

Review

The fundamental unit of pain is the cell



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ABSTRACT

The molecular/genetic era has seen the discovery of a staggering number of molecules implicated in pain mechanisms [18,35,61,69,96,133,150,202,224]. This has stimulated pharmaceutical and biotechnology companies to invest billions of dollars to develop drugs that enhance or inhibit the function of many these molecules. Unfortunately this effort has provided a remarkably small return on this investment. Inevitably, transformative progress in this field will require a better understanding of the functional links among the ever-growing ranks of “pain molecules,” as well as their links with an even larger number of molecules with which they interact. Importantly, all of these molecules exist side-by-side, within a functional unit, the cell, and its adjacent matrix of extracellular molecules. To paraphrase a recent editorial in *Science* magazine [223], although we live in the Golden age of Genetics, the fundamental unit of biology is still arguably the cell, and the cell is the critical structural and functional setting in which the function of pain-related molecules must be understood. This review summarizes our current understanding of the nociceptor as a cell-biological unit that responds to a variety of extracellular inputs with a complex and highly organized interaction of signaling molecules. We also discuss the insights that this approach is providing into peripheral mechanisms of chronic pain and sex dependence in pain.

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1. The nociceptor: a model cell

Among the earliest studies of the cell biology of pain were those performed by Perl and colleagues, starting nearly a half century ago [21,39,186,186]. Their work provided the fundamental insight that different nociceptors respond to different forms of noxious stimulation (ie, mechanical, thermal, and diverse chemicals), alone or in various combinations [186,221], those responding to multiple sensory modalities of noxious stimuli being referred to as polymodal nociceptors [157,185,188,205]. These studies introduced the critically important concept that primary afferent nociceptors are a heterogeneous group of cells that contribute to different forms of pain. It was not, however, until several decades later, that we began to elucidate the molecular basis of the transduction processes of these different forms of noxious stimuli. Although there remain gaps in our knowledge of the molecular identity of transducers for various forms of noxious stimuli, and even of which cells in each tissue the transducers are located, considerable progress has been made in our understanding of nociceptor transduction mechanisms [24,68,90,105,108].

For thermal transduction, the transient receptor potential (TRP) family of ligand-gated ion channels composes a group of transducing ion channels that gate at different temperatures, some in the noxious range [171,203,212,232]. This class of ion channels has been demonstrated to be present in sensory neurons that express other features of nociceptors (eg, expression of neuropeptides and specific types of sodium channels) [17,183,241]. However, TRP channels are not the only transducers implicated in detecting noxious thermal stimuli [49,170,182,190].

TRP channels [89,102,238] have also been implicated in transduction of noxious chemical stimuli, as have acid sensing ion channels (ASICs) [101,240]. A large number of other ligand-gated ion channels and G-protein-coupled receptors also contribute to chemical nociception, including ion channels for detection of hydrogen ions (acid, low pH) [24,25,119]; TRPA1, which responds to multiple noxious chemical substances [70,137,210]; ligand-gated ion channels (P2X) and G-protein-coupled (P2Y) receptors that detect purines [138,163,230]; and G-protein-coupled receptors for prostaglandins, the target of a major class of analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) [56,122], to name only a small number of a still-growing list of transducers for noxious chemical stimuli. Of note, progress has recently been made in studying the most recalcitrant sensory modality in the primary afferent nociceptor—mechanical transduction—with the recent identification of Piezos by Patapoutian and colleagues [54]. Some

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transducers respond to stimuli of more than 1 sensory modality; the most well studied being TRPV1, the “capsaicin receptor,” which responds to heat and low pH, as well as to the noxious component of the chili pepper, capsaicin [42,220], and recently evidence has been presented to suggest that it may even play a role in mechanical transduction [126,140,231]. Similarly, TRPA1 is considered to be a transducer for many noxious irritant substances [70,87,103].

The populations of nociceptors that contain various transducers terminate in different lamina of the spinal cord and at different depths in tissues, such as the skin [33,52,150,211,214,251], providing further support for the suggestion that they define groups of nociceptors that play very different roles in the cell biology of pain [32–34,68,154,193,217]. Although most of these transducers appear to be located on the peripheral terminals of primary afferent nociceptors, recent findings suggest that some may actually be located on non-neuronal cells, which in turn release mediators that signal to the nociceptor. The best-studied cell, in this regard, is the keratinocyte [134,204,235]. Although the most compelling evidence for a role of keratinocytes in sensory transduction relates to the detection of non-noxious warmth [51,192], keratinocytes contain transducers for a variety of noxious stimuli, for example, TRPV1 and TRPA1 [13,74,109]. The potential importance of this indirect transduction mechanism in peripheral pain mechanisms is currently being investigated.

