CHAPTER

23

Somatosensation and Pain

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Our body continuously surveys its external environment and its internal state. This is referred to as *exteroception* and *interoception*, respectively. Interoception is crucial for homeostatic regulation of physiological processes like breathing, but this information is most often used without us being aware of it. Similarly, we are typically unaware of our joint position or movement yet continuous proprioceptive feedback is critical for balance and coordinated locomotion. We are more aware of touch, temperature, and pain. Pain is especially powerful in drawing our attention, although protective reflexes are often initiated before we perceive the painful stimulus. Somatosensation is not unique in this regard; phenomena like blindsight—the ability of cortically blind individuals to respond to visual stimuli without conscious awareness of the stimulus—emphasize how much sensory processing occurs subconsciously even in the visual system.

These issues highlight the distinction between sensing and perceiving. *Sensation* refers to the detection of stimuli of different modalities. *Perception* refers to how our brain interprets that sensory input, which can be shaped by situational context, expectations, and a multitude of other factors. The two processes—sensing and perceiving—are obviously linked, so much so that we take the link for granted. Yet we do not always perceive a stimulus in the way one would expect. This is exemplified by illusions like the thermal grill in which interleaved warm and cool bars are misperceived as burning hot, and by clinical conditions such as ciguatera in which innocuous thermal stimuli are mistakenly perceived as burning hot. Pain is often described in terms of the stimuli that would normally evoke that percept regardless of what the stimulus really is. For instance, burning pain is often described as if *one's skin is on fire*. Perceived as pressure, cardiac ischemia is often likened to *an elephant sitting on one's chest*. Of course, the proper medical responses do not involve fire hoses or elephant removal.

This chapter focuses on somatosensory modalities including proprioception, thermoception, touch, and nociception. Given the clinical importance of chronic pain, later parts of the chapter are dedicated to discussion of how changes in somatosensory processing lead to chronic pain and how understanding the mechanisms underlying those changes can be used to help alleviate such pain. We begin with an introduction of concepts important for sensory physiology.

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BASIC CONCEPTS IN SENSORY PHYSIOLOGY

First-order sensory neurons—also known as primary afferents—are responsible for sensing stimuli on the skin or internal tissues and relaying that information to the central nervous system (CNS). Action potentials, or spikes, are used to convey that information over long distances, more than 1 m in some human axons and much farther in other species. Second-order sensory neurons in the spinal cord and brainstem receive that information via synaptic connections and relay signals to higher order sensory neurons deeper in the CNS. Fig. 23.1 illustrates the two basic pathways. Although Fig. 23.1 depicts strict feedforward pathways, local circuits and long-distance feedback loops play an important role in processing the information and modulating its transmission to the cortex. Central processing is critically important for how a given stimulus will ultimately be perceived but what

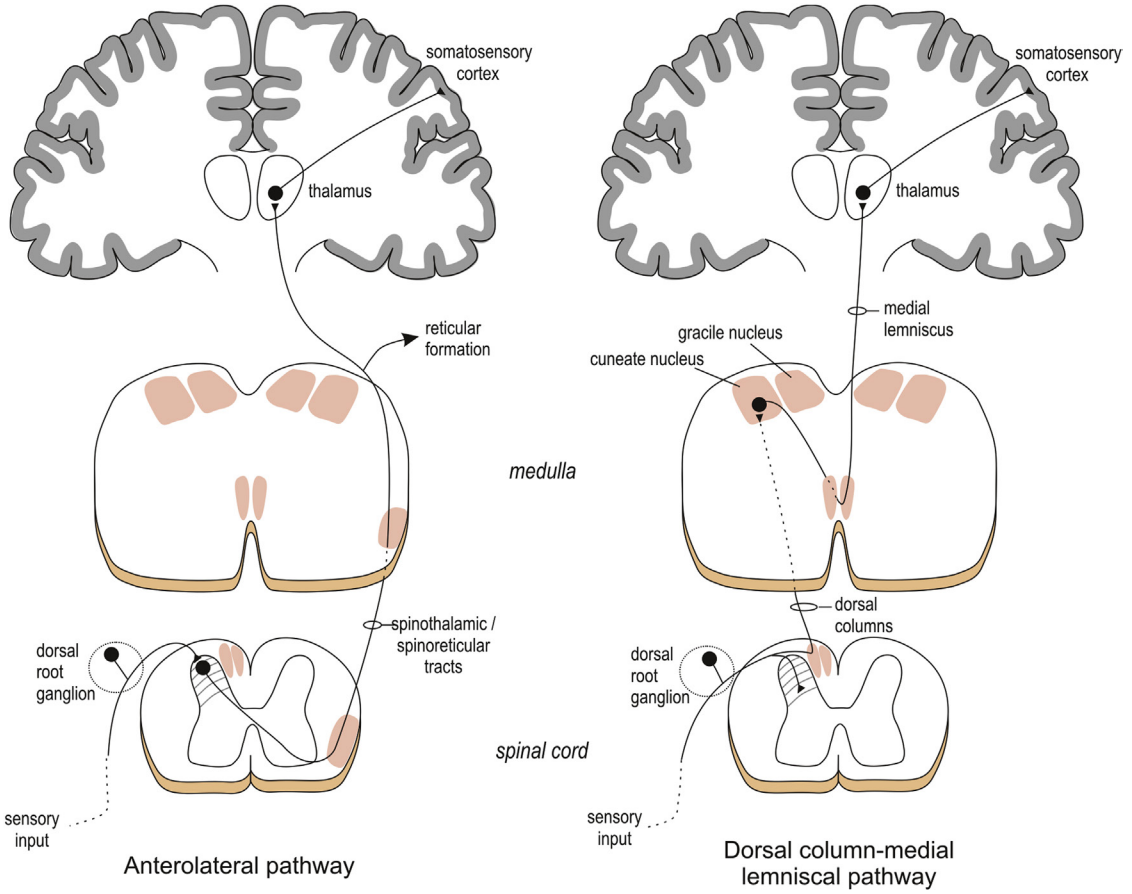


FIGURE 23.1 Somatosensory information from the periphery is routed through the central nervous system via two main pathways: the anterolateral pathway (left) and the dorsal column-medial lemniscal pathway (right). Fibers ascending in the dorsal columns carry information about proprioception and fine touch, while those ascending in the anterolateral tract carry information mostly about pain, temperature, and crude touch.

distinguishes sensory modalities (and submodalities) from one another is the type of physical stimuli to which primary sensory neurons respond. Accordingly, we dedicate a significant portion of this chapter to describing first-order sensory neurons.

Transduction is the process by which a physical stimulus is converted into a receptor potential in the peripheral endings of primary afferent neurons. This graded depolarization, also known as a generator potential, must be converted to a spike train in order for the sensory signal to reach the CNS. This second step depends on the local excitability, which reflects the complement of ion channels present in the axon terminal. The initial transduction step is mediated by the specific receptor molecules present in the fiber terminals and the association of those terminals with specialized end organs, that is, non-neural cells or capsules, such as Pacinian corpuscles (see section: Somatic Submodalities and Receptor Mechanisms). The *adequate stimulus* refers to the type of stimulus to which a fiber is most sensitive. This term has been largely replaced by the concept of tuning. A neuronal *tuning curve* shows the threshold stimulus intensity plotted against the stimulus parameter of interest, as illustrated for two different types of mechanoreceptors tested across a range of vibration frequencies in Fig. 23.2. The *x*-value at the minimum (trough) of the curve represents the stimulus to which the neuron is most sensitive. A narrow or broad tuning curve means that the neuron is more or less selective, respectively, for that stimulus parameter.

The *receptive field* of a neuron describes the portion of sensory space in which stimulation will activate that neuron (Fig. 23.3). In the somatosensory system, this typically refers to an area on the body surface, whereas in the visual system, for example, it refers to an area in visual space. The receptive field of a primary somatosensory afferent is determined by the area innervated by that particular fiber. Downstream neurons in the CNS can also be said to have a receptive field but, in their case, the receptive field reflects the sum of the receptive fields of upstream neurons converging onto the neuron of interest. Receptive fields can also be shaped by other aspects of the microcircuitry, most notably synaptic inhibition (see section: Central Pathways). The size of receptive fields affects tactile acuity: two points spaced closely together will be perceived as a single point if both points fall within the same receptive field. Therefore, two-point discrimination will be less precise where receptive fields are large, like on the torso, and more precise where receptive fields are small, like on the hands or lips. The smaller the receptive fields, the denser the innervation, implying that relatively more sensory neurons are dedicated to parts of the body with high acuity. The amount of somatosensory cortex dedicated to various body parts reflects the acuity of those body parts (see section: Thalamic and Cortical Regions Involved in Somatosensation).

