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Original article

Merkel-like basal cells in the nasal septal island of dromedaries: Ultrastructure and possible functions

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ABSTRACT

Unlike other Merkel cell types, the morphology and functions of the Merkel-like basal cells remain unclear. The aim of the present study was to investigate the ultrastructural features of Merkel-like basal cells in the nasal septal island (NSI) of dromedaries (*Camelus dromedarius*) using transmission electron microscopy and to speculate their potential functions. Ten pairs of nasal septal islands obtained from ten heads of dromedary camels were used for the current study. Interestingly, these cells have been identified in the basal layer of the neuroepithelium of the dromedary nasal septal island near the sensory nerve endings. These cells were ovoid to elliptical in shape and rested on the basal lamina. Their surface had spine like cytoplasmic processes which interwined with the adjacent basal cells. Their nuclei were large lobulated with 2–3 deep notches. Moreover, numerous dense-core granules surrounded by electron-lucent halo were aggregated in the basal portion of the cells close to the nerve ending as well as melanin pigments in the apical portion. The ultrastructural characteristics of the Merkel-like basal cells of NSI were typical to those of Merkel cells, but with some morphological differences, including their location, cellular attachments, and connections to other structures. The potential functions were discussed in the light of the cellular context and architecture. The Merkel-like basal cells of the NSI neuroepithelium might play a role in nociception and magnetoreception in dromedaries.
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1. Introduction

The septal organs are patches of chemosensory cells situated in the ventral parts of the nasal septum of many mammals and innervated by the olfactory nerve (Ma et al., 2003). However, a recent study revealed a unique nasal septal island of sensory epithelium situated in the dorso-medial part of the nasal vestibule of dromedaries (*Camelus dromedarius*) innervated by the ethmoidal branch of trigeminal nerve, and is believed to be involved in pain perception or nociception (Abo-Ahmed et al., 2021). Resembling other areas of somatosensory innervation, the trigeminal innervation contains Merkel cells, which are most frequently linked to sensory nerve ends. The trigeminal nerve endings in the NSI are surrounded by clusters of Merkel-like cells (Abo-Ahmed et al., 2021). However, during electron microscopic examination of the NSI tissues, the authors observed that some basal cells closely resembled Merkel cells. This prompted the authors to conduct this study to describe the ultrastructural characteristics of these Merkel-like basal (MLB) cells in more detail and elucidate their potential functions which might be essential for the dromedaries. Since Merkel cells are cutaneous receptor cells, they have a role in tactile sensation (Ramirez et al., 2016). The exact localization of these cells and their analogues has not been established throughout the dromedary nose, despite the extensive examination of Merkel cell distribution in humans, dogs, and rodents. It might be easier to comprehend their probable functions in detail with more information about their distribution.

Initially, the Merkel cell (MC) was misinterpreted as an artifact of histological sectioning, until Friedrich Merkel first described it in

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1875. The initial misclassification was attributed to the resemblance of Merkel cells to other non-keratinocytes, specifically, Langerhans and melanocytes, except for their pale cytoplasm and folded nucleus. Currently, the Merkel cell remains difficult to discern using light microscopy, and the ultrastructural techniques, especially transmission electron microscopy are necessary for accurate identification of Merkel or Merkel-like cells (Halata et al., 2010; Abraham and Mathew, 2019).

Ultrastructurally, several tissues have been found to contain Merkel cells, including skin and various areas of mucous membrane as revealed by Boot et al. (1992) and Moll et al. (2005). These cells are located in the basal layer of epidermis as shown by Halata et al. (2003). They can be differentiated from other non-keratinocytes by their distinguishing ultrastructural features, including a large, lobulated nucleus that sometimes presents nuclear inclusions (nuclear rodlets) and spine-like cytoplasmic processes interdigitating with neighboring cells to which they are attached via desmosomes. Their cytoplasm includes numerous dense-core granules that are surrounded by a clear halo and are clustered close to junctions with nerve fibers (Breathnath and Robin, 1970). Some melanin pigment is usually present where dense-cored granules are positioned opposite to the cell pole. Lastly, a synaptic junction is formed when the membrane of the cell is in close proximity to the membrane of the nerve terminals.

