Table 18–1 Classification of Sensory Fibers in Peripheral Nerves[1]

	Muscle nerve	Cutaneous nerve[2]	Fiber diameter (μm)	Conduction velocity (m/s)
Myelinated				
Large diameter	I	Aα	12–20	72–120
Medium diameter	II	Aβ	6–12	36–72
Small diameter	III	Aδ	1–6	4–36
Unmyelinated	IV	C	0.2–1.5	0.4–2.0

[1]Sensory fibers from muscle are classified according to their diameter, whereas those from the skin are classified by conduction velocity.
[2]The types of receptors innervated by each type of fiber are listed in Table 18–2.

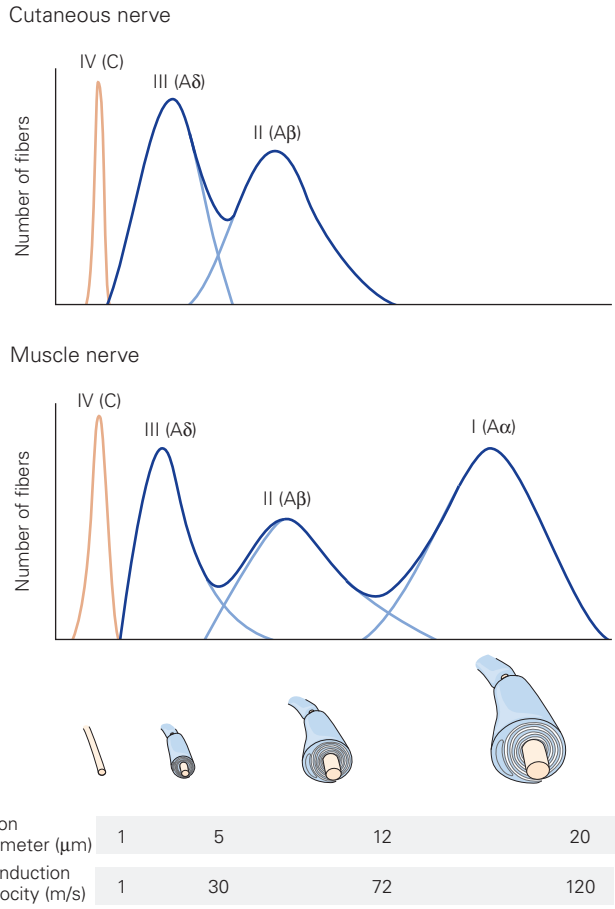


Figure 18–3 Classification of mammalian peripheral nerve fibers. The histograms illustrate the distribution of axon diameter for four groups of sensory nerve fibers innervating skeletal muscle and the skin. Each group has a characteristic axon diameter and conduction velocity (see Table 18–1). **Light blue lines** mark the boundaries of fiber profiles in each group in the zones of overlap. The conduction velocity (m/s) of myelinated peripheral nerve fibers is approximately six times the fiber diameter (μm). (Adapted, with permission, from Boyd and Davey 1968.)

organs, which signal muscle length and contractile force. Group II fibers innervate secondary spindle endings and receptors in joint capsules; these receptors also mediate proprioception. Group III fibers, the smallest myelinated muscle afferents, and the unmyelinated group IV afferents signal trauma or injuries in muscles and joints that are sensed as painful.

Nerves that innervate the skin contain two sets of myelinated fibers: Group II fibers innervate cutaneous mechanoreceptors that respond to touch, and group III fibers mediate thermal and noxious stimuli, as well as light touch in hairy skin. Unmyelinated group IV cutaneous afferents, like those in muscle, also mediate thermal and noxious stimuli.

Another method for classifying peripheral nerve fibers is based on electrical stimulation of whole nerves. In this widely used diagnostic technique, nerve conduction velocities are measured between pairs of stimulating and recording electrodes placed on the skin above a peripheral nerve. When studying conduction in the median or ulnar nerve, for example, the stimulation electrode might be placed at the wrist and the recording electrode on the upper arm. Brief electrical pulses applied through the stimulating electrode evoke action potentials in the nerve. The neural signal recorded a short time later in the arm represents the summed action potentials of all of the nerve fibers excited by the stimulus pulse and is called the *compound action potential* (Chapter 9). It increases in amplitude as more nerve fibers are stimulated; the summed activity is roughly proportional to the total number of active nerve fibers.

Electrical stimuli of increasing strength evoke action potentials first in the largest axons, because they have the lowest electrical resistance, and then progressively in smaller axons (Figure 18–4). Large-diameter fibers conduct action potentials more rapidly because