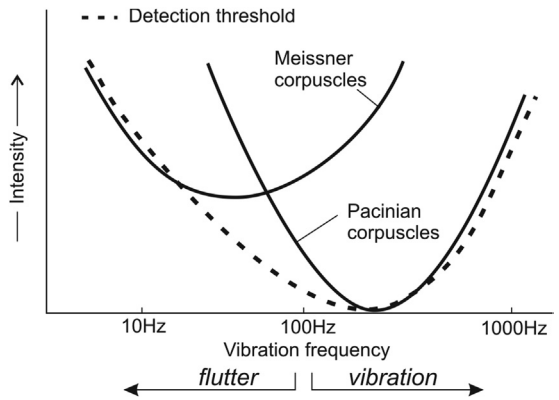


FIGURE 23.2 Tuning curves show the minimum stimulus intensity required to activate a given receptor type (*solid curves*) or to be detected by a person (*dashed curve*) at a given stimulus frequency. Meissner corpuscle-RA1 afferents are tuned to vibrations near 50 Hz, whereas Pacinian corpuscle-RA2 afferents are tuned to vibrations near 250 Hz. Vibrations <100 Hz are encoded by the former and are sensed as flutter. Vibrations >100 Hz are encoded by the latter and are sensed as vibration.

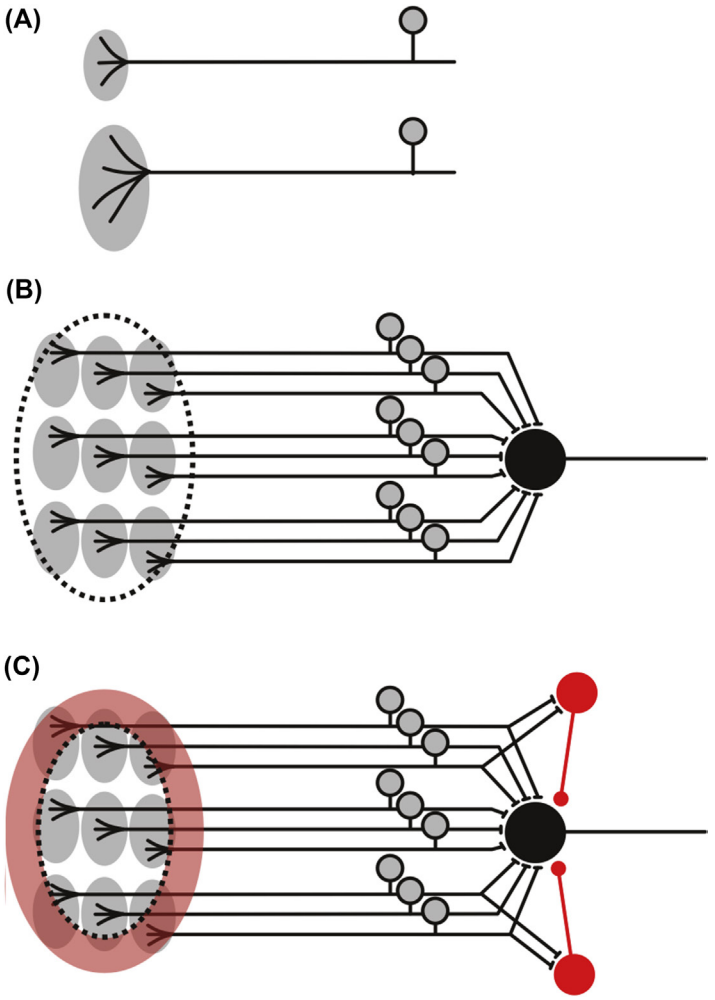


FIGURE 23.3 Receptive fields. (A) The receptive fields of first-order sensory neurons reflect the area innervated by their terminal branches. (B) For a second-order sensory neuron, its receptive field (*black dashed oval*) is the sum of the receptive fields of upstream neurons. Convergence of more first-order neurons onto second-order neurons translates into a larger receptive field. (C) Lateral inhibition evoked by first-order sensory neurons on the edge of the receptive field creates an inhibitory surround (*red shading*) that sharpens the second-order sensory neuron's receptive field.

FIRST-ORDER SOMATOSENSORY NEURONS

Unlike the other senses in which sensors are concentrated in dedicated sensory organs—the eyes, ears, nose, or tongue—primary somatosensory neurons innervate the entire surface of the body plus internal tissues. The cell body (soma) of each primary somatosensory neuron is located in a dorsal root ganglion (DRG) or trigeminal ganglion. Afferents from the trigeminal ganglia innervate the face and other cranial tissues like dura mater, and relay that information to trigeminal nucleus in the brainstem, while afferents from the DRG innervate the rest of the body and relay information into the dorsal horn

of the spinal cord. Located close to but officially outside the CNS, both sets of ganglia contain only sensory neurons. These neurons are pseudounipolar, which means that a single fiber exits the cell body and splits at a T-junction, with one end innervating peripheral tissue and the other end connecting with second-order sensory neurons in the CNS (see Fig. 23.1). The peripherally projecting fibers innervate skin, muscle, joints, and internal organs. The types of sensory neurons innervating a given tissue dictate the sensibility of that tissue: sensory neurons innervating the colon respond to stretch but not to temperature change, which is why burning the colon is not painful whereas stretching it is; in contrast, the skin is innervated by diverse sensory neurons, hence the rich sensory experience associated with cutaneous stimuli.

The peripheral terminals of primary afferent fibers are specialized to detect certain stimuli. This "tuning" is a direct reflection of the types of receptors they express and the specialized end organs with which they associate. But different fibers are *not* specialized to produce certain percepts. For example, fibers known as nociceptors are specialized to detect noxious stimuli, and while their activation will typically evoke pain, this is not always the case: in the heat of battle, injury may go completely unnoticed despite nociceptor activation until the stress of the situation recedes; on the other hand, the thermal grill illusion demonstrates burning pain in the absence of any nociceptor-activating stimulus. These two examples illustrate, respectively, that nociceptor activation is neither sufficient nor necessary to produce pain. "Pain" fibers simply do not exist. The neural code for pain and its relation to other submodalities has been the focus of significant debate (see Box 23.1).

Primary afferent fibers are classified according to several interrelated features (Fig. 23.4). Aα and Aβ fibers have the fastest conduction velocities due to their large diameter and thick myelination. These fibers convey information important for proprioception and light touch. Aδ fibers are intermediate in their conduction velocity, consistent with their medium diameter and thin myelination. Different subsets of these fibers are involved in light touch, thermosensation, and nociception. C fibers have the slowest conduction velocity due to their small diameter and lack of myelination. C fibers are involved in nociception, itch, thermosensation, and affective touch (which is distinct from discriminative touch). Most nociceptors are C fibers but not all C fibers are nociceptors, contrary to what is commonly assumed. C fibers significantly outnumber A fibers and are often subdivided based on whether they express peptide neurotransmitters. Fiber size has implications beyond conduction velocity (in part because of the different voltage-gated ion channels expressed in different fiber types). For instance, large fibers have the lowest threshold and are therefore the first to be recruited by electrical stimulation of a nerve. The largest fibers are also the first blocked by ischemia (eg, when a blood pressure cuff is applied) but the last to be blocked by local anesthetics. The capacity to differentially activate or block certain types of afferents has been used to help work out their relative contributions.

Before proceeding, it is important to reiterate that sensory input is transduced at the peripheral end of each primary afferent neuron. Mechanical, thermal, or chemical activation of receptors generates a receptor potential that is converted locally to a spike train, which is then relayed past the cell body and into the CNS. This distribution of responsibilities—spike initiation in the distal end of the axon and spike propagation toward the cell body—is unlike what occurs in most central neurons, where inputs are received on the dendrites and integrated in the cell body, with spikes being generated in the axon initial segment (near the cell body) before being relayed down the axon. Spikes can originate in the cell body, axon, or central terminals of primary somatosensory neurons, but this is atypical. Spikes originating from the "wrong" location are termed *ectopic*.

BOX 23.1

THEORIES OF SOMATOSENSORY CODING

In 1840, Müller outlined the concept of specific nerve energies, according to which each sense organ evokes a specific sensation regardless of how it is activated. Extending this, von Frey proposed in the 1890s that there are four cutaneous modalities—touch, warmth, cold, and pain—each subserved by distinct skin receptors. This was the origin of *specificity theory*, which posits that each sensation arises from the activation of distinct sensory neurons. According to this theory, primary sensory neurons must be specialized to detect (ie, are tuned to) different types of stimuli. Those primary sensory neurons should connect to equally specialized second-order neurons, and so on, forming *labeled lines*. According to the theory, the brain knows which type of sensory neuron got activated based on which brain area receives the resulting signal via its dedicated input line.