The general concept regarding Merkel cell function is that they are gradually adapting mechanoreceptors that respond to mechanical stimulation (touch) (Halata et al., 2010). However, recent experimental evidence has suggested other important roles of Merkel cells in immunity and nociception (Abraham and Mathew, 2019). In addition, they have been reported to release several active mediators that transfer nociceptive signals that are crucial for inflammatory reactions and immunological tolerance (Babu et al., 2016).

Unlike the other Merkel cell types, the morphology and functions of MLB cells are not well-established, and only minimally described in a few publications. For example, the taste bud's basal layer of some non-mammalian species contain MLB cells as reported by Delay & Roper (1988) and Delay et al. (1993). These basal cells are described as "Merkel-like" because of their ultrastructural features, including, a large, lobulated nucleus, dense-core granules, and synapse-like associations with adjacent cells (Delay & Roper, 1988). They are believed to have a crucial impact on neurotransmission processes, specifically, transduction of somatosensory perception (Delay et al., 1993). Still, MLB cells and their functional significance are poorly understood. Therefore, the ultrastructure of the MLB cells in the NSI of the dromedary camel was examined in the present study, with special consideration of their potential roles.

2. Material and methods

2.1. Tissue sampling

The protocols used in this study that involved animals were carried out in accordance with the animal use and care standards approved by the Scientific Research Ethics Committee, Faculty of Veterinary Medicine, Benha University, Egypt with approval number BUFVTM 01–12-22. Ten pairs of nasal septal organs were obtained from ten male dromedary camels. The animals were apparently healthy and their ages ranged from 3 to 6 years. All tissues used in this study were harvested immediately after slaughter, which took place at the Toukh and Qalioube slaughter houses, Egypt. Any tissues from animals that exhibited congenital or gained deformities of the nasal septum or the nose were excluded from this study.

2.2. Transmission electron microscopy (TEM)

Minute tissue samples of approximately 1–2 mm^3 were immediately immersion fixed for 3 hrs in 4% buffered glutaraldehyde, pH 7.2, at 4 °C. Subsequently, the tissue samples were then post-fixed in 1% osmium tetraoxide at room temperature for 2 hrs. The fixed tissue samples were dehydrated in a graded acetone series of 15 min each at 4 °C, ending with 100% acetone. Then, the tissues were embedded in Araldite resin, hardened and sectioned. After preparation of semithin sections, they were stained using 1% toluidine blue with 1% sodium borate. Ultrathin slices were placed on carbon-supported TEM grids and tarnished for 5 min using uranyl acetate, then, 2 min of staining with lead citrate to enhance the contrast. The sections were allowed to dry before being observed with a JEOL-JSM-1400 PLUS electron microscope (Tokyo, Japan) at Alexandria University, Egypt.

2.3. Statistical analysis

The statistical procedures in this study were performed with a readily accessible program (SPSS, Version 16.0; SPSS Inc., IL, USA). Shapiro-Wilk test was used to determine whether the data were normal and presented as average ± standard deviation.

3. Results

Pale oval shaped Merkel-like cells were detected in the neuroepithelium's basal layer of the dromedary NSI during examination of the semithin sections (Fig. 1&Fig. 2A). Notably, the nuclei of these cells were typically large and highly folded.

Examination of the ultrathin sections revealed the presence of Merkel-like cells that were ovoid to elliptical (Fig. 2B,C&D), rested on the basal lamina, and the surface presented spine like cytoplasmic processes or microvilli that were approximately 0.78 ± 0.163 μm in length. These processes were intertwined with the neighboring discoid basal cells, forming cellular bridges connected by desmosomes. The nucleus of each Merkel-like cell was large, lobulated and presented 2 to 3 deep notches (Fig. 3). Distinctive electron-dense aggregates of intranuclear rodlets or inclusions also were observed. Tonofibril-like aggregates of intermediate filaments were located around the nucleolus (Fig. 3). Typically, numerous dense-core granules or vesicles approximately 0.32 ± 0. 08 μm in diameter were concentrated near junctions with the nerve endings. These vesicles were surrounded by an electron-lucent halo. Some aggregates of melanin pigments were seen at the apical pole near the nucleus. The dilated nerve endings were in close proximity with the basal portion of the cells, forming Merkel cell-neurite complexes, immediately above the basement membrane. These nerve endings were remarkably large, discoid shaped, and 2.0 ± 0.60 ~ 2.6 ± 1.15 μm in diameter; they contained clear and dense-core granules (Fig. 3). The observed ultrastructural characteristics of the Merkel-like cells were summed up in Fig. 4.

