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## Abstract

The somatosensory system enables organisms to feel, to ache, to chill, and, perhaps most importantly, to know which parts of the body are involved in these sensations. This comprises proprioceptive and cutaneous sensitivity. Somatosensory receptors are distributed throughout the body rather than being concentrated at specialized locations and are able to sense different kinds of stimuli such as pressure against the skin, limb position, distention of the bladder, and body temperature. If a stimulus becomes so strong that it may be harmful, the somatosensory system is also responsible for feeling pain (nociception).

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The skin is the largest sensory organ, and a variety of stimuli from the external environment are constantly contacting its surface. These stimuli are sensed by specialized endings of sensory neurons called receptors, which then transmit signals to the spinal cord and brain for interpretation and response. A single stimulus usually activates many receptors, and each receptor is capable of encoding stimulus features such as intensity, duration, and direction. It is the central nervous system (CNS) that interprets the activity of the different receptors involved in the sensation and uses these interpretations to generate coherent perceptions.

In this chapter, the skin as a sensory organ will be discussed and its role in the sense of touch, nonpainful changes of temperature, itch, and pleasant touch.

### Keywords

Cutaneous sensitivity • Degenerin/epithelial sodium channel family • Dermal papillae • Dermatome • Epidermal keratinocytes • Gracile fasciculus • Itch • Keratinocytes • Krause end bulbs • Langerhans cells • Lissauer's tract • Mechanoelectric transduction • Mechanoreceptive afferents • Mechanoreceptive membrane • Meissner's corpuscles • Melanocytes • Merkel cells • Merkel's neurite complex • Pacinian corpuscles • Pain • Papillary layer • Pruritus • Purinergic receptor • Ruffini's corpuscles • Sensory afferent nerve fibers • Sensory axons • Skin morphology • Somatic sensory receptors • Somatosensation • Cortex • Impulse transmission • Ion channels • Sensory axons • Signal transduction • Skin morphology • Somatosensory cortex (SI) • Stimulus transduction • Stratum basale • Stratum spinosum • Thermoreceptors • Touch • Pleasant • Transient receptor potential (TRP)

### List of Abbreviations

ADP	Adenosine diphosphate
AM	A-mechanonociceptor
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ASIC	Acid – sensing ion channel
ATP	Adenosine triphosphate
BC	Basal cell
BL	Basal lamina
cAMP	Cyclic adenosine monophosphate
CF	Cuneate fascicle
cGMP	Cyclic guanosine monophosphate
CGRP	Calcitonin gene-related peptide
CLTM	Tactile fibers
CN	Clarke's nucleus
CNS	Central nervous system
CT	Unmyelinated fibers
D	Desmosome

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Deg/EnaC	Degenerin epithelial sodium channel
DM	Dermal papillae
DRG	Dorsal root ganglion
FA	Fast adapting
FNE	Free nerve endings
GF	Gracile fascicle
G-protein	Guanine nucleotide-binding protein
HFR	Hair follicle root
IN	Intermediolateral nucleus
K	Keratinocytes
MC	Meissner's corpuscles
MD	Merkel's disks
MEC	Ion channel
mGluR5	Metabotropic glutamate receptor 5
ML	Medial lemniscus
MN	Motor nucleus
MZ	Marginal zone
NGF	Nerve growth factor
NMDA	<i>N</i> -methyl <i>D</i> -aspartate
NP	Nucleus proprius
P2X	ATP activated purinergic receptor
P2Y	G-protein coupled receptor
PC	Paccinian corpuscles
PGP	Protein gene product
PV	Paraventricular nucleus
RA	Rapidly adapting
RE	Ruffini's endings
SA	Slowly adapting
SAM	Slowly adapting mechanoreceptor
SB	Stratum basale
SC	Caudal somatosensory area
SG	Substantia gelatinosa
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SP	Substance P (neuropeptide)
SR	Rostral somatosensory area
SSC	Somatic sensory cortex
T	Thalamus
TREK1	Mechanosensitive potassium channel
TRP	Transient receptor potential
UTP	Uridine triphosphate
VgluT	Vesicular glutamate transporter
VIP	Vasoactive intestinal peptide
VP	Ventro posterior nucleus

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VPLN	Ventral posterior lateral nucleus
VPM	Ventroposterior medial nucleus

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## Brief History

More than two centuries of studies had been devoted to determine the structure, distribution, and physiology of skin sensory receptors. Studies in the 1960s established the basic properties of cutaneous mechanoreceptors afferents in mammalian hairy skin and subdivided these into a number of categories according to the caliber of their axons (and whether myelinated or unmyelinated), the nature of any macroscopic structures associated with their terminations, their rate of adaptation to a constant displacement, and the form of their receptive fields.

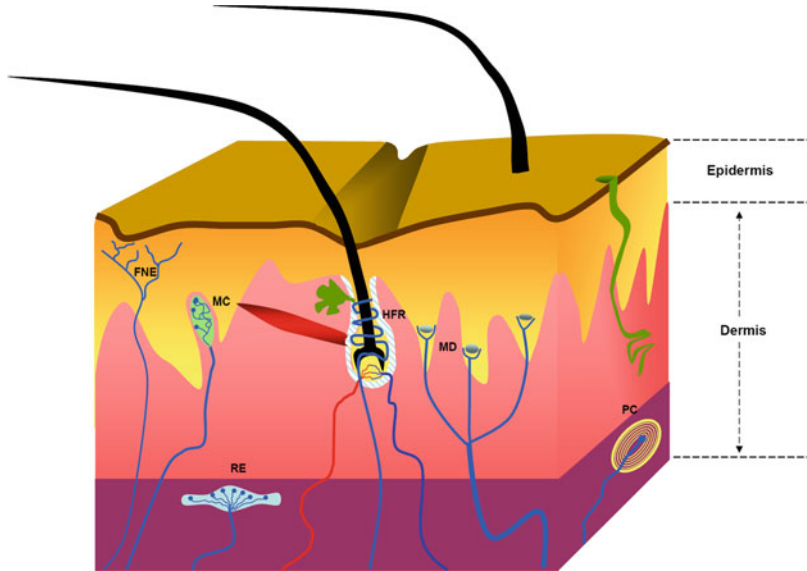
## Touch

The sensation of touch begins at the skin, a highly complex organ, innervated by a wide array of specialized sensory neurons sensitive to heat, cold, pressure, irritation, itch, and pain.

Touch is the first sense to develop. In utero tactile responses to a hair stroking the cheek of a fetus at around 8 weeks gestational age have been reported. Cutaneous sensitivity of the embryonic body extends to the genital area by week 10, the palms by week 11, the soles by week 12, and the abdomen and buttocks by week 17. By week 32 gestation, every part of the body is responsive to the gentle stroke of a single hair. This developmental hierarchy of tactile sensitivity is reflected anatomically, with the sites developing cutaneous sensitivity first possessing the greatest number and variety of sensory receptors in adults. Consequently, these sites are also represented cortically with larger areas of primary somatosensory cortex.

There are two major types of skin: hairy and glabrous (hairless). Skin consists of an outer stratified squamous epithelium of ectodermal origin – the epidermis – and an inner, thicker, supporting layer of connective tissue of mesodermal origin – the dermis. The skin is endowed with sensory receptors of various types that are peripheral terminals of sensory nerves. It is also well supplied with motor nerve endings to the blood vessels, arrector pili muscles, and sweat glands (Fig. 1). The nerve bundles course through the dermis vertically, forming a horizontal subepidermal neural plexus before losing their Schwann cell covering at the dermoepidermal junction, penetrating the epidermal basement membrane, ascending between keratinocytes, and terminating as free nerve endings.

In mammals, the sense of touch is initiated by more than a dozen morphologically distinct sensory afferents in the skin. These somatosensory afferents encode a wide range of stimuli, including hair movement, light touch, vibration, texture, itch, and pain. In the skin, the endings of a single afferent fiber form one kind of receptor. The process by which the receptive portion of an afferent fiber converts natural stimulus

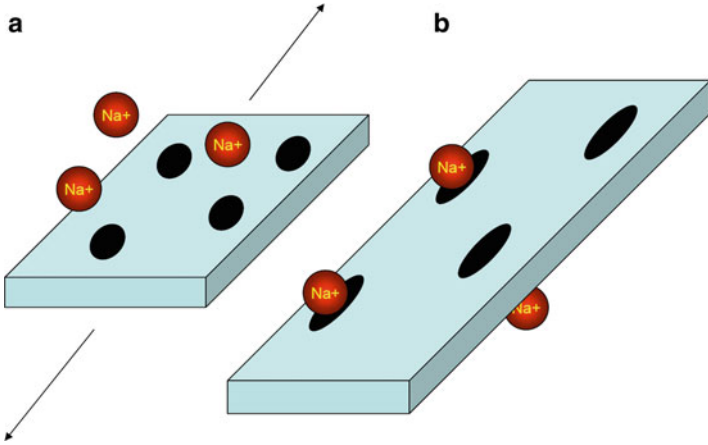


**Fig. 1** Somatic sensory receptors of the skin. Hairy and glabrous skin have a variety of sensory receptors in the dermal and epidermal layers: free nerve endings (*FNE*), Meissner's corpuscles (*MC*), Ruffini's endings (*RE*), nerve endings in the hair follicle root (*HFR*), Merkel's disks (*MD*), and Pacinian corpuscles (*PC*)

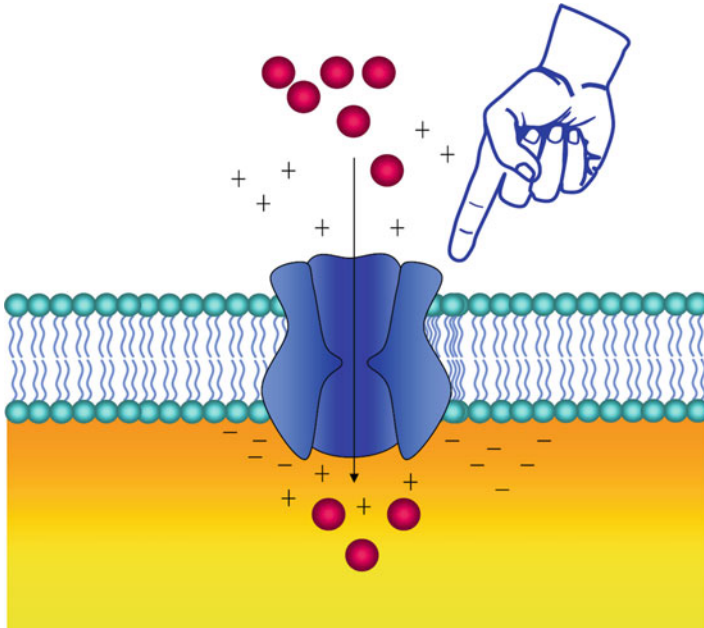
energy into neural activity is called stimulus transduction. To activate a receptor, a stimulus must be of suitable intensity and quality. Mechanoelectric transduction changes the mechanical energy of the stimulus into electrical energy that results in the receptor potential. In the resting condition, the mechanoreceptive membrane allows few  $\text{Na}^+$  ions to pass because the effective channel size is small. Stretching the membrane increases the effective channel size, thereby allowing more  $\text{Na}^+$  to flow across the membrane into the cell while  $\text{K}^+$  can simultaneously flow out (Fig. 2). Physiologically identified responses have been linked to the morphologically distinct cutaneous receptors. In the majority of receptors in the skin, mechanical energy presses on, displaces, or deforms the receptor (mechanoreceptor), which converts the energy into an electrochemical event, resulting in a nerve impulse (Fig. 3).

