Deprived of a sense of smell, worms live longer

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Many animals live longer when raised on low calorie diets. But now researchers at Washington University School of Medicine in St. Louis have shown that they can extend the life spans of roundworms even when the worms are well fed — it just takes a chemical that blocks their sense of smell.

Three years ago, the researchers, led by Kerry Kornfeld, M.D., Ph.D., reported they found that a class of anticonvulsant medications made the roundworm *Caenorhabditis elegans* live longer. But until now, they didn't quite know what the drugs did to give the worms their longevity. They report their latest findings in the Oct. 24 issue of the *Public Library of Science Genetics*.

"We've learned that the drugs inhibit neurons in the worm's head that sense chemicals in their surroundings — the neurons are like the worm's nose," says Kornfeld, professor of developmental biology. "Like roundworms that are grown in a food-scarce environment, the worms exposed to the anticonvulsant ethosuximide lived longer. But these worms ate plenty of food. That suggests that the worms' sensation of food is critical to controlling their metabolism and life span."

If roundworms sense that food is abundant, their metabolism adjusts accordingly. Their bodies respond to promote rapid ingestion, rapid growth and rapid aging, Kornfeld explains. In contrast, when the worms sense a shortage of food, they make "metabolic decisions" to delay growth, delay energy use and extend lifespan.

In the long term, Kornfeld's goal is to identify compounds that could potentially delay human aging. The research group for this project also included James Collins, Ph.D., Kim Evason, M.D., Ph.D., Chris Pickett, Ph.D., and Daniel Schneider.

Kornfeld's lab studies *C. elegans* because they live only about two to three weeks, so experimental results can be obtained quickly. In addition, the worms' genome has been sequenced and extensively studied.

The scientists' strategy has been to expose the roundworms to libraries of chemicals to identify compounds that delay aging and extend their lives. That approach led to the unexpected result that some human anticonvulsants slow aging in *C. elegans*.

Now, further investigating the effect of one of those compounds, ethosuximide, the researchers found that it had the same life-extending effect as some well-studied genetic mutations in *C. elegans*. These mutations inhibit the activity of some sensory neurons in the worm, and that helped the researchers conclude that ethosuximide also directly affected these neurons. Roundworms treated with ethosuximide lived up to 29 percent longer than normal.

"Now we know what cells ethosuximide targets in *C. elegans*," Kornfeld says. "It's likely that the drug prevents the nerve cells from being electrically active, but precisely how it does that is something we need to study further. We also want to find out how the effect on the neurons is translated into an effect on the worms' bodies to delay aging."

Ethosuximide is used to treat seizure disorders in people. Interestingly, a common side effect of the drug is the loss of the sense of taste. Does that mean the ability to taste or smell food affects aging in people? It's probably not that simple, but it does hint at some sort of connection,

Kornfeld says. He says it's possible that sensory perception cues have important metabolic consequences independent of what we actually eat.

"Emerging evidence suggests that core metabolic pathways that modulate lifespan in worms also modulate lifespan in vertebrates such as mice and perhaps humans," Kornfeld says. "Sensory pathways might also be fairly universal. In an ancient common ancestor, these pathways might have caused metabolic adjustments that affect lifespan. That could be reflected in our own biology."

Source: Washington University School of Medicine