4. Discussion

Merkel cells are mechanosensory epidermal cells that have long been proposed to activate neuronal afferents through chemical synaptic transmission (Hoffman et al., 2018); however, the distribution of these cells or their homologies has not yet been declared in the dromedary nasal septum. Therefore, this study was designated for deep investigation of these cells will help to speculate their probable functions.

This study revealed the presence of MLB cells in the basal layer of the dromedary NSI neuroepithelium, where they communicated with adjacent basal cells via their cytoplasmic processes, forming

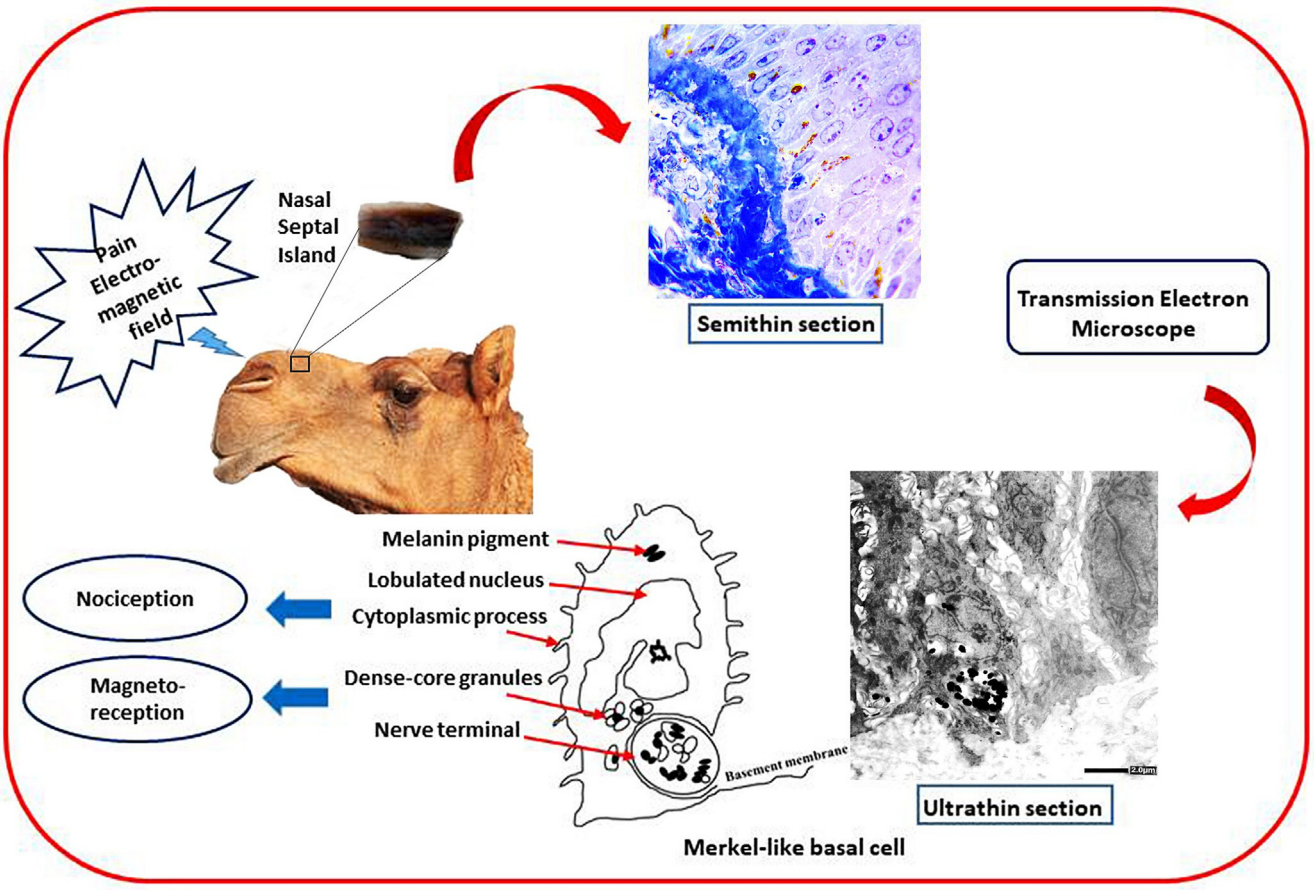

Fig. 1. A graphical abstract showing the Merkel-like basal cells of the nasal septal island of the dromedary camel with their proposed function.

cellular bridges connected by desmosomes. Furthermore, these cells contacted discoid-shaped nerve terminals. Ultrastructurally, these cells typically contained a folded nucleus with nuclear rodlets, while the cytoplasm contained osmophilic, dense-core, neurosecretory granules that were surrounded by a clear halo. These granules were usually seen in the cytoplasm near the nerve terminal. The structure described above was typical of Merkel cells reported by Zaghloul and Derbalah (2011) in the camel and Ramirez et al. (2015) in the dog. However, these authors suggested that the term Merkel-like cell was more suitable to discriminate NSI Merkel cells from typical cutaneous Merkel cells. This suggested distinction was attributed to the morphological differences that were present, including their location, cellular attachment, and connections to other cells. Specifically, the NSI MLB cells were situated only in the basal layer of the sensory neuroepithelium and attached to the basal lamina. The nerve terminals were notably large and located immediately above the basal lamina. Conversely, cutaneous Merkel cells are not attached to the basement membrane when they are occasionally found above the basal layer (Hashimoto, 1972). In addition, they