### Morphology of the Skin

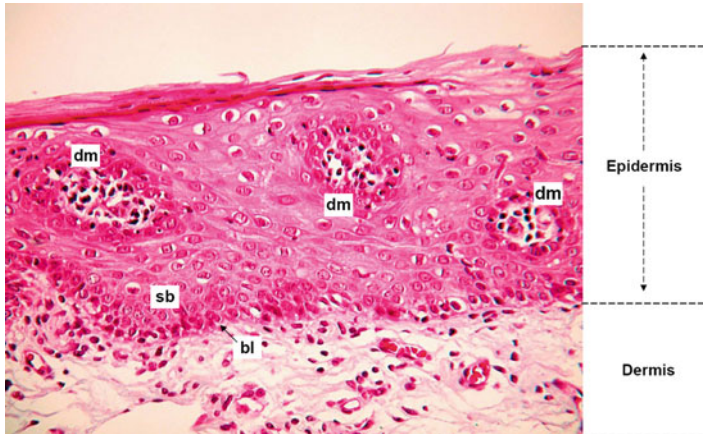
The skin can detect patterns on a very small scale; however, nerve fibers are not always so numerous, which suggests that nerve terminals are helped by epidermal sensors. In addition, the dimension of the receptive field typically exceeds the



**Fig. 2** Mechanoreceptive membrane in (a) resting and (b) stretching conditions. Mechanoelectric transduction changes the mechanical energy of the stimulus into electrical energy that results in the receptor potential (Modified from Martin (1985))



**Fig. 3** Mechanoreceptor. The mechanical energy presses on, displaces, or deforms the receptor, which converts the energy into a nerve impulse



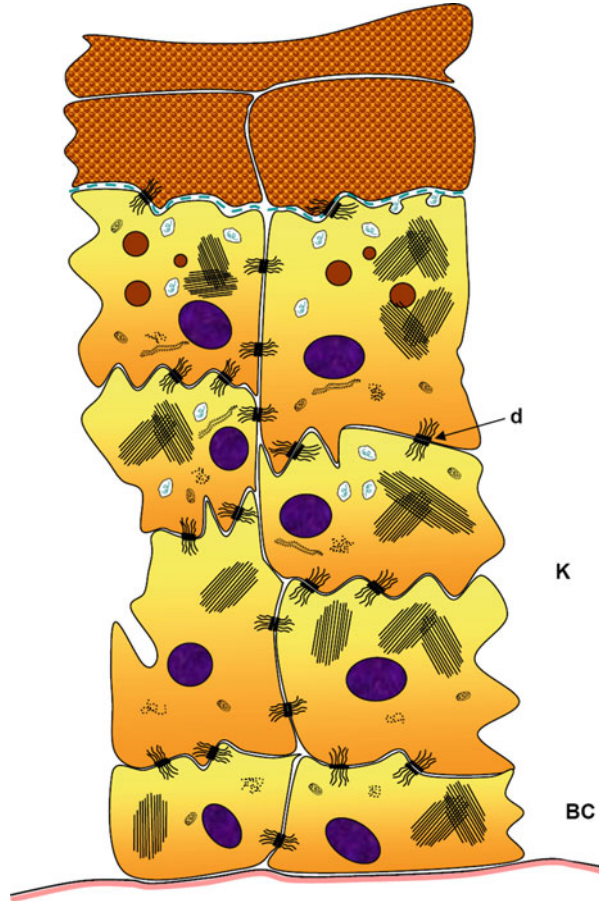
**Fig. 4** Section of human skin stained with hematoxylin eosin. Note the *dermal papillae* (*dm*), the *stratum basale* (*sb*), and the *basal lamina* (*bl*), within the epidermis (20 $\times$ )

regions of tissue directly innervated; thus, stimulus energy should be transmitted through different cells within the skin. In order to understand the role that epithelial cells play in the skin somatosensation, it is important to describe the skin morphology, how epidermal cells are arranged, and how they communicate.

The skin has an outer layer, the epidermis, and an inner layer, the dermis. The junction between the dermis and epidermis contains numerous finger-like connective tissue protrusions, *dermal papillae*, that project into the undersurface of the epidermis. Meissner's corpuscles are rapidly adapting receptors located in the *dermal papillae*. The papillae are complemented by what appear to be similar epidermis protrusions, called epidermal ridges, that project into the dermis. If the plane of section is parallel to the surface of the epidermis and passes at a level that includes the *dermal papillae*, the epidermal tissue appears as a continuous sheet of epithelium, containing circular islands of connective tissue (Fig. 4). At a site where increased mechanical stimuli is placed on the skin, the epidermal ridges are much deeper, and the derma papillae are much longer and more closely spaced, creating a more extensive interface between the dermis and the epidermis.

In the dermis, there are two structurally distinct layers, the papillary and the reticular layer. The papillary layer, the most superficial, consists of loose connective tissue (collagen and elastic fibers), blood vessels that do not enter the epidermis, and nerve processes that either terminate in the dermis, or penetrate the basal lamina, to enter the epithelial compartment. The reticular layer lies deeper than the papillary layer and is thicker and less cellular than the papillary layer. Pacinian corpuscles are rapidly adapting receptors usually located in the reticular dermis, and beneath that is a layer of adipose tissue that forms the hypodermis or subcutaneous layer. Individual smooth muscle cells that originate in this layer form the arrector pili muscles that connect the deeper part of hair follicles to the most superficial dermis. Contraction of

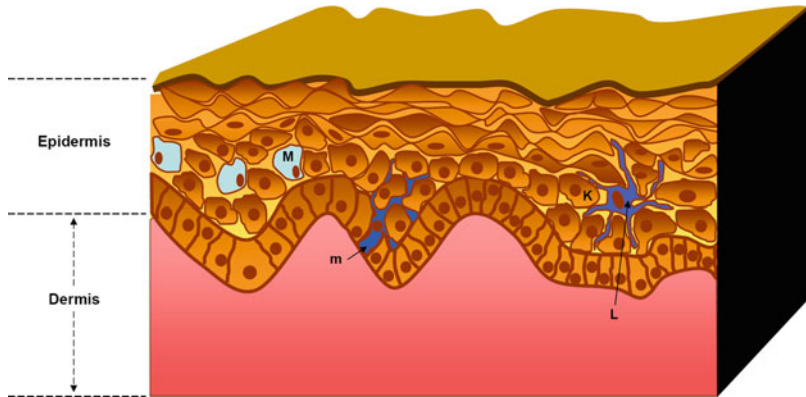
**Fig. 5** Epidermis. Basal cells (BC) connected to each other and to keratinocytes (K) by desmosomes (d)



these muscles in humans causes hairs to rise and skin to pucker, also known as goose bumps.

In the epidermis, four distinct layers can be identified, and in thick skin, a fifth layer can be found. The deepest layer is the *stratum basale*, a single layer of cells that rests on the basal lamina (Fig. 4). It contains the stem cells from which new keratinocytes are formed, basal cells, and melanocytes. Basal cells exhibit extensive cell junctions and are connected to each other, to keratinocytes, and to the underlying basal lamina by desmosomes. As new keratinocytes arise by mitotic division, they move into the next layer, the *stratum spinosum* which is several cells thick. The cells of this layer are larger than those of the stratum basale and exhibit numerous cytoplasmic processes or spines, which are attached to similar processes of adjacent cells by desmosomes (Fig. 5). As the cells mature and move to the surface, they increase in size and become flattened. This arrangement is particularly notable in the most superficial spinous cells, where the nuclei also become elongated instead of ovoid. The *stratum granulosum*, one to three cells thick, is the most superficial layer





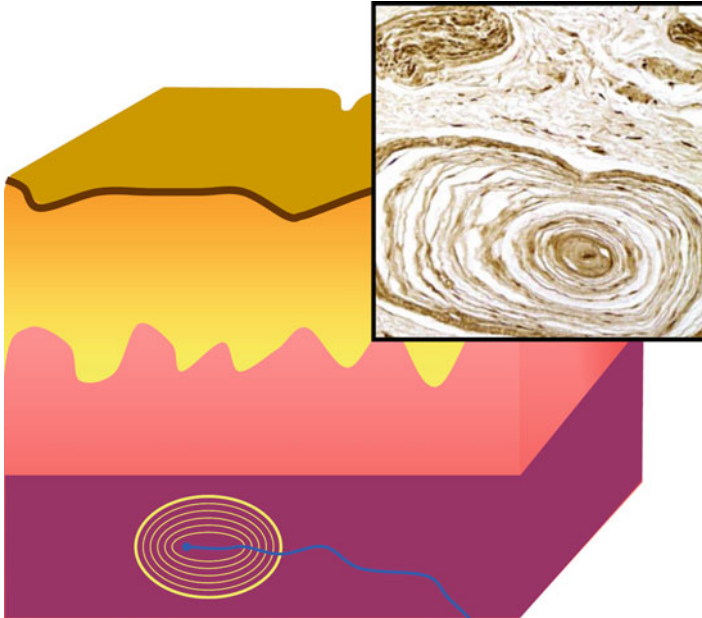
**Fig. 6** Epidermal cells of the skin: keratinocytes (*k*), melanocytes (*m*), Merkel's cells (*M*), and Langerhans cells (*L*)

of the nonkeratinized portion of the epidermis. These cells contain numerous keratohyalin granules, which vary in size and shape. The cells in the *stratum corneum* are the most differentiated cells in the skin. They lose their nucleus and cytoplasmic organelles and become filled almost entirely with keratin filaments. Other epidermal cells are melanocytes, Merkel and Langerhans cells (Fig. 6).

During embryonic life, melanocyte precursor cells migrate from the neural crest and enter the developing epidermis. A specific functional association is then established, the epidermal-melanin unit, in which one melanocyte maintains an association with a given number of keratinocytes. Neither the processes nor the cell body forms desmosomal attachments with neighboring keratinocytes. However, melanocytes that reside close to the basal lamina have structures that resemble hemidesmosomes. Merkel cells are modified epidermal cells located in the stratum basale and are bound to adjoining keratinocytes by desmosomes. They contain intermediate filaments in the cytoplasm and dense-cored neurosecretory granules.

In general, two types of mechanoreceptors can be morphologically distinguished within the skin, encapsulated and non encapsulated receptors. Pacinian corpuscles are large ovoid structures found in the deeper dermis and hypodermis and are composed of a myelinated nerve ending surrounded by a capsule structure. The axon is covered by a series of tightly packed, flattened Schwann cell lamellae, and the corpuscles respond to pressure and vibration through the displacement of the capsule lamellae. The Pacinian corpuscle is the most widely distributed of the encapsulated receptors and is also the largest, visible with the naked eye (1–2 mm). The lamination of the connective tissue capsule resembles a sliced onion with the laminae separated from one another by clear fluid (Fig. 7).

Meissner's corpuscles are receptors located in the dermal papillary layer just beneath the epidermal basal lamina of hairless skin (finger tips, the palm of the hands, soles of the feet, nipples, and female and male external genitalia). Meissner's corpuscle are tapered cylinders oriented perpendicular to the skin surface. They are

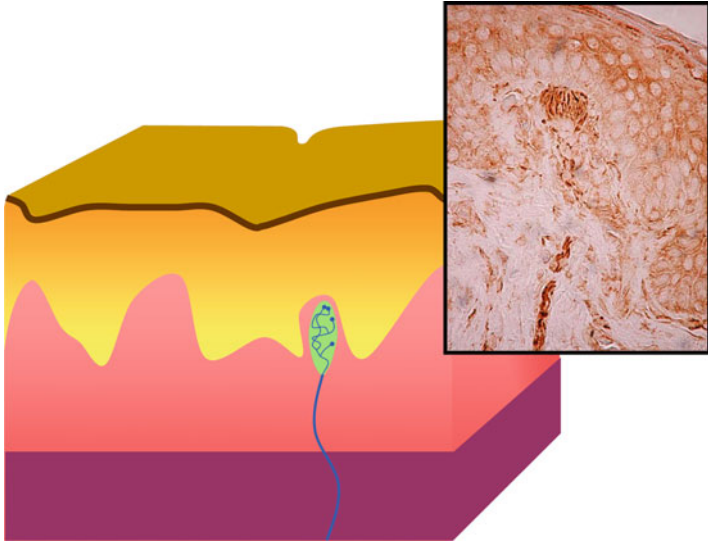


**Fig. 7** Pacinian corpuscle within the dermis, and Pacinian corpuscles immunostained with the neural marker PGP 9.5 as seen in light microscope section (40 $\times$ )

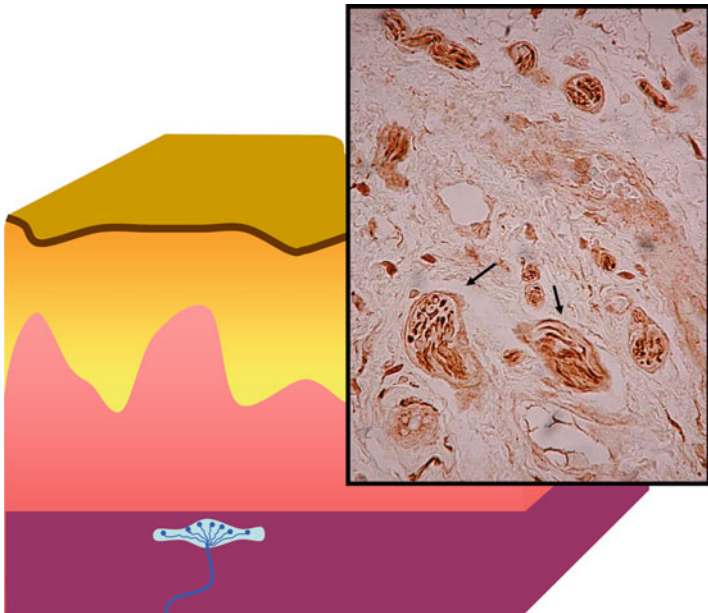
about one tenth the size of a Pacinian corpuscle and consist of a laminated capsule of connective tissue cells surrounding a spiral naked nerve ending. The sheaths of the nerve blend with the connective tissue capsule, at which point the myelin covering is lost (Fig. 8). Meissner's corpuscles are particularly receptive to mechanical shear forces applied to the skin, to low frequency stimuli, and probably participate in two-point discrimination.

