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Physiology in Medicine
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Annals of Internal Medicine
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REVIEW

Pain: Moving from Symptom Control toward Mechanism-Specific Pharmacologic Management

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Clinical Principles	Physiologic Principles
Nociceptive pain: transient pain in response to a noxious stimulus.	Nociception
Inflammatory pain: spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation.	Peripheral sensitization
Neuropathic pain: spontaneous pain and hypersensitivity to pain in association with damage to or a lesion of the nervous system.	Phenotype switch
Functional pain: hypersensitivity to pain resulting from abnormal central processing of normal input.	Central sensitization
	Neuron glial interaction
	Increased facilitation
	Structural reorganization
	Decreased inhibition

Pain is a multidimensional sensory experience that is intrinsically unpleasant and associated with hurting and soreness. It may vary in intensity (mild, moderate, or severe), quality (sharp, burning, or dull), duration (transient, intermittent, or persistent), and referral (superficial or deep, localized or diffuse). Although it is essentially a sensation, pain has strong cognitive and emotional components; it is linked to, or described in terms of, suffering. It is also associated with avoidance motor reflexes and alterations in autonomic output. All of these traits are inextricably linked in the experience of pain.

Although we tend to think of pain as a homogeneous sensory entity, several distinct types exist: nociceptive, inflammatory, neuropathic, and functional (**Figure 1**). The neurobiological mechanisms responsible for these different pains are beginning to be defined (1–3), providing insight into how distinct types of pain are generated by diverse etiologic factors, and in which patients (4). Moreover, we can now realistically expect to move from an empirical therapeutic approach to one that it is targeted specifically at the particular mechanisms of the type of pain experienced by an individual patient. Although current analgesic treatment is aimed at suppressing or controlling symptoms (5), interventions that can abort the development of pain mechanisms are beginning to be conceivable (1).

PAIN: THE GOOD, THE BAD, AND THE UGLY

Pain can be essentially divided into 2 broad categories: adaptive and maladaptive. Adaptive pain contributes to survival by protecting the organism from injury or promoting healing when injury has occurred. Maladaptive pain, in contrast, is an expression of the pathologic operation of the nervous system; it is pain as disease.

The sensory experience of acute pain caused by a noxious stimulus is mediated by a specialized high-threshold sensory system, the nociceptive system. This system extends from the periphery through the spinal cord, brain stem, and thalamus to the cerebral cortex, where the sensation is perceived. To prevent damage to tissue, we have learned to associate certain categories of stimuli with danger that must be avoided if at all possible. This association is formed by linking noxious stimuli with a sensation that is intense and unpleasant: that is, pain. The sensation of pain must be strong enough that it demands immediate attention.

Ann Intern Med. 2004;140:441-451.
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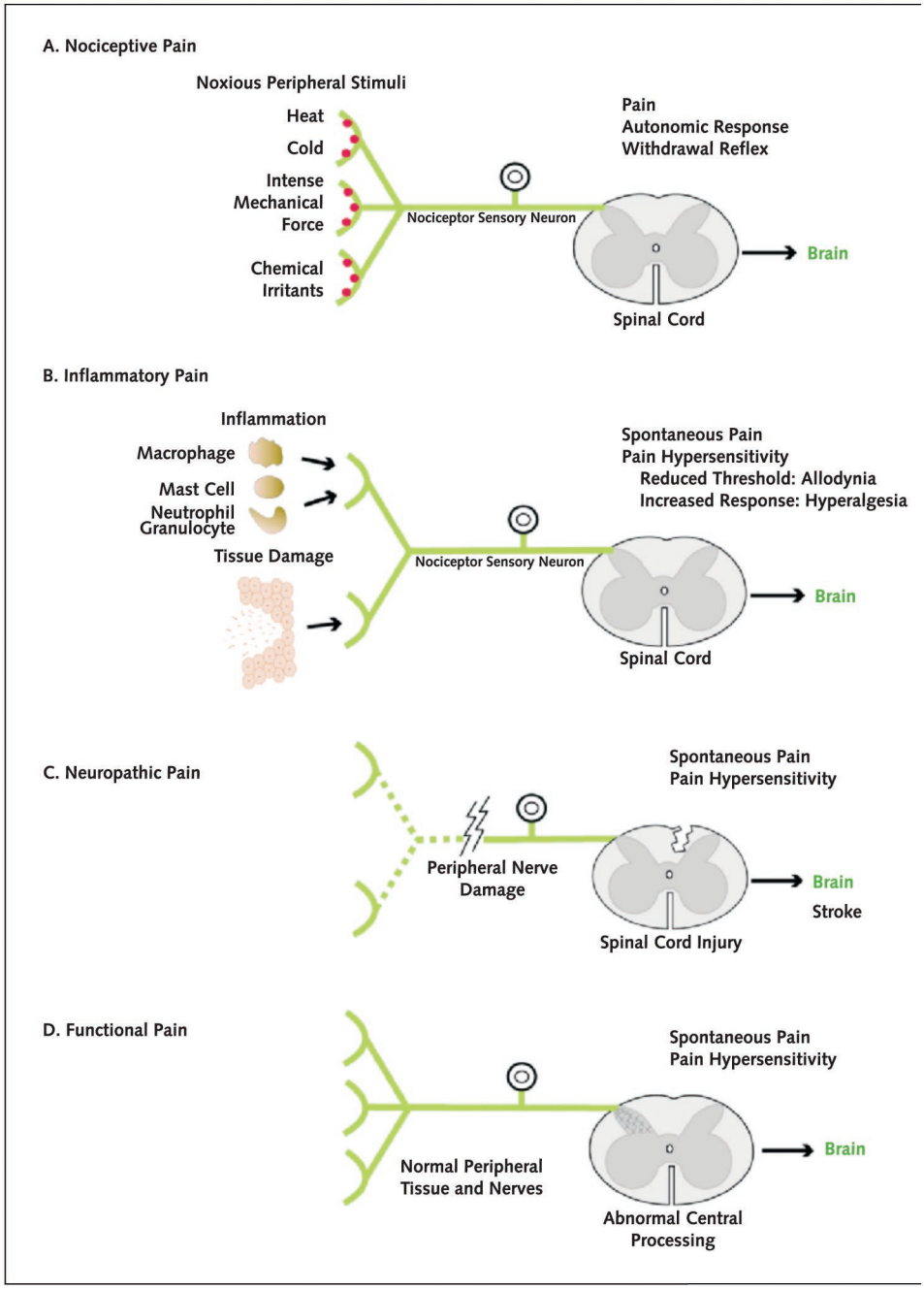
Figure 1. **The 4 primary types of pain.**



