Sensing light with two-pore domain potassium channels to control pain

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Optogenetics and photopharmacology enable light control of neuronal activity and are widely used to study pain signal transmission. However, their routine use is limited by costs, animal handling, and ethical concerns. To address these challenges, we introduce LAKI (Light Activated K+ channel Inhibitor), a photoswitchable inhibitor specifically designed to target the pain-relevant Two-Pore-Domain potassium channels, TREK and TRESK, in nociceptive neurons. LAKI remains inactive under dark or ambient lighting conditions, but alternating transdermal illumination at wavelengths of 365 nm and 480 nm blocks and unblocks TREK/TRESK currents in nociceptors. This wavelength tuned inhibition allows rapid, reversible control of pain in freely behaving mice and nematodes. Our findings reveal the subcellular distribution of TREK and TRESK channels at nociceptor free nerve endings and establish that their acute inhibition is sufficient to trigger pain perception. Furthermore, light control of nociceptive behavior in C. elegans demonstrates that TREK/TRESK orthologs act as transducers in conserved pain perception pathways. Finally, LAKI offers a non-invasive, physiological method to remotely control pain in naive animals, making it useful for pain research, analgesic drug screening in worms, and validation in mammals without requiring genetic manipulation or viral infection.

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