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AUTOCOMMENTARY



Sensing the cold: TRP channels in thermal nociception

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Nociception, a mechanism evolutionarily conserved throughout Metazoa, mediates protective behavioral responses to a range of stimuli, including noxious temperatures, chemicals, and mechanical insults. Noxious stimuli are transduced by specialized high threshold sensory neurons known as nociceptors. Thermosensory nociception is essential for survival and provides a mechanism for perception of noxious thermal stimuli; it alerts the organism to potential environmental dangers and, coupled with pain sensation and complex behavioral responses, protects the organism from incipient damage.

Drosophila melanogaster is a powerful model organism for dissecting the cellular and molecular mechanisms regulating nociception.¹ In *Drosophila* larvae, 2 types of sensory neurons innervate the epidermis: type I neurons, which have a single ciliated dendrite, and type II neurons – known as multidendritic (md) neurons – which have characteristic naked dendritic projections to the epidermis, similar to vertebrate nociceptors. class IV (CIV) md neurons have been demonstrated to function as polymodal nociceptors for noxious heat and mechanical detection,¹ however the fundamental cellular and molecular mechanisms underlying noxious cold detection are poorly understood.

Transient Receptor Potential (TRP) channels, variably selective cation channels, have well documented roles in thermosensation, as well as nociception, albeit their roles in noxious cold detection are less well defined.² TRPM8 functions in detection of both innocuous and noxious cold in rodents,^{3,4} and TRPA1 has been implicated as a vertebrate noxious cold

receptor⁵; however, select cold-sensing neurons fail to express either of these TRP channels⁶ suggesting that other noxious cold-sensing channels exist. In *Drosophila*, the potential role of TRP channels in acute noxious cold sensing was unknown.

In a recent study,⁷ we identified the cellular basis for noxious cold detection, implicating the TRP channels Pkd2, NompC, and Trpm in regulating cold-evoked nociceptive behavioral responses. When challenged with temperatures at and below 14°C, *Drosophila* larvae execute a full-body contraction (CT) behavior along the head-to-tail axis. Optogenetic activation and synaptic blockade analyses reveal class III (CIII) md neurons function as primary noxious cold nociceptors required for cold-evoked CT response. Moreover, *in vivo* Ca²⁺ imaging demonstrates CIII neurons are specifically activated by cold stimulation.

Neurogenomic investigations reveal that CIII neurons are enriched for a suite of TRP channel genes and genetic analyses implicate members of 3 distinct TRP family subtypes in mediating cold-elicited CT behavior, including the TRPP molecule Pkd2, the TRPN molecule NompC, and the TRPM molecule Trpm. Among these, Pkd2 appears to have a more direct role in cold sensing as mutants exhibit a significant reduction in cold-evoked Ca²⁺ responses in CIII neurons, whereas overexpression of Pkd2 in non-cold sensing CIV md neurons confers cold sensitivity as measured by increased Ca²⁺ response (Fig. 1). In contrast to Ca²⁺ responses observed in *Pkd2* mutants, *Trpm* mutant larvae exhibited a significant increase, whereas *nompC* mutants exhibited a modest, but non-significant increase, suggesting potentially complex

