



# Nociceptors: the sensors of the pain pathway

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**Specialized peripheral sensory neurons known as nociceptors alert us to potentially damaging stimuli at the skin by detecting extremes in temperature and pressure and injury-related chemicals, and transducing these stimuli into long-ranging electrical signals that are relayed to higher brain centers. The activation of functionally distinct cutaneous nociceptor populations and the processing of information they convey provide a rich diversity of pain qualities. Current work in this field is providing researchers with a more thorough understanding of nociceptor cell biology at molecular and systems levels and insight that will allow the targeted design of novel pain therapeutics.**

## Introduction

Pain, as a submodality of somatic sensation, has been defined as a “complex constellation of unpleasant sensory, emotional and cognitive experiences provoked by real or perceived tissue damage and manifested by certain autonomic, psychological, and behavioral reactions” (1). The benefit of these unpleasant sensations, however, is underscored by extreme cases: patients lacking the ability to perceive pain due to hereditary neuropathies often maintain unrealized infections, self mutilate, and have curtailed life spans (2). Normally, nociception (see Glossary, Sidebar 1) and the perception of pain are evoked only at pressures and temperatures extreme enough to potentially injure tissues and by toxic molecules and inflammatory mediators. These high threshold physical and noxious chemical stimuli are detected by specialized peripheral sensory neurons (nociceptors). This is in contrast to the high sensitivity of visual, auditory, olfactory, taste, and somatosensory organs to their adequate stimuli. Pain is described as having different qualities and temporal features depending on the modality and locality of the stimulus, respectively: first pain is described as lancinating, stabbing, or pricking; second pain is more pervasive and includes burning, throbbing, cramping, and aching and recruits sustained affective components with descriptors such as “sickening” (3). The intensity of these global reactions underscores the importance of avoiding damaging situations for survival and maintaining homeostasis. As opposed to the relatively more objective nature of other senses, pain is highly individual and subjective (4, 5) and the translation of nociception into pain perception can be curtailed by stress or exacerbated by anticipation (6).

Here, we review the nociceptive aspect of pain perception, focusing on nociceptors innervating the skin and subserving exteroception of noxious stimuli. Discussion of the similarities and differences among cutaneous, visceral, muscle, and joint nociception can be found elsewhere (7–9). We provide an overview of how noxious stimuli are detected, encoded, and conveyed to the CNS. Since recent reviews have described in detail the molecules involved in detecting noxious stimuli (10–13) and contributing to protective mechanisms mediating enhanced pain at the site of injury (14), we take an integrative approach that highlights recently discovered cellular transduction/conduction mechanisms in the context of different nociceptor fiber types identified *in vivo* and *ex vivo*. We further discuss innovations using genetic and pharmacological tools that begin to address how particular nociceptor populations

contribute to the perception of specific pain qualities. Since maladaptive changes in normal physiological mechanisms underlie a variety of pathologies leading to chronic pain, a thorough understanding of nociception is required to identify the interventions most likely to provide therapeutic benefit.

## Anatomy and physiology of cutaneous nociception

Significant insights into the cellular and molecular basis of cutaneous nociception have been realized from studies on conscious humans and surrogate animal models (15, 16), although we are far from understanding the cell biology of pain perception. Advances are hampered by the difficulties inherent in studying neuronal processes in humans, cellular changes in nociceptors induced by invasive methods, the inability to record directly from the tiny structures where transduction of noxious stimuli occurs, and the uncertainty in model systems that an animal’s behavior is due to its perception of pain (15, 17). Although the morphology of sensory nociceptive nerve endings is highly conserved in animals from rodents to humans (5, 9, 17–19), cutaneous nociceptors are an extremely heterogeneous group of neurons housed in peripheral sensory ganglia located just outside the CNS that transduce external noxious stimuli in the skin, up to meters away from their cell bodies.

Minimally invasive extracellular single unit recordings from nerve fibers in peripheral nerves (microneurography) and skin-nerve preparations in mammals (20) and microneurography combined with psychophysical measurements in human subjects (15, 16, 21) have revealed the existence of distinct classes of nociceptor activated by noxious stimuli. Adequate stimuli include temperature extremes ( $> \sim 40^{\circ}\text{C}$ – $45^{\circ}\text{C}$  or  $< \sim 15^{\circ}\text{C}$ ), intense pressure, and chemicals signaling potential or actual tissue damage. Nociceptors are generally electrically silent (12) and transmit all-or-none action potentials only when stimulated. However, nociceptor activity does not per se lead to the perception of pain. The latter requires peripheral information to reach higher centers and normally depends on the frequency of action potentials in primary afferents, temporal summation of pre- and postsynaptic signals, and central influences (7).

The speed of transmission is directly correlated to the diameter of axons of sensory neurons and whether or not they are myelinated. Most nociceptors have small diameter unmyelinated axons (C-fibers) (12) bundled in fascicles surrounded by Schwann cells and support conduction velocities of 0.4–1.4 m/s (22) (Figure 1). Initial fast-onset pain is mediated by A-fiber nociceptors whose axons are myelinated and support conduction velocities of approximately 5–30 m/s (and in the slower A $\delta$  range) (22). Nociceptive fibers have been

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**Sidebar 1****Glossary**

**Action potential**, actively propagating electric signal along neuronal processes that enables communication to postsynaptic neurons in the pain pathway

**Allodynia**, pain evoked by a normally innocuous stimulus

**Antidromic**, transmission of action potentials against the peripheral to central direction

**Axon reflex**, the invasion of orthodromic (afferent) action potentials into other terminal branches of the same axon innervating the skin (antidromic, efferent) can cause the release of proinflammatory substances (e.g., peptides) from those peripheral terminals to have a local effect on nearby terminals and nonneuronal components including the vasculature

**Central sensitization**, changes in synaptic efficacy between sensory neurons and central (spinal dorsal horn) neurons that increase the perception of pain, especially in regions adjacent to the primary site of injury

**Fatigue**, a decrement in response to repeated stimuli applied to the receptive field of sensory cell

**Hyperalgesia**, an increase in the perception of pain elicited by a *noxious* stimulus; **Hyperalgesic**, a treatment that increases the sensitivity to noxious stimuli; **Primary hyperalgesia**, increased pain perception in area of injury or exposure to noxious stimulus; **Secondary hyperalgesia**, increased pain perception in the region surrounding the area exposed to a noxious stimulus. Can be associated with a decrease in threshold and/or increase in suprathreshold response

**Inflammatory pain**, pain associated with tissue injury and inflammation characterized by reduced threshold and increased responsiveness

**Low threshold A-fibers**, sensory neurons that innervate nonneuronal Merkel cells (A $\beta$ -LTM SA I), Meissner corpuscle (A $\beta$ -LTM FA I), Ruffini corpuscle (sensitive to stretch; A $\beta$ -LTM SA II), pacinian corpuscle (vibration; A $\beta$ -LTM FAII), and hairs (hair movement; G1 hair (A $\beta$ -LTM FA1), and Down (D-) hair (A $\delta$ -LTM))

**Mechanical stimulation**, punctate mechanical stimulation: measuring reflex responses to constant force applied by calibrated filaments (often by Von Frey hairs). Pinch: Randall-Selitto increases pressure to the paw or tail via a clamp system. 1 bar = 14.51 psi = 0.987; atm = 760 mm Hg (Torr) = 101,325 Pa (N/m<sup>2</sup>) = ~10 g/mm<sup>2</sup>. Ambient pressure on the skin at sea level is 1 bar (~10 g/mm<sup>2</sup>)

