Endocannabinoid signaling in dietary restriction and lifespan extension

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There is no longer any doubt that dietary restriction (DR) extends lifespan. Many studies have shown that limiting nutrient intake extends lifespan in yeast, worms, flies and as well as postponing age-related diseases in mice. However, scientists are still puzzling over the exact mechanism of DR, convinced its secrets are the key to new therapies for diseases such as Alzheimer's, Parkinson's and even cancer. Research involving the nematode C. elegans at the Buck Institute for Research on Aging sheds new light on a possible mechanism of DR – revealing that a group of lipid signaling molecules called N-acylethanolamines (NAEs) informs the animal of limited or ample nutrients and helps regulate the worm's aging response to changes in its diet. Some of these worm (NAE's) are similar to endocannabinoids in humans, where they regulate many different physiological processes including nutrient intake and energy balance. Thus the link between endocannabinoids, DR and aging could be conserved among species. The study appears in the May 12th edition of *Nature*.

"This is a missing piece of the DR puzzle. We are now getting into the mechanics of the process," said Matthew S. Gill, PhD, who led the research. Gill, formerly an assistant research professor at the Buck Institute is now an assistant professor at The Scripps Research Institute in Jupiter, FL. In the study, Gill and his Buck Institute colleagues showed that NAE abundance in the worms is reduced during periods of dietary restriction, and that NAE deficiency in the presence of abundant food is sufficient to extend the animals lifespan.

According to Gill and Mark Lucanic, PhD, a Postdoctoral Fellow at the Buck and lead author of the study, most research on DR has focused on identifying individual proteins and genes that are players in the process. Gill said this new research identifies a novel small molecule signaling pathway in the worm that coordinates how the worm responds to being in environments of limited or abundant food. "The message about nutrient availability needs to be sent to every cell in the worm's body -- those types of messages tend to be delivered by small molecules, such as hormones and lipid-derived molecules like N-acyl ethanolamines and endocannabinoids."

Lucanic says up until this point, researchers did not think that short-lived nematode worms, used world-wide to study lifespan, had an endocannabinoid system. Even though specific endocannabinoid receptors have yet to be identified in the worm, Lucanic says there is no doubt the worm has components of an endocannabinoid system. "This research provides a new model -- an easily manipulated model for researchers who are studying N-acyl ethanolamines or endocannabinoids," said Lucanic.

Endocannabinoids are active in almost every system in mammalian physiology and have been implicated in learning and memory, appetite and energy metabolism, blood pressure, inflammation and bone growth among others. However, the new research opens up the possibility that NAEs and endocannabinoids influence aging in mammals as well. "There is a lot of interest in developing drugs that mimic the effects of DR, without patients having to reduce calories," said Lucanic. "This research shows that endocannabinoids should be added to the list of drug targets for aging."

More information: "N-Acylethanolamine Signaling Mediates the Effect of Diet on Lifespan in C. elegans," *Nature* (2011)

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