

Molecular mechanism of inflammatory pain

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Abstract

Chronic inflammatory pain resulting from arthritis, nerve injury and tumor growth is a serious public health issue. One of the major challenges in chronic inflammatory pain research is to develop new pharmacologic treatments with long-term efficacy and few side effects. The mediators released from inflamed sites induce complex changes in peripheral and central processing by directly acting on transducer receptors located on primary sensory neurons to transmit pain signals or indirectly modulating pain signals by activating receptors coupled with G-proteins and second messengers. High local proton concentration (acidosis) is thought to be a decisive factor in inflammatory pain and other mediators such as prostaglandin, bradykinin, and serotonin enhance proton-induced pain. Proton-sensing ion channels [transient receptor potential V1 (TRPV1) and the acid-sensing ion channel (ASIC) family] are major receptors for direct excitation of nociceptive sensory neurons in response to acidosis or inflammation.

G-protein-coupled receptors activated by prostaglandin, bradykinin, serotonin, and proton modulate functions of TRPV1, ASICs or other ion channels, thus leading to inflammation- or acidosis-linked hyperalgesia. Although detailed mechanisms remain unsolved, clearly different types of pain or hyperalgesia could be due to complex interactions between a distinct subset of inflammatory mediator receptors expressed in a subset of nociceptors. This review describes new directions for the development of novel therapeutic treatments in pain.

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Key words: Acid-sensing ion channel; Acidosis; G-protein-coupled receptor; Inflammation; Proton-sensing ion channel; Transient receptor potential V1

Core tip: Tissue acidosis that occurs during inflammation is central to the development and maintenance of chronic pain. Recent studies have revealed a variety of proton-sensing ion channels (*e.g.*, acid-sensing ion channels, transient receptor potential V1) and G-protein-coupled receptors (*e.g.*, G2 accumulation 2A, G-protein-coupled receptor 4, ovarian cancer G-protein-coupled receptor, T-cell death-associated gene 8) responsible for acid-induced pain. These cell-surface membrane proteins are promising therapeutic targets for the development of new analgesic drugs for chronic inflammatory pain.

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INTRODUCTION

Cancer, nerve injury, and arthritis often cause chronic inflammatory pain^[1]. Chronic pain may have a profound

effect on a person's life and society when not effectively treated. Although a variety of pharmacologic treatments are available, they are limited by unacceptable side effects or short-term efficacy. The development of long-acting pharmacologic therapies requires knowledge of how chronic inflammatory pain signals are initially interpreted and subsequently transmitted and perpetuated. This review focuses on recent findings from studies of the molecular mechanisms of inflammatory pain transmission and modulation, especially the roles of mediator-gated ion channels and G-protein-coupled receptors (GPCRs).

INFLAMMATORY PAIN

When our body senses noxious stimuli (such as a cut from a sharp knife, burn from an open flame, or contact with burning or erosive chemicals), the signal quickly activates primary sensory afferents (nociceptors) and delivers a message to the brain to elicit the pain feeling. When stimuli are absent, the painful experience disappears. The situation is called acute pain because the pain signal is transient^[2]. Noxious stimuli activate transducer receptors located on medium myelinated (A δ) and small unmyelinated (C) nociceptors to induce the receptor potential. The receptor potential activates a variety of voltage-gated ion channels to transmit pain signals to secondary nociceptors in the dorsal horn of the spinal cord, then to the brain^[3].

If the tissues are damaged mechanically or by pathogen infection, autoimmune disease, or tumor growth, the sites of the damaged or infected tissues usually show inflammatory responses such as redness, swelling and heat accompanied by persistent pain; endogenous mediators released from the damaged or infected tissues increase the extravasation of the vessels and attract the immune cells, including mast cells, macrophages, neutrophils, and platelets, to the injured site for the inflammatory response^[1]. The "inflammatory soup" is rich in purines, amines, cytokines, protons, ions and growth factors. These mediators can directly activate the nociceptors, evoking pain or modulating the sensitivity of the primary nociceptors, thus causing a hyperreactive reaction to stimuli. As a result, normal stimuli such as a light touch or a brush are perceived as painful (allodynia), or normally painful stimuli cause pain of greater intensity (hyperalgesia)^[4]. In the periphery, inflammatory mediators bind to GPCRs to activate protein kinases A and C (PKA and PKC) to phosphorylate receptors or increase receptor expression, which enhances the sensitivity of primary nociceptors, called peripheral sensitization. Primary nociceptor-driven transmitter release activates intracellular kinases to phosphorylate receptors. This situation leads to an immediate and activity-dependent increase in the excitability and responsiveness of dorsal horn neurons, called central sensitization. Central sensitization could be sustained for some time because of transcriptional changes^[2,4].

