

Intracellular Signaling in Primary Sensory Neurons and Persistent Pain

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Abstract During evolution, living organisms develop a specialized apparatus called nociceptors to sense their environment and avoid hazardous situations. Intense stimulation of high threshold C- and A δ -fibers of nociceptive primary sensory neurons will elicit pain, which is acute and protective under normal conditions. A further evolution of the early pain system results in the development of nociceptor sensitization under injury or disease conditions, leading to enhanced pain states. This sensitization in the peripheral nervous system is also called peripheral sensitization, as compared to its counterpart, central sensitization. Inflammatory mediators such as pro-inflammatory cytokines (TNF- α , IL-1 β), PGE₂, bradykinin, and NGF increase the sensitivity and excitability of nociceptors by enhancing the activity of pronociceptive receptors and ion channels (e.g., TRPV1 and Na_v1.8). We will review the evidence demonstrating that activation of multiple intracellular signal pathways such as MAPK pathways in primary sensory neurons results in the induction and maintenance of peripheral sensitization and produces persistent pain. Targeting the critical signaling pathways in the periphery will tackle pain at the source.

Keywords Peripheral sensitization · Dorsal root ganglion · Inflammatory pain · Neuropathic pain · MAP kinases · Neural plasticity

Introduction

It is absolutely essential for the survival of animals and human beings to be able to avoid hazardous situations. This capability is gained during evolution through the development a specialized apparatus by living organisms to sense their immediate environment in order to protect themselves from potentially dangerous inputs. This special apparatus is called *nociceptor* that can detect noxious stimuli from the environment. Intense stimulation of nociceptors that have high thresholds will elicit a pain sensation, through a pathway that is initiated from the action potential generated in the peripheral nociceptor terminal. This pain signal is conducted via thin fibers containing unmyelinated C-fibers and myelinated A δ -fibers of primary sensory neurons to secondary order neurons in the spinal cord dorsal horn, finally to the cortex via a relay in the thalamus. *Nociceptive pain* is an acute “ouch” pain, and has a protective role. In last decade, many pain transduction molecules have been identified, such as thermal receptors transient receptor potential (TRP) ion channel family. While TRPV1 and TRPV2 detect heat stimuli [1], TRPM8 [2, 3] and TRPA1 [4] sense cold stimuli. For example, activation of TRPV1 after a heat stimulus (>42°C) generates inward currents in the nociceptor peripheral terminal and results in action potentials in the nociceptor axon, leading to pain sensation [5–8].

A further evolution of the early pain system was development of the capacity to produce increases in sensitivity after injury, *nociceptor sensitization*, which will lead to the development of persistent pain.

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Electrophysiologically, this sensitization is characterized by increased background firing, increased responses to supra-threshold (noxious) stimuli, and decreased threshold for thermal and mechanical stimuli. These electrophysiological phenomena may underlie corresponding behavioral phenomena: spontaneous pain, hyperalgesia (increased responses to noxious stimuli), and allodynia (nociceptive response to previously innocuous stimuli). Nociceptive sensitization was found even in simple organisms such as *Aplysia*, where an intense noxious stimulus can produce a long lasting sensitization of the gill withdrawal reflex [9]. This sensitization is also referred to *peripheral sensitization* [6, 7, 10, 11], because it occurs in the peripheral nervous system. In contrast, *central sensitization*, a counterpart of peripheral sensitization, refers to an increased sensitivity in the central nervous system [12]. Although central sensitization after injury is also important for the development of persistent pain and especially important for the maintenance of persistent pain, this review will focus on peripheral sensitization.

While nociceptive pain or physiological pain is transient, clinical pain or pathological pain is often chronic. Animal models of persistent pain are often produced by peripheral tissue damage (inflammatory pain) or peripheral nerve lesions (neuropathic pain). Peripheral sensitization results in pain hypersensitivity in animals, such as spontaneous pain and hyperalgesia including heat hyperalgesia and mechanical hyperalgesia. Pain hypersensitivity is also manifested as allodynia. For example, animals normally do not respond to acetone (a cooling agent) or low force of von Frey hair stimulation (sub-threshold mechanical stimulation). However, after nerve injury, animals show robust painful responses to acetone application (cold allodynia) and low force mechanical stimulation (mechanical allodynia).

