Dietary restriction can improve learning in worms

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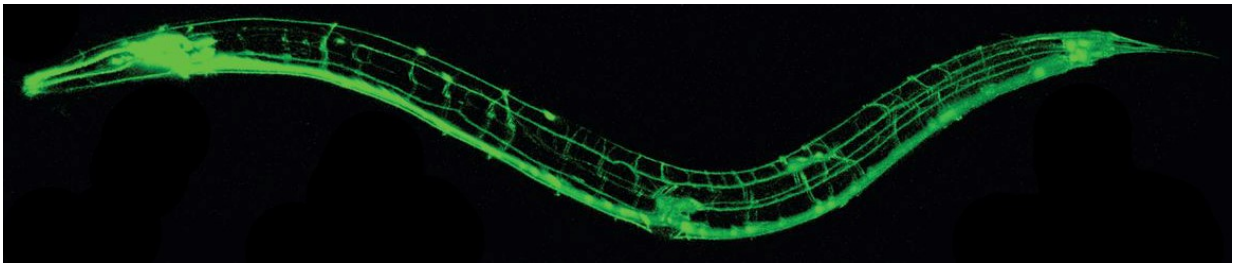

Body of the worm *Caenorhabditis elegans* with the entire nervous system visualized using green fluorescent protein. Credit: Hang Ung, Jean-Louis Bessereau laboratory, France

Dietary restriction - the reduction of a specific nutrient or total dietary intake without triggering malnutrition—increases longevity and improves learning, but are these processes regulated separately? A new study publishing on August 1 in the open access journal *PLOS Biology* by Mihir Vohra, Kaveh Ashrafi and colleagues at the University of California at San Francisco, indicates that the answer is "yes." The team shows that depletion of a single amino acid metabolite improves learning in an experimental animal, but has no effect on lifespan.

Reducing food intake is thought to improve cellular health in multiple ways, which are believed to contribute to the increase in longevity in animals deprived of calories over long periods. To explore neuron-

specific effects of dietary restriction, the authors used the nematode worm Caenorhabditis elegans as a model organism to test how food deprivation affected the ability of these animals to learn an association between a food source and a smelly chemical called butanone.

The authors found that dietary restriction increased the worm's ability to form associations (a type of learning) with butanone. The neurons responsible for the association are activated by the neurotransmitter glutamate, and the authors showed that kynurenic acid, a metabolic product of the amino acid L-tryptophan which inhibits glutamate signaling, could dampen the learning process. Dietary restriction improves learning by reducing levels of kynurenic acid. Reducing levels of kynurenic acid by knocking out a gene that regulates its production increased learning even in the absence of dietary restriction, and without increasing longevity, indicating that the learning pathway was distinct from the overall longevity effects of dietary restriction. The authors also showed that several molecular pathways known to be involved in diet-induced longevity, including insulin signaling, increased learning by altering the genes that regulate production of kynurenic acid.

According to the model proposed by the authors, restricted access to food limits the production of kynurenic acid, reducing the ability of this metabolite to inhibit glutamate signaling. This increases neuronal activity and increases learning. The results suggest that although dietary restriction exerts its effects on the organism through multiple independent pathways, the learning-specific effects can be separated from those acting on other aspects of cellular and organismic function, such as ageing.

"The kynurenic acid pathway and the inhibitory effects of the compound are also found in mammals," Ashrafi noted. "But it remains to be determined whether kynurenic acid influences learning in mammals as directly as it does in worms, and whether manipulation of the pathway

might offer new opportunities for therapeutic intervention in human disorders."

More information: Vohra M, Lemieux GA, Lin L, Ashrafi K (2017) The beneficial effects of dietary restriction on learning are distinct from its effects on longevity and mediated by depletion of a neuroinhibitory metabolite. *PLoS Biol* 15(8): e2002032. doi.org/10.1371/journal.pbio.2002032