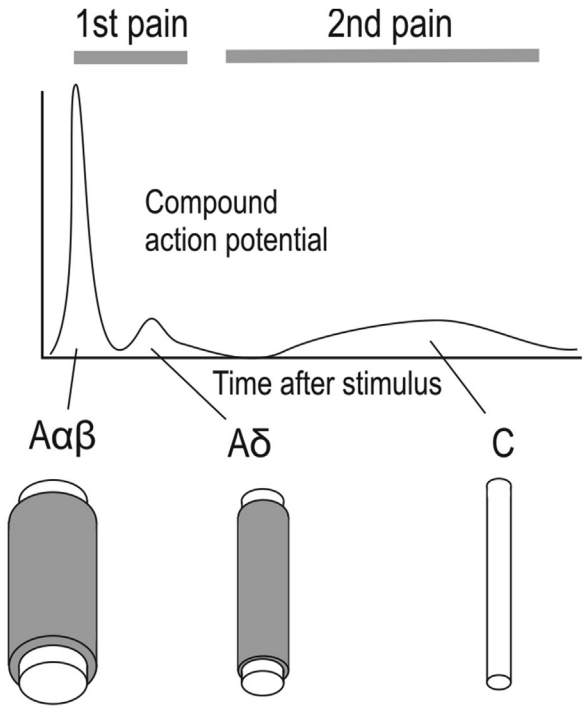
Notably, if differently tuned primary afferent neurons converge onto a second-order neuron, the second-order neuron will have broader tuning, which is to say that "labeling" is lost (or at least reconfigured). Although there is no denying that primary afferents are highly specialized, most higher-order neurons ultimately receive input from more than one type of primary afferent. This is not to say that all projections become equivalently tuned, but they are less specialized than the primary afferents. Observations that touch modulates pain, temperature modulates touch, and so on, contradict labeled lines and Specificity Theory, and are the motivation behind pattern theories. The best known pattern theory is the *gate control theory* of Melzack and Wall, which argues that low-threshold inputs normally inhibit high-threshold inputs and that the ratio of the two inputs, reflected in the output of the projection neuron, will dictate whether a stimulus is perceived as painful. Many of the original details of the gate control theory have been disproven (after bitter debate) but the core ideas survive and have been instrumental in driving pain research since mid-1960s.

Primary sensory neurons are highly *specialized*, but this means that they respond preferentially to certain stimuli, not that they respond exclusively (ie, *specifically*) to those stimuli. Realistic stimuli co-activate differently tuned neurons; in fact, meaningful co-activation patterns require heterogeneously tuned neurons (otherwise all neurons would be equivalently activated). This is to say that specialization is necessary for, not mutually exclusive of, most pattern-based codes. According to *combinatorial coding theory*, the richest and most robust coding strategies would exploit afferent co-activation patterns, consistent with the evidence available from other sensory systems, like color vision, which boils down to the relative activation of three differently tuned—red, green, and blue—photoreceptors. This is still very much an active area of research.

SOMATIC SUBMODALITIES AND RECEPTOR MECHANISMS

Proprioception

Proprioception refers to the sense of limb position and movement, where the latter is specifically referred to as kinesthesia. Proprioceptive feedback is critical for proper balance and motor control. Innervated by fast-conducting Aα fibers, muscles have receptors involved in proprioception. *Muscle spindles* comprise a bundle of thin muscle fibers that are enclosed within a capsule. Mechanosensitive afferents wrap around the muscle fibers and are activated by stretching such that their firing rate is proportional to muscle length. Contraction of the thin (intrafusal) muscle



Myelinated	Thinly myelinated	Non-myelinated
Large diameter	Medium diameter	Small diameter
Light touch Proprioception	Light touch Thermosensation Nociception	Thermosensation Nociception Itch Affective touch

FIGURE 23.4 Primary afferents are categorized by their size, myelination, and conduction velocity. Each fiber type is associated with different somatic submodalities. After a noxious stimulus, the immediate (first) and delayed (second) pain are linked with myelinated (A) and unmyelinated (C) fiber activation, respectively.

fibers, which are innervated by motoneurons, can effectively modulate the sensitivity of the muscle spindles. *Golgi tendon organs*, which are located between muscle and tendons, sense muscle force rather than length, and are an important component of reflex circuits. Joints are endowed with *joint-capsule receptors* that sense tension but, interestingly, individuals with artificial joints can still sense the angle and movement of their artificial joint reasonably well on the basis of input from muscle spindles.

Thermoception

Thermoception refers to temperature sensation. The temperature of the air or contacting object is sensed relative to skin temperature, which is typically maintained around 32°C. Rapid temperature changes are more readily sensed than slower changes; in fact, slow changes between 31°C and 36°C tend not to be detected because they are compensated for by dilation/constriction of cutaneous blood vessels. Slowly reducing the temperature will give a sensation of coolness near 31°C, with the sense of cold increasing until pain is felt near 12°C. Moving temperature slowly in the other direction, warmth is first felt near 36°C and the feeling of hot will increase until it is painful near 45°C. These sensations are subserved by a number of *transient receptor potential (TRP) channels* that are located in the membrane of primary afferent terminals and are active across different temperature ranges (Fig. 23.5). Notably, many TRP channels are also activated by specific chemicals, most notably food products like chili peppers and mint that give characteristic burning and cooling sensations, respectively. Importantly, the temperature-sensitivity of TRP channels can be significantly modulated by numerous factors including inflammation.

Hot receptors and high-threshold cold receptors correspond to different sets of C fibers, whereas low-threshold cold receptors (ie, cool receptors) correspond to Aδ fibers. Contrary to simplistic notions of temperature coding, these fiber populations do not operate independently. This is nicely illustrated by the fact that input from C-cold fibers is inhibited by input from Aδ-cool fibers; this "masking" can be revealed by selectively blocking the Aδ-cool fibers (which can be done with a blood pressure cuff), which results in a given temperature feeling colder than it really is, often as burning cold. Anyone who has felt burning pain after washing numb hands in lukewarm water has experienced this unmasking phenomenon. This argues that temperature perception does not depend only on which type of TRP channel is activated at a given temperature. Further to this point, capsaicin (the active ingredient of chilli peppers and an agonist of TRPV1 channels) can cause burning pain or itch depending on whether it is applied to the skin in a diffuse or punctate

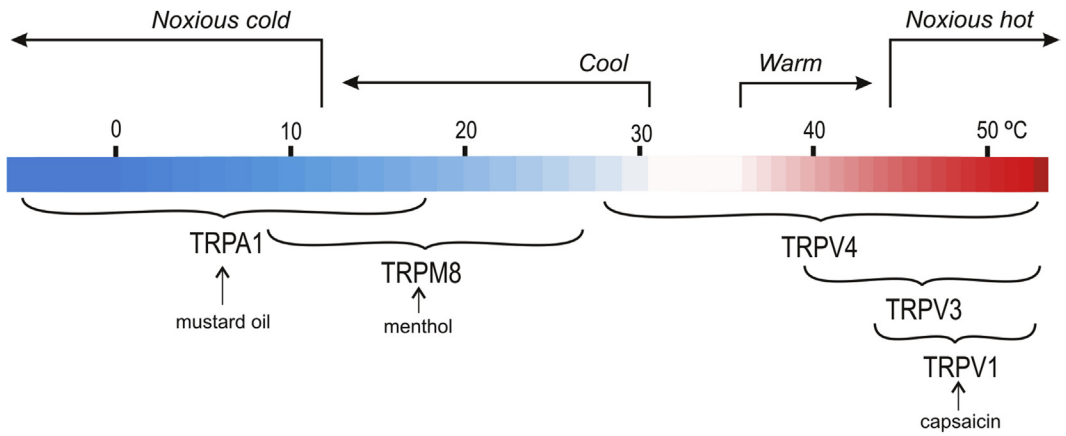


FIGURE 23.5 Thermal stimuli are sensed by transient receptor potential (TRP) channels tuned to different temperature ranges. Many of the channels also respond to chemicals. Temperature ranges associated with the sensation of noxious cold, cool, warm, and noxious hot are indicated.

manner, respectively. Unlike most other primary afferents that are silent unless stimulated, many thermosensitive afferents spike spontaneously and can modulate their firing rate up *or down* in response to temperature changes.

Touch

Our sense of touch relies on low-threshold mechanoreceptors (LTMRs). These LTMRs are subdivided into slow adapting (SA), which spike repetitively during a sustained stimulus, and rapid adapting (RA), which spike only transiently during stimulus onset and offset; each of these classes is subdivided based on subtler features like the regularity of spiking. Fig. 23.6 summarizes the distinguishing physiological and anatomical characteristics of the different fiber types and their associated end organs. Glabrous skin, the non-hairy skin covering the palms and soles, is endowed with a high density of end organs that underlie the discriminative capacity of this sort of skin. Hairy skin has the same end organs with the exception of Meissner corpuscles but the hair follicles themselves are also innervated by sensory fibers.

Rapid adapting type 1 (RA1) afferents are Aβ fibers associated with Meissner corpuscles. *Meissner corpuscles* are specialized end organs formed from Schwann cells arranged as horizontal layers embedded into the connective tissue, perpendicular to the innervating fiber. Indentation of the skin deforms the Meissner corpuscle, causing action potentials in its associated RA1 fiber. RA1 afferents are most sensitive to light touch repeating at frequencies around 50 Hz, which is perceived as flutter (see later). Whereas RA2 afferents innervate a single Pacinian corpuscle, a single RA1 afferent can innervate 30–80 Meissner corpuscles. RA1 afferents are very sensitive to movement across their receptive field and are thus thought to play an important role in sensing texture and detecting slip (which is an important feedback signal when grasping an object).

Rapid adapting type 2 (RA2) afferents are Aβ fibers associated with Pacinian corpuscles. *Pacinian corpuscles* have an onion-like structure, with layered Schwann cells encasing the terminal of the sensory fiber. This layering is parallel to the axis of the fiber, unlike in Meissner corpuscles, and Pacinian corpuscles are also located much deeper in the skin. Pacinian corpuscles are most sensitive (ie, have the lowest threshold) to vibration at 250 Hz. *Vibration* is perceived as a continuous sort of buzzing in response to mechanical stimuli repeating at rates >100 Hz, consistent with the activation of RA2 afferents via Pacinian corpuscles, whereas *flutter* is perceived as discontinuous (albeit rapid) tapping in response to mechanical stimuli repeating at rates <100 Hz, consistent with the activation of RA1 afferents via Meissner corpuscles (see Fig. 23.2). Impressively, RA2 afferents can fire at rates exceeding 500 Hz, thus allowing one spike per stimulus cycle such that stimulus frequency can be encoded by firing rate. That said, downstream neurons cannot fire at such high rates, which implies that the neural code for vibration must change as the signal passes from primary afferents to higher-order, central neurons. The receptive field of RA2 afferents is large due to the deep placement of Pacinian corpuscles within the dermis of the skin, which is consistent with our rather poor ability to localize vibratory stimuli.