Induction and Maintenance of Peripheral Sensitization

Tissue injury such as surgical incision [13] or injection of chemical substances (e.g., capsaicin, formalin, carrageenan, or complete Freund's adjuvant (CFA)) produces inflammation and heightened pain states [14]. This pain hypersensitivity arises from the production and release of inflammatory mediators such as prostaglandin E₂ (PGE₂), bradykinin, ATP, protons, nerve growth factor (NGF), and proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) from non-neuronal cells (e.g., fibroblasts, mast cells, neutrophils, monocytes, and platelets) as well as from primary sensory terminals. After nerve damage, these mediators can also be released from enclosing Schwann cells and damaged axons [15]. The soma and axons of primary sensory neurons contain

receptors for these inflammatory mediators, such as G-protein-coupled receptors for PGE₂ and bradykinin, ionotropic receptors for ATP and protons, tyrosine kinase receptors for NGF and cytokines [16, 17] (Fig. 1). Importantly, all these inflammatory mediators have been implicated in pain sensitization, and molecular mechanisms underlying the actions of these mediators have been intensively investigated [6, 7, 10, 11, 16–18].

Primary sensory neurons in the dorsal root ganglion (DRG) can be separated into two populations: neurofilament-200-positive (myelinated) and neurofilament-200-negative (unmyelinated). The majority of DRG neurons (around 70%) are unmyelinated (C-fiber) neurons that also express peripherin. These unmyelinated neurons are further divided into peptidergic neurons (40% of total DRG neurons) that express the neuropeptide calcitonin gene-related peptide (CGRP) and substance P, as well as NGF receptor TrkA and non-peptidergic neurons (30% of total DRG neurons) that express isolectin B4 (IB4) and glia-derived neurotrophic factor (GDNF) receptor c-ret [19–21]. Based on this neurochemical characterization, the majority of DRG neurons are nociceptors, which include (1) peripheral axonal terminals in the skin or muscle, (2) peripheral nerve axons (i.e., sciatic and saphenous nerves), (3) cell bodies in the DRG, (4) central axons in the dorsal root, and (5) central axonal terminals in the spinal cord. Although

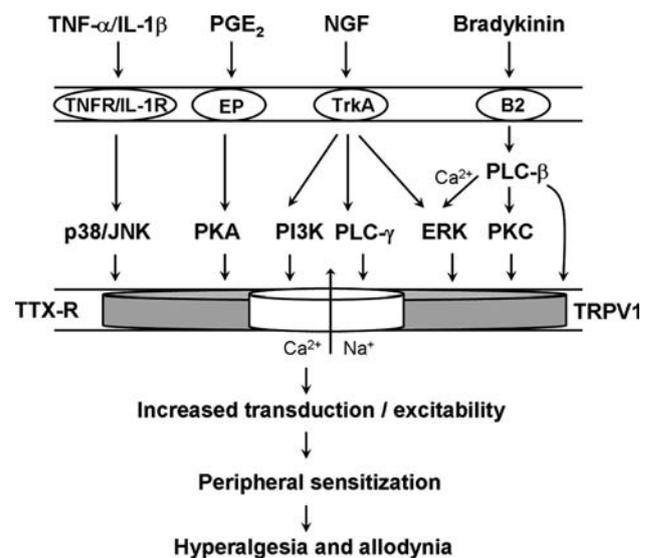


Fig. 1 Induction of peripheral sensitization. Peripheral tissue injury or nerve damage leads to the production of various inflammatory mediators, such as TNF- α , PGE₂, bradykinin, and NGF. These mediators are released and stimulate the corresponding receptors on terminals, axons, or cell body of nociceptive primary sensory neurons. Activation of different receptors results in the activation of multiple protein kinase pathways, leading to rapid posttranslational regulation of TRPV1 and TTX-R Na⁺ channels. Hyperactivity of TRPV1 and TTX-R Na⁺ channels induces peripheral sensitization and hyperalgesia

