Update Article

Pathophysiology of acute inflammatory pain: integration between inflammation and nociception

Fisiopatologia da dor aguda inflamatória: integração entre inflamação e nocicepção*

Talitha Koo Yen[1], Victor Ken Ishikawa[1], Jeniffer Charlene Silva Dalazen[1], Renan Peixoto Passos de Oliveira[1], Eduardo Alves de Almeida Silva[1], Walter Augusto Maciel Ramirez[1]

1. Hospital Geral de Itapecirica da Serra, Itapecirica da Serra, SP, Brazil

Abstract

Acute inflammatory pain represents an important clinical and public health challenge, being the main complaint in emergency services. It begins with tissue injury, which activates innate immune receptors and leads to the release of cytokines, prostaglandins, and algiogenic mediators, promoting vasodilation, edema, and sensitization of peripheral nociceptors. Among the main inflammatory mediators are PGE_2, NGF, IL-1β, TNF-α, as well as the chemokines CCL2 and CX3CL1 (fractalkine). This inflammatory environment decreases the activation threshold of nociceptors, intensifying the pain response. Transduction occurs through the activation of TRPV1 and Nav1.7/1.8 channels, resulting in action potentials that are transmitted by Aδ and C fibers to the dorsal horn of the spinal cord. There, synapses with second-order neurons trigger the ascending transmission of pain through the spinothalamic, spinomesencephalic, and spinoreticular tracts, reaching structures such as the thalamus, somatosensory, cingulate, and insular cortices, as well as limbic regions, shaping the sensory and emotional experience of pain. Modulation occurs both through local inhibitory interneurons and through descending pathways originating in the brainstem, using neurotransmitters such as GABA, serotonin, norepinephrine, and endogenous opioids. Microglial activation and central neuroinflammation may also perpetuate pain. An integrated understanding of the neurobiology of acute pain is essential to prevent its chronification and to propose effective therapeutic approaches.

Kewords: Acute Pain; Nociception; Inflammation; Prostaglandins; Neuroinflammation.

Resumo

A dor aguda inflamatória representa um importante desafio clínico e de saúde pública, sendo a principal queixa em serviços de urgência. Inicia-se com lesão tecidual, que ativa receptores imunes inatos e leva à liberação de citocinas, prostaglandinas e mediadores algiogênicos, promovendo vasodilatação, edema e sensibilização dos nociceptores periféricos. Entre os principais mediadores inflamatórios destacam-se a PGE_2, NGF, IL-1β, TNF-α, além das quimiocinas CCL2 e CX3CL1 (fractalina). Esse ambiente inflamatório diminui o limiar de ativação dos nociceptores, intensificando a resposta dolorosa. A transdução ocorre por meio da ativação de canais TRPV1 e Nav1.7/1.8, resultando em potenciais de ação que são transmitidos pelas fibras Aδ e C até o corno dorsal da medula espinal. Lá, sinapses com neurônios de segunda ordem desencadeiam a transmissão ascendente da dor por tratos espinotalâmico, espinomesencefálico e espinorreticular, alcançando estruturas como o tálamo, córtices somatossensorial, cingulado e insular, além de regiões límbicas, compondo a experiência sensorial e emocional da dor. A modulação ocorre tanto por interneurônios inibitórios locais quanto por vias descendentes oriundas do tronco encefálico, utilizando neurotransmissores como GABA, serotonina, noradrenalina e opioides endógenos. A ativação microglial e a neuroinflamação central também podem perpetuar a dor. O conhecimento integrado da neurobiologia da dor aguda é fundamental para prevenir sua cronificação e propor abordagens terapêuticas eficazes.

Palavras-chave: Dor aguda; Nocicepção; Inflamação; Prostaglandinas; Sensibilização periférica; Neuroinflamação.

Study performed at the Hospital Geral de Itapecirica da Serra, Itapecirica da Serra, SP, Brazil.
Correspondence: Talitha Koo Yen. R. Prof. Enéas de Siqueira Neto, 340 – Jardim das Imbuias, 04829-300, São Paulo, SP, Brazil.
Email: tkooyen@gmail.com.
Conflict of interest: None.
Source of funding: None.
Received: July 30, 2025.
Accepted: August 19, 2025.

Citation: Yen TK, Ishikawa VK, Dalazen JCS, Oliveira RPP, Silva EAA, Ramirez WAM. Pathophysiology of acute inflammatory pain: integration between inflammation and nociception. J. Braz. Musculoskelet. Pain Soc. 2025;1(2):e22

This content is licensed under a Creative Commons Attribution 4.0 International License.

Introduction

Acute pain is a highly prevalent condition and ranks among the leading reasons for seeking medical care in emergency departments. Studies indicate that between 60% and 90% of patients treated in hospital settings report pain as their chief complaint[1]. In the United Kingdom, pain-related demand exceeds 20 million visits annually, with an upward trend of approximately 6% to 7% per year[2]. In addition to its immediate clinical impact, acute pain carries significant socioeconomic consequences, being one of the main causes of work absenteeism and productivity loss. Economic estimates from the United States reveal that costs related to pain — including both acute and chronic forms — exceed US$ 635 billion per year[3]. Recognizing its importance, international guidelines have established pain as the fifth vital sign, highlighting its essential role in clinical assessment[4].

According to the definition proposed by the International Association for the Study of Pain (IASP), pain is understood as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[5]. Acute pain, in particular, is characterized by abrupt onset, limited duration, and a direct association with tissue injury and the subsequent inflammatory mechanisms[6]. From a physiological standpoint, it constitutes an adaptive response aimed at protecting the organism by inducing rest and immobility to promote recovery. Local inflammation triggered by cellular injury thus acts as a factor in the activation and maintenance of nociceptive stimuli[5,6].

