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Commentary

A thickening network of lipids

The lipids that make up the bulk of cell membranes are a rich source of signaling molecules, many of which trigger inflammation and magnify the response to painful stimuli. A classic example is provided by the eicosanoids, local mediators that are generated by enzymatic oxygenation of the polyunsaturated fatty acid, arachidonic acid, and bind to G protein-coupled receptors on sensory fibers, with a resultant lowering of the pain threshold during inflammation. A smaller, but growing number of lipid molecules act in an opposite way: they curb the inflammatory process, restore homeostasis in inflamed tissues, and blunt pain sensitivity by regulating neural pathways that transmit nociceptive signals from the periphery to the central nervous system (CNS). Among these membrane-derived analgesics is a small family of lipid molecules in which a saturated or monounsaturated fatty acid – such as palmitic or oleic acid – is chemically linked to ethanolamine through an amide bond. In neurons and innate immune cells, these endogenous lipid amides are formed by cleavage of the phospholipid precursor, *N*-acylphosphatidylethanolamine, a process that is carried out by a specialized phospholipase D enzyme. One of the best-known members of this family, palmitoylethanolamide (PEA), produces profound analgesic and anti-inflammatory effects in animals by recruiting a nuclear receptor called peroxisome proliferator-activated receptor-α (PPAR-α) [4] (see Fig. 1).

Initially identified as a receptor for peroxisome-stimulating plasticizers in the liver, PPAR-α is, in fact, a ubiquitous transcription factor that can be activated by a variety of endogenous fatty acid derivatives, including PEA and its monounsaturated analog, oleoylethanolamide [1]. Binding of an agonist ligand to PPAR-α promotes the translocation of this protein from the cytosol to the nucleus, and initiates a series of molecular events that culminate in the transcriptional repression of genes encoding for key pro-inflammatory proteins, such as tumor-necrosis factor-α, inducible nitric oxide synthase and cyclooxygenase-2 [11]. In addition to modulating gene expression, PPAR-α can suppress nociceptive fiber activity and behavioral pain responses through a rapid non-genomic mechanism, which might involve the opening of membrane potassium channels [4]. While the mechanism underlying PPAR-α-dependent antinociception is still unclear, its functional relevance is underscored by the marked analgesic properties demonstrated by PEA and other PPAR-α agonists in a variety of animal pain models [4].

In the current issue of *Pain*, Sasso and collaborators identify an unexpected new step in the molecular pathway through which PPAR-α regulates nociceptive responses [9]. Working with mice, these investigators observed that pharmacological blockade of neurosteroid biosynthesis reduces PEA's ability to alleviate pain-related behaviors elicited by chemical tissue damage (hindpaw injection of formalin) or acute inflammation produced by carrageenan. The authors used inhibitors that target two distinct enzymatic steps of neurosteroid biosynthesis: cytochrome P450scc (side-chain cleavage), which transforms cholesterol into pregnenolone, and 5α-reductase, which initiates the conversion of progesterone into allopregnanolone. Searching for biochemical correlates of these pharmacological observations, Sasso and coworkers found that administration of formalin or carrageenan causes a rapid drop in the spinal cord levels of cytochrome P450scc and steroidogenic acute regulatory protein (StAR, a mitochondrial cholesterol transporter required for neurosteroid biosynthesis). These effects, the researchers noted, were accompanied by a reduction in the levels of allopregnanolone in the spinal cord and could be prevented by treatment with PEA, leading them to propose the existence of an obligatory link between the antinociceptive effects of PEA and allopregnanolone production.

When administered as a drug, allopregnanolone can influence anxiety, mood and cognition in animal models through its action as a positive allosteric modulator of type-A γ-aminobutyric acid (GABA) receptors in the CNS. GABA receptor regulation may also underlie the neurosteroid's ability to alleviate acute and persistent pain responses [5,2] as well as nociceptive processing in the spinal cord [7]. Do these pharmacological properties reflect a role for endogenous allopregnanolone in nociception? Though the evidence is not entirely conclusive, a substantial amount of data suggests that this is possible. It has been shown, for example, that neural cells in the dorsal root ganglia and spinal cord express the enzyme complement necessary for allopregnanolone biosynthesis – including cytochrome P450scc, 5-α-reductase and 3-α-hydroxysteroid dehydrogenase [6]. Moreover, spinal-cord levels of these enzymes and their products are increased in a rat model of painful peripheral neuropathy [6]. Interestingly, in Iraq war veterans suffering from chronic pain, the plasma concentrations of allopregnanolone were inversely correlated with self-reported pain symptoms, which suggests that allopregnanolone may also have an intrinsic analgesic role in humans [3]. These findings leave unresolved, however, the essential issue of the mechanism(s) controlling neurosteroid mobilization during painful states.