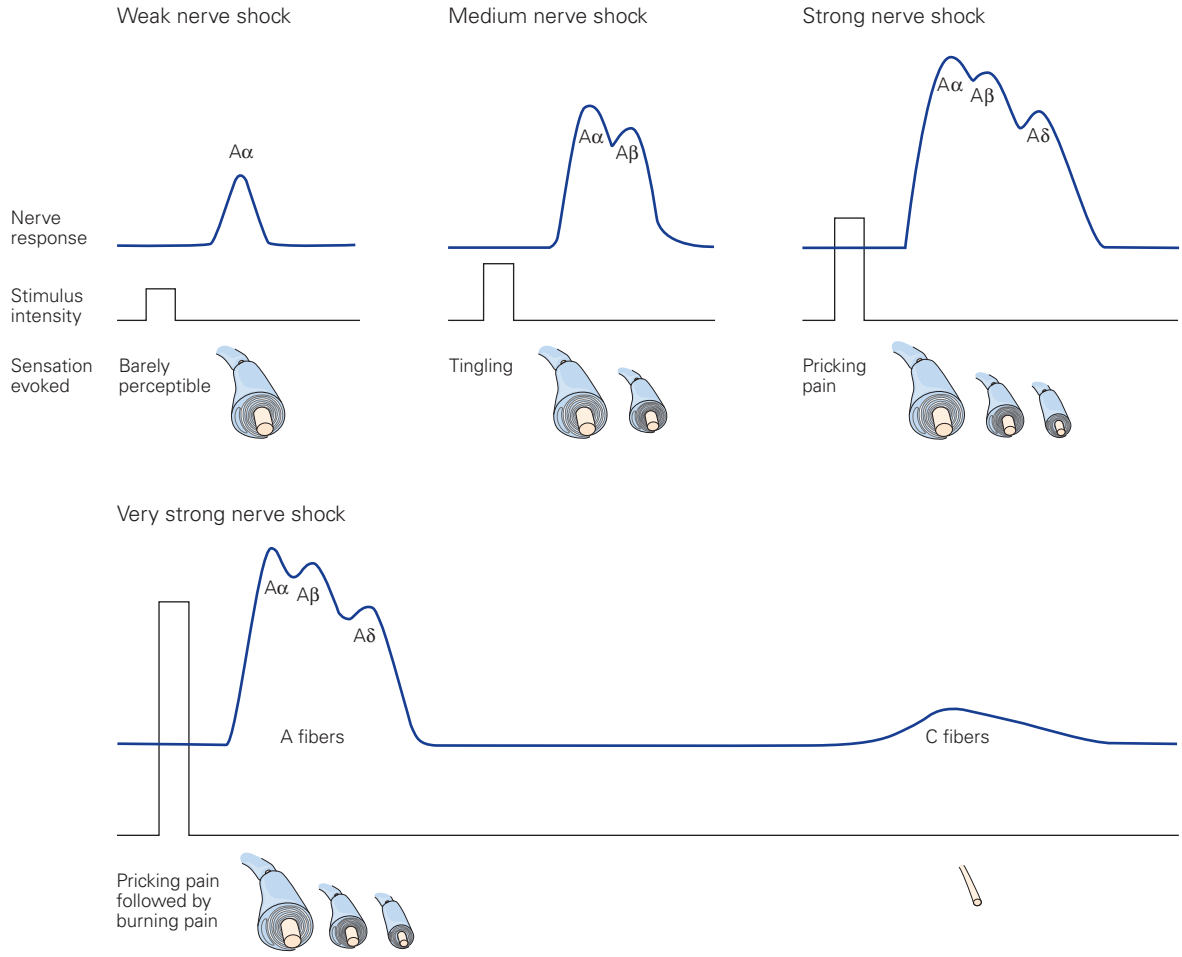


Figure 18–4 Conduction velocities of peripheral nerves are measured clinically from compound action potentials. Electrical stimulation of a peripheral nerve at varying intensities activates different types of nerve fibers. The action potentials of all the nerves stimulated by a particular amount of current are summed to create the compound action potential. The distinct conduction velocities of different classes of sensory and motor axons produce multiple peaks. (Adapted from Erlanger and Gasser 1938.)

the internal resistance to current flow along the axon is low, and the nodes of Ranvier are widely spaced along its length (Chapter 9). The conduction velocity of large myelinated fibers (in meters per second) is approximately six times the axon diameter (in micrometers), whereas thinly myelinated fibers conduct at five times the axon diameter. For unmyelinated fibers, the factor for converting axon diameter to conduction velocity is 1.5 to 2.5.

Following the stimulus artifact, the earliest neural signal recorded in the compound action potential occurs in fibers with conduction velocities greater than 90 m/s. Called the Aα wave (Figure 18–4), this signal reflects the action potentials generated in group I fibers and in motor neurons innervating skeletal muscle. The sensation is barely perceived by the subject in the region innervated.

As more large fibers are recruited, a second signal, the Aβ wave, appears. This component corresponds to group II fibers in skin or muscle nerves that innervate mechanoreceptors mediating touch and proprioception and becomes larger as the shock intensity is increased. At higher voltages, when axons in the smaller Aδ range are recruited, the stimulus becomes painful, resembling an electric shock produced by static electricity. Voltages sufficient to activate unmyelinated C fibers evoke sensations of burning pain. As we shall learn later in this chapter, some Aδ and C fibers also respond to light touch on hairy skin, but such gentle tactile stimuli are masked by concurrent activation of

pain fibers when whole nerves are stimulated electrically. Stimulation of motor neurons innervating the intrafusal fibers of muscle spindles (see Figure 18–9) evokes an intermediate wavelet called the Aγ wave, but this is usually difficult to discern because the conduction velocities of these motor neurons overlap those of Aβ and Aδ sensory axons. These differences in fiber diameter and conduction velocity of peripheral nerves allow signals of touch and proprioception to reach the spinal cord and higher brain centers earlier than noxious or thermal signals.