peripheral sensitization is best studied in the peripheral terminals and cell bodies, it can occur at all the sites of sensory neurons. Nociceptors express various types of ion channels such as TRP channels (TRPV1–V4, TRPA1, TRPM8) [4–6], ATP receptor P2X3 [22, 23], acid-sensitive channel (ASIC1–4) [24], and tetrodotoxin (TTX)-sensitive Na⁺ channels (TTX-S, such as Na_v1.1, Na_v1.2, Na_v1.3, Na_v1.6, and Na_v1.7) and TTX-resistant Na⁺ channels (TTX-R, such as Na_v1.8 and Na_v1.9) [25–28], as well as various kinds of Ca²⁺ channels [29] and K⁺ channels [30]. Notably, the sensitivity of these channels is strongly regulated by inflammatory mediators [6, 7, 17].

Current studies focus on two types of channels, TRP channels, especially TRPV1 (previously called vanilloid receptor subtype-1 (VR1)), a transduction molecule that can convert extracellular stimuli into electrical activity on the membrane [6, 7], and Na⁺ channels, especially TTX-R Na⁺ channels that are important for the conduction of action potentials [25–27], although other channels such as TRPA1 [31], Na_v1.7 [32], and purinergic receptors such as P2X3 [22, 23] are also well studied. TRPV1 is expressed in C-fiber nociceptive neurons and is required for the generation of heat hyperalgesia [6]. Inflammatory heat hypersensitivity following bradykinin [33], NGF [33], TNF- α [34], CFA [35], and carrageenan [36] is abolished in TRPV1 null mice. Persistent inflammation increases TRPV1 expression in DRG neurons [37, 38] and further increases TRPV1 transport to peripheral nociceptor terminals [37]. The peripheral input that drives pain perception depends on the presence of functional voltage-gated Na⁺ channels. Although fast-activating TTX-S Na⁺ channels may be sufficient for the conduction of action potentials, specific expression of TTX-R Na⁺ channels (Na_v1.8 and Na_v1.9) in nociceptors [39] and their slow-activating and slow-inactivating properties point to a specific role of these channels for sustained excitability of nociceptors after tissue injury [25–27]. Sensitization and hypersensitivity of TRPV1 and TTX-R Na⁺ channels has been strongly implicated in the generation of peripheral sensitization and persistent pain [6, 25–27, 33, 34, 36–38].

Sensitization of these ion channels can occur rapidly (within minutes) by posttranslational regulation via phosphorylation [17], and TRPV1 is known to have multiple phosphorylation sites for several protein kinases [11]. However, transcriptional regulation often takes hours to days to manifest, leading to increased expression of pronociceptive molecules to maintain peripheral sensitization and enhanced pain states (Fig. 2). Tissue injury and persistent inflammation are known to induce the expression of multiple pronociceptive genes in nociceptors, such as genes encoding for substance P, CGRP, brain-derived neurotrophic factor (BDNF), TRPV1, and Na_v1.8 [17, 37]. These changes in gene expression in peptidergic and TrkA-