It is essential that healthcare professionals understand the pathophysiological aspects involved in acute pain, as inadequate management may result in persistence of the pain condition. Evidence demonstrates that a considerable proportion of patients treated for acute pain progress to chronic pain, especially when adequate relief is not achieved in the hospital setting[7]. Cohort studies report transition rates ranging from 15% to 86%, depending on etiology and the management instituted[8,9]. The absence of systematized strategies, combined with underassessment of pain, directly contributes to increased morbidity, patient dissatisfaction, and healthcare system burden[10].

Therefore, this article aims to review the main mechanisms underlying acute pain of inflammatory origin, emphasizing the interaction between the peripheral nervous system and immune mediators released during tissue injury. Although the focus is on the acute phase of the process, aspects related to the transition to chronicity will also be addressed, such as glial activation and central neuroinflammation. The objective is to provide a solid scientific foundation to support clinical practices aimed not only at symptomatic relief but also at preventing long-term complications.

Pathophysiology of inflammation resulting from tissue injury

Acute pain of inflammatory origin begins with an event of tissue injury that causes disruption of cell membranes and results in the release of endogenous molecular danger signals known as damage-associated molecular patterns (DAMPs). These signals are promptly recognized by innate immune system receptors, such as Toll-like receptors (TLRs), expressed on cells including mast cells, resident macrophages, and endothelial cells. This activation triggers an inflammatory cascade with neutrophil recruitment and activation of other immunocompetent cells at the site of injury[11,12].

As a consequence, there is rapid release of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and nerve growth factor (NGF), which amplify the local inflammatory response by promoting vasodilation, increased vascular permeability, edema formation, and contributing to an environment conducive to activation and sensitization of nociceptive nerve endings. Several algogenic molecules are released in the injured tissue and play an essential role in the direct activation of peripheral nociceptors, such as bradykinin, histamine, serotonin, leukotrienes, substance P, platelet-activating factor (PAF), reactive oxygen species (free radicals), potassium ions, cyclic adenosine monophosphate (cAMP), thromboxanes, as well as the cytokines IL-1β, IL-6, TNF-α, and NGF[13]. Sustained exposure of these nerve endings to such mediators leads to functional modification of ion channels and sensory receptors, culminating in a state of hyperexcitability known as peripheral sensitization[11].

Among the inflammatory mediators released during tissue injury are the degradation products of arachidonic acid, which originates from membrane phospholipids of damaged cells through the catalytic action of the enzyme phospholipase A_2. Arachidonic acid is then metabolized through two main enzymatic pathways: the cyclooxygenase (COX) pathway and the lipoxygenase pathway. In the context of inflammatory pain, the COX pathway is of particular relevance. The COX-1 isoform, constitutively expressed, and COX-2,

CC BY

induced in response to inflammatory stimuli, convert arachidonic acid into prostaglandin H_2 (PGH_2), the common precursor of several bioactive prostanoids, including prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), and thromboxane A_2 (TXA_2)[14].

Prostaglandin E_2 (PGE_2), in particular, plays a central role in pain modulation by interacting with specific receptors on nociceptive terminals, lowering the neuronal excitation threshold and intensifying the pain response to mechanical, thermal, or chemical stimuli. In addition, prostaglandins exert important homeostatic physiological functions[12,13]. In the gastrointestinal tract, PGE_2 and PGI_2 protect the gastric mucosa by promoting local blood flow, stimulating mucus and bicarbonate production, and inhibiting acid secretion. In the renal system, they contribute to regulation of glomerular hemodynamics, while in the cardiovascular system they play a role in maintaining vascular tone and modulating platelet aggregation[14,15].

For these reasons, inhibition of COX enzymes—especially COX-1—by nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to clinically significant adverse effects. Among the main complications associated with the use of these medications are increased risk of gastroduodenal ulcers, acute kidney injury, and thromboembolic events, particularly in patients using selective COX-2 inhibitors[15]. These adverse effects highlight the importance of considering drug selectivity for COX isoforms in the therapeutic planning of acute inflammatory pain[15] (Figure 1).

Inflammation and the pathophysiology of pain

Nociceptive pain results from a highly organized neurophysiological process that begins in the periphery and ascends through neural pathways until it reaches higher centers of the central nervous system, where it