The clinician takes advantage of the known distribution of the conduction velocities of the various afferent fibers to diagnose diseases that result in sensory-fiber degeneration or motor neuron loss. In certain conditions, the loss of peripheral nerve axons is selective; in the neuropathy characteristic of diabetes, for example, the large-diameter sensory fibers degenerate. Such a selective loss is reflected in a reduction in the appropriate peak of the compound action potential, a slowing of nerve conduction, and a corresponding diminution of sensory capacity. Similarly, in multiple sclerosis, degeneration of the myelin sheath of large-diameter afferent fibers in the central nervous system results in slowing and, if severe enough, failure of nerve conduction.

A Variety of Specialized Receptors Are Employed by the Somatosensory System

The functional specialization of individual DRG neurons is determined by the molecular mechanisms of sensory transduction that occur at the distal nerve terminals in the body. When a somatic receptor is activated by an appropriate stimulus, its sensory terminal is typically depolarized. The amplitude and time course of the depolarization reflect the strength of the stimulus and its duration (see Figure 3–9A). Stimuli of sufficient strength produce action potentials that are transmitted along the peripheral branch of the DRG neuron's axon and into the central branch that terminates in the spinal cord or brain stem.

The sensory neurons that mediate touch and proprioception terminate in a nonneural capsule (Figure 18–1) or form morphologically distinctive endings surrounding hair follicles (Figure 18–2H) or intrafusal muscle fibers (see Figure 18–9A). They sense mechanical stimuli that indent or stretch their receptive surface. In contrast, the peripheral axons of neurons that detect noxious, thermal, or chemical events have unsheathed endings with multiple branches that terminate in the epidermis or in the viscera.

Several different morphologically specialized receptors underlie the various somatosensory submodalities. For example, the median nerve that innervates the skin of the hand and some of the muscles controlling the hand contains tens of thousands of nerve fibers that can be classified into 30 functional types. Of these, 22 types are afferent fibers (sensory axons conducting impulses toward the spinal cord), and eight types are efferent fibers (motor axons conducting impulses away from the spinal cord to skeletal muscle, blood vessels, and sweat glands). The afferent fibers convey signals from eight kinds of cutaneous mechanoreceptors that are sensitive to different kinds of skin deformation; five kinds of proprioceptors that signal information about muscle force, muscle length, and joint angle; four kinds of thermoreceptors that report the temperatures of objects touching the skin; and four kinds of nociceptors that signal potentially injurious stimuli. The major receptor groups within each submodality are listed in Table 18–2.

Mechanoreceptors Mediate Touch and Proprioception

A mechanoreceptor senses physical deformation of the tissue surrounding it. Mechanical distension—such as pressure on the skin, stretch of muscles, suction applied directly to cell membranes, or osmotic swelling of tissue—is transduced into electrical energy by the physical action of the stimulus on mechanoreceptor ion channels in the membrane. Mechanical stimulation deforms the receptor protein, thus opening stretch-sensitive ion channels and increasing nonspecific cation conductances that depolarize the receptor neuron (see Figure 3–9A). Removal of the stimulus relieves mechanical stress on the receptor and allows stretch-sensitive channels to close.

Various mechanisms for activation of mechanoreceptor ion channels have been proposed. Some mechanoreceptors appear to respond to forces conveyed through tension or deformation of the lipids of the plasma membrane, a mechanism called *force from lipids* (Figure 18–5A). Here, deformation of membrane lipids changes the cell surface curvature, exposing hydrophobic residues in the receptor protein to the membrane phospholipids, thereby opening the channel pore to cation flow. This may be the mechanism for detection of cellular swelling, which plays an important role in osmoregulation, or changes in shear stress on the walls of blood vessels due to altered fluid flow.

Another postulated mechanism for activation of mechanoreceptors involves linking the channel protein to the surrounding tissue through structural proteins,