**Myelinated neurons**, neurons whose axons are wrapped within a membrane-rich myelin sheath that enables the action potential to jump between axonal nodes of Ranvier (myelin-free areas) to increase the speed of its propagation (conduction velocity)

**Neurogenic inflammation**, a general term used to describe the effects of the local release of inflammatory mediators such as substance P and CGRP from afferent nerve terminals

**Nociception**, the neural process of encoding and processing noxious stimuli

**Nociceptor**, a peripherally localized neuron preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged; capable of encoding stimulus intensities within the noxious range; may have a wide dynamic range of thresholds from innocuous to noxious range but stimulus-response relationship peaks in the noxious range; these also include those that are not activated immediately but become responsive to heat and mechanical stimulation upon prolonged stimulation

**Nocifensive behaviors**, “signs” of pain including “pseudoaffective reflexes” (e.g., withdrawal, jumping, contractures) and conditioned motor responses (e.g., escape, avoidance, aggressiveness). Immobility (a behavior that could allow the animal to preserve a painless posture) is often not scored (15)

**Noxious stimuli**, damaging or potentially damaging stimuli including extremes of temperature, mechanical stimulation, and allergens that provoke an avoidance response

**Nocisensor**, a molecule that detects noxious stimuli and transduces the stimulus to a cellular response

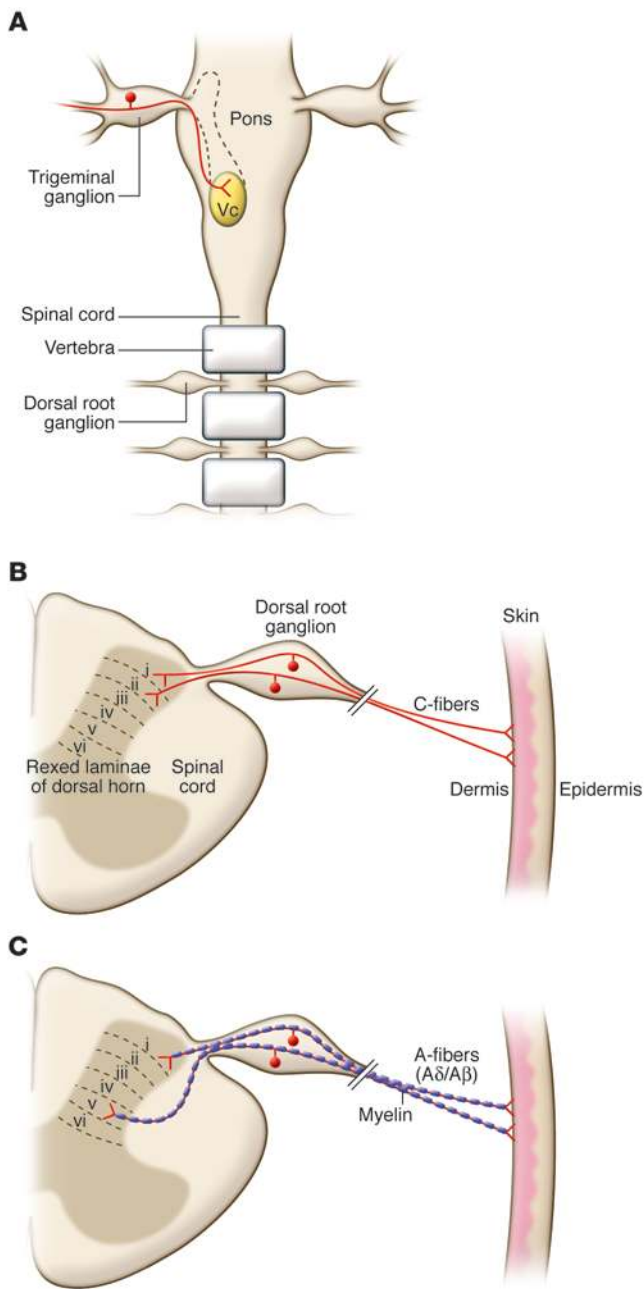
**Plasticity**, a dynamic modulation of signaling

**Receptive field (cutaneous)**, area of skin on which stimulation leads to response of a particular sensory neuron

**Receptor potential**, the change in membrane potential that occurs in the peripheral terminal due to transduction of a stimulus into ion flux, either through direct and/or indirect (through recruitment of second messenger cascades) modulation of ion channel activity

classified (23) on the basis of their conduction velocity and sensitivity and threshold to noxious mechanical (M), heat (H), and cold (C) (Tables 1 and 2) (9, 23). Units responding to thermal, mechanical, and chemical stimuli (polymodal) are the most common C-fiber type observed in fiber recordings (C-MH, C-MC, C-MHC) (7, 9, 24) (Table 1). The expression of differential repertoires of transduction molecules (particularly chemical sensors) confers a rich functional heterogeneity upon this class. The use of electrical stimulation to search for receptive fields, rather than mechani-

cal stimulation, identified nociceptors normally insensitive to mechanical and heat stimulation (silent; C-M<sub>i</sub>H<sub>i</sub>) that become sensitive to noxious mechanical or temperature only after being sensitized by inflammatory mediators (25, 26). C-fibers responsive to noxious heat (C-H; ~10% of C-nociceptors) play a major role in heat sensation (see below). A-fiber nociceptors are predominately heat- and or mechanosensitive (A-MH, A-H, A-M) (19, 27) (Table 2); however, sensitivity to noxious cold is also observed (27–29). Determining the contribution of each of these fiber types to pain



**Figure 1**

Anatomy of nociceptors. **(A)** Somatosensory neurons are located in peripheral ganglia (trigeminal and dorsal root ganglia) located alongside the spinal column and medulla. Afferent neurons project centrally to the brainstem (Vc) and dorsal horn of the spinal cord and peripherally to the skin and other organs. Vc, trigeminal brainstem sensory subnucleus caudalis. **(B)** Most nociceptors are unmyelinated with small diameter axons (C-fibers, red). Their peripheral afferent innervates the skin (dermis and/or epidermis) and central process projects to superficial laminae I and II of the dorsal horn. **(C)** A-fiber nociceptors are myelinated and usually have conduction velocities in the A $\delta$  range (red). A-fiber nociceptors project to superficial laminae I and V.