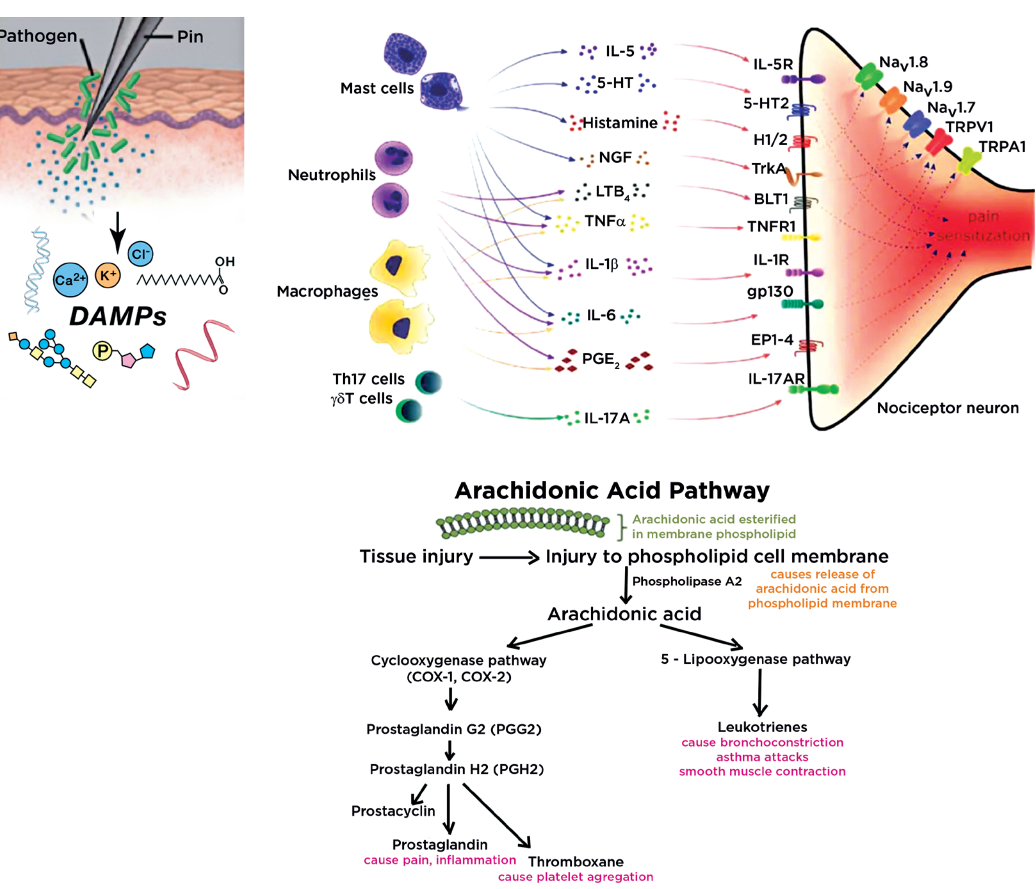

Figure 1. Inflammatory process resulting from tissue injury, with the release of DAMPs and inflammatory cytokines, emphasizing prostaglandins derived from the arachidonic acid degradation cascade and the binding of these substances to their respective receptors on the nociceptor.

Source: Adapted from https://www.cell.com/cms/10.1016/j.immuni.2024.03.002/asset/88fdde96-3bdc-47b0-9cf8-eb3b29b32ede/main.assets/gr1_lrg.jpg
https://genoskin.com/understanding-neurogenic-inflammation-pain/

CC BY

is consciously interpreted as pain. This process starts when potentially harmful stimuli — thermal, mechanical, or chemical in nature — activate the free nerve endings of nociceptors located in somatic and visceral tissues such as the skin, muscles, joints, and viscera. In situations of tissue injury, these nociceptors are immersed in an acidic inflammatory microenvironment rich in previously described chemical mediators, such as cytokines, prostanoids, and bradykinin[16].

The interaction of these mediators with their respective receptors on nerve terminals leads to the activation of specific ion channels, such as the TRPV1 channel — sensitive to heat, protons, and capsaicin — and the voltage-gated sodium channels Nav1.7 and Nav1.8[13,16]. Activation of these channels allows ion influx, resulting in neuronal membrane depolarization and generation of the initial action potential, a process known as transduction. This action potential is subsequently conducted along the axon to the spinal cord[11,16].

In addition to their activating function, inflammatory mediators contribute to peripheral sensitization, a phenomenon in which the excitation threshold of nociceptors is reduced, making them more responsive to subsequent stimuli[11]. This sensitization results not only from functional modulation of ion channels already present in the membrane, but also from induction of new channel expression, thereby increasing neuronal excitability. This hypersensitive state of the nociceptor is directly related to the clinically observed exacerbated pain responses, such as hyperalgesia and allodynia[17,18].

Table 1 lists the main inflammatory mediators and cytokines involved in this process, together with their receptors and the mechanisms by which they modulate nociceptor activation and sensitization, as well as their role in perpetuating the inflammatory cascade[12,16].

Transmission of the nociceptive stimulus begins with conduction of the action potential generated in

Table 1. Cytokines Involved in the Inflammatory Process, Their Receptors, and Mechanisms of Action

Inflammatory Mediator	Receptor(s)	Mechanism of Action
Prostaglandins	EP1–EP4	PGE_2 acts as a sensitizer of nociceptor activity by acting on proximal ion channels rather than directly activating nociceptive neurons, a key discovery for understanding the analgesic effects of NSAIDs. Over a longer time scale, PGE_2 also induces persistent hyperalgesia through PKA- and PKC-mediated activation of NF-κB in dorsal root ganglion (DRG) neurons.
Leukotrienes	BLT1, BLT2	Promote neutrophil chemotaxis and inflammation; involved in pain and bronchoconstriction. They sensitize nociceptors, and binding to BLT1 mediates calcium influx in TRPV1-positive neurons in the DRG.
Histamine	H1, H2	Rapid mediator of inflammation; induces vasodilation and increased vascular permeability. Histamine binds to H1 and H2 receptors on nociceptive neurons, increasing Nav1.8 sodium channel expression and enhancing sensitivity to mechanical and thermal stimuli.
5-HT (Serotonin)	5-HT2	Binding of 5-HT to the 5-HT2 receptor and activation of PKC increase the expression of acid-sensing ion channels (ASICs), which detect extracellular protons and mediate enhanced pain signaling.
NGF (Nerve Growth Factor)	TrkA	Sensitizes nociceptors via TrkA. TrkA activation triggers PI3K/Src kinase signaling, leading to TRPV1 phosphorylation and rapid membrane insertion, causing rapid peripheral sensitization, tissue repair, angiogenesis, and cell proliferation.
IL-1β	IL-1R	Sensitizes nociceptive neurons through p38 MAPK-mediated phosphorylation of Nav1.8 sodium channels, increasing action potential generation and resulting in mechanical and thermal hyperalgesia. IL-1β also activates IL-1R1 in nociceptive neurons, increasing TRPV1 expression and thermal pain sensitivity. Acts peripherally, in the DRG, and is released by microglia in the spinal dorsal horn.
TNF-α	TNFR1, TNFR2	Induces rapid modulation of nociceptor sensitivity through p38 MAPK-mediated phosphorylation of Nav1.8 and Nav1.9 sodium channels, increasing neuronal excitability. Triggers pro-inflammatory signaling cascades, activates glial cells, and promotes persistent pain.
IL-6	IL-6R/ gp130	Contributes to inflammatory pain by inducing prostaglandin production and binding to its signal transducer gp130 expressed on nociceptors, leading to increased TRPV1 and TRPA1 expression.
IL-5	IL-5R	Sensitizes nociceptive neurons expressing IL-5 receptors. Promotes eosinophil recruitment, allergic inflammation, and pain modulation.
IL-17 (IL-17A)	IL-17RA / IL-17RC	Induces chemokine production and autoimmune inflammation; contributes to chronic pain. IL-17A induces hyperalgesia through amplification of TNF-α, IL-1β, CXCL1, endothelin-1, and prostaglandins in antigen-induced arthritis. Also plays a role in neuroinflammation in the DRG.