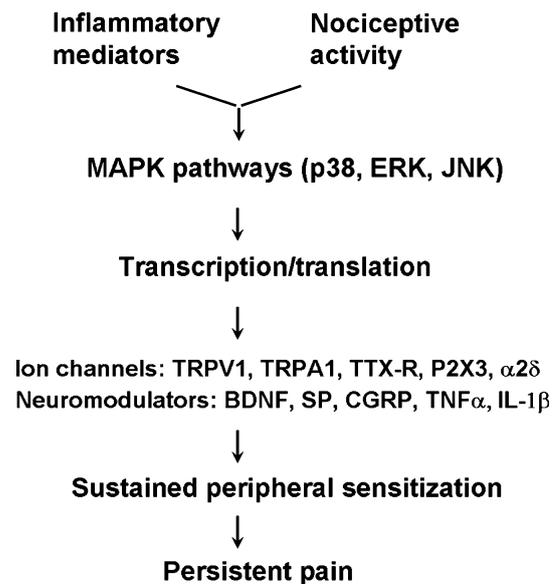


Fig. 2 Maintenance of peripheral sensitization by transcriptional or translational regulation. Inflammatory mediators produced after peripheral tissue injury or nerve damage (as shown in Fig. 1), as well as spontaneous electrical activity, induce the activation MAPK pathways (p38, ERK, JNK) in different subsets of nociceptive primary sensory neurons. Activation of these pathways results in transcriptional regulation via transcription factors CREB, ELK-1, Jun, and ATF and translational regulation via translation initiation factors. Consequently, there is increased synthesis of ion channels such as TRPV1, TRPA1, TTX-R Na⁺ channels, P2X3, and Ca²⁺ channel $\alpha 2\delta$ subunit and neuromodulators such as BDNF, substance P, CGRP, TNF- α , and IL-1 β . Persistent increase in the synthesis of these pronociceptive proteins in primary sensory neurons maintains hypersensitivity of these neurons and persistent pain

expressing nociceptors depend on NGF, whereas those changes in non-peptidergic nociceptors may depend on GDNF [17, 20]. After nerve injury, however, changes in DRG gene transcription are much more dynamic and complicated [40, 41], partly due to different processing of nerve degeneration and regeneration. Some of these changes such as upregulation of Ca²⁺ channel $\alpha 2\delta$ subunit [42] and Na⁺ channel $\beta 2$ subunit [43] in DRG neurons contributed to neuropathic pain sensitization.

Importantly, both rapid posttranslational and slow transcriptional regulations in sensory neurons require the activation of multiple protein kinases via intracellular signaling transductions.

Classic Protein Kinase Signaling Pathways and Peripheral Sensitization

Protein kinase A (PKA) is activated by cAMP, the first known second messenger. Activation of PKA in nociceptor terminal appears to be sufficient for producing hyperalgesia, since intradermal injection of cAMP analogue or adenylate

cyclase activator produce peripheral sensitization and hyperalgesia [10, 44, 45]. Peripheral PKA is also required for hyperalgesia after inflammation [10, 44, 45]. Mechanistically, cAMP/PKA cascade mediates PGE₂-induced enhancement of TRPV1 currents [46] and TTX-R Na⁺ currents [47]. PKA also prevents desensitization of TRPV1 by direct phosphorylation [11, 48]. In contrast, opioid receptor agonist morphine produces peripheral analgesia via inhibition of adenylate cyclase and PKA-potentiated TRPV1 responses [49]. PKA modulates spontaneous activity in chronically compressed DRG neurons and is required for TNF- α -induced neuronal discharges of C-fibers [50, 51]. Although it is generally believed that cAMP effects are mediated by PKA, PKA does not mediate all the cAMP-induced responses. Other kinases may also participate. For example, cAMP could activate Epac (exchange protein directly activated by cAMP), a guanine nucleotide exchange factor, leading to the activation of epsilon isoform of protein kinase C (PKC ϵ) [10].

The role of PKC in peripheral sensitization is well studied. Activation of PKC in nociceptor terminals is both sufficient and required for producing hyperalgesia [52]. PKC can sensitize TRPV1 [11, 53] and TTX-R Na⁺ channels [47]. In particular, the PKC ϵ , a Ca²⁺-independent member of PKC family, can be translocated to the plasma membrane of nociceptors in response to inflammatory mediators such as bradykinin and substance P and plays a major role in peripheral sensitization in inflammatory and neuropathic pain conditions [10, 54, 55]. Indeed, sensitization of TRPV1 requires PKC ϵ -mediated phosphorylation at S800 [10, 11, 56]. Other PKC isoforms such as PKC δ [57] and PKC μ [58] may also play a role in TRPV1 sensitization.

