Anatomy of receptors

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The human hand is a complex organ serving the functions of grip and touch. The mechanoreceptors of the hand can be categorised into those located within skin and subcutaneous tissues and those associated with joints and muscles providing the central nervous system with information about position of movement of hand and fingers. In addition to mechanoreceptors there are numerous free nerve endings reacting to thermal and/or painful stimuli generally referred to as polymodal nociceptors. They are found in the connective tissue of the locomotion apparatus as well as the skin and even enter the epidermis. Morphologically these are terminal branches of afferent nerve fibres without any specific structures around these 'free' nerve endings in marked contrast to the different types of mechanoreceptors.

Mechanoreceptors of joints

Joints are surrounded by mechanoreceptors in the connective tissue forming the joint capsules. The first type – Ruffini corpuscle – is found in the outer fibrous layer (membrana fibrosa) of the joint capsules. A Ruffini corpuscle consists of one or several cylinders formed by flat perineural cells and is supplied by one myelinated axon (5–10 µm diameter) loosing its myelin sheath on entering the cylinder and branching several times (Fig. 1). Each branch is covered incompletely by terminal Schwann cells anchoring between the fibrils with differently shaped nerve terminals. The nerve terminals contain accumulations of mitochondria and empty vesicles. Free surfaces are coved by basal lamina of the termi-

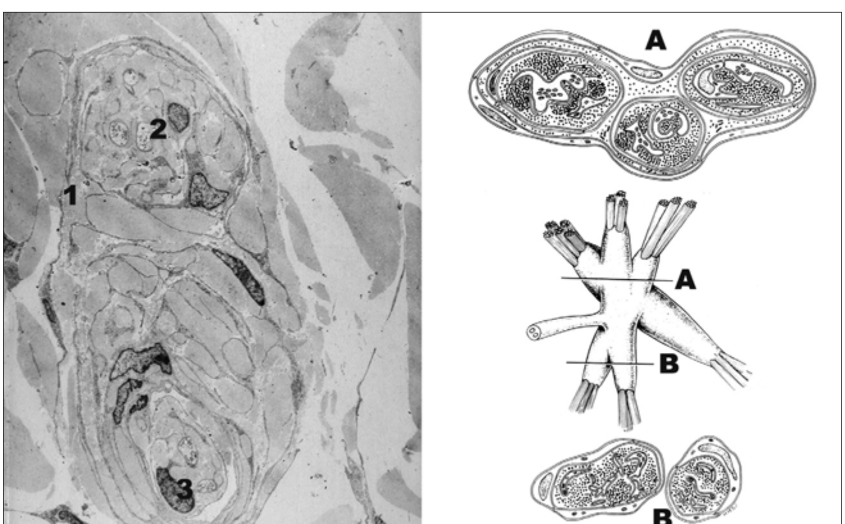

Figure 1. Ruffini corpuscles
Left: Electronmicrograph of a cross section through a Ruffini corpuscle. (1) perineural capsule, (2) nerve terminal. (3) nucleus of terminal Schwann cell. Magnification × 6,000.
Right: Diagrammatic representation of a Ruffini corpuscle from a joint capsule. The longitudinal axis of the cylinders run parallel to the collagen fibrils of the fibrous layer. A and B represent cross sectional images through the planes as indicated.