Table 18–2 Receptor Types Active in Somatic Sensory Processing

Receptor type	Fiber group[1]	Fiber name	Receptor	Marker(s)	Modality
Cutaneous mechanoreceptors					Touch
Meissner corpuscle	Aα,β	RA1	Piezo2	*cRet*/*Npy2r*/NFH	Stroking, flutter
Merkel disk receptor	Aα,β	SA1	Piezo2	Troma1/Keratin8/*Npy2r*	Pressure, texture
Pacinian corpuscle[2]	Aα,β	RA2	Piezo2	*cRet*/*Npy2r*/NFH	Vibration
Ruffini ending	Aα,β	SA2	Piezo2		Skin stretch
Hair (guard)	Aα,β	Aβ RA-LTMR	Piezo2	*cRet*/*Npy2r*/NFH	Stroking, hair movement
Hair (awl/auchene)	Aδ	Aδ-LTMR	Piezo2	TrkB	Light stroking, air puff
Field receptor (circumferential endings)	Aβ	Aβ Field-LTMR	Piezo2	NFH	Skin stretch
Hair (zigzag)	C	C-LTMR		TH	Slow stroking, gentle touch
Thermal receptors					Temperature
Cool receptors	Aδ	III	TRPM8		Skin cooling (<25°C)
Warm receptors	C	IV	TRPV3		Skin warming (>35°C)
Heat nociceptors	Aδ	III	TRPV1/TRPV2		Hot temperature (>45°C)
Cold nociceptors	C	IV	TRPA1/TRPM8		Cold temperature (<5°C)
Nociceptors					Pain
Mechanical	Aδ	III		CGRP	Sharp, pricking pain
Thermal-mechanical (heat)	Aδ	III	TRPV2		Burning pain
Thermal-mechanical (cold)	C	IV	TRPV1/TRPA1	IB4	Freezing pain
Polymodal	C	IV	TRPV1/TRPA1		Slow, burning pain
Muscle and skeletal mechanoreceptors					Limb proprioception
Muscle spindle primary	Aα	Ia	Piezo2	PV/NFH	Muscle length and speed
Muscle spindle secondary	Aβ	II	Piezo2	PV/NFH	Muscle stretch
Golgi tendon organ	Aα	Ib	Piezo2	PV/NFH	Muscle contraction
Joint capsule receptors	Aβ	II			Joint angle
Stretch-sensitive free endings	Aδ	III			Excess stretch or force

[1]See Table 18–1.
[2]Pacinian corpuscles are also located in the mesentery, between layers of muscle, and on interosseous membranes.

a mechanism termed *force from filaments* (Figure 18–5B). In this arrangement, mechanical force applied to the skin or muscle by direct pressure or lateral stretch of the tissue distorts the extracellular matrix or intracellular cytoskeletal proteins (actin, integrins, microtubules). These tethering molecules interact with the receptor-channel proteins, change their conformation, and open cation channels. The extracellular linkage to the channel proteins is elastic and often represented as a spring-loaded gate. Direct channel gating in this model may be produced by forces that stretch the extracellular linkage protein. The channel closes when the force is removed. This type of direct channel gating is used by hair cells of the inner ear and by some touch receptors in the skin.

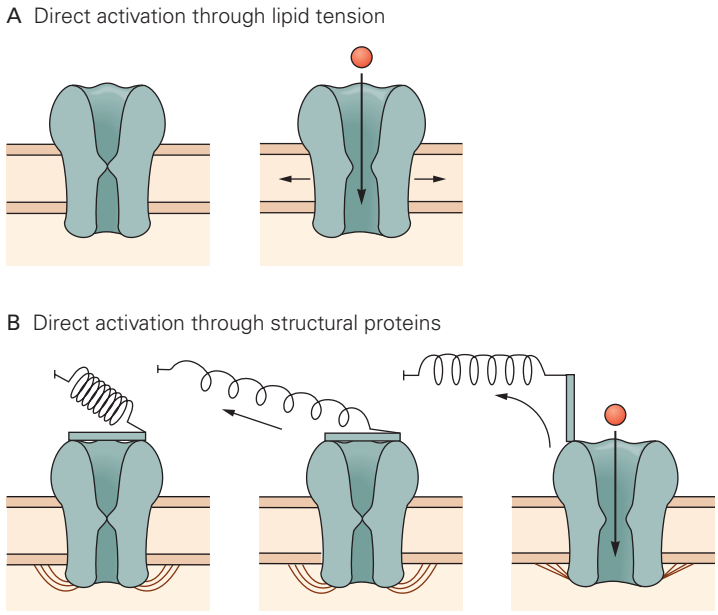


Figure 18–5 Ion channels in mechanoreceptor nerve terminals are activated by mechanical stimuli that stretch or deform the cell membrane. Mechanical displacement leads to channel opening, permitting the influx of cations. (Adapted, with permission, from Lin and Corey 2005. Copyright © 2005 Elsevier Ltd.)

A. Force from lipids. Channels can be directly activated by forces conveyed through lipid tension in the cell membrane, such as changes in blood pressure.

B. Force from filaments. Forces conveyed through structural proteins linked to the ion channel can also directly activate mechanosensory channels. The linking structural proteins may be extracellular (attached to the surrounding tissue) or intracellular (bound to the cytoskeleton) or both.

It is remarkable that although the receptor end organs for touch in the skin were first studied by Edgar Adrian and Yngve Zotterman in the 1920s and receptor potentials were recorded from isolated touch receptors from the mesentery (Pacinian corpuscles) in the 1960s, there was little consensus about the molecular biology of mechanosensation in mammalian touch. The leading candidates were derived from invertebrate model organisms such as the nematode worm *Caenorhabditis elegans* whose touch receptors were identified as members of the degenerin superfamily of ion channels and are similar to vertebrate epithelial Na^+ channels (DEG/ENac channels). Other candidate molecules included TRPV4 receptors (members of the transient receptor potential [TRP] receptors that are also involved in thermal senses), and NOMPC, a *Drosophila* member of the TRPN family. However, these molecules are not expressed in mammalian DRG neurons.