This nociceptive pain system is a key early warning device, an alarm system that announces the presence of a potentially damaging stimulus. Nociceptive pain must be controlled only under specific clinical situations, such as during surgery or medical procedures that damage tissue and after trauma. It is important that this system not be chronically disabled, because loss of its protective function inevitably leads to tissue damage, including self-induced mutilation of the tongue and lips, destruction of joints, loss of the tips of fingers, and pressure ulcers. Nociceptive pain is therefore a vital physiologic sensation. Lack of it in patients with congenital insensitivity to pain due to a mutation of the nerve growth factor tyrosine kinase A receptor, which results in a loss of high-threshold sensory neurons, reduces life expectancy (6).

If tissue damage occurs despite the nociceptive defensive system (for example, through trauma, surgery, or inflammatory diseases), the body's imperative shifts from protecting against noxious, potentially damaging stimuli to promoting healing of the injured tissue. Inflammatory pain

is used to accomplish this goal. In this state, sensitivity is increased such that stimuli to the affected part that would normally not cause pain now do so. As a result, we prevent contact with or movement of the injured part until repair is complete, minimizing further damage. Inflammatory pain typically decreases as the damage and inflammatory response resolve (**Figure 1**).

Although inflammatory pain is adaptive, evolution has not taken into account the ability to inflict elective injury (that is, to undergo surgery) or survive severe trauma. We need to be able to actively manage inflammatory pain after surgery or trauma as well as in patients with inflammatory diseases, such as rheumatoid arthritis, without removing or severely blunting the warning system of nociceptive pain or impairing the healing process by allowing excessive inflamed or damaged tissue to form. The aim is to normalize pain sensitivity, not remove it.

Maladaptive pain is uncoupled from a noxious stimulus or healing tissue. Such pain may occur in response to damage to the nervous system (neuropathic pain) or result from abnormal operation of the nervous system (functional pain) (**Figure 1**). Maladaptive pain is the expression of abnormal sensory processing and usually is persistent or recurrent. This is an area of enormous unmet clinical need because treatment options are limited and our understanding incomplete. Essentially, in maladaptive pain, the fire alarm system is constantly switched on even though there is no emergency, or repeated false alarms occur.

Neuropathic pain may result from lesions to the peripheral nervous system, as in patients with diabetic or AIDS polyneuropathy, post-herpetic neuralgia, or lumbar radiculopathy, or to the central nervous system, such as in patients with spinal cord injury, multiple sclerosis, or stroke (7). Functional pain is an evolving concept. In this form of pain sensitivity, no neurologic deficit or peripheral abnormality can be detected. The pain is due to an abnormal responsiveness or function of the nervous system, in which heightened gain or sensitivity of the sensory apparatus amplifies symptoms. Several common conditions have features that may place them this category: for example, fibromyalgia, irritable bowel syndrome, some forms of noncardiac chest pain, and tension-type headache (8–10). It is not known why the central nervous system of patients with functional pain displays abnormal sensitivity or hyperresponsiveness.

