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Beyond the classic eicosanoids: Peripherally-acting oxygenated metabolites of polyunsaturated fatty acids mediate pain associated with tissue injury and inflammation

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ABSTRACT

Pain is a complex sensation that may be protective or cause undue suffering and loss of function, depending on the circumstances. Peripheral nociceptor neurons (PNs) innervate most tissues, and express ion channels, nocisensors, which depolarize the cell in response to intense stimuli and numerous substances. Inflamed tissues manifest inflammatory hyperalgesia in which the threshold for pain and the response to painful stimuli are decreased and increased, respectively. Constituents of the inflammatory milieu sensitize PNs, thereby contributing to hyperalgesia.

Polyunsaturated fatty acids undergo enzymatic and free radical-mediated oxygenation into an array of bioactive metabolites, oxygenated polyunsaturated fatty acids (oxy-PUFAs), including the classic eicosanoids. Oxy-PUFA production is enhanced during inflammation. Pioneering studies by Vane and colleagues from the early 1970s first implicated classic eicosanoids in the pain associated with inflammation. Here, we review the production and action of oxy-PUFAs that are not classic eicosanoids, but nevertheless are produced in injured/ inflamed tissues and activate or sensitize PNs. In general, oxy-PUFAs that sensitize PNs may do so directly, by activation of nocisensors, ion channels or GPCRs expressed on the surface of PNs, or indirectly, by increasing the production of inflammatory mediators that activate or sensitize PNs. We focus on oxy-PUFAs that act directly on PNs. Specifically, we discuss the role of arachidonic acid-derived 12S-HpETE, HNE, ONE, PGA_2, iso-PGA_2 and 15D-PGJ_2, 5,6-and 8,9-EET, PGE_2-G and 8R,15S-diHETE, as well as the linoleic acid-derived 9-and 13-HODE in inducing acute nocifensive behavior and/or inflammatory hyperalgesia in rodents. The nocisensors TRPV1, TRPV4 and TRPA1, and putative Gαs-type GPCRs are the PN targets of these oxy-PUFAs.

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Abbreviations: ALOX, arachidonic acid lipoxygenase; AITC, allyl isothiocyanate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPA-R, AMPA receptor; AP, action potential; B2, bradykinin receptor 2; $[Ca^{++}]_{in}$, intracellular calcium concentration; Ca_V, voltage-gated calcium channel; CFA, complete Freund's adjuvant; CGRP, calcitonin gene-related peptide; CN, central nociceptor neuron; DG/ DRG, dorsal ganglion/dorsal root ganglion; DH, dorsal horn; EC, endocannabinoid; EpDPE, epoxy-docosapentaenoic acid; EpETE, epoxy-eicosatetraenoic acid; GPCR, G-protein coupled receptor; HMGB1, high mobility group box 1; HPLC-MS, high-performance liquid chromatography - mass spectrometry; i.pl., intraplantar; MaR, maresin; Na_V, voltage-gated sodium channel; NDGA, nordihydroguaiaretic acid; NMDA, N-methyl-D-aspartate receptor; ONE, oxo-nonenal; oxy-PUFA, oxygenated polyunsaturated fatty acid; PGE_2-G, prostaglandin E_2 glycerol ester; PKA, protein kinase A; PKC, protein kinase C; $PMF_{2\alpha}$, prostamide $F_{2\alpha}$; PN, peripheral nociceptor neuron; RTX, resinferatoxin; sEH, soluble epoxide hydrolase; SP, substance P; TG, trigeminal ganglion; TRP, transient receptor potential (ion channel superfamily); 15d-PGJD-PGJ_2, 15-deoxy-prostaglandin J_2

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1. Introduction

Injured and inflamed tissues are often painful. Following a burn injury, for example, pain is ongoing, contact with hot water is more painful than usual, and the normally innocuous contact with clothing or lukewarm water is painful. These three forms of amplified pain that typify significant inflammation, termed collectively inflammatory hyperalgesia, are a consequence of the sensitization of pain-encoding neurons, the peripheral and central nociceptor neurons (PNs and CNs, respectively) [1–3]. Inflammatory hyperalgesia is implicated in the pain accompanying numerous acute and chronic clinical scenarios, including post-operative pain, burns, osteoarthritis (OA), rheumatoid arthritis (RA), and Inflammatory Bowel Disease (IBD).