Ruffini's corpuscles are the simplest encapsulated mechanoreceptors. They have an elongated fusiform shape and consist of a thin connective tissue capsule enclosing a fluid-filled space. The neural element consists of a single myelinated fiber that enters the capsule where it loses its myelin sheath and branches to form a dense arborization of fine axonal endings, each terminating in a small knob-like bulb (Fig. 9). The axonal endings are dispersed and intertwined inside the capsule. Ruffini's endings are located deep in the dermis in both hairy and glabrous skin. The axonal endings respond to the displacement of collagen fibers induced by sustained or continuous mechanical stimuli.

Unencapsulated nerve endings can terminate as free branched fibers in the papillary dermis or in the epithelial layers of the skin. In hairy skin areas, they can end in the dermis as free endings or surround a hair follicle and attach to their outer root sheath (Fig. 10). In this position, they are particularly sensitive to hair movement and serve as mechanoreceptors. The bending of hair causes a deformation of

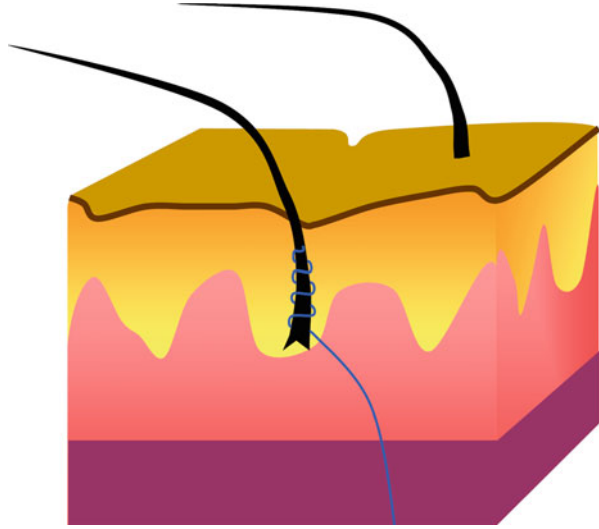


**Fig. 8** Meissner corpuscle in the *dermal papillae*, and Meissner corpuscles immunostained with the neural marker PGP 9.5 as seen in light microscope section (40 $\times$ )



**Fig. 9** Ruffini's ending in the dermis, and Ruffini's ending immunostained with the neural marker PGP 9.5 as seen in light microscope section (40 $\times$ )

**Fig. 10** Nerve ending surrounding a hair follicle



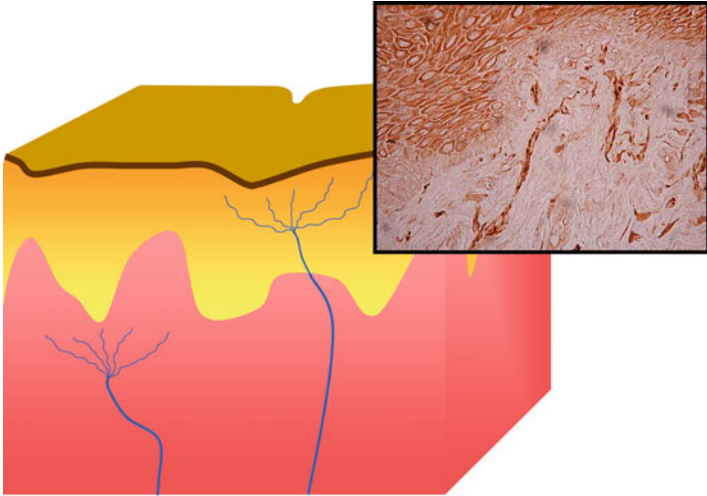
the follicle and surrounding skin tissues. This in turn stretches, bends, or flattens the nearby nerve endings, which then increases or decreases their action potential.

Sensory neurons of the peripheral nervous system send many primary afferent fibers to the skin. They pass through the dermis and penetrate the basement membrane to innervate epidermal cells or remain as free endings.

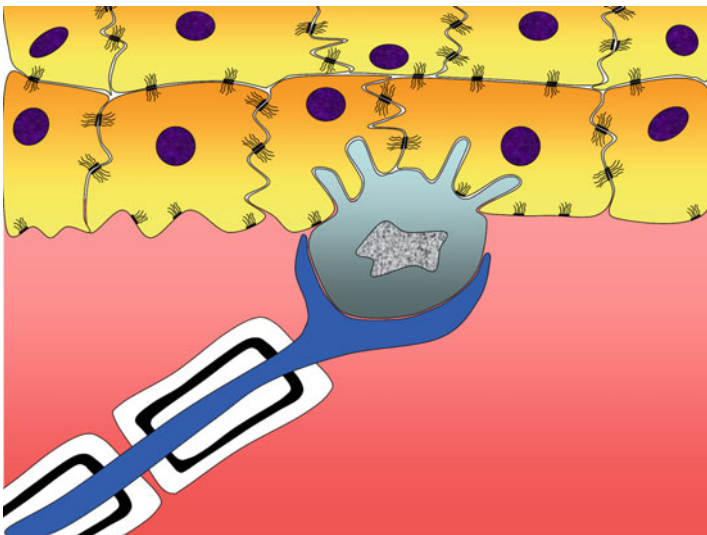
In glabrous skin, the axon reaches the epithelial layers, loses its Schwann cell sheath, and forms numerous unmyelinated branches (Fig. 11) throughout the granular layer. Free nerve endings are receptive to touch, temperature, and pain. In areas such as lips and fingertips, nerve endings may be free, form-flattened disks abutted against modified epithelial cells or may be surrounded by bulblike structures. In the border regions of dry skin and mucous membrane (around the lips and genitals), the nerve terminals look like knotted balls of string and are called Krause end bulbs. Free nerve endings are the simplest type of receptors.

Merkel cells are closely associated with the expanded terminal bulb of afferent myelinated nerve fibers. The neuron terminal loses its Schwann cell covering and immediately penetrates the basal lamina, where it expands into a disk- or platelike ending that lies in close apposition to the base of the Merkel cell. The combination of the neuron and epidermal cell, called a Merkel's neurite complex, is a sensitive mechanoreceptor (Fig. 12).

Merkel's disks consist of a nerve terminal and a flattened, nonneural epithelial cell. Each of these disks lies adjacent to vesicles within the epithelial cell. The epithelial cell is the mechanically sensitive part because it makes a synapse-like junction with the nerve terminal. There is some evidence that light pressure (touch) on the epithelial cell releases a transmitter from the vesicles that stimulate the Merkel's disk. Merkel cells can be grouped as Merkel ending complexes that are disklike endings flattened against specialized Merkel cells, clustered in the basal



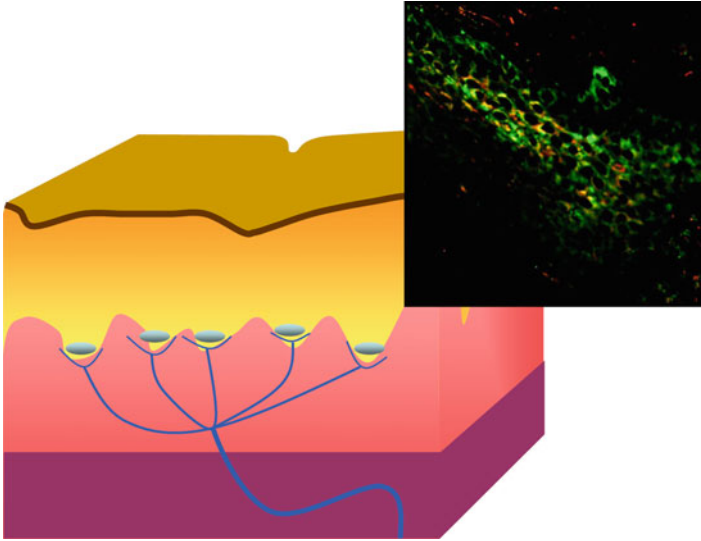
**Fig. 11** Nerve endings in the skin, and nerve endings immunostained with the neural marker PGP 9.5 as seen in light microscope section (40×)



**Fig. 12** Merkel's neurite complex diagram

lamina at the base of the thickened intermediate epidermal ridges (Fig. 13). They are most abundant in the skin where sensory perception is acute.

The epidermis and its sensory endings are morphologically and chemically organized into a stratified sensory transducing and integrating organ.



**Fig. 13** Merkel's neurite complex diagram and double immunofluorescence of the epidermis with cytokeratin 20 and the neural marker PGP9.5 as seen in laser confocal microscope (40 $\times$ )

## The Role of the Skin in Signal Transduction

Skin responds to external stimuli, either directly, through transduction of the stimulus energy by receptors on nerve terminals, or indirectly, through activation of channels on epidermal cells and/or the release of intermediate molecules, which, in turn, act on sensory neuron receptors.

All epidermal cells (keratinocytes, melanocytes, Langerhans cells, and Merkel cells) express sensor proteins and neuropeptides regulating the neuro-immuno-cutaneous system (Table 1). The epidermis acts as sensory tissue where sensor proteins with neuron-like properties, enable epidermal cells to participate in skin surface perception through interactions with nerve fibers. Epidermal cells express many sensor proteins like those found in neurons. These proteins are mainly transmembrane proteins (Fig. 14), which transform stimuli like touch, osmotic pressure, temperature, or chemical stimulations into biochemical intracellular messages (Table 2). Such neuron-like properties permit the whole epidermis to have sensory functions.

The molecular transduction mechanisms of touch are largely unknown, but three models have been postulated to explain touch perception: (a) high-speed channels convert stimuli into an electrical signal, (b) ion channels are tethered to the cytoskeleton or extracellular matrix in which membrane movements induce the opening of ion channels to generate electrical activity, and (c) a mechanosensory protein initiates a second messenger cascade leading to the opening of the ion channels, thus producing depolarization.

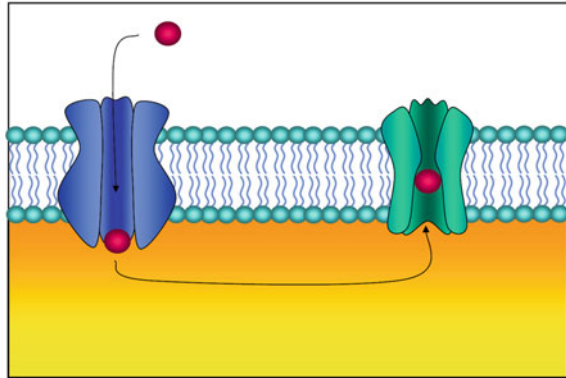
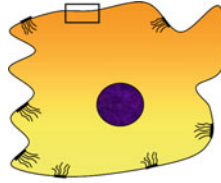
**Table 1** Ion channels believed to be implied in somatosensation in mammals (Modified from Boulais and Misery 2008)

Channel	Physical stimuli	Chemical stimuli	Cells and fibers
TRPA1	Thermal, mechanical	Isothiocyanates, Ca <sup>2+</sup> , icilin	C-fibers
TRPC1	Mechanical	Stored-operated calcium channel	Mechanosensory neurons
TRPM8	Thermal	Menthol, icilin	C-fibers
TRPN1	Mechanical	None known	Hair cell, bristles
TRPV1	Thermal, osmotic	Capsaicin, proton, endocannabinoids, amandamide, protons, diphenyl compounds	C, A $\delta$ -fibers, keratinocytes
TRPV2	Thermal, osmotic, mechanical	Diphenyl compounds	A $\delta$ , A $\beta$ -fibers, immune cells
TRPV3	Thermal	Camphor, carvacrol, diphenyl compounds	Keratinocytes, C-fibers
TRPV4	Thermal, osmotic cell swelling	Phorbol ester (4 $\alpha$ PDD), epoxyeicosatrienoic acid	Keratinocytes, Merkel cells, A $\delta$ , and C-fibers
ASIC1	Mechanical	Protons	A $\delta$ , A $\beta$ and C-fibers
ASIC2	Mechanical	Protons	A $\delta$ , and A $\beta$ fibers
ASIC3	Mechanical	Protons	A $\delta$ , and A $\beta$ fibers
MEC4	Mechanical	None known	Mechanosensory neurones
MEC10	Mechanical	None known	Mechanosensory neurones

