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Reducing caloric intake delays nerve cell loss

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To delay the onset of neurodegeneration, mice have the option to undergo a regimen of caloric restriction (represented by the scale) or a pharmacological treatment with a SIRT1-activation compound (SRT), both of which result in reduced memory loss and preserved synaptic plasticity. Credit: Li-Huei Tsai, Ph.D.

Activating an enzyme known to play a role in the anti-aging benefits of calorie restriction delays the loss of brain cells and preserves cognitive function in mice, according to a study published in the May 22 issue of *The Journal of Neuroscience*. The findings could one day guide

researchers to discover drug alternatives that slow the progress of age-associated impairments in the brain.

Previous studies have shown that reducing calorie consumption extends the lifespan of a variety of species and decreases the brain changes that often accompany aging and neurodegenerative diseases such as Alzheimer's. There is also evidence that caloric restriction activates an enzyme called Sirtuin 1 (SIRT1), which studies suggest offers some protection against age-associated impairments in the brain.

In the current study, Li-Huei Tsai, PhD, Johannes Gräff, PhD, and others at the Picower Institute For Learning and Memory, Massachusetts Institute of Technology, and Howard Hughes Medical Institute, tested whether reducing caloric intake would delay the onset of nerve cell loss that is common in neurodegenerative disease, and if so, whether SIRT1 activation was driving this effect. The group not only confirmed that caloric restriction delays nerve cell loss, but also found that a drug that activates SIRT1 produces the same effects.

"There has been great interest in finding compounds that mimic the benefits of caloric restriction that could be used to delay the onset of age-associated problems and/or diseases," said Luigi Puglielli, MD, PhD, who studies aging at the University of Wisconsin, Madison, and was not involved in this study. "If proven safe for humans, this study suggests such a drug could be used as a preventive tool to delay the onset of neurodegeneration associated with several diseases that affect the aging brain," Puglielli added.

In the study, Tsai's team first decreased by 30 percent the normal diets of mice genetically engineered to rapidly undergo changes in the brain associated with neurodegeneration. Following three months on the diet, the mice completed several learning and memory tests. "We not only observed a delay in the onset of neurodegeneration in the calorie-

restricted mice, but the animals were spared the learning and memory deficits of mice that did not consume reduced-calorie diets," Tsai explained.

Curious if they could recreate the benefits of caloric restriction without changing the animals' diets, the scientists gave a separate group of mice a drug that activates SIRT1. Similar to what the researchers found in the mice exposed to reduced-calorie diets, the mice that received the drug had less cell loss and better cellular connectivity than the mice that did not receive the drug. Additionally, the mice that received the drug treatment performed as well as normal mice in learning and memory tests.

"The question now is whether this type of treatment will work in other animal models, whether it's safe for use over time, and whether it only temporarily slows down the progression of neurodegeneration or stops it altogether," Tsai said.

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