Comparatively, less is known about the role of protein kinase G (PKG), which is activated by nitric oxide/cGMP pathway [10]. The role of nitric oxide/cGMP in pain control appears to be contradictory, ranging from hyperalgesia [59, 60] to antinociception [61, 62], depending on the dose and spatial locations [11]. However, nerve injury upregulates the neuronal nitric oxide synthase in DRG neurons [63]. In Aplysia sensory neurons, PKG couples to extracellular signal-regulated kinase (ERK) pathway and contributes to axotomy-induced long-term hyperexcitability [64]. In particular, GTP cyclohydrolase contributes to peripheral neuropathic and inflammatory pain, via the synthesis of tetrahydrobiopterin, an essential cofactor for nitric oxide synthesis [65].

MAPK Signaling Pathways and Peripheral Sensitization

Mitogen-activated protein kinases (MAPKs) are a family of evolutionally conserved molecules that play a critical role

in cell signaling. There are three major family members: ERK (ERK1/2 or p44/42 MAPK), p38, and c-Jun N-terminal kinase (JNK) that represent three different signaling cascades. MAPK transduces a broad range of extracellular stimuli into diverse intracellular responses by both transcriptional and non-transcriptional regulation [66–69]. Although ERK was originally implicated in regulating mitosis, proliferation, differentiation, and survival of mammalian cells during development, it also plays an important role in regulating neuronal plasticity and inflammatory responses in the adult [66, 70]. p38 and JNK are typically activated by cellular stress (ultraviolet irradiation, osmotic shock, heat shock), lipopolysaccharide, and proinflammatory cytokines such as TNF- α and IL-1 β [70]. MAPKs are activated by upstream kinases via phosphorylation. Notably, MAPK studies greatly benefit from phosphorylation-specific antibodies available to investigate the activation of each MAPK pathway. Unlike many other kinases, relatively specific inhibitors are available to study the function of MAPK pathways. Inhibition of all three MAPK pathways with multiple inhibitors has been shown to attenuate persistent pain after tissue and nerve injuries without changing basal pain perception [67–69].

ERK activation involves sequential activation of a cascade including Ras, Raf, MEK, and ERK [66]. As a major effector of growth factors, ERK is strongly activated by NGF in DRG neurons [71]. Unlike embryonic DRG neurons, adult DRG neurons do not require NGF for survival, but require NGF for maintaining nociceptor phenotype [20]. As an inflammatory mediator generated in inflamed tissue, NGF also sensitizes nociceptors and ion channels (e.g., TRPV1 and TTX-R Na⁺ channels) [72]. In addition to acting on high affinity TrkA receptor, NGF at high concentrations may also bind low affinity p75 receptor to sensitize TTX-R Na⁺ currents via the putative second messenger ceramide [73]. Blocking the ERK cascade using a MEK1/2 inhibitor, PD98059, abrogated NGF dependent capsaicin sensitivity [74], but this result was not confirmed in another study [75]. The discrepancy may result from chronic [74] versus acute [75] NGF treatment. It is also important to point out that the MEK inhibitor PD98059 requires sufficient pretreatment time (>20 min) to get optimal membrane permeability. We have shown that ERK activation is also required for NGF-induced TRPV1 sensitization and heat hyperalgesia [71]. ERK is not only activated by growth factors but also by nociceptive activities both in central dorsal horn neurons [76] and peripheral DRG neurons [68]. Activation of C-fiber nociceptors by capsaicin induces a rapid and transient ERK activation in cultured DRG neurons [71]. This transient ERK activation is also observed in vivo following peripheral noxious stimuli [77]. In addition, ERK activation is found both in the soma and axonal terminals of nociceptors [71, 77]. Inhibition of ERK pathway attenuates heat or mechanical hyperalgesia induced by capsaicin [77], NGF

[71], and epinephrine [78]. ERK is likely to mediate heat hyperalgesia by sensitizing TRPV1 [71]. Interestingly, in normal conditions PGE₂-induced hyperalgesia is ERK-independent. However, when the tissue is “primed” by carrageenan pretreatment, PGE₂-induced hyperalgesia becomes ERK-dependent [79], suggesting an important role of ERK in nociceptor plasticity. In addition to aforementioned posttranslational regulation, ERK also maintains pain sensitization by transcriptional regulations in DRG neurons [68].