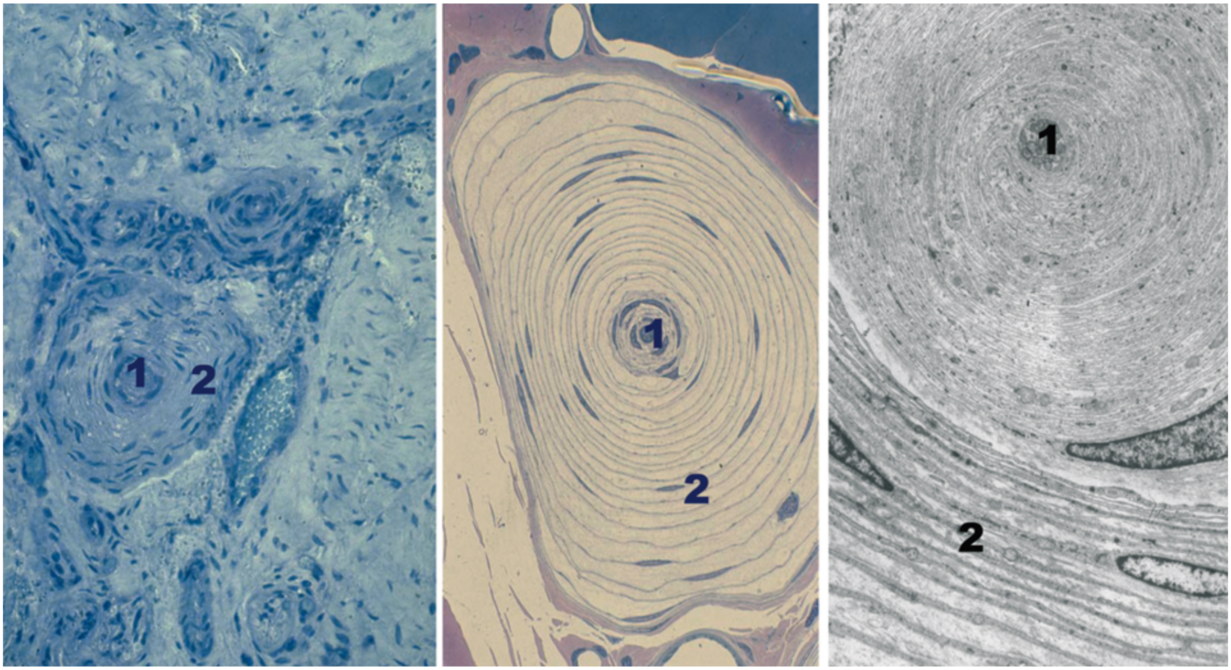

FIGURE 2. VATER-PACINI CORPUSCLES: CROSS SECTIONS THROUGH VATER-PACINI CORPUSCLES
Left: Paraffin section of the fibrous layer of a joint capsule showing a Vater-Pacini corpuscle. (1) inner core, (2) perineural capsule. Magnification × 800.
Middle: Vater-Pacini corpuscle from the epimysium of hand muscles. (1) inner core with nerve terminal, (2) perineural capsule. Magnification × 1,200.
Right: Electron micrograph showing the central part of a Vater-Pacini corpuscle. (1) axon with inner core, (2) perineural capsule. Magnification × 6,000

nal Schwann cells. The longitudinal axis of the cylinders measures approximately 200–300 µm and follows the direction of the collagen fibrils in the fibrous layer of the joint capsule. Structurally the Ruffini corpuscles of the locomotion apparatus are identical with those of the skin.

Functionally Ruffini corpuscles were found to respond with high sensitivity to stretching of the collagen fibres. The discharge pattern of the action potentials is slowly adapting with very regular interspike intervals during maintained stimulation [1].

The second type of joint mechanoreceptor is the so called Vater-Pacini corpuscle, also referred to as Pacinian corpuscle. They are the largest type of mechanoreceptors found in mammals with a length of up to 2 mm and a diameter of up to 1 mm (Fig. 2). The myelinated axon of 6–10 µm diameter looses the myelin sheath on entering the inner part or the corpuscle, but in older people the myelin sheath may extend up to one third of the inner core of the corpuscle. The axon ends in the centre of the corpuscle with a ball shaped thickening.