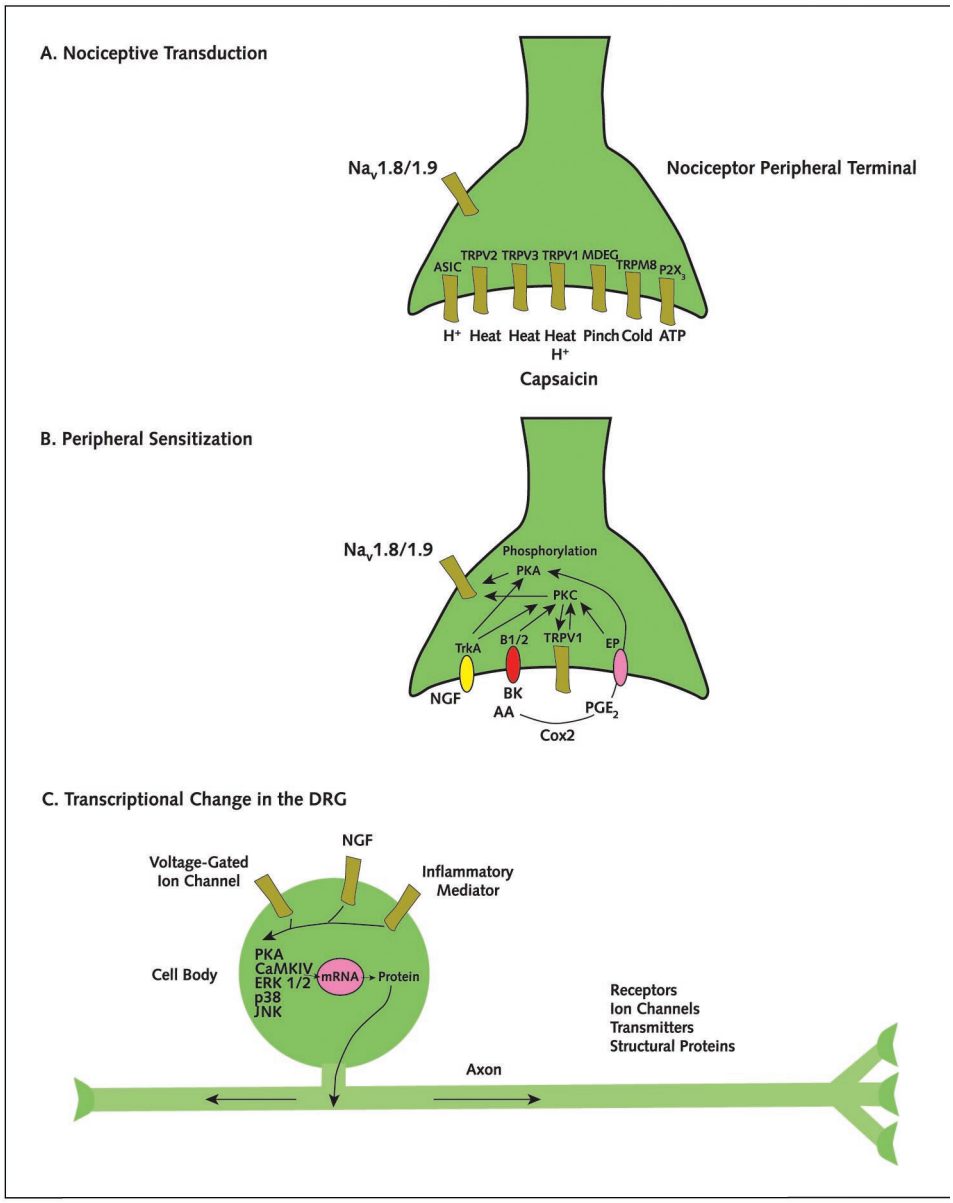
Classic migraine is in a category of its own. It is an episodic neurologic condition related to abnormal cortical activity that alters sensory input from dural and cerebrovascular sensory fibers and is associated with an abnormal sensory processing in the brain stem. It possesses features of inflammatory and functional pain, as well as of objective neurologic dysfunction (11, 12). Pain caused by cancer varies greatly in character and source; it depends on the tumor, its location, and its proximity to other tissues. In some cases, tumor cells produce chemical signals that contribute directly to the pain, as in osteosarcomas. In other tumors, the pain may be due to mechanical compression or invasion of a nerve, distention of an organ, ischemia, or an inflammatory reaction to tissue necrosis. It may also represent a neurotoxic side effect of chemotherapy (13).

Although inflammatory, neuropathic, and functional pain each have different causes, they share some characteristics. The pain in these syndromes may arise spontaneously in the apparent absence of any peripheral stimulus, or it may be evoked by stimuli. Evoked pain may arise from a low-intensity, normally innocuous stimulus, such as a light touch to the skin in a patient with post-herpetic neuralgia or vibration during an acute attack of gout, or it may be an exaggerated and prolonged response to a noxious stimulus. The former condition is called *allodynia* and the latter *hyperalgesia.* Spontaneous pain and changes in sensitivity to stimuli are fundamental features of clinical pain, distinguishing it from nociceptive pain, in which pain occurs only in the presence of an intense or noxious stimulus. Because nociceptive pain constitutes our everyday experience of pain, the lack of an identifiable peripheral stimulus in some patients can lead to the assumption that their pain is "hysterical" in origin. However, the increased sensitivity of the nervous system during inflammatory, neuropathic, or functional pain can lead to pain in the absence of any peripheral noxious stimulus. Two major challenges in pain management are to identify the mechanisms responsible for producing hypersensitivity to pain and to find a means of normalizing sensitivity or preventing hypersensitivity from becoming established.

Mechanisms of Pain

Multiple mechanisms that can produce pain have been identified; they include nociception, peripheral sensitization, phenotypic switches, central sensitization, ectopic excitability, structural reorganization, and decreased inhibition (1, 2, 14, 15). Nociception is the sole mechanism that causes nociceptive pain and comprises the processes of transduction, conduction, transmission, and perception. *Transduction* is the conversion of a noxious thermal, mechanical, or chemical stimulus into electrical activity in the peripheral terminals of nociceptor sensory fibers. This process is mediated by specific receptor ion channels expressed only by nociceptors (**Figure 2A**). *Conduction* is the passage of action potentials from the peripheral terminal along axons to the central terminal of nociceptors in the central nervous system, and *transmission* is the synaptic transfer and modulation of input from one neuron to another. Ectopic excitability, structural reorganization, and decreased inhibition are unique to neuropathic pain, whereas peripheral sensitization occurs in inflammatory and some forms of neuropathic pain (post-herpetic neuralgia, the only documented form) (**Figure 2B**). Central sensitization, in contrast, contributes to inflammatory, neuropathic, and functional pain (**Figure 3**). Mechanisms are therefore not synonymous with pain syndromes. Because mechanisms