INFLAMMATORY MEDIATORS OF PAIN

The endogenous mediators, such as prostaglandin E₂

(PGE₂), bradykinin (BK), serotonin [5-hydroxytryptamine (5-HT)], proton, histamine, and ATP, are released from the damaged site of the tissue and immune cells to induce inflammation and nociception^[2]. These mediators act on transducer receptors situated on sensory neurons to induce complex changes in peripheral and central signal processing. Although some mediators can act directly on ion channels to induce receptor potential, for the most part these chemical interactions occur through the activation of receptors coupled with G-proteins and second messengers, thus activating protein kinases. Such activated kinases phosphorylate ion channels to alter ion permeability or phosphorylate cellular proteins to increase gene expression.

Earlier studies of single mediators demonstrated that BK, PGE₂, 5-HT, and proton have excitatory action on cutaneous nociceptors and induces transient pain^[5-8]. More sustained effects are achieved only in a high-concentration (10^{-5} mol/L) combination of inflammatory mediators (BK, 5-HT, PGE₂, and histamine)^[9]. Steen *et al.*^[10] proposed that the combination of inflammatory mediators plays a role in sensitizing the low pH effect. The acidosis in inflamed tissues is the decisive factor for ongoing nociceptor excitation and sustained pain. However, the interaction between various mediators remains unclear.

TISSUE ACIDOSIS AND ACID-SENSING RECEPTORS

Tissue acidosis is a common phenomenon found in inflammation (reduced to pH 5.4)^[11], in lesions or incisions (reduced to pH 6.5)^[12], in ischemic heart or muscle (pH 5.7-7.0)^[13,14], and even in malignant tumors (pH 5.8-7.4)^[15]. High local proton concentrations in inflamed tissues can excite and sensitize rat skin nociceptors and can cause sustained pain in human skin^[7,16,17]. As well, the combination of inflammatory mediators (BK, 5-HT, PGE₂, and histamine) in acid solution (pH 6.1) can excite and sensitize rat skin nociceptors^[18]. Injections of the inflammatory mediator combination in neutral solution in human skin induces dose-dependent, transient, burning pain, but the effects become more intense and prolonged when the mediator combination is in acidic solution^[10]. Studies of rat dorsal root ganglion (DRG) neurons revealed that acidic solutions induced a cation conductance in a subset of neurons^[19], and a proton-activated sustained current is potentiated more by the mediator combination than each mediator alone^[20]. Proton-activated currents found in the sensory neurons are due to direct activation of the non-selective cation channels and indirect modulation of ion channels^[21]. Proton-gated ion channels and proton-sensing GPCRs expressed on nociceptors are potential candidates responsible for acidosis-induced pain.

PROTON-GATED ION CHANNELS: ACID-SENSING ION CHANNELS

Acid-sensing ion channels (ASICs), which belong to

the family of degenerin/epithelial amiloride-sensitive Na^+ channels, are voltage-insensitive cationic channels activated by extracellular protons^[22-25]. The ASIC family, comprising ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, ASIC4 and ASIC5, is expressed in the peripheral and central nervous systems^[26-28].

Among ASICs, ASIC3 is the most sensitive receptor to protons, with pH 0.5 for activation around 6.7, and is expressed in both small- and large-diameter DRG neurons^[29-31]. The expression of ASIC3 in DRG is increased with hind paw inflammation in rats^[32,33]. As well, ASIC3 channel activity is enhanced by several components of the inflammatory soup, such as BK, 5-HT, hypertonicity, arachidonic acid, and nitric oxide^[34-38]. Thus, ASIC3 is considered a sensor of acidic and primary inflammatory pain^[34]. Study of skin nerves revealed that loss of ASIC3 increases the sensitivity of mechanoreceptors to light touch but decreases that of mechanoreceptors to a noxious pinch^[39,40]. Surprisingly, mice lacking the ASIC3 gene still respond to acid stimuli and have acid-induced pain or primary inflammatory pain^[39,41-43]. However, inhibiting ASIC3 function with a specific peptide or small interfering RNA significantly reduces cutaneous acidic pain under normal or inflammatory conditions and postoperative pain^[34,44].

