Fat location defines sensation

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Arachidonic acid metabolites have long been known to potentiate inflammation and sensitize sensory neurons. Now linoleic acid, an essential ω-6 fatty acid precursor of arachidonic acid and a major membrane constituent of mammalian cells, has been found to have a related role. Hargreaves and colleagues (1) have shown that oxidized linoleic acid products produced from heated skin are potent activators of TRPV1, the capsaicin receptor, which plays a major role in thermal hyperalgesia. They make a strong case that these mediators contribute substantially to heat-activated TRPV1 currents in sensory neurons. In this issue of PNAS, Patwardhan et al. (2) extend the group's findings to show that depolarized spinal cord neurons also release the same oxidized linoleic acid metabolites that act on TRPV1. This release causes not only thermal hyperalgesia but also mechanical allodynia (pain associated with a normally nonnoxious mechanical stimulus). Thus the same chemical mediators [9- and 13-hydroxyoctadecanoic acid (9-HODE and 13-HODE) and related molecules] acting through the same receptor, TRPV1, appear to have distinct effects on sensation when released either peripherally or centrally. How can we explain these fascinating observations?

Heat Sensing

The molecular cloning of the heat-activated capsaicin receptor TRPV1 by Caterina, Julius, and their colleagues (3) provided a satisfying explanation for the hot sensation evoked by chili peppers and a potential identity for the heat-sensitive channels originally described by Cesare and McNaughton (4). As soon as the TRPV1-knockout mouse was generated, however, it became clear that there must be other heat sensors in sensory neurons (5). Although TRPV1 plays a major role in heat hyperalgesia, deletion of TRPV1 or even the cells that express TRPV1 (6) has little effect on heat sensing at threshold noxious temperatures (as opposed to very high temperatures) measured with Hargreaves's eponymous apparatus. This observation suggests that other heat receptors in other cells have lower heat thresholds than TRPV1 and signal noxious heat independently (7). Is the principal role of TRPV1 heat sensing? This possibility seems unlikely. The activation of TRPV1 by low pH, characteristic of damaged tissue (8), its demonstrated importance in inflammatory hyperalgesia (5), and the evidence presented here of an important role for presynaptic TRPV1 in thermal and mechanical sensitization (2) support a role for TRPV1 as an inflammatory amplifier. It is also possible that TRPV1 in CNS locations that are not involved in pain perception may also regulate synaptic signaling.

Suprathreshold noxious temperatures, linoleic acid metabolites, and capsaicin in the periphery activate TRPV1 to evoke heat pain. The voltage-dependent mechanism of TRP activation that underlies this form of heat sensing has been described by Nilius and colleagues (9), and other TRPVs have been investigated as potential heat sensors (8). At the moment, however, the molecular identity of the threshold acute noxious heat sensor that may also be sensitized by pro-inflammatory lipids remains unknown, as do the set of sensory neurons that first respond to tissue-damaging heat.

Lipid Activators of TRPV1

A range of fats activate TRPV1, including anandamide, diacylglycerol and lipoxygenase metabolites of arachidonic acid, the unsaturated long-chain *N*-acylethanolamines, and unsaturated long-chain *N*-acyldopamines (10). Interestingly, lipid activators have been associated with G-protein-coupled receptor (GPCR) systems, some of which are apparently analgesic—e.g., CB1 and 2 receptors activated by anandamide (11). This association makes unraveling the physiological actions of lipid metabolites in pain pathways problematic. Interestingly, there is an association between linoleic acid release and inflammation, raising the possibility that the neutralizing antibodies described by Patwardhan et al. (2) could have some therapeutic utility. Linoleic acid metabolites have been associated with GPCR-mediated signaling, as well as human pathologies ranging from type II diabetes to Alzheimer's disease (12, 13).

Mechanisms of Allodynia

Although the expression of channels in sensory neurons that contribute to mechanosensation has been shown to be up-regulated both transcriptionally and in terms of membrane trafficking by inflammatory mediators, the development of allodynia has often been associated with events in the dorsal horn (14). Intriguingly, many peptide mediators associated with small-diameter sensory neurons [calcitonin gene-related peptide (CGRP), substance P, brain-derived neurotrophic factor (BDNF)] have been shown to evoke allodynia when applied intrathecally (15–17). Thus a major afferent barrage from peptidergic nociceptive neurons is likely to sensitize dorsal horn neurons that are normally wired for mechanosensitive input through the (extrasynaptic?) actions of these mediators. Killing the dorsal horn neurons that express NK1 receptors suppresses allodynia, and deleting the gene for BDNF in Nav1.8$^+$ neurons also inhibits central sensitization (18, 19). Specific antagonists of TRPV1 can block mechanical allodynia, suggesting that presynaptic TRPV1 activation is an important element in the release of pro-allodynic mediators (20). Thus afferent barrage leading to second-order neural depolarization may cause the release of 9-HODE that amplifies the release of neuromodulators in the dorsal horn. In this way, despite the known mechanoinsensitivity of TRPV1, presynaptic amplification of nociceptive input through this receptor contributes to allodynia. High-dose peripheral capsaicin, which causes a sustained depolarization of peptidergic neurons, can cause allodynia, consistent with the present model (21). Pain research (with drugs in mind) has focused on mediators, rather than neuronal pathways, and we have limited insight into the innervation of dorsal horn neurons above a simple lamina specificity. Given the importance of presynaptic TRPV1 within the dorsal horn in central sensitization, it will be fascinating to see which dorsal horn neurons are innervated by these TRPV1$^+$ terminals, where they project, and whether they also receive input from other sensory neurons. One caveat to these findings results from the fact that TRPV1-null mutant mice can develop some mechanical hypersensitivity (5). There must, therefore, be mechanisms that contrib-

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ute to mechanosensitization that do not require TRPV1.

Mediators, Receptors, Drugs, and Wiring

The role of linoleic acid metabolites as activators of TRPV1 and effectors of central sensitization was unexpected. The enzymes that produce 9-HODE and related metabolites thus become potentially interesting analgesic drug targets. The present findings provide an insight into how wiring dictates the actions of mediators. TRPV1 clearly has a number of distinct functions, not all of which, particularly in the CNS, are understood. Will the enzymes that generate oxidized linoleic acid products prove a useful target for analgesic intervention? If these mediators are associated with other physiological functions, such a program may be frustrated. Does depolarization of CNS neurons cause related fatty acid mediators to be released, perhaps acting on other transient receptor potential ion channels? Do these mediators cause TRPV1 activation directly or through membrane effects? The recent paper (2) is likely to stimulate a wave of research to answer these intriguing questions.

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