ized nonneuronal structures conferring high sensitivity to light touch, stretch, vibration, and hair movement are innervated by low threshold A-fibers (11). Nociceptive endings are in the vicinity of keratinocytes, mast cells, and Langerhans cells, indicating the capacity of peripheral sensory endings to monitor the status of the skin (31). Nociceptors, like other primary somatosensory neurons, are pseudounipolar (Figure 1): a single process emanates from the cell body in the dorsal root ganglion (DRG) or trigeminal ganglion (TG) and bifurcates, sending a peripheral axon to innervate the skin and a central axon to synapse on second-order neurons in the dorsal horn of the spinal cord or the trigeminal subnucleus caudalis (Vc) (13), respectively (Figure 1A). In this way, propagating electrical signals between periphery and spinal cord (or brainstem) follow a direct axonal pathway, thus reducing the risk of conduction failure (32). Nociceptors are excitatory neurons and release glutamate as their primary neurotransmitter as well as other components including peptides (e.g., substance P, calcitonin gene-related peptide [CGRP], somatostatin) important in both central synaptic signaling and efferent signaling in the skin (13). Invasion of action potentials into the nociceptor soma via the short stem axon (32) can lead to biochemical changes (e.g., phosphorylation and activation of MAPK superfamily of signaling pathways) that ultimately alter gene expression and functional phenotype (33, 34). Although it is thought that direct communication between the soma of primary sensory neurons does not occur, vesicle exocytosis is observed in dissociated soma and may influence associated Schwann cells and possibly nearby neurons (35, 36). The central axon of DRG neurons enters the spinal cord via the dorsal root and sprouts branches that innervate multiple spinal segments in the rostral and caudal direction as well as the segment associated with the particular DRG and dorsal column nuclei of the caudal medulla (7). They terminate predominantly in laminae I, II, and V of the dorsal horn on relay neurons and local interneurons important for signal modification (13, 37, 38) (Figure 1, B and C). The relay neurons project to the medulla, mesencephalon, and thalamus, which in turn project to somatosensory and anterior cingulate cortices to drive sensory-discriminative and affective-cognitive aspects of pain, respectively (38). Local inhibitory and excitatory interneurons in the dorsal horn as well as descending inhibitory and facilitatory pathways originating in the brain modulate the transmission of nociceptive signals, thus contributing to the prioritization of pain perception relative to other competing behavioral needs and homeostatic demands (39).

The cell body (soma) has served as an extremely useful model to study molecules and modulatory mechanisms mediating transduction of noxious stimuli, transmission of electrical signals to the CNS, and release of neurotransmitters and neuropeptides

perception requires an understanding of the molecular mechanisms underlying the detection of particular stimulus modalities and nociceptor connectivity in central circuits.

Noxious stimuli are transduced into electrical signals in free “unencapsulated” nerve endings that have branched from the main axon and terminate in the wall of arterioles and surrounding connective tissue, and may innervate distinct regions in the dermis and epidermis (17, 30). The endings are ensheathed by Schwann cells except at the end bulb and at mitochondria- and vesicle-rich varicosities (17). A-fibers lose their myelin sheath and the unmyelinated A-fiber branches cluster in separated small spots within a small area, the anatomical substrate for their receptive field (17). C-fiber branches are generally more broadly distributed, precluding precise localization of the stimulus (17). In contrast, special-



**Table 1**  
Major heat and/or mechanosensitive nociceptor C-fiber classes

	Mechanical sensitivity		Mechanical insensitivity		References
	C-MH	C-M	C-H	C-MiH <sub>i</sub> (“silent”)	
Percentage observed	35–approaching 100	10–15	5–10	10–25	25, 50, 67
CV (m/s)	0.8–1.0 (human, monkey); ~0.5 (mouse)	0.84 (human); ~0.5 (mouse)	0.81 (human); 0.87 (monkey); 0.35 (mouse); slower than mechanically sensitive C-fibers)	0.80 (human); 0.82 (monkey); slower than mechanically sensitive C-fibers	25, 50, 55, 123, 124
Correlation of heat response and PR	Yes/repeated stimulation sensitizes (hairy, not glabrous)	NA	Unknown	NA	24, 67, 106
Heat threshold	39°C–51°C	NA	42°C, 48°C (>C-MH)	NA	50, 55, 67, 123, 124
Correlation of mechanical response to punctuate stimulation and PR	Static: no; accelerating: yes	Accelerating: yes	NA	NA	24, 125
Mechanical threshold	30 mN (human); 25 mN (monkey); 17 mN (mouse)	30 mN (human); 18 mN (mouse)	High	High	25, 26, 50, 55
Correlation of tonic pinch response to tonic pinch and PR	Yes; initial pain; adapting	Yes; initial pain; adapting	Yes: slow development of pain; sensitization; perhaps indirect	Yes: slow development of pain; sensitization; perhaps indirect	9, 18, 126
Electrical stimulation of axon → flare	No: uninjured skin Yes: UV-B–treated skin	No: uninjured skin	Yes: restricted to receptive field	Yes	127–130
Known chemical activators	Cap → TRPV1 (transient); AITC → TRPA1 (58%); diversity of chemical activators: e.g., pH)	AITC → TRPA1 (36%)	Cap → TRPV1 (prolonged); histamine, BK, PGE2	Cap → TRPV1 (prolonged); AITC → TRPA1, 32%; MH sensitivity unmasked by CAP; histamine, BK, PGE2	16, 25, 60, 124, 131
Effect of injury/inflammation	Nonuniform changes in activity after burn: hypoalgesia (glabrous); sensitization (hairy)	Unknown	Inflammation: hyperalgesia; sensitive to mechanical stimuli after injection of inflammatory soup; BK: sensitization	Thresholds for mechanical and heat stimuli in “sensitive” range; sensitization to suprathreshold stimuli	26, 60, 106, 123, 124, 128, 132
Comments	Heat responses independent of TRPV1; may provide neural code for magnitude judgments of heat pain; contribute to stimulus localization		Responsible for TRPV1-heat hyperalgesia; not capable of precise localization of stimulus	May be “C-H” fibers with higher heat thresholds or peripheral endings deeper in the skin	50, 124

Classification of nociceptors on the basis of mechanical sensitivity varies among investigators using different cut-off values and methods. For clarity, cold-sensitive fibers are not included. Cap, capsaicin; CV, conduction velocity; PR, human subject pain ratings; +, immunoreactive.

at central and peripheral terminals (40, 41). The soma expresses many molecular entities that are expressed in free nerve endings, central terminals, and axon (13). However, data from whole-cell soma recordings have been shown in a few cases to be at odds with behavioral or peripheral physiological data (e.g., heat transduction, refs. 42–44; and proton responsiveness, ref. 45). Although the underlying differences in these cases may be due to differential distribution of transduction molecules, it is also possible that nonneuronal peripheral components are required *in vivo* and lacking in dissociated neuronal cultures. This underscores the importance of corroborating results from cultured neurons with behavior and/or acute preparations retaining intact terminal fields. Labeling with retrograde dyes injected into the target tissue has enabled characterization of functional attributes of the soma of

nociceptors innervating those tissues. The heterogeneity of functional phenotypes observed in isolated sensory cell bodies (46, 47) appears to reflect the variability observed in cutaneous nociceptor fiber types observed in studies in which recordings from fiber or soma during receptive field stimulation are combined with subsequent nociceptor labeling to identify terminal morphology (48, 49) and the expression of nocisensors (50), markers, and peptides (48) (Table 1). Nociceptors differentially express a variety of anatomical and biochemical markers (e.g., the expression of versican, the binding partner for the isolectin B4 [IB4]; ref. 51), however the functional significance of these markers, especially given striking species differences (49, 52), are unknown. Here, we will address how the functional heterogeneity of the nociceptor has an impact on the perception of pain.