Given that ASIC3 is predominantly expressed in muscle nociceptors rather than in cutaneous nociceptors^[45], ASIC3 should be required for development of secondary mechanical hyperalgesia induced by acid injection in skeletal muscle or by muscle inflammation^[46-48]. Although the ASIC3 requirement for development and maintenance of muscle inflammatory pain is argued, selective microRNA-targeted ASIC3 inhibits primary and secondary hyperalgesia induced by muscle inflammation^[49]. Interestingly, a recent study by Lin *et al.*^[50] suggested that ASIC3-mediated muscle pain is negatively modulated by substance P *via* regulation of the M channel in a G-protein-independent pathway.

ASIC1a is predominantly expressed in small-diameter DRG neurons^[23,51] and is less sensitive than ASIC3 with pH 0.5 for activation around 6.5^[29,30]. Mice lacking ASIC1a show normal mechanical sensitivity in cutaneous afferents but enhanced mechanically evoked firing rate in gastrointestinal afferents^[52,53]. In contrast to the ASIC3 role in secondary hyperalgesia, ASIC1a-deficient mice do not develop primary hyperalgesia induced by muscle inflammation, so ASIC1a and ASIC3 may play distinct roles in the development and maintenance of hyperalgesia, respectively^[43]. Downregulation of ASIC1a expression in spinal dorsal horn neurons by using selective inhibitor or antisense oligonucleotides reduces complete Freund's adjuvant (CFA)-induced thermal and mechanical hypersensitivity, which suggests that ASIC1a contributes to central sensitization in inflammatory pain^[54]. A recent study provides a new view for ASIC1a and ASIC3 roles in inflammatory pain in that acidosis may induce endocytosis and maturation of macrophages through ASIC1a and ASIC3^[55]. Mice lacking ASIC1a, ASIC2 and ASIC3 genes lost acid-induced transient currents, but their be-

havioral sensitivity to mechanical stimuli was increased, so ASICs indeed contribute cutaneous mechanosensation but in complex behavioral changes^[56].

PROTON-GATED ION CHANNELS: TRPV1

Transient receptor potential/vanilloid receptor subtype 1 (TRPV1/VR1) is a 6-transmembrane domain, non-selective cation channel and activated by vanilloid, heat, capsaicin, and proton^[57,58]. TRPV1 is predominantly expressed in small-diameter DRG neurons in rats and mice^[57]. Disruption of the TRPV1 gene in mice reduces responses of DRG neurons to acid and thermal stimuli and eliminates carrageenan-induced thermal hyperalgesia, so TRPV1 may be involved in acid-induced pain and inflammation-induced thermal hyperalgesia^[59,60]. However, surprisingly, blockage of the TRPV1 function in peripheral or spinal loci by selective antagonists inhibits mechanical hyperalgesia induced by CFA, capsaicin, or bone cancer^[61-64]. Although TRPV1 participates in both mechanical allodynia and thermal hyperalgesia induced by cutaneous inflammation, it does not participate in muscle inflammation^[65]. TRPV1 mediates the development of heat but not mechanical hypersensitivity after muscle inflammation^[66]. With peripheral inflammation, the mRNA TRPV1 expression is increased and the channel function enhanced in DRG neurons^[67-69]. Interestingly, DRG neurons with increased TRPV1 expression and function are mainly non-peptidergic rather than peptidergic neurons^[69]. Since most non-peptidergic neurons project to skin targets, TRPV1 would mainly participate in cutaneous inflammatory pain^[70,71]. Okun *et al.*^[72] suggested that CFA-induced ongoing pain is transient and depends on TRPV1-positive afferents but cannot be blocked by TRPV1 antagonism. TRPV1 may be responsive to noxious stimuli while nociceptors are sensitized (inflammation). Its function could be sensitized by inflammatory mediators such as BK^[73,74], chemokines (CCL3)^[75], 5-HT^[76], PGE₂^[77,78], proton^[79] or by protease-activated receptor 2^[80,81]. A recent study suggested that TRPV1 and TRPA1 are involved in the transition of acute to chronic pain in a chronic pancreatitis model^[82].