The identification of receptor proteins activated by different stimuli, in particular ion channels of the Transient Receptor Potential (TRP) superfamily, has put forward the concept that specificity of peripheral sensory receptor neurons is determined by their expression of a particular molecular sensor that confers to each functional type its selective response of a discharge of nerve impulses to stimuli of a given quality. The TRP family members have been reported to be activated by mechanical stress, temperature, or other physical or chemical factors. TRPV1, TRPV3, and TRPV4 have been shown to be present in epidermal keratinocytes. TRPV4 is expressed in the Merkel-neurite complexes, which play a key role in the slowly adapting type I mechanoreception; however, it is also highly expressed in nonsensory tissues. TRPV3 and TRPV4 channels have been identified as thermosensitive channels that are activated by warm temperatures. TRPM8 is a nonselective cation channel of the TRPM8 (melastatine) family with a modest permeability to calcium. The channel is specifically expressed in small diameter trigeminal and dorsal root ganglion neurons, in which cooling evokes inward depolarizing currents and intracellular calcium rises. Thus, TRPM8 has been proposed as the cold sensor molecule that confers to the peripheral thermoreceptor neuron, the specific ability to respond



**Fig. 14** Epidermal cells express transmembrane proteins, which transform external stimuli into biochemical intracellular messages



**Table 2** Physiological classification of cutaneous sensory endings (Modified from Boulais and Misery 2008)

Type	Sub-type	Stimuli	Type of fiber
Mechanoreceptor	Type I	Quivering	Meissner, A $\beta$ -fibers
		Touch	Merkel cells, A $\beta$ -fibers, low-threshold C-fibers
	Type II	Vibration	Pacini, A $\beta$ -fibers
		Pressure	Ruffini endings
Thermoreceptor	Cold	<30 °C	C and A $\delta$ -fibers
	Heat	32–48 °C	C-fibers predominantly
Nociceptors	Mechano	Significant pressure, inflammatory mediators, ischemia mediators	A $\delta$ , and A $\beta$ fibers
	Polymodal	Inflammatory mediators	C-fibers
Puriceptors		Histamine, inflammatory mediators	Histaminergic C-fibers

to small temperature reductions, ultimately causing well-defined innocuous cold temperature sensations. TRPM8 is gated by lysophospholipids and other chemical agents that induce mechanical deformation in the membrane bilayer, suggesting a possible mechanosensitive role. The multimodality of the TRP channels is a well-established concept. Similar multimodal gating mechanisms are also frequent among two-pore-domain K<sup>+</sup> channels, another extended family of ion channels with prominent sensing roles in the somatosensory system.



Another receptor family thought to participate in many cutaneous events is the purinergic receptor. Two types of receptors belong to this family and are grouped according to the ligand they bind. P1 receptors bind adenosine and are divided into four subtypes, whereas P2 receptors, which bind ATP, ADP, and UTP, are divided into ionotropic P2X receptors and metabotropic G-protein-coupled P2Y receptors. The nervous system contains two distinct families of ATP receptors. One is the ATP-activated purinergic receptor (P2X) family, which is a ligand-gated channel, and the other is the P2Y family of metabotropic, heptahelical G-protein-coupled receptors. P2X3 was first identified as a pain receptor in the peripheral nervous system. P2X3 is expressed in human epidermal keratinocytes. P2Y2 receptors have been identified in Merkel cells, and this channel may have a role in mechanoreception.

Keratinocytes play an important role at the forefront of the sensory system because they are equipped with sensing proteins similar to those found in neurons. Keratinocytes express receptors like TRPV1, TRPV3, and TRPV4. TRPV channels enable them to sense thermal and noxious stimuli and perhaps osmotic variation. The stimulation of these receptors is followed by the release of neuropeptides like SP, which can act as neurotransmitters onto target cells or modulators of epidermal functions.

The ability of keratinocytes to interact with neurons has been demonstrated *in vitro*. In co-cultured models, keratinocytes exhibit a strong trophic effect toward sensory neurons, and close contact was found between these two elements. The mechanism involved in signal transduction from keratinocytes to sensory neurons remains unclear. One hypothesis is that the signal goes through the purinergic receptors P2X2, P2X3, and P2Y2. It has been shown that ATP-activated cells can increase their intracellular calcium concentration, producing a calcium wave able to propagate to neighboring cells. The ATP-dependant calcium waves produced by keratinocytes can induce an increase in intracellular calcium concentration not only in adjacent keratinocytes but also in sensory neurons. These events are interesting because keratinocytes are in such close contact with sensory neurons that synaptic transmission was considered. But, ATP-dependant calcium waves may also allow keratinocytes to communicate with neurons from a long range as well. Another putative pathway of communication from keratinocytes to neurons implicates that activation of bioactive substances like NGF or the inflammatory cytokine interleukins, IL-1 $\alpha$  and IL-8, released subsequent to the receptor activation. These mediators are released upon activation of the keratinocytes by neuropeptides like SP, CGRP, VIP, galanin, and probably other proteins expressed by keratinocytes themselves.

Both TRP and ATP receptors on keratinocytes might play a role in a variety of skin sensations. Activation of P2Y receptor reduced the threshold temperature of TRPV1. Such interaction between receptors could play a regulatory role in complex signaling systems. Further study is needed to reach a better understanding of the role of each receptor in keratinocytes in relation to the skin sensory system. Of the major types of known ion channels, mechanosensitive channels are the least understood.

Various environmental stimuli or neurotransmitters often cause changes in Ca<sup>2+</sup> in the skin. Epidermal keratinocytes are nonexcitable cells and do not produce action

potentials. Given that  $\text{Ca}^{2+}$  waves in keratinocytes are mediated by the release of extracellular molecules, such signals may also affect the activities of surrounding cells such as sensory neurons. The expression of a functional voltage-gated calcium channel in epidermal keratinocytes has been demonstrated. An electrochemical communication between adjacent cells (keratinocyte-keratinocyte or keratinocyte-neuron) might play a crucial role in both epidermis-nervous system communication and epidermal homeostasis. A synapse-like connection between keratinocytes and nerve endings has been identified.

Epidermal keratinocytes in the different layers of the epidermis show variable responses to ATP. The calcium concentration is highest in the upper layer of the epidermis. The increase of intracellular calcium in response to ATP is different in each layer of the epidermis and is greater at the bottom layer than in the uppermost layer. ATP plays a crucial role in calcium propagation via P2Y<sub>2</sub>, a G-protein-coupled purinergic receptor in the epidermis. Direct intracellular communication might occur in the epidermis, and if so, gap junctions must play an important role. Second messengers, such as ATP, cAMP, and cGMP might be transferred via specific gap junctions. Gap junctions are important for the transmission of mechanosensory signals in the epidermis. They might play an important role in intercellular communication, such as calcium propagation, especially at the uppermost layer, whereas in the basal layer of the epidermis, cell-cell communication via P2Y<sub>2</sub> probably plays the major role. Thus, epidermal keratinocytes in the various layers of the epidermis might undertake different tasks in sensation and signal transmission. The uppermost layer of the epidermis might be more sensitive to environmental stimuli, whereas the basal layer might be more sensitive to second messengers, such as ATP.

Nerve endings reach the uppermost layer of the epidermis, whereas nerve plexus are observed in deeper areas. Keratinocytes and nerve cells are in contact with each other. Thus, in the uppermost layer of the epidermis, the external stimuli might be transmitted from keratinocytes to nerve endings, whereas a second message might be transferred to the nerve plexuses in deeper areas of the epidermis via ATP. A wide range of receptors are expressed in epidermal keratinocytes, and receptors are specifically distributed in each layer of the epidermis. Ions such as calcium, magnesium, and potassium are also distributed heterogeneously. Through these receptors, epidermal keratinocytes might mediate information transfer from the interface between the body and environment.

Mechanical stimulation of a single keratinocyte has been shown to induce intracellular calcium elevation not only in that cell but also in its neighbors. This response was shown to be prevented by application of an ATP receptor blocker. Thus, mechanical stress applied to a single keratinocyte can be signaled to surrounding cells and can also evoke excitation of the peripheral nervous system. Although no junctions have been found between keratinocytes and sensory termini, ultrastructural studies have shown that keratinocytes come into contact with dorsal root ganglion neurons through membrane-membrane apposition. There is also evidence that keratinocytes communicate with sensory neurons via extracellular molecules. Sensory neurons themselves sense various external stimuli, but there may also be skin-derived regulatory mechanisms by which sensory signaling is modulated.

ATP plays an important role in signal transduction between keratinocytes and might also play a crucial role in signal transduction between keratinocytes and the nervous system.

The involvement of Degenerin/Epithelial sodium channel family (Deg/ENaC) in mechanotransduction was conveyed by their expression in many mechanosensory neurons of the dorsal root, trigeminal ganglia, and hair cells of the inner ear. Due to their broad expression in the nervous system, it is possible that they regulate synapse excitability. The acid-sensing ion channel (ASIC) family are the mammalian homologs of DEG/ENaC channels.

The capacity exhibited by the different functional types of somatosensory receptor neurons to preferentially detect and encode specific stimuli into a discharge of nerve impulses appears to be the result of a characteristic combinatorial expression of different ion channels in each neuronal type that finally determines their transduction and impulse firing properties. Further studies of the interaction of keratinocytes sensors, such as TRP and purinergic receptors, with the endocrine system are needed to understand the role of the epidermis in relation to the whole body.

A key question in recent years has been whether the sensory neurons are the primary transduction element, or whether nonneuronal cells can act as the key signaling pathway. Subsequent activation of adjacent nerve terminals, or neuronal structures, results in a perception of touch, temperature, pain, or pleasure. Specialized epithelial structures such as hair cells, Merkel cells, and receptors on taste buds are known to play a role in sensory transduction. Recent evidence suggests that other candidates, such as keratinocytes, may also be primary transducers of mechanical stimuli.

The presence of sensory receptors on epidermal keratinocytes suggested a functional role. Denda et al. suggested that keratinocytes could be the primary transduction pathway, using signal transduction cascade mechanisms such as intracellular  $\text{Ca}^{2+}$  fluxes to evoke a response in adjacent C-fibers. Putative keratinocyte-neuron interactions, intermediate molecules, and second messenger cascades have been proposed and await validation.

A tonal balance in terms of mechanotransduction is achieved via several interconnected mechanisms: modulation of growth factors and receptors, second messenger signaling pathways, interaction with cytoskeletal elements, alteration of nerve firing thresholds following presentation of the stimulus, and consequent perceptual processing (e.g., the increase in touch sensitivity and hyperalgesia following inflammation reactions such as sunburn). Without this intricate level of control, the sensory system would be swamped with redundant signals, or worse, would fail to recognize noxious and threatening stimuli and, thus, fail to act, or to remove, neutralize, or repair the threat. This ensures that at all times an appropriate response is mounted by the organism, whether it is in response to touch, temperature, pain, or pleasure.

Epidermal keratinocytes contain a series of receptors, which were originally found in the central nervous system as neurotransmitter receptors. Several sensory receptors have been reported in epidermal keratinocytes. Thus, it could be that

environmental signals are sensed by keratinocytes, and then processed, before being passed to C-fibers in the epidermis. A specific electrochemical information processing system might exist in the epidermis, and calcium permeable channels could play a role in information processing by epidermal keratinocytes.

It had long been considered that only nerve C-terminals in the epidermis play a role in skin surface perception. However, epidermal keratinocytes appear to be equipped with sensing systems similar to those of the peripheral and central nervous systems.

Melanocytes are often in close contact with sensory endings and electron microscopy has revealed a thickening of the apposing membrane, suggesting a synaptic communication. Melanocytes appear to be sensory and regulatory cells for epidermis homeostasis. Until now, melanocytes have never been clearly implicated in touch reception, thermal sensation, or nociception. However, they are found in the outer root sheath, often as precursors, or as poorly differentiated cells. The outer root sheath is the location of Merkel cells, where they are found in number, and therefore, it is a place of mechanotransduction. The TRP receptors are present on melanocytes, which express voltage-gated sodium and potassium channels and have a rectifying potassium current, similar to those observed in neurons. Nevertheless, melanocytes are not considered to be excitable cells, like Merkel cells, even if synaptic-like structures and excitable cell-specific ion channels are present.

Langerhans cells are antigen-presenting cells. Like other dendritic cells, Langerhans cells are sensitive to thermal stimulation. However, sensor channels were not demonstrated to be present, thus the thermal perception by dendritic cells might involve sensory molecules with a second messenger cascade rather than common thermosensitive ion channels. Langerhans cells express ionotropic ATP-specific and P2X receptors. They also express numerous neuropeptides, and their receptors. This allows them to communicate with other cutaneous cells like Merkel cells, or with sensory neurons. The functional role of the Merkel cell-Langerhans cell complex has not been further investigated.

Merkel cells are located in glabrous skin, hairy skin, and in some mucosa. They are epidermal cells scattered in the basal layer of the epidermis and in the outer root sheath of hair follicles. They are characterized by dense core secretory granules and cytoskeletal filaments and synthesize numerous neuropeptides inside the secretory granules. The corresponding receptors are also present at the surface of Merkel cells. The neuropeptide-containing granules are mainly located facing the low-threshold sensory neurons that supply nearly all epidermal Merkel cells. The cluster of Merkel cells with sensory neurons is named the Merkel cell-neurite complex. It constitutes the slowly adapting mechanoreceptor (SAM) reacting in nearby fashion and thus is named type I. Conversely, Ruffini corpuscles within the dermis feel pressure in a wider area and are thus called type II (SAM).