Slow adapting type 1 (SA1) afferents are Aβ fibers associated with Merkel cells. *Merkel cells* are located near the basal layer of the epidermis. In glabrous skin, Merkel cells are located on rete ridges (epidermal thickenings that extend downward between the dermal papillae), while in the hairy skin, Merkel cells form touch domes. Merkel cells communicate with SA1 afferents through synapse-like contacts. Both Merkel cells and their innervating fibers are mechanosensitive but Merkel cells are now known to be primarily responsible for transducing the sustained component of the signal (ie, pressure), whereas SA1 afferents respond directly to the dynamic component of the signal. In other

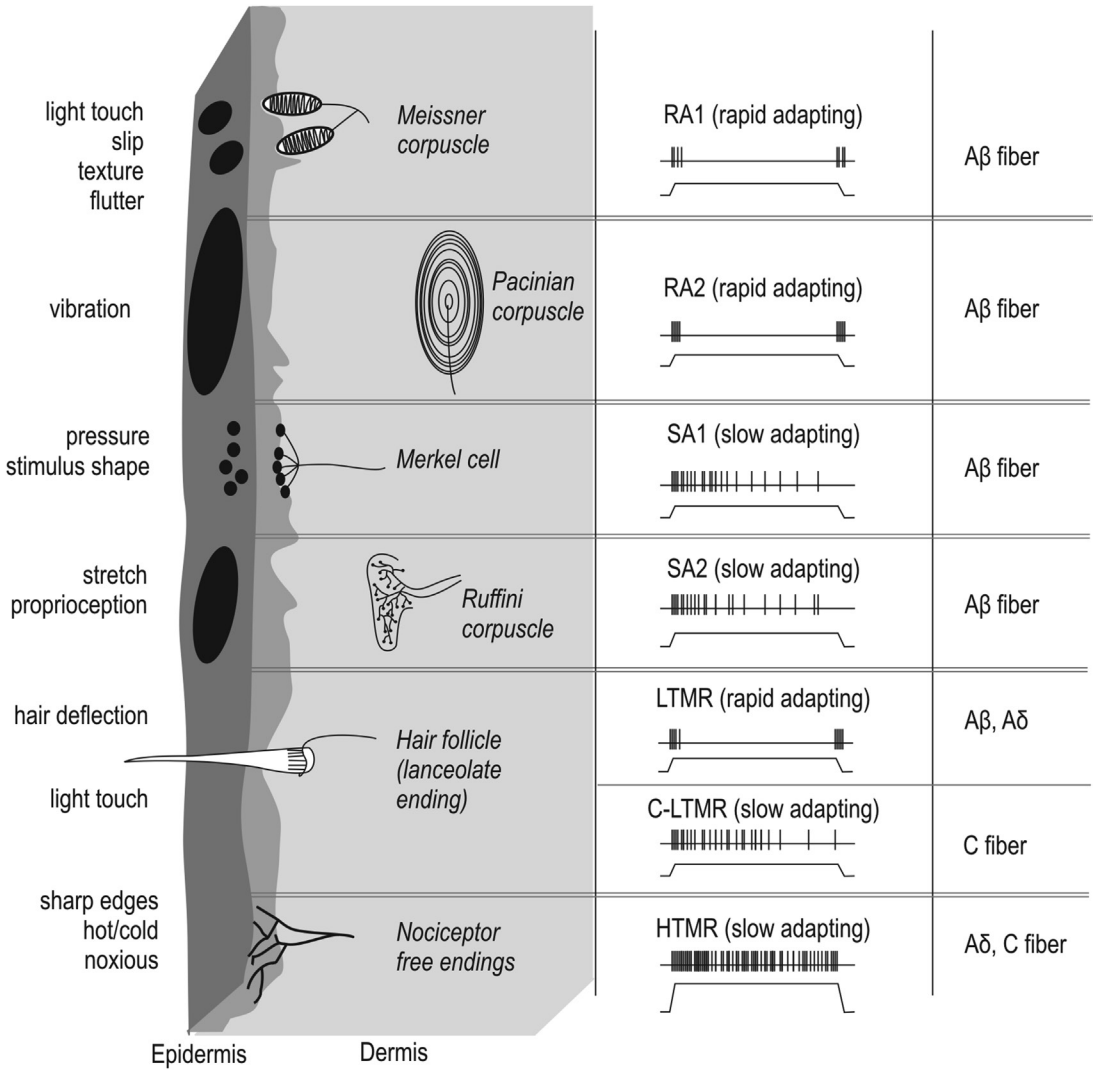


FIGURE 23.6 Skin is innervated by primary sensory fibers capable of detecting different aspects of mechanical stimulation based on their association with distinct end organs. Spiking patterns fall in two broad categories: slow adapting in which spikes occur throughout the stimulus and rapid adapting in which spikes occur at the stimulus onset and offset. Stimulus waveform is shown below each spiking response. *HTMR*, high-threshold mechanoreceptor; *LTMR*, low-threshold mechanoreceptor.

words, chemical transmission from the Merkel cell to the sensory fiber encourages the fiber to spike repetitively during sustained indentation, thus allowing that indentation to be encoded by the firing rate of SA1 afferents. Among the touch receptors, SA1 afferents have the highest spatial acuity and tend to respond strongly to edges and corners, which makes them a prime candidate to encode stimulus shape.

Slow adapting type 2 (SA2) afferents are Aβ fibers associated with Ruffini endings located deep in the skin. *Ruffini endings* are

spindle-shaped cylinders that resemble Golgi tendon organs. Compared with SA1 afferents, SA2 afferents are less sensitive to skin indentation but more sensitive to skin stretch, and their receptive field is also several times larger. SA2 afferents are also sensitive to hand shape, which suggests a role in proprioception. Skin stretching normally results from shear force (ie, acting parallel to the skin surface), whereas indentation results from compressive force (ie, acting perpendicular to the skin surface). Encoding shear force is distinct from detecting movement across the skin (ie, slip), which is ascribed to RA1 afferents, but both senses provide important sensory feedback for modulating the grip when handling an object.

This discussion of fiber types and their association with certain sensations must be placed in context. For experimental purposes, stimuli can be designed to preferentially activate a certain type of end organ and the associated sensation can be ascertained. However, under natural conditions, complex stimuli co-activate sets of differently tuned afferents and the resulting sensation depends not on which one type of afferent is activated but, instead, on which combination is activated. Textures—the smoothness of silk or the roughness of wool—are good examples of complex stimuli whose encoding depends of multiple types of afferents. The fact that stimuli co-activate different afferents becomes even more obvious when considering the hairy skin, where each hair follicle is itself a specialized mechanosensory organ innervated by >1 type of afferent.

In mammals, there are three types of hairs: guard (or tylotrich), awl/auchene, and zigzag. The distinction is important insofar as the follicle of each hair type is innervated by a different complement of sensory fibers, which can include Aβ, Aδ, and C fibers. Guard hair follicles are innervated by Aβ fibers; awl/auchene hair follicles are innervated by Aβ, Aδ, and C fibers; and zigzag hairs are innervated by Aδ and C fibers. In each of the aforementioned cases, the fibers form *longitudinal lanceolate endings*, which are fence-like structures involving Schwann cells, that transduce hair deflection into an RA spiking response. In the case of Aδ fibers, their response to hair deflection is direction sensitive because their longitudinal lanceolate endings are not evenly distributed around the follicle. Each type of hair follicle is also innervated by fibers that form circumferential endings around the hair follicle, but the response properties of such fibers remain unknown. It should be emphasized that the C fibers innervating hair follicles are indeed LTMRs and are thought to underlie tickle and affective or emotional touch (as opposed to discriminative touch). C-LTMRs are absent from glabrous skin. In hairy skin, Merkel cells are concentrated in touch domes located near the top of guard hair follicles, and serve to translate guard hair deflection into a sustained (SA1-like) spiking response in the associated Aβ fibers. An important point alluded to at the end of the preceding paragraph is that stimulation of a single hair will necessarily co-activate the multiple fiber types innervating that hair. Moreover, a realistic stimulus that affects different types of hairs will activate an even larger array of fiber types, arguing that one's perception of a somatosensory stimulus depends not on any one fiber type, but, rather, on an orchestra of different fiber types.

The search for the ion channel(s) responsible for transducing mechanical forces into a receptor potential has been a difficult one. Certain channels like TRPA1 have been implicated in mechanotransduction but turned out to be only indirectly involved. There are several mechanically sensitive ion channels that could, in theory, act as the transducer but recent evidence points most convincingly to Piezo channels in the case of mammalian touch. Piezo2 is expressed in mechanosensitive afferents and in Merkel cells, which, as explained, help shape the responses of SA1 afferents. Piezo proteins oligomerize, forming a huge, mechanically activated channel complex estimated to have between 120 and 160

transmembrane segments. Mechanotransduction in other tissues is critical for proprioception, visceral sensations, such as bloating and pain, and blood pressure regulation (by baroreceptors), not to mention transduction in the auditory and vestibular systems. The molecular identity of the mechanotransducer in these other cases remains uncertain.

