This Week in The Journal

Phosphoinositides Limit TRPV1 Sensitivity

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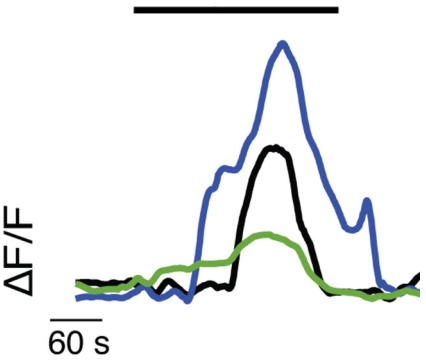
(see pages 408–423)

Phosphatidylinositol 4,5-bisphosphate (PIP_2), a minor phospholipid of the plasma membrane, is best known for its involvement in signaling downstream of Gq-coupled receptors; these receptors activate phospholipase C, which cleaves PIP_2 to form inositol trisphosphate and diacylglycerol, which in turn trigger calcium release and activation of protein kinase C (PKC). But PIP_2 also interacts with other membrane-associated proteins, and it modulates the function of various ion channels, including transient receptor potential (TRP) channels. These interactions may be disrupted by depletion of membrane PIP_2 by phospholipase C. Therefore, understanding how membrane-associated proteins are regulated by PIP_2 is important for appreciating the full effects of Gq signaling.

Sensitization of TRPV1 channels after tissue injury results in pain hypersensitivity and depends partly on Gq signaling. For example, the activation of Gq-coupled receptors by bradykinin sensitizes nociceptors by inducing PKC-dependent phosphorylation of TRPV1. Whether and how channel function is altered by depletion of PIP_2 is unclear, however: some studies have shown that PIP_2 and other phosphoinositides enhance TRPV1 function, whereas other studies indicated that phosphoinositides inhibit channel function (Rohacs, 2015, Pflugers Arch 467:1851).

To clarify how TRPV1 is affected by phosphoinositides *in vivo*, Caires et al. turned to *Caenorhabditis elegans*. TRPV1 is not expressed in these worms, but when the rat channel was expressed in a particular class of worm sensory neurons, the worms acquired aversive responses to capsaicin. Importantly, reducing PIP_2 levels by knocking out an enzyme involved in phosphoinositide recycling (TTX-7) increased capsaicin-induced calcium transients in TRPV1-expressing neurons and increased behavioral responses to capsaicin. In contrast, increasing PIP_2 levels by feeding worms PIP_2-supplemented food reduced neuronal and behavioral responses to capsaicin. Finally, deleting a putative phosphoinositide interaction domain in the TRPV1 C terminus increased capsaicin-induced calcium and behavioral responses and prevented modulation of these responses by PIP_2 supplementation.

These data suggest that interaction between the C terminus of TRPV1 and plasma membrane PIP_2 limits calcium flux through the channel. Therefore, depletion of membrane PIP_2 downstream of Gq signaling is expected to enhance TRPV1 function. This likely contributes to sensitization of nociceptor neurons by inflammatory molecules and other neuromodulators that activate Gq-coupled receptors.



Capsaicin (applied during period indicated by bar, top) evokes calcium transients (measured with a fluorescent calcium indicator) in nematode neurons expressing rat TRPV1 (black trace). Knocking out *ttx-7* reduced PIP_2 levels and increased capsaicin-induced transients (blue), whereas dietary supplementation with PIP_2 increased PIP_2 levels and reduced calcium transients (green). See Caires et al. for details.

RFRP-3 Neurons Regulate Reproductive Hormone Release

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(see pages 474–488)

Hypothalamic neurons that release gonadotropin-releasing hormone (GnRH) are key regulators of reproduction. Pulsatile release of GnRH into the anterior pituitary stimulates release of luteinizing hormone (LH) and follicle-stimulating hormone, which act on the gonads to promote the development of eggs and sperm and the release of estrogen, progesterone, and testosterone. The activity of GnRH neurons is regulated by feedback from these sex hormones, as well as by upstream hypothalamic neurons—most notably those that release kisspeptin or RF-amide related peptide 3 (RFRP-3). Whereas kisspeptin promotes firing of GnRH neurons, RFRP-3 inhibits this activity. The opposing action of these neuropeptides is thought to regulate the timing of puberty onset and ovulation. In addition, because RFRP-3 neurons are activated by glucocorticoid stress hormones, they have been proposed to contribute to stress-induced suppression of reproduction. Mamgain et al. provide support for these hypotheses using mice in which RFRP-3 neurons could be selectively activated, inhibited, or ablated.

Persistent activation of mouse RFRP-3 neurons with designer receptors exclusively activated by designer drugs (DREADDs) led to significant increases in plasma corticosterone levels and delayed puberty onset in male mice. Although puberty onset was not affected in female mice, the length of the estrous cycle was increased. In contrast, ablating RFRP-3 neurons using diphtheria toxin did not affect corticosterone levels, even in mice subjected to restraint stress, and it did not affect the estrous cycle or indicators of testosterone or estradiol levels in unstressed mice. Nevertheless, ablation of RFRP-3 neurons prevented stress-induced decreases in LH release in male and female mice. Chronic DREADDs-mediated inhibition of RFRP-3 neurons also prevented corticosterone-induced suppression of LH release in female mice, but males were not affected.

These results suggest that RFRP-3 neurons have sex-specific roles in the regulation of reproduction under normal and stressful conditions. They also suggest that RFRP-3 neurons provide positive feedback for stress signaling: they are activated by glucocorticoids and enhance corticosterone release, possibly through stimulation of corticotropin-releasing hormone neurons in the hypothalamus. Future work should determine whether RFRP-3 neurons also contribute to suppression of reproduction under circumstances that do not involve increases in glucocorticoids.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.41.3.2021