Investigations into the exact role of Merkel cells in the perception of touch within the SAM-I have produced conflicting results. Either they are themselves mechanoreceptors, acting as a synaptic transducer to signal sensory neurons, or, rather than the trigger of the neuronal activity, they are the target of sensory neurons in an efferent signal. The synaptic transmission between Merkel cells and neurons has

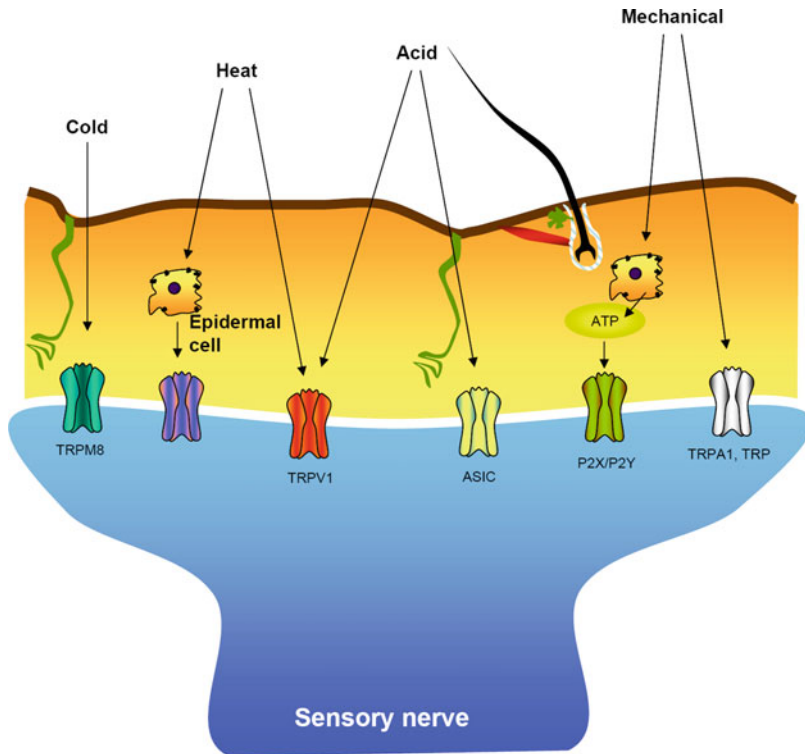
been demonstrated by molecular biology. Merkel cells express most of the proteins involved in vesicle trafficking and recycling; they have many components of the glutamatergic transmission machinery, and they bear P/Q-type voltage-gated calcium channels. The latter are normally found in excitable cells, and reveal synaptic capability, since quick calcium currents are believed to be involved in cell depolarization and neurotransmitter release. Nevertheless, there is still a lack of structural evidence of a synaptic connection, identification of neurotransmitters and the stimuli that activate Merkel cells.

Ionic channels, like the osmotic receptor TRPV4 and the purinergic receptor P2Y2, are present on Merkel cells. Swelling-induced hypo-osmolarity may be able to activate Merkel cells through the TRPV4 receptor, while the P2Y2 receptor may mobilize the intracellular calcium required for cell excitability and neuropeptide release. The presence of one stretch-activated channel in Merkel cells would support the idea that they are mechanosensory cells. The glutamatergic components present in Merkel cells (mGluR5 receptor, subunits of the AMPA and NMDA receptors, VgluT1, VgluT2, and VgluT3) reveal their capacity to modulate excitability of neurons rather than signal transduction. Furthermore, the glutamate receptors are more specific to postsynaptic elements than presynaptic ones. However, they also should be capable of activating sensory neurons of the SAM following their depolarization, and the release of their neurosecretory granules (transduced information from touch). Hence, Merkel cells appear to be excitable cells, able to transduce stimuli toward several sensory nerve types and other epidermal cells, and they are involved in touch perception directly or indirectly.

Merkel cells are attached to neighboring keratinocytes by desmosomes and contain melanosomes similar to keratinocytes. They are excitable multisensory cells in close contact with sensory nerve endings that can receive almost all environmental stimuli including electromagnetic and ultraviolet radiation, temperature, and humidity.

Merkel and other epidermal cells allow molecular exchanges, thereby modulating the functions of the skin. Merkel cells are multisensory cells that can receive almost all environmental information and are multifunctional cells. They are excitable cells containing the molecular components of synaptic connections, and so they transduce the stimuli synaptically. The mechanisms of communication between keratinocytes, Langerhans cells, or melanocytes and sensory neurons are not clear. They are not excitable cells containing the molecular components of synaptic connections. Paracrine function is supposed, but the mediator used to transmit rapid stimuli as fast as they occur must exhibit the characteristics of a neurotransmitter. It must be specific enough to carry a unique signal and quickly degraded to transmit a short stimulation. A possible candidate might be calcium, which can activate neighboring cells once released by keratinocytes.

Unfortunately, the molecular identity of ion channels involved in the transduction of mechanical stimuli by mammalian somatosensory endings is still uncertain. The fact that mechanosensation requires the concerted function of several proteins acting in an ensemble (transduction apparatus) makes this study particularly challenging. The list of candidate transducer molecules for mechanotransduction includes several



**Fig. 15** Putative ion channels involved in mechanisms of stimuli transduction in the skin (Modified from Marchan et al. (2005))

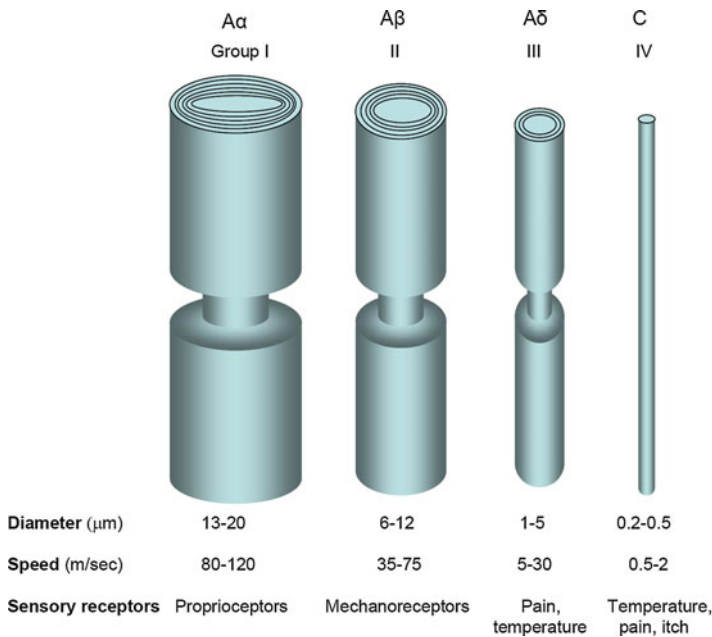
TRP channels, members of the acid-sensing ion channel (ASIC), two-pore-domain  $K^+$  channels, and P2X purinergic receptors (Fig. 15).

Not only are many transducing molecules multimodal for different energy forms, but several of the molecular sensors associated to stimulus, and hence to a sensory modality, are concomitantly expressed in sensory neurons that are functionally defined as specific for another stimulus quality. For example, a fraction of low-threshold cutaneous mechanoreceptors are activated by cooling, suggesting that they possess some of the transducing mechanisms for temperature, present in specific thermoreceptor neurons. In addition, separate molecular sensors detecting the same type of physical or chemical stimulus may coexist in an individual receptor type. In other words, there are complex interactions between transducers and signal modulators. Sensory transduction channels do not operate in isolation but rather show important direct and indirect interactions with other ion channels and signaling molecules. The functional overlap provides sensory neurons with a larger operating range than that offered by a single transduction channel and additionally offers the possibility of different responses to internal and external modulators.

In any case, the physiological unit of transduction is the sensory ending which, in many cases, coexpresses different transduction channels with different activation profiles. The differential sensitivity of receptor endings results from the expression of a particular protein whose presence would be necessary and sufficient to determine the capacity to transduce the specific stimulus into a propagated sensory message and ultimately the modality of the evoked sensation. Much needs to be learned about the transduction process and the properties of native channels and their functional interactions with other molecules elements on nerve terminals.

### Sensory Axons

The skin is densely innervated by a network of different afferent fibers that respond to specific sensation, including noci-, thermo-, chemo-, and mechanostimulation. The peripheral nervous system innervating the skin originates from the dorsal root ganglia. The neurites get into the skin and form a subepidermal plexus from which some fibers cross the dermoepidermal junction to innervate epidermal cells or to remain apparently free of targets. Sensory axons are classified according to their degree of myelination, the fatty sheath that surrounds the nerve fiber. The degree of myelination determines the speed with which the axon can conduct nerve impulses and hence the nerve’s conduction velocity (Fig. 16). Cutaneous innervation consists



**Fig. 16** Primary afferents axons. The diameter of an axon is correlated with its conduction velocity and with the type of sensory receptor (Modified from Bear et al. (2001))

**Table 3** Classification of sensory afferent nerve fibers (Modified from McGlone and Reilly (2010))

Sensory afferent nerves			
Class	Modality	Axonal diameter (μm)	Conduction velocity (m/s)
<i>Myelinated</i>			
Aα	Proprioceptors from muscles and tendons	20	120
Aβ	Low-threshold mechanoreceptors	10	80
Aδ	Cold, noxious, thermal	2.5	12
<i>Unmyelinated</i>			
C-pain	Noxious, heat, thermal	1	<1
C-tactile	Light stroking, gentle touch	1	<1
C-autonomic	Autonomic, sweat glands, vasculature	1	<1

mainly of unmyelinated fibers, accounting for around 90 % of all dermal nerve fibers.

The largest and fastest axons are called Aα and include some of the proprioceptive neurons, such as the muscle stretch receptors. The second largest group, called Aβ, includes all of the discriminative touch receptors. Pain and temperature include the third and fourth groups, A-δ and C-fibers (Table 3). They can be also classified according to the neuropeptides present at the nerve terminals and the information they transduce to the central nervous system. Functional properties are not strictly related to morphological aspects. However, it is currently accepted that cutaneous, large-myelinated Aβ-fibers of low-threshold are suited to be mechanoreceptors, which feel pressure, stretch, or hair movement. Unmyelinated C-fibers and lightly myelinated Aδ-fibers are often thermoreceptors, which respond to heat and cold with different thresholds of activation. Cold receptors are coupled to Aδ and C fibers, while warm receptors are coupled only to C fibers. In the epidermis, the cutaneous myelinated terminations are thinner terminal branches of large myelinated Aβ fibers, whereas cutaneous terminations of small myelinated Aδ fibers lose their myelin before entering the dermis and become indistinguishable from C-fiber termination.

Correlative electrophysiological and morphological studies in the glabrous or hairy skin of mammals have attempted to establish the signaling characteristics of the peripheral receptors. At the heart of each mechanoreceptor are unmyelinated axon branches. These axons have mechanosensitive ion channels, whose gating depends on stretching or changes in tension of the surrounding membrane. Four classes of mechanoreceptive afferents have been described in different parts of the human skin: slowly adapting (SA) I, SA II, rapidly adapting (RA) I, and RA II afferents. SA I and SA II afferents supply Merkel endings and Ruffini corpuscles, respectively, and exhibit a relatively prolonged response related to the magnitude of maintained skin deformation. In addition to responding to forces applied normally to the skin, a unique feature attributed to SA II primary afferents is the capacity to



**Table 4** Mechanoreceptive afferents in human nerves from glabrous and hairy skin (Modified from Olausson et al. (2010))

Sensory endings and afferent unit acronyms		
Glabrous skin	Hairy skin	Adaptation
Merkel SAI	Merkel SAI	Slow
Ruffini SAI	Ruffini SAI	Slow
Pacini FAII (PC)	Pacini FAII (PC)	Fast
Meissner FAI (RA, QA)	Hair follicle unit	Fast
	Field	Fast
	C-tactile CT (CLTM)	Intermediate

The different unit types were identified on the basis of microneurography of recording in man while types of end organs were inferred on the basis of physiological and morphological studies in various species

respond to lateral skin stretch. The different mechanoreceptors that innervate the human skin are summarized in Table 4. The best characterized light-touch response is the SA I afferent, which was identified arising from Merkel cell-neurite complexes.

Cutaneous mechanosensitive afferents in vertebrate models have traditionally been divided primarily by conduction velocity in physiological assays. Fast, myelinated afferents, or A-afferents, are subdivided into A $\beta$ - and A $\delta$ - afferents, whereas unmyelinated afferents are dubbed C-fibers. In addition to conduction velocity, cutaneous afferents are often divided into touch receptors and nociceptors based on sensory threshold. A-mechanociceptor (AM) afferents are thinly myelinated, falling primarily into the A $\delta$  conduction velocity range, and are responsible for quick, prickling pain sensations, whereas unmyelinated nociceptors convey slow, sustained responses. Low-threshold C-fibers, which represent a rare population of unmyelinated afferents, appear to be important for the onset of mechanical hypersensitivity during inflammation or injury. Low-threshold A $\delta$ -afferents include down hair receptors, whose response properties and extreme sensitivity place them firmly in the category of light-touch receptors.