Figure 2. **Contributions of primary sensory neurons to pain.**



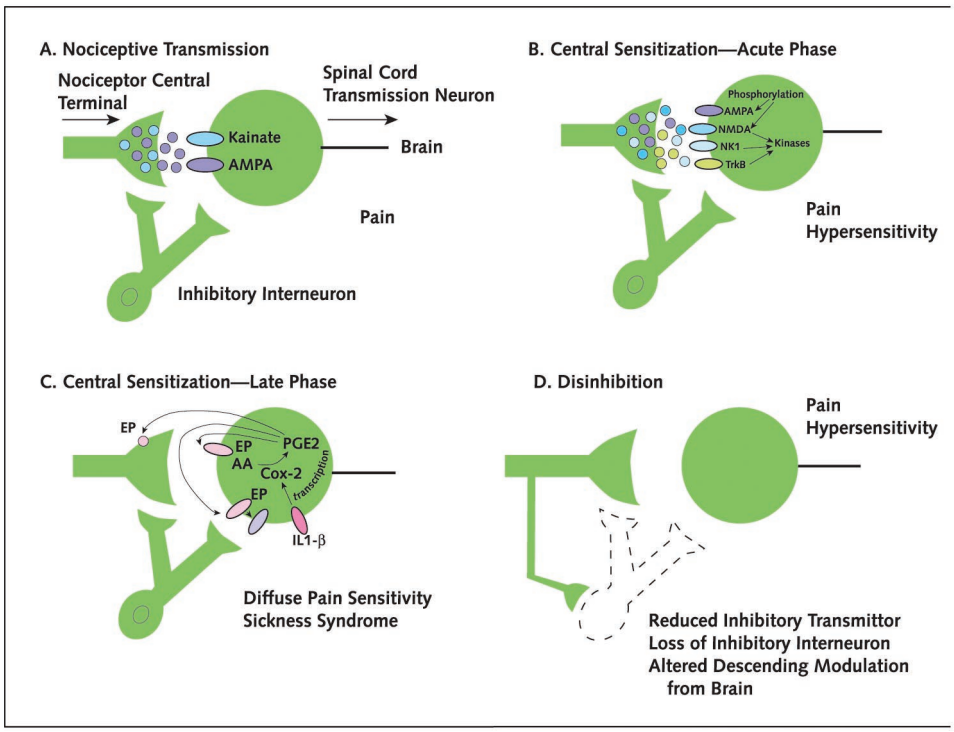
A. The peripheral terminal of a nociceptor sensory neuron. The different transducing receptor and ion channels that respond to thermal, mechanical, and chemical stimuli are shown. **B.** The mechanism of peripheral sensitization. Inflammatory mediators, such as prostaglandin E_2 (*PGE_2*), bradykinin (*BK*), and nerve growth factor (*NGF*), activate intracellular kinases in the peripheral terminal that phosphorylate transducer channels to reduce their threshold or sodium channels to increase excitability. **C.** Transcriptional changes in the dorsal root ganglion. Activity, growth factors, and inflammatory mediators act on sensory neurons to activate intracellular transduction cascades. These cascades control the transcription factors that modulate gene expression, leading to changes in the levels of receptors, ion channels, and other functional proteins. AA = archidonic acid; ASIC = acid-sensing ion channel; ATP = adenosine triphosphate; CaMKIV = camkinase IV; COX-2 = cyclooxygenase-2; ERK = extracellular signal-regulated kinase; EP = prostaglandin E receptor; JNK = jun kinase; mRNA = messenger RNA; PKA = protein kinase A; PKC = protein kinase C; TRP = transient receptor potential receptor.

can be the target of treatment (4), we must develop both diagnostic tools to identify these mechanisms as well as mechanism-specific pharmacologic agents.

Nociception

Nociception, the perception of noxious stimuli, is initiated by stimuli that activate the peripheral terminals of nociceptors, a highly specialized subset of primary sensory neurons that respond only to intense stimuli. Nociceptors have unmyelinated (C-fiber) or thinly myelinated (Aδ-fiber) axons (16). The receptive properties of these sensory neurons are determined by their expression of transducing ion-channel receptors, which have a high threshold of activation to external stimuli (2). Many (but not all) of these transducers have been identified, including those that cause

Figure 3. **Contributions of spinal cord dorsal horn neurons to pain.**



A. Nociceptive transmission. **B.** The acute phase of central sensitization. **C.** The late phase of central sensitization. Some alterations in gene expression are activity-driven and restricted, such as dynorphin, whereas others are widespread and produce diverse changes in function, such as induction of cyclooxygenase-2 (*COX-2*) in central neurons after peripheral inflammation. **D.** Disinhibition. AA = arachidonic acid; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; EP = prostaglandin E receptor; IL-1β = interleukin-1β; NK1 = neurokinin 1; NMDA = *N*-methyl-D-aspartic acid; PGE_2 = prostaglandin E_2; TrkB = tyrosine kinase B_2.

the response to noxious heat (>42 °C) and cold (<10 °C) and direct chemical irritants, such as capsaicin (**Figure 2A**) (2). In general, the transducer ion channels are nonselective cation or sodium channels that are gated not by voltage but by temperature, chemical ligands, and mechanical shearing forces. Once they are activated, the channels open and sodium and calcium ions flow into the nociceptor peripheral terminal, producing an inward current that depolarizes the membrane. If the depolarizing current is sufficient to activate voltage-gated sodium channels, they too will open, further depolarizing the membrane and initiating a burst of action potentials, the frequency and duration of which reflect the intensity and duration of the noxious stimulus. The presence, specificity, and threshold of the nociceptor transducers is thus the first and most important filter in the activation of nociception and defines the different classes of primary sensory neurons: unimodal, which react only to one form of stimulus (for example, noxious heat) or polymodal, which react to several kinds of stimuli. Polymodal primary sensory neurons are more common than the unimodal variety. Some nociceptor neurons are effectively silent: They fail to react under normal circumstances to any nondamaging stimulus because the basal threshold of their transducers is so high.