Sasso and collaborators suggest that one such mechanism might involve PEA activation of PPAR-α. Drawing from another study conducted in C6 glioma cells [8], these investigators propose that PPAR-α stimulates the transcription of genes encoding for steroidogenic enzymes, resulting in an up-regulation of neurosteroids that contribute to the analgesic effects of PEA. This hypothesis ties together two distinct membrane-derived signaling pathways – lipid amide PPAR-α agonists and GABA-modulating neurosteroids – and will undoubtedly prompt new questions about the role of these pathways in nociceptive control. For example, the rapid decreases in neurosteroid production that accompany formalin or

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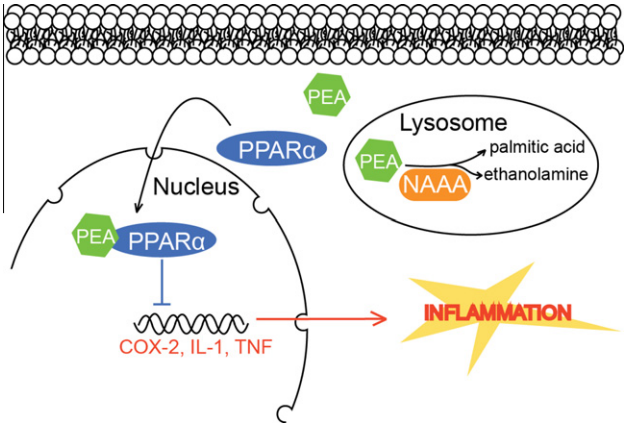

Fig. 1. Hypothetical role of PEA in inflammation and pain. According to this model, PEA acts as an endogenous anti-inflammatory and analgesic factor, by activating the nuclear receptor PPARα. PPARα down-regulates transcription of a number of pro-inflammatory proteins in macrophages, including cyclooxygenase-2 (Cox-2), interleukin-1 (IL-1) and tumor necrosis factor (TNF). The effects of PEA are terminated by the cysteine amidase N-acylphosphatidylethanolamine (NAAA), which catalyzes the hydrolysis of PEA into palmitic acid and ethanolamine. NAAA is localized to lysosomes. (Modified from [4].)

carrageenan injection raise the possibility that neurosteroid activity at GABA-A receptors in the spinal cord may help maintain normal pain thresholds, and that this analgesic tone might be turned down during inflammation and other painful conditions. Interestingly, the biosynthesis of PEA in innate immune cells is also suppressed by pro-inflammatory stimuli [10], confirming the suspicion that a thick network of interactions may link lipid amides and neurosteroids.

Conflict of interest statement

The author has no conflicts of interest regarding this commentary.

References

[1] Fu J, Gaetani S, Oveisi F, Lo Verme J, Serrano A, Rodríguez De Fonseca F, Rosengarth A, Luecke H, Di Giacomo B, Tarzia G, Piomelli D. Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. Nature 2003;425:90–3.

[2] Kawano T, Soga T, Chi H, Eguchi S, Yamazaki F, Kumagai N, Yokoyama M. Role of the neurosteroid allopregnanolone in the hyperalgesic behavior induced by painful nerve injury in rats. J Anesth; 2011 August 31 [Epub ahead of print].

[3] Kilts JD, Tupler LA, Keefe FJ, Payne VM, Hamer RM, Naylor JC, Calnaido RP, Morey RA, Strauss JL, Parke G, Massing MW, Youssef NA, Shampine LJ. Veterans Affairs Mid-Atlantic Mental Illness, Research, Education and Clinical Center Workgroup, Marx CE. Neurosteroids and self-reported pain in veterans who served in the U.S. Military after September 11, 2001. Pain Med 2010;11:1469–76.

[4] LoVerme J, Russo R, La Rana G, Fu J, Farthing J, Mattace-Raso G, Meli R, Hohmann A, Calignano A, Piomelli D. Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-alpha. J Pharmacol Exp Ther 2006;319:1051–61.

[5] Ocvirk R, Pearson Murphy BE, Franklin KB, Abbott FV. Antinociceptive profile of ring A-reduced progesterone metabolites in the formalin test. Pain 2008;138:402–9.

[6] Patte-Mensah C, Meyer L, Schaeffer V, Mensah-Nyagan AG. Selective regulation of 3 alpha-hydroxysteroid oxido-reductase expression in dorsal root ganglion neurons: a possible mechanism to cope with peripheral nerve injury-induced chronic pain. Pain 2010;150:522–34.

[7] Peng HY, Chen GD, Lee SD, Lai CY, Chiu CH, Cheng CL, Chang YS, Hsieh MC, Tung KC, Lin TB. Neuroactive steroids inhibit spinal reflex potentiation by selectively enhancing specific spinal GABA(A) receptor subtypes. Pain 2009;143:12–20.

[8] Raso GM, Esposito E, Vitiello S, Iacono A, Santoro A, D'Agostino G, Sasso O, Russo R, Piazza PV, Calignano A, Meli R. Palmitoylethanolamide stimulation induces allopregnanolone synthesis in C6 Cells and primary astrocytes: involvement of peroxisome-proliferator activated receptor-α. J Neuroendocrinol 2011;23:591–600.

[9] Sasso O, Russo R, Vitiello S, Mattace Raso G, D'Agostino G, Iacono A, La Rana G, Vallée M, Cuzzocrea S, Piazza PV, Meli R, Calignano A. Implication of allopregnanolone in the antinociceptive effect of N-palmitoylethanolamide in acute or persistent pain. Pain 2011;153:33–41.

[10] Solorzano C, Zhu C, Battista N, Astarita G, Lodola A, Rivara S, Mor M, Russo R, Maccarrone M, Antonietti F, Duranti A, Tontini A, Cuzzocrea S, Tarzia G, Piomelli D. Selective N-acylethanolamine-hydrolyzing acid amidase inhibition reveals a key role for endogenous palmitoylethanolamide in inflammation. Proc Natl Acad Sci USA 2009;106:20966–71.

[11] Zandbergen F, Plutzky J. PPARalpha in atherosclerosis and inflammation. Biochim Biophys Acta 2007;1771:972–82.

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