Cytoplasmic spines extend from the non-myelinated part of the axon anchoring between the lamellae of the inner core of the corpuscle. The axoplasm of the 'ball' and near the origins of the cytoplasmic processes contains accumulations of mitochondria and empty vesicles. The inner core of the corpuscle is formed by symmetrically arranged lamellae of terminal glial cells. In a longitudinal section these lamellae are shaped

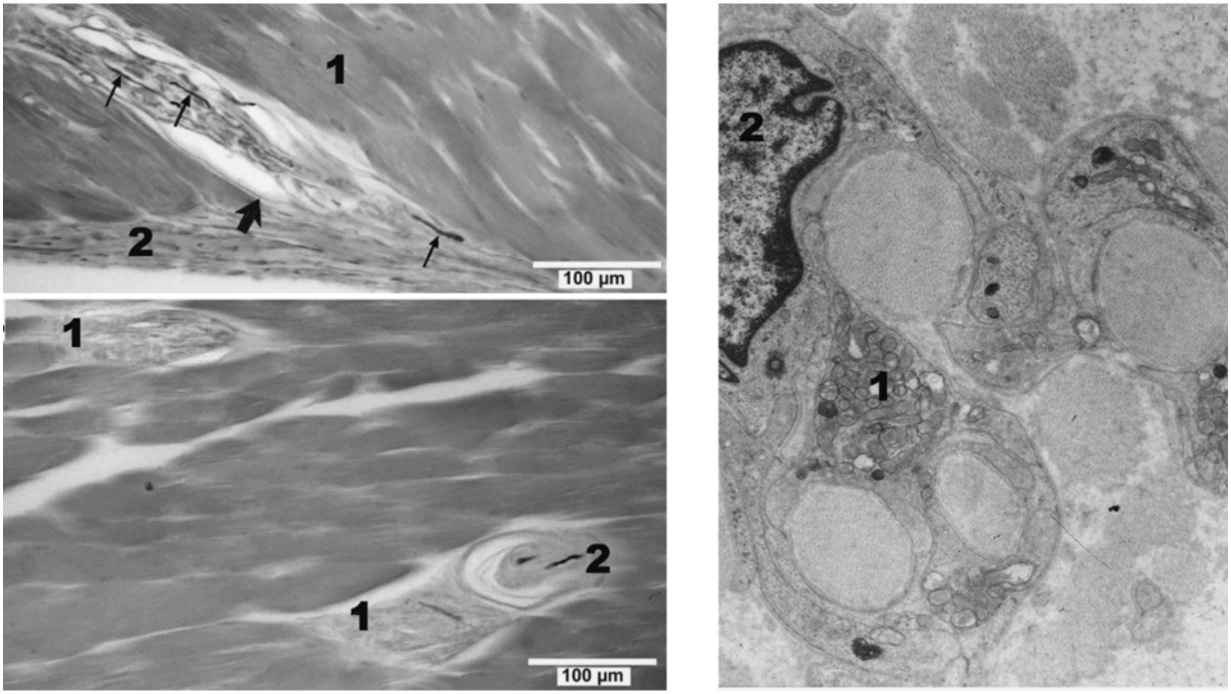

Figure 3. Golgi tendon organs
Left: Silver stained longitudinal section (above) and oblique section (below) of Golgi tendon organs (1). Small Pacini corpuscles (2) are also seen. The nerve terminals are indicated by thin arrows, the thick arrow marks the perineural capsule.
Right: Electronmicrograph of a cross section through a Golgi tendon organ. (1) nerve terminal with accumulation of mitochondria, (2) nucleus of a terminal Schwann cell. Magnification × 12,000.

like half moons on either side of the axon resembling a 'hot dog'. Two symmetric longitudinal clefts separate the two lamellar systems. Thin collagen fibrils are running as spirals through the longitudinal cleft and between the lamellae. The number of lamellae varies with the size of the corpuscle and can reach up to 60 layers. The perineural capsule consists of layers of thin perineural cells extending from the perineurium of the nerve. The cells are flat and show micropinocytotic vesicles. The outer side is surrounded by a basal lamina. Collagen fibrils also run through the clefts between these flat perineural cells. The number of layers of perineural cells forming the capsule depends on the size of the corpuscle. Large corpuscles may have up to 70 layers.

Functionally Pacinian corpuscles respond to vibration stimuli with an optimum of sensitivity in the frequency range of about 200 Hz and vibration amplitudes below 0.1 µm [2].

