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Review

Hyperalgesia and allodynia: peripheral mechanisms

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Abstract

Nociceptive signals are generated by peripheral sensory organs called nociceptors, which are endings of small-diameter nerve fibers responsive to the tissue environment. The myriad chemical mediators capable of activating, sensitizing, or arousing nociceptors include kinins, proinflammatory and anti-inflammatory cytokines, prostanoids, lipooxygenases, the "central immune response mediator" NF-κB, neurotrophins and other growth factors, neuropeptides, nitric oxide, histamine, serotonin, proteases, excitatory amino acids, adrenergic amines, and opioids. These mediators may act in combination or at a given time in the inflammatory process, producing subtle changes that result in hyperalgesia or allodynia. We will review the most extensively studied molecular and cellular mechanisms underlying these two clinical abnormalities. The role of the peripheral nervous system in progression of inflammatory joint disease to chronicity is discussed.

Keywords: Nociceptors; Pain; Hyperalgesia; Allodynia; Inflammation

1. Introduction

Studies into the immunopathology of inflammatory joint disease have unraveled the mechanisms responsible for joint damage, providing a rationale for novel treatment approaches, which have been validated. These new treatments are now used in substantial proportions of patients. The most striking example is probably anti-TNFα therapy, an effective approach in patients with rheumatoid arthritis (RA) or spondyloarthropathies. At the same time, dramatic strides have been made in understanding the pathophysiology of pain, so that in this area also new therapeutic targets are being identified. A large body of clinical evidence supports a role for the nervous system in the pathophysiology of inflammatory joint disease. For instance, RA and other diseases that usually cause bilateral symmetric joint involvement spare the side with nerve damage in patients who have hemiplegia or poliomyelitis [1–5]. In rats with polyarthritis induced by Freund's adjuvant, severing one of the sciatic nerves delays and reduces the severity of the joint manifestations on that side [6,7]. Many aspects of the interactions between the nervous system and the immune system remain nebulous. For instance, the potential role for the nervous system in generating and perpetuating chronic inflammatory disorders is unclear. Among medications widely used by rheumatologists to treat patients with inflammatory disorders or immune disorders, many play a crucial role in activating and sensitizing the nerve fibers involved in pain.

We will discuss the cellular and molecular mechanisms involved in clinical manifestations such as allodynia and hyperalgesia, which are commonly encountered by rheumatologists, for instance when examining inflammatory joints. Although spinal and cerebral mechanisms participate in the generation and perpetuation of pain, we will confine our discussion to peripheral mechanisms, about which knowledge has expanded considerably in recent years, suggesting new treatment possibilities.

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2. Polymodal nociceptors

In the early 20th century, Sherrington coined the term "nociception" (from the Latin "nocere", to hurt) to designate a physiological sensory phenomenon. Nociceptive stimuli cause tissue damage, thereby activating a discrete set of peripheral sensory organs called nociceptors. These organs are the endings of small-diameter nerve fibers that are either nonmyelinated (C fibers) or minimally myelinated (Aδ fibers). These nerve fibers form arborizations throughout tissues. Nociceptors can be activated by various forms of energy, including mechanical, electromagnetic, electrical, thermal, and chemical stimuli. High stimulus intensity, indicating that there is a risk of tissue damage, seems necessary for nociceptor activation to occur. An algogenic stimulus is defined as a nociceptive stimulus that causes pain. If the stimulus is noxious, tissue damage occurs, producing the classic cardinal manifestations of redness, warmth, swelling, and pain. Subsequently, pain may occur in the absence of a local stimulus (spontaneous pain) or in response to a previously nonalgogenic stimulus (allodynia) such as gently stroking the skin over a site of inflammatory arthritis. Finally, a nociceptive stimulus may produce pain that is disproportionately severe compared to the intensity of the stimulus (hyperalgesia).

Sensory fibers fall into four groups. Aα (Group I) fibers are characterized by a thick coat of myelin (diameter, 12–22 μm) and a fast conduction velocity (70–120 m/s); they capture afferent impulses from the neuromuscular spindles and Golgi tendon organs. Aβ (Group II) fibers have a thinner myelin coat (diameter, 6–12 μm) and connect to touch receptors. The two other fiber groups encode and transmit nociceptive and thermal stimuli. Aδ (Group III) fibers have a thin myelin sheath (diameter, 1–5 μm) and intermediate conduction velocity (4–30 m/s), whereas C (Group IV) fibers are nonmyelinated (diameter, 0.3–1.5 μm) slow-conducting (0.4–2 m/s) fibers. C fibers contribute 60–90% of all afferent fibers from the skin and the overwhelming majority of afferent fibers from the internal organs. Among C fibers, the most important are the polymodal nociceptors, which respond to thermal, mechanical, and chemical nociceptive stimuli. Their response is dependent on both a mosaic of membrane receptors and a distinctive neurochemical profile whose two variants differentiate two C-fiber subsets [8–10] (Fig. 1, Table 1).

Aδ fibers are less well known. In general, they seem to be polymodal. The activation threshold is higher than that of C fibers. Although many Aδ fibers are sensitive to peptides, their role in inflammation remains to be determined. The spinal projections of Aδ fibers are not confined to the superficial layers.

Normally, a rich supply of myelinated and nonmyelinated fibers innervates the joint capsule, subchondral bone, periosteum, ligaments, and menisci. The synovial membrane receives only nonmyelinated fibers and the cartilage has no nerve supply. The sensory fibers found in joints fall into four groups each connected to specific receptor types [11]. The Aα, Aβ, Aδ, and C fibers are Group I–IV fibers, respectively, and these group numbers are often used to designate the corresponding receptors. Aα and Aβ fibers, which are myelinated, respond to nonnociceptive mechanical stimuli including stretch and pressure conveyed by mechanoreceptors (Golgi receptors, Paccini corpuscles, Ruffini corpuscles). Mechanoreceptors are found in the capsule, ligaments, and menisci and contribute to proprioception. Aδ fibers, which are scantily myelinated, receive information from receptors located at the surface of ligaments and sensitive to mechanical stimuli and, to a lesser extent, to high-intensity thermal stimuli (high-threshold dynamic mechanoreceptors). Finally, C fibers connect to the predominant contingent of intra-articular receptors, which are found in all joint structures except the cartilage. Pain associated with joint disease may be related to activation of Aδ and C nociceptors. Roughly, mechanical pain in patients with lower limb osteoarthritis is triggered by mechanical activation (stretching and pressure) of the receptors located in the subchondral bone, periosteum, capsule, and ligaments. Interactions between nociceptors and inflammatory processes are discussed below. In addition, muscle tissue contains slender nerve fibers that are activated during muscle contraction. These fibers play no role in nociception but may be involved in the cardiovascular and respiratory adjustments that occur during physical activity.

Tissue damage triggers a chain of events intimately linked to inflammatory processes. These events prolong nociceptor activation and enhance nociceptor sensitivity. About 10–20% of C fibers are silent nociceptors that are normally inactive [12] and unresponsive to acute nociceptive stimuli. Silent C fibers undergo gradual activation during the inflammatory response, contributing actively to the development of hyperalgesia. Via peripheral nociceptor activation, perpetuation of the inflammatory process results in central sensitization, which plays a major role in progression to chronicity, even after elimination of the primary cause.

3. Inflammation and pain: the cast

Inflammation results from the release of myriad substances, many of which are neuroactive. These substances stimulate chemosensitive nociceptors, thus playing a major part in the development of inflammatory pain. Potassium ions, hydrogen ions, and adenosine triphosphate (ATP) released by damaged cells, together with bradykinin, are the only endogenous substances with excitatory effects; the other substances act mainly via sensitization. Sensitization decreases the depolarization threshold of nociceptors, which therefore become responsive to low-intensity stimuli. In addition, sensory fiber endings are protected by the perineurium, which isolates the endoneural tissue, preventing the passage of large molecules and hydrophobic molecules such as peptides. At sites of inflammation, this barrier is disrupted, so that peptides can access their potential targets.

