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Review

# Prostanoids and inflammatory pain

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ABSTRACT

Prostanoids play pivotal roles in inflammation and pain. Cyclooxygenase (COX) inhibitors, the nonsteroidal anti-inflammatory drugs (NSAIDs), depress prostanoid formation and are widely used to treat inflammatory pain. However, their therapeutic benefit is offset by serious side-effects, primarily gastrointestinal and cardiovascular complications. Pathway elements downstream of the COX enzymes, particularly the terminal synthases and receptors of prostaglandin $E_2$, have been proposed as alternative targets for the development of novel NSAID like drugs. Here, we summarize the current knowledge on the roles of individual prostanoids in modulating inflammatory pain.



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## 1. Inflammatory pain

Pain produced by intense, potentially harmful stimuli is an important early warning sign that helps avoid tissue damage. This type of pain is known as nociceptive pain. Nociceptive pain signaling is initiated by peripheral terminals of sensory neurons, the nociceptors, which respond to heat, acids or severe mechanical stress resulting from direct pressure. Peripheral nociceptor terminals express molecules such as the transient receptor potential cation channel subtype V1 (TRPV1) and voltage-gated sodium channels (e.g. Nav1.8 or 1.9) to detect noxious stimuli and transduce them into electrical energy. Inflammatory pain develops when the sensitivity of the nociceptive system increases after the tissue integrity is disrupted by trauma, heat, infection, toxins, inadequate immune responses, tumors or other insults [1].

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Once tissue damage has occurred, multiple chemical mediators are released from the injured cells and the infiltrating immune cells to create an "inflammatory soup" that contains proinflammatory cytokines [such as interleukin 1β (IL-1β) and tumor necrosis factor (TNF)-α], chemokines [such as monocyte chemotactic protein-1 (MCP-1)], prostaglandins [such as prostaglandin (PG) $E_2$ and prostacyclin ($PGI_2$)], bradykinins, nerve growth factors, purines, amines, ions, and many others. The peripheral terminals of nociceptors express receptors for many of these inflammatory mediators. They act to lower the activation threshold of the TRPV1 and the Nav ion channels, for example, by inducing phosphorylation events at regulatory amino acid residues or by increasing expression levels [2,3]. This increase in the sensitivity of the peripheral terminals of nociceptors in inflamed tissue is termed peripheral sensitization and contributes to inflammatory pain hypersensitivity or hyperalgesia [4]. Stimuli that would normally cause mild pain now evoke strong pain; normally unpainful sensations such as pressure or warmth at the site of inflammation now feel painful. Pain hypersensitivity helps protect injured tissues from further damage as it discourages physical activity and, thus, reduces mechanical stress.

The second mechanism underlying pain hypersensitivity is termed central sensitization [5]. In addition to creating the peripheral "inflammatory soup", tissue injury also stimulates the release of neurotransmitters (e.g. glutamate, substance P) from the central terminals of nociceptors and augments the production of $PGE_2$ or proinflammatory cytokines (e.g. IL-1β, TNF-α) in the spinal cord. This causes additional excitation and disinhibition of dorsal horn neurons and generates abnormal responses to sensory signals from the periphery [6]. The pain spreads to regions beyond the site of tissue damage and innocuous tactile stimulation now is processed to cause a painful sensation. The processes underlying central sensitization reflect the plasticity of the nociceptive system that is invoked by injury. They are usually reversible within hours to days following adequate responses of the nociceptive system (e.g. in postoperative pain). Chronic inflammatory disease may condition persistent modification of the architecture of the nociceptive system, which may lead to long lasting changes in its responsiveness. These mechanisms contribute to chronic pain.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, naproxen, ibuprofen, and acetaminophen, are the most commonly used drugs for the treatment of inflammatory pain. These therapeutic agents inhibit cyclooxygenase (COX)-1 and -2, thereby reducing the production of prostanoids, lipid mediators that contribute to both peripheral and central sensitization in inflammatory pain. Thus, the analgesic effect of NSAIDs is partially explained by the reduction or reversal of peripheral sensitization when the prostanoid concentration in the "inflammatory soup" is reduced. NSAIDs also modulate pain intensity by suppressing prostanoid formation in the spinal cord and perhaps the brain, thus affecting central sensitization. Indeed, the mixed COX-1 and -2 inhibitor acetaminophen is thought to relieve pain largely by inhibition of prostanoid production in the CNS, while its peripheral anti-inflammatory activity is limited.

