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LPA activates TRPV1—and it hurts

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Abstract

Lysophosphatidic acid, a lipid mediator, second messenger and intermediate in lipid biosynthesis, finds a new intracellular target in TRPV1. This nonselective cation channel is also targeted by the analgesic capsaicin, which acts to desensitize the channel

Pain has been categorized into three types: nociceptive (physiological), inflammatory and neuropathic (chronic) pain. Acute inflammatory pain is caused by tissue injury and is reversible upon the elimination of inflammatory mediators, which can be controlled by the many available painkillers. Neuropathic pain generally results from damage to the nervous system and is characterized by stimulus-independent, persistent pain or by abnormal pain perception triggered by innocuous stimuli. A decade ago, pioneering work established the role of LPA in neuropathic pain through the activation of the LPA₁ G protein-coupled receptor (GPCR)¹. Recently, it has been found that inhibitors of autotaxin, the enzyme that produces LPA from lysophosphatidylcholine, provide pain relief in neuropathic pain models². Nieto-Posadas *et al.*³ now build a compelling case that LPA directly activates the transient receptor potential channel TRPV1 by binding to its intracellular C terminus to mediate acute inflammatory pain sensation.

The TRPV1 channel is known to be an originator of acute inflammatory pain⁴ as it is rapidly activated by low pH, temperature and pungent compounds, including capsaicin from hot peppers. The analgesic effect of capsaicin is thought to be mediated by the desensitization of TRPV1 (ref. 5), which is known to be modulated by another lipid second messenger, phosphatidylinositol-4,5-bisphosphate (PIP₂)⁶. TRPV1 is widely expressed in neurons of the pain pathways in the nervous system; for this reason, the molecules directly activating it are of enormous interest for pharmaceutical industries.

The case for TRPV1's involvement in mediating LPA-induced pain sensation began with the authors' use of the receptor pan-antagonist analog and inhibitor of autotaxin-mediated LPA biosynthesis⁷ bromo LPA-phosphonate (LPA-BrP), which led to the finding that LPA₁ is not directly involved. In dissociated dorsal root ganglion cells, the authors demonstrate using electrophysiological techniques that application of LPA and LPA-BrP leads to the firing of action potentials, which are absent in cells from *Trpv1* knockout mice. The authors also use *Trpv1*, *Lpp3* and double *Trpv1 Lpp3* knockout mice to investigate pain-like behaviors. LPP3 is a lipid phosphate phosphatase that breaks down several lysophospholipids, and *Lpp3* knockout mice have elevated LPA concentrations that the authors link to increased pain responses in these animals. LPA-induced pain hypersensitivity is largely reversed in *Trpv1* knockout and *Trpv1 Lpp3* double-knockout mice. The authors also show that the TRPV1 antagonist capsazepine inhibits activation of the channel by LPA.

They establish that other TRP family channels do not respond to LPA and that other lysophospholipids, such as sphingosine-1-phosphate, do not activate TRPV1.

The authors show that although LPA applied extracellularly can activate TRPV1, application to the intracellular side is more effective. A very interesting structural aspect of the new findings is that LPA interacts with a site on the TRPV1 intracellular C terminus that partially overlaps with the PIP₂ binding site and also is allosterically regulated by PIP₂. The authors demonstrate direct physical interaction between TRPV1 and LPA in pull-down experiments and identify Lys710 as a requirement for LPA and LPA-BrP binding. Taken together, these findings point to the exciting new possibility that LPA is an activator of acute inflammatory pain through TRPV1 and also has a role in neuropathic pain via the LPA₁ GPCR (Fig. 1).

This work places LPA at the center stage of pain research and also provides a paradigm-shifting challenge to lipidologists by demonstrating that an extracellularly applied long-chain lysophospholipid can rapidly enter cells to directly activate intracellular targets. This latter paradigm lays ground for a new transcellular signaling mechanism in which lipid mediators excreted by one cell can access intracellular targets within another cell. The source of LPA in inflammatory and TRPV-mediated neuropathic pain is yet unknown. Extracellularly, LPA is produced in blood via stimulus-coupled mechanisms involving phospholipases A1 and A2 and autotaxin⁸. Intracellularly, LPA can be generated by the Ca²⁺-independent class of phospholipase A2 and phospholipase D and via glycerol-3-phosphate acyltransferase-1 (ref. 9). Which of these mechanisms is responsible for TRPV1 activation remains to be determined. In biological fluids, LPA is bound to carrier proteins, mostly albumin. The biophysical mechanism that transfers LPA from its carrier across the bilayer to the C terminus of TRPV1 is another subject that begs to be elucidated. For the pharmaceutical industry, the task now is to generate LPA analogs that selectively block TRPV1 activation and LPA₁ as well as autotaxin. Thus, it is not hard to envision that analgesics specific for LPA targets will be vigorously sought in the future.

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Figure 1.

LPA-activated pain mechanisms. Acute pain is mediated via LPA activation of TRPV1 channels present in the sensory nerve endings and some dorsal root ganglion cells (DRGs). Center inset shows the intracellular site marked by Lys710 where LPA and PIP₂ bind. The sources of LPA accessing the C terminus of TRPV1 are unclear and are indicated by a question mark. Chronic pain is mediated by the GPCR LPA₁ expressed in DRG and Schwann cells. Activation of the latter pool of LPA₁ receptors leads to demyelination, whereas LPA₁ expressed in the DRG modulates neurotransmitter release, neurite retraction and sprouting.