**Table 2**  
Major heat and/or mechanosensitive nociceptor A-fiber classes

	A-MH II	A-MH I	A-M	References
Percentage observed	~10 (hairy skin)	~20 (hairy skin)	15–50	50, 55
CV (m/s)	11, 15 (monkey)	11, 25 (monkey)	14 (monkey)	55, 57
Correlation of heat response and PR	Yes; response is transient (rapid onset [ $<1$ s], early peak discharge [ $<1$ s], adapting); fatigue to repeated stimuli	Yes; long latency to respond and late peak discharge; shows sensitization	NA	55
Heat threshold	43°C–47°C	$>53$ °C	NA	55
Correlation of mechanical response to punctate stimulation and PR	Yes but with threshold offset	YES	YES	78, 132
Mechanical threshold	11–15 bar (monkey)	3.7–5 bar (monkey)	8.2 bar (monkey); 25 mN (mouse)	50, 55, 59
Known chemical activators	Cap $\rightarrow$ TRPV1	Cap insensitive	Cap insensitive	57, 59
Effect of injury/inflammation	Unknown	Burn: heat sensitization, hyperalgesia in glabrous skin; may mediate 2° punctate mechanohyperalgesia	Punctate hyperalgesia; may mediate 2° punctate mechanohyperalgesia	19, 55, 130, 133
Comments	Mediates first pain to heat and provides precise localization of stimulus; not observed in glabrous skin; eliminated in skin desensitized by Cap	Mediates 2° punctate hyperalgesia due to central sensitization; May contribute to slowly developing pain to heat	Mediates 2° punctate hyperalgesia due to central sensitization; Most TRPV2 <sup>+</sup> but insensitive to 54°C; HTMs	50, 55, 78, 130

For clarity, A-H and A-MH, (“MIA,” ref. 26), which give long-lasting responses to capsaicin (57), are not included in this table. HTM, high threshold mechanoreceptor.

### The response of nociceptors to noxious stimuli

Close proximity of distal extremities to a hot or cold surface, intense pressure or squeezing, and irritating chemicals can result in a sub-second somatopic withdrawal response. Activation of nociceptors requires that adequate stimuli depolarize peripheral terminals (producing a receptor potential) with sufficient amplitude and duration. This ensures that despite any attenuation and slowing of the receptor potential by passive propagation between the sites of transduction and action potential generation, information such as stimulus intensity will be encoded in the resulting train of impulses. Although the distance to action potential initiation is not known for fibers innervating the skin, action potential generation has been proposed to be at or near the site of transduction in A $\delta$  cold fibers innervating the guinea pig cornea (53). In this model, action potentials can be generated at differing distances from the terminal ending depending on the extent of depolarization of the fiber and resulting inactivation of voltage-gated channels involved in conduction (53). Theoretically, the depolarizing receptor potential can be accomplished by multiple membrane conductance changes and electrogenic pump activity. Since the electrochemical gradients for sodium (Na<sup>+</sup>), calcium (Ca<sup>2+</sup>), and chloride (Cl<sup>-</sup>) (37) are more positive than the resting membrane potential in sensory neurons, the opening of ion channels permeable to these ions will cause the membrane potential to shift in the positive direction (depolarize). Since the electrochemical gradient for potassium (K<sup>+</sup>) is more negative than resting potential, closure of active potassium channels not only depolarizes the membrane potential but amplifies current-induced voltage fluctuations due to the resulting increase in membrane resistance (54).

The identification of the molecules that mediate or contribute to heat-, cold-, mechanical-, and chemical-induced generator potentials has been achieved by careful characterization of currents in native cells, the use of novel approaches to identify genes encoding channels and receptors, genome sequencing and bioinformatics, chemical tools (e.g., calcium dyes, pharmacological agents), and innovative genetic approaches. Although significant progress has been made in the study of heat and chemical transduction, many pieces of the puzzle are still missing (Table 3 and Figure 2).

### Transduction of noxious heat

At least 5 classes of nociceptor reveal an increase in activity dependent on the intensity of the heat stimulus beyond the threshold for pain perception ( $\sim 40$ °C–45°°C) into the noxious range (9, 24). Microneurography studies on conscious human subjects have addressed whether activity in a particular fiber correlates with the psychological rating of pain. Under normal conditions, the activity in only a subset of heat-responsive fibers correlates to the degree of pain perceived (C-MH, A-MH type I, A-MH type II; Tables 1 and 2). A-fibers (A-MH Type II innervating hairy skin) responding to temperatures slightly cooler than the perceptual pain threshold for heat are proposed to mediate first pain in humans (55). These fibers rapidly activate, adapt during prolonged heat stimulation, fatigue between heat stimuli, and are sensitive to capsaicin (55–57), a selective agonist of the mammalian heat-activated nonselective cation (NSC) channel transient receptor potential VI (TRPV1) (58) (Table 3). In humans and monkeys, slowly developing second pain is evoked by activation of C-fibers and A-MH type I-fibers



(9, 24), the latter requiring longer exposures to noxious temperatures to achieve maximal firing rates (Tables 1 and 2). Heat-induced C-MH fiber activity in primates correlates with human pain perception in the absence of injury (9). In human glabrous skin, however, neither first pain (56) nor A-MH type II-fiber innervation is observed (59). Investigation of noxious heat transduction in animal models is complicated because the conservation of these pathways is unknown.

Although human C-MH polymodal nociceptors are activated in a temperature range (39°C–51°C) similar to recombinant TRPV1 (58) and have been reported to be transiently activated by capsaicin (60), genetic deletion of TRPV1 in mice only partially reduces noxious heat sensitivity in behavioral assays (42, 43) and has no effect on heat responsiveness of the C-fibers tested (42, 44, 49). This suggests that, at least in mice, heat sensors other than TRPV1 are the major contributors to acute heat-induced pain. Cultures of rodent sensory ganglia indicate expression of TRPV1 in approximately 50% of neurons (61) and 75% of small-medium diameter neurons (43), similar to the proportion of C-MH fibers in a skin-nerve-sensory ganglion-spinal cord preparation (49). Although functionally characterized mouse C-MH neurons were not immunoreactive for TRPV1 (50), neurons with low expression levels may have been missed. Importantly, every identified mouse C-H neuron (~10% of the population) revealed TRPV1-like immunoreactivity (50) and no functionally identified C-H nociceptors were observed in TRPV1-deficient animals. This result cannot be explained by a phenotypic switch to C-MH fibers in these mice since mechanical sensitivity of the C-fiber population was unchanged (50). Furthermore, noxious acute heat responses evoked in rat C-MH saphenous fibers were not decreased by ruthenium red at concentrations that block the capsaicin response (45). In humans, the prolonged time course of the strong C-H response to capsaicin applied to the receptive field matched the duration of the perceived pain (60) and is consistent with the results of rodent studies (50). Disparities regarding the contribution of TRPV1 to fiber subtype functionality (especially C-MH fibers) may depend on species, stimulation techniques, tissue preparation, and sensitivity of the assay. However, it is clear that acute heat responses are mediated by mechanisms in addition to TRPV1 activation, at least in mouse. In the context of tissue injury, however, polymodal C-MH fibers are certainly important in TRPV1-mediated thermal hyperalgesia, indicating that inflammation upregulates the contribution of TRPV1 to heat-evoked nocifensive behaviors in mouse (see below). TRPV2 (Table 3) has been suggested to mediate, at least in part, the receptor potential in A-MH type I-fibers, since it is activated by temperatures greater than 52°C in recombinant expression studies (62); however, the lack of selective pharmacological tools for manipulation of TRPV2 activity has hindered rigorous evaluation of this hypothesis. Transducers of heat stimuli into the noxious range other than TRPV1 and TRPV2 (45, 49) include other TRPV channels (TRPV3 and TRPV4) that have been reported to exist on sensory neurons (10) as well as constitutively active K<sup>+</sup> channels (KCNK2) inhibited by heat (63) (Table 3). Although TRPV3 undergoes dramatic sensitization to repeated heat stimuli, TRPV3 does not appear to be involved in agonist sensitization of C-fiber heat responses (44). Nociceptors directly activated by heat are also expressed on resident skin cells (e.g., TRPV3 and TRPV4 on keratinocytes; refs. 10 and 31) and cause the release of allogenic substances that indirectly influence nociceptor firing (64) (Table 3).