The Piezo protein family of transmembrane ion channels was recently identified by Ardem Patapoutian and colleagues as molecular mediators of mechanoreception in mammals. Piezo1 proteins are composed of approximately 2,500 amino acids, with at least 26 transmembrane α-helices (Figure 18–6A). The ion channel is a trimer formed from three identical Piezo protein subunits, with two pore-forming α-helices at the C-terminal end of each Piezo protein. The N-terminals of the subunits form a propeller-like structure (Figure 18–6B), which is thought to be involved in coupling mechanical stimuli to channel gating. Piezo proteins form nonspecific cation-permeable channels that conduct excitatory depolarizing current.

Two different isoforms of the Piezo proteins serve as mechanosensors: Piezo1 is found primarily in nonneural tissue, such as epithelia in blood vessels, the kidney, and bladder, and in red blood cells. Piezo2 is expressed in mechanosensory DRG and trigeminal neurons that mediate the senses of touch and proprioception and in vagal afferents innervating smooth muscle of the lung, where they mediate the Hering-Breuer reflex by sensing lung stretch (Chapter 32).

Specialized End Organs Contribute to Mechanosensation

In addition to the molecular composition of the ion channels expressed in the distal nerve endings, components of surrounding tissue such as epithelial cells or muscle fibers play a significant role in mechanotransduction. The specialized nonneural end organs that surround the nerve terminals of a DRG neuron must be deformed in specific ways to excite the fiber. For example, individual mechanoreceptors respond selectively to pressure or motion, and thereby detect the direction of force applied to the skin, joints, or muscle fibers. The end organ can also amplify or modulate the sensitivity of the receptor axon to mechanical displacement.

Specialized epithelial cells in the skin—such as Merkel cells, the epithelium lining hair follicles, and the papillary ridges that form the fingerprints of glabrous

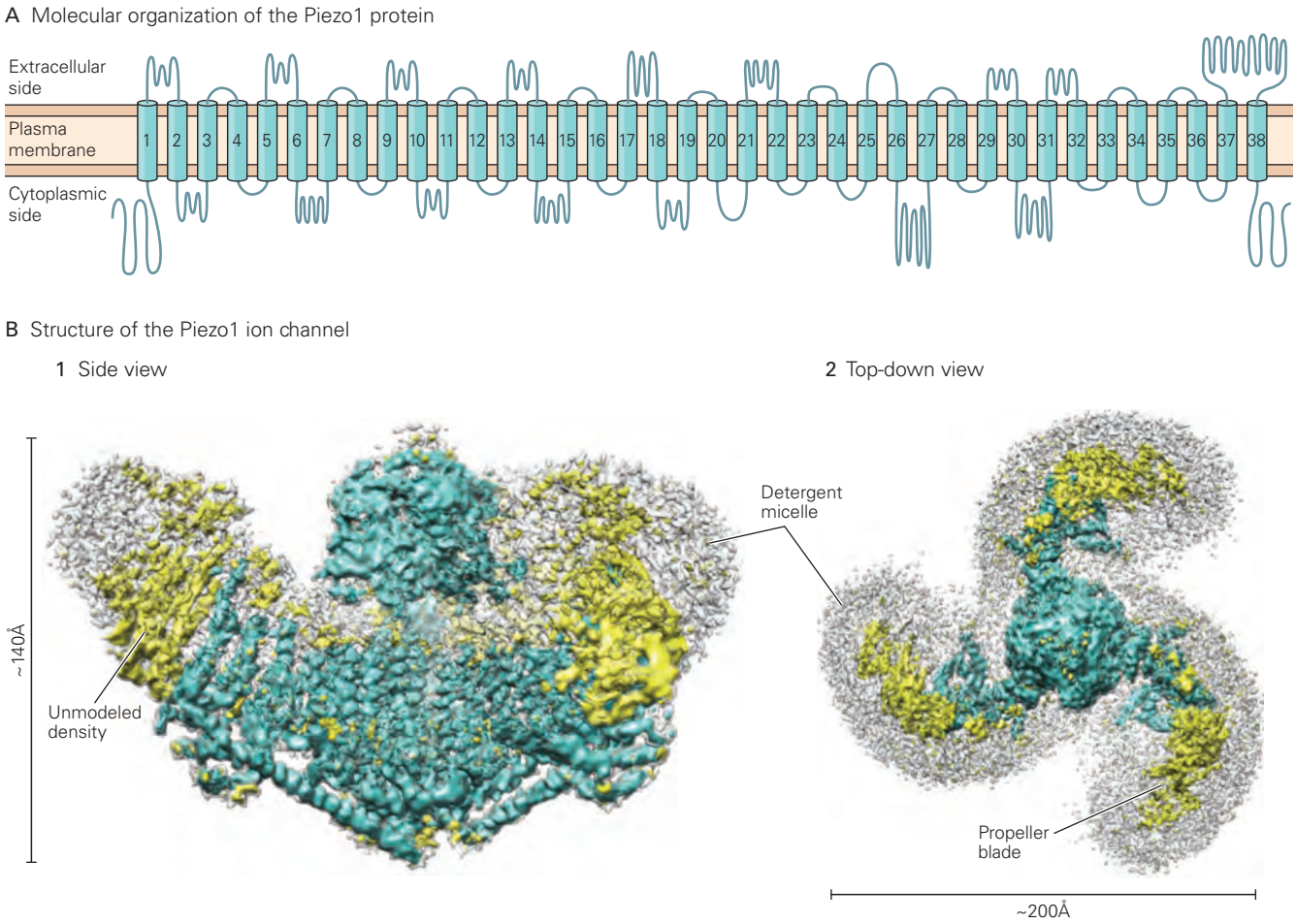


Figure 18–6 Structure and molecular organization of Piezo1 ion channels.

