Sensory response to environmental stimuli modulated by form of vitamin B3 in worms

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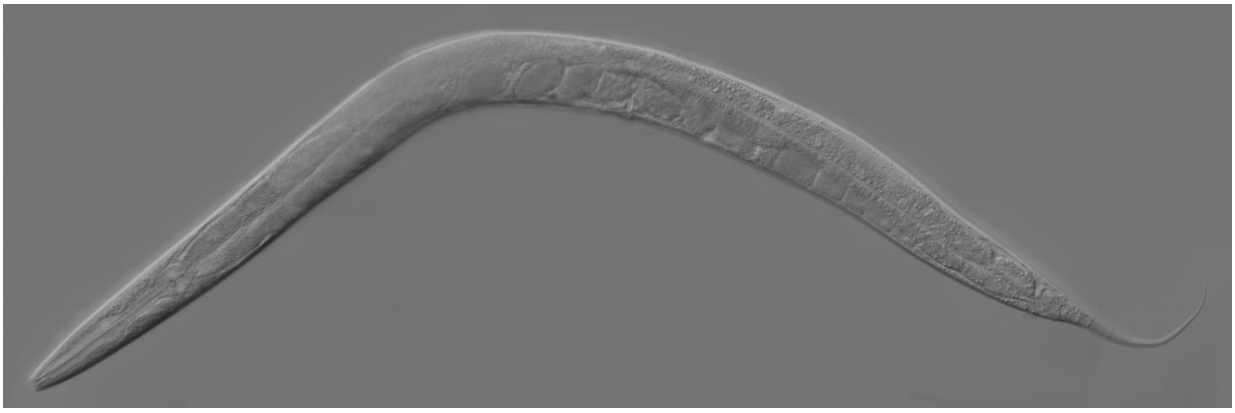

Adult *Caenorhabditis elegans* worm. A form of vitamin B3, nicotinamide, modulates the worm's sensory response to environmental stimuli. Credit: Kbradnam, CC 2.5

Experiments show that too much of a form of vitamin B3—nicotinamide—that is produced naturally inside of cells can lead to cell death in certain sensory cells and cause behavioral changes in the worm, *Caenorhabditis elegans*. The research, by a team of Penn State scientists, shows that excess nicotinamide causes overactivity of the TRPV ion channel that is involved in sensory perception by controlling the movement of certain charged particles in and out of cells. The work also provides clues to the mechanism causing the cells to die, and links these cellular processes to behavior. A paper describing the research is

published in the October 12, 2016 edition of the journal *Nature Communications*.

"We didn't set out to study the TRPV ion channel, but we found out that vitamin B3 is having physical and behavioral effects on the worm that we study and when we followed these effects using genetics we found that the nicotinamide form of vitamin B3 is toxic to certain cells that use the TRPV ion channel," said Wendy Hanna-Rose, associate professor of biochemistry and molecular biology at Penn State and the lead author of the study. "We were able to show that nicotinamide is an agonist of the TRPV channel—it causes it to be overactive—which causes the cells to die. What's really cool about this is the idea that the TRPV ion channel which is involved in sensory perception—it responds to things like pain, touch, or temperature changes—is regulated by a natural byproduct of the cell's metabolism which in turn influences the worm's behavior."

The research team had previously shown that when a gene, pnc-1, that is involved in nicotinamide metabolization in cells is mutated in the worm, nicotinamide can build up to ten times its normal level in sensory cells in the worm's uterus, causing the cells to die. In the current paper, the researchers experimentally expose the worms to excess nicotinamide and identify another type of sensory nerve cell that dies from the resulting overactivity of the TRPV channel.

The two cell types affected by nicotinamide share the expression of the genes osm-9 and ocr-4—two of the several genes that encode TRPV ion channel subunits in worms. The researchers labeled these two genes with a fluorescent marker and showed that the overactive TRPV channel in the cells is made up of two copies each of the proteins encoded by these two genes.

"We intuitively understand that metabolism can affect a sensory input—how good something smells might be affected by how hungry

you are—but we don't know much about how that happens," said Hanna-Rose. "With this research we are opening a door to identifying a mechanism for how a cell's metabolic state can directly affect a sensory channel."

Because the TRPV ion channel is involved in sensory perception, the researchers next explored whether cell death as a result of overexposure to nicotinamide effects the worm's behavior. The nerve cells that die are exposed to the environment through the worm's nose and are used by the worm to sense food while foraging. Worms exposed to excess nicotinamide, either experimentally or by mutation of the pnc-1 gene, expressed an abnormal head-bending behavior while foraging compared to wild-type worms. The researchers also linked an egg-laying defect in the worms to the excess nicotinamide and overactive TRPV channels.

The researchers also showed that the ability of nicotinamide to overexcite the TRPV channel is evolutionarily conserved. They exposed larvae of the fly, Drosophila melanogaster, to nicotinamide and found that the response of the larvae to vibration was reduced. This mirrored the effect of loss-of-function mutations to the fly versions of the TRPV genes, but it did not result in cell death.

"TRPV ion channels are not just evolutionarily conserved in worms and flies," said Hanna-Rose. "These sensory receptors are found in mammals as well—capsaicin receptors for example—and many others like them. Our work opens a new avenue for studying the mechanism by which these receptors function, showing that they can be regulated by naturally occurring products of a cell's metabolism"

More information: "Nicotinamide is an endogenous agonist for a C. elegans TRPV OSM-9 and OCR-4 channel," DOI: 10.1038/ncomms13135

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