### Transduction of noxious cold

Identifying the mechanisms used by nociceptors to transduce noxious cold has lagged behind progress in understanding heat transduction mechanisms (65). The intensity of cold pain in humans increases linearly with stimulus intensity between about 20°C and 0°C. The threshold for pain perception to cold is much less precise than that for heat, but is about 15°C (66). There is tremendous variability in threshold for cutaneous cold-evoked fiber activity observed in mammals in part due to the rate of cooling (approximately +30°C to -18°C; refs. 27, 66–68). Homeostatic processes engaged during *in vivo* studies (e.g., vasculature changes) and potential tissue damage occurring at subfreezing temperatures are likely to indirectly influence nociceptor responsiveness. Furthermore, measuring cold nocifensive behavior in animals has proven to be challenging, perhaps due to the prolonged exposure time in most assays (68).

Cooling the skin to 4°C activates A- and C-fibers sensitive to innocuous cooling and cold-sensitive nociceptors (27–29, 67, 69), consistent with the presence of two populations of cold-sensitive neurons observed in culture (70–72). Cool-sensitive nonnociceptive afferents are spontaneously active at normal skin temperature and their excitability increases with decreasing temperature (53, 67). The menthol-activated NSC channel TRPM8 (10) is responsible for the detection of innocuous cooling (69, 73, 74) and contributes to spontaneous firing (69) in mice. The effective range for TRPM8-mediated cold coding extends from just below skin temperature into the noxious range (10°C–15°C and below; ref. 10). Although mouse studies have yielded conflicting results regarding the requirement of TRPM8 in behavioral responses to noxious stimuli, more recent work using a novel cold-plate assay convincingly demonstrates a role for mouse TRPM8 in sensing noxious cold (75). Furthermore, the analgesic effects of cold temperature (17°C) were lost in mice lacking TRPM8 in the context of formalin-induced inflammation (74). Whether TRPM8-mediated analgesia is dependent on peripheral and/or central sites of action is unknown but may be addressed now that TRPM8-expressing neurons and their peripheral and central fibers can be visualized by GFP expression driven by the TRPM8 promoter (76, 77). Importantly, studies in humans and mice reveal species differences in pathways sensing innocuous cold: A-fiber block completely suppresses the cold response in humans (78), yet the majority of TRPM8-expressing fibers responsible for innocuous cold transduction in mice have small diameters (76, 77).

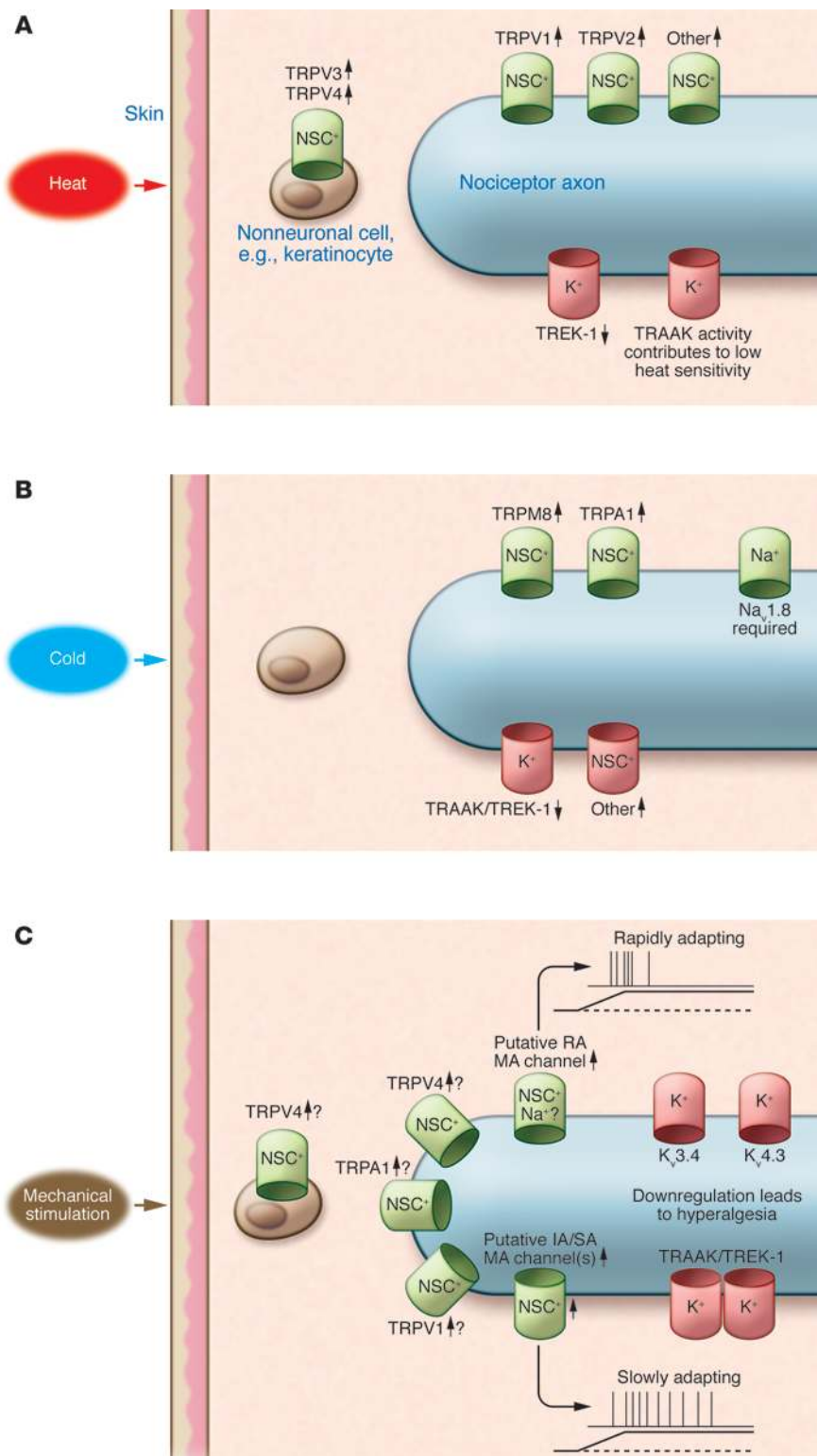
Noxious cold stimuli activate NSC currents and calcium influx (10, 79) and decrease K<sup>+</sup> channel activity (80) and Na<sup>+</sup>/K<sup>+</sup>-ATPase function (65) (Table 3). The temporal dissociation of the qualities of pain/ache vs. prickle/heat to noxious cold (3°C) suggest underlying differences in transduction mechanisms or information processing (66). The cation channel TRPA1 (10) has been proposed to play a role in this process because it has a threshold near 17°C, is expressed in nociceptors together with TRPV1 (10), and is required for cold sensation in mice (81, 82). Human genetic studies have suggested TRPA1 contributes to variation in cold-pain sensitivity (5). Although TRPA1 may respond to cold indirectly through cold-induced intracellular calcium release (10), slow temperature ramps can activate TRPA1 in excised patches in the absence of calcium (82, 83). However, the contribution of TRPA1 to cold sensation is debated since TRPA1 activation was not observed in a heterologous expression system or cultured TG neurons to which relatively short cold stimuli to 5°C were applied (84), and not all



