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Can we extend healthspan by altering the perception of food?

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Researchers at the Buck Institute have shown a new effect on aging via a small drug-like molecule that alters the perception of food in the nematode *C. elegans*. Publishing in *Aging Cell*, researchers "tricked" the worm's metabolism into a state of caloric restriction, extending the animal's lifespan by 50 percent. The study provides a new avenue of inquiry for researchers around the world who are attempting to develop human drugs that mimic the positive effects of a Spartan diet. Caloric restriction has shown to extend life-and-healthspan in simple animals and mice.

"This small molecule blocks the detection of food in the worm's mouth," said Buck faculty and senior author Gordon Lithgow, PhD. "The worm senses that its mouth is empty even when it is full of food, tricking the animal into shifting its physiology into a caloric restricted-state even when it's eating normally," he said. "Our study suggests that primary sensory pathways represent new targets for human pharmacology."

Lead author Mark Lucanic, PhD, a postdoctoral research fellow in the Lithgow lab, screened 30,000 synthetic, drug-like compounds in nematodes and identified several structurally related compounds that acted on mechanisms tied to caloric restriction. He found that the small molecule, NP1, impinged upon a food perception pathway by promoting glutamate signaling in the pharynx of the animal. "The chemical activated a neurotransmitter-controlled food deprivation signal which altered the animal's normal metabolism into a caloric restriction state," Lucanic said.

Lithgow said exploring sensory pathways as potential drug targets should be of interest to age researchers interested in mimicking caloric restriction in order to extend healthspan. "The mechanisms involved in sensory pathways may be more specific than secondary pathways that detect energy levels or absorbed nutrients at the cellular level," he said, noting the current interest in intracellular pathways such as mTOR and AMPK which are under study in many labs around the world. "Targeting sensory pathways may lead to a more rapid response to changing diet," said Lithgow, "Altering these higher level, specific response mechanisms may also have fewer effects on other systems in the body."

Lucanic will work on identifying the specific molecule that NP1 activates in the sensory pathway in the worm. He also hopes to look at 59 other synthetic compounds that "hit" known aging pathways during his initial screening process. Lithgow said this study highlights the need to bring more resources to the effort to test promising compounds, "Aging researchers have found scores of both natural and synthetic compounds that affect aging in simple animals - I tell people that we have at least 100 of those compounds in our freezer and that any one of them could hold the key to extending human healthspan," he said. "We want to look at all of them, but we can only do what our resources will allow."

More information: Mark Lucanic et al, Chemical activation of a food deprivation signal extends lifespan, *Aging Cell* (2016). DOI: 10.1111/acel.12492

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