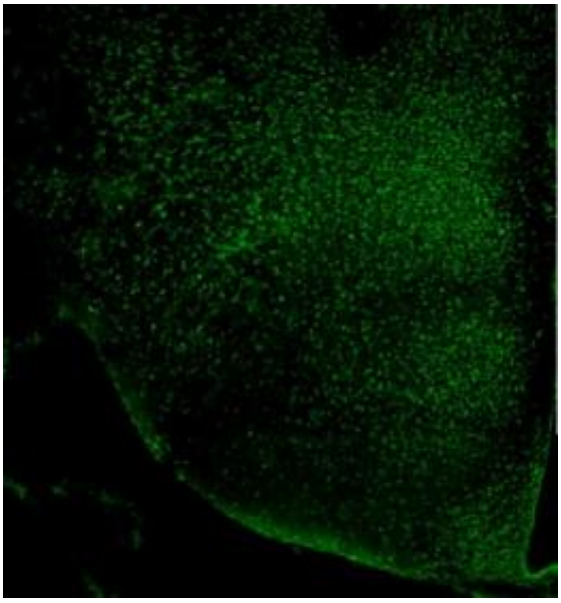
MedicalXpress

Aging and longevity tied to specific brain region in mice

July 28 2010



A green stain lights up a protein tied to aging, showing that it is abundant in the hypothalamus region of mice brains. Credit: Shin-ichiro Imai, Washington University in St. Louis

Researchers watched two groups of mice, both nearing the end of a two-day fast. One group was quietly huddled together, but the other group was active and alert. The difference? The second set of mice had been engineered so their brains produced more SIRT1, a protein known to play a role in aging and longevity.

"This result surprised us," says the study's senior author Shin-ichiro Imai,

MD, PhD, an expert in aging research at Washington University School of Medicine in St. Louis. "It demonstrates that SIRT1 in the brain is tied into a mechanism that allows animals to survive when food is scarce. And this might be involved with the lifespan-increasing effect of low-calorie diets."

Imai explains that the mice with increased brain SIRT1 have internal mechanisms that make them use energy more efficiently, which helps them move around in search of food even after a long fast. This increased energy-efficiency could help delay aging and extend lifespan.

The research findings are published in the July 28 issue of the Journal of Neuroscience.

Imai's past research demonstrated that SIRT1 is at the center of a network that connects metabolism and aging. A form of the gene is found in every organism on earth. The gene coordinates metabolic reactions throughout the body and manages the body's response to nutrition. SIRT1 is activated under low-calorie conditions, which have been shown to extend the life spans of laboratory animals.

The researchers found that the key to the mice's extra activity lies in a small region of the brain called the hypothalamus, which controls basic life functions such as hunger, body temperature, stress response and sleep-wake cycles.

At the start of the research project, the study's lead author Akiko Satoh, PhD, a postdoctoral research associate in developmental biology, saw that mice on low-calorie diets had increased amounts of SIRT1 in specific regions of the hypothalamus and that neurons in the same regions were activated.

So the research team developed mice that continually produced higher

amounts of SIRT1 in their brains to see what the effect would be. That's when Satoh observed the mice's unusual level of activity under fasting conditions.

"This is the first time that it has been demonstrated that SIRT1 is a central mediator for behavior adaptation to low-calorie conditions," Satoh says.

Interestingly, these mice, called BRASTO (brain-specific SIRT1-overexpressing) mice, also maintained higher body temperatures after a 48-hour fast than ordinary mice, which experience a drop in body temperature during fasting.

"The BRASTO mice have a better capability to come up with energy to achieve a higher body temperature and increased activity level when food is restricted," says Imai, associate professor of developmental biology and of medicine.

The team also examined mice that had no ability to produce SIRT1 in their brains. During diet-restricting conditions, these mice did not increase their activity, and their body temperature dropped more than normal, giving further evidence that SIRT1 was essential for high-activity, high-temperature responses.

As the researchers looked further into the role of SIRT1 in the hypothalamus, they found that during diet restriction, SIRT1 enhanced the production of a specific neural receptor in the hypothalamus involved in regulating metabolic rate, food intake and insulin sensitivity. Furthermore, mice with increased brain SIRT1 had a higher neural response to the gut hormone, ghrelin, which is known to stimulate the hypothalamus during low-calorie conditions. Both findings add weight to a significant role for SIRT1 in the hypothalamic response to a restricted diet.

The scientists are continuing to study the BRASTO mice to see if they live longer than ordinary mice.

Their work suggests that the brain, and particularly the hypothalamus, might play a dominant role in governing the pace of aging. They believe their studies could eventually provide clues for increasing productive aging in people.

"If we can enhance the function of the human hypothalamus by manipulating SIRT1, we could potentially overcome some health problems associated with aging," Imai says. "One example is anorexia of aging in which elderly people lose the drive to eat. It is possible that enhancing SIRT1 could alleviate behavioral problems like this."

More information: Satoh A, Brace CS, Ben-Josef G, West T, Wozniak DF, Holtzman DM, Herzog ED, Imai S. SIRT1 promotes the central adaptive response to diet restriction through activation of the dorsomedial and lateral nuclei of the hypothalamus. Journal of Neuroscience. July 28, 2010.

Provided by Washington University School of Medicine