nociceptors along Aδ (myelinated) and C (unmyelinated) fibers, which reach the dorsal horn of the spinal cord. In these fibers, whose cell bodies are located in the dorsal root ganglia, axons enter the spinal cord and distribute through the tract of Lissauer, ascending or descending before establishing synapses with second-order neurons, predominantly in Rexed laminae I, II, and V[19] (Table 2).

At the spinal synapse, excitatory neurotransmitters such as glutamate — which acts on AMPA and NMDA receptors — and substance P, which binds to NK1 receptors, are released. Activation of these receptors promotes depolarization of second-order neurons, driving the pain signal to higher levels of the central nervous system. Lamina I responds preferentially to noxious and thermal stimuli and projects to the contralateral spinothalamic tract. Lamina II, also known as the substantia gelatinosa, contains inhibitory interneurons rich in GABA and neuropeptide Y, responsible for modulation of nociception. Laminae III and IV receive afferents from larger myelinated fibers as well as serotonergic projections originating in the raphe nuclei. Lamina V integrates information from Aβ, Aδ, and C fibers, including visceral nociceptive input[20].

Several ascending pathways are involved in conducting pain signals to the brain, including the spinothalamic, spinoreticular, and spinomesencephalic tracts. The spinothalamic tract, the principal pathway responsible for discrimination of pain in terms of location and intensity, consists of two divisions: the lateral division, which carries pain and temperature signals, and the anterior division, responsible for conduction of crude touch and firm pressure. Axons originating from neurons in the dorsal horn and intermediate gray matter cross to the contralateral side of the spinal cord and ascend in the anterolateral quadrant to reach the brainstem or diencephalon[21,22].

The terminals of these axons reach multiple structures, such as the reticular formation of the brainstem (spinoreticular tract), the periaqueductal gray (spinomesencephalic tract), and thalamic nuclei — including the ventral posterolateral nucleus and the intralaminar nuclei[21]. Other accessory pathways include direct projections to the hypothalamus, specific routes for visceral pain through the dorsal columns, and connections with limbic structures such as the cingulate and insular cortices, mediated by the parabrachial nuclei and the amygdala. These routes contribute significantly to the affective-emotional dimension of pain[21,22,23] (Figure 2).

Within the central nervous system, pain modulation may occur through inhibitory or facilitatory mechanisms, influencing nociceptive transmission in the dorsal horn of the spinal cord. Inhibition is mediated by local interneurons that predominantly use GABA and glycine, producing pre- and postsynaptic effects that reduce neuronal excitability. Some of these interneurons also release endogenous opioids such as enkephalins, endorphins, and dynorphins, which increase potassium conductance, hyperpolarize neurons, and inhibit

Table 2. Ion Channels of Nociceptors Involved in Transduction of the Inflammatory Nociceptive Stimulus

Ion Channel	Action
TRPV1	TRPV1 is a large-pore cation channel activated by noxious heat (≥43 °C), protons, and capsaicin. During inflammation or tissue injury, cytokines, prostaglandins, NGF, and bradykinin signal neurons to increase TRPV1 expression and/or activity. Immune mediators activate MAPK, PKC, and PKA, which phosphorylate membrane or cytoplasmic residues of TRPV1, altering gating properties and facilitating channel opening.
TRPA1	TRPA1 is a nociceptive ion channel responsive to electrophilic reactive chemicals and inflammatory products such as prostaglandins. It is predominantly expressed in sensory nociceptive neurons of vagal ganglia, trigeminal ganglia, and DRG neurons (both peptidergic and non-peptidergic). Bradykinin activates TRPA1, and other inflammatory mediators increase its membrane expression and phosphorylation cascades, enhancing cold pain sensitization.
TRPV4	TRPV4 is a calcium-permeable ion channel activated by warm temperatures (>25 °C), hypotonicity, and acidic pH. It also responds to inflammatory mediators and chemotherapy-induced neuropathy. TRPV4 contributes to carrageenan- or inflammatory soup–induced mechanical hyperalgesia (bradykinin, substance P, PGE_2, serotonin, histamine) through cAMP–PKA and PKC signaling pathways.
NaV1.7, NaV1.8, NaV1.9	Voltage-gated sodium channels NaV1.7, NaV1.8, and NaV1.9 are highly expressed in peripheral nociceptors. Pro-inflammatory mediators, including IL-1β and TNF-α, signal through kinases to phosphorylate these sodium channels and facilitate their opening. IL-1β and TNF-α induce p38-mediated changes in TTX-resistant sodium currents, increasing nociceptive excitability. Inflammation also modulates sodium channel expression; NaV1.7 and NaV1.8 are upregulated in the DRG.

