Controlling key enzyme in brain offers clue for future obesity treatment

December 15 2009

Eduardo Nillni is a professor of medicine at Brown University. Credit: Photo Provided

The Sirt1 enzyme in the body has generated enormous attention as a possible secret to living longer. Some scientists believe that fasting and drinking wine appear to aid in this quest because both likely activate Sirt1, unleashing its power.

But researchers from Brown University, Rhode Island Hospital and the University of Texas Southwestern Medical Center have discovered that Sirt1 in the brain has its own potential health benefit: It may keep people thinner. They determined that inhibiting the activity of Sirt1 in the brain's hypothalamic region appears to help control food intake — a

finding that potentially lays the groundwork for new treatments for obesity. Details will be published online Dec. 15, 2009, at PLoS ONE.

The discovery is the culmination of the first in-depth study of the metabolic role of Sirt1 in the brain. It suggests that Sirt1 behaves differently in the brain than in organs such as the liver and pancreas, where the enzyme has been more commonly studied.

Sirt1 research so far has posited that fasting activates Sirt1 and thereby helps extend life. Drug companies and scientists have also thrown their support behind resveratrol, a compound found in red wine, thought to be beneficial to the body because it may activate Sirt1. The new Brown research challenges at least some of the preexisting findings, because scientists found that inhibiting the activity of Sirt1 in the brains of rats, rather than stimulating it, appeared to reduce appetite, leading to a smaller weight gain compared to untreated animals. They believe a similar mechanism exists in human brains.

"It's still controversial whether calorie restriction or resveratrol are Sirt1 stimulators," said Eduardo Nillni, the study's lead author. Nillni is professor of medicine (research) at the Warren Alpert Medical School of Brown University and a member of the Department of Molecular Biology, Cell Biology and Biochemistry. At Rhode Island Hospital, Nillni is senior investigator in the Division of Endocrinology. Other authors include researchers from Brown and the University of Texas Southwestern Medical Center.

Nillni's team did find that fasting helped increase Sirt1 production and activity in the brain, consistent with the view that reducing food intake stimulates Sirt1 elsewhere in the body. But they generated clear data showing that pharmacologically or genetically inhibiting Sirt1 activity in the brain led to the animals eating less food and gaining fewer pounds compared to their untreated counterparts.

The study also indentified specific brain receptors or sites where Sirt1 induced food intake — the melanocortin receptors.

Nillni said that more work should be done to investigate whether or how the brain pathways involving Sirt1 and food intake are affected in obese animals.

Provided by Brown University