Nociception

Nociceptive pain is pain originating from the activation of high-threshold afferents known as *nociceptors*. Pathological forms of pain can occur without nociceptor activation, but we will defer discussion of those pathological conditions until later and focus here on high-threshold fibers activated by mechanical, thermal, and/or chemical stimuli. By definition, nociceptors have a high activation threshold, which is to say that they are activated only by intense (ie, noxious) stimuli that risk causing tissue damage. Nociceptors often correspond to C fibers, but can also be Aδ or even Aβ fibers; it should be clear from previous discussion that not all C fibers are nociceptors. The sharp pain felt almost instantaneously upon stubbing your toe is mediated by A fibers, whereas the slightly delayed but longer lasting pain is mediated by C fibers (see Fig. 23.4). Unlike LTMRs, which are associated with specialized end organs, nociceptors have free nerve endings (see Fig. 23.6). Mechano-nociceptors are activated uniquely by strong mechanical stimulation, especially sharp edges or points. Thermo-nociceptors are activated uniquely by noxious hot or cold (see section: Thermoception). Polymodal nociceptors respond to noxious mechanical, thermal, and chemical stimulation. Skin, muscles, joints, and many other tissues are innervated by nociceptors.

Itch

Also known as pruritus, itch is best described as an irritating cutaneous sensation that elicits the desire to scratch. This is distinct from pain, which tends to elicit withdrawal, yet both are protective. Itch originating in the skin is known as pruritoceptive itch and can be evoked by chemical, mechanical, thermal, or electrical stimulation. The sensation of itch relies on C fibers terminating superficially within the skin. Histamine, whether injected intradermally or released from mast cells (as occurs during an allergic reaction), activates a subset of C fibers that express histamine receptors. These particular C fibers are mechanically insensitive but respond to chemicals like capsaicin and mustard oil that normally elicit pain. Interestingly, capsaicin elicits different sensations depending on how it is applied to the skin, with punctate application evoking itch and diffuse application evoking burning pain. This contradicts the simplistic notion that specific C fibers underlie the sensation of each, and argues in favor of a more sophisticated neural coding scheme that remains as yet unclear. Like with pain (see section: Neuropathic Pain), abnormal neural processing can result in neuropathic itch, which occurs in the absence of a pruritogenic stimulus. The responsible changes can occur in the peripheral nervous system (PNS) or CNS. Unresponsive to interventions that would normally soothe pruritoceptive itch, neuropathic itch can be very difficult to treat and, undiminished by scratching, can lead to significant skin lesions and discomfort.

Visceral Sensations

Sensations originating from the viscera (ie, internal organs) differ from the skin, muscle, and joints. For instance, we can identify the location of cutaneous stimuli very precisely, and although we are less precise in localizing muscle or joint stimuli, visceral inputs are especially diffuse and poorly localizable. This results from a relatively small number of sensory neurons (mostly C fibers with free nerve endings) innervating large areas of a given organ, and

branching extensively within the spinal dorsal horn to connect with many second-order neurons. Convergence of visceral and somatic inputs onto common second-order neurons can lead to referred pain (see section: Nociceptive Pain). Beyond pain, visceral sensations include dyspnea (shortness of breath), nausea, and bloating/distension, all of which function as warning signals yet are distinct from somatic sensations; the viscera do not give rise to sensations of touch, vibration, hot, or cold. Most mechanosensitive visceral afferents have low activation threshold but can encode (ie, continue to increase their firing rate) into the noxious range. These and other afferents that are normally unresponsive—referred to as "silent" nociceptors—can be sensitized by inflammation and presumably by other factors. This sensitization plays a significant role in dysfunctional pain syndromes, such as irritable bowel syndrome and painful bladder syndrome (interstitial cystitis). Parenchymous viscera like the liver and pancreas to not give rise to pain unless there is inflammation or involvement of the organ capsule. Likewise, the brain is insensate; electrically stimulating sensory areas can evoke sensations felt in the body part represented by stimulated neurons, but this is not equivalent to sensing the electrical stimulus as an electric shock to the brain. On the other hand, stimulation of the dura mater is painful and the sensitization of dural afferents contributes to headache and migraine.

CENTRAL PATHWAYS

As already explained, the cell body of each first-order sensory neuron is located in a DRG or trigeminal ganglion. Those ganglia contain only sensory neurons. One branch of each sensory neuron projects peripherally via a peripheral nerve, often joined by motor and autonomic fibers. The other branch projects centrally via a dorsal root, entering the brainstem (for afferents from the trigeminal ganglia) or spinal cord (for afferents from the DRG). Upon entering the CNS, different fiber types follow different routes. Aα fibers from golgi tendon organs connect directly to motoneurons in the ventral horn of the spinal cord, creating a monosynaptic circuit responsible for stretch reflexes. A variety of fibers enter the spinal dorsal horn, forming synapses on second-order, spinal neurons. Certain fibers ascend ipsilaterally, forming synapses in the dorsal column nuclei located in the medulla. Fig. 23.1 illustrates the major ascending pathways. The schematic in Fig. 23.7 highlights key cortical areas and subcortical structures, the organization and function of which are discussed further.

Anterolateral Pathway

Fibers branch upon entering into the spinal cord, sending collaterals a few spinal segments rostral and caudal to their entry level via Lissauer's tract. The dorsal (or posterior) horn is divided in six layers (laminae) of grey matter, with numbering starting at the dorsal-most edge. Different fiber types terminate in different lamina: fibers carrying noxious and thermal information tend to terminate superficially, in laminae 1 and 2, whereas fibers carrying low-threshold mechanosensory information terminate more deeply. All layers except lamina 2 (also known as the substantia gelatinosa) contain projection neurons that take input from primary sensory neurons, directly and via excitatory interneurons, and relay that information to the thalamus and other supraspinal targets. Those project neurons cross to the other side of the spinal cord and then ascend in the anterolateral section of the spinal cord white matter. Notably, projection neurons constitute a relatively small proportion of all neurons in the dorsal horn, the majority being local (segmental) excitatory or inhibitory interneurons. The variety of interneuron types and how they are synaptically interconnected are still an active area of research. That said, it is important to appreciate

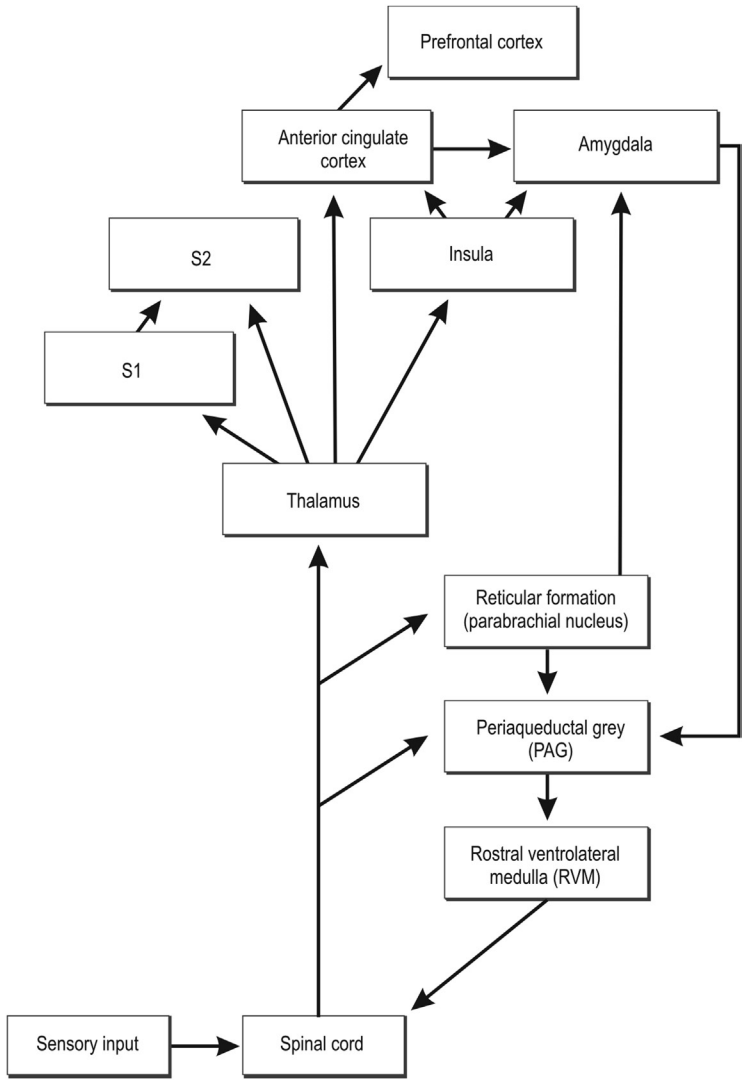


FIGURE 23.7 Schematic illustrating the key subcortical and cortical areas involved in processing ascending somatosensory information and for mediating descending modulation. *S1*, primary somatosensory cortex; *S2*, secondary somatosensory cortex.

the crucial role of synaptic inhibition in modulating the transmission of information through dorsal horn circuits.