CC BY

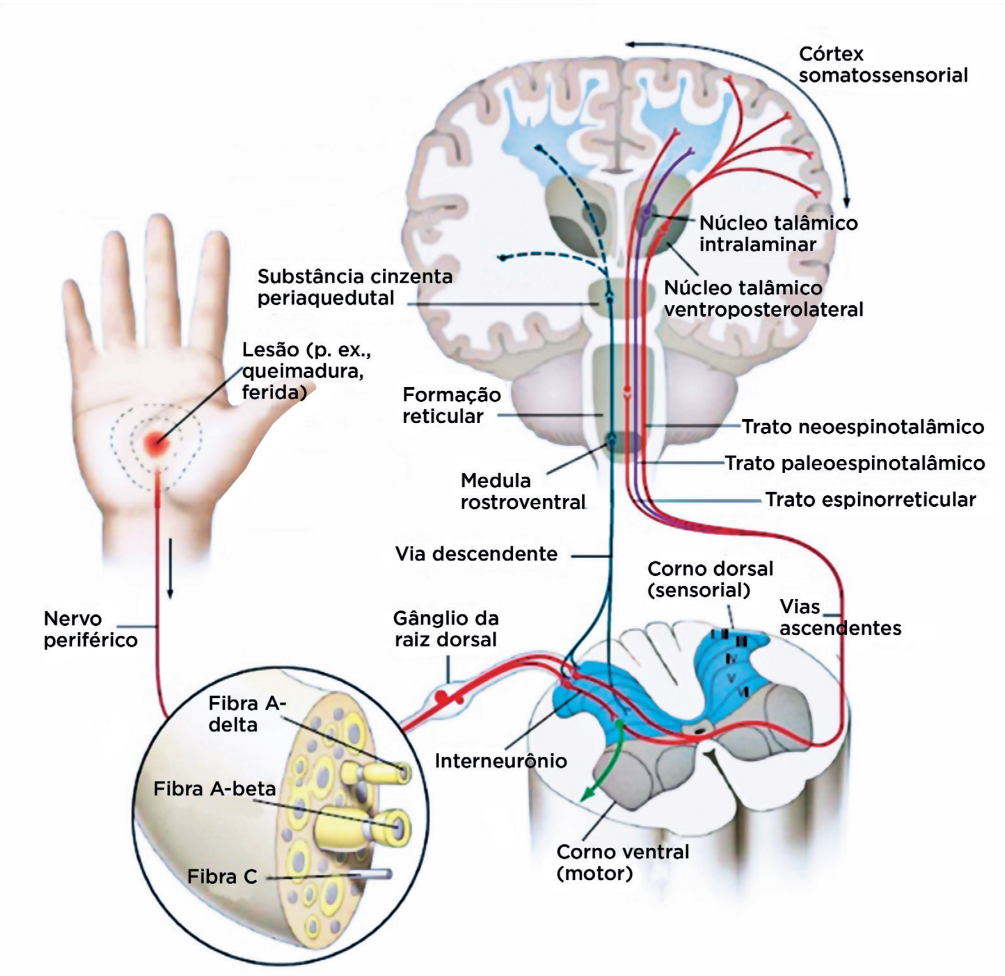

Figure 2. Ascending nociceptive pain pathway (red) and descending modulatory pain pathway (green).
Source: Albuquerque[30].

neurotransmitter release from primary afferent fibers by blocking voltage-gated calcium channels[17,22].

Descending inhibitory pathways originate from structures such as the rostroventral medulla, brainstem nuclei (including the nucleus of the solitary tract, parabrachial nucleus, and dorsal reticular nucleus), hypothalamus, and cortex. These tracts utilize neurotransmitters such as norepinephrine (α_2-adrenergic receptors), serotonin (5-HT_1, 5-HT_2, 5-HT_3), GABA, glycine, endocannabinoids (CB_1, CB_2), and endogenous opioids (μ, κ, δ), promoting inhibitory modulation of pain. In contrast, central facilitation — generally associated with the transition to chronic pain — occurs through sustained activation of NMDA receptors by glutamate, release of substance P, inflammatory cytokines, and microglial activation, characterizing a state of central neuroinflammation[24].

Table 3 further details the excitatory and inhibitory neurotransmitters acting in the synaptic cleft, their receptors, and their actions[21].

Pain perception involves multiple cortical regions and subcortical structures that integrate the sensory, emotional, and cognitive components of the painful experience. The primary somatosensory cortex, located in the postcentral gyrus of the parietal lobe, is responsible for encoding the location and intensity of the nociceptive stimulus, maintaining precise somatotopic organization. Third-order axons originating from the thalamus travel through the posterior limb of the internal capsule and terminate in these cortical areas. The intralaminar thalamic nuclei project to the insula and anterior cingulate gyrus, regions involved in deep, poorly localized pain with strong affective components[25].

CC BY

The insula and anterior cingulate cortex are associated with conscious perception and emotional evaluation of pain, while the prefrontal cortex participates in cognitive interpretation of the painful stimulus. The limbic system, particularly the amygdala and hippocampus, regulates emotional response, memory, and learning related to pain. This cortical-limbic circuit explains why psychological factors — such as depression, anxiety, selective attention, and catastrophizing — may lower the pain threshold and amplify its perception. Individuals with depressive symptoms, for example, report greater pain intensity in response to identical stimuli, and learned negative emotional experiences may perpetuate hyperalgesic states[23,26].