Algogenic substances may be formed locally or present in the bloodstream. Aδ and C endings are often in intimate con-

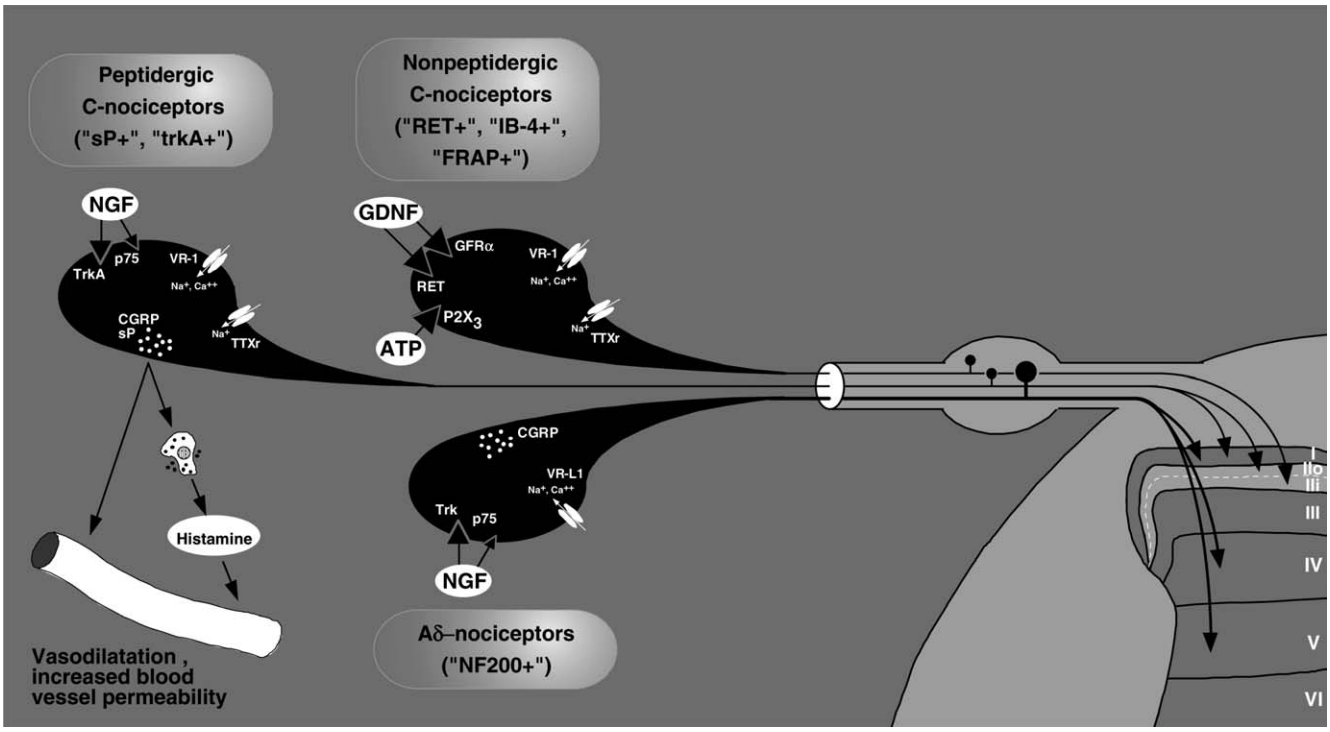

Fig. 1. Peptidergic and nonpeptidergic C nociceptors and Aδ nociceptors. Nonmyelinated nociceptors fall into two groups. One group expresses peptides, including substance P (sP+ nociceptors) and responds to NGF (produced by fibroblasts, keratinocytes, and Schwann cells). This group mediates the neurogenic inflammation inducted by small vasoactive peptides, either directly or indirectly via mastocyte degranulation, which releases histamine (left side of the figure). These fibers project to the outermost layers I and IIo ("o" for "outer" of the dorsal horn of the spinal cord) (right side of the figure). The second group is nonpeptidergic, i.e., does not express substance P or CGRP, but is sensitive to one of the four glial-derived neurotrophic factors (GDNF, produced by the Schwann cells) via a common specific receptor called tyrosine-kinase RET (RET+). These nociceptors contain a distinctive phosphatase called thiamine monophosphatase or fluoride-resistant acid phosphatase (FRAP+). They also express a subset of purinergic receptors ($P2X_3$), whose naturally occurring ligand is adenosine triphosphate (ATP). Another unique feature of nociceptors in this group is a high density of tetrodotoxin-resistant sodium channels SNS/PN3. They project only to the innermost IIi layer ("i" for "inner" in the dorsal horn of the spinal cord (right side of the figure). The third group is myelinated and therefore can be characterized based on its neurofilaments (NF200). These nociceptors contain CGRP and other peptides. Their membrane expresses receptors for neurotrophins belonging to the NGF family (TrkA, TrkB, and TrkC) and probably a high-temperature receptor different from VR-1 and called VRL-1 (vanilloid receptor-like-1). The fibers project to layer I and to the deeper layers of the dorsal horn of the spinal cord (right side of the figure). Layers I and IIo contain neurons that express substance P receptor. Layer IIi comprises only interneurons whose main characteristics are responsiveness confined to nonnociceptive mechanical stimuli and expression of protein kinase Cγ (PKCγ), whose synthesis can be increased by subcutaneous injection of an inflammatory agent. See Table 1 for abbreviations.

tact with arterioles and venules, a configuration favorable to effects from substances in the bloodstream. Algogenic substances fall into three groups based on whether they are released from damaged cells, inflammatory cells, or nociceptors. In patients with cancer pain, other substances such as endothelins probably contribute to pain generation [13]. Fig. 2 recapitulates these mechanisms.

Amplification of nociceptive messages is produced not only by the substances released within the site of inflammation, but also by the recruitment of adjacent activated or sensitized fibers, in particular via the axon reflex: this phenomenon is known as neurogenic inflammation (Fig. 3). Thus, the primary afferent fibers contribute to the "inflammatory soup" by releasing neuropeptides. This subtle set of neurochemical interactions is the basis for hyperalgesia, which originates both within the damaged tissue (primary hyperalgesia) and within the surrounding healthy tissue (secondary hyperalgesia). These interactions produce the erythema, edema, and cutaneous hyperalgesia seen at sites of inflammatory arthritis, where gently stroking the skin causes pain, although the initial abnormality is intraarticular [14].

4. Elementary receptors located on nociceptors

Recent developments in molecular biology have allowed researchers to identify, clone, and investigate biochemical receptors found on the membrane of primary afferent fibers. Among these receptors, some are transducers, i.e., structures capable of converting a physical stimulus into a depolarizing current that runs through the cell membrane. The plasticity that characterizes polymodal nociceptors is ascribable to the mosaic of specialized biochemical receptors present on the nociceptor membrane.

4.1. Vanilloid (pepper) receptors [15]

Vanilloids are naturally occurring irritants responsible for the "hot" taste of spices. They include capsaicin, piperine,