If action potentials are initiated by a noxious stimulus applied to the peripheral terminal of a nociceptor, they are conducted from the periphery to the central nervous system along the sensory neuron axon, which runs through peripheral nerves to the dorsal root ganglion and into the spinal cord through the dorsal root, where the central terminals of the neurons make synaptic contact with dorsal horn neurons. Sensory neurons express several voltage-gated sodium channels that mediate conduction of the action potentials, including 2 that are unique to nociceptors: $Na_v1.8$ and $Na_v1.9$ (17, 18). If it were possible to selectively block these channels, local anesthetics that block only pain and leave innocuous sensation, motor, and autonomic output intact could be developed. All of the currently available sodium-channel blockers have a poor therapeutic index because they are nonselective, acting on sodium channels in the peripheral and central nervous systems and cardiovascular system (19).

Transfer of input from nociceptors to neurons in the dorsal horn of the spinal cord that project to the brain is mediated by direct monosynaptic contact or through multiple interneurons, some of which are excitatory and some inhibitory. The encoding in the central nervous system of the initiation, duration, intensity, and location of peripheral noxious stimuli results from fast synaptic activation by nociceptors of neurons in the spinal cord (which receive inputs from the body) or the spinal nucleus of the trigem-

inal in the medulla (which receive nociceptor inputs from the head). Some of these neurons send axon projections to the thalamus, transferring the sensory information to the brain. The fast excitatory synaptic potentials are mediated by the release from the nociceptor central terminals of the excitatory amino acid glutamate and its action on ligand-gated ion channel receptors on the postsynaptic membrane of the central neurons (14). The thalamus receives only a small fraction of the sensory input that enters the spinal cord as a result of the activation of action potentials in dorsal horn projecting neurons, and it relays this information to the cortex. Most input fails to evoke an action potential output or is involved in local processing, refining, modulating, and controlling of the sensory transfer. The central terminals of nociceptors contain presynaptic receptors that can alter transmitter release. The presynaptic central axonal terminal is a major site of the action of opioids, cannabinoids, γ-aminobutyric acid (GABA) receptor ligands, and the anticonvulsant gabapentin, which acts on the $\alpha_2\delta$ subunit of voltage-gated calcium channels to reduce transmitter release. Postsynaptic inhibition involves a hyperpolarizing inhibitory potential evoked in dorsal horn neurons by the opening of potassium or chloride channels in response to opioids and GABA. Opioids are effective because they act at multiple sites simultaneously (presynaptic and postsynaptic regions, as well as various areas of the nervous system).

Sensory processing is controlled through local segmental circuits in the spinal cord and by descending tonic and phasic inhibitory and facilitatory influences arising from the brain. The inhibitory mechanisms are sufficiently powerful that they can override nociception, stopping transfer of sensory inflow to the pain perception areas in the cortex. This inhibition is a feature of the fight-or-flight reaction to life-threatening situations: Reaction to danger takes precedence over pain even in the face of severe injury. Inhibition can also be activated by complex inputs, contributing to placebo analgesia and the pain relief produced by such ritualized treatments as acupuncture or osteopathic manipulations. However, these effects are generally unpredictable and rely heavily on the suggestibility and belief system of the patient. Counterirritation and low-threshold afferent inputs (transcutaneous electrical nerve stimulation or dorsal column stimulation) also activate inhibitory mechanisms, but efficacy is generally small and short lasting. Greater success is achieved by pharmacologic manipulation of inhibitory circuits, in particular ligands for the μ opioid receptor, which mediate all of the actions of morphine (20). This receptor is also widely expressed outside of pain-related parts of the nervous system, which accounts for the common side effects of its agonists: nausea, sedation, cognitive dysfunction, constipation, and respiratory depression.

The more intense the peripheral noxious stimulus, the higher the frequency and the longer the duration of the train of action potentials activated in the nociceptors. High-frequency action potentials result in release of neuropeptides, such as substance P; the neuromodulator brain-derived neurotrophic factor; and the fast synaptic transmitter glutamate from the nociceptor central terminals in the spinal cord. The neuropeptides act on G-protein–coupled receptors to produce slow, more sustained synaptic currents than does glutamate, and brain-derived neurotrophic factor acts on tyrosine kinase receptor B to modify membrane excitability (14). Neuropeptide-mediated slow synaptic potentials, together with activation by glutamate of the *N*-methyl-D-aspartic acid (NMDA) receptor, provides an opportunity for activity- or use-dependent plasticity to occur (14). At resting membrane potentials, the NMDA receptor ion channel is physically blocked by a magnesium ion so that no current flows if glutamate binds to the receptor; activation of the NMDA receptor by glutamate produces excitation only when this block is relieved by depolarization. One form of activity-dependent plasticity is a progressive increase in the output from dorsal horn neurons in response to closely timed repeated input; this phenomenon, known as *wind-up,* represents an acute form of pain amplification during the course of a train of stimuli and is responsible for the increasing pain experienced in response to closely repeated stimulation of the skin by noxious heat.

Projection neurons in the dorsal horn transfer nociceptive input to the brainstem, hypothalamus, and thalamus and then, through relay neurons, to the cortex. Functional imaging and positron emission transmission scanning permit precise mapping of the cortical areas activated by noxious stimuli that produce the perceptual and aversive components of pain and provide indications of cortical activation during pain, an objective surrogate for the subjective experience (12).

