



What is this thing called pain?

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To paraphrase Cole Porter's famous 1926 song, "What is this thing called pain? This funny thing called pain, just who can solve its mystery?" Pain, like love, is all consuming: when you have it, not much else matters, and there is nothing you can do about it. Unlike love, however, we are actually beginning to tease apart the mystery of pain. The substantial progress made over the last decade in revealing the genes, molecules, cells, and circuits that determine the sensation of pain offers new opportunities to manage it, as revealed in this Review series by some of the foremost experts in the field.

Classifying pain

What exactly, from a neurobiological perspective, is pain? Pain is actually three quite different things, although we and many of our physicians commonly fail to make the distinction. First, there is the pain that is an early-warning physiological protective system, essential to detect and minimize contact with damaging or noxious stimuli. This is the pain we feel when touching something too hot, cold, or sharp. Because this pain is concerned with the sensing of noxious stimuli, it is called *nociceptive* pain (Figure 1A), a high-threshold pain only activated in the presence of intense stimuli (1). The neurobiological apparatus that generates nociceptive pain evolved from the capacity of even the most primitive of nervous systems to signal impending or actual tissue damage from environmental stimuli. Its protective role demands immediate attention and action, which occur by virtue of the withdrawal reflex it activates, the intrinsic unpleasantness of the sensation elicited, and the emotional anguish it engages. Nociceptive pain presents itself as something to avoid now, and when engaged, the system overrules most other neural functions.

The second kind of pain is also adaptive and protective. By heightening sensory sensitivity after unavoidable tissue damage, this pain assists in the healing of the injured body part by creating a situation that discourages physical contact and movement. Pain hypersensitivity, or tenderness, reduces further risk of damage and promotes recovery, as after a surgical wound or in an inflamed joint, where normally innocuous stimuli now elicit pain. This pain is caused by activation of the immune system by tissue injury or infection, and is therefore called *inflammatory* pain (Figure 1B); indeed, pain is one of the cardinal features of inflammation. While this pain is adaptive, it still needs to be reduced in patients with ongoing inflammation, as with rheumatoid arthritis or in cases of severe or extensive injury.

Finally, there is the pain that is not protective, but maladaptive, resulting from abnormal functioning of the nervous system. This *pathological* pain (Figure 1C), which is not a symptom of some disorder but rather a disease state of the nervous system, can occur after damage to the nervous system (neuropathic pain), but also in conditions in which there is no such damage or inflammation (dysfunctional pain). Conditions that evoke dysfunctional pain include fibromyalgia, irritable bowel syndrome, tension type headache, temporomandibular joint disease, interstitial cystitis,