Table 1
Abbreviations used in the figures

5-HT: 5-hydroxytryptamine (serotonin)	NK1: substance P receptor
AC: adenylate cyclase	NMDA: *N*-methyl-D-aspartate
ADP: adenosine triphosphate	NO: nitric oxide
AMPc: cyclic adenosine monophosphate	NOS: nitric oxide synthase
ASIC: acid-sensing ionic channel	NPY: neuropeptide Y
ATP: adenosine triphosphate	NSAID: nonsteroidal anti-inflammatory drugs
BDNF: brain-derived neurotrophic factor	NT: neurotrophin
BK: bradykinin	P1: purinergic receptors 1, bind adenosine
CB: cannabinoid receptor	P2: purinergic receptors 2, bind ATP
CCK: cholecystokinin	P2X: ionotropic ATP receptors
CGRP: calcitonin gene-related peptide	P2Y: metabotropic ATP receptors
COX: cyclooxygenase	PAF: platelet-activating factor
CyPG: cyclic prostaglandin	PAR: protease-activated receptors
DAG: diacylglycerol	PG: prostaglandin
DRASIC: dorsal root acid-sensing ionic channel, or ASIC-3	PIP_2: phosphatidylinositol biphosphonate
EP: prostaglandin E (PGE) receptor	PKA: protein kinase A
ERK: extracellular signal-regulated protein kinase	PKC: protein kinase C
FRAP: fluoride-resistant acid phosphatase, or thiamine monophosphatase	PLC: phospholipase C
GAL: galanin	PPAR: peroxisome proliferator-activated receptor
GDNF: glial cell-derived neurotrophic factor	RET: rearranged in transfection, tyrosine-kinase RET, GDNF receptor
GDP: guanosine diphosphate	SNS: sensory-neuron-specific sodium channel
GMPc: cyclic guanosine monophosphate	sP: substance P
GTP: guanosine triphosphate	TNF: tumor necrosis factor
HETE: hydroxyeicosatetraenoic acid	Trk: tyrosine kinase
IB-4: isolectin B-4	TrkA: tyrosine kinase A, NGF receptor
IKK: IκB kinase	TTXr: tetrodotoxin-resistant (sodium channel)
iNOS: inducible nitric oxide synthase	TTXs: tetrodotoxin-sensitive (sodium channel)
IP: prostaglandin receptor	VDCC: voltage-dependent calcium channel
IP_3: inositol triphosphate	VGSC: voltage-gated sodium channel
IκB: NF-κB inhibitor	VIP: vasoactive intestinal peptide
LTB_4: leukotriene B_4	VR: vanilloid receptor
NF200: 200-kDa neurofilament, characteristic of myelinated peripheral fibers	VRL: vanilloid receptor-like
NF-κB: nuclear factor κB	
NGF: nerve growth factor	

and zingerone, which are found in peppers, black peppercorns, and ginger [16]. Capsaicin applied to the skin causes a burning sensation in humans, which is abolished by cold and exacerbated by warmth. Capsaicin activates polymodal C fibers via a specific receptor, the ionotropic vanilloid receptor VR-1. VR-1 normally responds to intense heat.

The VR-1 receptor (Fig. 4) is a nonselective channel open to all cations, with, however, a preference for calcium [17]. Protons and capsaicin do not cause direct VR-1 activation; rather, they markedly decrease its activation threshold, so that ambient temperatures become nociceptive stimuli, causing allodynia. The VR-1 receptor has been found to belong to a vast family of temperature-activated transient receptor potential ion channels, or TRPs, and its name has therefore been changed to Trpv1. Three TRPs have been cloned and found sensitive to intense heat [18].

4.2. Acid-sensing receptors

The acid-sensing ionic channel (ASIC) superfamily is composed of sodium channels that are blocked by amiloride. Of the six ASIC receptor subtypes described to date, five are expressed in small-diameter primary afferent fibers [19]. They undergo activation when the pH falls below 6.9, a threshold not very distant from physiological pH values [20]. At sites of inflammation, tissue pH values can drop to 5.5 [21]. Thus, tissue inflammation or damage results in ASIC receptor activation. This property is unique: elsewhere in the nervous system, low extracellular pH is associated with decreased neuronal excitability [22–26].

4.3. NMDA and AMPA/kainite receptors [27–29]

The membrane of primary afferent fibers and sympathetic nerve endings expresses glutaminergic receptors, of which the most important are the ionotropic AMPA/kainite and NMDA receptors, whose density increases at sites of inflammation. Similar to peptides, excitatory amino acids are produced by the afferent sensory fibers themselves. The result is a local mechanism that self-perpetuates the nociceptive activity.

4.4. Adrenoceptors

Epinephrine and norepinephrine do not normally activate nociceptors but may sensitize them under specific condi-