Mechanoreceptors of the musculature

Two types of mechanoreceptors are found in the musculature: muscle spindles and Golgi tendon organs.

Golgi tenton organs (GTO) were first described by Golgi in 1880 and are found at the juncture between skeletal muscle and tendon, rarely also between muscles and their fascia (Fig. 3). GTOs have the shape of a spindle with a maximum

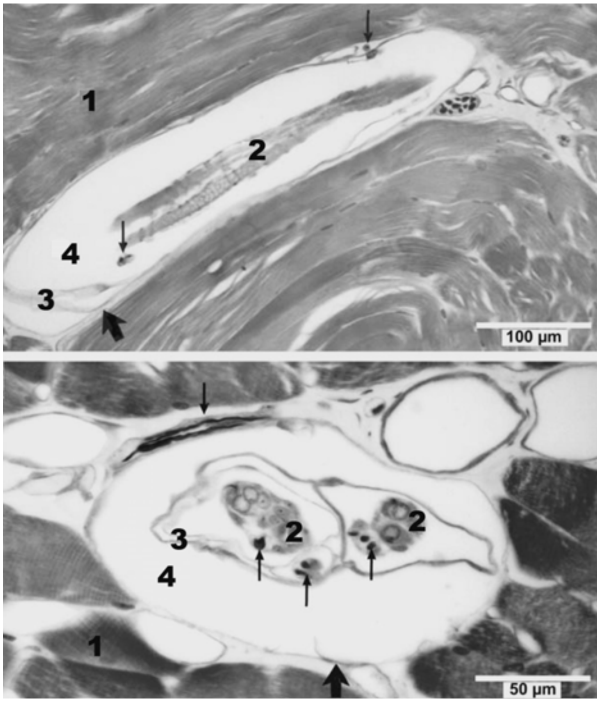

Figure 4. Muscle spindles in silver staining
Above: Longitudinal section of a muscle spindle.
Below: Cross section through a muscle spindle. (1) Extrafusal muscle fibres, (2) intrafusal fibre, (3) inner spindle sheath, (4) subcapsular space. Thin arrows incidate nerve fibres, thick arrow the perineural capsule.

length of about 1,600 µm and a width of up to 120 µm [3, 4]. The spindles are pointed on both sides towards the muscle and towards the tendon, but the end facing the muscle is usually about 25% thicker than the end facing the tendon. Most GTOs are simple spindles, but sometimes one or the other side can branch into 2 or 3 lappets. Occasionally small Pacinian corpuscles can be found within GTOs.

GTOs are usually supplied by several (3 to 6) myelinated afferent axons (5–15 µm diameter) entering the GTO on the long side where the perineurium verges into the capsule of the GTO formed by flat perineural cells surrounded by a basal lamina. The capsule is open at the pointed ends of the GTO. Within the GTO, the afferent nerve looses its myelin sheath and branches several times. Lamellae of terminal glial cells anchor the afferent nerve terminals between collagen fibres. Blood vessels enter the GTO together with the afferent nerve while the venous outlet is usually at the pointed ends.

Functionally, GTOs monitor the tension developed by the muscle and are able to elicit protective spinal reflexes *via* inhibitory synapses with the corresponding motor neurons [5, 6].

Muscle spindles (Figs 4 and 10) belong together with the GTOs to the group of encapsulated mechanoreceptors of the locomotion apparatus. They are 2–10 mm long and about 0.2 mm thick. In the lumbrical muscles, the longest muscle spindles are found in the middle of the muscles while those closer to the muscle ends are shorter.