Table 3. Excitatory and Inhibitory Neurotransmitters Acting in the Synaptic Cleft, Their Receptors, and Actions

Neurotransmitter	Type	Main Action	Receptor	Site
Glutamate	Amino acid	Excitatory	NMDA, AMPA, mGlu	CNS, PNS
Aspartate	Amino acid	Excitatory	AMPA, NMDA, Kainate	CNS
Substance P	Peptide	Excitatory and inflammatory	NK1, NK2, NK3	CNS and PNS
CGRP	Peptide	Excitatory and inflammatory	RAMP1, CLR, RCP	CNS and PNS
Nitric Oxide (NO)	Diffusible gas	Excitatory or inhibitory	Membrane diffusion activates sGC	CNS, PNS
GABA	Amino acid	Inhibitory	GABA_A, GABA_B	CNS, PNS
Glycine	Amino acid	Inhibitory	GlyR	CNS
Endogenous Opioids (Enkephalins)	Peptide	Inhibitory (analgesia and pain modulation)	μ-, κ-, δ-receptors	CNS, PNS
Cannabinoids	Lipid	Inhibitory	CB1, CB2	CNS, PNS
Serotonin (5-HT)	Indole derivative	Receptor-dependent (excitatory or inhibitory)	5-HT1–4, 7	CNS, PNS
Norepinephrine	Monoamine	Excitatory (α1, β), inhibitory (α2)	α1, α2, β-adrenergic receptors	CNS, PNS

Table 4. Neurotransmitter Receptors in the Synaptic Cleft

Receptor	Main Action	Mechanism of Action	Principal Sites of Action
AMPA Receptor	Mediates fast excitatory transmission in the CNS; crucial for synaptic plasticity, learning, and memory.	Ionotropic receptor. Upon neurotransmitter binding, rapidly opens allowing sodium (Na^+) influx, causing depolarization.	CNS, especially postsynaptic membranes.
NMDA Receptor	Essential for long-term synaptic plasticity (LTP), a key process for learning and memory. Requires neurotransmitter binding (glutamate and co-agonist such as glycine) and membrane depolarization.	Ionotropic receptor and ion channel. Blocked by magnesium (Mg^{2+}) at rest. Activation requires glutamate/glycine binding and Mg^{2+} block removal by depolarization. Allows calcium (Ca^{2+}) and sodium (Na^+) influx.	Widely distributed in the CNS, particularly in glutamatergic synapses of the hippocampus, cortex, and spinal cord; mainly postsynaptic membranes.
Metabotropic Receptor	Modulates neuronal and synaptic activity more slowly and persistently than ionotropic receptors; may be excitatory or inhibitory.	G protein–coupled receptor (GPCR). Lacks ion channel. Neurotransmitter binding activates intracellular G proteins, triggering cascades via cAMP, IP_3, DAG that open/close ion channels, activate enzymes, and regulate gene expression.	Widely distributed in CNS and PNS; located on pre- and postsynaptic membranes.
Opioid Receptors	Mediate analgesic effects of endogenous opioids (enkephalins, endorphins, dynorphins) and exogenous opioids (morphine). Also involved in mood, reward, respiration, gastrointestinal function, and stress responses.	Metabotropic receptors coupled to inhibitory G proteins. Activation inhibits cAMP, opens potassium (K^+) channels, and closes calcium (Ca^{2+}) channels, leading to hyperpolarization and reduced neurotransmitter release.	CNS (spinal cord, brainstem, thalamus, limbic system, cortex), PNS (sensory neurons), gastrointestinal tract. Subtypes (μ, δ, κ) have slightly different distributions and actions.

The role of microglia in inflammation and pain

Although microglial activation is widely associated with chronic, neuropathic, or nociplastic pain, growing evidence indicates that it may also occur early in acute pain contexts, particularly when there is intense inflammatory stimulation or significant tissue injury. Microglia are the principal resident immune cells of the central nervous system (CNS) and respond to signals of injury or inflammation by releasing pro-inflammatory mediators that amplify neuronal excitability[26].

In acute inflammatory pain, peripheral stimuli can activate microglia in the dorsal horn of the spinal cord through cytokines such as IL-1β, TNF-α, and IL-6, as well as mediators including extracellular ATP, fractalkine (CX3CL1), and MCP-1 (CCL2), which bind to microglial receptors and promote phenotypic activation[27].

Once activated, microglia secrete a range of molecules that potentiate nociceptive pathways: IL-1β and TNF-α enhance synaptic transmission in second-order neurons via effects on AMPA and NMDA receptors; prostaglandins and nitric oxide increase central sensitization and promote hyperalgesia; additionally, fractalkine acting on the CX3CR1 receptor stimulates the release of brain-derived neurotrophic factor (BDNF), which alters ionic gradients in neurons, facilitating depolarization. These mechanisms position microglia as key contributors to pain perpetuation and to the transition from acute to chronic pain.

Therefore, even in cases of acute pain, early modulation of microglial activation may represent a promising therapeutic strategy to prevent pain chronification[19] (Figure 3).

Table 5 presents the inflammatory mediators most commonly associated with neuroinflammation and microglial activity.

Multimodal treatment of inflammatory nociceptive pain

Based on current understanding of inflammation pathophysiology and the nociceptive pain pathway, the management of acute pain should be multimodal,