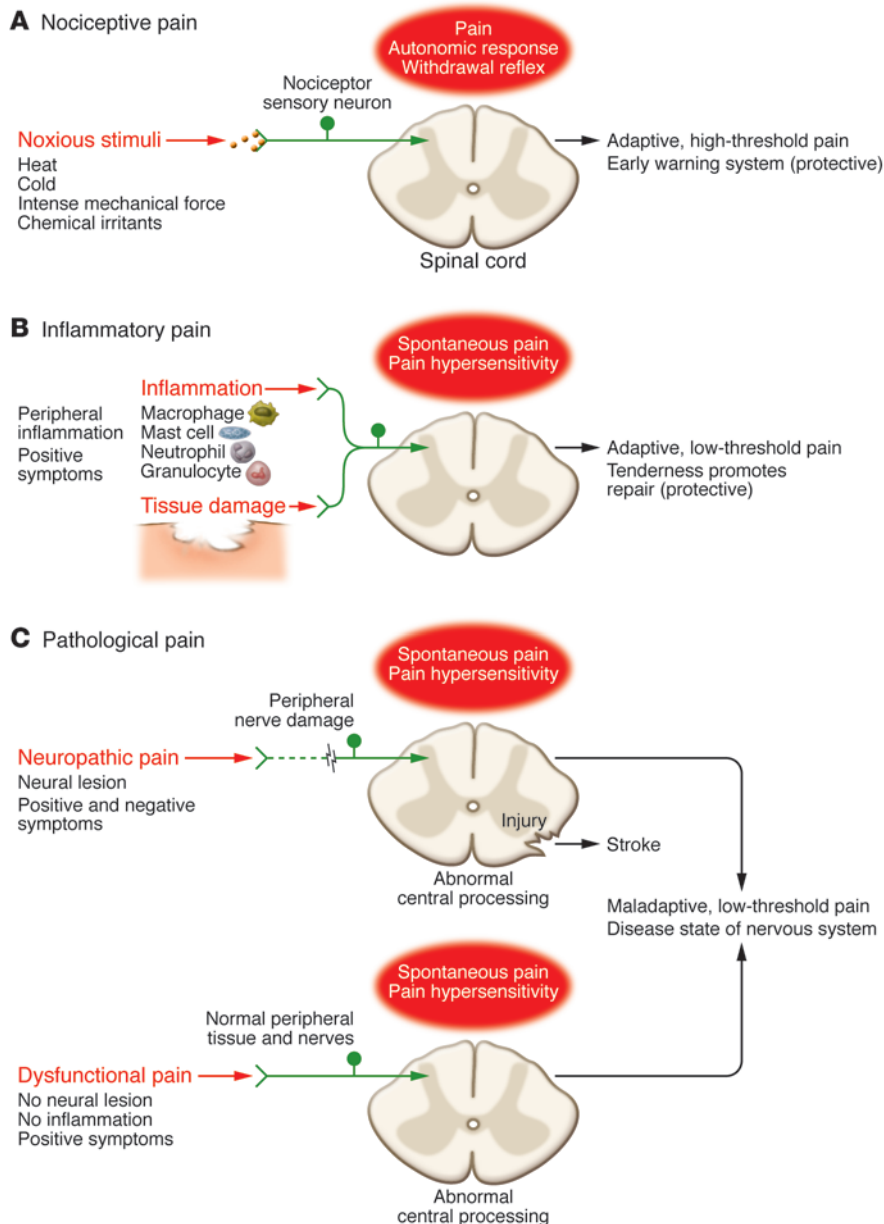
and other syndromes in which there exists substantial pain but no noxious stimulus and no, or minimal, peripheral inflammatory pathology. The clinical pain syndrome with the greatest unmet need, pathological pain is largely the consequence of amplified sensory signals in the central nervous system and is a low-threshold pain. By analogy, if pain were a fire alarm, the nociceptive type would be activated appropriately only by the presence of intense heat, inflammatory pain would be activated by warm temperatures, and pathological pain would be a false alarm caused by malfunction of the system itself. The net effect in all three cases is the sensation we call pain. However, because the processes that drive each are quite different, treatments must be targeted at the distinct mechanisms responsible.

The upside of pain

Nociceptive pain is not a clinical problem, except in the specific context of surgery and other clinical procedures that necessarily involve noxious stimuli, where it must be suppressed by local and general anesthetics or high-dose opioids. Lack of nociceptive pain is, however, a problem. Congenital insensitivity or indifference to pain due to rare missense or in-frame deletions of *SC9A*, the gene that encodes the voltage-gated sodium channel $Na_v1.7$ (as reviewed by Raouf et al.; ref. 2), or loss-of-function mutations in the neurotrophic tyrosine kinase receptor TrkA and nerve growth factor (hereditary sensory and autonomic neuropathy type IV) typically result in self mutilation, bone fractures, multiple scars, joint deformities, amputations, and early death, underscoring the important protective role of nociceptive pain (3). The importance of preserving nociceptive pain is also revealed when peripheral neuropathy leads to a sensory denervation of joints, resulting in Charcot neuro-osteoarthropathy, with severe deformities due to joints damaged because of a lack of pain sensitivity (4, 5). Nociceptive pain is, therefore, a pain essential for maintaining bodily integrity. Although we use analgesics clinically to reduce pain (as reviewed by Burgess and Williams; ref. 6), we nevertheless need to be careful that patients' nociceptive pain is not so blunted by the therapy that its protective role is lost (7). An expected side effect of antagonists for TRPV1, the noxious heat detector, would be that patients may burn themselves because they cannot differentiate warm and hot stimuli. Even in disease states, nociceptive pain may be protective; for example, excessive use of an osteoarthritic joint because of complete pain relief could conceivably accelerate joint destruction. Thus, symptomatic treatment without disease-modifying interventions may be problematic in some settings.