**Table 3**  
Proposed ion channel sensors of cutaneous noxious stimuli

Noxious stimulus	Transduction channel	Evidence for role in acute nociception	Role in hyperalgesia	Comments	Refs
Heat $\geq 43^{\circ}\text{C}$	TRPV1 $\geq 43^{\circ}\text{C}$ (unsensitized); specific receptor for sub- $\mu\text{M}$ Cap	Chemical activation (Cap, resiniferatoxin); heat nociception by activating C-H fibers (mouse); reduced central wide dynamic range neuron response to $49^{\circ}\text{C}$ in null mice	Major contributor to thermal (heat) after carrageenan or CFA-induced inflammation; heat threshold decreased by inflammatory mediators (e.g., BK, NGF-mediated phosphorylation via P-p38); after burn, heat hyperalgesia reduced in KO; upregulation and enhanced activity in inflammation	Only heat receptor that releases CGRP and substance P in periphery when activated; Cap induces predominantly stinging and burning pain	10, 34, 42–44, 50, 134
	TRPV2 $\geq 52^{\circ}\text{C}$ , recombinant	No evidence for a loss of heat sensitive fibers in mice lacking TRPV2 together with TRPV1	ND	Proposed to mediate heat response in A-MH type II-fibers (human/primate)	49
	TRPV3; threshold $32^{\circ}\text{C}$ – $39^{\circ}\text{C}$ into noxious range	Heat: increased withdrawal latency on hot plate $\geq 50^{\circ}\text{C}$	Null mice reveal no deficits in thermal (heat) or mechanical hyperalgesia induced by CFA or BK and formalin-induced behaviors	Reveals strong sensitization by repeated heating; mediates ATP release from keratinocytes and $\text{PGE}_2$ release from keratinocytes overexpressing TRPV3	64, 135–138
	TRPV4; threshold $27^{\circ}\text{C}$ – $34^{\circ}\text{C}$ into noxious range	No contribution to $50^{\circ}\text{C}$ -induced spike frequency at $40^{\circ}\text{C}$ ; no phenotype on hot plate to $50^{\circ}\text{C}$	Thermal (heat): slight increase in withdrawal latency at $45^{\circ}\text{C}$ – $46^{\circ}\text{C}$ ; activated by concerted action of components in inflammatory soup	Protein has been detected in DRG that depends on an intact <i>TRPV4</i> gene; high expression in keratinocytes	10, 67, 139–142
	KCNK2 (TREK-1) $30^{\circ}\text{C}$ – $45^{\circ}\text{C}$	Null mice reveal: enhanced heat-dependent ( $30^{\circ}\text{C}$ – $45^{\circ}\text{C}$ ) saphenous C-fiber activity; decreased thermal ( $46^{\circ}\text{C}$ – $50^{\circ}\text{C}$ ) tail withdrawal latency; higher percentage of heat-sensitive/TRPV1-negative fibers	Recombinant channel activity inhibited by $\text{H}^+$ ; LPA; Inflammation increased heat ( $46^{\circ}\text{C}$ ) (but not cold) hyperalgesia in C-MH fibers in null mice; LPA and protons inhibit channel activity	2-pore potassium channel reduced activity causes increased excitability; contributes to suppression of heat activation of C-MH fibers; negatively regulated by $\text{G}_s$ and $\text{G}_i$ protein-coupled receptors, such as $\text{PGE}_2$ , serotonin, and glutamate	63, 143, 144
	KCNK4 (TRAAK)	Null mice reveal: higher percentage of heat-sensitive/TRPV1-negative fibers and heat hyperalgesia	Null mice reveal heat ( $46^{\circ}\text{C}$ ) hyperalgesia after carrageenan	Two pore potassium channel	144
Cold	TRPM8; threshold near $26^{\circ}\text{C}$ and active into the noxious range	Severe deficit in cooling-induced behavior and sensory neuronal responses in null mice; contributes to avoidance of moderately low temperature; contributes to avoidance at noxious cold temperatures and cold hypersensitivity	Contributes to cold allodynia in CFA model of inflammation	Predominant detector of innocuous cold <i>in vivo</i> ; responsible for the analgesic effect produced by cold or chemical cooling compounds	10, 69, 73–75, 145
	TRPA1; moderately specific receptor for mid- $\mu\text{M}$ AITC	Contributes to nocifensive behaviors on $0^{\circ}\text{C}$ cold plate and acetone-induced nocifensive behaviors; and cold hypersensitivity at $10^{\circ}\text{C}$	Contributes to CFA-induced cold hyperalgesia and BK-induced hyperalgesia; null mice reveal increased threshold to punctate mechanical stimuli (von Frey) and reduced inflammatory hyperalgesia	Controversial (see text); does not contribute to heat hyperalgesia during CFA-induced inflammation	10, 75, 81, 82, 85, 146–148
	KCNK4 (TRAAK)	Together with KCNK2 (but not alone) contributes to noxious cold-induced C-fiber activity (lowered threshold) and behavior	ND	Combination of TREK-1 and TRAAK important	144
Intense punctate and/or pinch pressure	KCNK2 (TREK-1)	Contributes to von Frey punctate mechanical-induced pain, but not pressure-induced pain	Null mice reveal inflammation-induced mechanical (von Frey) hyperalgesia and reduced $\text{PGE}_2$ -induced pain	Hypertonic (10%) saline-induced pain reduced in null mice	63
	KCNK4 (TRAAK)	Contributes to punctate von Frey-induced pain; together with KCNK2 contributes to osmotic pain	ND	Combination of TREK-1 and TRAAK important	144
	TRPV4	TRPV4 KO: reduced response to tail clamp	Mechanical hyperalgesia	Although activated by hypotonicity, there is lack of consensus for a role of TRPV4 in noxious mechanical stimulus transduction; protein has been detected in DRG that depends on an intact <i>TRPV4</i> gene	142, 149
	TRPA1	Cutaneous nociceptor fibers from TRPA1-null mice exhibit lower firing rates in response to mechanical stimuli	Mechanical hyperalgesia BK-induced reduction in mechanical withdrawal threshold required TRPA1	A direct effect of mechanical stimuli on mammalian TRPA1 has not been demonstrated	81, 147, 148
	TRPV1	Null mice have normal threshold for punctate and pinch stimuli	After burn, mechanical hyperalgesia reduced in KO; BK-induced reduction in mechanical withdrawal threshold required TRPV1; no defects in mechanical sensitivity after AITC or CFA injection in null mice	Role in mechanical hyperalgesia	42, 85, 134
	Kv3.4	Mechanical hyperalgesia after i.t. antisense ODN injection (rat lumbar DRG); no effect on heat response	ND	Reduced activity causes increased hyperalgesia	150
Kv4.3	Mechanical hyperalgesia after i.t. antisense ODN injection (rat lumbar DRG); no effect on heat response	ND	Reduced activity causes increased hyperalgesia	150	

NGF, nerve growth factor; ND, not determined; i.t., intrathecal.