According to Robertson [7], the fusiform capsule of muscle spindles consists of an inner spindle sheath, an outer spindle sheath. Both layers are formed of flat perineural cells. Thin collagen fibres are running in spirals through the periaxial space between the two layers. The outer layer is surrounded by endomysium of the extrafusal muscle fibres. The perineurium of the supplying nerve is a continuation of the arachnoid matter and extends into the capsule of the muscle spindle, explaining the assumption that cerebro spinal fluid can be found within the muscle spindles [8]. Thin muscle fibres are running through the muscle spindles and referred to as intrafusal fibres. They are encased by connective tissue of the endomysium. Two types of intrafusal fibres can be distinguished depending on the arrangement of their nuclei in the middle (equator) of the muscle spindle: thin nuclear chain fibres, where the nuclei form a row, and thick nuclear bag fibres, where the nuclei are accumulated like in a bag. There are more nuclear chain than nuclear bag fibres and one human muscle spindle contains 1 to 5 nuclear bag fibres and 2 to 11 nuclear chain fibres [9]. The nuclear bag fibres insert into collagen fibres of the endomysium of the extrafusal muscle fibres outside the capsule of the the muscle spindle. In

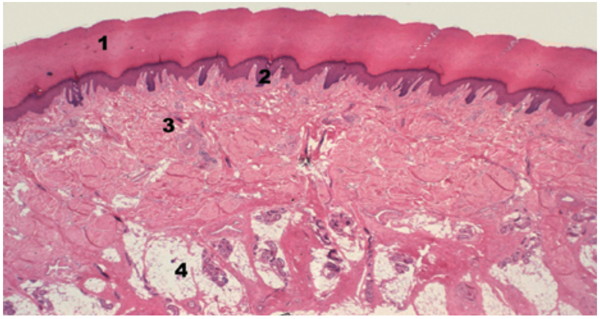

Figure 5. Ridged skin from human finger skin.
(1) stratum corneum, (2) glandular ridge, (3) reticular layer of the dermis, (4) subcutaneous adipose tissue. Paraffin section, HE, magnification × 400.

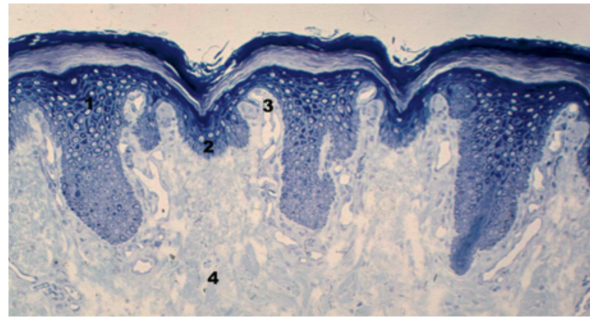

Figure 6. Cross section through the skin of a monkey finger tip with glandular and adhesive ridges.
(1) glandular ridge, (2) adhesive ridge, (3) papilla of the papillary layer of the dermis, (4) reticular layer of the dermis. Semithin section, magnification × 1,500.

contrast, the nuclear chain fibres insert on the inner side of the capsule [10]. Intrafusal muscle fibres have more satellite cells than extrafusal fibres. Similar to the extrafusal muscle fibres, three different types of intrafusal fibres can be distinguished: type A – fast twitch fibres, type B – slow twitch fibres and type C – fast twitch fibres with small diameter.

Afferent axons entering the periaxial space near the equator of the spindle with diameters of 6–15 µm (Ia-fibres) or about 5 µm (group II-fibres) branch several times before forming characteristic nerve endings around the intrafusal fibres. Ia-fibres form primary nerve endings (also called anulospiral endings) near the equator of nuclear bag and nuclear chain fibres. In contrast, group II nerve fibres form secondary nerve endings above and below the equator of the muscle spindles mainly of nuclear chain fibres. These can be of anulospiral or flower spray type. In the polar regions of muscle spindles thin myelinated nerve fibres (group III) and non-myelinated nerve fibres (group IV) form free nerve endings. In addition to sensory innervation, muscle fibres are supplied by axons of motor neurons of Aβ- and Aγ-type.

Muscle spindles monitor the length or changes in length of muscles. For a detailed review see [11].