are separated from the basement membrane via a mass of epithelial cells that encircle them (Ramirez et al., 2015). Furthermore, typical Merkel cells often have nerve terminals that are located on the dermis, where they are situated either underneath the basement membrane or beside the Merkel cells opposite to the basal lamina as shown by Halata and Baumann (2000). Finally, the morphology of MLB cells was typical to other Merkel cells, except for their attachment to the basal lamina, and the cellular context in which no keratinocytes were present in their vicinity as expected.

Typical Merkel cells of any mammalian species are pale oval cells containing dense-cored neurosecretory vesicles that are localized in the cells' basal region, and frequently associated with a nerve terminal (Halata et al., 2003). Sometimes, melanin granules are detected on the opposite side of the clusters of dense-core granules (Ramirez et al., 2015). Mammalian Merkel cells also have a characteristic set of cytoplasmic processes that are typically interdigitated with the surrounding keratinocytes of the suprabasal epidermal layer or an ectodermally derived mucosa (Halata et al., 2003; Ramirez et al., 2015). Structurally, Merkel cells of camels are similar to those of other domestic animals (Zaghloul and Derbalah, 2011). However, the MLB cells situated in the NSI neuroepithelium of dromedary camels were similar to those found in some non-mammalian species, including the mudpuppy, *Necturus maculosus*, where such cells were found in the taste bud's neuroepithelium (Delay and Roper, 1988; Delay et al., 1994) and in the lingual epithelium of regions other than taste buds in the axolotl (Nagai and Koyama, 1994). The primary distinction between the mudpuppy and camel MLB cells is their involvement in the mudpuppy mainly in serotonin secretion. However, in the camel, the possibly neurosecretory function of these cells requires additional investigation. Furthermore, the presence of nerve terminals in the vicinity of these cells would indicated sensory functions.