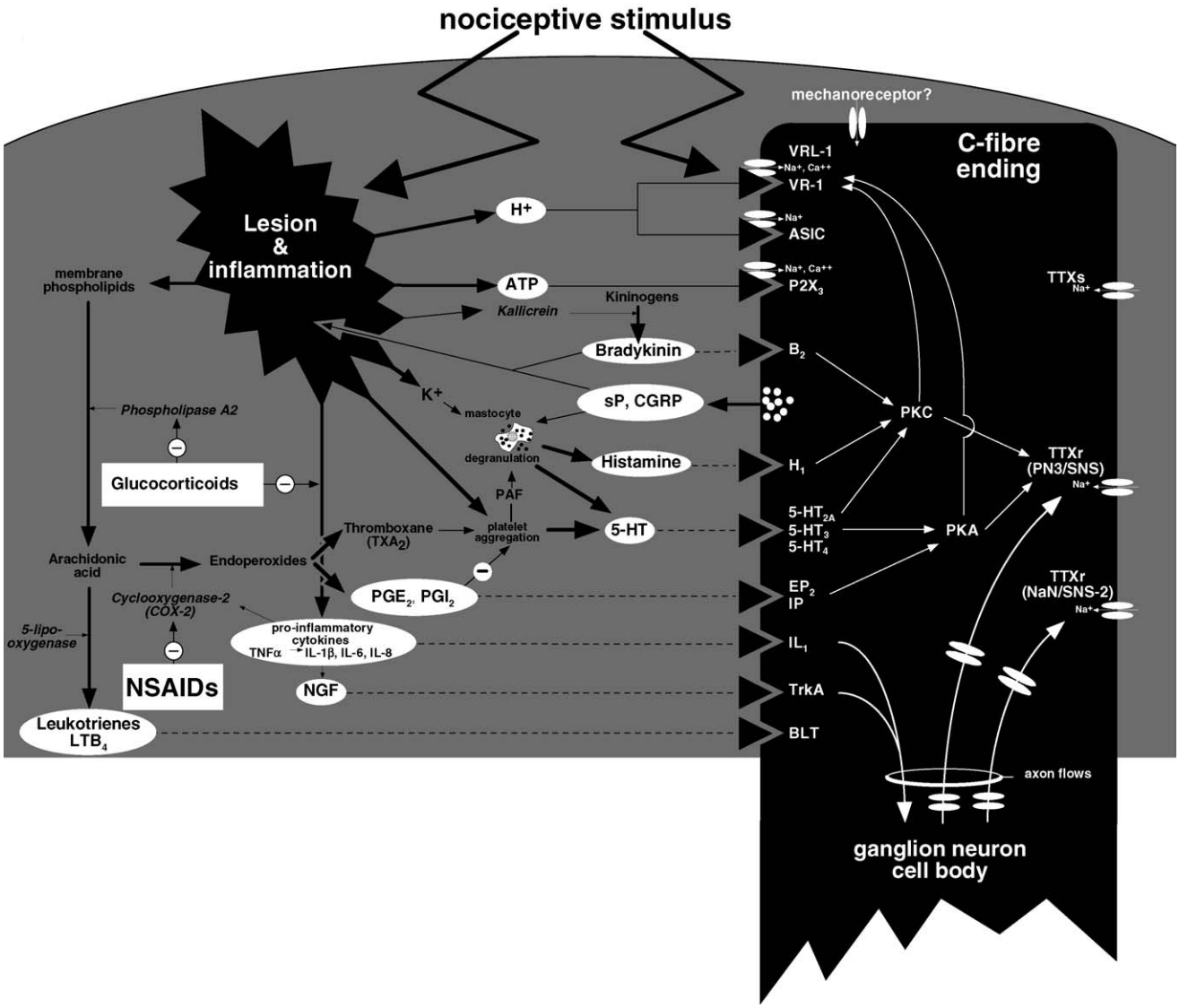

Fig. 2. Receptors, nociception, and inflammation. This figure shows the factors that can activate (----->) and/or sensitize (- - - >) nociceptors at sites of tissue damage. Three groups of factors are involved. One group is composed of factors directly related to tissue damage. These factors activate the nociceptors, previously excited directly by the causal stimulus itself. They include hydrogen ions (H^+) and adenosine triphosphate (ATP) released by damaged tissue. Hydrogen ions interact with the ASIC-1 receptor and sensitize the VR-1 receptor. Binding of these two receptors and of the ATP receptor ($P2X_3$) to their respective ligands results in opening of the cation channels, which depolarizes the nerve fiber ending. The second group is related to inflammatory processes and includes bradykinin, prostaglandins, leukotrienes, proinflammatory cytokines, and NGF. Bradykinin increases capillary permeability and is among the most potent algogenic substances identified to date. The factors in this group exert specific effects and sensitize the receptors to other factors. They cause primary hyperalgesia. In addition, serotonin (5-HT), released during platelet aggregation and mastocyte degranulation, and histamine, released by mastocyte degranulation, belong to this group. Histamine induces pruritus followed by pain as the concentrations increase. These substances bind to specific receptors, inducing phosphorylation of protein kinases (PKA and PKC), which (a) enhance the efficiency of tetrodotoxin-resistant (TTXr) sodium channels and (b) lower the threshold of receptor-transducers such as VR-1. Finally, NGF binds to the high-affinity TrkA receptor, forming an NGF/TrkA complex, which is internalized then transported to the neuron cell body in the spinal ganglion. There, the complex induces changes in protein synthesis, including an increase in the production of tetradotoxin-resistant sodium channels. These channels are then carried along the retrograde axonal flow to enrich the fiber endings. The third group comprises substance P (sP) and calcitonin gene-related peptide (CRGP). These substances are released by the nociceptors. They can activate these nociceptors either directly or indirectly. These mechanisms result in a vicious circle. Influences from norepinephrine (and co-localized neuropeptide Y) released by postganglion sympathetic fibers occur in addition to these local responses. They may be enhanced by a number of cytokines, such as IL-8, and excitatory amino acids. For clarity, they are not indicated in the figure. Glucocorticoids block the enzyme phospholipase A2 and, therefore, the metabolism of leukotrienes and prostaglandins, whereas nonsteroidal anti-inflammatory drugs (NSAIDs) block only cyclooxygenase-2 (COX-2).

tions, generating hyperalgesia. This sensitizing effect is probably mediated by protein kinases, mainly PKA and, to a lesser extent, PKC, which regulate tetrodotoxin-resistant sodium channels [30,31]. Stress, for instance, can amplify nociceptive messages as soon as peripheral perception occurs.

5. Voltage-dependent sodium channels [32,33]

Voltage-dependent sodium channels are extremely important in clinical practice, as they are the target of several medications including local anesthetics. Two groups can be differ-

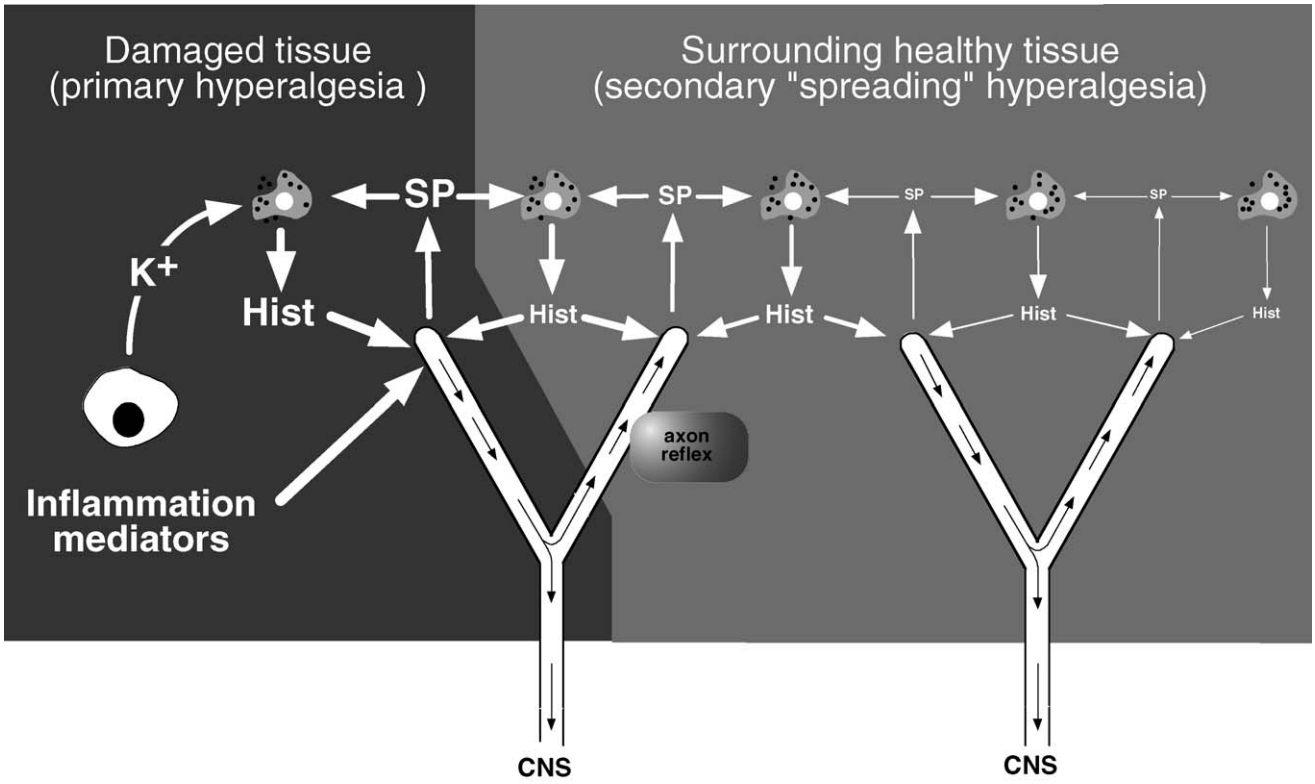

Fig. 3. Neurogenic inflammation. The left side of the figure recapitulates the processes that unfold within sites of tissue damage, resulting in primary hyperalgesia. These factors work in concert to directly or indirectly activate the nociceptors, which send nociceptive signals not only to the central nervous system (CNS), but also to the periphery via axon reflexes. This antidromic activation causes the nonmyelinated nerve endings to release substance P (sP), which binds to its specific receptor, NK1. This interaction directly induces both vasodilation with increased blood vessel permeability allowing plasma extravasation and mastocyte degranulation. The mastocyte granules release histamine, which amplifies the vascular processes and activates and sensitizes the nociceptors. Calcitonin gene-related peptide (CGRP) and neurokinin A probably exert similar effects. These mechanisms involve not only sites of tissue damage, producing the vicious circle depicted in Fig. 2, but also healthy tissue, where they cause secondary or spreading hyperalgesia (right side of the figure).

entiated based on action and inactivation kinetics. When depolarization of a neuron membrane reaches a threshold, the voltage-dependent sodium channels open suddenly, triggering an action potential. These are usually low-threshold channels with fast inactivation kinetics and sensitivity to blockade by tetrodotoxin (tetrodotoxin-sensitive channels, TTXs). They are found on the membrane of myelinated and nonmyelinated primary afferent fiber endings.

The C-fiber membrane also contains sodium channels, but these are resistant to tetrodotoxin (TTXr). In contrast to TTXs, TTXr have a high activation threshold and slow inactivation kinetics, so that they produce few but long-lasting action potentials. These properties enhance nociceptor synaptic efficiency. Extremely high efficiency levels occur when the TTXr threshold is lowered as a result of phosphorylation triggered by hyperalgesia-inducing mediators, via protein-kinases A (prostaglandin and serotonin) or protein kinases C (bradykinin and histamine). TTXr channel production increases during inflammation, potentiating this hyperalgesia-inducing mechanism.

Anti-arrhythmic agents, anti-convulsants, and local anesthetics such as lidocaine act mainly by blocking the TTXs channels responsible for triggering action potentials [34,35]. The development of specific TTXr antagonists is a promising avenue of research in the field of pain control.

6. Substances involved in inflammation

Most of the substances involved in inflammation interact with the nociceptive fibers present within the joint and induce the hyperalgesia and allodynia seen in patients with chronic inflammatory joint disease. However, pain is probably not the only effect of this interaction, although the other consequences on the course of inflammatory joint disease remain unclear.

6.1. Kinins [36–38]

Bradykinin and kallidin are peptides produced when plasma or tissue kallicreines act on α2-globulins (called kininogens). The B_2 receptor is responsible for the short-term effects of bradykinin (Fig. 5). Several authors have argued for a key role of kininogens in perpetuation of chronic inflammation [37,39].