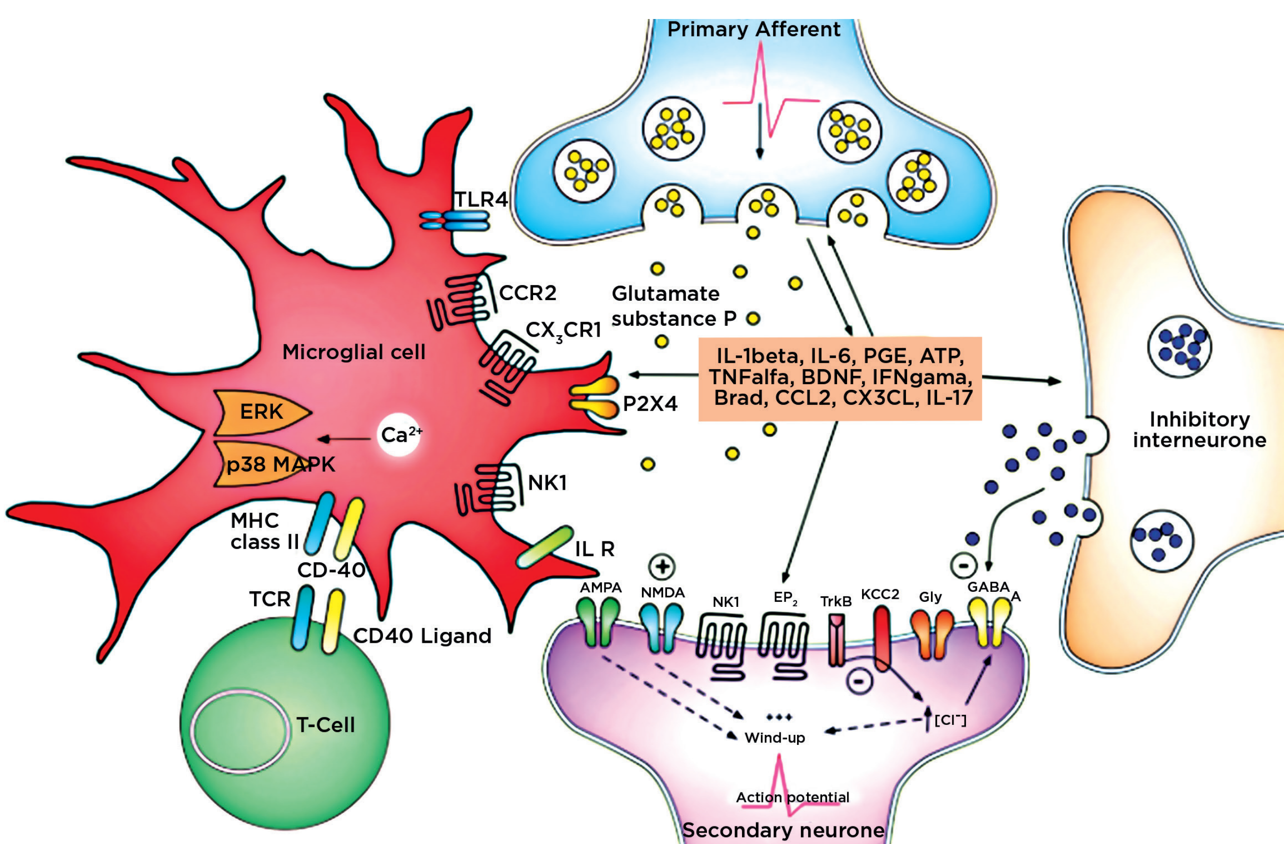

Figure 3. Inflammatory mediators present in the synaptic cleft between first- and second-order neurons in the dorsal horn of the spinal cord, and the role of microglia in neuroinflammation.

Source: Sikandar et al.[31]

CC BY

Table 5. Inflammatory Mediators Associated with Neuroinflammation and Microglial Activity

Inflammatory Mediator	Receptor(s)	Mechanism of Action
Bradykinin	B1, B2	Increases vascular permeability and pro-inflammatory cytokine release. B2 acts in peripheral and central tissues mediating acute pain sensitization, whereas B1 acts on microglial cells, contributing to transition to chronic pain.
ATP	P2X, P2Y	Activates nociceptors via P2X3 and P2X7 ion channels; promotes inflammation and sensitization.
BDNF	TrkB	Induces synaptic plasticity and chronic pain via TrkB signaling and central modulation.
IFN-γ	IFNGR1/2	Activates macrophages and promotes Th1 inflammation, exacerbating inflammatory pain.
IL-15	IL-15Rα/β/γc	Stimulates NK and T cells, promoting cytotoxicity and chronic inflammation.
CCL2 (MCP-1)	CCR2	Recruits monocytes, activates microglia, and stimulates central neurons via CCR2, culminating in neuropathic pain.
CX3CL1 (Fractalkine)	CX3CR1	Mediates leukocyte adhesion, activates microglial TNF-α production in a p38 MAPK–dependent manner, and modulates chronic pain.

combining pharmacological and non-pharmacological strategies to reduce inflammation, modulate nociceptive transmission, and prevent chronification[13].

The first step in treating acute inflammatory pain is addressing or controlling the underlying tissue injury — for example, fracture stabilization through immobilization or surgical intervention.

From a pharmacological perspective, simple analgesics such as acetaminophen (paracetamol) and dipyrone are effective for mild to moderate pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and diclofenac, inhibit COX-1 and COX-2, reducing prostaglandin production responsible for pain and inflammation; however, caution is required due to the risk of gastrointestinal, renal, and thromboembolic events[15,28].

Corticosteroids (e.g., dexamethasone, betamethasone) are useful in cases of intense inflammation and edema, particularly in orthopedic conditions. For severe pain, the WHO analgesic ladder may be applied, beginning with weak opioids (e.g., tramadol, codeine) and, if necessary, progressing to strong opioids (e.g., morphine, oxycodone, fentanyl), with careful monitoring of adverse effects[29].

The combination of adjuvant medications such as serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (e.g., nortriptyline), and gabapentinoids may play a role in acute pain management, particularly as preemptive analgesia before surgical procedures to prevent central sensitization and reduce the transition to chronic pain[15].

The use of minimally invasive techniques, such as ultrasound-guided infiltrations or nerve blocks (e.g., erector spinae plane block – ESPB), provides effective local analgesia, reduces opioid and NSAID requirements, mitigates side effects, and accelerates recovery. These methods have been associated with significant reductions in postoperative opioid consumption and improvements in pain scores and patient satisfaction[13].

Other non-pharmacological approaches, such as acupuncture and early physical therapy — including cryotherapy, transcutaneous electrical nerve stimulation (TENS), manual therapy, and therapeutic exercises — are fundamental for restoring mobility, reducing muscle spasm, and activating descending inhibitory pathways, thereby complementing pharmacological analgesia.