A. Piezo1 and Piezo2 have homologous protein structures, containing approximately 2,500 amino acids, with at least 26 putative transmembrane segments. Combined as trimers, they form the largest membrane ion channels in mammals. (Adapted, with permission, from Murthy, Dubin, and Patapoutian 2017. Copyright © 2017 Springer Nature.)

B. Putative structure of the Piezo1 ion channel deduced from cryo-electron microscopy. **1.** Side view, cytoplasmic surface down. **2.** Top-down view from extracellular side. The receptor is a triskelion made up of three identical Piezo1 subunits. The C-terminals of the three Piezo proteins form a central extracellular cap tethered to the extracellular surface of the transmembrane pore, which extends beyond the membrane into a cytoplasmic tail domain. The aqueous pore through the channel extends through the central axis of the cap, the transmembrane pore, and the cytoplasmic tail domain. The N-terminals of the three protein subunits are arrayed peripherally, forming a propeller-like helical structure. **Blue** indicates area of high-resolution modeling. (Adapted, with permission, from Saotome et al. 2018. Copyright © 2018 Springer Nature.)

skin—play important auxiliary roles in the sense of touch. The best studied of these end organs are Merkel cells—sensory epithelial cells that form close contacts with the terminals of large-diameter (Aβ) sensory nerve axons at the epidermal–dermal junction, forming Merkel cell–neurite complexes. Merkel cells cluster in swellings of the epidermis in hairy skin called touch domes (Figure 18–7A) and near the center of the fingerprint ridges in glabrous skin (see Figure 19–3). When a probe contacts the touch dome, the sensory nerve responds with a train of action potentials whose frequency is proportional to the velocity and amplitude of pressure applied to the skin (Figure 18–7A2). These spike trains typically last throughout the period of stimulation and are termed *slowly adapting* because the firing persists for periods of up to 30 minutes. Likewise, the sensory nerve is called an *SA1 fiber* (slowly adapting type 1 fiber).

Merkel cells serve a similar receptive function in the sense of touch as auditory hair cells in the cochlea