Newer NSAIDs such as celecoxib have been purposefully developed to inhibit COX-2 selectively with the intent to reduce the risk of gastrointestinal bleeding caused primarily by COX-1 inhibition. However, placebo-controlled trials revealed that three structurally distinct NSAIDs selective for inhibition of COX-2 – rofecoxib, celecoxib, and valdecoxib – predisposed patients to myocardial infarction and stroke. The molecular mechanism underlying these complications is amongst the best studied of any adverse drug effect [7,8]. COX-2 inhibition depresses prostanoid formation in the vasculature [9], which restrain platelet activation by prothrombotic stimuli, contributes to renal blood pressure homeostasis and may slow atherogenesis [9,10]. Inhibition of these mediators, particularly of $PGI_2$, increases the likelihood of thrombotic events, hypertension, and heart failure particularly in patients at elevated cardiovascular risk.

These side effects have led researchers to investigate more specific approaches to targeting prostanoid signaling in inflammatory pain such as the inhibition of prostanoid terminal synthases and receptors as potential therapeutics. For example, deletion or inhibition of the inducible $PGE_2$ terminal synthase, membrane-associated PGE synthase-1 (mPGES-1), has been shown to reduce pain and inflammation in murine models [11,12], while no mechanistic basis for an enhanced cardiovascular risk was observed in mice [13]. Similarly, targeting the G-protein-coupled receptor subtypes for $PGE_2$ (EP1, EP2, EP3, and EP4) is being pursued as an alternative approach to developing analgesics with potentially fewer side-effects. Interestingly, $PGI_2$ was also reported to play crucial roles in the induction of inflammation and pain by activating the prostacyclin receptor (IP) which has been identified as another potential target in the therapy of inflammatory pain [14].

## 2. Prostanoid biosynthesis and receptors

Prostanoids are produced via three sequential enzymatic reactions that begin with the release of arachidonic acid (AA) from membrane phospholipids by phospholipase $A_2$ ($PLA_2$), in many cells cytosolic $PLA_2$ ($cPLA_2$). Arachidonic acid is metabolized by three major groups of enzymes, the COXs, lipoxygenases, or epoxygenases to form the prostanoids, the leukotrienes, or the epoxyeicosatrienoic acids. Eicosanoid products of all three pathways have been implicated in inflammatory pain signaling. Here, we focus on the prostanoids. Both COX-1 and -2 convert AA to the unstable endoperoxide intermediates $PGG_2$ and $PGH_2$. $PGH_2$ is isomerized to different prostanoids by their respective terminal synthases. To date, five bioactive prostanoids are known to be generated by the COXs in mammals: $PGE_2$, $PGI_2$, $PGD_2$, $PGF_{2\alpha}$ and thromboxane (Tx) $A_2$. The corresponding synthases are PGE synthase (PGES), PGIS, PGDS, PGFS and TxAS, respectively. Three forms of PGES – mPGES-1, mPGES-2 and cytosolic PGES (cPGES), two forms of PGDS – lipocalin-type (L-PGDS) and hematopoietic-type (H-PGDS), two forms of PGFS (PGFS-1 and PGFS-2) have been identified, underscoring the diversity of the prostanoid biosynthetic system [15].

COX-1 is constitutively expressed in most tissues and responsible for the basal production of prostanoids with homeostatic functions, such as gastric epithelial cytoprotection and renal blood flow maintenance. COX-2 is not expressed or expressed only at marginal levels under basal conditions in many tissues, but is upregulated in response to proinflammatory factors, hormones and growth factors. Its role in the production of prostanoids during inflammation and in cancerous states provided the rationale for the development of COX-2 selective NSAIDs [16]. Several compounds, such as celecoxib, valdecoxib, and rofecoxib entered the market. However, the paradigm of distinct homeostatic and pathological functions of COX-1 and COX-2 turned out to be an oversimplification, with ample of evidence now showing contributions of COX-2 to healthy cardiovascular, renal and gastric physiology and roles of COX-1 in inflammation [17–20]. Indeed, the cardiovascular hazard associated with COX-2 selective NSAIDs led all compounds except celecoxib to be withdrawn from the market [8].

The prostanoid synthases, cPGES, PGDSs, PGFSs and TXAS were reported to be preferentially, but not exclusively, coupled functionally with COX-1, while mPGES-1 and PGIS are often coupled and co-induced with COX-2 to mediate $PGE_2$ and $PGI_2$ synthesis, respectively, in response to acute and chronic inflammatory stimuli. mPGES-2 has been functionally linked to both COX-1 and COX-2 [15]. Expression levels of prostanoid synthases within various cells are important determinants of the prostanoid production