PROTON-SENSING G-PROTEIN-COUPLED RECEPTORS: OGR1 FAMILY

In 2003, Ludwig *et al.*^[83] found two GPCRs, ovarian cancer GPR 1 (OGR1) and G protein-coupled receptor 4 (GPR4), fully responsive to protons at pH 6.8 and stimulating inositol triphosphate and cAMP formation, respectively. Later, the 2 other family members, G2 accumulation (G2A) and T-cell death-associated gene 8 (TDAG8) were identified as proton receptors, with full activation at pH 6.4-6.8^[84-86]. OGR1, GPR4, and G2A were previously identified as receptors for sphingosylphosphorylcholine (SPC) or lysophosphatidylcholine (LPC), but the original publications have now been retracted^[87-89]. Whether OGR1, GPR4, and G2A are SPC or LPC receptors

remains unclear. In addition to responding to protons, TDAG8 also responds to psychosine^[85,89]. Although G2A was considered a proton-sensing receptor, Radu *et al*^[90] suggested that G2A is less likely to be a pH sensor because it does not generate a significant response after acid stimulation. G2A shows conservation of only 1 of 5 critical histidine residues that are involved in pH-sensing of OGR1, so G2A may be less sensitive to protons^[83]. Later, Obinata *et al*^[91] found that G2A can respond to oxidized free fatty acid (9-hydroxyoctadecadienoic acid, 9-HODE). Recent studies with gene-knockout techniques have revealed the absence of some but not all pH-induced cellular effects in OGR1-, TDAG8- or GPR4-deficient mice or cells, so OGR1 family members are indeed involved in proton sensing, and the pH-dependent activities could be highly cell-type- or signaling-pathway-specific^[90,92-94]. Interestingly, mice lacking G2A show some deficiencies in LPC- or acid-related cellular effects^[90,95-97]. Whether G2A is a proton, LPC or fatty acid receptor remains debated.

Proton-sensing GPCRs are widely expressed in non-neuronal and neuronal tissues^[98]. Approximately 75% to 82% of OGR1 family members are found in small-diameter DRG neurons responsible for nociception and 61% to 74% are present in isolectin B(4) (IB4)-positive neurons, so they may be involved in chronic pain^[79,98]. Indeed, one of the members, TDAG8, showed increased expression after CFA-induced inflammation, and its activation sensitizes TRPV1 function^[79]. TDAG8 is involved in CFA-induced inflammatory pain by modulating TRPV1 function. Later, knockdown of spinal TDAG8 expression was found to reduce bone cancer pain^[99]. Thus, TDAG8 could have pro-nociceptive roles in the peripheral and central nervous system. Although a recent study suggested that TDAG8 is a negative regulator in inflammation because of exacerbation of arthritis induced by anti-type II collagen antibody in TDAG8-deficient mice, whether TDAG8 has an anti-nociceptive role in inflammatory pain remains unclear^[100].

In endothelial cells, G2A expression blocks NF- κ B activation and chemokine expression, thus inhibiting macrophage accumulation, which suggests that G2A expression may have a protective role in preventing early events of inflammation^[96]. This situation could explain why G2A expression is downregulated in capsaicin- and CFA-induced inflammatory pain, so G2A could have an anti-nociceptive role in inflammatory pain^[79]. GPR4 is present in endothelial cells of blood vessels, and mice lacking GPR4 show vascular abnormalities, which suggests that GPR4 has a role in vascular growth and vascular stability^[93]. Vascular stability is important for leukocyte adhesion and function^[101]. GPR4 antagonism attenuates acidosis-induced inflammation and modulate a wide range of inflammatory genes in endothelial cells^[102].