The B_1 receptor is virtually absent from normal tissue but is expressed in response to proinflammatory agents (polysaccharides and cytokines), NGF, and bradykinin. Bradykinin binds to the B_1 receptor. The B_1 receptor is inducible and resistant to desensitization [40]. Thus, interaction with the B_1 receptor may explain the long-term effects of bradykinin occurring after the B_2 receptors are desensitized.

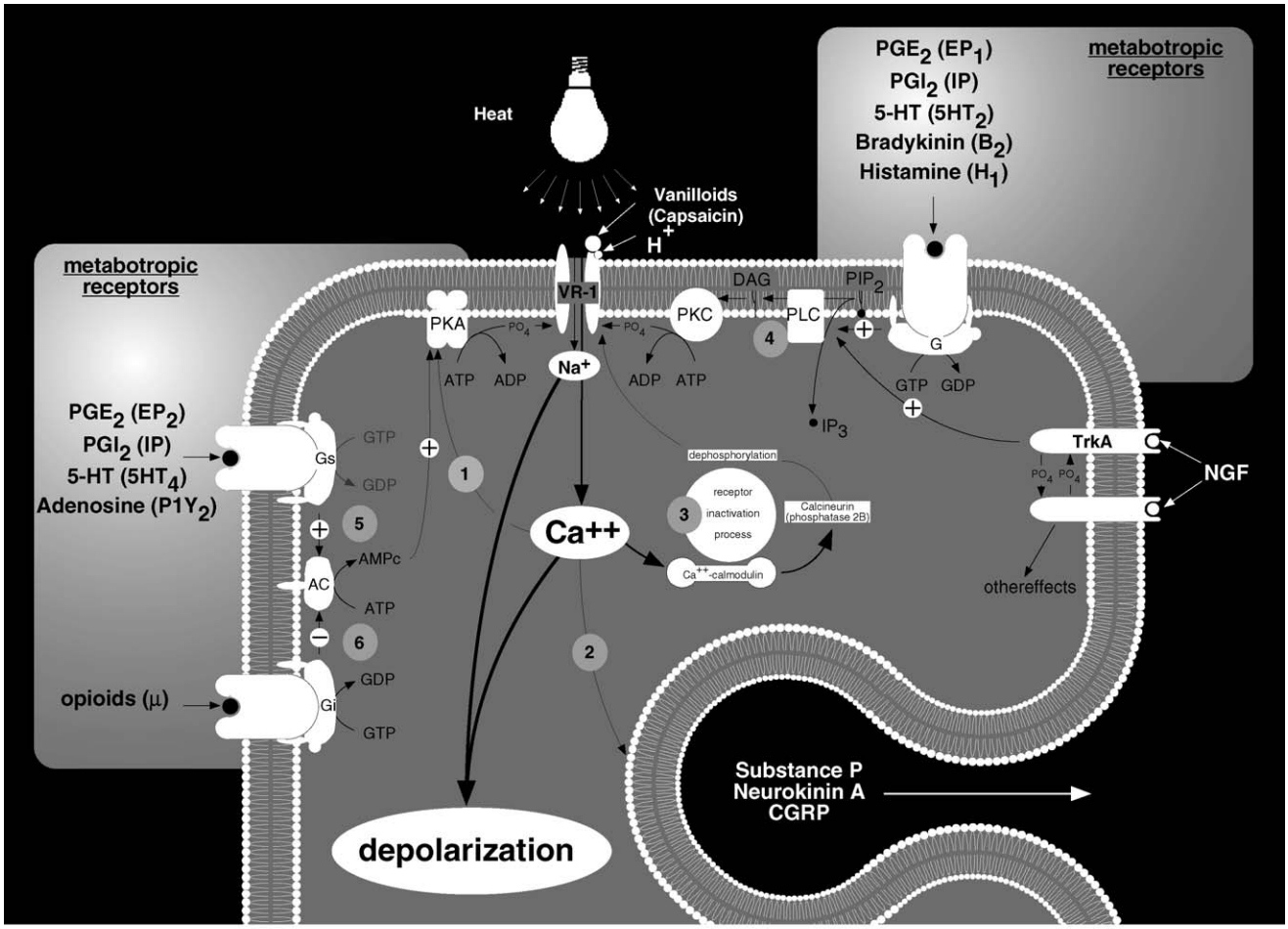

Fig. 4. The capsaicin receptor. The capsaicin receptor is a channel protein with six membrane-spanning domains. The channel opens in response to heat. The opening threshold varies with the biochemical environment. The receptor is directly sensitized by the extracellular pH and by vanilloids and indirectly sensitized by various inflammatory substances. Once sensitized, the capsaicin receptor can respond to ambient temperatures. This property explains why cold application relieves pain in some situations. Calcium influx sets off a chain of reactions that is not specific to nociceptors; (a) amplification of the phenomenon by phosphorylation of the receptor via protein kinases, (b) exocytosis, in particular of peptides; and (c) inactivation via dephosphorylation induced by calcineurin, which in turn is dependent on the Ca^{++}-calmodulin complex. A property that is more characteristic of nociceptors is that the cytosolic calcium originates mainly from the extracellular compartment because the fiber endings contain no endoplasmic reticulum. Protein kinases C (PKC) are activated by a phospholipase C (PLC) (4), which is dependent on a metabotropic receptor (upper right part of the figure) and on tyrosine kinases, such as TrkA, which is a high-affinity receptor for NGF (right side of the figure). The protein kinases A (PKA) are activated by cyclic AMP produced by the enzyme adenylate cyclase (AC) coupled to metabotropic receptors bound to stimulating G proteins (Gs) (5) or inhibitory G proteins (Gi) (6) (left side of the figure).

Because bradykinin acts on multiple targets, it orchestrates the inflammatory process and the generation of inflammation-related pain. For many years, bradykinin has been a therapeutic target of choice. Until recently, most bradykinin receptor antagonists were peptides and, consequently, showed poor diffusion to the therapeutic targets. The development of nonpeptide antagonists holds promise as a source of therapeutic agents for a vast array of conditions (inflammation, asthma, and pain) [41].

6.2. Cytokines [42–44]

Cytokines are small proteins released by lymphocytes, monocytes, and macrophages. Some cytokines are proinflammatory (TNFα, IL-1β, and IL-8), whereas others are anti-inflammatory (IL-4, IL-10, IL-13, and IL-1ra), and yet others have both categories of effects. In addition, when present in the bloodstream, IL-6 can trigger a febrile response, which can occur in association with focal inflammation [45]. Proinflammatory cytokines cause cells to release prostaglandins and sympathomimetic amines. Their order of potency in inducing hyperalgesia is as follows: IL-1β > TNFα >> IL-8 >> IL-6. In some situations, sympathetic system stimulation by IL-8 may contribute to induce hyperalgesia.

Thus, together with bradykinin, cytokines form the link between tissue damage and inflammatory responses. IL-1 and TNFα play a pivotal role in the tissue destruction seen in chronic inflammatory joint diseases such as rheumatoid arthritis or Crohn's disease [46]. The development of cytokine antagonists is probably the most important advance achieved in recent years in the treatment of inflammatory disease. Nociceptors carry receptors to some cytokines. Thus, TNFα

