MECHANOSENSING DENDRITES

The elegance of prickly sensations

Neurons sensing harmful mechanical forces in the larvae of fruit flies have a striking architecture of dendrites that are optimized to detect pointy objects.

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How do we distinguish between being poked by something benign like a cotton swab and a sharp nail that could harm us? This is achieved through neurons lying beneath our skin called nociceptors which are tuned to detect painful, or noxious, stimuli (Basbaum et al., 2009). A lot of what is known about nociceptors comes from studying cells called class IV dendritic arborization neurons (or cd4a neurons for short) in larvae of the fruit fly Drosophila melanogaster (Grueber et al., 2002).

Protruding from the cell body of cd4a neurons is a mesh of branches known as dendrites, which can sense noxious environmental cues (Tracey, 2017). This includes the ovipositor of parasitic wasps, a needle-like structure used to lay eggs in live hosts. When the larvae feel the mechanical pressure of the ovipositor poking their skin, they react by rolling away to escape being punctured by the wasp (Figure 1A). However, it is poorly understood how these sensory neurons with their astounding architecture can capture such potentially life-threatening mechanical forces.

As shown by the famous drawings of the neuroscientist Santiago Ramón y Cajal, cells in the nervous system come in a range of shapes and sizes. One might therefore wonder whether the elegant structure of cd4a neurons allows them to perform their sophisticated mechanosensing role. Now, in eLife, Xin Liang and colleagues from Tsinghua University – including Zhen Liu and Meng-Hua Wu as joint first authors – report that cd4a dendrites are pressure sensors which are shaped and tuned to maximize detection of local mechanical forces (Liu et al., 2022).

The team designed and built an experimental setup to monitor the activity of cd4a neurons in semi-intact preparations preserving the ‘skin’ of the larvae (containing the epithelial cell layer, sensory neurons and muscle cells) as well as their nervous system. The cd4a neurons were then imaged to see how they responded to different sized probes that were applied with varying force to dendrites that were either close (proximal) to the cell body of the neuron (the soma) or were far away (distal) from the soma, of the neuron. This revealed that cd4a dendrites were more sensitive to small probes (30µm), which could even be sensed by dendrites outside the local area of where the force was applied.

To find out if the dendritic architecture of cd4a neurons is required for sensing localized forces, the team studied larvae lacking the gene for cut, a transcription factor that gives the neurons their complex structure. The cd4a neurons of the mutant larvae were less responsive to small probes applied to their distal dendrites, and the larvae displayed reduced rolling escape behavior.

Using mathematical simulations, Liu et al. showed that their probe exerted both a perpendicular pressure at its tip, and lateral forces up...
Figure 1. Sensing noxious touch in *Drosophila* larvae. (A) Schematic of a *Drosophila* larva with nociceptive cells called c4da neurons covering its entire body. The c4da neurons can sense noxious touch (here provided by a small diameter probe) resulting in the larva undergoing a rolling escape response. (B) Schematic side view of c4da neurons in the larval body sandwiched between the epidermal cell layer (beige) and the extracellular matrix (green). The noxious touch of the probe deforms the body wall including c4da dendrites and generates perpendicular and lateral forces (indicated by arrows) (C) The force applied by the probe (yellow-blue color code) activates c4da neurons by triggering two mechanosensory channels – Ppk1/Ppk26 (cyan) and Piezo (red) – located on its dendrites. Voltage-gated calcium channels (grey) then allow information to reach the soma so they can elicit a response in the c4da neuron soma.

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Mechanosensing channels are crucial for sensing the local stimuli applied to dendritic branches, but how is this information reaching the cell body of the neuron? Liu et al. found that voltage-gated calcium channels – which when open permit an influx of calcium – play a critical role in this process. In their experiments, low doses of a drug that inhibits these voltage-gated calcium channels strongly affected calcium responses in the neurons when the mechanical stimulus targeted dendrites further away from the soma, suggesting decreased information flow. Further experiments revealed a specific
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References

Basbaum AI, Bautista DM, Scherrer G, Julius D. 2009. Cellular and molecular mechanisms of pain. Cell 139:267–284. DOI: https://doi.org/10.1016/j.cell.2009.09.028, PMID: 19837031

Gorzyczka DA, Younger S, Meltzer S, Kim SE, Cheng L, Song W, Lee HY, Jan LY, Jan YN. 2014. Identification of Ppk26, a DEG/ENaC channel functioning with Ppk1 in a mutually dependent manner to guide locomotion behavior in Drosophila. Cell Reports 9:1446–1458. DOI: https://doi.org/10.1016/j.celrep.2014.10.034, PMID: 25456135

Grueber WB, Jan LY, Jan YN. 2002. Tiling of the Drosophila epidermis by multidendritic sensory neurons. Development 129:2867–2878. DOI: https://doi.org/10.1242/dev.129.12.2867, PMID: 12050135

Guo Y, Wang Y, Wang Q, Wang Z. 2014. The role of PPK26 in Drosophila larval mechanical nociception. Cell Reports 9:1183–1190. DOI: https://doi.org/10.1016/j.celrep.2014.10.020, PMID: 25457610

Han C, Wang D, Soba P, Zhu S, Lin X, Jan LY, Jan YN. 2012. Integrons regulate repulsion-mediated dendritic patterning of Drosophila sensory neurons by restricting dendrites in a 2D space. Neuron 73:64–78. DOI: https://doi.org/10.1016/j.neuron.2011.10.036, PMID: 22243747

Jiang N, Rasmussen JP, Clanton JA, Rosenberg MF, Luedke KP, Cronan MR, Parker ED, Kim H-J, Vaughan JC, Sagasti A, Parrish JZ. 2019. A conserved morphogenetic mechanism for epidermal ensheathment of nociceptive sensory neurites. eLife 8:e42455. DOI: https://doi.org/10.7554/eLife.42455, PMID: 30855229

Kim SE, Coste B, Chada B, Cook B, Patapoutian A. 2012a. The role of Drosophila Piezo in mechanical nociception. Nature 483:209–212. DOI: https://doi.org/10.1038/nature10801

Kim ME, Shrestha BR, Blazeski R, Mason CA, Grueber WB. 2012b. Integrons establish dendrite-substrate relationships that promote dendritic self-avoidance and patterning in Drosophila sensory neurons. Neuron 73:79–91. DOI: https://doi.org/10.1016/j.neuron.2011.10.033

Liu Z, Wu MH, Wang QX, Lin SZ, Feng XQ, Li B, Liang X. 2014. Drosophila mechanical nociceptors preferentially sense localized poking. eLife 9:e65987. DOI: https://doi.org/10.7554/eLife.65987, PMID: 25454784

Mauthner S, Huang Y, Lewis AH, Xiao Q, Tsubouchi A, Wang Y, Honko K, Skene JHP, Grandl J, Tracey WD Jr. 2014. Balboa binds to pickpocket in vivo and is required for mechanical nociception in Drosophila larvae. Current Biology 24:2920–2925. DOI: https://doi.org/10.1016/j.cub.2014.10.038, PMID: 25454784

Mikesell AR, Isaeva O, Moehring F, Sadler KE, Menzel AD, Stucky CL. 2022. Keratinocyte PIEZO1 modulates cutaneous mechanosensation. eLife 11:e65987. DOI: https://doi.org/10.7554/eLife.65987, PMID: 36053009

Tracey WD. 2017. Nociception. Current Biology 27:R129–R133. DOI: https://doi.org/10.1016/j.cub.2017.01.037, PMID: 28222285

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