Both gamma-aminobutyric acid (GABA) and glycine are used as inhibitory neurotransmitters in the spinal dorsal horn. In addition to being expressed on spinal neurons (see later), $GABA_A$ receptors are present "presynaptically," on the central terminals of primary sensory neurons. Because primary sensory neurons maintain a high intracellular chloride concentration, activation of presynaptic $GABA_A$ receptors causes depolarization; in contrast, $GABA_A$ receptor activation causes hyperpolarization in most

central neurons because those neurons maintain a lower intracellular chloride concentration. However, primary afferent depolarization (PAD) is nonetheless inhibitory because it tends to reduce the excitability of the central terminals (by inactivating sodium channels and otherwise impeding spike propagation) so that less transmitter is ultimately released. Activation of the $GABA_A$ and glycine receptors on spinal neurons hyperpolarizes those neurons, or at least it reduces the depolarization caused by excitatory (ie, glutamatergic) input, which is referred to as shunting. Pharmacological blockade of synaptic inhibition in the spinal dorsal horn causes severe pain and hypersensitivity, consistent with the Gate Control Theory of pain (see Box 23.1), and as one might expect, inhibition is pathologically reduced in neuropathic pain conditions. Inhibition should not, however, be thought of as a simply gating the transmission of information through the spinal cord; instead, synaptic inhibition contributes to subtler yet important computations, such as shaping receptive fields by creating inhibitory surrounds (see Fig. 23.3).

Projection neuron axons ascend contralaterally in the anterolateral quadrant of the spinal cord. Some axons project to the thalamus, whereas others terminate in the brainstem. These tracts are named according to their origin and their target. The spinothalamic tract connects to third-order neurons in thalamus that project to the cerebral cortex, where continued processing of the signal ultimately leads to perception. The spinoreticular tract ends in the reticular formation of the medulla and pons, from which information is relayed to thalamus and elsewhere. Located in the reticular formation, the parabrachial nucleus routes information to the periaqueductal gray (PAG), amygdala, and hypothalamus. The spinomesencephalic tract ends near the midbrain tectum and PAG, where descending pathways that modulate function in the spinal cord originate (see section: Descending Modulation).

Dorsal Column–Medial Lemniscal Pathway

Many Aβ fibers ascend ipsilaterally in the dorsal columns, although they still give off collaterals that enter the spinal cord grey matter near the spinal segment where the fiber first enters. The dorsal column on each side includes the gracile fascicle, which is located medially and carries fibers from the lower limb and trunk, and the cuneate fascicle, which is located laterally and carries fibers from the upper limb and neck. The fibers terminate in the gracile and cuneate nuclei, respectively, which together constitute the dorsal column nuclei. Second-order neurons whose cell bodies are in the dorsal column nuclei send axons across the midline and up the medial lemniscus pathway to the thalamus. Like for the first synaptic relay point in the spinal dorsal horn (for the anterolateral pathway), there are interneurons in the dorsal column nuclei that process the incoming information before it is conveyed to the thalamus.

The Aβ fibers ascending in the dorsal columns carry information about proprioception and touch. By comparison, the fibers ascending in the anterolateral tract carry information mostly about pain, temperature, and crude touch. The separation is not complete but it is significant enough to be clinically recognizable in patients who experience hemisection of their spinal cord. The outcome, which is termed Brown–Séquard syndrome, is characterized by loss of fine touch and vibration sensation as well as proprioception ipsilateral to the injury, plus loss of pain, temperature, and crude touch sensation contralaterally. This results from interrupting the ascending pathways before or after the cross-over point (ie, decussation) of the ascending fibers—the dorsal column-medial lemniscal pathway decussates at the level of the medulla, whereas the anterolateral pathway decussates near the spinal levels where the afferent fibers arrive. Notably, pain and temperature sensation is often spared for the two or three

segments immediately below (ie, caudal to) the lesion because primary afferents send collaterals this number of segments rostral, thus bypassing damage to the anterolateral tract on the contralateral side. Ipsilateral paralysis also occurs due to interruption of descending motor fibers.

Thalamic and Cortical Regions Involved in Somatosensation

The ascending fibers in the medial lemniscus terminate mostly in the ventral posterior nuclei of the thalamus, with inputs from the face in the medial division (ie, ventral posterior medial) and inputs from the rest of the body arriving in the lateral division (ie, ventral posterior lateral). Ascending fibers in the spinothalamic tract of the anterolateral system terminate mostly in ventral posterior nuclei, intralaminar nuclei, and posterior nuclei. Fibers from ventral posterior nuclei project to primary somatosensory cortex (S1), fibers from the posterior nuclei project to secondary somatosensory cortex (S2), while those from the intralaminar nuclei project elsewhere in cortex and to the basal ganglia. Somatosensory information can arrive in the cortex after crossing as few as two synapses but, as already explained, significant processing occurs prior to the signal arriving in cortex and the information is, evidently, broadcast to multiple cortical (and subcortical) areas. Moreover, despite ascending signals being partitioned between the dorsal column-medial lemniscus and anteroloateral pathways, to some extent, these signals re-converge in thalamus and cortex. The processing that occurs within the cortex is remarkably complex and not yet fully understood. Neocortex is organized into six layers, with thalamic input arriving primarily in layer 4 before being sent up to layer 3 and down to layer 5. In addition to processing the information with local microcircuits, neurons in superficial layers communicate directly with other areas of cortex while neurons in deeper layers send information back to thalamus and other areas outside cortex. Neurons with similar response properties (eg, rapid-adapting vs. slow-adapting) tend to be organized as columns that span across the layers.

Primary somatosensory cortex (S1) is located in the postcentral gyrus. It comprises four areas known as Brodmann's areas 1, 2, 3a, and 3b. Each area is somatotopically organized, meaning that the (contralateral) body surface maps in a spatially organized way to the cortex. This is often represented as a homunculus (little man) reclined across the cortex, with his foot positioned medially and his face more lateral. Notably, the amount of cortex dedicated to a certain body region is not proportional to the surface area of that region but, instead, is proportional to its innervation density and tactile acuity. Hence, the hands and face, which are densely innervated, are allotted more cortical real estate than the torso. This somatotopic organization is hinted at by the sequence of body regions affected during a Jacksonian seizure, with numbness progressing across one half of the body, from the fingers to the toes, as epileptiform activity shifts medially across the contralateral somatosensory cortex. Yet another complete representation of the body surface is present in the secondary somatosensory cortex (S2), which is located just posterior and lateral to S1. It should be noted that other areas of cortex, such as the insula and anterior cingulate are particularly important for pain, especially the affective/motivational aspects of pain. Lesioning connections to the frontal lobes (ie, lobotomy) was very effective in relieving the suffering caused by chronic pain (but had other significant negative effects). To be clear, lobotomized patients could still sense pain but did not perceive it as something unpleasant. The affective component of the pain experience—its unpleasantness—is ultimately what makes pain "pain." These sorts of clinical observations point to the importance of cortical processing for ultimately generating what we think of as true pain.

Descending Modulation

The PAG receives bottom-up signals from the spinal cord and top-down signals from the cortex. The PAG in turn connects to the rostroventral medulla (RVM), which sends fibers down the spinal dorsal horn, thus forming a feedback loop. Releasing serotonin, noradrenaline, and GABA, these descending fibers modulate the activity of spinal neurons, thereby modulating the ascending signals carried by spinal projection neurons. Neurons of the PAG and RVM both express opioid receptors, the activation of which by opiates like morphine produces analgesia by engaging the descending modulatory pathways. Opioid receptors are also present on certain spinal neurons. The endogenous opioids enkephalin and dynorphin are expressed by neurons in the RVM, PAG, and spinal cord. This provides for powerful endogenous modulation that can be engaged during fight-or-flight situations, such as in the heat of battle. This modulatory system is also important for the placebo effect, and for the emotional and attentional modulation of pain based on top-down signals from cortex. The direct engagement of descending modulation by bottom-up signals is illustrated by the phenomenon known as *diffuse noxious inhibitory control (DNIC)*: if a painful test stimulus is applied in the presence of a second painful (conditioning) stimulus applied elsewhere on the body, the test stimulus will feel less painful than if the test stimulus were applied alone. This spatially diffuse form of counter-irritation, whereby pain inhibits pain, involves the descending modulatory pathways described before. Although the activation of opioid receptors (by endogenous or exogenous ligands) causes powerful analgesia under normal conditions, this modulation becomes less effective under neuropathic conditions, for example, DNIC is reduced in patients with neuropathic pain. Opioids tend to be less effective against neuropathic pain and, paradoxically, can exacerbate pain under certain conditions. These changes seriously compromise our ability to treat neuropathic pain.

TYPES OF PAIN

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is a subjective experience that depends on sensory input and how that input is processed by the nervous system—from the transduction step in primary afferent neurons to complex distributed processing within neocortical networks. Pain can serve as a diagnostic tool, providing critical information about underlying diseases or injury, but pain can also be a difficult clinical problem in its own right. We distinguish between three types of pain on the basis of mechanistic differences—nociceptive pain, inflammatory pain, and neuropathic pain. Pain can be described in many other ways, including its duration—acute vs. chronic—and anatomical origin—somatic vs. visceral. Many of these descriptors are relatively self-explanatory but a number of noteworthy concepts will be introduced in the following text.