A second, unique, dimension of the function of the primary afferent nociceptor is its ability to be sensitized—that is, to undergo a decrease in threshold for activation as well as enhanced response to a stimulus of the same intensity. Sensitization is thought to play an important role in diverse pain syndromes, both inflammatory and neuropathic [26,65,76,78,114,115,117,118,179–181,194]. Sensitization in the primary afferent nociceptor contrasts with the function of sensory neurons that transduce other somatic (eg, touch, tickle, pressure) and special (eg, vision, taste, smell, and hearing) sensory modalities in that repeated stimulation tends to desensitize those neurons [85,120,128,142,168,198]. A large number of studies of nociceptor sensitization have elucidated the role of 2 classic second messenger signaling pathways in which cAMP/protein kinase A (PKA) and protein kinase C (PKC) play key roles [6,46,48,64,162,179,194,237]. As it is beyond the scope of this review to trace in detail the second messenger signaling pathways involved in nociceptor sensitization, the reader is referred to reviews that develop this aspect of the cell biology of the nociceptor in more detail [194].

The targets of these second messenger signaling pathways, for the most part voltage- and ligand-gated ion channels, have also been studied in detail. Thus, multiple members of sodium [15,45,91,202], potassium [37,97,249], and calcium [45,144,169] ion channel families have been demonstrated to play a role in nociceptor sensitization. This can occur by phosphorylation of the channels [23,139,184,248] or by their insertion or removal from the plasma membrane [47,110,173,200,248]. One novel association between transduction and sensitization is found in a population of nociceptors that, under basal conditions, are mechanically insensitive, and are thus termed mechanically insensitive afferents [36,160] or “silent” nociceptors [88,206], but which, on exposure to inflammatory mediators, develop the ability to respond to mechanical stimulation [197,199]. Given that such mechanically insensitive afferents may play a role in some forms of pain [84,88,107], the mechanisms underlying the development of mechanical transduction of silent nociceptors on exposure to inflammatory mediators remains an important question.

It is on this historical foundation of the biology of the primary afferent nociceptor that we will discuss cell biology approaches to primary afferent nociceptor function and what they have begun to teach us about mechanisms of acute and chronic pain.

2. Contributions to pain from the extracellular environment of the nociceptor

The extracellular environment of the nociceptor relevant to the production of pain has classically been considered to consist of inflammatory mediators—cytokines and chemokines that are products of immune system cells that can sensitize nociceptors, and neurotrophic factors that, in addition to being important for the health of sensory neurons, can also contribute to the development of pain when present at elevated levels [158,172,174,189,201,202]. Of note, the observation that individual neurotrophic factors act on different populations of nociceptors has helped to establish the idea that subpopulations of nociceptors contribute to the development of specific pain syndromes. Among the earliest studies of the role of inflammatory mediators in peripheral pain mechanisms, the prostaglandins, cyclooxygenase products of arachidonic acid metabolism, were identified, and are the target of 1 of the most important and widely used classes of analgesics, NSAIDs [80,81,216,226]. Novel therapeutic possibilities for the treatment of some forms of chronic intractable pain are presented by more recently developed inhibitors (eg, cytokine and chemokine antagonists) for other inflammatory mediators that include tumor necrosis factor- α (TNF α) [2,191], interleukin 6 (IL-6) [12,40], and interleukin 1 β (IL-1 β) [177].

The first neurotrophic factor implicated in producing pain, nerve growth factor (NGF) [146,176], serves as a neurotrophin for a population of nociceptors that are also characterized by expression of the high-affinity NGF receptor, TrkA [129,148] and neuropeptides (eg, substance P and calcitonin gene-related peptide), and are thus referred to as TrkA-positive or peptidergic nociceptors [148,209,241]. The finding that NGF levels increase in the setting of inflammation [7,10,225] and nerve injury [9,141] led to the suggestion that NGF might also play a role in inflammatory and neuropathic pain [10,43,234,242]. This hypothesis has culminated in the recent demonstration that an anti-NGF antibody can be effective in the treatment of some clinical pain syndromes [38,121].