Thus, an integrated, evidence-based, and personalized approach is essential to ensure effective pain relief, safety, and improved functional prognosis.

Conclusion

Acute inflammatory pain is a complex clinical manifestation resulting from the interaction between biological mechanisms of tissue inflammation and coordinated activation of the nociceptive pathway.

A thorough understanding of the pathophysiology of acute inflammatory pain is indispensable for sound clinical reasoning, more effective and safer therapeutic decision-making, and, most importantly, for preventing pain chronification.

With early, precise, and evidence-based intervention, it is possible to achieve not only symptomatic relief but also functional preservation and improved patient quality of life.

Author's Contributions: TKY and VKI: conceived and planned the activities that led to the study, wrote the manuscript, participated in the review process, and approved the final version; **JCSD** and **RPPO** interpreted the study results and participated in the review process; **EAAS** and **WAMR** participated in the review process and approved the final version.

References

1. Cordell WH, Keene KK, Giles BK, Jones JB, Jones JH, Brizendine EJ. The high prevalence of pain in emergency medical care. Am J Emerg Med. 2002;20(3):165-9.
2. Yu D, Missen M, Jordan KP, Edwards JJ, Bailey J, Wilkie R, et al. Trends in the annual consultation incidence and prevalence of low back pain and osteoarthritis in England from 2000 to 2019: comparative estimates from two clinical practice databases. Clin Epidemiol. 2022;14:179-89.
3. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012 Aug;13(8):715-24.
4. Morone NE, Weiner DK. Pain as the fifth vital sign: exposing the vital need for pain education. Clin Ther. 2013;35(11):1728-32.
5. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.
6. Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. J Pain. 2017;18(4):359.e1-359.e38.
7. Pines JM, Hollander JE. Emergency department crowding is associated with poor care for patients with severe pain. Ann Emerg Med. 2008;51(1):1-5.
8. Kemp HI, Laycock H, Costello A, Brett SJ. Chronic pain in critical care survivors: a narrative review. Br J Anaesth. 2019;123(2):e372-84.
9. Friedman BW, Abril L, Naeem F, Irizarry E, Chertoff A, McGregor M, et al. Predicting the transition to chronic pain 6 months after an emergency department visit for acute pain: a prospective cohort study. J Emerg Med. 2020;59(6):805-11.
10. Admassie BM, Lema GF, Ferede YA, Tegegne BA. Emergency nurses perceived barriers to effective pain management at emergency department in Amhara region referral hospitals, Northwest Ethiopia, 2021: multi-center cross-sectional study. Ann Med Surg. 2022;81:104338.
11. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018;129(2):343-66.
12. Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of inflammation. Methods Mol Biol. 2018;1803:57-79.
13. Vardeh D, Mannion RJ, Woolf CJ. Toward a mechanism-based approach to pain diagnosis. J Pain. 2016;17(9 Suppl):T50-69.
14. Mahesh G, Anil Kumar K, Reddanna P. Overview on the discovery and development of anti-inflammatory drugs: should the focus be on synthesis or degradation of PGE2? J Inflamm Res. 2021 Feb 3;14:253-63.
15. Kianian S, Bansal J, Lee C, Zhang K, Bergese SD. Perioperative multimodal analgesia: efficacy and safety of options. Anesth Perioper Sci. 2024;2(9):9.
16. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. Nat Rev Immunol. 2019;19(7):433-47.
17. Oliveira Júnior JO, Portella Junior CSA, Cohen CP. Inflammatory mediators of neuropathic pain. Rev Dor. 2016; 17:35-42.
18. Dehghan B, Abolhasanzadeh N, Shademan B, Nourazarian A. Deciphering pain: molecular mechanisms and neurochemical pathways—challenges and future opportunities. Front Mol Biosci. 2024;11:1382555.
19. Carvalho WA, Lemônica L. Mecanismos centrais de transmissão e de modulação da dor. Rev Bras Anestesiol. 1998;48:221-41.
20. Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci. 2010;11(12):823-36.
21. Yam MF, Loh YC, Tan CS, Adam SK, Abdul Manan N, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8):2164.
22. Khalid S, Tubbs R. Neuroanatomy and neuropsychology of pain. Cureus. 2017;9(10):e1754.
23. Bushnell MC, Čeko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci. 2013;14(7):502-11.
24. Yoshimura M, Furue H. Mechanisms for the anti-nociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord. J Pharmacol Sci. 2006;101(2): 107-17.
25. Lee TH. Zero pain is not the goal. JAMA. 2016;315(15):1575-7.
26. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.
27. Karavis MY, Siafaka I, Vadalouca A, Georgoudis G. Role of microglia in neuropathic pain. Cureus. 2023;15(8):e43555.
28. Amaechi O, Huffman MM, Featherstone K. Pharmacologic therapy for acute pain. Am Fam Physician. 2021;104(1):63-72.
29. Anekar AA, Hendrix JM, Cascella M. WHO analgesic ladder. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554435/
30. Albuquerque APS. O efeito da microcorrente sobre o acuponto Zusanli nos modelos de dor incisional, inflamatória e neuropática em ratos Wistar [dissertação]. Alfenas: Universidade Federal de Alfenas; 2018. Disponível em: https://bdtd.unifal-mg.edu.br:8443/bitstream/tede/1140/5/Disserta%C3%A7%C3%A3o%20de%20Ang%C3%A9lica%20Pontes%20e%20Silva%20de%20Albuquerque.pdf.
31. Sikandar S, Patel R, Patel S, Sikander S, Bennett DL, Dickenson AH. Genes, molecules and patients—emerging topics to guide clinical pain research. Eur J Pharmacol. 2013;716(1-3): 188-202.