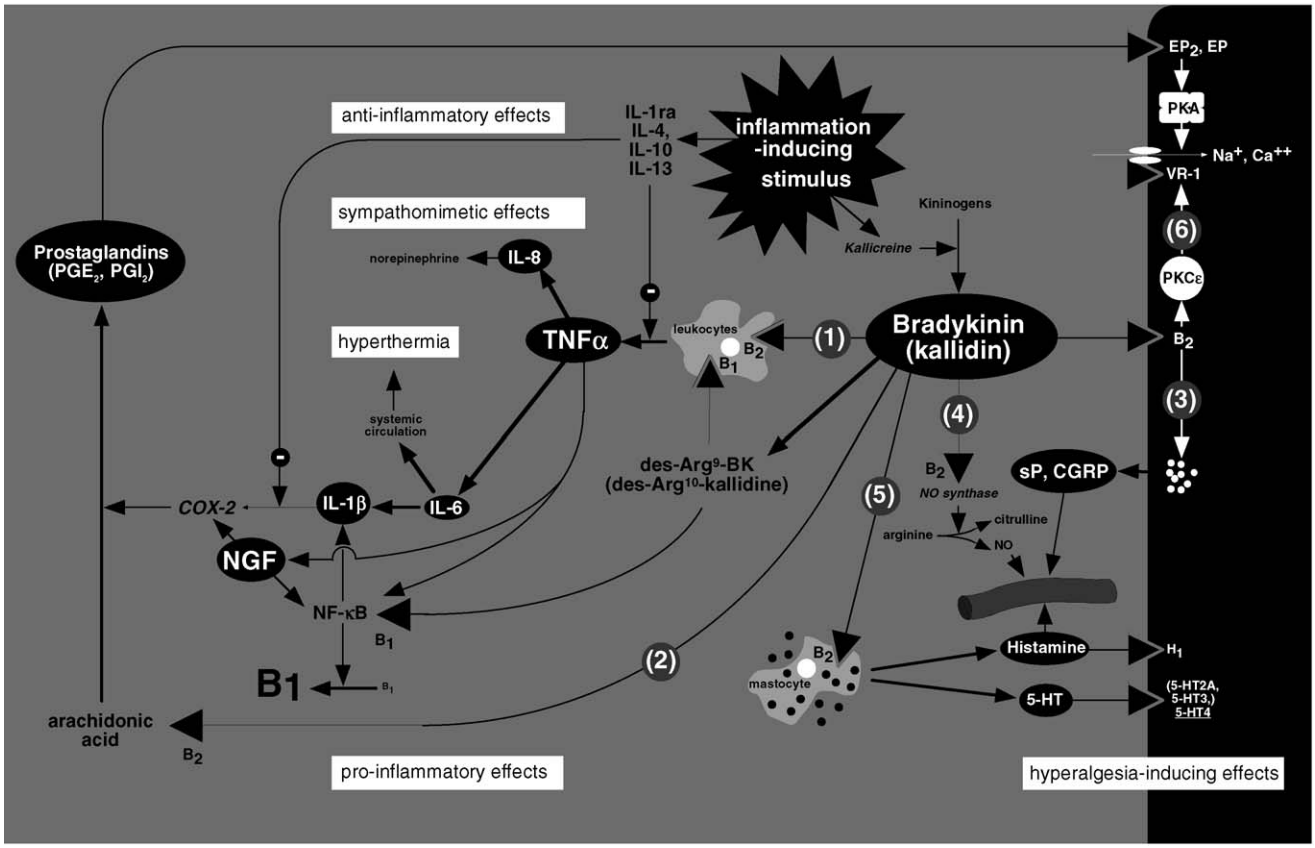

Fig. 5. Kinins and the cytokine chain. Cytokines are mainly proinflammatory and hyperalgesia-inducing, in particular via the chain from TNFα to IL-6 and from there to IL-1β, which induces COX-2 synthesis and therefore prostaglandin release. Via IL-8, TNFα also results in release of sympathomimetic amines. These mechanisms are counteracted by anti-inflammatory cytokines, including IL-1ra, IL-4, IL-10, and IL-13. Bradykinin (or kallicrein in humans) triggers the proinflammatory cytokine chain (TNFα, IL-6, IL-1β, and IL-8) (1) and stimulates the release of arachidonic acid (2), thereby promoting the production of prostaglandins. Bradykinin causes primary afferent fiber endings to release peptides (neurokinins and CGRP) (3) and enhances the production of nitric oxide (4). Another effect of bradykinin is mastocyte degranulation (5), which leads to release of histamine and serotonin. Steps (3), (4), and (5) act in concert to cause vasodilation and increased blood vessel permeability. Finally, bradykinin induces phosphorylation of the VR-1 receptor (6), which then is responsive to ambient temperatures. Bradykinin and kallidin exhibit high affinity for the B_2 receptor, which is constitutively expressed. The B_1 receptor is preferentially activated by their respective metabolites. B_1 receptor synthesis is virtually nonexistent in normal tissue but is induced by NF-κB, which is activated by numerous endogenous factors, including bradykinin, TNFα, and NGF (see Fig. 5).

may induce nociceptor sensitization. These mechanisms may explain why patients started on TNFα antagonist therapy sometimes experience pain relief within 24 h, before the local inflammation is controlled [47].

6.3. Prostanoids

Prostaglandins and probably leukotrienes sensitize nociceptors to physical stimuli and to the effects of other substances. Proinflammatory agents including cytokines, mitogens, and endotoxins, trigger prostaglandin synthesis from arachidonic acid by inducing the enzyme cyclooxygenase 2 (COX-2). To date, two COX isoforms have been identified, COX-1 and COX-2. These isoforms share similar enzyme activity and substrate affinity but differ in their location and synthesis regulation. Many review articles on the COX isoforms are readily available in the medical literature. Although the improved gastrointestinal safety profile of COX-2 inhibitors is a valuable advance, additional studies will have to define the long-term effects of inhibiting COX-2 synthesis.

Prostanoids interact with G proteins via eight specific receptors. Three of these receptors sensitize primary afferent fibers: the prostaglandin E_2 (PGE_2) receptors EP_1 and EP_2 and the prostaglandin I_2 (PGI_2 or prostacyclin) receptor IP (Fig. 6).

7. The central immune response mediator NF-κB

The transcription factor NF-κB is found in many cell types. This substance is often called the “central immune response mediator,” because as many as 150 or so inducers have been identified to date, some exogenous (e.g., bacterial and viral components) and others endogenous, as well as a commensurate number of targets [48,49]. Activators relevant to primary afferent nociceptor fibers include bradykinin, potassium ions, platelet-activating factor (PAF), TNFα and perhaps other growth factors, LTB_4 and possibly other prostanoids, and glutamate (Fig. 7). Genes targeted by NF-κB include genes which, when activated, trigger the production of recep-