Mechanoreceptors of the connective tissue between skin and muscle fascia

Within the subcutaneous tissue between skin and muscles large Pacinian corpuscles can be found often arranged in groups of up to three corpuscles. Their structure is identical to those described in the joint capsules. In addition, Ruffini corpuscles are found in the reticular layer of the dermis. They have the same structure as described above for those in the fibrous layer of the joint capsules.

Cutaneous mechanoreceptors

Among the cutaneous mechanoreceptors, estimated to reach a total number of 17,000 per hand [12], one type – Merkel cell nerve endings – is found close to the surface of the skin within the epithelium, while the other types of mechanoreceptors are found in the dermis – either in the papillary layer close to the epidermis (Meissner corpuscles) or lower down in the reticular layer (Ruffini corpuscles). All types are adapted to the typical structure of the skin in fingers and palms which is ideally suited to deal with mechanical stimuli. A schematic drawing showing the loca-

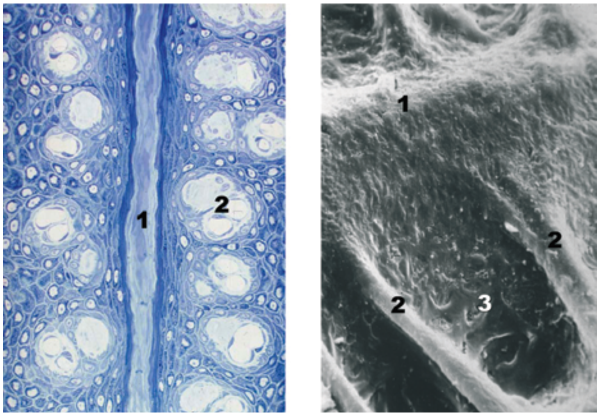

Figure 7
Left: Horizontal section through the skin of a monkey finger tip parallel to the surface. (1) superficial furrow between two glandular ridges. (2) dermal papillae of the papillary layer. Semithin section, magnification × 1,500.
Right: scanning electronmicrograph of the basal layer of the epidermis from below. (1) glandular ridge, (2) adhesive ridge, (3) epithelial crypt. Magnification × 1,600.

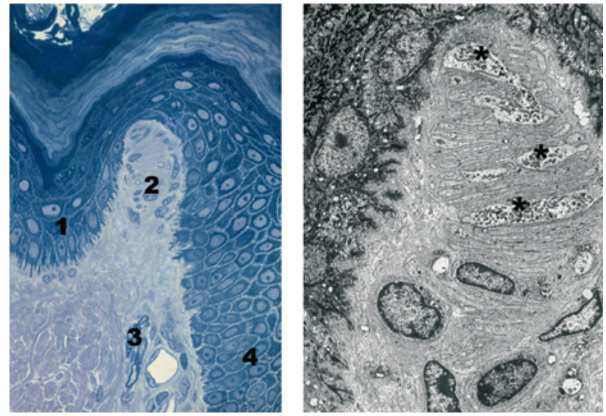

Figure 8 Cross sections through the skin of a monkey finger tip. Meissner corpuscles
Left: Light micrograph of a Meissner corpuscle. (1) adhesive ridge, (2) Meissner corpuscle within the papillary layer of the dermis, (3) myelinated axons of the Meissner corpuscle, (4) glandular ridge. Semithin section, magnification × 3,000.
*Right: Electron micrograph of a Meissner corpuscle. *nerve terminals with accumulation of mitochondria. Magnification × 5,000.*

tion and characteristic features of all types of cutaneous mechanoreceptors is shown in Figure 10.

The surface has skin lines visible with the naked eye. The basal side of the epidermis shows below the epithelial ridges glandular ridges through which sweat ducts pass to the surface (Figs 5, 6 , 7 and 10). Below the groves on the epithelial surface are adhesive ridges. They run parallel to the glandular ridges but are thinner and less deep. Perpendicular to both are cross ridges. In this way, the lower surface of the epidermis forms crypts between glandular and adhesive ridges and perpendicular running cross ridges (Fig. 7). These crypts contain the papillary layer of the dermis and Meissner corpuscles (Figs 8 and 10).