SEROTONIN AND SEROTONIN RECEPTORS

In the periphery, serotonin (5-HT) released from plate-

lets, mast cells, and endothelial cells into the inflamed site is pro-inflammatory and pro-nociceptive, exciting nociceptive afferents and inducing hyperalgesia^[9,103-106]. In central loci, the descending pathway on serotonergic neurons from the rostral ventromedial medulla to the spinal cord has facilitatory or inhibitory effects on DRG neurons depending on the activation of 5-HT receptor subtypes^[107]. Seven subgroups of serotonin receptors (5-HT₁₋₇) have been identified, and some subtypes have more than one receptor (*e.g.*, 5-HT₁ has 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}; and 5-HT₂ has 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C})^[108]. Although Sufka *et al*^[103] (1992) suggested that all of the 5-HT_{1A}, 5-HT_{2A}, and 5-HT₃ subtypes participate in 5-HT-induced pain, the presence of multiple 5-HT receptors on afferent nociceptors reflects distinct pain models or mechanisms.

Taiwo *et al*^[104] reported that only the 5-HT_{1A} agonist mimics the 5-HT effect to induce hyperalgesia and 5-HT_{1A} antagonists block mechanical hyperalgesia induced by 5-HT. Nevertheless, Kayser *et al*^[109] suggested that mice lacking 5-HT_{1A} show increased sensitivity to noxious heat but not mechanical pain stimuli. The other study of formalin testing also suggested that 5-HT_{1A} mediates antinociception^[110]. In addition to 5-HT_{1A}, the receptors 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} also have anti-nociceptive effects in heat-evoked or formalin-induced nociceptive responses^[109,110]. Later, 5-HT_{2B/2C} but not 5-HT_{1A} was found to mediate 5-HT-induced mechanical hyperalgesia^[111]. Spinal and peripheral injection of a specific antagonist (RS127445) of 5-HT_{2B} reduced formalin-induced flinching behavior, which suggests that 5-HT_{2B} has a pro-nociceptive role in peripheral as well as spinal loci^[112]. However, Urtikova *et al*^[113] suggested that blockage of peripheral or spinal 5-HT_{2B} by a specific antagonist (RS127445) could enhance hyperalgesia induced by chronic constriction nerve injury. 5-HT_{2B} may have distinct roles in different pain models.

Ionotropic 5-HT₃ is directly responsible for inflammatory pain^[109,114,115]. Lack of the 5-HT₃ gene in mice or blocking with the 5-HT₃ antagonist granisetron elicited normal acute pain responses but reduced persistent pain responses^[109,115]. Giordano *et al*^[116] showed that 5-HT₃ contributes to chemical but not thermal and mechanical nociceptive pain. 5-HT_{2A} potentiates the effects of other inflammatory mediators^[117]. In the study by Tokunaga *et al*^[118], only the 5-HT_{2A} agonist but not 5-HT_{1A} and 5-HT_{3A} agonists mimicked 5-HT-induced thermal hyperalgesia, which was blocked by the 5-HT_{2A} antagonist ketanserin. However, Loyd *et al*^[119] suggested that both 5-HT-induced and 5-HT-enhanced capsaicin-evoked thermal hyperalgesia require 5-HT_{2A} and 5-HT₃. Likely, 5-HT_{2A} potentiates 5-HT₃-mediated nociceptive responses to thermal stimuli. Recent studies show that 5-HT_{2A} has a pronociceptive role in spinal nociceptive transmission and seems to be involved in both mechanical and thermal hyperalgesia in the spinal nerve ligation model^[120,121].

In addition, 5-HT₄ enhances the inflammatory pain signal^[122]. 5-HT₇ inhibits capsaicin-induced mechanical

sensitivity^[123]. Intrathecal injection of 5-HT_{2A}, 5-HT₃ and 5-HT₄ antagonists significantly reduced spinal cord stimulation-induced long-lasting pain in rat models, with no effect by administration of 5-HT_{1,6,7} antagonists^[124]. 5-HT₂ and 5-HT₇ are major receptors to potentiate TRPV1 function in inflammatory pain^[76].