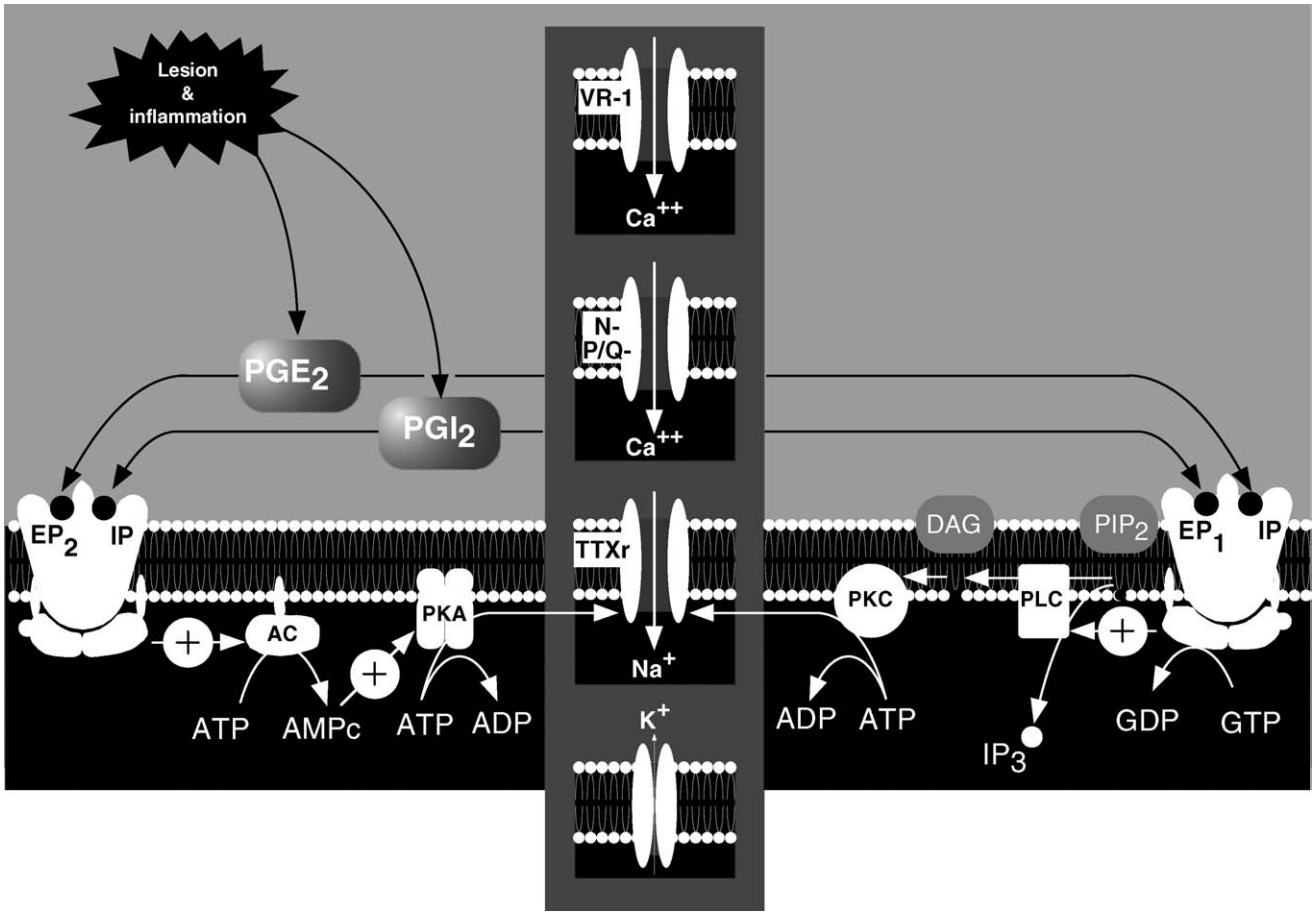

Fig. 6. Recapitulation of effects of prostaglandins on nociceptors. Prostaglandins (PGE_2, PGI_2) interact with specific receptors (EP_1, EP_2, and IP), inducing phosphorylation of ionic channels, which then show increased sensitivity to other agents. Phosphorylation is induced via a protein kinase A, which is activated by adenylate cyclase (left side of the figure), or via a protein kinase C, activated by a phospholipase (right side of the figure). Phosphorylation promotes opening of the vanilloid receptor VR-1, calcium channels (including N and P/Q), and voltage-dependent sodium channels (TTXr) and closure of potassium channels (shown in the center from top to bottom). All these effects increase membrane sensitivity to depolarization. Prostaglandin synthesis from arachidonic acid is induced in cells exposed to proinflammatory substances; this is shown in the upper left part of the figure.

tors (B_1 as mentioned above, PAF_1, NPY_1, and P1), enzymes involved in prostanoid synthesis (phospholipase A2, 5-lipooxygenase, and COX-2), cytokines (TNFα, IL-1β, IL-6, and IL-8), and the inducible nitric oxide synthase isoform (iNOS). Not surprisingly, NF-κB expression is exacerbated during inflammation [52,53].

8. Growth factors [54,55]

Macrophages release neurotrophins, which act as growth factors during the development of the nervous system. Once development is complete, the function of neurotrophins changes radically. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) induce hyperalgesia by binding with high affinity to their specific receptors. Thus, the peripheral effect of NGF is that of a co-adjuvant to the inflammatory response [56]. The production of NGF increases in response to TNFα, other cytokines, and interleukins released by inflammatory cells. NGF binds to its high-affinity receptor TrkA (see lower right-hand part of Fig. 2). The NGF/TrkA complex is then internalized and transported to the neuron cell body located in the spinal ganglion, where it modifies the transcription of precursors for various peptides (increasing the transcription of substance P and CGRP and decreasing the transcription of VIP, CCK, NPY, and GAL), growth factors (GDNF and BDNF), and the tetrodotoxin-resistant sodium channels NaN/SNS-2. This mechanism undoubtedly contributes to the long-term perpetuation of hyperalgesia-producing processes. NGF induces overexpression of BDNF in the peptidergic C fibers. BDNF is released in the dorsal horn of the spinal cord, where it binds to its high-affinity TrkB receptor, causing phosphorylation of the NMDA receptor via a protein kinase C. Thus, BDNF is pivotal to the induction of "central sensitization" by inflammatory processes.

9. Neuropeptides [57–59]

Stimulating the distal end of a nerve root or the proximal end of a severed nerve induces antidromic vasodilation mediated by the release of vasodilating agents (substance P, CGRP, neurokinin A), which increase blood vessel permeability and