Peripheral Sensitization

Injury to and inflammation of tissue result in profound changes to the chemical environment of the peripheral terminal of nociceptors. Damaged cells release intracellular contents, such as adenosine triphosphatase and K^+ ions; pH decreases; and cytokines, chemokines, and growth factors, are produced by inflammatory cells recruited to the site of damage (21). Some of these factors act directly on the nociceptor terminal to activate it and produce pain (*nociceptor activators*), and others sensitize the terminal so that it becomes hypersensitive to subsequent stimuli (*nociceptor sensitizers*) (**Figure 2B**). Adenosine triphosphatase, for example, is released in millimolar quantities by injured cells into the extracellular space. Activation by adenosine triphosphatase of the ligand-gated $P_{2\times3}$ purinoreceptor enables immediate detection by nociceptors of tissue damage (16). Protons, in contrast, build up slowly after tissue damage and act on acid-sensitive ion channels and the transient receptor potential V1 channel expressed by nociceptors to produce pain some time after injury (22). The prostanoid prostaglandin E_2 and nerve growth factor

bind to G-protein–coupled prostaglandin E and tyrosine kinase A receptors, respectively, to alter the sensitivity of the terminal without producing direct nociceptor activation (23). Bradykinin, a peptide produced by kallikrein-mediated cleavage of kininogens, activates and sensitizes the terminal through its constitutive B_2 receptor (24). B_1 bradykinin receptors are expressed only after injury or inflammation.

Prostanoid production at the site of tissue injury, a major element of the inflammatory reaction, results from generation of arachidonic acid from membrane phospholipids by phospholipase A_2. Cyclooxygenase-2 (COX-2) converts arachidonic acid into prostaglandin H, which is converted into specific prostanoid species, such as prostaglandin E_2, by prostaglandin synthases (25). Cyclooxygenase-2, phospholipase A_2, and prostaglandin E synthases are inducible enzymes that are not constitutively present in most noninflamed tissues. Cyclooxygenase-2 is induced in response to interleukin-1β and tumor necrosis factor-α. Because this induction occurs several hours after initiation of the inflammation (**Figure 2B**) (25), nonsteroidal anti-inflammatory drugs or COX-2 selective agents have no effect on nociceptive or immediate inflammatory pain. They do, however, have an immediate analgesic action in such conditions as rheumatoid arthritis, in which COX-2 is expressed chronically as a result of maintained inflammation.

Sensitizing agents, such as prostaglandin E_2, reduce the threshold of activation of nociceptor terminals and increase the responsiveness of the terminal by binding to specific receptors expressed on the membrane of the nociceptor terminal (for example, the prostaglandin E receptor). These receptors are coupled to intracellular kinases in the cytoplasm of the terminal. Activation of adenyl cyclase by prostaglandin E increases levels of cyclic adenosine monophosphate, which activates cyclic adenosine monophosphate–dependent protein kinase A. Release of calcium stores from microsomes in the terminal or calcium entry through channels in the membrane activates the calcium-activated protein kinase C (**Figure 2B**) (16). Protein kinase A and protein kinase C phosphorylate the amino acids serine and threonine in many proteins. Phosphorylation of proteins constitutes post-translational processing, a change in the chemical make-up of a protein produced after its synthesis (or translation) from messenger RNA. Such phosphorylation can dramatically alter the activity of receptors and ion channels. The heat-sensitive transducer transient receptor potential V1 channel, for example, normally has a threshold of activation of 42 °C, the temperature at which we begin to experience heat as painful. After its phosphorylation, however, the threshold decreases to close to normal body temperature (26). Production of prostaglandin E_2 after COX-2 induction in such conditions as sunburn causes the threshold of pain due to heat to decrease. This effect, which is restricted to the site of the inflammation, accounts for the burning pain experienced in response to a warm shower in persons with sunburn. The threshold and kinetics of voltage-gated sodium ion channels, such as Nav1.8, are also altered by phosphorylation, increasing membrane excitability. More action potentials than normal are produced in the nociceptor terminal (27). Because several sensitizers are present (prostaglandin E_2, nerve growth factor, and bradykinin), blocking production of only 1 of these substances at any time will not eliminate peripheral sensitization. This factor contributes to the ceiling effect of such drugs as COX-2 inhibitors. Peripheral sensitization decreases the threshold of high-threshold and silent nociceptors and plays a major role in increasing sensitivity to pain at the site of injury or inflammation. Several features of peripheral sensitization manifest early during post-herpetic neuralgia, including a reduction in the threshold of pain caused by heat at the site of erythematous skin (28). Later in the natural history of the disease, innervation of the skin by nociceptors is lost, sensitivity to heat pain caused by heat is reduced, and the severe sensitivity to tactile pain experienced by many patients reflects abnormal responses in the central nervous system to low-threshold fibers that usually elicit only innocuous sensations rather than altered peripheral sensitivity.

Transcriptional and Post-Transcriptional Regulation in Sensory Neurons

The functional properties, intrinsic excitability, and susceptibility to pharmacologic agents of sensory neurons are not fixed but rather depend on the nature and levels of the different proteins expressed by the sensory neurons (**Figure 2C**). For example, after peripheral inflammation, there is an increase in the level of the heat-sensitive transient receptor potential V1 channel in the peripheral terminal of nociceptors, increasing peripheral sensitivity to heat (29), and in levels of the synaptic modulators substance P and brain-derived neurotrophic factor (30), amplifying central input to the spinal cord. These changes result from increased production of nerve growth factor in the inflamed tissue. This growth factor is transported from the periphery to the cell body of the sensory neuron in the dorsal root ganglion, where it activates intracellular signaling pathways that include the mitogen-activated protein kinase p38 (**Figure 2C**) (29). After a peripheral axonal injury, the number of μ opiate receptors decreases and the number of $\alpha_2\delta$ calcium-channel subunits increases, contributing to reduced sensitivity to morphine and increased sensitivity to gabapentin (31). Alterations in the expression and distribution of sodium and potassium ion channels after nerve injury increase membrane excitability such that ectopic impulses begin to be generated without any peripheral stimulus; this ectopic excitability is a major contributor to spontaneous neuropathic pain (32).