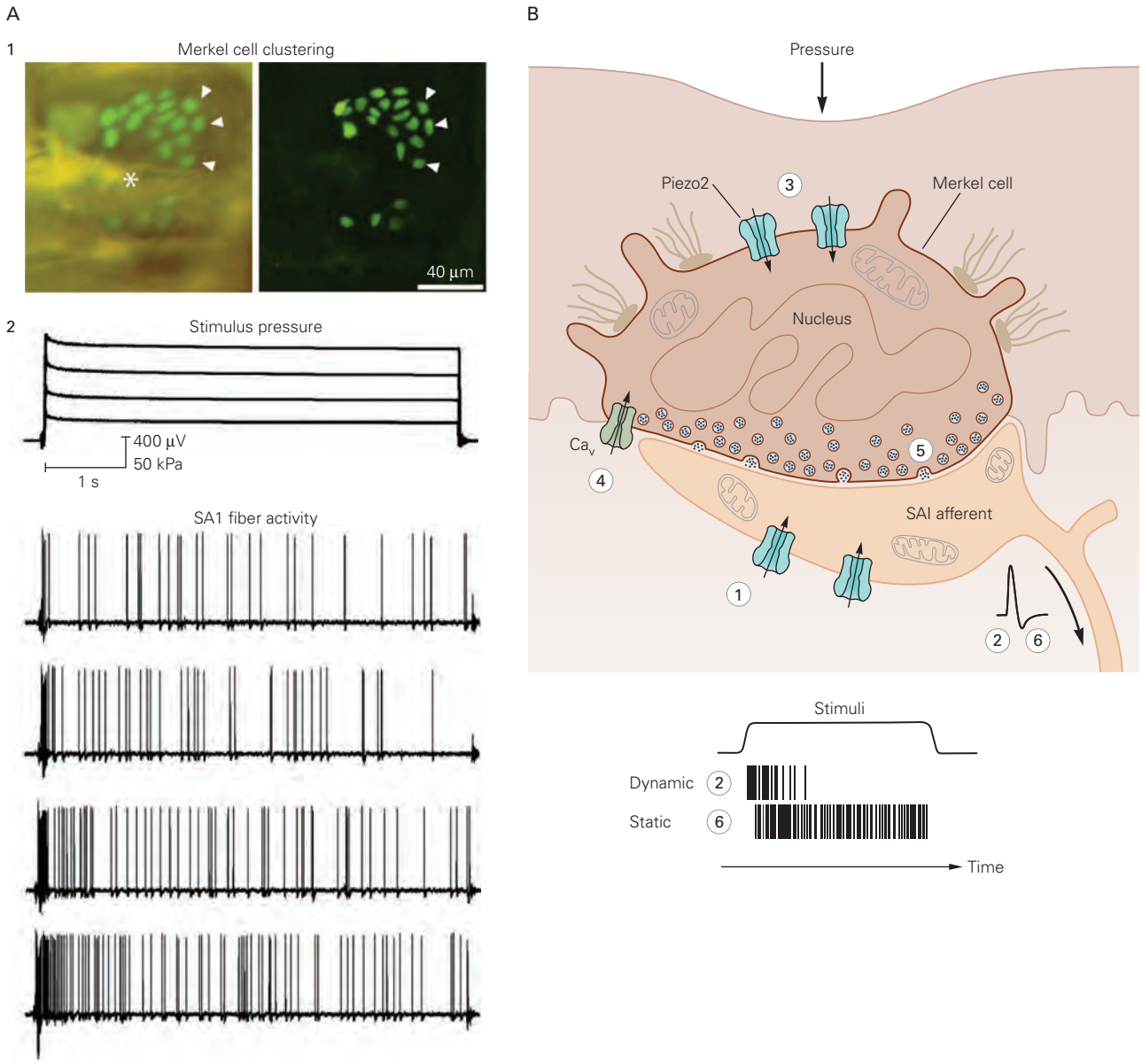


Figure 18–7 Afferent fibers innervating Merkel cells respond continuously to pressure on the skin.

A. 1. An individual slowly adapting type 1 (**SA1**) mechanoreceptive fiber innervates a cluster of 22 Merkel cells (each labeled with enhanced green fluorescent protein [eGFP]) in a touch dome of the hairy skin. *Left*: In vivo epifluorescent images of the isolated skin-nerve recording preparation. Asterisk (*) indicates the location of the associated guard hair within the touch dome. *Right*: Confocal z-series projections of the entire touch dome innervated by the SA1 fiber. **Arrowheads** are used to align Merkel cells in the two images. **2.** The SA1 fiber responds to 5-second duration steps of pressure (measured in kilopascals [**kPa**]) applied over the touch dome (upper records) with irregular, slowly adapting spike trains (recorded extracellularly), whose mean frequency of firing is proportional to the applied force (lower records). The neuron fires at its highest rate at the start of stimulation and fires fewer spikes during maintained pressure. (Reproduced, with permission, from Wellnitz et al. 2010.)

B. A model of sensory transduction in SA1 mechanoreceptors. Pressure on the skin opens Piezo2 channels (**blue**) in the Merkel cell and in the peripheral neurite of the SA1 fiber that receives synaptic input from the Merkel cell. Piezo2 channels in the neurite open at the onset of stimulation (**1**) generating the initial dynamic response to touch (**2**). Skin deformation simultaneously activates Piezo2 channels in the Merkel cell (**3**), depolarizing it and allowing voltage-gated Ca_V channels in the Merkel cell (**4**) to open and release neurotransmitter continuously (**5**). Binding of the neurotransmitter further depolarizes the SA1 neurite, producing sustained firing in the principal axon (**6**). (Reproduced, with permission, from Maksimovic et al. 2014. Copyright © 2014 Springer Nature.)

(Chapter 26) and taste cells in the tongue (Chapter 32). Merkel cells studied in vitro respond to mechanical force such as pressure or suction with depolarizing currents that are similar in time course and conductance to those evoked in isolated DRG neurons. They express synaptic release proteins and contain vesicles that release excitatory neurotransmitters during sustained pressure. Merkel cells express Piezo2 proteins and show increased cytoplasmic Ca^{2+} levels when stimulated by pressure.

The importance of Merkel cells for physiological responses to touch is seen in mice that fail to develop Merkel cells in the epidermis (*Atoh1* conditional knockout mice). The firing rates of SA1 fibers in these animals are reduced in amplitude and duration compared to wild-type. These experiments indicate that Merkel cells are responsible for the sustained response to static touch. Recently, Ellen Lumpkin and colleagues used optogenetic stimulation of Merkel cells rather than direct pressure on the skin to demonstrate that SA1 fibers innervating touch domes use a dual-mechanism to sense pressure on the skin (Figure 18–7B). The initial dynamic response to touch is generated primarily by current flow through Piezo2 channels in the SA1 nerve terminal. The subsequent static response results from excitatory synaptic transmission from Merkel cells that express Piezo2 channels and continuously release neurotransmitter during sustained pressure on the skin.

Hairs that protrude from the surface of the skin provide another important set of touch end organs. Sensory hair fibers are extremely sensitive to motion. Deflection of hairs by light breezes or air puffs evokes one or more action potentials from hair follicle afferent fibers. Humans can perceive motion of individual hairs and localize the sensation to the base of the hair, where it emerges from the skin. Sensory hairs serve an important protective function as they detect objects, other organisms, or obstacles in the environment at a distance before they impact the body. Hairs or sensory antennae detect important object features such as texture, curvature, and rigidity that aid recognition as friend or foe. These neurons are named *rapidly adapting low-threshold mechanoreceptors* (RA-LTMRs) because they respond to gentle touch or hair movement with brief bursts of spikes when the hair is moved by external forces.