It is becoming clear that the extracellular matrix, which used to be considered little more than glue holding together the various cells in a tissue, plays a key role in the physiologic functions of cells, including the primary afferent nociceptor. For example, extracellular matrix is a ligand for a class of receptors on the cell surface, the integrins, which have the unique feature of signaling both from inside the cell out to the extracellular matrix, as well as from the extracellular environment into the cell [58,228,243]. Importantly, interrupting this signaling mechanism has been shown to affect nociceptor function. For example, blocking antibodies or oligodeoxynucleotides antisense to mRNA for specific integrins selectively attenuate mechanical hyperalgesia induced by specific proinflammatory cytokines [27,29,62,63,153]. One intriguing recent example is the demonstration that the extracellular proteoglycan, versican, an extracellular matrix molecule that binds isolectin B4 (IB4) on a sub-population of nociceptors [78,165], may be necessary for the transduction of low pH by those IB4-positive nociceptors [131]; in addition, the attenuation of versican levels selectively attenuates signaling in this population of nociceptors [29]. Another function of the extracellular matrix is its ability to concentrate specific molecules (chemokines and neurotrophic factors) to present them to their cell surface receptors. Related to nociceptor function, versican can concentrate the chemokine, monocyte chemoattractant protein 1 (MCP1) [27], the receptor for which is present on the IB4-positive subpopulation of nociceptors [28], to produce mechanical hyperalgesia. Whether specific integrins and extracellular matrix molecules can be used to categorize functional populations of nociceptors, in addition to the IB4-positive population, is an important unanswered question.

Other neurotrophic factors, most notably members of the glial cell line–derived neurotrophic factor (GDNF) family (ie, GDNF, artemin, neurturin and persephin [3,20]), whose cognate receptors (ie, GFR α_{1-4} [14,207]) are present on subpopulations of nociceptors, have been shown to be up-regulated in the setting of pain [19,67,95,233]. The possibility that populations of nociceptors may be eliminated, for example, by the neurotoxin saporin coupled to IB4, to selectively eliminate IB4-positive nociceptors [8,219,246], provides an intriguing prototype for an approach to the treatment of pain syndromes that are mediated by a subpopulation of nociceptors [16,125,144,213] while preserving protective responses to noxious, potentially tissue-injuring stimuli, necessary for the survival of the organism. This aspect of the cell biology of the nociceptor promises to provide insights into diverse pain syndromes as well as to provide targets for the treatment of currently intractable pain syndromes.

3. Cell contents

The concept of second messengers took root with the discovery of cyclic adenosine monophosphate (cAMP) [195], which subsequently was the first signaling molecule implicated in nociceptor sensitization [79,82]. This pathway is activated by a G-protein–coupled receptor coupled to a stimulatory G-protein (G α_s), which in turn activates adenylyl cyclase, leading to production of cAMP and the downstream activation of protein kinase A (PKA). PKA phosphorylates voltage-gated ion channels, regulating neuronal excitability [22,44,59]. Over time, several other second messengers, especially other kinases, have been implicated in nociceptor sensitization. Probably the next most well-studied second messenger in nociceptor sensitization is protein kinase C (PKC) [46,48,227]. However, why there are multiple second messengers capable of leading to nociceptor sensitization and how these signaling pathways might be involved in different pain syndromes by selectively affecting different populations of nociceptors or different ion channels and receptors [1,57,68,135,148] are just beginning to be elucidated. In this regard, it is worth noting that the epsilon isoform of PKC (PKC ϵ) is found in almost all dorsal root ganglion neurons, but its pain-related function operates only in a particular subpopulation of nociceptors. Thus, PKC ϵ plays a role in the transition from acute to chronic pain, but only when it acts in the IB4-positive nociceptors [78].

Interaction between cAMP/PKA and PKC signaling pathways are just beginning to be elucidated. The recent discovery of an exchange protein activated by cAMP (EPAC), a cAMP-dependent guanine–nucleotide exchange factor [30,100], has provided 1 mechanism by which cAMP/PKA and PKC signaling pathways can interact. Further discussion of the interaction between cAMP/PKA and PKC signaling pathways will be deferred to the discussion of nociceptor neuroplasticity, a mechanism implicated in the transition from acute to chronic pain.