Central Sensitization

In the same way that the peripheral terminal of the nociceptor can be sensitized, central nociceptor transmission neurons in the dorsal horn of the spinal cord or in the

spinal nucleus of the trigeminal can also be sensitized. Central and peripheral sensitization are the major causes of hypersensitivity to pain after injury. Central sensitization amplifies and facilitates the synaptic transfer from the nociceptor central terminal to dorsal horn neurons (**Figure 3A**). Initially, it is triggered in central neurons by nociceptor input into the spinal cord (that is, it is activity dependent) (**Figure 3B**). Later, it is sustained beyond the initiating stimulus by transcriptional changes in the molecular machinery of the cell (that is, it becomes transcription dependent) (**Figure 3C**) (14, 33).

In general, the alterations underlying central sensitization are similar to those that produce peripheral sensitization. Intracellular kinases are activated, leading to phosphorylation of ion channels and receptors, and genes are then induced, changing the chemical character or phenotype of the neuron. Peripheral and central sensitization are an expression of the plasticity or modifiability of the nervous system, which molds itself to new functions in response to changing inputs (in this case, tissue injury). Within seconds of a massive barrage of sensory inflow from an injured tissue or a damaged nerve, neurons in the spinal cord that receive this sensory input become hyperresponsive. After this reaction, inputs that would normally have been undetectable now evoke outputs; normally innocuous stimuli, such as a light touch to the skin, now elicit pain; and areas well outside an injured site become tender (secondary hyperalgesia) (14).

Central sensitization requires brief but intense nociceptor activity to be initiated: for example, a surgeon's cutting through skin by using a scalpel. It is also produced by sensitized nociceptors during inflammation and by spontaneous ectopic activity generated in sensory neurons after nerve injury. Central sensitization begins with a cascade of events in the dorsal horn of the spinal cord that are triggered by release of transmitters from nociceptor central terminals, leading to alterations in synaptic receptor density, threshold, kinetics, and activation, and thus dramatically increasing transmission of pain. One key receptor involved in these changes is the glutamate-activated NMDA receptor. During central sensitization, this receptor is phosphorylated, which increases its distribution from intracellular stores to the synaptic membrane and its responsiveness to glutamate. Increased responsiveness to glutamate occurs by removal of the voltage-dependent Mg^{2+} ion block of the NMDA channel and increasing the time during which the channel is open. The increase in excitability of the cell means that it can be activated by inputs that are normally subthreshold and that its response to suprathreshold inputs increases. The recruitment of subthreshold inputs manifests as a reduced threshold for eliciting pain (allodynia), an exaggerated or amplified response to noxious stimuli (hyperalgesia), and the spread of sensitivity to noninjured areas (secondary hyperalgesia). Inhibition of the NMDA receptor by using the competitive NMDA receptor antagonist ketamine, a short-lasting anesthetic, reduces the early phase of central sensitization (34) and the resultant hypersensitivity to pain (35). However, the widespread distribution of the NMDA receptor in the brain means that unacceptable psychotomimetic effects accompany this analgesic activity. Thus, ketamine has good efficacy but poor clinical utility. Development of drugs that block central sensitization without side effects is being actively pursued.

After these early activity-dependent post-translational changes to existing proteins that alter their distribution and function, changes occur in gene regulation in central neurons, including induction of new proteins and effects on the levels of expression of existing proteins (**Figure 3C**). Some of the changes in gene expression are driven by synaptic-mediated activation of intracellular signal transduction pathways and are restricted to parts of the nervous system that receive inputs from the injured tissue. One example is the endogenous opioid peptide dynorphin, which is regulated by mitogen-activated protein kinases (36) and a repressor, downstream regulatory element-antagonist modulator (37).

Other genes are more widely activated. Cyclooxygenase-2, for example, begins to be expressed in neurons in many areas of the central nervous system several hours after a localized peripheral tissue injury (38). This expression is initiated not by sensory inflow into the spinal cord but by a circulating humoral factor released by inflammatory cells that acts on the endothelial cells of the cerebral vasculature to produce interleukin-1β. The interleukin-1β enters the cerebrospinal fluid and acts on neurons that express the interleukin-1 receptor to produce COX-2 (38). The resultant increase in prostaglandin E_2 has many presynaptic and postsynaptic actions that facilitate synaptic transmission and increase excitability, contributing to a late-onset, prolonged, and diffuse phase of central sensitization (**Figure 3**) (38). The widespread central induction of COX-2 contributes to the generalized aches and pains, loss of appetite, and changes in mood and sleep cycle that together constitute the sickness or illness syndrome, a feature of inflammatory diseases.

These findings have important implications for therapy. First, COX-2 inhibitors must be targeted to central as well as peripherally induced COX-2. The central site of their action appears to be a major component of their analgesic activity. In addition, treatment aimed at reducing sensory inflow into the central nervous system, such as regional or epidural local anesthesia during surgery, will not prevent the humoral-mediated central induction of COX-2 and may need to be supplemented by therapy with COX-2 inhibitors. Central sensitization contributes to the hyperresponsive conditions of postoperative pain, migraine, neuropathic pain, fibromyalgia, and gastrointestinal tract pain.

Neuroimmune and Neuron–Glial Interactions

Peripheral sensitization is a form of neuroimmune interaction that results from the action of chemical signals produced by inflammatory cells on nerve fibers. Other, similar interactions are central induction of COX-2 in central neurons in response to a humoral inflammatory signal and the consequent central release of interleukin-1 and the massive activation of microglia in the spinal cord in response to peripheral nerve injury (39, 40). These macrophage-like cells are quiescent in the normal spinal cord but are rapidly activated after nerve injury and are probably a source of many cytokines and chemokines that act on neurons and their supporting glia to alter their properties or patterns of gene transcription. Changes in peripheral glia (Schwann cells) after nerve injury contribute to the direct activation of neighboring injured and noninjured sensory fibers by releasing such signaling substances as tumor necrosis factor-α and growth factors (39). Central glia (astrocytes) may play a similar role.