p38 is typically activated by cellular stresses and inflammatory mediators [70]. p38 activation in DRG neurons is also induced by nociceptive activities [80]. Downstream, activation of phospholipase A2 leads to the generation of arachidonic acid for prostaglandin production [70]. Further, activated p38 is translocated to the nucleus phosphorylating the transcriptional factors and increasing the biosynthesis of multiple inflammatory mediators such as TNF- α and IL-1 β [66, 70, 81]. Phospho-p38 (p-p38), the active form of p38, is normally expressed in 10–15% of DRG neurons that are primary C-fiber nociceptors [37, 82]. p-p38 is increased in DRG neurons following peripheral inflammation and nerve injuries [37, 82, 83]. After nerve injuries, p38 is activated not only in injured DRG neurons but also in adjacent intact neurons [82, 84]. While TNF- α produces early p38 activation [85, 86], NGF induces more persistent p38 activation after inflammation and nerve injury [37, 87]. Importantly, intrathecal injection of p38 inhibitors inhibits heat and cold hypersensitivity after inflammation and nerve injury [37, 82, 85]. NGF plays a pivotal role in triggering p38-mediated thermal hypersensitivity [88]. Target-derived NGF is retrogradely transported to the soma in the DRG where it activates p38, leading to an upregulation of TRPV1 [37] and TRPA1 [87]. Consistently, p-p38 is co-expressed with TRPV1 and TRPA1 in DRG nociceptors, and inhibition of p38 suppresses the upregulation of TRPV1 and TRPA1 following inflammation [37, 87]. Since increase of TRPV1 protein level is much more robust than that of TRPV1 mRNA level, p38 appears to increase TRPV1 expression via translational regulation [37] (Fig. 2), although transcriptional [66, 89] and posttranscriptional regulation [70, 90] of p38 on other targets cannot be denied. Additionally, p38 can sensitize nociceptors via fast posttranslational regulation. For example, TNF- α activates p38 and rapidly enhances TTX-R Na⁺ currents in isolated DRG neurons, and this enhancement is blocked by the p38 inhibitor SB202190 [34].

Compared with ERK and p38, less is known about the role of JNK in pain regulation. JNK can be activated by cell stresses such as heat shock, direct DNA damage, and reactive oxygen species [66], and plays an important role in the induction of apoptosis [91]. Nerve injury induces a rapid (<1 day) but transient (<10 days) JNK activation in

DRG nociceptors [92]. Unlike p38, JNK is only activated in injured neurons [82, 92]. JNK activation in DRG neurons is not associated with apoptosis, because neuronal apoptosis after nerve injury is not noticeable in the first several weeks [93]. Instead, the transient JNK activation is involved in the early development of mechanical allodynia after nerve injury, because DRG infusion of the peptide JNK inhibitor D-JNKI-1 prevents mechanical allodynia for a week but does not reverse mechanical allodynia [92]. Downstream, JNK is known to activate the transcription factor c-Jun that is also activated in injured DRG neurons [92, 94], leading to the transcription of many genes containing AP-1 binding sites [95]. Apart from transcriptional regulation, JNK is also involved in fast posttranslational regulation. Acute hyperalgesia induced by intraplantar capsaicin, endothelin-1, CFA, or bee venom is suppressed by the JNK inhibitor SP600125 [95–98].

PI3K Signaling Pathway and Peripheral Sensitization

Phosphatidylinositol 3-kinase (PI3K) is a lipid kinase that phosphorylates the D-3 position of phosphatidylinositol lipids to produce PI(3,4,5)P₃, acting as a membrane-embedded second messenger to activate serine/threonine kinase Akt (also called protein kinase B). Akt is postulated to mediate most of PI3K's effects [99]. PI3K/Akt is a major pathway activated by growth factors. For example, NGF can strongly activate PI3K pathway in DRG neurons [71, 100]. Capsaicin also activates PI3K in DRG neurons via intracellular Ca²⁺ increase [71]. Further, Akt activation in DRG neurons was shown to be activity-dependent [101]. Intraplantar injection of PI3K inhibitors prevents heat hyperalgesia induced by both NGF and capsaicin [71]. Consistently, activation of Akt in the periphery contributes to pain behaviors induced by capsaicin [102]. PI3K was shown to mediate NGF-induced acute sensitization of TRPV1 [71, 100]. In particular, NGF induces sequential activation of PI3K and Src kinase, and Src then binds to TRPV1 and phosphorylates TRPV1 [103]. Phosphorylation of TRPV1 at a single tyrosine residue Y200 by Src results in insertion of TRPV1 channels into the surface membrane, which may underlie NGF-induced rapid sensitization of TRPV1 [103]. Apart from acute pain sensitization, activation of PI3K and Akt in DRG nociceptors also contributes to the development of nerve injury-induced neuropathic pain [104].