The role of cellular organelles is another cell-biological subject that is beginning to emerge in studies of nociceptor sensitization. Because of space limitations, we will restrict our discussion to the example of the role of mitochondria in the primary afferent nociceptor. Given the immense distance between the transduction mechanisms in the peripheral terminal of the nociceptor and its cell body, the function of the nociceptor is heavily dependent on machinery in its peripheral terminal, which, compared to the conducting axon, contains a very high abundance of mitochondria [98,159]. The regulation of intracellular Ca²⁺, aerobic energy metabolism, generation of reactive oxygen species, and apoptosis are but a few of the better-known mitochondrial functions [11,41,72]. Inhibitors of any of the 5 mitochondrial electron transport chain complexes inhibit pain in models of human

immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) therapy, cancer therapy, and diabetic painful peripheral neuropathy [78,113,116]. Furthermore, caspase signaling in the apoptotic pathway as well as all 5 electron transport chain complexes have been implicated in hyperalgesia induced by TNF α and NGF [50,112]. In addition, mitochondria-derived reactive oxygen species and mitochondria-regulated intracellular calcium influence physiological and pathological nociceptor function [50,75,117,130,208,236]. The cell biology by which these various mitochondrial functions interact to produce nociceptor sensitization remains to be fully described. We have, however, recently provided evidence that mitochondrial fission, an important component of mitochondrial dynamics that regulates multiple mitochondrial functions, may provide a target for the treatment of neuropathic pain [77].

A more detailed elucidation of the intracellular mechanisms involved in nociceptor sensitization, a key component of diverse clinical pain syndromes [90,187,194], will likely provide insight into the complex intracellular molecular interactions producing the hypersensitive state and how disease states that alter cellular function may lead to clinical pain syndromes.

4. The plasma membrane of the cell: organized interaction of signaling molecules

Although most pain research being performed at the cellular level has focused on transducers and ion channels in the plasma membrane and on second messenger signaling pathways in the cytoplasm, it has not, until relatively recently, directed attention to higher-order organizational units in the cell such as the extracellular matrix, multi-molecular complexes in the plasma membrane (eg, lipid rafts and caveolae), and intracellular organelles in the cytoplasm (eg, mitochondria, Golgi apparatus, endoplasmic reticulum, and cytoskeleton) that, together, provide a framework for piecing together the puzzle of pain molecules. In this review, we explore the power that a more integrative cell biological approach provides to development of a fuller understanding of the neurobiology of pain. Building from the unitary domain (single molecules or pairs of molecules in linear signaling pathways) in classic studies of pain mechanisms, to the more complex multi-molecular components of the cell, provides important insight into the organizational principles of the neurobiology of pain.

The classic view of the cell's plasma membrane was that of a lipid bilayer containing uniformly distributed signaling proteins. Thus, a thermal transducer might be a protein floating in the lipid membrane that had a high temperature coefficient for change in its molecular structure (Q10), producing a conducting pore for ions when a certain temperature in the environment is exceeded. In this view, sensitization reflected phosphorylation of voltage-gated ion channels in the membrane, such that a small depolarization produced by a transducer would be amplified, lowering the threshold for production of an action potential, which then propagates to the dorsal horn of the spinal cord. This simplified model of the plasma membrane of the primary afferent nociceptor has been immensely successful, and recent cell biological approaches to the system have added an additional level of nuance and complexity to our understanding of this membrane's structure and function.

Arguably, the most dramatic change in our view of the cell's plasma membrane has been the description of micro-domains that support very specific functions by bringing molecular elements of a signaling pathway together, and excluding members of other pathways, producing a highly efficient signaling complex or “signalosome” [104,175]. Structures such as lipid rafts contain elements necessary to execute specific signaling events, including nociceptor sensitization, by activation of a specific cell-surface receptor, and

signaling to a specific second-messenger–signaling pathway. As an example, we have shown that integrins play a critical role in inflammatory pain by interacting with components of second messenger cascades [4,5,62,153]—from G-protein–coupled receptors to kinases—that mediate inflammatory hyperalgesia. Specifically, interactions with the cyclooxygenase product of arachidonic acid, prostaglandin E₂ (PGE₂), may be mediated by a signalosome organized by lipid rafts, as disrupting lipid rafts interrupts this signaling pathway [62].