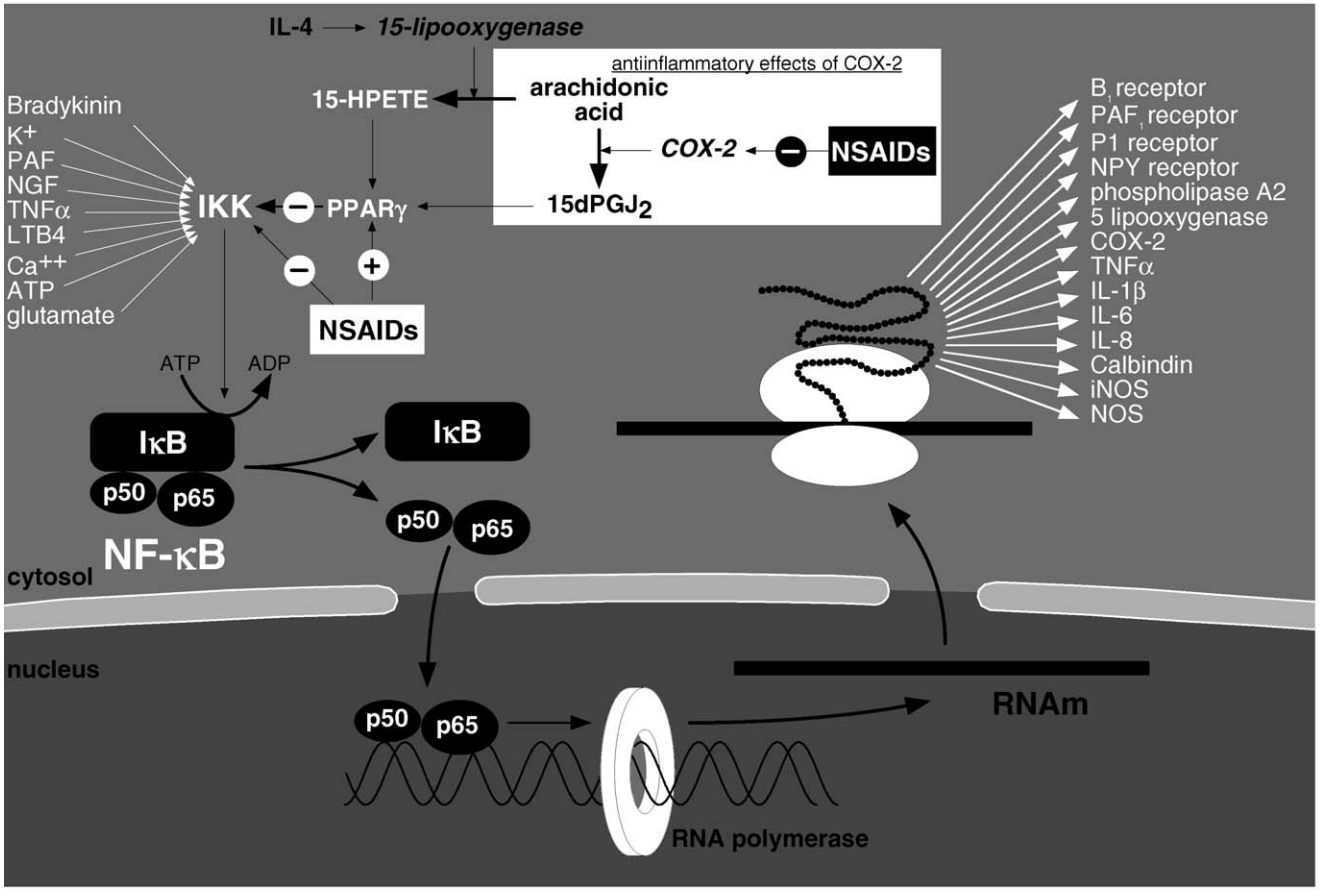

Fig. 7. The NF-κB transcription factor. The inactive form of NF-κB, present in the cytosol, is a complex of three subunits, of which two (p50 and p65) form the active transcription dimer. These two subunits are inhibited by the third subunit (IκB). The many NF-κB activation pathways result ultimately in phosphorylation of the inhibitory IκB protein by specific kinases (IKK), causing the p50–p65 dimer to be released. The dimer is then translocated to the nucleus, where it binds to the appropriate receptor sequences in the DNA chain. In the nucleus, the dimer induces synthesis of transcripts that induce the production of many proteins. Those relevant to primary afferent nociceptive fibers are shown in the upper right part of the figure. Endogenous IKK inducers relevant to primary afferent nociceptive fibers are shown in the upper left part of the Figure. In addition, IKK activity is modulated by the PPARg receptor, which can be activated by arachidonic acid metabolites, namely leukotrienes (15-HPETE) and prostaglandins ($15dPGJ_2$). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit IKKs, either directly or indirectly via PPARγ activation; this results in inhibition of all the effects ascribed to NF-κB [50,51]. This is the second mechanism underlying the anti-inflammatory effects of NSAIDs.
15-HPETE is produced via a 15-lipooxygenase that can be activated by IL-4. The pentacyclic prostacyclin $15dPGJ_2$ prostaglandin is produced via the enzyme COX-2, most notably during remission of acute inflammation (white inset). Inhibition of the enzyme leads to a proinflammatory effect that offsets the expected effects of NSAID therapy.

allow plasma extravasation. Little is known about the role for the other peptides found in thin primary afferent fibers, such as somatostatin, vasoactive intestinal peptide (VIP), galanin, and others. However, these substances probably add to the complexity of the "inflammatory soup".

10. Therapeutic targets for today and tomorrow

The data reviewed above establish a strong role for nonsteroidal anti-inflammatory drugs (NSAIDs) in pain management. Here, we will discuss targets for other medications that are already used or are being developed for pain control.

10.1. Opioids

Morphine is well known as a centrally acting agent. However, the anti-diarrheal effects of morphine are classic also. In addition, opioid receptors are found on the peripheral sensory nerve endings. About one third of C fibers carry μ or δ receptors that may contribute to the peripheral anti-nociceptive effect of opioids, which is significant only at sites of inflammation [60]. Opioid receptors can be activated by exogenous agonists, with μ ligands showing the greatest efficacy in this respect, or by endogenous opioid peptides released locally by immune cells (lymphocytes and monocytes). However, these cells are not the only peripheral sources of endogenous opioids, as met-enkephalin is found in a nonnegligeable number of primary afferent fibers.

The expression of the enkephalin precursor pro-enkephalin A in the spinal ganglions is almost completely abolished in rats with polyarthritis. Met-enkephalin overexpression following administration of a recombinant vector to the animals results in (a) anti-inflammatory effects, (b) polyarthritis remission, and (c) reductions in pain-related behaviors [61]. These

data support not only a role for enkephalinergic sensory neurons in peripheral pain control but also the involvement of these neurons in the modulation of inflammatory and immune responses.

In animals, locally administered opioids exhibit anti-inflammatory and analgesic effects [60]. In humans, intraarticular injection of morphine after arthroscopy seems to have modest effects similar to those obtained with local anesthetics [62]; these effects are more marked, however, in patients with chronic inflammation [63].

10.2. Cannabinoids [64–66]

In the late 1980s, two cannabinoid receptors were identified, CB_1, found chiefly in the central nervous system, and CB_2, found only in peripheral tissues including afferent fiber endings. The anti-inflammatory effects of CB_2 receptor agonists result from decreases in histamine and serotonin secretion via inhibition of mastocyte degranulation. The antinociceptive effects of cannabinoids on the CB_1 receptor are probably mediated by central mechanisms, although peripherally these agents diminish blood vessel permeability and plasma extravasation. Synthetic cannabinoids devoid of psychoactive effects are being evaluated in humans.

10.3. Capsaicin

Capsaicin is a potent sensitizer [67] that lowers the nociceptor activation threshold, enhances nociceptor responsiveness to nociceptive stimuli, and arouses silent nociceptors. Capsaicin can induce neurogenic inflammation. Conversely, capsaicin has no effect on mechanoreceptors or cold receptors. Vanilloids have been used as rubefacients in many popular remedies and in a few pharmaceutical preparations. Capsaicin as a pharmaceutical preparation is used in some forms of focal chronic pain syndrome. Repeated capsaicin applications deplete the C fibers of their neurotransmitters, thereby decreasing C-fiber sensitivity to nociceptive stimuli.

Purinergic receptors are activated by adenosine triphosphate. They are under study as therapeutic targets for developing new analgesic medications.

11. Piecing the puzzle

A number of proinflammatory agents directly activate the primary afferent fibers by depolarizing their endings. Examples include protons and ATP, as discussed above. Another example is heat, which is among the cardinal features of inflammation. Other proinflammatory agents sensitize the primary afferent fiber endings by enhancing their responsiveness to physical and chemical depolarizing agents, via two categories of mechanisms. One is amplification of the generating potential produced in the channel receptors by the stimulus. The other involves a modification in membrane excitability via lowering of the threshold at which voltage-dependent sodium channels open, i.e., lowering of the threshold at which an action potential occurs. These mechanisms are occasionally direct (VR-1 receptor sensitization by protons when the pH is acidic) but more often depend on a chain of second messengers, most notably kinases. Examples include VR-1, as discussed above, and voltage-dependent sodium channels. Thus, phosphorylation lowers the opening threshold of the tetrodotoxin-resistant sodium channel SNS/PN3. Phosphorylation is induced by a protein kinase A, which is activated by prostaglandins and serotonin or by a protein kinase C, itself activated by bradykinin and histamine. Phosphorylation increases the sodium currents that enter the nerve ending, thereby lowering the nerve ending activation threshold.

This is a highly sophisticated fine-tuning system dependent on many variables characterizing the physical and chemical environment of sensory nerve endings. The mosaic of biochemical receptors and second messengers that coats these endings adds to the complexity of the system.

In addition to this "direct" activation, several substances can act peripherally to modify protein synthesis in the cell bodies of primary sensory neurons located in the spinal ganglions [68]. For instance, once released, NGF binds to high-affinity TrkA receptors, as indicated above. The NGF–TrkA complex is internalized, and transported to the neuron cell body, where it modifies the transcription of various proteins. These proteins are carried in the retrograde direction to the peripheral endings and in the orthograde direction to the central endings. The ultimate result may be an increase in the number of ion channels (such as VR-1 and TTXr sodium channels) peripherally. Under the influence of NGF, BNDF is overexpressed in the peptidergic C fibers then released in the dorsal horn of the spinal cord. The phenotype modifications induced by these mechanisms contribute to perpetuate the inflammation and the primary and secondary hyperalgesia. Protein kinases A, which then no longer seem to require activation by AMPc, play a similar complementary role [39].

The NF-κB transcription factor is probably a second major source of long-term modifications. Relevant mechanisms may include induction of synthesis of the bradykinin B_1 receptor and changes in the production of prostanoids, cytokines, and nitric oxide (iNOS). These changes in protein synthesis are not confined to sensory neurons but occur throughout the site of inflammation.

These mechanisms acting in concert undoubtedly participate in the progression of hyperalgesia to chronicity in some situations.

12. Conclusion

We focused on current knowledge regarding the biology of the distal end of the first-line neuron linking sites of pain to the central nervous system. The multiplicity of the elementary modulating mechanisms involved is astounding. At sites of tissue damage, the nociceptors are activated and sensitized not only by substances released within the focus of inflam-

mation but also via recruitment of adjacent fibers, in particular by means of the axon reflex mechanism. This web of subtle neurochemical interactions constitutes the foundation of hyperalgesia. However, vicious circles are not confined to peripheral sites. For instance, NMDA receptors, prostaglandins, and nitric oxide send positive feedback signals to central presynaptic endings in the dorsal horn of the spinal cord. Although these mechanisms are not discussed in the present review, they should be borne in mind. Their existence indicates that the separation between "peripheral" and "central" mechanisms to sensitization is probably simplistic: peripheral and central mechanisms seem to be closely intertwined [69].

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