Nociceptive Pain

Nociceptive pain is the normal response to noxious (intense) stimulation. This type of pain can range from sharp, pricking, or shock-like to dull, aching, or burning depending on the responsible stimulus. Nociceptive pain is predictably initiated by the activation of nociceptors, which as explained in section "Nociception," are primary afferent neurons with a high activation threshold. Sharp pain is due to the activation of myelinated (mostly Aδ) nociceptors, whereas dull, aching pain is due to activation of unmyelinated (C) nociceptors (see Fig. 23.4). Nociceptor activation initiates protective withdrawal

reflexes and draws our immediate attention, which helps us learn which stimuli are dangerous and should, in future, be avoided—the motivation to avoid pain is a strong one. In other words, nociceptive pain acts as an important alarm system, alerting us to danger and helping teach us what to avoid in the future. Such pain also warns us about internal problems, from cardiac ischemia to a burst appendix. The importance of this alarm system is illustrated by individuals with congenital insensitivity to pain who, in the absence of pain, sustain repeated injury and fail to seek medical attention, oblivious to infection and other conditions that would normally manifest pain.

Nociceptive pain continues only as long as the noxious stimulus is maintained. That said, sustained or recurrent noxious stimulation can occur in certain disease states like osteoarthritis, where changes in the joint can allow normal weight bearing to produce forces sufficient to activate nociceptors. While nociceptive pain originating from the skin can usually be well localized, enabling you to escape from or remove the noxious stimulus, nociceptive pain originating from deeper structures, including muscle and viscera, tends to be more diffuse and may in fact be very difficult to localize. *Referred pain* is pain attributed to somewhere on the body surface despite the noxious stimulus originating in a deep structure. In cardiac ischemia, for example, the noxious input (ie, ischemia) is detected by fibers innervating the heart but the tightness and crushing pain is felt in the chest and down the left arm. This pattern is no coincidence, as the sensory input from these regions of the body surface and sensory input from the heart both arriving in the lower cervical and upper thoracic levels of the spinal cord (Fig. 23.8). Certain projection neurons receive convergent input from skin and deep structures, but their activation is perceived as if stimulation originated from the skin (which is where most stimulation occurs). In the case of appendicitis, pain is initially felt near the umbilicus because both the appendix and umbilicus are innervated by sensory afferents entering the spinal cord as the T10 level; it is only when the adjacent peritoneum becomes inflamed that pain becomes more clearly localized to the right lower quadrant of the abdomen. It goes without saying that efficiently diagnosing a variety of conditions relies on learning the patterns of referral, which is facilitated by understanding the underlying anatomy.

Inflammatory Pain

Inflammatory pain refers to increased sensitivity due to the inflammatory response associated with tissue damage. Under these sensitized conditions, an innocuous stimulus can be perceived as painful—this is known as *allodynia*—and the pain evoked by a noxious stimulus is exaggerated in both amplitude and duration—this is known as *hyperalgesia*. These two forms of hypersensitivity do not necessarily reflect changes in the same neurons and, moreover, can apply to mechanical or thermal stimulation. After a bad sunburn, for example, clothes brushing lightly against your skin or a lukewarm shower can be painful, while a slap or hot shower can be downright excruciating. Inflammatory pain serves not so much as an alarm, but more as a reminder of recent injury, discouraging activities that risk reinjury so that recovery can proceed quickly.

Primary hyperalgesia refers to hypersensitivity at the site of injury, within the area of inflammation, whereas secondary hyperalgesia refers to hypersensitivity extending outside the area of injury. Primary hyperalgesia is a direct consequence of *peripheral sensitization*, the process whereby inflammatory mediators and other local factors—prostaglandin, bradykinin, cytokines (eg, interleukin), histamine, serotonin, protons, potassium, ATP, glutamate, and so on—trigger intracellular signaling pathways in the peripheral terminals of primary afferents, leading to changes in the function and/or expression of receptor molecules and voltage-gated ion channels, which ultimately causes those afferents to

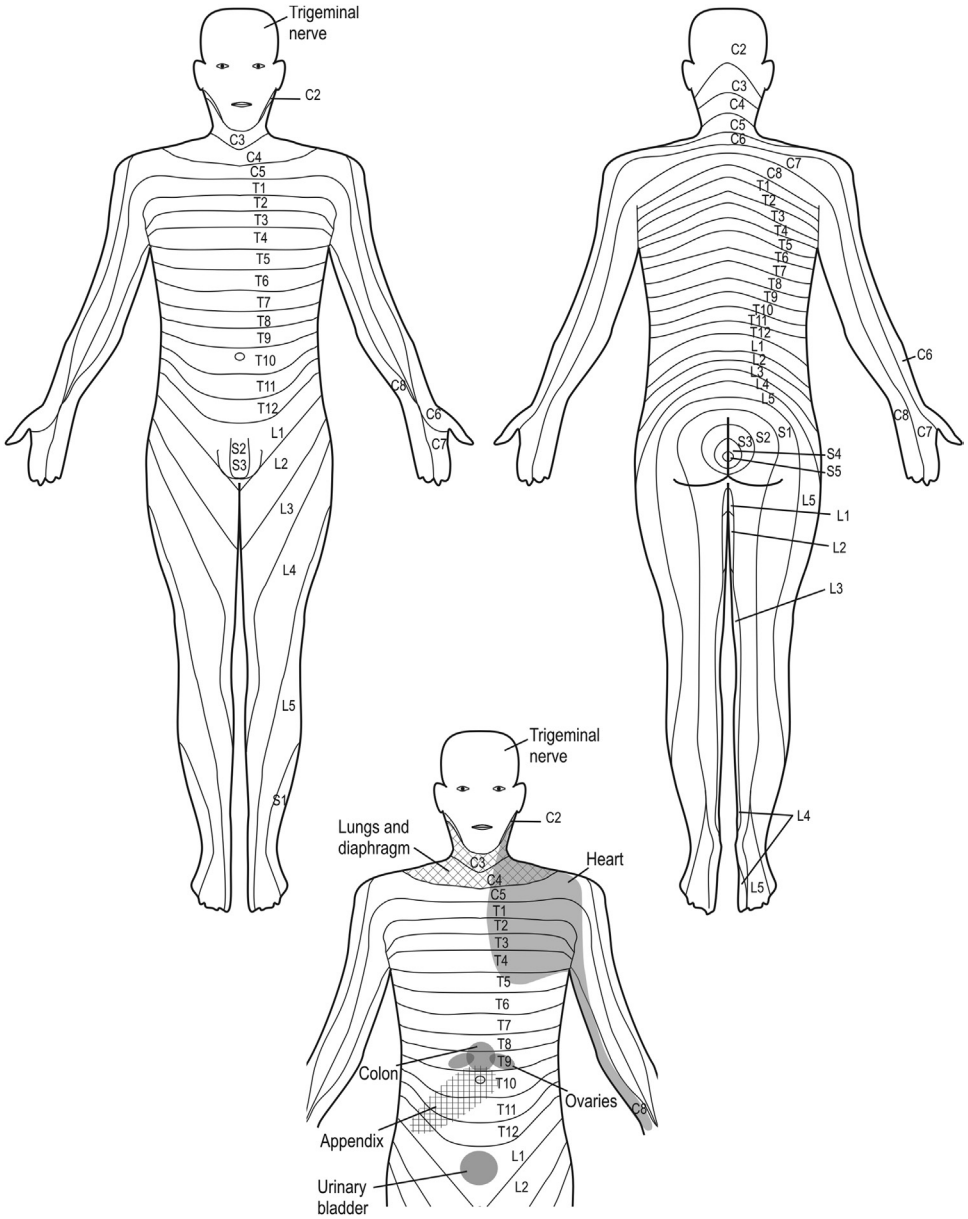


FIGURE 23.8 Each dermatome represents the body surface area innervated by primary afferents originating from a given pair of dorsal root ganglia (DRG) and projecting to the corresponding spinal segment. The face and other cranial tissues are innervated by afferents from the trigeminal ganglia. Primary afferents innervating internal organs often converge onto spinal neurons that also receive input from the body surface. This can result in pain that is referred (sensed in) the dermatomes corresponding to the spinal segments in which convergence occurs. *C*, cervical; *L*, lumbar; *S*, sacral; *T*, thoracic.

become hyperresponsive to stimulation. Notably, peptidergic C fibers can release substance P and calcitonin gene–related peptide (CGRP) from their peripheral terminals, causing *neurogenic inflammation*, thus forming a nasty positive feedback loop. Through a phenomenon known as an *axon reflex*, in which spikes initiated in one fiber branch propagate antidromically down neighboring fiber branches, neurogenic inflammation can extend throughout the receptive field of a peptidergic C fiber. The hypersensitivity can spread even further through the effects of *central sensitization*, which involves synaptic plasticity and other changes in the downstream central circuits. Synaptic plasticity and numerous other changes contribute to making the pain persistent but, generally speaking, inflammatory pain persists only as long as the inflammation. Reducing the inflammation is therefore a logical way to reduce the pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin block the synthesis of prostaglandins and thromboxanes via the enzyme cyclooxygenase.