PROSTAGLANDIN E2

Prostaglandin E2 (PGE₂), derived from an arachidonic acid by the cyclooxygenase (COX) pathway, is released from damaged cells and contributes to inflammatory pain^[125]. Non-steroidal anti-inflammatory drugs are the commonly used analgesics that reduce prostaglandin synthesis by inhibiting COX-1 and COX-2^[126]. Four subtypes of PGE₂ receptors (EP₁, EP₂, EP₃ and EP₄) belong to GPCRs^[125,127]. The roles of PGE₂ receptor subtypes in pain are undefined because of inconsistent results from studies involving gene targeting techniques, but are better resolved in combined studies with pharmacological approaches^[126]. PGE₂-induced thermal hyperalgesia is mediated by EP₁ predominantly through a PKC-dependent pathway and is due to potentiation or sensitization of TRPV1^[77]. Wang and colleagues showed that PGE₂-induced pain is mediated by EP₃ through PKA and Epac/PKC pathways to sensitize purinergic P2X₃ receptors^[78,128]. Several lines of evidence also support the roles of PGE₂ in modulating pain transduction. PGE₂ potentiates the TRPV1 function in response to capsaicin^[78]. Repeated administration of PGE₂ sensitizes T-type calcium channels, thus resulting in mechanical hyperalgesia^[129]. PGE₂ potentiates the voltage-gated tetrodotoxin-resistant sodium channels (Nav1.5, Nav1.8 and Nav1.9) by a cAMP-PKA signaling pathway^[130,131].

TRANSITION FROM ACUTE TO CHRONIC PAIN

The possible mechanisms of chronic inflammatory pain could be that continuous sensitization induced by inflammatory mediators in primary afferent nociceptors results in persistent and long-lasting pain or neuroplastic changes in primary afferent nociceptors after initiating insults lead to enhanced and prolonged sensitization of nociceptors even with low-level exposure of pro-nociceptive inflammatory mediators. The mechanisms of chronic pain and the regulation of the transition from short-term to long-lasting pain have become clearer from studies with the PGE₂ priming model.

Administration of PGE₂ in rat induces short-term hyperalgesia that depends on PKA activity^[132]. With carageenan pre-injection, rats display long-lasting hyperalgesia induced by PGE₂, and the prolonged effect can be inhibited by PKC ϵ blocker or attenuated by antisense oligonucleotides for PKC ϵ ^[133,134]. Therefore, PKC ϵ may be necessary to maintain hyperalgesic priming. Indeed, a highly selective PKC agonist can induce hyperalgesic priming in rat^[134]. In contrast, the study by Ferrari *et*

al^[135] proposed that a transient decrease in GRK2 levels leads to increased nociceptor response to inflammatory mediators, and the reduced GRK2 levels are PKA- but not PKC-dependent. Ferrari *et al*^[136] later proposed that the prolongation of PGE₂-induced hyperalgesia is mediated by an autocrine mechanism. PGE₂ activates EP receptors followed by cAMP production, which in turn activates PKA and induces hyperalgesia. The increase in intracellular cAMP level triggers the transporter to transport cAMP outside the cell. The extracellular cAMP is metabolized to AMP and adenosine, thus activating the Gi-coupled A₁ adenosine receptor. The Gi pathway stimulates PKC ϵ , which is responsible for the late phase of PGE₂-induced hyperalgesia, although evidence has shown that after injury, the inflammatory mediators may release and reach the effective concentration in a different time course. Each mediator activates its own receptor subtypes, thus contributing to the development of hyperalgesia. However, which receptor is the major receptor causing the acute to chronic pain remains unclear.

ESTABLISHMENT AND MAINTENANCE OF CHRONIC PAIN: THE ROLE OF AN EXCITATORY AMINO ACID IN CENTRAL SENSITIZATION

The establishment and maintenance of chronic pain is not simply a reflection of peripheral inputs or abnormality but is also a dynamic reflection of central neuronal plasticity. Once the central sensitization occurs, painful sensations are generated even in the absence of the noxious stimulus^[137]. Several lines of evidence implicate the contribution of excitatory amino acids in neuroplasticity and central sensitization in the spinal cord. Noxious stimulation or peripheral inflammation causes the release of an excitatory amino acid, glutamate, in the spinal dorsal horn^[138,139]. Dorsal horn neurons that are sensitized with peripheral inflammation show increased responsiveness to the iontophoretic application of the excitatory amino acid^[139,140], and such responsiveness or sensitization is reduced after the administration of glutamate receptor antagonists^[141,142].