Thus, *Meissner corpuscles* are positioned just below the basement membrane in dermal papillae adjacent to adhesive ridges. On the other side, between Meissner corpuscles and the glandular ridges are capillary loops. In relation to the skin surface, Meissner corpuscles are found below the epidermal grooves and are thus more superficially located than the intraepidermal Merkel cell receptors at the bottom of the glandular ridges (Fig. 10). One square millimetre of skin can contain up to 24 Meissner corpuscles [13]. However, this number decreases with age to about 6 per mm^2 in 70–84 year old human subjects [14].

Meissner corpuscles are oval in shape. The longitudinal axis measures 100–150 µm and is perpendicular to the skin surface. The width of the corpuscles is in the range of 40–70 µm [15]. The corpuscle consists of terminals from myelinated nerve fibres separated by thin lamellae of terminal glial cells also called lamellar cells [16]. The proximal part of the corpuscle has a cup shaped perineural capsule. Collagen fibres of the dermal papilla run between the lamellae of the distal part without capsule and anchor in semi-

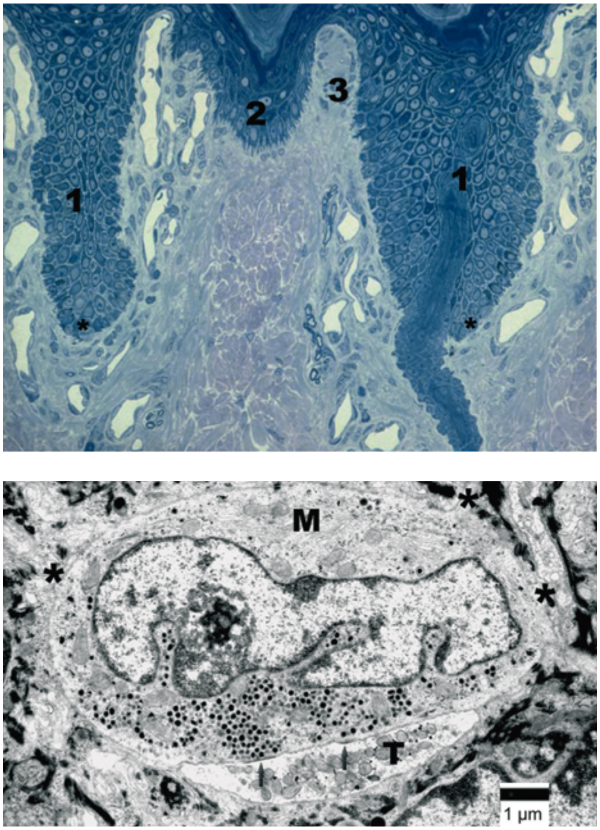

Figure 9. Cross sections through the skin of a monkey finger tip. Merkel cell nerve endings

Above: Light micrograph of two glandular ridges (1) with Merkel cells (*) in the basal layer of the epithelium. (3) Meissner corpuscle. Semithin section, magnification × 1,500.

Below: Electron micrograph of a Merkel cell (M) with associated nerve terminal (T). Characteristic finger-like cytoplasmic processes are marked by asterix, synapse-like contacts between Merkel cell and nerve terminal are marked by arrows.

desmosomes of the epidermis. One corpuscle can be supplied by several myelinated axons of 3–5 µm. The axons loose their myelin sheath on entering the corpuscle and branch into discoid terminals containing large numbers of mitochondria and vesicles of about 80 nm in diameter.

Meissner corpuscles are known to respond to small changes (tens of µm) of indentation of the skin with short, rapidly adapting spike trains. In contrast to Pacinian corpuscles their optimum frequency is in the range of 20–30 Hz [17, 18].