**Figure 2**

Known or proposed transduction mechanisms in uninjured mammalian nociceptor peripheral terminals. Ion channels that transduce heat (A), cold (B), and mechanical stimuli (C) are depicted. Stimuli are presented to the skin, which is depicted as containing representative nonneuronal cells (such as keratinocytes) (brown cells) and the free nerve endings of nociceptor axons (blue). Arrows next to channels indicate whether their activity is increased or decreased upon stimulation. Note that these nociceptors are not necessarily coexpressed in the same terminal. The curved arrow in C refers to the transducer(s) and other channels and molecules that contribute to the firing pattern (e.g., rapidly adapting vs. slowly adapting) in these fibers. Molecularly unidentified channels with indicated ion permeabilities inside drawing of channel are referred to as "putative RA MA channel" and "putative IA/SA MA channel." MA, mechanically activated; RA, rapidly adapting; IA, intermediate adapting; SA, slowly adapting.

mouse lines constitutively lacking TRPA1 reveal a cold phenotype in behavioral and neural assays (85). However, two independent studies recently demonstrated a role of TRPA1 in noxious cold sensitivity (75, 82). TRPA1 is established as a general sensor for noxious irritating electrophilic compounds (including allyl iso-

thiocyanate [mustard oil] [AITC] and cinnamaldehyde, the active pungent ingredients in hot mustard and cinnamon, respectively; refs. 84 and 86) and is sensitized by inflammatory mediators (87). These electrophilic agonists open an integral channel pore by covalent binding to the intracellular N terminus of the channel protein





(88, 89). Importantly, endogenous reactive chemicals are also effective agonists of TRPA1 (90). How TRPA1-expressing neurons might mediate the burning sensation of hot mustard (AITC) may be explained by anatomical and psychophysical results: AITC is a strong chemical activator of a subset of TRPV1-expressing neurons, and activity in peripheral fibers transmitting information about cold stimuli in the presence of an A-fiber block (presumably C-fibers) evoke burning, aching, and pricking qualities (67). Interestingly, the activation of some cold fibers by noxious heat may be the basis for the paradoxical cold sensation felt by stimulating cold spots with noxious heat stimuli (67).

### Transduction of noxious mechanical stimuli

Whereas heat- and chemical-induced nociceptor responses correlate with pain perception in humans (9, 24), mechanical stimulation of C-MH (24) and rapidly adapting A-HTM (18) fibers may not (24) (Tables 1 and 2). The perception of pinprick pain intensity, however, is related to activity in capsaicin-insensitive A-fiber nociceptors (e.g., A-M and A-MH type I) (78). Transduction channels mediating mammalian noxious (and innocuous) mechanical stimuli have been elusive (5, 91, 92). Transduction in soma membranes on a submillisecond time scale suggests direct gating by pressure of ion channels with NSC and possibly Na<sup>+</sup> permeability (91). No orthologs for the well-studied prokaryotic mechanosensitive channels MscL and MscS are present in mammalian genomes (93). In addition, there is no strong evidence that mammalian orthologs of invertebrate components of structures involved in mechanosensation (92) are the transduction channel in cutaneous sensory neurons, although acid-sensitive ion channels (ASICs) appear to play a role (11). Some progress has been made in the identification of proteins (e.g., stomatin-like protein 3; ref. 94) involved in sensing innocuous touch, but their genetic deletion in mouse does not compromise behavioral responses to noxious pressure. TRP channels are candidates based on expression and functional similarities to evolutionary counterparts, but whether these contribute to the molecular sensor/transducer or function in a sensitizing role is still unclear (11) (Table 3). The challenges encountered in assigning a role for transducers of noxious mechanical stimuli include the efficacy of stimulation protocols applied in behavioral and *ex vivo* tissue assays (e.g., phenotypes can differ when challenged with thin calibrated von Frey nylon filaments vs. distributed pinch that may also induce local ischemia; ref. 95), the suppressive influence of innocuous A-fiber mechanosensitive inputs at a systems level (18), and the extrapolation of cellular assays to nociception (e.g., poking, ref. 96; stretching, ref. 97; hypo-osmotic-induced swelling, ref. 98). This topic is reviewed in more detail elsewhere (12, 19, 91–93).

### Conduction

Nociceptors express a wide variety of voltage-gated channels (e.g., Na<sub>v</sub>, Ca<sub>v</sub>, K<sub>v</sub>) that transduce the receptor potential into an action potential or, more commonly, a set of action potentials that encode the intensity of a noxious stimulus applied within their receptive fields. There are 9 known Na<sub>v</sub>, 10 Ca<sub>v</sub>, and 40 K<sub>v</sub> genes in mammals (<http://www.iuphar-db.org/DATABASE/>), many of which have multiple splice variants with different functional characteristics (99). Cell excitability and firing behavior (e.g., threshold for action potential generation, action potential and undershoot amplitude and duration, and maximal firing frequency) depend on the complement of these channels as well as those contributing to frequency modulation (e.g., hyperpolarization-activated

cyclic nucleotide-gated cation channel [HCN] and A-type K<sub>v</sub>4.3 and K<sub>v</sub>3.4 channels) (54). For instance, nociceptors responsive to noxious cold require the expression of the tetrodotoxin-resistant (TTX-resistant) Na<sub>v</sub>1.8 channel at the peripheral terminal (100), and mice lacking Na<sub>v</sub>1.8 and Na<sub>v</sub>1.7 display deficits in mechanosensation (95, 101). Peripheral CGRP release by inflammatory mediators is unaffected by TTX, suggesting an important role of TTX-resistant Na<sub>v</sub> in regulated pain thresholds, consistent with their robust modulation by bradykinin (BK) and PGE<sub>2</sub> (102) (see below). Since enhanced excitability of primary sensory neurons in inflammatory and pathologic pain states is a major contributor to the perception of pain, specific pharmacological agents that specifically dampen aberrant activity are desirable in the design of pain therapeutics. To this end, an understanding of species-specific differences is critical, as exemplified by the dramatically different phenotypes in mice and humans lacking Na<sub>v</sub>1.7: although mice lacking Na<sub>v</sub>1.7 show a mechanosensory (pinch) and formalin-induced (5%) pain phenotype (103), humans lacking Na<sub>v</sub>1.7 are insensitive to pain altogether (104).

### Central modulation

Nociceptors release a variety of substances from their central terminals that have the potential of exciting second-order neurons through multiple mechanisms. Fast and slow synaptic transmission are mediated in large part by glutamate and peptides (e.g., substance P, CGRP), respectively (7, 38). Of particular importance to pain perception is the plasticity in synaptic strength (i.e., the ability to enhance homosynaptic as well as heterosynaptic connections) between primary afferents and the relay and interneurons they drive, presynaptic and postsynaptic modulation by descending facilitatory and inhibitory pathways in the spinal cord, and the efferent aspects of nociceptor function activated by strong GABAergic/glycinergic depolarization of presynaptic terminals leading to the dorsal root reflex (37, 105). Anterograde transmission of action potentials from the spinal cord to the periphery results in release of peptides and other inflammatory mediators in the skin and exacerbates nociceptor excitability and pain (see below). It is at the spinal level that nonnociceptive neurons are recruited by strong nociceptor activation through functional modulation of local circuits (105).