Elucidation of other aspects of the cell biology of the nociceptor plasma membrane has suggested novel approaches to treat pain. As an example, it has long been known that certain viruses (eg, herpes simplex) can gain entry into a population of nociceptors, where they can continue to replicate [92]. Investigators have taken advantage of this bit of virological cell biology to create genetically engineered viruses that are able to produce molecules within the infected nociceptor that have the potential to attenuate nociceptor signaling and neurotransmission to the spinal cord [92,94,222,247]. The potential to selectively manipulate the function of the nociceptor without affecting other cells hints at the possibility of developing highly selective analgesic therapies, while minimizing their side effects.

5. Chronic pain

Most often one can find chronic pain defined as pain that has persisted for some period of time (eg, 1 month [111,152], 3 months [31,166], 6 months [53,136], or 12 months [229]), which is not, however, justified by any specific mechanism separating the acute and chronic phase of the pain syndrome. As a starting point, we propose that there are at least 2 mechanistically distinct types of chronic pain, which we will refer to as type I and type II. Type I chronic pain is here defined as acute pain that persists for a prolonged period of time. In contrast, type II chronic pain involves a mechanistic transition from the acute to the chronic phase of the pain syndrome. This transition involves the disconnection of the generation of pain by the initial tissue injury, and/or loss of responsiveness to therapies that successfully treat acute pain. Clinical observation supports this distinction: (1) patients who have experienced inflammatory pain for a prolonged period of time, such as patients with previously untreated rheumatoid arthritis, can experience dramatic relief of their pain by treatment with an inhibitor of the pronociceptive inflammatory mediator, TNF α [86] (type I chronic pain), whereas (2) other patients who initially responded well to treatment, for example with NSAIDs, for osteoarthritis or rheumatoid arthritis, may then experience loss of efficacy over time [151,239] (type II chronic pain).

Of all the pieces of the pain puzzle, unraveling the mechanisms underlying the transition from acute to chronic pain has been 1 of the most challenging. We have described 1 candidate mechanism of neuronal plasticity in primary afferent nociceptive nerve fibers (nociceptors) by which an acute inflammatory insult or environmental stressor can trigger long-lasting hypersensitivity of nociceptors in response to a subsequent exposure to a low concentration of an inflammatory mediator. This phenomenon, which we have referred to as “hyperalgesic priming,” is dependent on activation of PKC ϵ and a switch in intracellular signaling pathways that mediates cytokine-induced nociceptor hyperexcitability from PKA alone to also include signaling via PKC ϵ [66,194]. Importantly, other mechanisms, in both the peripheral and central nervous systems, have also been implicated in the persistence of sensitized states. For example, Price [127], and McMahon [156] have provided evidence that chronic changes may also depend on the activity of protein kinase M ζ (PKM ζ), an essential mechanism in the neuroplasticity associated with late-phase long-term

potentiation (LTP), a well-established memory mechanism [99,147].

6. Nociceptor sex

It is now well recognized that pain is sexually dimorphic, with differences between males and females demonstrated in multiple studies, in human diseases and animal models [55,83,93,124,145,155,164,196,215]. Both androgen and estrogen receptors, as well as synthetic pathways for sex hormones, have been found in pain circuits in the peripheral and central nervous system [60,73,149,218,244,250]. The primary afferent nociceptor has been shown to contain receptors for male and female sex hormones [71,123,178,245]. Many of the differences in pain between males and females are sex hormone dependent. For example, we have demonstrated that the second-messenger signaling pathways in nociceptors for induction of mechanical hyperalgesia is estrogen dependent [106]. Similarly, on the cellular level, estrogen can sensitize nociceptors by acting on the nociceptive neuron [132]. In sensory neurons, the action of estrogen can be rapid, occurring over a matter of seconds [143,161,167], implicating unknown actions beyond their classical actions on gene transcription. There remain many other unanswered questions related to fundamental aspects of sexual dimorphism in pain syndromes. For example, whereas it is known that females of multiple species have lower mechanical pain thresholds than males, we still do not know whether these differences are due to sexual dimorphism in mechanisms in the peripheral and/or central nervous system.

7. Looking forward

Although in this review we have summarized only a relatively small fraction of the growing literature on the cell biology of pain, and focused on the primary afferent nociceptor, we have attempted to demonstrate the power of cell biology in addressing key questions related to the neurobiology of pain, and to suggest ways in which this approach can enhance the development of novel treatments for currently intractable chronic pain syndromes.

Conflict of interest statement

The authors report no conflict of interest.

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