Most cutaneous A $\beta$ -afferents are slow-threshold mechanoreceptors that can be divided into the slowly adapting and rapidly adapting (RA) categories, based on whether they maintain action potential discharge throughout a sustained mechanical stimulus. Based on their low mechanical threshold and cutaneous location, it is likely these somatosensory afferents subservise the sensation of touch. RA afferents fire only in response to a changing stimulus, providing the brain with a neural image of moving or vibrating stimuli. Sensory structures associated with RA responses include hair-follicle afferents, Meissner's corpuscles, and Pacinian corpuscles, which are innervated by early Ret + neurons.

Slowly adapting afferents maintain firing during sustained indentation and have been divided into two types in all vertebrate models. SA I responses convey high-resolution spatial information to the brain and are thought to be responsible for the ability to discriminate texture, curvature, patterns such as Braille, and some components of proprioception.

**Table 5** Channels mediating tactile perception in the glabrous skin (Modified from McGlone and Reilly (2010))

Channel	Pacinian	NPI	NPII	NPIII
Frequency response	40–80 Hz	3–100 Hz	15–400 Hz	<0.3 to >100 Hz
Receptor type	FAI pacinian	FAII meissner	SAII ruffini	SAI merkel

Mechanoreceptive A $\beta$ -neurons are the most represented subset of neurons supplying Merkel cells in slow-adapting mechanoreceptors (SAM-I). However, recent findings show that C and A $\delta$ -fibers also innervate Merkel cells, demonstrating that the formation of the SAM is dependent on multiple neurotrophins and their receptors.

The Merkel cell-neurite complexes that generate SA I responses are located in highly touch-sensitive skin structures including finger tips, whisker follicles, and touch domes of hairy skin. SA II responses have been postulated to arise from Ruffini endings; however, direct evidence supporting this correlation is still lacking.

There are at least four distinct channels mediating tactile perception in the glabrous skin. Each specific channel is represented by one of the four anatomical end organs and nerve fiber subtypes. Frequencies in the 40–500 Hz range provide a sense of vibration, transmitted by Pacinian corpuscles (PC channels or RA II), Meissner corpuscles transmit a sense of flutter in the 2–40 Hz range (RA I), while pressure is mediated by Merkel's disks in the 0.4–2.0 Hz range (SA I) and Ruffini organs produce a buzzing sensation in the 100–500 Hz range (SA II) (Table 5). The oral-facial region, unlike the hand, is notably insensitive to high-frequency vibrations and mechanical transients, the stimuli to which the Pacinian corpuscles are most sensitive. This is in agreement with the studies that indicate that Pacinian corpuscles are largely absent from the oral-facial region.

Descriptive statistics compiled from information provided in a number of publications suggest that the proportion of RA and SA units varies considerably between different body areas. The surfaces of the two body areas that serve to manipulate and explore objects – the glabrous skin of the hand and the masticatory mucosa of the anterior tongue – appear to have the largest proportion of FA units. Thus, FA units may be of particular importance for active touch and manipulation of objects. In contrast with the hairy skin of the arm, hand, and face, the oral mucosa that lines inside of the lips appears to have a higher proportion of SA units.

## Touch and Pain

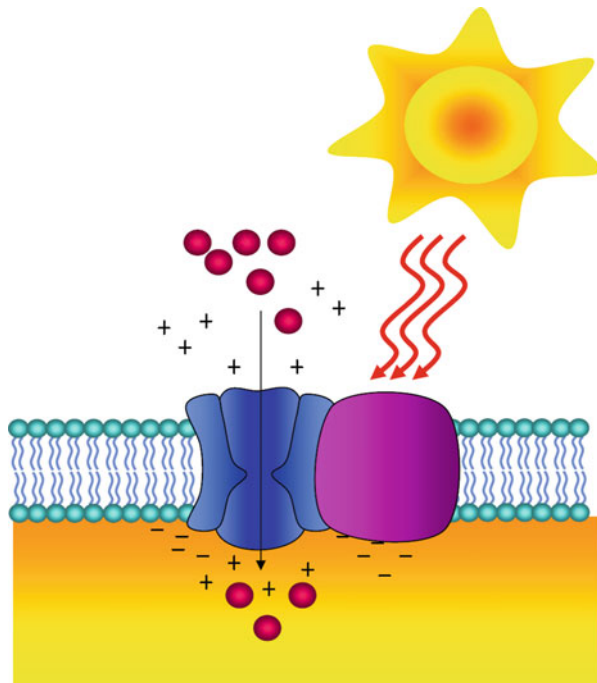
Light touch can evoke pain via the mechanisms of hyperalgesia. Pain evoked by activity in nociceptors can be reduced by simultaneous activity in low-threshold mechanoreceptors (A $\beta$  fibers). Presumably, this is why it feels good to rub the skin around your shin when you bruise it (Melzack and Wall's gate theory of pain).

## Temperature

The cutaneous somatosensory system detects changes in ambient temperature over a wide range, initiated when thermal stimuli that differ from a homeostatic set point excite temperature-specific sensory receptors in the skin. Thermoreceptors are neurons with specific membrane mechanisms extremely sensitive to temperature (Fig. 17). Within the innocuous thermal sensing range, there are two populations of thermosensory fibers, one responding to warmth and the other to cold, and also fibers from the A $\delta$  and C range. Specific cutaneous cold and warm receptors have been defined as slowly conducting units that exhibit a steady-state discharge at constant skin temperature and a dynamic response to temperature changes.

Cold-specific and warm-specific receptors can be distinguished from nociceptors that respond to noxious low and high temperatures, and also from thermosensitive mechanoreceptors. Free nerve endings for cold-sensitive or warm-sensitive nerve fibers are located just beneath the skin surface. These fiber endings form a small sensitive point, separate from the sensitive points of neighboring fibers. Sensitivity to temperature changes of the skin can be mapped by taking small cold or warm probes. Some spots are especially sensitive to either hot or cold but not sensitive to both. Also, small areas of the skin between the hot and cold spots are relatively insensitive to temperature. The total area of skin occupied by the receptor endings of

**Fig. 17** Thermoreceptor. The thermal energy presses on, displaces, or deforms the receptor, which converts the energy into a nerve impulse



a single temperature-sensitive nerve fiber is relatively small (~1 mm in diameter) with the density of these thermo-sensitive points varying in different body regions; thus, temperature sensitivity is not spread uniformly across the skin.

## Itch

Itch or pruritus is described as an unpleasant sensation provoking the desire to scratch. The pathway processing the itch is functionally and anatomically separate from the pain pathway. The itch pathway employs its own subgroup of peripheral, mainly mechano-insensitive, C-fibers in the skin. In the central nervous system, histaminergic spinal neurons transduce the itch sensation initiated by dedicated pruriceptors to the thalamus. The pruriceptors are activated by histamine, which consistently provokes pruritus but rarely pain. However, other inflammatory molecules such as prostaglandin E<sub>2</sub>, serotonin, acetylcholine, bradykinin, or even capsaicin may induce a moderate itching sensation. As with the existence of multiple types of pain afferents, different classes of itch nerves are also likely to account for the various experiences of itch reported by patients.

In recent years, a growing body of evidence has been accumulating from anatomical, psychophysical, electrophysiological, and neuroimaging studies for the presence of a population of C-fibers, found only in hairy skin that are neither nociceptive nor pruritic but respond preferentially to low force, slow movement.

## Pleasant Touch

The cutaneous senses are classically defined as including tactile, thermal, pain, and itch sensing submodalities, and there is a growing evidence for an additional cutaneous sensory channel that subserves positively affective aspects of touch, such as those generated during grooming and nurturing behaviors. Recent studies indicate a dual mechanoreceptive innervation. Besides the known A fibers, human skin is also innervated by slow-conducting, low-threshold mechanoreceptors with unmyelinated (CT) afferents, existing in the hairy but not glabrous skin.

The functional role of CT afferents is not fully understood, but their neurophysiological response properties, fiber class, and slow conducting velocities preclude their role in any form of rapid mechanical discriminative or cognitive tasks and point to a more limbic function, particularly the emotional aspects of tactile perception. Direct evidence for a specific role of CT afferents has been difficult to achieve; a major reason being that is not possible to stimulate CT afferents without also activating A $\beta$  afferents. This system is poor in encoding discriminative aspects of touch, but well suited to encoding slow, gentle touch; CT fibers in hairy skin may be part of a system for processing pleasant and socially relevant aspects of touch. CT fiber activation may also have a role in pain inhibition. Evidence from patients lacking myelinated tactile afferents indicates that signaling in these fibers project to lamina II of spinal cord and form synapses with the secondary sensory neurons. The

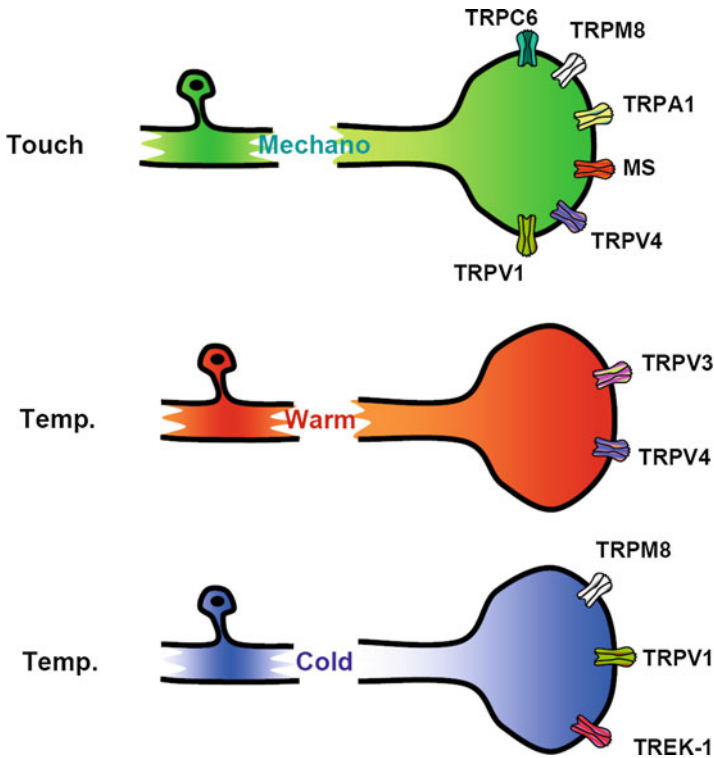
latter then project to insular cortex via the spinothalamic tract. CT afferents may constitute a privileged peripheral pathway for tactile stimulation. The role of CT afferents in sexual functions has not been studied. Interestingly, studies on the distribution of the apparent mouse homolog of human CT afferents suggest they are lacking in the genital region. CT afferents are likely to play an important role, together with A $\beta$  afferents, in human social interactions involving touch. Social touch has a characteristic subjective quality, such as the feeling of well-being from the touch of a loved one. However, light touch can also be distinctly unpleasant such as the disgust associated with an unwanted touch, illustrating the importance of higher-level contextual processing.

Research on touch in humans has focused mostly on the sensory and multisensory aspects of discriminative touch rather than on the social and emotional dimension. Interestingly, the emotion of love was typically communicated as a slow and moderately intense stroking over the skin. Research in rodents indicates that slow skin stroking promotes hormonal responses, i.e., endorphins and oxytocin. Properties of the CT system suggest a role related to pain perception. CT afferents have partly similar projections as nociceptive afferents in the central nervous system, and CT afferents have been shown to reduce nociceptive signaling at the level of lamina II of the dorsal root in rats. CT stimulation is effective in reducing experimental pain. CT afferents have to be fully characterized functionally. Much work also remains to be done in charting their central pathways from the dorsal horn to the brain and determining the relevant receptor channels of the sensory terminals in the skin.

McGlone and Reilly proposed that touch as pain is also characterized by sensory/discriminative and affective/motivational components and that there are two touch systems parallel to the two pain systems. First touch is subserved by fast-conducting A $\beta$  afferents responsible for rapid identification of the physical properties of a tactile stimulus. The sensory information is primarily discriminative and nonemotional, conveying qualitative states such as “wet, hard, rough, etc.” and is essentially “immediate” in terms of conscious awareness. By contrast, second touch, mediated by slow-conducting mechanosensitive C-fibers (CTs), conveys information related to tactile inputs associated with affiliative and affective touch, such as those gentle and slow stroking touches experienced during grooming or nurturing behaviors. Work is in progress to identify this class of C-fibers histologically within the epidermis.