Merkel nerve endings are the only mechanoreceptors found within the epithelium. Groups of up to 19 Merkel cells are positioned in the basal layer of the glandular ridges of the epidermis near the ducts of sweat glands (Figs 9 and 10). Merkel nerve endings consist of Merkel cells and discoid nerve terminals. In contrast to keratinocytes, Merkel cells are oval in shape and have spiny cytoplasmic protrusions anchoring between keratinocytes (Fig. 9). The nucleus is characteristically lobulated. In the cytoplasm facing the nerve terminal are typical osmiophilic (dense cored) granules of 80–120 nm in diameter (for review see [19]). Each group of Merkel cells is supplied by one myelinated nerve fibre (3–5 µm) from the superficial nerve plexus of the dermis. The axon loses its myelin sheath within the papillary layer of the dermis. Covered by a Schwann cell without forming a myelin sheath the axon approaches the basement membrane. Dichotome branchings of the axon are seen at the last Ranvier node and at the epidermo-dermal border. Within the epidermis the axon is ‘naked’ and branches further finally forming discoid terminals with accumulations of mitochondria and empty vesicles (20–40 nm) at the basal side of Merkel cells. Synapse-like connections can be seen between Merkel cells and nerve terminals.

Merkel nerve endings respond to indentation of the skin with long lasting, slowly adapting trains of action potentials [20]. There has been a long controversy whether the Merkel cell is involved in the mechano-electric transduction process or not (for review see [19]). Recent experimental data suggest a glutamatergic synaptic transmission between Merkel cell and nerve terminal [21–24]. Thus, it appears likely, that a dual transduction mechanism may exist with the Merkel cell responsible for the slowly adapting responses [19, 25, 26].

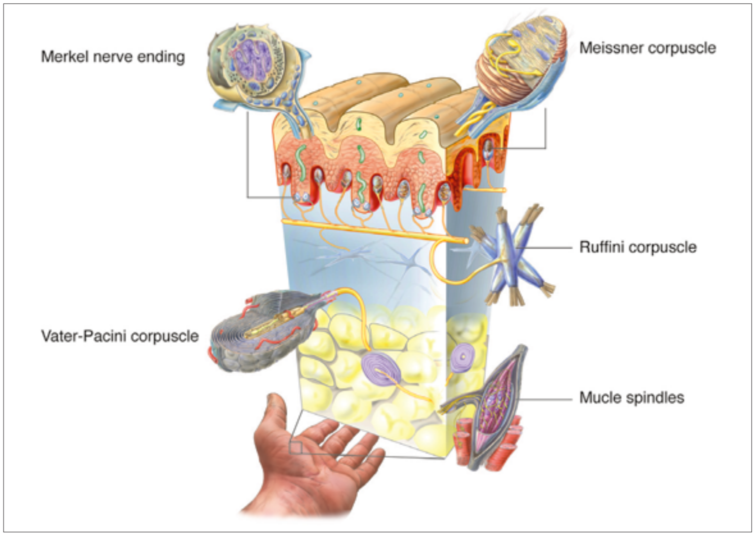

Figure 10. Schematic drawing of mechanoreceptors in the skin and muscles of the hand
In the epidermis, Merkel nerve endings are located in the basal layer of glandular ridges. Meissner corpuscles can be found in the papillary layer of the dermis, while in the reticular layer Ruffini corpuscles are seen. Deep in the subcutis are large Vater-Pacini corpuscles and in the muscles (especially lumbrical muscles) muscle spindles are found between 'extrafusal'

Summary

The human hand serves important functions of grip and touch. Numerous specialised nerve endings are found in the skin, subcutaneous tissues, muscles, ligaments and joint capsules. Some of them form corpuscular mechanoreceptors specialised in monitoring pressure or changes in pressure exerted on the skin surface (Merkel and Meissner corpuscles), stretching of the dermis or ligaments and joint capsules (Ruffini corpuscles) and vibrations transmitted from tools to the hand (Pacinian corpuscles). In addition the length and tension of muscles is controlled *via* information provided by muscle spindles and Golgi tendon organs. A vast number of free nerve endings are distributed throughout the skin and locomotion apparatus serving as polymodal nociceptors responding to various potentially harmful stimuli and partly also to changes in temperature.

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