Augmented Facilitation

The powerful controls exerted by the brain on sensory processing in the spinal cord, and on its equivalent for the face—the trigeminal nucleus of the medulla—are both inhibitory and facilitatory. Relatively little is known about the normal role of descending facilitatory influences, but indications exist that these positive controls are activated or augmented after both inflammation and peripheral nerve injury and in this way contribute to the general increase in sensory transmission (41). Prevention of such facilitation may help reduce hypersensitivity to pain.

Structural Reorganization

The central terminals of nociceptor sensory neurons terminate in a distinct area of the spinal cord, the most superficial laminae of the dorsal horn. In contrast, low-threshold sensory fibers activated by touch, pressure, vibration, and normal ranges of movement of joints terminate in the deep laminae of the dorsal horn. Experiments in rodents have shown that physical rearrangement of this circuitry occurs after peripheral nerve injury: In several weeks, new growth or sprouting of the central terminals of the low-threshold afferents into the zone normally occupied exclusively by the nociceptor terminals is observed (42). It has not been possible to determine whether a similar structural rewiring of the connectivity of the spinal cord occurs in patients and underlies their heightened sensitivity to pain. Such a phenomenon would explain the intractability of many neuropathic pain conditions and raise the issues of how to prevent these changes and whether they are irreversible. It is known that the exquisite pain sensitivity to light touch in patients with neuropathic pain is due an abnormal central response to low-threshold sensory fibers that usually elicit only touch sensations (43). This abnormal central reaction to normal sensory input could be due to central sensitization and structural reorganization, as well as to loss of inhibition (disinhibition).

Disinhibition

Powerful tonic and phasic inhibitory mechanisms that act presynaptically and postsynaptically focus sensory input so that it produces a limited, appropriate, and brief response to any given input. Within the spinal cord, this inhibition is mediated by inhibitory neurons that release the inhibitory transmitters glycine and GABA. Descending inhibitory inputs from the brain stem operate through norepinephrine and serotonin. Pharmacologic removal of spinal GABA and glycine inhibition by injection of receptor antagonists produces a hypersensitivity to pain similar to that associated with peripheral nerve injury, indicating that the ongoing inhibition substantially affects the pain system.

Central sensitization produces hypersensitivity to pain, by directly increasing excitation. However, pathologic loss of inhibition (disinhibition) can also lead to increased excitability and pain. Peripheral nerve injury results in substantial loss of inhibitory currents, particularly those mediated by GABA (44), and administration of GABA-mimetics reduces neuropathic pain (45). This suggests that disinhibition contributes to hypersensitivity in patients with neuropathic pain (**Figure 3D**). One cause of such disinhibition is a selective death of GABAergic inhibitory interneurons after nerve injury. One week after nerve injury that produces hypersensitivity to pain, neurons begin to undergo apoptosis in the dorsal horn (44). The apoptosis may be excitotoxic, due to excessive glutamate release or failure of glutamate uptake, or result from cell death–inducing signals, such as release of tumor necrosis factor-α from activated microglia. If disinhibition is a major feature of the neuropathic pain experienced by patients, the syndrome may be at least in part a neurodegenerative disease. We should consider treatment aimed at preventing loss of neurons and, thereby, development of pain. Such a strategy requires identification of patients at risk and development of therapy that prevents activation of apoptotic pathways.

The Future of Pain Management

Identification of the multiple mechanisms responsible for production of distinct pain syndromes and their molecular components has been a major advance in our understanding of pain. Future steps require the development of diagnostic tools that will allow us to identify the mechanisms of pain in an individual patient and pharmacologic tools that act specifically on these mechanisms. This strategy will allow us to take a rational rather than an empirical trial-and-error approach to controlling pain. Treatment with COX-2 inhibitors has a clear role if induction of COX-2 is substantially contributing to a patient's pain, as is the case in most inflammatory conditions. However, such drugs offer no benefit to patients whose pain is due mainly to ectopic excitability caused by abnormal sodium-channel activity after nerve injury, as in those with painful diabetic peripheral neuropathy. Since mechanisms of pain

may coexist, a polypharmacy approach may be indicated to target each cause, thereby achieving additive effects.

Definition of analgesics by the severity (mild, moderate, or severe) or duration (acute or chronic) of pain is not informative, although the U.S. Food and Drug Administration still uses these descriptions on labels for these drugs. Not all patients with persistent pain have similar mechanisms (for example, osteoarthritis is sensitive to COX-2 inhibitors, whereas the pain of spinal cord injury is not). Similarly, intensity does not reflect the neurobiological causes, only the extent to which they are activated. The relatively poor efficacy of current treatment for neuropathic pain may reflect that even in single disease entities, only some patients respond to the therapy. Response or lack thereof may be due to the presence or absence of the targeted mechanism at a particular time in the natural history of the syndrome. This idea is true for post-herpetic neuralgia, in which topical lidocaine works only in patients with sensitized nociceptors; once these are lost as the disease progresses, tactile pain is centrally driven and centrally acting treatment is required.

Now that we are beginning to appreciate that some aspects of pain are an expression of a malfunction or disease of the nervous system, we must develop a disease-modifying treatment strategy to complement the existing approach of symptom control. The means to prevent the phenotypic switches, structural reorganization, and loss of inhibitory circuits that seem to underlie the most severe and intractable forms of pain will be required. The challenge is certainly great, but so is the need.

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Potential Financial Conflicts of Interest: None disclosed.

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