Neuropathic Pain

Neuropathic pain refers to pain arising from damage to or dysfunction of the nervous system. The pathological changes responsible for this type of pain can occur in the PNS or in the CNS, originating from any one of a number of etiologies including trauma (eg, nerve compression and spinal cord injury), disease (eg, diabetes and multiple sclerosis), infection (eg, HIV, varicella zoster/shingles), and neurotoxic chemicals (eg, chemotherapeutic and antiretroviral agents). The pain occurs spontaneously, either as a persistent burning sensation or as a paroxysm (sudden burst); the intense electric shooting pains associated with trigeminal neuralgia and sciatica are two examples of paroxysmal pain. Neuropathic pain is also associated with hypersensitivity—allodynia and hyperalgesia—to mechanical and/or thermal stimuli. Ironically, the most obvious consequence of nerve damage is loss of function (negative symptoms), not gain of function (positive symptoms). Spontaneous pain, allodynia, and hyperalgesia are all positive symptoms. But in fact, quantitative sensory testing has clearly established that many patients with neuropathic pain also experience negative symptoms evidenced by sensory deficits. In other words, those with neuropathic pain are often less able to detect a light touch or subtle temperature change, but when the stimulus is detected, it is more likely to be mistakenly perceived as painful. Another notable feature of neuropathic pain is that it often takes days, or even weeks or months, to manifest following the injury or exposure responsible for the neural damage, although this long latency is less obvious when the underlying pathology is subtle and more protracted. The timescale suggests that neuropathic pain really represents the maladaptive response of the nervous system to damage, as opposed to the immediate consequence of that damage. The result is a difficult-to-treat mix of varied symptoms. It should also be recognized that many chronic pain conditions can involve more than one type of pain (eg, a neuropathic component and an inflammatory component); each component is liable to respond to different therapeutic interventions.

Dysfunctional pain refers to chronic pain conditions in which there is no noxious stimulus, no inflammation, and no damage to the nervous system; in other words, nociceptive pain, inflammatory pain, and neuropathic pain are all excluded. The caveat here is that ruling out inflammation and neural damage is difficult, especially since neural "damage" might occur in different ways and at many different spots throughout the nervous system. Indeed, dysfunctional pain syndromes, such as irritable bowel syndrome, painful bladder syndrome (interstitial cystitis), and fibromyalgia share certain features with neuropathic pain. Primary erythromelalgia and paroxysmal extreme pain disorder might be considered dysfunctional pain syndromes but, in both these cases, the cause of the pain has been traced back to mutations in NaV1.7 sodium channels, which are expressed in

primary sensory neurons. Although there is no damage per se, the channel mutation evidently alters how sensory information is processed and how it is ultimately perceived, which is the same problem as in neuropathic pain. Intriguingly, other mutations in the NaV1.7 channel are responsible for congenital insensitivity to pain.

NEUROPATHIC PAIN: AN UNMET CLINICAL CHALLENGE

For a given injury or disease, only a subset of unfortunate individuals will go on to develop chronic neuropathic pain. A person's genetic background is evidently very important but, with the exception of a few monogenic disorders, such as the channelopathies mentioned before, one's susceptibility to develop chronic neuropathic pain depends on numerous genes and environmental factors that interact in complex ways. Notably, sex is an important factor, with many chronic pain conditions being more prevalent in women than in men. The hope is to develop personalized, precise interventions that can alleviate neuropathic pain while leaving other sensations, including (beneficial) nociceptive pain, intact. We have a long way to go. Many patients, despite receiving the best available treatment, continue to experience unremitting pain and have significantly reduced quality of life because of it. According to a 2011 report from the Institute of Medicine, approximately 100 million adults in the United States suffer from chronic pain (much of which has a neuropathic component). Between the direct costs of treatment and lost productivity, chronic pain is estimated to cost $560–635 billion annually. This is a huge burden on the economy. The personal toll on those with chronic pain is incalculable. The reality is that despite intense research and the identification of many promising drug targets, development of new, more efficacious analgesics has been disappointingly slow.

Neuropathic pain is difficult to treat in part because it involves diverse pathophysiological changes occurring in both the PNS and CNS. In many cases, damage to primary afferents causes the surviving afferents to become hyperexcitable, spiking spontaneously and producing exaggerated responses to stimulation. Interestingly, Aβ fibers have been shown to underlie injury-induced mechanical allodynia. Whereas reducing the activation threshold of nociceptors would be a straightforward way to cause allodynia (by allowing innocuous input to produce a signal normally interpreted as pain), one would predict that enhancing the activation of Aβ fibers should evoke a sense of more intense touch, not burning pain. Furthermore, according to the gate control theory (see Box 23.1), touch is supposed to inhibit pain, not evoke it. This confusing situation points to changes in central processing. It is now firmly established that low-threshold afferents connect via polysynaptic pathways (ie, excitatory interneurons) to projection neurons that are normally activated only by high-threshold input. Those polysynaptic pathways are typically ineffective because of synaptic inhibition but, if that inhibition is compromised, the polysynaptic pathways can be opened and the resulting activation of ascending pathways causes the low-threshold input to be misperceived as painful. Notably, inhibition is reduced in many neuropathic pain conditions; however, inhibition can be reduced through different mechanisms, including reduced transmitter release and altered chloride regulation in the postsynaptic neuron. Correcting different disinhibitory mechanisms requires different therapeutic interventions, but it is not trivial to identify which disinhibitory mechanism is at play and which therapy to apply. Moreover, many other forms of plasticity occur at synapses and within individual neurons. That plasticity is driven (or at least accompanied) by a pronounced neuroimmune response. Reversing these changes has proven extremely difficult.

There is good evidence that abnormal input from hyperexcitable afferents initiates and helps maintain the downstream changes occurring in the spinal cord. Indeed, blocking this afferent

input can relieve or significantly attenuate many instances of neuropathic pain. This provides significant motivation to try to therapeutically modulate afferent excitability. Nerve blocks using local anesthetics can provide relief but ideally one would reverse hyperexcitability rather than block all activity. It should be mentioned that the antiepileptic drug Carbamazepine, which acts by stabilizing the inactivated state of voltage-gated sodium channels, is effective against trigeminal neuralgia and is also used for other forms of neuropathic pain. There has been a major push to identify more selective blockers of ion channels, such as NaV1.7, but there is also reason to suspect that the therapeutic effects of very selective drugs will be circumvented by pathophysiological changes that involve up- or downregulation of several different ion channels. Some of the more recently developed drugs that are effective in reducing neuropathic pain—namely gabapentin, pregabalin, and ω-conotoxin—act via calcium channels involved in synaptic transmission.

Other commonly used pharmacological interventions include tricyclic antidepressants, SNRIs (serotonin–norepinephrine reuptake inhibitors), and opioids. As mentioned earlier, opioids tend to be less effective against neuropathic pain than they are against nociceptive or inflammatory pain; moreover, opioids have significant adverse effects and abuse potential that complicate their long-term use. There are also neuromodulation techniques, such as transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS). Both approaches involve stimulating primary afferents in order to engage inhibitory mechanisms in the spinal dorsal horn. In SCS, electrodes are placed over the dorsal columns in order to selectively activate myelinated sensory fibers (since those are the only fibers present in the dorsal columns). The spikes are conducted antidromically reaching caudal segments of the spinal cord via collaterals. The SCS-evoked paresthesia (sensation of "pins and needles") is used to help position the stimulating electrodes so that inhibition is engaged in the correct spinal segments, but that paresthesia can itself be unpleasant and the analgesic effects of SCS often decrease over time. New variations of SCS avoid causing paresthesia by applying short electrical pulses at very high frequency, but the mechanism by which this reduces pain remains unclear. Other therapies, from acupuncture to relaxation, are also beneficial. A comprehensive treatment plan will consider all of these options, combining interventions in ways that maximize benefit (ideally through synergistic interactions) while minimizing adverse effects. The problem is that without more effective treatment options, even the best treatment plans tend to fall short of providing adequate pain relief.

Despite the emphasis on pathological changes occurring in the peripheral and spinal cord, one must bear in mind that chronic pain is associated with changes through the somatosensory system. In fact, structural changes in the neocortex of chronic pain sufferers are well documented and are correlated with psychological changes. Descending modulatory systems are also compromised. With so many different changes occurring, it is difficult to disentangle which contribute to the abnormal perception of the pain and which are simply correlated with that abnormal perception.

SUMMARY

Humans rely heavily on their visual and auditory systems to communicate and to interact with the world. Although less appreciated, somatosensation is also critical in many ways. Proprioception and touch are used subconsciously to coordinate movement and to manipulate objects. Our very survival relies on nociceptive pain to alert us to danger. But the perception of somatosensory input is not as simple as receiving a signal generated through activation of a certain receptor; instead, incoming signals are processed at multiple points within the circuit, which includes modulation by top-down signals (reflecting our expectations, mood, and so on) before it gives

rise to perception. If that processing goes awry, as in neuropathic pain, we can misperceive the lightest touch as excruciating pain. Our inability to alleviate such pain reveals the gaps in our current understanding of how somatosensory information is normally processed and how that processing becomes pathologically altered. These are intriguing basic scientific questions whose answers will have huge clinical implications for countless people suffering from chronic pain.

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