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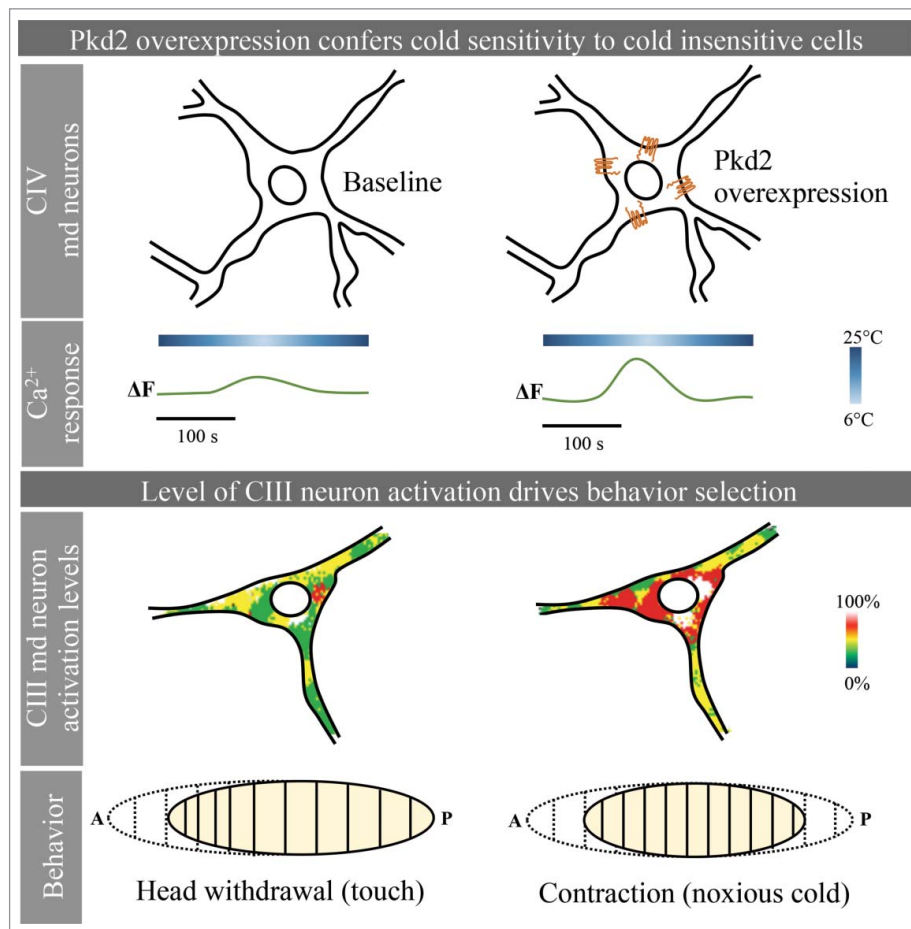


Figure 1. Pkd2 overexpression confers cold sensitivity (upper panel). Pkd2 overexpression in cold insensitive CIV neurons confers cold sensitivity as measured by increased GCaMP6 Ca^{2+} responses relative to baseline (ΔF). CIII neuron activation levels drive behavioral selection in response to gentle touch vs. noxious cold (lower panel). The magnitude of CaMPARI Ca^{2+} response reveals low-level activation evokes HW behavior, while high-level activation elicits CT behavior. Abbreviations: ΔF (change in fluorescence); A (anterior); P (posterior).

roles for these TRPs in regulating Ca^{2+} homeostasis in response to noxious cold exposure.

Intriguingly, previous analyses revealed that NompC functions in CIII neurons to mediate gentle touch mechanosensation.⁸ In contrast to cold-elicited CT behavior, the predominant larval response to gentle touch is a head withdrawal (HW). We independently confirmed NompC function in gentle touch mechanosensation, thereby demonstrating that CIII neurons are multimodal for noxious cold and gentle touch, and that the response to both sensory stimuli requires NompC. We also discovered that *Pkd2* and *Trpm* mutant larva displayed mechanosensory defects. Thus, like NompC and CIII neurons, these TRP channels are themselves multimodal and respond to innocuous touch and noxious cold. To elucidate how CIII neurons may discriminate between gentle touch and noxious cold in terms of driving distinct sensory

behaviors (HW vs. CT, respectively), we performed optogenetic dose response assays revealing that CIII-mediated behavior selection is regulated in a dose-dependent fashion – CT is the predominant behavior at high levels of optogenetic stimulation, and HW at low levels. These analyses suggest that CIII neurons may be high threshold cold nociceptors and low threshold mechanosensors. To investigate that question we performed CaMPARI-mediated Ca^{2+} analyses demonstrating that cold more robustly activates CIII neurons relative to gentle touch. Therefore, CIII-mediated multimodal behavior is dependent upon activation levels (Fig. 1). Given the requirement for Pkd2, NompC, and Trpm in both behaviors, perhaps these channels may exhibit different biophysical properties (e.g. gating/ion permeation) in response to diverse sensory stimuli, thereby modulating behavioral selection. Alternatively, or in concert, these TRP

channels may coordinate with different sets of partially overlapping channels or transporters to perform distinct cellular functions, such as regulation of ionic homeostasis, that ultimately impact behavioral output. These questions merit further consideration.

The present study⁷ establishes a genetically tractable platform for elucidating conserved molecular bases of cold nociception and for revealing generalizable mechanisms underlying TRP channel mediated multimodality. The novel assays implemented in this work should also prove powerful tools in unraveling the neural circuit architecture by which complex multimodal stimuli are processed to drive behavioral selection. Finally, the identification of Pkd2 in multimodal sensory function may have diagnostic or clinical implications as disruptions in this gene are causatively linked to autosomal dominant polycystic kidney disease; however, it is presently unknown whether patients having this common monogenic disorder have defects in cold thermosensation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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