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Caloric restriction can be beneficial to the brain, study shows

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Studies of different animal species suggest a link between eating less and living longer, but the molecular mechanisms by which caloric restriction affords protection against disease and extends longevity are not well understood.

New clues to help solve the mystery are presented in an article published in the September issue of *Aging Cell* by scientists at the Center for Research on Redox Processes in Biomedicine (Redoxoma), one of the Research, Innovation and Dissemination Centers (RIDCs) funded by FAPESP.

The results of in vitro and in vivo experiments performed by the Redoxoma team included the finding that a 40% reduction in dietary caloric intake increases mitochondrial calcium retention in situations where intracellular calcium levels are pathologically high. In the brain, this can help avoid the death of neurons that is associated with Alzheimer's disease, Parkinson's disease, epilepsy and stroke, among other neurodegenerative conditions.

Mitochondria are organelles that keep cells full of energy and regulate cellular metabolism.

"More than promoting the advantages of eating frugally, we aim to understand the mechanisms that make not overconsuming calories better for health. This can point to new targets for the development of drugs against various diseases," said Ignacio Amigo, lead author of the article.

The investigation was conducted at the University of São Paulo's Chemistry Institute (IQ-USP) in Brazil during Amigo's postdoctoral research.

According to Amigo, calcium participates in the process of communication between neurons. However, Alzheimer's disease and other neurological disorders can cause an excessive influx of calcium ions into brain cells due to overactivation of neuronal glutamate receptors. This condition, known as excitotoxicity, can damage and even kill neurons.

To verify the effect of caloric restriction on excitotoxicity, Redoxoma's scientists compared two groups of mice and rats. The control animals were given food and water ad libitum for 14 weeks and were overweight at the end of the experiment. The other group received a 40% caloric restriction (CR) diet for the same period.

"We calculated the daily amount of calories consumed on average by the control group and offered the other group 40% less," Amigo explained. "They didn't become underweight and remained healthy, although we supplemented their diet with vitamins and minerals to avoid malnutrition due to the restricted amount of food."

In the first test, the animals were injected with kainic acid, a glutamate analogue with a similar effect in terms of inducing neuronal calcium influx, albeit more persistent. In rodents, it can cause brain damage, seizures and neuronal cell death due to overactivation of glutamate receptors in the hippocampus. It is used in the laboratory to mimic epilepsy.

"We administered a small dose to avoid killing the animal. Even so, kainic acid caused seizures in the control group. It had no effect on the CR group," Amigo said.

Because previous research had shown that increasing mitochondrial calcium uptake can afford protection against excitotoxicity, he continued, "we decided to verify in vitro whether this was the case in our model. We isolated brain mitochondria from rats and again compared those fed ad libitum with those on a 40% CR diet. As we added calcium to the medium, we observed higher levels of mitochondrial calcium uptake in the CR group."

The next step was to see what happened when the mitochondria isolated from each group were treated with cyclosporin, a drug known to increase calcium retention. While calcium uptake did indeed increase in the mitochondria from the control group, it remained unchanged in the CR group, eliminating the difference observed in the previous test.

"Cyclosporin's target in mitochondria is well known," Amigo said. "The drug inhibits the action of a protein called cyclophilin D, leading to increased mitochondrial calcium retention."

In this case, however, cyclophilin D levels were found to be the same in both groups. The researchers therefore decided to measure the levels of other proteins that might be interfering with cyclophilin D's action in the organism.

"We discovered that caloric restriction induces an increase in levels of a protein called SIRT3, which is capable of modifying the structure of cyclophilin D. It removes an acetyl group from the molecule in a process known as deacetylation, and this inhibits cyclophilin D, so that the mitochondria retain more calcium and become insensitive to cyclosporin," Amigo said.

Just as other research groups had already found, the Redoxoma team also observed an increase in the activity of antioxidant enzymes such as glutathione peroxidase, glutathione reductase and superoxide dismutase

in the CR rodents' mitochondria. According to the scientists, these results suggest an enhanced capacity to manage cerebral oxidative stress, a condition that contributes to the onset of several degenerative diseases.

Many studies on the effects of caloric restriction on metabolism and cell signaling have been conducted at IQ-USP. Preliminary data suggest the change in mitochondrial calcium transport induced by caloric restriction may also occur in other tissues besides the brain, with different repercussions.

For Amigo, the proteins with activity affected by nutritional intervention in this recent study are potential targets to be explored for treatment of diseases in which excitotoxicity causes loss of neurons.

More information: Ignacio Amigo et al. Caloric restriction increases brain mitochondrial calcium retention capacity and protects against excitotoxicity, *Aging Cell* (2016). DOI: 10.1111/acel.12527

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