HHS Public Access

Author manuscript

Pain. Author manuscript; available in PMC 2016 June 20.

Published in final edited form as:

Pain. 2016 April ; 157(4): 786–787. doi:10.1097/j.pain.0000000000000490.

Keratinocytes as modulators of sensory afferent firing

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Skin keratinocytes release several neuroactivator compounds, eg, CGRP, ATP, acetylcholine, glutamate, growth factors and cytokines, in response to various stimuli.[3] Keratinocytes also express ligand-gated and voltage-gated ion channels and growth factor/cytokine receptors, suggesting complex autocrine and paracrine signaling occurs between epithelial cells and sensory afferents.[8] Furthermore, this signaling may change in chronic disease where inflammation, changes in nerve innervation, parathesias, pain/itch are common.[4,9,10]

1. Light-activated opsin proteins allow separable activation of neurons and keratinocytes

Understanding of neuro-epithelial communication in cutaneous sensory transduction has been hindered because of the complexity of the skin-neural interface. It is also impossible to apply natural (thermal, mechanical) stimuli in a manner that does not simultaneously affect both nerves and keratinocytes. To evaluate the contribution of each cell type to sensory transduction, optogenetic rodent models that target channelrhodopsin (ChR2), a blue light-gated cation channel, or halorhodopsin, a yellow light-stimulated chloride pump, to subsets of sensory neurons,[2,6] to Merkel cells,[5,7] or to epidermal keratinocytes1 are being used.

Blue light illumination of the skin of mice that expresses ChR2-YFP in sensory neurons causes robust nocifensive behaviors and light-induced action potential (AP) firing. However, neural responses to light differed from responses generated by direct stimulation of the skin,[1] eg, for Aδ-HTMRs, mechanical stimulation evoked a tonic response, whereas blue light evoked a phasic response. This suggests activation of intrinsic afferent properties is not sufficient to reproduce the firing pattern elicited by natural stimulation, ie, light stimulation of sensory fibers alone lacks a skin-specific signal that also contributes to the activation of sensory endings.

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The authors have no conflicts of interest to declare.

2. Opsins in keratinocytes

2.1. Light-mediated activation of ChR2 expressed in keratinocytes elicits nociceptive behavioral responses and action potential firing in nociceptor-type cutaneous afferents

Analysis of mice that express ChR2 exclusively in epidermal keratinocytes shows keratinocyte activation can induce afferent firing.[1] In response to blue light stimulation of the skin, K14-ChR2 mice exhibit nocifensive behaviors and AP firing in C-, HTMR-, and SA1-fiber subtypes. Interestingly, Aβ– and Aδ–LTMR fiber types were unresponsive to light stimulation of keratinocytes. These findings support a model in which neuroactivators released from activated ChR2-keratinocytes evoke AP firing in specific subtypes of cutaneous afferents.

2.2. Activation of halorhodopsin in keratinocytes blocks action potential firing in cutaneous afferents

Yellow light stimulation of keratinocytes that express the halorhodopsin chloride pump blocks AP firing in response to mechanical or heat stimulation. AP firing is decreased in C fibers, A-HTMRs, and SA1 fibers.[1]

Peripheral drivers of pain are located in both target tissues and sensory afferents. Mouse models that allow specific targeting of light-activated opsins to nonneuronal cells and specific neuronal populations will allow us to investigate the extent and nature of this communication and advance understanding of sensory transduction and how it changes in pathological states.

Acknowledgments

This work was supported by the National Institutes of Health Grant AR066371.

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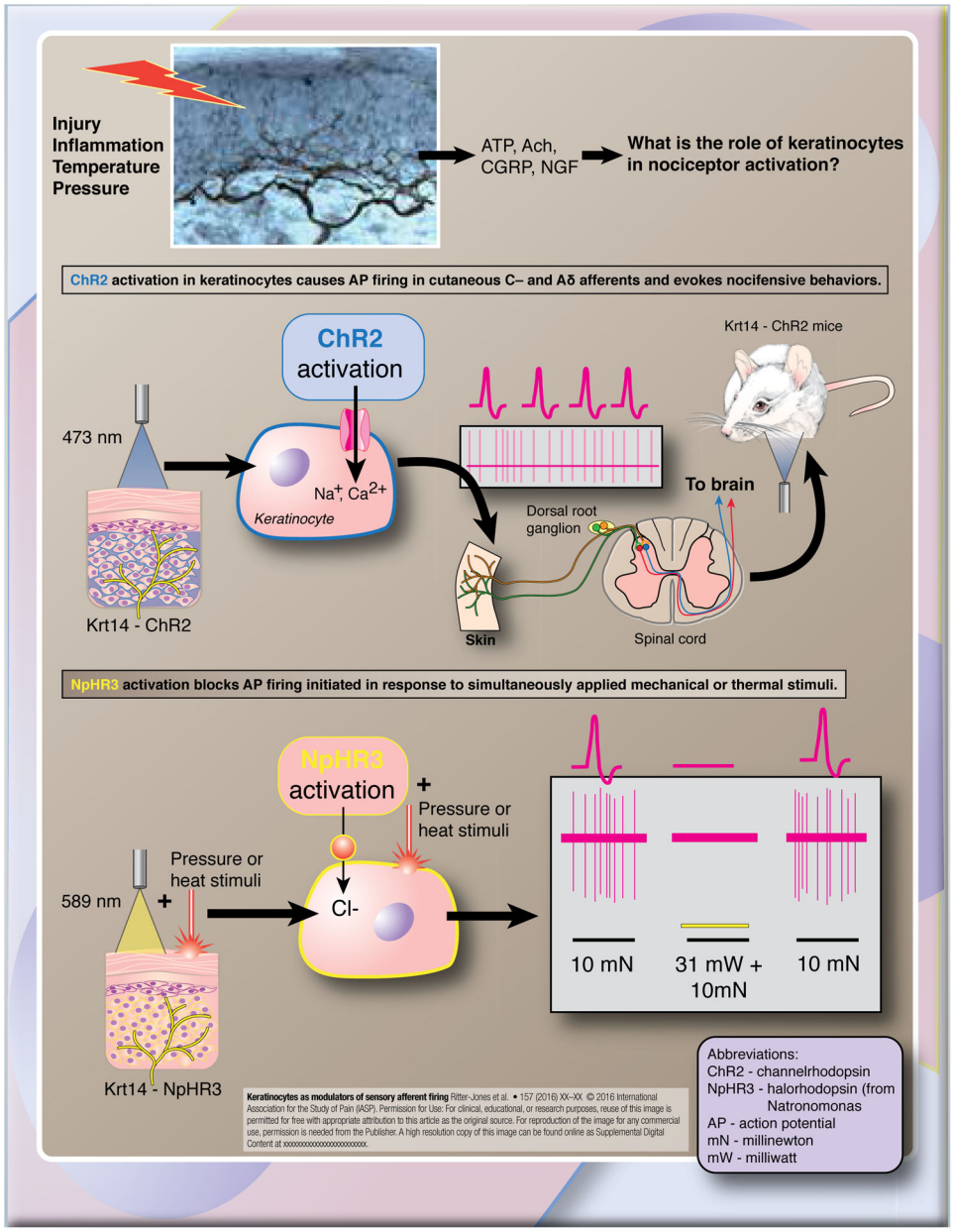

Figure.