A thickening network of lipids.
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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 as a positive allosteric modulator of type-A cannabinoid receptors and GABA-modulating neurosteroids – and will undoubtedly prompt new questions about the role of these pathways in nociceptive control. For example, the rapid – and will undoubtedly prompt new questions about the role of these pathways in nociceptive control. For example, the rapid

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 mood, anxiety, 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, 5α-reductase and 3α-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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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.

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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]).