### Adaptive and maladaptive shifts in pain threshold

Injury to the skin induces protective physiological responses aimed at decreasing the likelihood of exacerbating the injury. After an injury induced by pungent chemicals (e.g., capsaicin, mustard oil) and burn, stimulation of the injured area produces enhanced pain to noxious stimuli (primary mechanical and thermal hyperalgesia) dependent on C-fiber activity that manifests as a decrease in threshold to activate C-MH fibers and to perceive pain (9, 19, 106). Immediately surrounding the injured area, a zone of flare (reddening) develops and stimulation of even a larger secondary zone produces pain in response to normally innocuous stimuli (e.g., brush stroke) (secondary mechanical allodynia) as well as enhanced responsiveness to noxious mechanical (secondary mechanical hyperalgesia) and thermal (heat) hyperalgesia if spatial summation is invoked (secondary thermal hyperalgesia) (21, 105, 107). Here, noxious punctate stimulation of C-nociceptors induces secondary mechanical hyperalgesia mediated by A-nociceptors (7) and innocuous dynamic mechanical stimuli (gentle stroking) provokes nonnociceptor A-fiber-mediated pain



(108). Cellular mechanisms underlying this complicated response involve both peripheral and central processes (14, 38, 105, 107) and require nociceptor input, particularly A-MH and C-MH fibers (19, 91, 105). After a burn, A-MH fibers (most likely type I) mediate primary heat hyperalgesia in glabrous skin (9).

What are the cellular mechanisms mediating hyperalgesia? Electrical stimulation of the majority of C-polymodal fibers produced plasma extravasation in their peripheral receptor field (109). Centrally propagating impulses can antidromically invade peripheral arborizations innervating other areas in the afferent's receptive field (axon reflex), causing the release of peptides (e.g., substance P, CGRP, somatostatin) and/or other bioactive substances from the terminal (e.g., cytokines) into the interstitial tissue (17). The released substances produce a myriad of autocrine or paracrine effects on endothelial, epithelial, and resident immune cells (Langerhans), which lead to arteriolar vasodilatation ("flare," via CGRP) and/or increased vascular permeability and plasma extravasation from venules (edema, via substance P). Liberated enzymes (e.g., kallikreins) and blood cells (e.g., platelets, mast cells) further contribute to the accumulation of inflammatory mediators and neurogenic inflammation (110, 111). A large variety of substances feed back onto nociceptors innervating the injured region and sensitize peripheral terminals by direct and indirect actions at ion channels, receptors, and second messenger cascades (87, 102, 111, 112). The mechanisms by which inflammatory mediators recruit "silent" C-MH<sub>1</sub> fibers by endowing these fibers with prolonged mechanical and heat sensitivity (25, 60) is unknown but may involve long-lasting alterations in second messenger signaling cascades and sensitization of nociceptors. Decreased thermal and chemical thresholds in the primary area are due in part to sensitization of TRPV1 and TRPA1 by numerous components of the "inflammatory soup" including BK (36, 85–87, 112). Although TRPV1 is not the only transducer of acute noxious heat, it is the major contributor to the development of heat hyperalgesia, perhaps due to its expression in polymodal neurons capable of inducing neurogenic inflammation and modifying central connections (42, 43). As a polymodal nociceptor, TRPV1 is the target for acute acid responsiveness in the skin of mice, although species differences are apparent (113). A recently described phenomenon ("hyperalgesic priming") evoked by cytokine- and neurotrophin-induced recruitment of  $G_{i/o}$ -PKC $\epsilon$  signaling in nociceptors can produce prolonged sensitization and mechanical hyperalgesia and may contribute to chronic pain (114). Prolonged pain perception observed in inflammatory pain models is generally believed to be produced by ongoing nociceptor activity (15); formalin, for instance, produces nocifensive behaviors through its activation of TRPA1 (115, 116). Secondary hyperalgesia to punctate pinprick stimuli is mediated at least in part by capsaicin-insensitive A-fiber nociceptors (e.g., A-MH type I and A-M; Table 2) by central sensitization processes (78, 108).

### Do labeled lines transmit noxious stimulus information?

Determining the extent to which pain qualities are dependent on the activation of subpopulations of neurons and intensity coding poses a considerable challenge and is an active area of research (13). Psychophysical studies on spinal cord injury patients suffering from partial or complete loss of thermal sensitivity support a model in which both pain-specific pathways and nonnociceptive pathways are integrated (117). Significant crosstalk between these pathways exists at multiple levels including stimulus transduction

(118), peripheral terminals during neurogenic inflammation, and central connections during central sensitization and may underlie paradoxical temperature sensation. To address the extent by which particular nociceptive signaling pathways encode particular modalities, a number of approaches have been taken. Genetically encoded tracers have enabled visualization of specific subpopulations of sensory neurons (e.g., *Mrgpr* family, ref. 30; TRPM8, refs. 76 and 77) and determination of their innervation patterns as well as cellular function. Pharmacologic and hereditary genetic ablations have defined the role of nociceptors in pain but until recently have included multiple or entire nociceptor populations (e.g., capsaicin-induced ablation of TRPV1-expressing neurons; refs. 42 and 119) or sensory and autonomic populations (2). Genetically mediated ablation using toxins (e.g., diphtheria A) transcribed by promoters of genes expressed in specific neuronal subtypes (e.g.,  $Na_v1.8$ -expressing neurons, ref. 120) provides a means to address the contributions of particular cells to acute nociception and hyperalgesia and allodynia after injury.

Mice expressing diphtheria toxin under the  $Na_v1.8$  promoter reveal significant loss of sensory neurons (85% and 13% of unmyelinated and myelinated neurons, respectively, consistent with  $Na_v1.8$  expression in most nociceptors as well as some myelinated sensory neurons). These mice are unresponsive to acute noxious mechanical (pressure-induced, not punctate) and cold stimuli and defective in the development of inflammatory pain, but are normal with regard to acute responsiveness to heat stimuli and the ability to develop neuropathic pain (120). These data are remarkably consistent with gene-deletion studies (103). The sensitivity of C-MH fibers innervating hairy skin to cold, heat, and mechanical stimuli is reduced in mice constitutively lacking *MrgprD*-expressing cells reported to be TRPV1 and peptide negative (121). However, when genetic ablation of this population of cells is done in adulthood, behavioral deficits were observed to mechanical but not thermal stimuli (122). An additive loss of both mechanical- and heat-induced nocifensive behaviors was achieved after further pharmacologic ablation of central TRPV1<sup>+</sup> terminals, suggesting a separation of mechanical and thermal modalities at all levels of sensory processing in the pain pathways subserved by *MrgprD*- and TRPV1-expressing cells (122). The extent to which this separation is maintained for other murine nociceptor populations is a subject of active research.

### Future challenges

Despite significant progress in understanding the complexities of mammalian nociception and pain perception in the last half century, our knowledge is far from complete with regard to the identity of the full complement of sensors of noxious stimuli (particularly with regard to mechanotransduction), the role of nociceptor heterogeneity in physiological and pathological pain, the coding of the quality of the stimulus, and the modulation of pain pathways by peripheral and central mechanisms. A focus on mechanisms underlying thermal nociception and hyperalgesia is in large part due to the identification of the TRP family of channels. The future identification of elusive mechanotransducers in somatosensory neurons will likewise thrust the direction of research toward a cellular/molecular understanding of mechanical hyperalgesia and allodynia. The application of genetic technologies and pharmacological approaches to understanding the contributions of molecules, signaling pathways, and cell populations to nocifensive behaviors to particular stimulus modalities in normal



and pathophysiological states in rodents will inspire hypotheses that ultimately must be tested in humans.

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