Concluding Remarks and Future Directions

It is estimated that chronic pain affects 20% of the population worldwide. Current treatments only have limited

success in attenuating this pain. Chronic pain is initially evoked by peripheral sensitization in primary sensory neurons that is triggered by inflammatory mediators produced after tissue injury or nerve damage. Activation of multiple intracellular signal pathways such as PKA, PKC, PKG, PI3K, and three MAPK pathways has been implicated in the induction and/or maintenance of peripheral sensitization and persistent pain. Other kinase pathways such as Ca²⁺/calmodulin-dependent kinase-II (CaMKII) [105] and cyclin-dependent kinase 5 (Cdk5) [106] may also be involved. These kinase pathways act via the following mechanisms. First, the rapid posttranslational regulation by these signaling pathways leads to phosphorylation and hyperactivity of TRPV1, TTX-R Na⁺ channels, and other pain-promoting molecules in primary nociceptive neurons, inducing peripheral sensitization and hyperalgesia (Fig. 1). Second, the slow transcriptional or translational regulation by these pathways leads to increased synthesis of ion channels (e.g., TRPV1 and TTX-R Na⁺ channels) and neuromodulators (e.g., BDNF, substance P) in nociceptors, therefore, maintaining peripheral sensitization and persistence of pain (Fig. 2). Moreover, the sensitivity of nociceptors can also be regulated by stimulus-induced surface insertion of receptors and ion channels that may involve some of these pathways [103, 107].

Although all these signaling pathways are involved in peripheral sensitization and pain hypersensitivity, two critical questions remain to be answered. First, what is the distinct role of each pathway in peripheral sensitization? To address this issue, distinct activation pattern (e.g., time course and cellular localization) of these signaling pathways in primary sensory neurons should be compared after stimulation with the same inflammatory mediator or under the same injury condition. Also, the effects of inhibition of different pathways should be compared in the same pain model at the same time points. A more difficult task is to elucidate the molecular targets (e.g., critical ion channels and receptors) that are regulated by these pathways. Second, are there interactions or cross-talks between these signal pathways? ERK pathway appears to be downstream of PI3K [71, 100], PKG [64], cAMP/Epac [108], as well as PKA and PKC [109, 110], indicating a crucial role of this pathway in integrating multiple signal cascades. Further investigation of cross-talks among different signal pathways in sensory neurons is of great importance to reveal essential signaling mechanisms and validate critical drug targets.

Sensory neurons express hundred's of ion channels and G-protein-coupled receptors that may contribute to peripheral sensitization and are considered as drug targets for developing new analgesics. However, given the large number of these receptors and channels, the antinociceptive effect of blocking a single channel or receptor could be limited. Instead, targeting a critical signal transduction

pathway such as MAPK pathway that can regulate the activity of multiple channels and receptors should be a more effective strategy for pain management. Inhibition of all three MAPK pathways with multiple inhibitors has been shown to attenuate persistent pain after tissue and nerve injury without affecting basal pain perception [67–69], which is quite different from traditional analgesics such as opioids and ion channel blockers that also inhibit basal pain perception. It is important to keep normal pain sensation intact, since the physiological pain is protective in our daily life. In summary, blockade of a critical signaling pathway in primary sensory neurons with a kinase inhibitor can effectively tackle abnormal pain at the source. Development of peripheral acting kinase inhibitors will also minimize the side effects of these inhibitors.

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