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**Figure 1**

Pain classification. Pain can be broadly divided into three classes. **(A)** Nociceptive pain represents the sensation associated with the detection of potentially tissue-damaging noxious stimuli and is protective. **(B)** Inflammatory pain is associated with tissue damage and the infiltration of immune cells and can promote repair by causing pain hypersensitivity until healing occurs. **(C)** Pathological pain is a disease state caused by damage to the nervous system (neuropathic) or by its abnormal function (dysfunctional).

scious awareness of the sensation occurs. As reviewed by Ossipov et al., pain involves active regulation by excitatory and inhibitory circuits in the central nervous system, controlled primarily by nuclei in the brainstem that can either diminish or exaggerate pain depending on mood, cognitive function, and memories (10). The function of these pain modulatory circuits appears to be disturbed in diverse pathological conditions, contributing to the abnormal pain amplification. While cortical influences commonly increase pain, they also can reduce it, and this provides the neurobiological basis for placebo and suggestion (11), the basis for alternative therapies like acupuncture. Some analgesics, such as opioids, mimic activity in inhibitory circuits (12); others, like dual amine uptake inhibitors, increase the inhibitory tone generated by norepinephrine (13).

Visualizing pain

For many years, the study of nociceptive pain was restricted to analysis of sensory neurons and circuits in the spinal cord because it was difficult to examine how the brain processed pain signals in anesthetized animals, where the standard definition of adequate anesthesia is loss of pain-related behavior. However,

functional imaging in human volunteers and patients has allowed for definition of those brain areas activated by nociceptive inputs, as reviewed by Schweinhardt and Bushnell (14). This work has revealed a wide range of different brain areas that constitute what has been called the pain matrix; these areas are activated during the encoding of nociceptive pain's location, intensity, duration, quality, and emotional associations and show how pain can be influenced by attention, distraction, and manipulation of mood. Indeed, these studies have both focused attention on the important nonsensory components of pain and revealed that chronic pain is associated with apparent structural changes in the brain, reinforcing the notion of chronic pain as a disease of the nervous system.

Targeting sensitivity

The major characteristics of inflammatory and pathological pain are that noxious stimuli are no longer required to generate pain;

Decoding molecular sensation

Dubin and Patapoutian review how a specific subset of sensory neurons is specialized to respond only to noxious stimuli by expressing proteins that detect intense hot, cold, mechanical, and chemical stimuli and transduce these into currents in the sensory fiber peripheral terminals that then activate action potential signaling (8). In many respects, the molecular elucidation of different noxious stimulus detectors has been one of the great achievements in modern pain neurobiology. However, although it is clear that there are specific pain-related sensory channels in the peripheral nervous system that drive nociceptive pain, it is also clear that sensation arises both from activation of these "labeled lines" and from the interactions between different sensory channels, as reviewed by Ma (9). In addition, pain is not simply a switch that, once activated in the periphery, inevitably results in the transmission of signals to the part of the cortex where con-



indeed, pain may arise spontaneously in the absence of any stimulus. Considerable effort devoted to elucidating the mechanisms responsible has revealed that the nociceptive system is capable of undergoing enormous change or plasticity when exposed to inflammatory mediators and growth factors, in response to activity, and after injury (15). The changes occur in nociceptors, whose peripheral terminals become sensitized during inflammation. Furthermore, axons can become sufficiently hyperexcitable to generate spontaneous action potentials, cell bodies undergo dramatic changes in the expression and trafficking of proteins, and synapses in the spinal cord can change their strength or undergo structural reorganization. Similar changes take place in the spinal cord and brain, involving neurons and non-neuronal cells, and these changes are responsible for facilitating the responses to peripheral inputs – a phenomenon known as central sensitization – so that the threshold for generating pain falls and its duration, amplitude, and spatial distribution increase (16). In essence, this represents an uncoupling of nociceptive pain from its absolute need for noxious stimuli. A big difference between inflammatory and pathological pain is that the former represents hypersensitivity in reaction to a defined peripheral pathology, whereas the latter is the result of altered neural processing. Nevertheless, defining what the changes in the system are, when and how they occur, and what molecular

mechanisms are responsible provides enormous opportunity for therapeutic intervention, although this has not yet been successfully tapped by the pharmaceutical industry (6). Intriguingly, it seems clear that susceptibility to pain hypersensitivity and conversion from acute to chronic pain has a large heritable component (17–19), and we now need to define exactly who is at risk as well as discover means of reducing such risk pharmacologically.

Given the complexity of pain, it is extremely encouraging that it has turned out to be surprisingly amenable to formal study using genetic, molecular, electrophysiological, imaging, and behavioral techniques, as discussed in the Reviews in this series. Moreover, such study has provided both insight into the nature and mechanisms of pain and a path to developing novel analgesics with greater efficacy and less side-effect burden, something that is much needed.

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