double transgenic mice in which Merkel cells like all neural crest-derived cells are marked by the reporter gene LacZ. Thus, there is now unambiguous evidence for a neural crest origin of avian and mammalian Merkel cells.

5.02.9 Mechanoreceptor Function of Merkel Cells s0045

p0070 Merkel's original description of touch corpuscles clearly described these complexes as mechanoreceptors (Merkel, F., 1875). They respond to punctate pressure on the skin (Iggo, A. and Muir, A. R., 1969) or bending of whiskers with long-lasting spike trains

(Gottschaldt, K.-M. *et al*., 1973). In all locations, the Merkel cells are positioned between the direction of the physiological mechanical stimulus and the nerve terminal. The surface of Merkel cells is equipped with protoplasmic protrusions anchoring between keratinocytes (Halata, Z. *et al*., 2003), which has led to comparisons with inner ear hair cells (Iggo, A. and Findlater, G. S., 1984; Baumann, K. I. *et al*., 1990) where bending of the hairs opens mechanically gated ion channels resulting in depolarization, increase of free intracellular calcium, and transmitter release (Crawford *et al*., 1991).

p0075 There have been long controversies, whether the mechanoelectric transduction process occurs in the Merkel cell or whether the Merkel cell only directs the mechanical stimulus toward the nerve terminal. Unfortunately, the location of these receptors makes direct electrophysiological recordings with microelectrodes impossible. The slowly adapting responses of these receptors and the characteristic impulse pattern of action potentials with rather irregular interspike intervals were interpreted as an indication of a synaptic link (Iggo, A. and Muir, A. R., 1969; Horch, K. W. *et al*., 1974).

p0080 Various potential neurotransmitters were found in the dense-core granules of Merkel cells (Hartschuh, W. *et al*., 1979; Hartschuh, W. and Weihe, E., 1988; Cheng Chew, S. B. and Leung, P. Y., 1991; English, K. B. *et al*., 1992). However, attempts to impair transmission with the respective receptor blockers failed to show clear effects on receptor responses (Gottschaldt, K.-M. and Vahle-Hinz, C., 1982). Using calcium indicator dyes, increases of intracellular calcium concentration in Merkel cells during mechanical stimulation have been observed consistently in different species and locations (Chan, E. *et al*., 1996; Tazaki, M. and Suzuki, T., 1998). In spite of mechanical stimulation, no such increases are seen if the extracellular fluid is calcium free or amiloride (known to block mechanosensitive ion channels; Hamill, O. P. *et al*., 1992) is added to the solution (Halata, Z. *et al*., 2003). Further studies revealed the existence of voltage-gated calcium channels and presynaptic proteins in Merkel cells (Yamashita, Y. *et al*., 1992; Chan, E. *et al*., 1996; Haeberle, H. *et al*., 2004). Thus, mechanical stimulation causes an influx of calcium into Merkel cells, which in turn appears to trigger further release of calcium from intracellular stores (Calcium-induced calcium release; Senok, S. S. and Baumann, K. I., 1997). It has long been established that increase in free calcium is a requirement for synaptic transmitter release.

p0085 Recent experimental evidence suggests that glutamatergic transmission occurs at Merkel cell receptors although the specific type of glutamate receptor involved is still unclear (Fagan, B. M. and Cahusac, P. M. B., 2001; Hitchcock, I. S. *et al*., 2004; Haeberle, H. *et al*., 2004; Cahusac, P. M. B. *et al*., 2005). This synaptic transmission is probably essential for the slowly adapting responses during maintained mechanical stimuli (Ogawa, H., 1996; Senok, S. S. and Baumann, K. I., 1997).

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