Cells transform omega-6 and omega-3 polyunsaturated fatty acids (ω−6 and ω−3 PUFAs) such as arachidonic acid (AA; C20:4;ω−6) into an array of lipid mediators that orchestrate basal tissue function and the response to deviations from homeostasis. AA metabolites are central to pain processing, as exemplified by the prostaglandins and the endocannabinoids (ECs) [4], which amplify and suppress pain, respectively [5]. Numerous other oxygenated and non-oxygenated PUFA-derived mediators modulate pain as well [5–7].

The ancient Greek physician Celsus described the cardinal sign of inflammation, which include “dolor”: the painfulness of inflamed tissues. The recognition that pain responds to naturally-occurring aspirin-like substances (i.e. salicylates originating in medicinal plants) also dates back to ancient times. Vane and colleagues [8] provided the molecular link between these two observations in 1971, demonstrating that aspirin and NSAIDs ameliorate inflammation and the pain associated with inflammation through inhibition of prostanoid synthesis [8]. Since then, a plethora of original studies have confirmed the role of PGE_2, alongside other prostanoids (particularly PGI_2), and other classic eicosanoids (LTB_4) in producing inflammatory hyperalgesia, and have been reviewed over the years as data accumulates [9–17]. Inhibition of COX isoforms (1 or 2) or 5-LOX attenuates inflammatory hyperalgesia but does not completely normalize sensitivity to pain, suggesting the involvement of mediators other than classic eicosanoids. Several articles, mainly from the early 2000s, reported that oxy-PUFAs are produced in peripheral tissues upon injury and inflammation, and although not classic eicosanoids they participate in acute pain and/or inflammatory hyperalgesia. To date, the oxy-PUFAs found to mediate acute pain and/or inflammatory hyperalgesia are all derived from ω−6 PUFAs: AA, dihomo-γ-linolenic acid (DGLA; C20:3;ω−6) and linoleic acid (LA; C18:2;ω−6) [18]. Here we describe the studies implicating these oxy-PUFAs' role in inflammatory hyperalgesia and attempt to categorize the oxy-PUFAs according to their mechanism of action on PNs.

2. Pain and oxy-PUFAs: an overview of their physiology and pathophysiology

2.1. Acute nociceptive pain

Peripheral and central nociceptor neurons detect stimuli that are potentially or actually injurious to tissues and relay the sensory input to the brain (Fig. 1). PNs are unmyelinated or thinly-myelinated sensory neurons with un-encapsulated peripheral terminals. PN axons are contained within spinal or trigeminal nerves, and their cell bodies (somata) are housed in the dorsal root or trigeminal nerve ganglia (DRG, TG), adjacent to the CNS. Ion channels embedded in the PN peripheral terminal, called nocisensors [2], couple cell injury and noxious stimuli to depolarization of the PN membrane potential (Fig. 1). Most nocisensors conduct sodium and/or calcium upon activation, which leads to depolarization. Nocisensors may be activated by thermal and mechanical stimuli in the noxious range, by injurious substances (H^+, Reactive Oxygen or Nitrogen Species, chemical irritants), or by substances released from injured cells (e.g. ATP) [2,3]. Transient receptor potential cation channel, vanilloid subfamily V, member 1 (TRPV1) is an informative example of a nocisensor. Heat in the painful range (temp $>42\,^{\circ}C$) transforms TRPV1 into a cation-(sodium and calcium) conducting channel *in vitro* and *in vivo*, and depolarizes TRPV1-expressing PNs [2,19,20–23]. Several nocisensors other than the TRP have been identified, as detailed elsewhere [2,3,5,24].

A robust generator potential initiates action potentials (APs) by activating voltage-gated sodium channels (Na_v). APs propagate to the PN central terminals, such as those located in the dorsal horn (DH) of the spinal cord, leading to release of excitatory neurotransmitters such as glutamate. Post-synaptic AMPA ion receptors are activated by glutamate, and CNs relay the encoded pain signal to