The different conduction speeds of cutaneous sensation that are conveyed to the CNS, by myelinated A $\beta$  and unmyelinated CT fibers, lead to the distinction of first and second touch, with the former having a discriminative quality and the latter an emotional one.

Signaling of stimuli such as touch, temperature, pain, itch, and pleasure requires molecular recognition of stimulus and mobilization of a response in the form of an electrical signal. A perception of a single stimulus often requires several transduction mechanisms. Touch and tactile sensitivity require rapid and direct signaling that is provided by ion channels via interaction with both intracellular cytoskeletal and extracellular matrix proteins. The key mammalian ion channel candidates are the epithelial sodium channels and the acid-sensing ion channels (ASICs), both of which belong to the Degenerin/epithelial amiloride sensitive Na<sup>+</sup> channel (DEG/ENaC)



**Fig. 18** TRP channels in C and A $\delta$  sensory neurons (Modified from Belmonte and Viana (2008))

superfamily of ion channels mentioned before. The presence of multiple TRP channels, with distinct localization on subsets of C- and A $\delta$ -sensory neurons allows for a wide spectrum of physiological activities to be regulated by these channels and accounts, at least in part, for the complexity of these transducer systems (Fig. 18).

Once activated, cutaneous sensory neurons induce action potentials as well as the release of neurotransmitters, which modulate inflammation, cell growth, or pruritus. Such neuronal modulations of cutaneous properties regularly bring heterotrimeric G proteins into play at the beginning of the metabolic cascade and endopeptidases at the end for termination of the response degrading the messengers. Finally, cutaneous neuritis plays a major role in sensory behavior, but there is much evidence suggesting a modulation of sensitivity by epidermal cells.

### Transmission of Impulses to CNS

Information from the skin is brought into the central nervous system by afferent nerve fibers that run together with efferent fibers in peripheral nerves. As the peripheral nerves approach the spinal cord, they join together into spinal nerves.

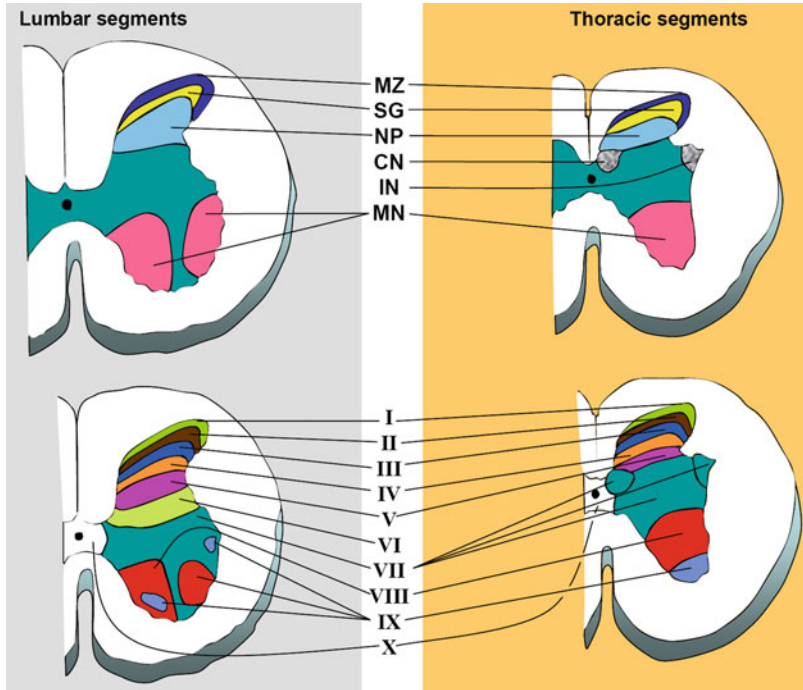
Afferent nerve impulses are conveyed by fibers of primary sensory neurons located in trigeminal and dorsal root ganglia, which are comprised of a heterogeneous population of cell bodies of all the peripheral afferents innervating the skin. Efferent axons of dorsal root ganglia neurons terminate in the skin where they innervate a variety of cutaneous structures such as sweat glands, hair follicles, Merkel cells, Meissner corpuscles, and blood vessels. The basic somatosensory system includes afferents from the peripheral receptors that terminate in the spinal cord or brain stem, a relay of second-order neurons from these structures to the thalamus, projections from the thalamus to different areas that project to motor cortex, other cortical areas, and subcortical structures. Afferents include those from several types of mechanoreceptors in the skin, muscle-spindle, and joint receptors that signal movement and position and afferents mediating temperature and pain.

To convey sensory information from the skin to the brain for perception, the somatic sensory pathways must first traverse the spinal cord. The spinal cord is a relay for sensory information. It carries both ascending afferent pathways and descending motor tracts. A transverse section of the spinal cord shows that it is organized into a butterfly-shaped central gray area (gray matter), where the cell bodies of spinal neurons are located, and a surrounding region of white matter that contains afferent and efferent axons, most of which are myelinated. The gray matter is divided into a dorsal horn, intermediate zone, and a ventral horn. The dorsal horn is radially laminar structure; the thin outermost layer is the posterior marginalis layer, the second layer the substantia gelatinosa, and the layer medial to that, the nucleus proprius (Fig. 19). In 1952, Bror Rexed proposed a classification for understanding the organization of the gray matter of the spinal cord based on ten layers or laminae. Laminae I–V are roughly equivalent to the dorsal horn, laminae VI and VII are roughly equivalent to the intermediate zone, and laminae VIII and IX are equivalent to the ventral horn. Lamina X consists of the gray matter surrounding the central canal (Fig. 19).

The white matter is divided into three bilaterally paired columns, dorsal, ventral, and lateral columns. In addition to the major ascending and descending tracts, the spinal cord contains pathways to connect different regions of the spinal cord (*fasciculus proprius*).

The afferent fibers in the spinal nerves separate from the efferent fibers and enter the spinal cord as the dorsal roots. Each dorsal root innervates a restricted peripheral region called a dermatome (Fig. 20). At plexuses, located between the spinal cord and the periphery, the afferent fibers are regrouped so that each spinal nerve receives afferents from several peripheral nerves (Fig. 21).

All the primary sensory neurons have their cell bodies situated outside the spinal cord in the dorsal root ganglion, where there is one ganglion for every spinal nerve. Dorsal root fibers enter the spinal cord at its dorsolateral margin. Because axons of different diameters serve different somatic modalities, the neurons are located in different regions of the dorsal horn. The axons from collaterals and large-diameter fibers, which mediate tactile sense, enter the lateral aspect of the dorsal columns and enter the dorsal horn from its medial aspect (Fig. 22). There is evidence from cats that the rapidly adapting (RA) and slowly adapting (SA) classes of afferents



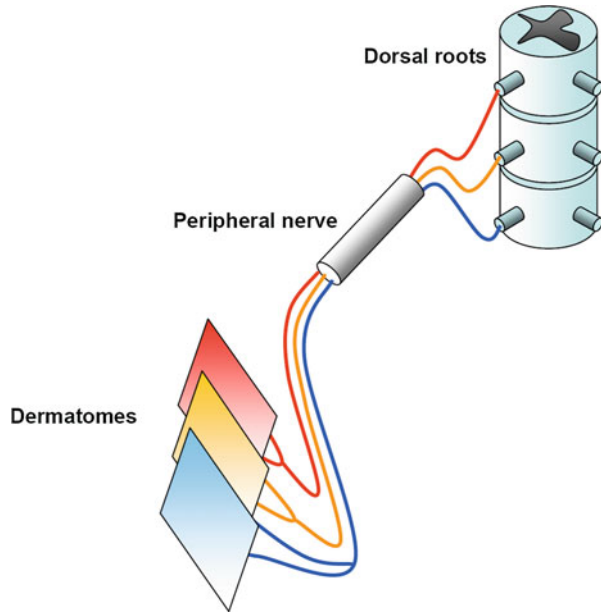
**Fig. 19** Nuclei and laminae of the spinal gray matter. *MZ* marginal zone, *SG* substantia gelatinosa, *NP* nucleus proprius, *CN* Clarke's nucleus, *IN* intermediolateral nucleus, *MN* motor nuclei. Laminae I–V are roughly equivalent to the dorsal horn, laminae VI and VII are roughly equivalent to the intermediate zone, and laminae VIII and IX are equivalent to the ventral horn. Lamina X consists of the gray matter surrounding the central canal (Modified from Martin (1985))

terminate in separate clusters of cells in the posterior column nuclei. Tactile primary afferents, or first-order neurons, turn up the spinal cord toward the brain, ascending in the dorsal white matter forming the posterior columns. The posterior columns primarily contain  $A\beta$  fibers which project rostrally toward the brain and terminate in the posterior column nuclei of the medulla.

In a cross section at the cervical level of the spinal cord, two separate tracts can be seen: the midline tracts comprise the *gracile fasciculus* conveying information from the lower half of the body and the outer tracts comprise the *cuneate fasciculus* conveying information from the upper half of the body. Primary tactile afferents make their first synapse with second-order neurons at the medulla where fibers from each tract synapse in a nucleus of the same name: the *gracile fasciculus* axons synapse in the *gracile nucleus* and the *cuneate* axons synapse in the *cuneate nucleus*. The neurons receiving the synapse provide the secondary afferents and cross the midline immediately to form a tract on the contralateral side of the brain – the medial lemniscus – which ascends through the brainstem to the next relay station in the midbrain, specifically, in the lateral region of the posterolateral thalamus. Ultimately,



**Fig. 20** Each dorsal root innervates a restricted peripheral region called a dermatome. There is an overlap in the peripheral innervation (Modified from Martin (1985))

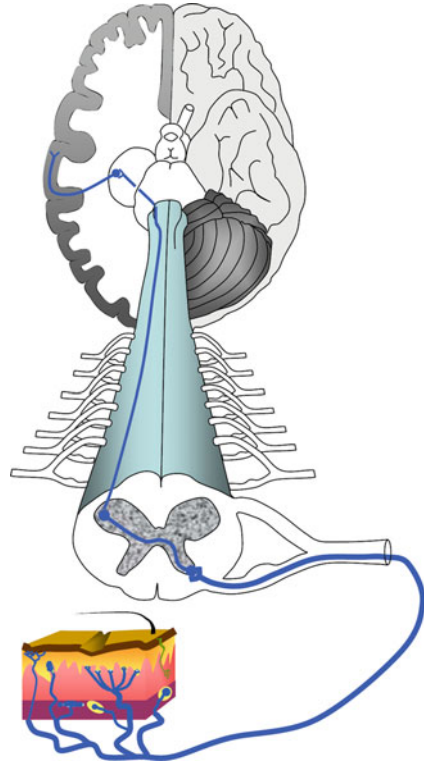


third-order neurons terminate in the primary and secondary somatosensory cortices (Fig. 22).

The different skin sensory receptors and nerves that convey information to the brain about mechanical, thermal, and pruritic stimulation of the skin are grouped into three different pathways in the spinal cord and project to different target areas in the brain. They differ in their receptors, pathways, and targets and also in the level of decussation (crossing over) within the CNS.

As with the tactile system, thermal primary afferents synapse ipsilaterally and the secondary afferents cross, but the crossing occurs at different levels. Temperature afferents enter the dorsal horn of the spine and synapse within one or two segments, forming Lissauer's tract. The two types of fibers, C and A $\delta$ , enter different layers of the dorsal horn. A $\delta$  fibers enter the posterior marginalis and the nucleus proprius and synapse on a second set of neurons which are the secondary afferents, which relay the signal to the thalamus. The secondary afferents from both layers cross to the opposite side of the spinal cord and ascend in the spinothalamic tract. C-fibers enter the substantia gelatinosa and synapse on interneurons – neurons which do not project out of the immediate area but relay to secondary afferents in either the posterior marginalis or the nucleus proprius (Fig. 23). Certain neurons of the dorsal horn, which project an axon up the spinothalamic tract, are excited by both large-diameter sensory axons and unmyelinated pain axons. The projection neuron is also inhibited by an interneuron, and the interneuron is both excited by the large sensory axons and inhibited by the pain axon (Melzack and Wall's gate theory of pain). The spinothalamic tract ascends the entire length of the spinal cord and the entire

**Fig. 21** Afferents fibers from the skin entering the spinal cord to the somatic sensory cortex. Fibers are regrouped so that each spinal nerve receives afferents from several peripheral nerves

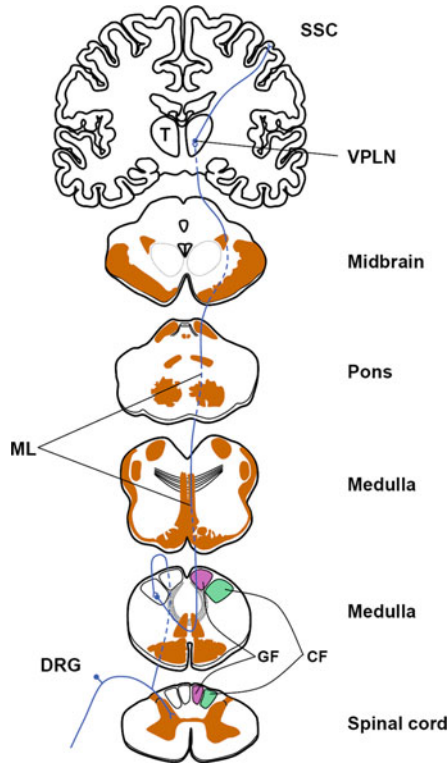


brainstem and, on reaching the midbrain, is continuous with the medial lemniscus. These tracts enter the thalamus together.