Hairs are embedded in skin invaginations called hair follicles. Three types of hairs are found in mammalian skin (Figure 18–8A). The largest, longest, and stiffest hairs (named guard hairs) are the first to emerge from the skin during development. *Guard hairs* are innervated by the largest-diameter and fastest-conducting sensory nerve fibers (type Aβ); these fibers form lanceolate (comb-like) endings in the epidermis of the follicle surrounding the hair (Figure 18–2H). Aβ RA-LTMR nerve fibers also innervate intermediate-sized hairs (called *awl/auchene hairs*) with lanceolate endings. Awl/auchene hairs are triply innervated: They provide inputs to fast-conducting (Aβ) myelinated fibers; smaller-diameter, slower-conducting myelinated (Aδ) fibers; and unmyelinated C fibers. The smallest and most numerous hairs (called *zigzag* or *down hairs*) are also innervated by Aδ and C fibers.

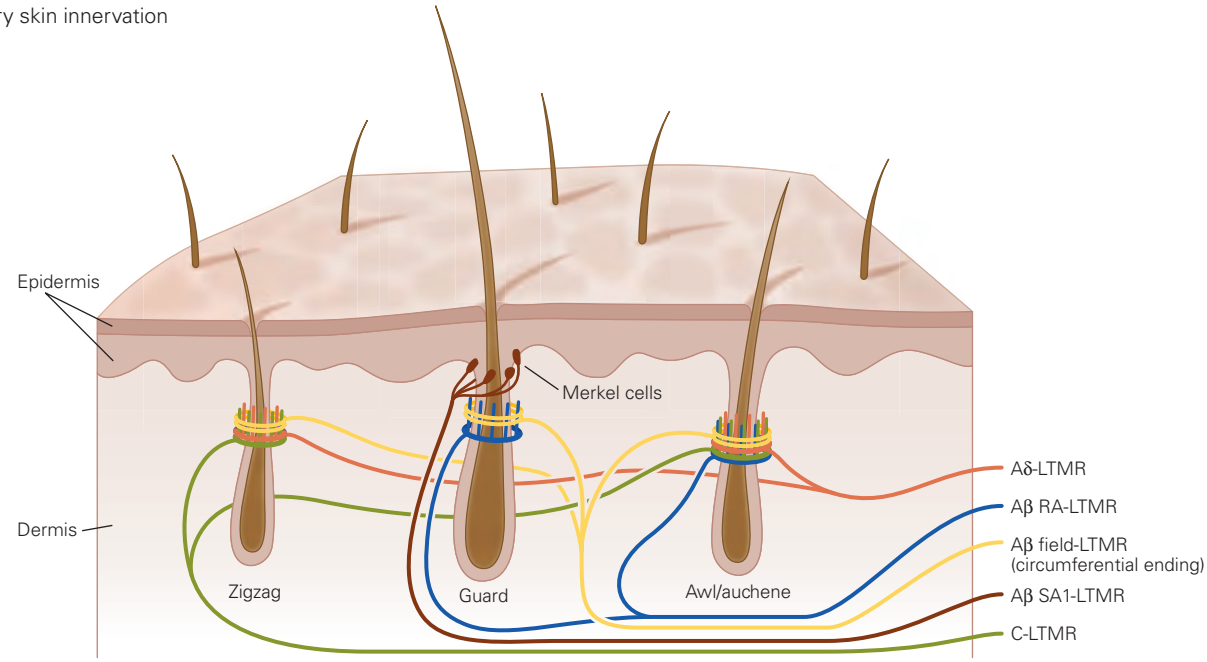
Until recently, Aδ and C fibers were thought to mediate only thermal or painful sensations. However, microneurography studies in humans by Johan Wessberg, Håkan Olausson, and Åke Vallbo demonstrated that hairy skin is also innervated by unmyelinated C-LTMR fibers that respond to slowly moving tactile stimuli and are thought to mediate social or pleasurable touch. They may also play a role in pain inhibition in the spinal cord dorsal horn.

The innervation pattern of hair follicles in the skin illustrates two important principles of sensory innervation of the body: convergence and divergence. Each individual hair follicle in the skin provides input to multiple sensory afferent fibers. This pattern of overlap provides redundancy of sensory input from a small patch of skin. Shared lines of communication innervate each hair follicle, rather than a single labeled line. Tactile information from the skin is therefore transmitted in parallel by an ensemble of sensory neurons.

The skin area innervated by the sensory nerve terminals of a DRG neuron defines the cell's *receptive field*, the region of the body that can excite the cell. Each sensory nerve fiber collects information from a wide area of skin because its distal terminals have multiple branches that can be activated independently. This morphology enables each afferent fiber to provide unique patterns of sensory input to the brain.

The diversity of receptive field sizes and territories encompassed by individual classes of DRG neurons is illustrated in Figure 18–8B. Because of the large size of tactile receptive fields, gentle touch excites many different sensory fibers at the site of contact, each conveying a specific sensory message. The smallest tactile receptive fields are the touch domes innervated by SA1 fibers (see Figure 19–8B Aβ SA1). An individual SA1 fiber innervates all of the Merkel cells in a touch dome and typically collects information from one to three touch domes in adjacent skin regions. Hair follicles innervated by individual RA fibers are spread further apart and the sensory endings differ somewhat in size, with the largest-diameter Aβ fibers encompassing the

A Hairy skin innervation



B Receptive fields of low-threshold mechanoreceptors