The authors have proposed several functions for the MLB cells in dromedaries based on their intimate anatomical relationship with the somatosensory nerve endings of the NSI neuroepithelium. Given that Merkel cells are the primary active mediators for transmitting nociception information via Merkel cell-neurite complexes, it is likely that they are involved in nociception

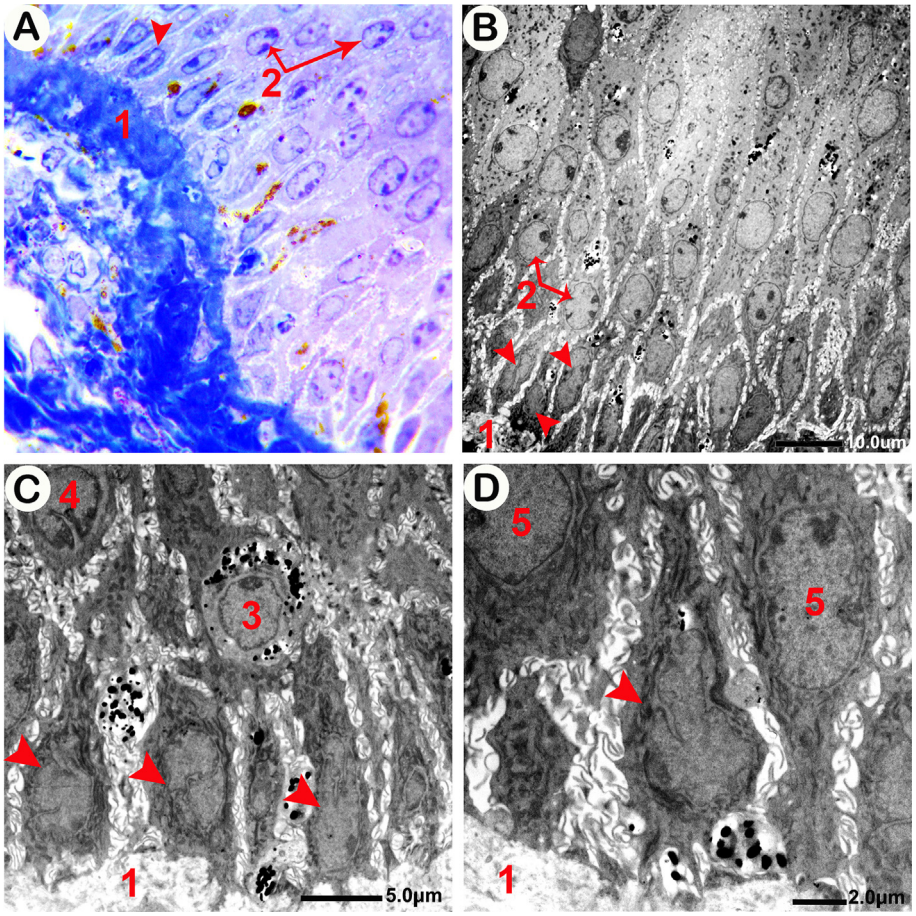

Fig. 2. Light and transmission electron micrographs of the neuroepithelial basal cell layer of camel nasal septal island (NSI) showing: (A) Light micrograph of a semithin section stained with Toluidine blue, showing a Merkel-like basal cell (red arrowhead), which rests on the basement membrane (1), bipolar cells of NSI (2). **(B, C & D)** Transmission electron micrographs at X500, X1200, and X2000 respectively, showing Merkel-like basal cells (red arrowheads), which rest on the basement membrane (1), bipolar cells (2), Langerhans cells (3), macrophages, or mononuclear phagocytic cells (4). Note that the Merkel-like basal cells are scattered between the typical basal cells (5). Scale bars = 10 µm (B), 5 µm (C), 2 µm (D).

(Tachibana et al., 2001; Hoffman et al., 2018; Jeon et al., 2021). However, mechanistic studies are still required to elucidate this possible role. Notably, the MLB cells in our study possessed dense-core granules that were comparable to the secretory vesicles of APUD cells (Boyd, 2001) as well as Merkel cells, which are believed to be a component of the diffuse neuroendocrine system (Gauweiler et al., 1988; Hartschuh et al., 1989; Ramírez et al., 2014). Because these cells secrete various amines, neuropeptides and biologically active mediators, it has been hypothesized that MLB cells have an endocrine function in addition to their somatosensory role. Moreover, the neuropeptides found in the cytoplasmic vesicles in MLB cells might exert a paracrine effect on the nerve terminals and neighboring epithelial cells as well as an autocrine effect on the MLB cells.