Glutamate receptors include ionotropic amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartate (NMDA), kainate receptors and metabotropic G-protein-coupled glutamate receptors (mGluRs). The contribution of ionotropic glutamate receptors to the central sensitization are considered the ability of AMPA and NMDA receptor antagonists to reduce the responsiveness of dorsal horn neurons and in producing analgesic effects^[142]. Intrathecal injection of NMDA leads to hyperalgesia, which can be reversed by application of an NMDA antagonist^[143]. The NMDA antagonist MK-801 reduces the hyperalgesia that develops in rats with adjuvant-induced inflammation^[144] or reduces the inflammation-induced expansion of the receptive field of spinal nociceptive neurons^[145].

Peripheral inflammation elevates levels of phosphorylated NMDA receptors in the spinal dorsal horn^[146,147]. The sustained release of the neuropeptides (such as substance P and CGRP) and glutamate causes PKC activation and Ca²⁺ influxes through NMDA receptors. With Ca²⁺ influx, several intracellular signal pathways, including the phospholipase C-PKC pathway, phosphatidylinositol-3-kinase (PI3K) pathway, and mitogen-activated protein kinase (MAPK) pathway, are activated. Activated intracellular signaling pathways result in phosphorylation of spinal NMDA receptors, enhancing Ca²⁺ currents at NMDA receptors. Activated intracellular signaling pathways also phosphorylate AMPA receptors, thus increasing the density of AMPA receptors on the membrane^[148]. These mechanisms create a positive feedback loop for glutamate transmission and alter the neuronal plasticity in the dorsal horn. In the formalin-induced inflammatory pain model, intrathecal injection of the MEK inhibitor PD98059 can reduce the second phase of the licking/lifting behavior and attenuate extracellular signal-regulated kinase activity, so some intracellular signaling pathways may also be involved in central sensitization^[149].

CONCLUSION

At the inflamed site of the tissue, endogenous mediators (5-HT, PGE₂, BK, and proton) are released from damaged cells and accumulate. Nociceptors innervating the skin, muscle and organs detect the noxious stimuli and express one or more cell-surface receptors to respond to these inflammatory mediators. The mediators can directly or indirectly alter the sensitivity of the receptors on nociceptors. ASIC3, ASIC1a and TRPV1 seem to be important transducer receptors contributing to hyperalgesia induced by inflammation. ASIC1a participates in primary mechanical hyperalgesia induced by muscle inflammation, but ASIC3 may have a predominant role in secondary mechanical hyperalgesia. TRPV1 could be responsible for mechanical and thermal hyperalgesia induced by cutaneous inflammation. Inflammatory mediators such as 5-HT, PGE₂, BK, and proton sensitize TRPV1 or ASIC3 to prolong the hyperalgesia. PGE₂ acts on EP₁ to sensitize TRPV1 or on EP₃ to sensitize P2X₃. Proton and BK sensitize TRPV1 through TDAG8 and B₂, respectively. 5-HT potentiates TRPV1 function, possibly through 5-HT₂ and 5-HT₇. Although each mediator receptor has its own dominant second-messenger signaling cascade, each could also be coupled in part to other second-messenger pathways. For short-term hyperalgesia, the cAMP-PKA pathway is dominant, but prolonged hyperalgesia is regulated by PKC ϵ -dependent or -independent pathway.

The signal of a stimulus is triggered by a peripheral nociceptor, followed by conduction to central neurons. In acute pain, the signal is mediated by glutamate acting on AMPA and kainate subtypes of ionotropic glutamate receptors of postsynaptic neurons and generating the excitatory postsynaptic potential. If the signal is generated by intense or persistent noxious stimuli, the depolarization of the postsynaptic neurons will activate NMDA re-

ceptors. NMDA receptor activation induces Ca²⁺ influx, which activates intracellular signaling pathways to further enhance Ca²⁺ influx through NMDA receptors. NMDA receptors can also be modulated by GPCRs such as NK1, EP or mGlu receptors that are also expressed on the superficial dorsal horn of nociceptor terminals^[150]. All these NMDA-receptor-mediated mechanisms contribute to central sensitization, which is important for establishing and maintaining chronic pain^[151].

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