It is important to note that there is a degree of mixing information in the tracts. Some light touch, proprioceptive conscious awareness of body position and movements information travel in the spinothalamic tract.

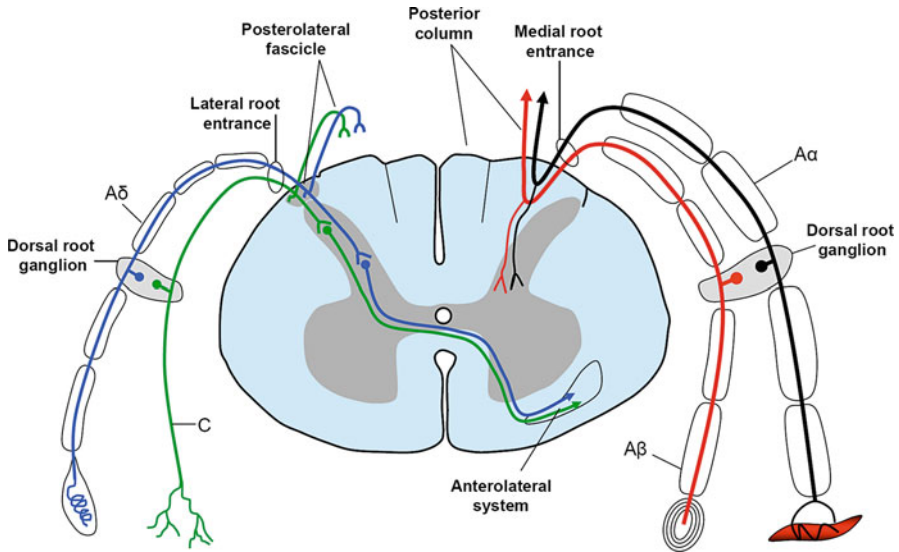
In humans and primates, neurons responding to noxious and temperature stimuli project from the marginal zone through the spinothalamic pathway to the ventral posterior nucleus of the thalamus. Subsequently, temperature fibers project to the posterior insular cortex in a somatotopically organized fashion.

In facial skin, the fifth cranial nerve or trigeminal nerve innervates all facial skin structures including oral mucosa. These neurons have their cell bodies outside of the CNS in the trigeminal ganglion with their proximal processes entering the brainstem. As in the spinal cord, the four modalities of touch, temperature, pain, and itch have different receptors in the facial skin, travel along different tracts, and have different targets in the brainstem – the trigeminal nuclei extending from the midbrain to the medulla. The large-diameter ( $A\beta$ ) fibers enter directly into the main sensory nucleus of the trigeminal nuclei and, as with the somatosensory neurons of the body, synapse and decussate with the secondary afferents joining the medial lemniscus as it projects to the thalamus. The small-diameter fibers conveying pain and temperature enter the



**Fig. 22** Organization of the dorsal column-medial lemniscal system. Dorsal root ganglion (*DRG*), gracile fascicle (*GF*), cuneate fascicle (*CF*), medial lemniscus (*ML*), thalamus (*T*), ventral posterior lateral nucleus (*VPLN*), and somatic sensory cortex (*SSC*) (Modified from Carpenter (1976))

midbrain with the main trigeminal nerve but then descend through the brainstem to the caudal medulla where they synapse and cross the midline. These descending axons form a tract, the spinal tract of V, and synapse in the spinal nucleus of V, so called because it reaches as far down as the upper cervical spinal cord, comprising three regions along its length: the subnucleus oralis, the subnucleus interpolaris, and the subnucleus caudalis. The secondary afferents from the subnucleus caudalis cross to the opposite side and join the spinothalamic tract where somatosensory information from the face joins that from the body, entering the thalamus in a separate nucleus, the ventroposterior medial nucleus (VPM). The slowly adapting afferents (SA I and SA II) associated with Merkel cells and Ruffini endings, the two types of rapidly adapting afferents (RA I and RA II) associated with Meissner corpuscles and Pacinian corpuscles, hair follicle receptors, and other afferents related to pain and temperature sensibilities also terminate in the dorsal horn of the spinal cord and the brain stem equivalent, where second-order neurons cross to form the ascending spinothalamic tract. Which pathway CT afferents travel in is not yet known, but low-threshold tactile inputs to spinothalamic projection cells have been documented.



**Fig. 23** Diagram of the cervical spinal cord, showing thick  $A\alpha$  and  $A\beta$ , and thin  $A\delta$  and C fibers (Modified from Warren et al. (2002))

The second-order neurons in the dorsal column-trigeminal complex cross and ascend to the contralateral ventroposterior nucleus (VP) in the thalamus. The RA and SA response classes are preserved in this relay, and these two types constitute the major inputs to VP, where they activate separate groups of neurons in cats, monkeys, and perhaps other mammals. The thalamus is not simply a relay structure; its sensory inputs are both discriminative and affective and are critical in adjusting affective scale. The third-order thalamocortical afferents travel up through the internal capsule to reach the primary somatosensory cortex, located in the postcentral gyrus, a fold of cortex just posterior to the central sulcus.

The ascending spinothalamic information is clearly important, but after a thalamic relay, its role in the traditional areas of somatosensory cortex seems to be one of modulation rather than activation. The thalamocortical afferents convey all signals to the primary somatosensory cortex where sensory information from the entire body surface is mapped contralaterally in a somatotopic manner.

The component of the cutaneous senses that is relayed to the somatosensory cortex includes the entire body from the neck down; sensation from the face are relayed via cranial nerves, with both parts sharing a common central organization.

There are eight separate areas primarily subserving somatosensation within the cortex: primary somatosensory cortex (SI) with four subregions (1, 2, 3a, and 3b), secondary somatosensory cortex (SII), located along the superior bank of the lateral sulcus, the insular cortex, and the posterior parietal cortex, areas 5 and 7b. The SII receives inputs primarily from SI and in turn projects to the somatic sensory fields in the insular region.

After sectioning of the afferents in the dorsal columns of rats, the deprived areas of at least SI are totally and persistently deactivated. Similarly, in monkeys, dorsal column sections abolish all evoked activity in all four areas of the anterior parietal cortex (areas 3b or SI, 3a, 1, and 2). The dorsal column-medial lemniscus system is capable of independently activating primary and most likely secondary areas of somatosensory cortex. While other afferents may have an important modulating role, and they are certainly critical in mediating pain and temperature sensations, dorsal column afferents are capable of mediating tactile discrimination independently.

In all investigated mammals, SI systematically represents the mechanoreceptors of the skin of the opposite side of the body. The body parts are usually represented from tail to tongue in a mediolateral sequence. The representations of different body parts often have a morphological counterpart in the cortex that can be visualized using appropriate histochemical techniques. These isomorphs of the body are best known for SI of rats and mice where an orderly arrangement of oval-like aggregates of neurons, one for each whisker on the side of the face, have long been described as the cortical barrels. Metabolic markers, cytochrome oxidase, and succinic dehydrogenase have been used to reveal more of the isomorphic including discrete cellular clusters for other whiskers and for the digits and pads of the forepaws and hind paws.

In a wide range of mammals, SI projects directly to S2, PV, SR, and SC. All of these areas are involved in further processing of information from SI, as well as processing inputs from the thalamus. S2 and PV receive VP inputs, while SR and SC receive most of their thalamic inputs from neurons just outside of VP.

Both S2 and PV respond throughout to cutaneous stimuli. PV is characterized by a convergence of thalamic VP and cortical SI and S2 inputs. Projections from PV include an even more ventral and rostral cortical regions, parietal rostral.

CT afferents project to the dorsal posterior part of the insular, presumably bypassing SI, since patients with no A $\beta$  afferents demonstrate a lack of activation to brush stroking of hairy skin in this region. In addition to the primary and secondary somatosensory cortices, the posterior parietal lobe also receives somatic inputs. This region is a higher-order sensory cortex, similar in function to an association cortex; it relates sensory and motor processing and is concerned with integrating the different somatic sensory modalities necessary for perception.

The forward projections from these primary somatosensory areas to limbic and prefrontal structures have been studied with fMRI and PET in order to understand the affective representations of skin stimulation for both pain and pleasure.

The discriminative and affective aspects of touch are processed in different brain areas by stroking the skin with either a wooden dowel or a piece of velvet. Activation of primary somatosensory cortex was found to be greater to the wood stimulus, whereas the orbitofrontal cortex (area involved in emotions) was activated more by the velvet stimulus. This area has also been shown to represent painful as well as pleasant touch, demonstrating the relevance of this brain region for representing the emotional dimensions of skin sensitivity, the positive and the negative.

Thus, signals from touch receptors pass via sensory nerves to the spinal cord, where they synapse and then travel to the thalamus and sensory cortex. The transmission of this information is highly topographic, meaning that the body is

represented in an orderly fashion at different levels of the nervous system. Larger areas of the cortex are devoted to sensations from the hands and lips; much smaller cortical regions represent less sensitive parts of the body.

The receptive field of a single mechanoreceptor has been mapped. Meissner corpuscles and Merkel disks have small receptive fields, only a few millimeters wide, while Pacinian corpuscles and Ruffini endings have large receptive fields that could cover an entire finger or half the palm. Mechanoreceptors also vary in the persistence of their response to long-lasting stimuli. Some mechanoreceptors such as Meissner and Pacinian corpuscles tend to respond quickly at first, but then stop firing, even though the stimulus continues; these receptors are said to be rapidly adapting. Other receptors, such as Merkel disks and Ruffini endings, are slowly adapting; they generate a more sustained response during a long stimulus.

Different parts of the body vary in their sensitivity to touch discrimination according to the number and distribution of the different receptors. The fingertips are good at touch discrimination, but the chest and back are less sensitive (and less discriminating).

Not surprisingly, acuity is greatest in the most densely nerve-packed areas of the body. This feature, in fact, is used to test clinically for the integrity of these somatosensory pathways. For example, a neurologist can run tests by using a two-point threshold. This method involves touching the skin with calipers at two points. The two-point threshold is the distance between the two points that is necessary for the individual to distinguish two distinct stimuli from one.

The richness of perceived skin sensations is dependent upon the diversity of many channels of cutaneous sensory input to the CNS, as well as to the integrative properties of the various stages at which these inputs are processed, from the dorsal horn to the sensory awareness stages in SI and SII, to the affective representation in insula and orbitofrontal cortices. Results of anatomical, psychophysical, behavioral, neurophysiological, and neuroimaging studies have shown that separate information processing channels, each with its own neurobiological mechanism, exist for the perception of tactile, thermal, pruritic, pleasant tactile, and pain stimuli. However, fundamental questions remain concerning the nature of how these channels, with their individual properties, operate together in the perception of the different stimuli encountered by the skin.

Coactivation of channels is the norm. Mechanical stimuli may also activate thermal channels, scratching reduces itch while rubbing reduces pain, and with all forms of affective and affiliative touch, there is coactivation of mechanosensitive A-fibers as well as, in hairy skin, mechanosensitive CT fibers. In order to fully characterize the perception of complex skin sensations, it will require a full understanding of the properties of each channel, and the mechanisms by which they interact.

It has been recognized for some time that the mind can affect the skin. It is now time to recognize that the skin can affect the mind. The skin's capabilities as a sensory organ very much like the central nervous system make it understandable why some authors would consider the label "spread brain" in reference to the epithelium. However, the relationship between skin and brain is still incompletely

understood. The functional complexity and overlap of sensory and mechanical capabilities give clues to the absolute importance of sensory function for preservation of the body covered by this most valuable source of sensation.

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## Outlook

The role of the epidermis as a sensory system has been worked on intensively using anatomical and physiological techniques, but is, nevertheless, not completely understood. In the future, it will be necessary to define, in molecular chemical terms, which are the most critical sensor proteins and neuron-like properties within epidermal cells that enable them to participate in the skin surface perception through interactions with nerve fibers. We offer the vision that the sensory neurons and cells in the skin may participate in a bidirectional molecular “dialogue,” and that this dialogue is *sine qua non*, for maintaining adequate perception of external stimuli by the skin receptors. At the present time, little is known about the set of molecules engaged in this “dialogue.” From a practical point of view, a deeper understanding of this chemistry could lead to two positive outcomes: the heightening of skin sensitivity under conditions where that is desirable and the restoration of normal sensitivity following skin damage or disease.

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