The morphological features described in this study should be taken into consideration to more fully understand the potential function of MLB cells in camels. These features, include the basal attachment, cytoplasmic processes, neurosecretory vesicles, and the presence of melanin pigment. Initially, these features appeared isolated, but collectively, they point to a little-studied function, known as magnetoreception. It is well established that Merkel cells have a common function in mechanotransduction as reported by Ikeda et al. (2014), Woo et al. (2014) and García-Mesa (2017). However, other studies have suggested additional interesting functions, including magnetoreception, which is critical for animal navigation, sense direction, and telekinesis (Kirschvink & Gould, 1981; Toyoshima et al., 1993; Diebel et al., 2000; Irmak, 2010). Consequently, Merkel cell attachment to the basal lamina is crucial for their ability to assess their immediate environment and provide orientation (Woodley et al., 1983). Such attachment also is present in hair sinuses, where Merkel cells are oriented similar to scales in a pine cone, vertical or oblique to the basal lamina. This pattern is thought to enable Merkel cells as mechanosensors to immediately recognize direction and spatial orientation, which, together with the extensive neural representation in the somatosensory cortex might work as a biological navigation system (Irmak, 2010).

Surprisingly, an interesting theory regarding the role of melanin pigment in Merkel cells for mammalian magnetoreception was described by Irmak (2010) and Xiao et al. (2014). They hypothesized that Merkel cells contain transferred melanosomes, which contain iron molecules that serve as a "biological magnet". The movable melanosomes or melanin pigments are linked to ion channels with a mechanical gate located in the membrane of Merkel cell. Consequently, the melanin pigments could open the ion channels in response to a changing electromagnetic field, creating a receptor potential sent from the sensory pathway to the brain.

Therefore, the possible mechanism of action of MLB cells in response to electromagnetic fields can be presented as follows: in a changing electromagnetic field, the melanin pigments move via the cytoskeleton, open particular cell membrane ion channels, and generate a cell potential (Irmak, 2010). These conformational changes in the cell membrane could cause the Merkel cells' cyto-

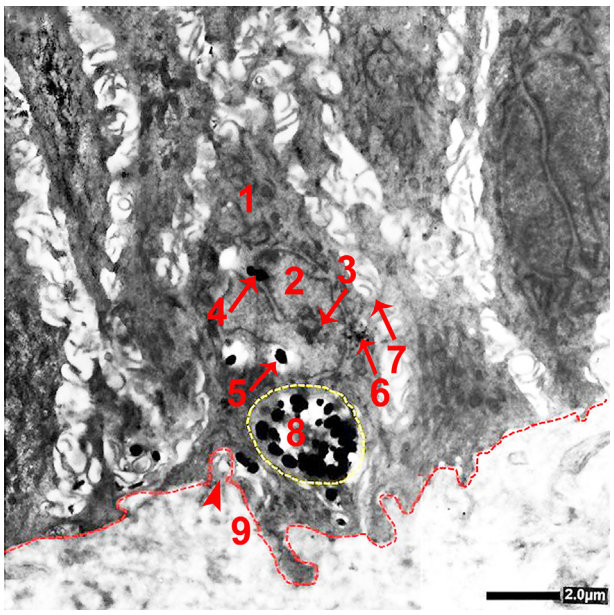

Fig. 3. Transmission electron micrograph of the neuroepithelial basal cell layer of camel nasal septal island showing a Merkel-like basal cell (MLB) (1), characterized by a large, folded nucleus (2), with nuclear inclusions or rodlets (3), melanin pigments (4), Merkel granules (5), which are dense-core granules with a clear halo near the area of nerve terminal, tonofilament-like aggregations (6), cytoplasmic processes or microvilli (7), which are interwined with the discoid neighboring basal cell, and a discoid-shaped nerve terminal (8). The MLB cell rests on the basement membrane (9) with a basal invagination (red arrowhead) of the MLB cell with the basement membrane. Scale bar = 2 µm.

plasmic processes to bend in a specific direction as indicated by their proposed function, and eject their secretory vesicles (Ramirez et al., 2015). The arrangement of MLB cells in the basal layer of the NSI neuroepithelium might provide a mechanism by which the animal's environment might be scanned in detail. The significance of this capability would be the ability to generate a GPS-like picture in the brain to provide real-time perceptions of the environment, yielding animal-specific factors crucial to navigation.

Finally, it is well-established that Merkel cells are multifunctional, excitable mechanosensory cells that express presynaptic molecules and biosynthetic machinery critical for nociception and touch (Irmak, 2010; Woo et al., 2014; Hoffman et al., 2018; Bataille et al., 2022). It is noted in this study that the NSI neuroepithelium is located inside the nasal cavity, where the typical mechanical (touch) perception does not appear to be critical. However, other functions, including neuroendocrine properties and magnetoreception especially the later are proposed for MLB cells. Nevertheless, prospective studies are required to further dissect the molecular machinery of the nociceptive and magnetoreceptive roles of the MLB cells in the dromedary camel.

5. Conclusion

The Merkel-like basal cells, as their name implies, are morphologically distinct from typical Merkel cells and are located in the neuroepithelium's basal layer of the nasal septa island. Functionally, these cells might be necessary for magnetoreception, which is the detection of electromagnetic fields in mammals. This function is essential for camels in the vast extent of the desert environment, to help with navigation and provide a sense of direction. However, further mechanistic studies are required to verify this theory.

6. Compliance with ethical standards

This study's techniques were executed in agreement with the standards for the animal use and care approved by the Scientific Research Ethics Committee, Faculty of Veterinary Medicine, Benha University, Egypt (BUFVTM 01–12-22).

Author contribution

The experimental procedures were designed by AIA and FL. AIA and RIE conducted the experiments. Analysis of data, and interpretation of results was completed by AIA, RIE, and IG. AIA, FL, and IG wrote the initial manuscript draft. AIA and IG made significant revisions to the text. The final manuscript was read and approved by all authors.

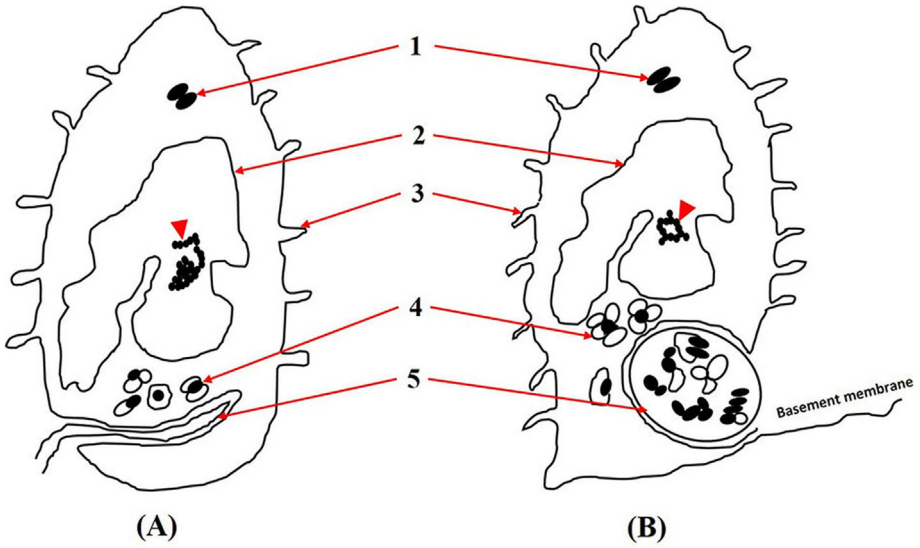

Fig. 4. A conceptual illustration of the ultrastructure of Merkel cells (A) vs. Merkel-like basal cells (B) showing: the presence of melanin pigments (1), the characteristic, highly folded nucleus of Merkel cells (2) with electron-dense nuclear rodlets (red arrowheads), cytoplasmic processes that interdigitate with adjacent cells (3), dense-core secretory granules surrounded by a clear halo (4) that are gathered close to the nerve fiber junction; they contact a dilated nerve ending (5).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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